



Australian Academy of Science

**SUBMISSION TO THE THERAPEUTIC
GOODS ADMINISTRATION CONSULTATION
ON REGULATION OF AUTOLOGOUS STEM
CELL THERAPIES**

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Australian Academy of Science submission to the TGA Consultation on regulation of autologous stem cell therapies

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1 Summary of Key Points

- Stem cell science has the potential to provide innovative new therapies for treatment of injury and disease.
- Most potential treatments are still experimental and require further research to fully evaluate and verify their safety and potential benefit.
- Evidence collected in clinical trials is usually required before a new product or treatment can be approved to be marketed and used in routine medical care.
- In some countries, exemptions exist in regulatory instruments that allow proven and routine therapies, such as bone marrow transplants, coronary artery bypass grafts and skin grafts, to proceed without regulatory interference. Exemptions also exist that allow innovative but unproven stem cell therapies to go ahead in defined, low-risk circumstances outside of the clinical trials framework.
- There is a weakness in current regulations under the *Therapeutic Goods Act* in Australia that allows doctors to bypass all regulatory constraints on manufacture, manipulation, efficacy and safety reporting, if they use cells extracted directly from a patient - so-called autologous cell therapy.
- The instrument of the *Therapeutic Goods Act* that excludes autologous cell therapy from regulation is called the *Excluded Goods Order*.
 - The *Excluded Goods Order* is very broad and has had the unintended consequence of facilitating the proliferation of unfounded, unproven, and potentially unsafe cell treatments.
- Under the current Excluded Goods Order, the only oversight of the growing “stem cell therapy marketplace” lies with the Australian Health Practitioners’ Regulation Agency (AHPRA) and the Australian Competition and Consumer Commission (ACCC).
 - There is little or no scope for prevention of unproven therapies or unsound practices, and no ability to police unethical practices unless an adverse event is reported.
- Medical tourism, where patients travel overseas for treatment, is a global multi-billion dollar industry.
 - There is a lack of understanding of the difference between experimental medicine and approved therapeutic procedures in sectors of the community, and naïve acceptance of the risks associated with unproven therapies.
- At least three companies in Australia currently appear to be promoting therapies using cell-derivatives of “reprogrammed” autologous cells.
 - Cell therapy involving such cells or their derivatives may come with many additional risks to the patient, including tumor formation, unless stringent safeguards are in place.
- The International Society of Stem Cell Research (ISCCR), recommends that development of innovative therapeutic strategies be conducted in the context of clinical trials and in exceptional cases in the context of individualised care.
- Governmental regulation of unproven autologous stem cell therapies in Australia providing a blanket exemption on the use of autologous cell or stem cell therapies (irrespective of the level of manipulation of cells and whether they are for homologous or non-homologous use) falls short of both international expert opinion and the regulatory trends emerging in America and Europe.

- The National Health and Medical Research Council (NHMRC) of Australia is aware of the dichotomy between regulations in Australia and those in other jurisdictions, and has published statements targeting the public and medical practitioners advising them on the risks of unproven autologous stem cells offered by clinics.
- There is a clear opportunity for the Therapeutic Goods Administration (TGA) to harmonise Australian regulation of the provision of autologous cell and stem cell therapies with current international expert opinion and regulatory trends in other jurisdictions.
- The Australian Academy of Science supports regulatory change to protect vulnerable patients from exploitation and risk at the hands of unethical practitioners, and to promote the progression of evidence-based medicine.
- New regulations should provide the TGA, AHPRA and ACCC with the “teeth” to curb the expansion of unproven therapies becoming available in Australia, and the perception that Australia is a destination for stem cell tourism.

2 Summary of Recommendations

The Australian Academy of Science recommends:

- 1. Immediate modification of the current *Excluded Goods Order* allowing exemption of unproven autologous cell and stem cell therapies on the condition that a) they are for homologous applications and b) that they use no more than minimally manipulated cells.**
- 2. Clarification and modernisation of the terms “homologous use”, “non-homologous use”, “minimally manipulated” and “more than minimally manipulated” in the Biologicals Framework of the Therapeutic Goods Act.**
- 3. Substantial reform of regulations governing the commercial provision of all autologous cell therapies as under Option 5 of the TGA Discussion Paper.**
- 4. Clear incentives for practitioners to provide evidence of efficacy as well as safety and quality of manufacturing.**
- 5. Clarification of the responsibilities of the TGA, AHPRA and ACCC in oversight of the regulation of autologous cell and stem cell therapies under the Act including false advertising and misrepresentation of medical expertise.**

3 Background

3.1 Introduction

Stem cell science has the potential to provide innovative new therapies for treatment of injury and disease. While the last decade has seen enormous advances in the understanding of the biology of stem cells, the field is not yet at a stage where it is able to routinely use stem cells to treat the many patients that suffer from debilitating illness. Specifically, while there is growing evidence from laboratory and animal studies that stem cells may have a role in treating a range of conditions, **most potential treatments are still experimental and require further research to fully evaluate and verify their safety and potential benefit** to human health.

As a consequence, the range of diseases for which there are proven stem cell treatments available in Australia is small and limited to hematopoietic or blood stem cell transplants that aid treatment of blood and autoimmune diseases.

Clinical trials are the gold standard for evaluation of new therapies. These research studies are conducted with a high level of regulatory oversight and are designed to first assess safety, then efficacy so as to prevent dangerous or ineffective therapies moving beyond early stages of development. **Evidence collected in clinical trials is usually required before a new product or treatment can be approved to be marketed and used in routine medical care.**

In some countries, exemptions exist in regulatory instruments that allow proven and routine therapies, such as bone marrow transplants, coronary artery bypass grafts and skin grafts, to proceed without regulatory interference. Exemptions also exist to allow innovative but unproven stem cell therapies to go ahead in defined, low-risk circumstances outside of the clinical trials framework (Lysaght *et al.* 2013, *Cell Stem Cell* 13:647).

However, this creates a regulatory weakness that can be exploited by practitioners who seek to market new and unproven therapies to sick and often desperate or frightened patients. Such treatments are often expensive, attracting fees in the order of tens-of-thousands of dollars, with multiple treatments encouraged.

It is clear that a growing number of doctors and medical clinics worldwide are electing to provide such experimental cell and stem cell therapies to patients at high cost under the banner of individualised medical care. As has been identified in the TGA Discussion Paper, and by others, this raises significant concerns regarding patient safety and medical ethics, and is a situation that should be addressed through regulatory change.

In the sections below, we elaborate on the regulation of autologous cell and stem cell therapies in Australia and how this contrasts to regulation internationally, before addressing the Discussion Questions.

3.2 Regulation of autologous stem cell therapies in Australia

The use of therapeutic products and the conduct of medical practitioners in Australia are governed by different statutory bodies. Medical procedures and the conduct of medical practitioners are regulated by the Australian Health Practitioners' Regulation Agency (AHPRA), which manages the 14 national Medical Boards across Australia, and the Australian Competition and Consumer Commission (ACCC). Therapeutic products, on the other hand, are regulated by the TGA under the *Therapeutic Goods Act (1989)*, in particular the Biologicals Framework introduced in 2011.

The proliferation of unproven stem cell therapies is becoming increasingly evident in Australia and internationally. The Australian Academy of Science believe that this is in part due to the fact that **there is a weakness in current regulations under the *Therapeutic Goods Act* in Australia that allows doctors to bypass all regulatory constraints on manufacture, manipulation, efficacy and safety reporting, if they use cells extracted directly from a patient - so-called autologous cell therapy** – and as long as they administer cells to the patient for a single condition in a single course of treatment.

The instrument of the *Therapeutic Goods Act* that excludes autologous cell therapy from regulation is called the *Excluded Goods Order*. Although originally introduced to exempt straightforward and proven procedures - such as the use of a patient's veins for grafts in cardiac bypass surgery - from undue regulatory interference, ***the current exclusion is in fact very broad and has had the unintended consequence of facilitating the proliferation of unfounded, unproven, and potentially unsafe cell treatments*** by clinics in the private sector. In general, there is the view that autologous cell therapies involve much lower risk when compared to using cells from a different donor individual, a situation which would provoke much higher levels of regulation by the TGA. However, the current *Excluded Goods Order* of the *Therapeutic Goods Act* broadly exempts all autologous cell and stem cell therapies from meeting the requirements set out under the Biologicals Framework.

At present in Australia, cells can be taken from a patient and then put back into the same patient without regard for how the cells are prepared, how much they are manipulated, or how they are delivered back to the patient, and without the need to formally establish safety. There is no requirement for any independent verification of protocols or standards. Thus, it is far from clear exactly what is being injected and how one therapy relates to another.

Nor is there a requirement for practitioners to prove the effectiveness of new or unproven cell therapies that fall within this category through pilot studies or through clinical trials before marketing those therapies to patients, and there is no requirement to report back to the TGA on adverse events that arise. Thus, there is no incentive for the sector to advance evidence-based medical practice by engaging in properly controlled clinical trials, or reporting on their findings.

While the majority of interventions being offered in Australia involve injection of adipose cell or stem cell extracts directly into the joints of affected patients for musculoskeletal ailments, some doctors and clinics offer to treat a wide range of serious medical conditions - such as stroke, multiple sclerosis, retinal neuropathy, spinal cord injury, motor neuron disease and even autism – with an intravenous injection of crudely prepared cell extracts. None of these procedures are routine medical practice and most are not supported by peer-reviewed scientific evidence. Most are conducted outside of the framework of a clinical trial. Claiming that a single stem cell therapy can be used to treat such a range of serious diseases without provision of scientific evidence and safety data is an extremely optimistic, and misguided, portrayal of regenerative medicine (Bianco *et al.* 2013, *Nature Medicine* 19:35). Indeed, the assumption underpinning this approach – that mesenchymal stem cells from any tissue (including adipose tissue which is readily accessible) have the potential to differentiate into a broad range of cell types well beyond their normal functions in the body, and/or express factors that support reparative processes that are universally applicable to *any* disease context - has been extremely controversial from the outset (Bianco *et al.* 2013, *Nature Medicine* 19:35). Indeed, it has been likened to the alchemic principle of a “panacea” - a single cure for all ills. In contemporary scientific literature, it is an outdated and erroneous concept.

When a therapeutic benefit is claimed as a result of a mesenchymal stem cell clinical trial, most stem cell scientists agree that this does not occur through a stem cell mechanism (see for example Fisher

et al. 2015, *Circ Res*, Epub ahead of print: PMID: 25632038). Indeed, many clinics use crude cell preparations in which stem cells will be rare or absent. Cell preparations used for therapy, whether enriched for stem cells or not, invariably die soon after delivery, and while they may stimulate the host tissue to activate natural repair processes, they do not participate directly to any significant extent in replacement of lost or injured tissue. Advertising such treatments as “stem cell therapy” is a deception.

Under the current *Excluded Goods Order*, the only oversight of the growing “stem cell therapy marketplace” lies with the Australian Health Practitioners’ Regulation Agency (AHPRA) and the Australian Competition and Consumer Commission (ACCC). While these bodies have the authority to investigate unsafe and unsound medical practices, as well as false and misleading advertising, such inquiries can only be triggered on a case-by-case basis following an unsatisfactory experience and formal complaint. **There is little or no scope for prevention of unproven therapies or unsound practices, and no ability to police unethical practices unless an adverse event is reported.** With limited resources and expertise in cell therapy and manufacturing, it is difficult for these agencies to tackle this growing problem in Australia.

3.3 The stem cell tourism industry

The current discussion about unproven autologous stem cell therapies can be framed in the broader context of ‘stem cell tourism’, where patients travel to overseas clinics for expensive unproven ‘stem cell’ treatments (National Stem Cell Foundation of Australia *Australian Stem Cell Handbook*, 2013).

Medical tourism, where patients travel overseas for treatment, is a global multi-billion dollar industry predicted to grow exponentially over the next decade. Without medical advice, patients are increasingly using the internet to identify treatments that are either too expensive or not available in their home countries. **There is a lack of understanding of the difference between experimental medicine and approved therapeutic procedures in sectors of the community, and naïve acceptance of the risks associated with unproven therapies.**

Medical tourism thrives in countries where regulation of emerging therapies is not onerous. False advertising exploits the vulnerability of patients with serious illnesses. The industry is also promoting purely cosmetic therapies involving unproven autologous cell or stem cell applications, such as facelifts, breast augmentations, vaginal rejuvenation, and anti-aging therapy. While clinics offering autologous cell or stem cell therapies have been the subject of intense scrutiny (Cattaneo and Corbellini, *Nature* 2014, 510:333), they continue to proliferate because patient demand exceeds the level of therapy that the regenerative medicine community can currently safely provide. As discussed in a recent article, stem cells are an effective “wedge” in a broader push by vested organisations to allow commercialisation of unproven therapies and to reduce the power of regulators (Bianco and Sipp, *Nature* 510:337). Recent events in Italy show how opposition to this push by concerned scientists can pit scientists, patients, their advocates, governments, lawyers, the public and media against each other with costly consequences (Cattaneo and Corbellini, *Nature* 2014, 510:333).

In a recent survey of clinics offering autologous cell or stem cell therapies online (Connolly et al. 2014, *Travel Medicine and Infectious Diseases*, 12:695), most clinics were in the USA (27%), some offering cross border treatments with Mexico, which had 9% of clinics. Asia had a larger number of clinics (around 40%), likely aided by state-backed initiatives that foster medical tourism. Australia

currently has around 3% of clinics worldwide offering unproven autologous cell or stem cell therapies.

3.4 The scale of the problem in Australia

The number of commercial clinics offering autologous cell or stem cell therapies in Australia has grown exponentially from 1-2 in 2011, to over 40 currently (Munsie and Pera 2014, *Stem Cells Dev.* 23:34). Given the possibility that some commercial clinics may not be listed as such (*eg.*, they do not have a website and rely on patient-to-patient or clinician-patient referrals), the number may be higher.

The therapies offered by the majority of these Australian clinics involve use of adipose tissue-derived extracts, readily accessible by liposuction. These extracts are usually marketed as stem cells or stromal vascular fractions under the assumption, usually not quantified or verified, that they contain mesenchymal stem cells. Indications for treatment include osteoarthritis and cartilage repair, stroke, multiple sclerosis, retinal neuropathy, spinal cord injury amyotrophic lateral sclerosis, autism, myocardial infarction and aging. One Australian clinic even listed cancer as one of the conditions it could treat (since rescinded) (McLean *et al.* 2014, *J. Law Med.* 22:65). Clinics, particularly those with links to US concerns, are well organised and active in advertising in the media, including on television news programs and panel shows, drawing on patient and particularly celebrity testimonials.

At least three companies in Australia currently appear to be promoting therapies using cell-derivatives of “reprogrammed” autologous cells. One company claims to reprogram specialised immune cells (leucocytes) from the blood into “multipotent stem cells” - capable of differentiating into many lineages. Another company claims to produce autologous cells for therapy by “direct reprogramming” of blood cells into neurons. While this is potentially exciting technology and has some basis in research settings, there are many manufacturing and safety issues to consider. A third company claims to reprogram autologous adult cells to a state of “pluripotency” – the ability to differentiate into all lineages of the body. This latter case is truly alarming. While their reprogramming methods have not been disclosed, it is claimed that they are safe and do not require genetic engineering. What is not included in the public material available from these companies however is that reprogramming to pluripotent cells usually involves major genetic manipulation of cells harvested from the patient in the laboratory, and imposes major changes to the epigenetic regulation of gene expression in those cells. The reprogramming method may be accompanied by other unintended and unpredictable genetic changes to the chromosomes of the reprogrammed cells (Hussein *et al.* 2013, *Bioessays* 35:152). **Cell therapy involving such cells or their derivatives may come with many additional risks to the patient, including tumor formation, unless stringent safeguards are in place.**

3.5 International expert opinion

In 2013, the International Society of Stem Cell Research (ISSCR), the umbrella society for stem cell research internationally, issued a statement on the use of unproven autologous cell-based interventions in patients (<http://www.isscr.org/home/about-us/news-press-releases/2013/2013/09/12/isscr-statement-of-delivery-of-unproven-autologous-cell-based-interventions-to-patients>). ISSCR recognises that development of innovative therapeutic strategies to

patients is essential for the advancement of medicine. **The International Society of Stem Cell Research (ISCCR), recommends that development of innovative therapeutic strategies be conducted in the context of clinical trials and in exceptional cases in the context of individualised care.** However it condemns the provision of unproven treatments to large populations of patients for profit and furthermore states that it is “*unethical and unprofessional to market such interventions directly to patients*”. It recommends that unproven therapies provided outside of the context of a clinical trial should satisfy a number of criteria:

- Provision to at most a small number of patients
- A scientific rationale, including pre-clinical evidence of efficacy and safety
- Full characterization of the types of cell being transplanted and their processing
- Plans for peer-review, clinical follow-up and data collection to assess efficacy and safety
- An action plan for adverse events
- A commitment to report results
- A commitment to move to a clinical trial in a timely manner after experience on a few patients.

3.6 Regulation in Australia relative to other jurisdictions

The approach in Australia to regulation of biologicals and in particular stem cell-based therapeutics, as in many jurisdictions around the globe, is based on perceived risk. The approach recognises the need to preserve the clinical autonomy of medical professionals as well as patient choice, and to allow proven and low-risk therapies to be used unimpeded by regulation. It also seeks to balance patient access to evidence-based innovative, but not yet fully proven, and routine therapies with the inherent risks of clinical research (Lysaght *et al.* 2013, *Cell Stem Cell* 13:647). However, variations in regulatory approach arise depending on which cells and procedures are classified as having “minimal risk” (Lysaght *et al.* 2013, *Cell Stem Cell* 13:647). In some countries, autologous cell products that are “minimally manipulated” and for “homologous use” are excluded from regulation as medicinal products under various exemptions, such as the Specials Scheme and Hospital Exemption Scheme in the UK, however, consistent with guidelines published by the ISCCR, these are designed for application of innovative therapies only in special circumstances and to small numbers of patients. As acknowledged in the TGA Discussion Paper, definitions of the terms “more than minimal manipulation” and “non-homologous use” vary in different jurisdictions.

In the US, under the Public Health Safety Act, any stem cell product containing cells that are cultured in the laboratory or processed in other ways (“more than minimally manipulated”) or used for other than their normal function (“non-homologous use”), would require the submission of an investigational new drug application to the Food and Drug Administration (FDA), requiring strict oversight (Halme *et al.* 2006, *N Engl J Med* 355:1730). With specific respect to adipose-derived cellular extracts, in 2014 the FDA issued a draft guidance statement that recommended that interventions utilising adipose derived tissue, including stromal vascular fraction, should be regulated as a drug where their production involves more than minimal manipulation and/or non-homologous use (FDA Draft guidance: **Minimal manipulation of human cells, tissues and cellular and tissue-based products**).

The FDA also provides warnings to consumers concerning unproven stem cell therapies. Furthermore, the FDA demonstrates its intention to prosecute stem cell therapists who flaunt regulation. On its website, the TGA cites prosecution of three individuals in 2011 with links to a Mexican clinic, for manufacturing, selling and using stem cells without FDA approval. In 2014, the FDA Office of Criminal Investigations issued a release concerning sentencing of an individual in the

Southern District of Texas to 78 months jail for falsely promoting therapy involving stem cells for multiple sclerosis, Parkinson's and other neurological diseases, and falsely claiming that their procedures had been reviewed by the FDA. Also in 2014, the District of Columbia Court of Appeals, in a case against the stem cell company Regenerative Sciences, upheld the FDA's position that stem cells grown in the laboratory are in fact drugs requiring FDA regulation. The FDA has also recently issued warning letters to cosmetics companies marketing stem cell creams, putting them on notice that their creams are promoted for uses that cause them to be considered as biological drugs.

In the European Union, regulation is complex and conducted through multiple agencies across multiple jurisdictions (PAS 83:2012 British Standards Institution, 2012). However, human cells that are expanded in culture are deemed "more than minimally manipulated". Cell products that are more than minimally manipulated or for non-homologous use are considered *medicinal products*, and the developer is required to demonstrate that they are manufactured to an appropriate and consistent standard, and are acceptably safe and efficacious. The overall risk/benefit to the proposed patient population is evaluated considering available data on quality, safety and efficacy on a case-by-case basis. Furthermore, demonstrated good manufacturing practice (GMP) is mandatory.

Governmental regulation of unproven autologous stem cell therapies in Australia providing a blanket exemption on the use of autologous cell or stem cell therapies (irrespective of the level of manipulation of cells and whether they are for homologous or non-homologous use) falls short of both international expert opinion and the regulatory trends emerging in America and Europe. Oversight is provided only by the AHPRA; however, the AHPRA only oversees registration and professional standards, and does not register or exert any regulatory control of unproven or unethical therapeutic practice unless an adverse event comes to light and a complaint is made (Lysaght *et al.* 2013, *Cell Stem Cell* 13:647). This extends to false advertising that may breach consumer protection laws (McLean *et al.* 2014, *JML* 22:65).

The National Health and Medical Research Council (NHMRC) of Australia is aware of the dichotomy between regulations in Australia and those in other jurisdictions, and has published statements targeting the public and medical practitioners advising them on the risks of unproven autologous stem cells offered by clinics (NHMRC Media Release, Dec 19 2013). These views are echoed in the *Australian Stem Cell Handbook* (2013), published by the National Stem Cell Foundation of Australia and statements from patient groups (Motor Neuron Disease Australia: Position Statement Jun 2014) and professional bodies (Australian Rheumatology Association [<https://www.rheumatology.org.au/downloads/ARA%20Position%20Statement%20042014.pdf>]; Royal Australasian College of Physicians: Media Release 21 Nov 2014).

4 Response to TGA Discussion paper

The Australian Academy of Science acknowledges that the risks of acute adverse events associated with autologous stem cell therapies as judged by published clinical trials data appear to be low. However, information on risk derived from clinical trials data cannot be extrapolated to risk from new and unproven cell or stem cell therapies. Furthermore, as the level of unregulated manipulation of cell or stem cell fractions used in autologous therapies increases, as we believe it will, it is entirely possible that the risk of adverse events will increase. Therefore, the evaluation of risk must be ongoing, and perception of risk may change as the long-term impact of clinical trials and exempt therapies are fully evaluated.

There is a clear opportunity for the TGA to harmonise Australian regulation of the provision of autologous cell and stem cell therapies with current international expert opinion and regulatory trends in other jurisdictions. While full harmony would be difficult, clarification of terms such as “more than minimally manipulated” and “non-homologous use” in ways that align in spirit with the definitions of other jurisdictions, and regulation of autologous therapies in the context of these definitions, should be achievable. **The Australian Academy of Science supports regulatory change to protect vulnerable patients from exploitation and risk at the hands of unethical practitioners, and to promote the progression of evidence-based medicine.** The Australian Academy of Science supports Australia as a leader in global efforts by scientists and regulators to curb unethical practices associated with stem cell tourism and to promote evidence-based medicine. It calls for regulation of this sector in Australia as described under Option 5 in the TGA Discussion paper. **New regulations should provide the TGA, AHPRA and ACCC with the “teeth” to curb the expansion of unproven therapies becoming available in Australia, and the perception that Australia is a destination for stem cell tourism.** Stronger harmony between the TGA and other regulatory agencies including AHPRA and ACCC is also desirable under any new regulations, so that false advertising of the nature and likely benefits of unproven cell therapies, inappropriate patient consent, and misrepresentation of clinical expertise can be discouraged and prosecuted. This should apply to any unregulated homologous and minimally manipulated autologous cell therapies.

Self-regulation of the sector in the form of a Code of Conduct has been mooted by representatives of nine companies offering autologous stem cell therapies in Australia as a first step towards a more adequate regulatory framework provided by Government instruments (Tuch and Wall 2014, *Med J Aust.* 200:196). This has not yet been published and not all companies offering autologous stem cell therapies have been represented in discussions (Vesey 2014, *Med J Aust* 201:514). We believe that formally protecting patient safety is paramount and commercial interests secondary. Self-regulation is an admirable short-term goal if there are significant delays in regulatory reform, but should not prevail as a long-term solution.

We expand on these points individually as we address the specific Discussion Questions below.

Response to Discussion Questions

4.1 What are the public health risks of ‘autologous stem cells’? What is the evidence for these risks?

4.1.1 Overall risk

Few studies adequately address the inherent risk in autologous stem cell therapies. However, data emerging from clinical trials, mostly using bone marrow fractions or mesenchymal stem cells from bone marrow or adipose tissue, suggests that only few serious adverse effects arise in the short or medium-term with autologous stem cell therapies for a range of medical conditions (Lalu *et al.* 2012, *PLoS One* 7:e47559). Extensive data is accumulating for some clinical applications. For example, a number of clinical trials evaluating cell therapies for ischemic and dilated cardiomyopathy, and heart failure, have now been published, and have been the subject of recent meta-analyses (see for example Fisher *et al.* 2015, *Circulation Research* Epub ahead of print: PMID: 25632038). Overall, Fisher *et al.* conclude that autologous cell-based therapies are safe as a treatment for ischemic heart failure, with minimal major adverse effects and no increase in the incidence of arrhythmias.

Some additional data can be gleaned from animal studies. In a review of safety and efficacy of mesenchymal stem cell therapy for intervertebral disc degeneration in animal models (a relatively high-risk procedure), it was concluded that this therapy is *largely* safe, albeit that 2 of 24 studies reported ectopic ossifications in 5% of animals, potentially the result of leakage of injected cells from the disc (Yim *et al.* 2014, *Stem Cells and Development*, 23:2553). However, it is likely that animal studies under-report adverse events.

It is important to stress that most current clinical trials using autologous cell therapies are Phase I and Phase II, in which only small numbers of patients are recruited. Thus, the scale of adverse events that may emerge as much larger Phase III and IV clinical trials are conducted in the future is difficult to predict. Fisher *et al.* and other authors have also noted the potential for reporting bias in published studies on cardiac stem cell clinical trials, highlighting the need for trials on larger groups of patients with more rigorous reporting.

We are unaware of any adverse events from unregulated autologous stem cell therapies in Australia thus far, although it is likely that adverse events will occur as activity in the sector increases. Serious adverse events are likely to receive significant publicity, as they have elsewhere.

4.1.2 Background risk

An increasing number of isolated serious adverse events involving different types of autologous cell and stem cell therapies are being reported in the literature. These indicate that therapies of this nature do have a background risk of serious adverse events that is greater than the general risk associated with injection of other substances. These include lethality, tumours, leukemia, hypoplasia and differentiated cell masses (Amarigli *et al.* 2009 *PLoS Medicine* 6:221; Thirabanjasak *et al.* 2010, *CJASN* 21:121; Folkerth *et al.* 1996, *Neurology* 46:1219; Dlouhy *et al.* 2014, *J Neurosurg Spine* 21:618), pulmonary embolism (Jung *et al.* 2013, *Yonsei Med J.* 54:1293), arrhythmias (Pytel *et al.* 2010, *Cardiovasc Pathology*, 19:e33) and acute demyelinating illness (Kishk *et al.* 2013, *J. Clin. Neurosci.* 20:310). Intravenous injection of autologous mesenchymal stem cells embolise the circulation of the lungs and other organs, where they cause endothelial damage – a general and potentially significant adverse effect (Lee *et al.* 2009, *Cell Stem Cell* 5:54; Schrepfer *et al.* 2007, *Transplant. Proc.* 39:573). Patients are also at risk of cerebrovascular events. In a recent

announcement (Aug 2014), the San Diego-based company Cytori Therapeutics halted two clinical trials using adipocyte stem cell therapy for heart failure (ATHENA and ATHENA II), after adverse cerebrovascular events in 3 patients. Additional adverse events may be recognised over a longer time frame. It is likely that abnormal growth or differentiation of injected stem cells occurs more frequently than is appreciated; as such events come to light only when clinical symptoms appear.

4.1.3 Other current or future risk considerations

4.1.3.1 *Extrapolating risk from clinical trials data to unregulated autologous stem cell therapies performed in clinics*

Conclusions about the safety or efficacy of autologous bone marrow or adipose cell therapy, or mesenchymal stem cell therapy, reported in the clinical trials literature cannot be generalised to predict safety or efficacy in autologous cell therapies offered in Australia under the *Excluded Goods Order*.

The cell therapy clinical trials reported in the literature have a high degree of oversight over conditions of cell manufacture, delivery methods, patient safety and clinical outcomes. Patient recruitment and protocols are subject to review by human research ethics committees and other regulatory bodies, and trials will be registered with the NIH Clinical Trials website or regional equivalent. Patients are, in general, carefully stratified according to disease and their condition carefully followed by specialist clinicians.

By contrast, autologous therapies offered in Australia under the *Excluded Goods Order* by medical practitioners or clinics target a vast range of medical conditions often with a single type of treatment, without the necessary stem cell expertise or indeed specialist medical expertise related to the particular conditions being treated, and without obligation for clinical follow up. There is no obligation to adhere to any particular standard or protocol for cell isolation, manufacture or delivery, and therefore cell populations may vary enormously in composition and stem cell content (Shen 2013, *Nature* 499:38). There is a risk of contaminating cell types or that there is a complete lack of the desired cell type (see for example Cattaneo and Corbellini, *Nature* 2014, 510:333). This lack of standardisation of cell preparation and quality control has been identified as a major impediment for the field in advancing evidence-based medicine (Shen 2013, *Nature* 499:38). Furthermore, because there is little appetite for self-regulation within clinics providing unproven autologous cell therapies, and reporting of methods is vague (McLean *et al.* 2014, *JML* 22:65), the prospect of any progression towards standardisation of methodologies seems remote (Shen 2013, *Nature* 499:38).

Adding to this, there is no obligation or incentive under the current Order to report adverse events to regulatory bodies in an unbiased way or to respond to them through modifications to protocols. Indeed, the unregulated environment for the conduction of autologous cell or stem cell therapies in Australia is also conducive of misleading advertising to vulnerable patients (McLean *et al.* 2014, *JML* 22:65). The well-established peer-review process for publication of scientific data that limits false or misleading claims, and demands reporting of adverse events and financial or other conflicts of interest, is completely bypassed. An additional major concern is the misrepresentation of clinical expertise (McLean *et al.* 2014, *JML* 22:65). Misleading advertising on the nature or promoting the efficacy of autologous cell or stem cell therapies, in addition to potentially breaching consumer protection laws, violates a number of other medical professional codes, undermines the integrity of

the medical profession and breaches the trust invested in doctors who have a duty of care to their patients.

The clinical literature fully recognises that mesenchymal and adipose tissue stem cell therapies are experimental medicine and that “larger scale controlled clinical trials with rigorous reporting of adverse events are required to further define the safety profile of MSCs” (Lalu *et al.* 2012, *PLoS One* 7:e47559). Clinics offering stem cell therapies for high fees under the *Excluded Goods Order* are under no obligation to recognise or acknowledge the experimental nature of treatments, and generally do not do so explicitly on their websites or promotional material. Evidence for efficacy is usually anecdotal. In effect, the Order allows clinics to bypass proper patient informed consent and the need for reporting of adverse events in this context. The questionable legality of these conditions has been discussed (McLean *et al.* 2014, *JML* 22:65).

4.1.3.2 *Increased risks associated with more than minimally manipulated cells and non-homologous use*

The *Excluded Goods Order* does not distinguish in regulatory terms between autologous cells that have been “minimally manipulated” and those that have been “more than minimally manipulated”. The latter might include cells that have been cultured for the purpose of expansion or to enrich for stem cells, or manipulated in other ways, including genetic manipulation, reprogramming or combining cells with animal products or chemicals that alter their natural state. Nor does it distinguish between cells for “homologous” and “non-homologous” use. Homologous use may be the application of autologous bone marrow mesenchymal stem cells for musculoskeletal repair (Bianco *et al.* 2013, *Nature Medicine* 19:35). Non-homologous use may be the application of the same bone marrow stem cells for spinal cord repair or to treat heart failure. The US-based clinical trials registry, ClinicalTrials.gov, lists 204 clinical trials involving autologous mesenchymal stem cells for diseases including spinal cord injury, inflammatory bowel disease, multiple sclerosis, Parkinson’s disease, multiple system atrophy, emphysema, stroke, infarction of the cerebral artery, alcoholic liver cirrhosis, ovarian failure, pulmonary fibrosis, diabetes type I and II, dilated cardiomyopathy, osteoarthritis, intervertebral disc degeneration, chronic renal failure, tendonopathy, bone fractures *etc.* Most of these therapies involve non-homologous use of cells.

The use of more than minimally manipulated cells introduces additional risks, including an increased risk of infectious disease and the accumulation of genetic or epigenetic changes to the DNA in cells that could alter their state or increase the risk of tumour formation. While stem cells have their own intrinsic identity, they are also instructed by their tissue environment, which may not be optimal for regeneration in the setting of non-homologous therapies. While the modern concept of mesenchymal stem cell biology introduced by Caplan in the early 1990s, emphasises the broad potency of these cells and their apparent suitability for use in non-homologous therapies, this assumption has been vigorously contested (Bianco *et al.* 2013, *Nature Medicine* 19:35). Non-homologous use increases the risk of invoking an abnormal tissue response to a foreign environment.

4.1.3.3 *Increased risks associated with reprogramming*

The *Excluded Goods Order* does not distinguish in regulatory terms between cells that have been minimally manipulated and those that have been manipulated in ways that alter their natural state. We note a move in Australia towards the promotion of therapies involving the cellular derivatives of “reprogrammed” autologous cells (see Section 2.5 above), including cells reprogrammed to pluripotency. Pluripotent stem cells are a form of super-stem cell with characteristics similar to stem cells obtained directly from very early pre-implantation human embryos (embryonic stem cells).

Pluripotent cells are highly tumorigenic. Reprogramming techniques that generate pluripotent or multipotent stem cells is a focus of basic research in many labs around the world, but this collective work is still a long way from achieving a clear understanding of the mechanisms of reprogramming, and optimal processes or potential impacts that cause genetic instability or unpredictable changes in cell state, particularly as relates to human application (see, for example, Hussein *et al.* 2014, *Nature* 516:198). Manipulations of this sort are allowed under the *Excluded Goods Order* because the initial cells harvested from the patient are autologous. However, as noted above (Section 2.5), there is likely to be much higher levels of risk associated with cell therapies using reprogrammed cells unless stringent safeguards are in place. In contrast to the many autologous and allogenic mesenchymal stem cell clinical trials currently underway, only few trials utilising cells derived from pluripotent stem cells have been approved in the US (for example, Cyranoski 2013, *Nature Biotechnology* 31:775) because of the complex safety considerations.

4.1.3.4 *Risks associated with manipulations that increase stem cell survival and tissue replacement*

For most autologous stem cell therapies, the literature remains equivocal as to whether there is a benefit to patients. Where a benefit is claimed as a result of clinical trial evidence, most scientists agree that this is unlikely to occur through a stem cell mechanism (Bianco *et al.* 2013, *Nature Medicine* 19:35). In animal models, cell preparations infused systemically are embolised by the lungs and other organs and are subsequently cleared (Lee *et al.* 2009, *Cell Stem Cell* 5:54; Schrepfer *et al.* 2007, *Transplant. Proc.* 39:573). If they are introduced directly into an organ, while some cells may engraft, any positive benefit to organ function is likely to be due to the release of paracrine factors (for example, Tang *et al.*, 2010, *Circulation* 121:293). Introduced cells can stimulate the host tissue to activate natural repair processes, or modify the immune system, but in most therapeutic settings it is unlikely that they will participate significantly in replacement of lost or injured tissue. A natural progression for the field will be to identify the factors responsible for regenerative effects and to develop these as therapies. However, others will explore methods that encourage the survival of injected stem cells, and promote their participation in tissue replacement (see for example Mohsin *et al.* 2012 *J. Am. Coll. Cardiol.* 60:1278). Under such circumstances of donor cell survival, risks are likely to increase, particularly for malignant transformation. The identity of stem cells is determined in part by the hormonal signals they receive from the tissue environment. Such signals are complex and heterogeneous, and influenced by injury and disease. There is no guarantee that long-lived stem cells will differentiate into the tissue types appropriate for regeneration, particularly under non-homologous use.

For all of these reasons, clinics marketing these therapies to patients with the implied assertion that clinical benefit will be derived as a direct result of the action of autologous stem cells are likely to be at best misrepresenting the state of the science, and at worse, deliberately misleading.

4.1.3.5 *Indirect risks to patients enrolled in unproven autologous cell therapies*

Because there is no obligation for clinics promoting autologous cell or stem cell therapies to offer evidence of efficacy as a rationale for such treatments, or report their findings, the public is missing out on the benefits of the knowledge accumulated from the conduction of properly configured trials. Patients treated at unregulated clinics may find that they are excluded from enrolment in a registered clinical trial or properly configured trial of an innovative therapy due to the unpredictable effects of their treatment on trial outputs. There may also be a delay in implementation of standard care. Patients may incur greater costs associated with unproven treatments. An additional consideration is the lack of long-term follow-up in clinical care associated with un-regulated clinics. This is a direct consequence of both the business model of these clinics and of the lack of any

requirement for them to report adverse events. These factors add additional levels of risk for patients seeking the most up to date but unproven medical treatments.

4.2 What identified risks should have highest priority for resolving?

There are quantifiable risks associated with autologous cell therapies that include death, tumour formation, pulmonary embolism, cerebrovascular events and the development of ectopic differentiated tissues masses. While apparently low, the level of risk will only become apparent as data from clinical trials accumulates. Thus, assessment of risk is ongoing. Risk is likely to be higher in unregulated autologous cell therapies for non-homologous use provided by clinics for pecuniary gain. Any unregulated increase in the level of manipulation of cells used in cell therapies, including prior cell culture to expand cells or to enrich for stem cells, concomitant use of animal products, reprogramming, or augmentation of cell survival, self-renewal, growth or differentiation pathways, will likely further increase the level of risk to patients. Such manipulations may already be a reality in Australia. Non-homologous use and more than minimal manipulation of cell fractions should be the highest priority for regulation. The Australian Academy of Science takes the view that regulation in this sector must harmonise not only with current expert opinion internationally and regulation in other jurisdictions such as the USA and Europe, but also with regulatory vehicles in Australia that have oversight of the registration and ethical conduct of practitioners and the legality of their actions (see McLean *et al.* 2014 *J. Law Med.* 22:65).

4.3 Are there public health benefits, such as patient access to new and novel treatments, to consider?

Innovative but unproven therapies are legitimate tools for advancing medical knowledge and can be used to provide the foundation for further explorations through clinical trials. The ISCCR recognises the need for innovative therapies on small numbers of patients, however with clear expectations surrounding the provision of pre-clinical data on safety and efficacy, a plan for peer-review and for moving forward to clinical trials, and an action plan for adverse events. The Academy of Science supports this view and believes that unproven innovative cell and stem cell therapies that have the potential to advance medical knowledge and alleviate suffering, should be made available to Australian patients in need. However, it is imperative that such therapies be regulated in the context of a pilot study or clinical trial, and in a way that ensures patient safety and promotes evidence-based approaches to medicine and ethical practice amongst clinicians.

We reject the implication that regulation of this sector will stifle access of patients to innovative therapies or prevent Australia from becoming a world leader in clinical trials of autologous stem cell therapies (see Rollins, AMA Local News, “Stem cell cowboys bring the watchdog sniffing” 16th Feb 2015). Provision of unregulated therapies without safety and efficacy reporting does not advance evidence-based medicine. Regulation of the sector under all Options suggested under the TGA Discussion paper does not affect the use of autologous cells in clinical trials.

5 Call for increased regulation

The Australian Academy of Science supports the principal of evidence-based medicine underpinning responsible translation of stem cell science and regenerative medicine into accepted clinical practice in Australia and throughout the world.

We concur with the ISSCR Guidelines on Clinical Translation of Stem Cells and in particular their recent statement that it should be considered unethical to market unproven cell-based interventions outside of clinical trials – even when the patient’s own cells are used. We also echo their call on medical licensing bodies, legal authorities, patient advocacy organisations, physicians, and others to exercise their influence to discourage commercial provision of unproven autologous cell-based interventions outside of clinical trials.

The Australian Academy of Science believes that the responsibility for regulatory change rests not only with the TGA, but also allied agencies such as the AHPRA and ACCC who share responsibility for oversight of unethical medical and other practices.

The Australian Academy of Science recommends the following regulatory changes in Australia:

1. An immediate implementation of Option 2 of the TGA Discussion Paper (*Regulation of autologous stem cell therapies*) using legislative instruments available to the Minister for Health and Secretary; *ie. Immediate modification of the current Excluded Goods Order allowing exemption of unproven autologous cell and stem cell therapies on the condition that a) they are for homologous applications and b) that they use no more than minimally manipulated cells.*
2. Autologous stem cells not meeting these conditions should be regulated under the Act as a biological at the level of Class 2, 3 or 4. Such amendments to the *Excluded Goods Order* would curb the most dangerous and untested current practices and avoid putting patients and indeed the sector at an unacceptable risk. Option 2 would also forbid advertising of unproven cell and stem cell therapies to the public, which will curb false and unethical advertising on the nature and benefits of such therapies and incentivise the sector to contribute to the evolution of therapies through evidence based medicine. This implementation will require a **clarification and modernisation of the terms “homologous use”, “non-homologous use”, “minimally manipulated” and “more than minimally manipulated” in the Biologicals Framework of the Therapeutic Goods Act.** This should ideally be harmonised with the spirit of definitions used in the US and Europe. Cells that are expanded in culture, altered genetically, treated with drugs that alter wholesale the epigenetic makeup of cells, or are reprogrammed to a higher stem cell state, must be constituted “more than minimally manipulated”. It is our understanding that the Secretary of the Department of Health, or a delegate of the Secretary, has the authority to make or change Orders under Section 7 of the Act as with the *Therapeutic Goods (Excluded Goods) Order No. 1* of 2011. Therefore, the implementation of Option 2 could be done quickly and would bring some of the currently excluded therapies back under the control of the Act as biologicals.
3. **Substantial reform of regulations governing the commercial provision of all autologous cell therapies as under Option 5 of the TGA Discussion Paper.** – regulation under the Act as a Class2, Class3 or Class4 biological. Under this Option, all autologous cells used for therapies are

regulated as a biological of Class 2 or above, and must be evaluated by the TGA for their quality, safety, and efficacy for their intended purpose, prior to inclusion in the Australian Registry of Therapeutic Goods (ARTG). This is the only Option that provides **clear incentives for practitioners to provide evidence of efficacy as well as safety and quality of manufacturing**, and is therefore the only Option that protects patients from actions that exploit their vulnerability for commercial gain, and ensure their safety. Under this Option, Australia will be seen as a world leader in advancing evidence-based medicine aligned with international expert opinion and efforts to curb stem cell tourism. It is our understanding that implementation of Option 5 would require use of a legislative instrument as specified in the *Legislative Instruments Act 2003 S 3 (b)* to the Regulations defining a biological under Section 32A of the Act by the Minister or the Minister's delegate, after appropriate consultation.

Options 4 and below are inadequate. Under Option 4, autologous stem cells for homologous use and which are minimally manipulated require registration in the ARTG as a Class 1 biological. Those for non-homologous use and more than minimally manipulated would require registration as a Class 2, 3 or 4 biological. However, a Class 1 biological (of which there are currently none) represents the lowest level of risk and is associated with the lowest level of regulation. While requiring certifications on safety and applicable standards of quality and advertising, and reporting of adverse events, the TGA is not actually required to evaluate a Class 1 biological for their safety and quality. Importantly, users are not required to attest to the *efficacy* of proposed therapies under this Option, and neither the manufacturer nor the manufacturing process requires licensing. This is inadequate oversight, as it does not discourage proliferation and commercialization of unproven therapies, and potentially exposes patients to considerable and unquantifiable risks of serious adverse events for no therapeutic gain. Furthermore, as noted by the TGA in their Discussion Paper, this Option “may, inadvertently, provide an inappropriate level of confidence in the products as they will be seen to be regulated by the TGA, but without strict assessment of safety, quality and efficacy. This may then perpetuate patients exposing themselves to risk with insufficient evidence of benefit”.

4. **Regulation of autologous cell therapies in Australia is to be based on a risk/benefit analysis rather than assessment of risk alone. Of the Options presented in the TGA Discussion Paper, Option 5 is the only suitable instrument for regulation based on risk/benefit.**
5. **Clarification of the responsibilities of the TGA, AHPRA and ACCC in oversight of the regulation of autologous cell and stem cell therapies under the Act including false advertising and misrepresentation of medical expertise.** Collectively, these bodies should have the will and teeth to enforce regulations through prosecution. This would largely be achieved through regulation by the TGA under Option 5 of the Discussion Paper and this would place responsibilities for all dimensions of regulation of unproven autologous cell and stem cell therapies in the hands of the single most appropriate body, the TGA. It will create a regulatory environment in which there is no uncertainty concerning expectations under the Act and the penalties associated with breaches of the Act.