Australian Academy of Science

SUBMISSION TO THE

TGA CONSULTATION ON REGULATION OF CELL AND TISSUE PRODUCTS AND PROPOSED CONSEQUENTIAL CHANGES TO CLASSIFICATION OF BIOLOGICALS

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Australian Academy of Science submission to the TGA Consultation on regulation of cell and tissue products and proposed consequential changes to classification of biologicals

1 Summary of key messages

1. Stem cell science has the potential to provide innovative new therapies for treatment of injury and disease.
2. Most potential treatments are still experimental and require further research to fully evaluate and verify their safety and potential benefit.
3. 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.
4. 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-based interventions to go ahead in defined, low-risk circumstances outside of the clinical trials framework.
5. There is a weakness in current regulations under the *Therapeutic Goods Act 1989* in Australia that allows Australian medical practitioners 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'.
6. The instrument of the Therapeutic Goods Act that excludes autologous cell therapy from regulation is called the *Therapeutic Goods (Excluded Goods) Order No 1 of 2011*.

   The term pertaining to the use of human cells and tissues is very broad and has had the unintended consequence of facilitating the proliferation of unfounded, unproven, and potentially unsafe cell treatments often marketed as 'stem cell' treatments.
7. 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), State/Territory regulators 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.
8. 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.
9. At least one company in Australia currently appears to be promoting therapies using cell-derivatives of autologous cells that have been 'converted' to a more pluripotent state.

   Cell therapy involving such cells or their derivatives may impose many additional risks to the patient, including tumour formation, unless stringent safeguards are in place.
10. The International Society of Stem Cell Research (ISSCR) and the International Cell Therapy Society (ISCT) recommend that development of innovative therapeutic strategies be conducted in the context of clinical trials and in exceptional cases in the context of individualised care.
11. 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, and runs the risk of positioning Australia as a destination for unregulated 'stem cell tourism'.

12. 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.
13. There is a clear opportunity for the Therapeutic Good 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.
14. 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. Section 4 of this document outlines the Australian Academy of Science's support for Option 4 and provides detailed response to questions raised in the TGA 2016 consultation paper.
15. New regulations should be introduced without delay to 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 Recommendations

The Australian Academy of Science recommends:

1. **Immediate modification of the current Excluded Goods Order allowing exemption of autologous cells and tissue from TGA oversight only where a) preparation involves minimal manipulation; b) the cells or tissue are for homologous applications; c) they are not advertised directly to consumers, and d) the use is under the supervision of a registered Australian medical or dental practitioner.**
2. **Immediate adoption of Option 4 outlined in the 2016 TGA Discussion Paper, together with the inclusion of "homologous" in modifications, to avoid any further confusion regarding the remit of TGA's oversight in relation to autologous cells and tissues.**
3. **Adoption of the revised definition of "minimal manipulation" in the Biologicals Framework of the Therapeutic Goods Act.**
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, State and Territory regulators and ACCC in oversight of the regulation of autologous cell-based therapies to avoid duplication of endeavour and to ensure a more prompt and coordinated response to systemic misrepresentation of therapeutic benefit and safety of unproven 'stem cell' therapies in Australia.**

3 Background

This section provides an update to the information provided to the TGA by the Australian Academy of Science as part of the 2015 public consultation on the regulation of autologous stem cell therapies. Concerns regarding the extent of the Australian 'stem cell marketplace' and the lack of effective regulation of autologous therapies have not diminished over the last eighteen months. Action in the form of regulatory change is required to protect vulnerable patients from exploitation and risk at the hands of unethical practitioners, and to promote the progression of evidence-based medicine in Australia.

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 cell-based interventions 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, and skin grafts.

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. Autologous cell-based products should not be an exception.**

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. A recent review of online direct-to-consumer marketing of stem-cell-based interventions illustrates that there are hundreds of clinics operating around the globe, including in countries such as the United States, Ireland, Australia, and Germany (Berger *et al.* 2016 *Cell Stem Cell* 9(2):158). As has been identified in the 2016 TGA Consultation Paper, and by others, such practices have the potential for increased risk to patient safety and should be addressed through regulatory change to ensure appropriate oversight is in place.

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 specific questions raised in the 2016 Consultation Paper (see Section 4).

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 and state and territory regulators, with regulation of consumer goods and false and misleading advertising under the remit of the Australian Competition and Consumer Commission. 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 believes 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 Australian medical practitioners 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 *Therapeutic Goods (Excluded Goods) Order No 1 of 2011* or 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 (Munsie and Pera 2014 *Stem Cells Dev* 23:34; McLean et al. 2015 *Stem Cell Res Ther*. 2015 6:33). 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 that 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, irrespective of the level of manipulation or intended use.

In Australia at present, cells can be taken from a patient and then put back into the same patient without regard for how the cells are prepared, the exact cellular composition of the preparation, 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 aliments, 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. In some cases the site of administration of cell preparations—for example intravitrial and trans-thecal injections—are of considerable concern in of themselves with respect to patient safety, as evidenced by the recent cases of blinding after administration of autologous cell into the vitreous of the eye for macular degeneration in the US (Ledford 2016 *Nature* 537:148). None of these treatments is 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, the universality of a single cell or stem cell therapy is an out-dated and erroneous concept.Furthermore, 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*, 16(8):1361). 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, are invariably embolised by the lungs and other organs, and cleared by the immune system, 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 autologous 'stem cell therapy marketplace' lies with the Australian Health Practitioners' Regulation Agency and the Australian Competition and Consumer Commission. 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*, 2015). **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, and because the regulation and scrutiny of unproven autologous cell therapies is low. In some countries, there is state or national-level support for stem cell therapies for commercial reasons, and lower regulatory oversight, despite such therapies being unproven and potentially unsafe. 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, 2014 *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).

However, the provision of unproven stem cell interventions is not just a hallmark of countries with lax or limited regulatory oversight. A recent survey of 'stem cell' clinics marketing their services online (Berger *et al.* 2016 *Cell Stem Cell* 9(2):158), reported that the top ten countries by number of clinics were USA (187 clinics), India (35), Mexico (28), China (23), Australia (19), UK (16), Thailand (14), Malaysia (12), Germany (11), and Indonesia (7). Another report suggests that the number of USA businesses engaged direct-to-consumer marketing is actually 351 with authors commenting that "regulatory inaction [by the Food and Drug Administration and others] has emboldened entrepreneurial physicians and other market participants" (Turner and Knoepfler, 2016 *Cell Stem Cell* 19(2):154).

3.4 The scale of the problem in Australia

The number of commercial medical practitioners offering autologous cell or stem cell therapies in Australia has grown exponentially from 1-2 in 2011, to over 40 by 2014 (Munsie and Pera 2014, *Stem Cells Dev.* 23:34). Given the possibility that some commercial clinics may not be listed as such (*e.g.* 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. Such direct-to-consumer advertising can also be augmented by aggressive marketing tactics. In the extreme this can include bombarding those contemplating treatment with further

information regarding the unsubstantiated but alleged benefits of such therapy (see ABC 730 report, 21 September 2016).

While most clinics appear to use cells that have not been extensively manipulated *ex vivo*, **at least one company in Australia currently appears to be promoting therapies using cell-derivatives of autologous cells that have been 'converted' to a more pluripotent state.** While specific details regarding the manufacturing are limited, the description available on-line states that the cells are "extracted from the patient's own blood" and converted in their laboratory over a period of four days into cells with "the ability to turn into every cell type". These Autologous Multi-lineage Potential Cells (AMPC) are promoted for cosmetic rejuvenation, disease prevention, revitalisation, and anti-ageing with claims that they have "been applied in over 300 instances and recipients have reported beneficial effects ranging from improved vitality to alleviation of chronic joint pains". Because such an approach has some parallels to the new field of induced pluripotent stem cells, it raises substantial manufacturing and safety issues. While their reprogramming or 'conversion' methods have not been disclosed, it is claimed that they are the "best product in the market in terms of safety and treatment efficacy", "can do its job better and more quickly" and is "non-invasive" despite being applied via "intravenous reinfusion", directly into the "joint" or via "dermal injections" depending on the "type of treatment sought by the client". What is not included in the public material available however is that conversion 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 tumour formation, unless stringent safeguards are in place.**

Risks to patient health are not limited to the introduction of infection or aberrant growth following administration of poorly characterised autologous cell 'products'. As the unfortunate death of an Australian woman who was 'treated' for dementia at a Sydney clinic clearly illustrates, procedures used to obtain the cells can in themselves cause harm and in this case contributed to the patient's death (NSW Coroner's Court Findings, 2016). As stated in the Findings, the patient was subjected to a procedure that was of "unproven nature and efficacy" and due to the severity of her dementia "unlikely to be beneficial to any significant degree" and that steps are taken by TGA and other agencies to "consider how best to manage and regulate the provision of 'experimental' or 'innovative' medical or surgical procedures that have not yet been approved". We echo the Deputy Coroner's call that "legal protection against the exploitation of severely and chronically ill people by purveyors of scientifically dubious 'therapies' is needed".

3.5 International expert opinion

The International Society of Stem Cell Research (ISSCR) and the International Cell Therapy Society (ISCT), 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.

In 2016, the International Society of Stem Cell Research, the umbrella society for stem cell research internationally, published revised guidelines pertaining to human stem cell research and, clinical translation (Daley *et al.* 2016 *Stem Cell Reports* 6(6): 787). These most recent guidelines reinforces the ISSCR position that development of innovative therapeutic strategies for patients must be underpinned by a sound scientific rationale, a plausible mechanism, and evidence collected in

clinical trials. Furthermore, the 2016 guidelines reiterate that "the premature commercialization of unproven stem cell treatments, and other cell-based interventions inaccurately marketed as containing or acting on stem cells, not only puts patients at risk but also represents one of the most serious threats to the stem cell research community, as it may jeopardize the reputation of the field and cause confusion about the actual state of scientific and clinical development".

For example, the ISSCR guidelines (Recommendation 3.4.1) stipulate that unproven stem cell-based interventions are provided outside of the context of a formal clinical trial where highly restrictive provisions are met including:

- provision limited to 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
- explanation of why the proposed stem cell-based intervention should be attempted compared to existing treatments
- peer-review by experts with no vested interest in proposed procedure
- patient is not eligible for an existing stem cell-based trial
- an action plan for adverse events
- a commitment to report results
- institutional support and accountability
- personnel have appropriate qualifications
- a commitment to move to a clinical trial in a timely manner after experience on a few patients.

The International Cell Therapy Society has also recommended a series of actions to ensure that patient welfare remains of foremost concern in generating an increased level of public awareness of cellular therapy (Dominici *et al.* 2015 *Cytotherapy* 17:1663). Included in these recommendation was the need to "implement a long-term program to promote global regulatory harmonization, including early access programs for unmet needs that permit cost recovery and reimbursement, and regulation that recognizes different tiers of risks and benefit and provides appropriate levels of regulation".

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 International Society of Stem Cell Research, 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*). Although proposed in 2014, the draft guidelines are yet to be adopted prompting criticism that the lack of action by the FDA has contributed to the rampant growth of unproven autologous cell 'industry' in the USA (Turner and Knoepfler, 2016 *Cell Stem Cells* 19(2):154; Editorial 2016 *Nature* 535:7). Indeed examples of serious harm have now been reported. For example an ophthalmologist in Florida has recently described how three of his patients have been rendered legally blind following autologous cell 'treatment' for macular degeneration (Ledford 2016 *Nature* 537:148).

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 at least six 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 Australian Health Practitioners' Regulation Agency; however, the Australian Health Practitioners' Regulation Agency 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* (2015), 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).

The Australasian College of Sports and Exercise Physicians (ACSEP) has recently published a position statement calling for any use of mesenchymal stem cells for musculoskeletal conditions to be only available as through participation in a registered clinical trial or through innovative therapy in specific, rare circumstances (Osbourne *et al.* 2016, *Br J Sports Med* 50:1228). In response to recent developments the ACSEP have issued a follow-up statement to restrict use of mesenchymal stem cells to clinical trials only (see http://www.acsep.org.au/content/Document/Policy Documents).

4 Response to 2016 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 (as outlined in Academy's 2015 submission to TGA). However, information on risk derived from clinical trials data cannot be extrapolated to risk from new and unproven cell or stem cell therapies. Recent reports of paralysis, blindness and even death illustrate that there are real risks to the health of those pursuing unproven interventions marketed as stem cell treatments (Berkowitz et al., 2016 *N Engl J Med* 375:196; NSW Coroners Court Findings, 2016; Ledford 2016 *Nature* 537:148). 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 tissue therapies with current international expert opinion and regulatory trends in other jurisdictions. While full harmony would be difficult, incorporation of the revised definition of minimal manipulation into the biological framework will greatly address the current regulatory impasse. Furthermore, we continue to urge the TGA to reconsider incorporating the term 'homologous' use into modifications to the Excluded Goods Order to ensure the change will provide clarity regarding the intended remit of the TGA and prevent any further non-evidence based, exploitative and undesirable autologous cell-based interventions. **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 4 in the 2016 TGA consultation paper. While we support broadening item 4q of the Excluded Goods Order to

dental practitioners supervising the manufacturing and administration of accepted dental procedures, this should only be considered in conjunction with Option 4. The Australian Academy Science remains concerned that any lesser regulation could foster a further expansion of non-evidence based practices. **New regulations should provide the TGA, the Australian Health Practitioners' Regulation Agency and the Australian Competition and Consumer Commission 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 the Australian Health Practitioners' Regulation Agency and the Australian Competition and Consumer Commission 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 in a timely manner. This should apply to any unregulated non-homologous and more than minimally manipulated autologous cell interventions.

We expand on these points individually as we address the specific questions raised within Chapter 2 and Part A of Chapter 3 of the 2016 TGA consultation paper.

4.1 Description of the 'problem'

Overall, Part B of Chapter 2 in the consultation paper provides a reasonable summary of the concerns that have been raised in relation to the largely unregulated Australian autologous cell 'industry'.

Stem cell science and regenerative medicine has the potential to provide innovative new therapies for treatment of injury and disease. However, most potential interventions are considered experimental and require further research to fully evaluate and verify their safety and potential benefit. Leading international bodies, including those representing clinicians (such as Australasian College of Sports and Exercise Physicians), are calling for evidence to be collected in clinical trials prior to the marketing and used of an autologous product in routine medical care (Osbourne *et al.* 2016, *Br J Sports Med* 50:1228).

Broadly excluding all autologous biologicals from appropriate regulation under the Therapeutic Goods Act has allowed a growing number of Australian medical practitioners to market their 'products' and services directly to patients without oversight.

While there are prohibitions regarding false, misleading or deceptive advertising under the Health Practitioner Regulation National Law and under the Australian Consumer Law, these have proved an ineffective way to address the issue. The reliance on case-by-case consumer-driven complaints to trigger an investigation of the practitioner is a poor instrument to address a systemic and increasingly sophisticated network of individuals and companies supporting Australian providers of unproven autologous cell therapies (see ABC 730 report, 21 September 2016).

In addition to a change to bring autologous cell products under the remit of the TGA, there needs to be greater co-ordination and clarification of responsibilities and roles of the various state/territory and federal agencies to ensure a more streamlined and responsible approach to the systemic misrepresentation of therapeutic benefit and safety of unproven 'stem cell' and other 'cell-based' therapies in Australia.

Such efforts need to extend to the development of a reliable, national system shared across the agencies to record and monitor the nature and extent of those involved. The current consumer

complaint model alone is inadequate. It is based on the assumption that the consumer (in this case the patient or their family member or treating doctor) has the motivation, time and energy to lodge a formal complaint. Without an effective system to capture adverse events and other egregious activities it can't be assumed that the 'absence of reliable evidence' means there is 'no issue to be addressed'.

4.2 Risks to patient health by failing to act

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 accumulate. 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).

As we described in our 2015 submission 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, suggest 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 are 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* 116:1361-1377; 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. It is noteworthy, however, that a recent meta-analysis of cardiac cell-based therapies drawn on primary safety and efficacy data from 12 randomised trials concludes that there were no effects on major adverse cardiac or cerebrovascular events, and no changes in cardiac functional parameters (Gyongyosi et al. 2015, *Circulation Research* 116;1346-1360). Yet another meta-analysis concluded that "It is plausible that the significant positive effects on LVEF [left ventricular ejection fraction] (ranging from 2%-4%) shown in some meta-analyses may represent too optimistic or spurious results".

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.

With the exception of the death of Shelia Drysdale (NSW Coroners Court Findings, 2016) who died following complications of an unproven 'stem cell' treatment for her dementia, we are unaware of any adverse events from unregulated autologous stem cell therapies in Australia. However, this particular case illustrates how the under-regulated environment in Australia contributed to her untimely death. First alerted to the possibility of 'stem cell' arthritis treatment by an advertisement on the radio, Mr Drysdale was able to access intra-articular autologous 'treatment' for himself before petitioning and obtaining 'treatment' for his wife with advanced dementia. This treatment involved intravenous delivery of "stromal vascular fraction" derived from liposuction for which the doctor was initially prepared to "accept a large bundle of shares of unknown future value". As the Deputy Coroners finds, the cause of death was due to hypovolemic shock following uncontrolled blood loss associated with the liposuction procedure. The fact that the doctor was able to provide this "unproven, dubious procedure" in Australia highlights the need for greater clarity regarding the regulation of "'experimental' or 'innovative' medical or surgical procedures that have not yet been approved following clinical trials or other recognised peer-reviewed evaluation process".

Until a firmer stance is taken by TGA and other regulators to curb the activities of the Australian illegitimate stem cell 'industry', it is likely that others will be subjected to harm. Surely one life lost in the pursuit of bogus therapy should be sufficient justification.

4.2.1 Increased risks associated with more than minimal manipulation and non-homologous use

As raised in the Australian Academy of Science 2015 submission, the Excluded Goods Order as it currently stands 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 over 270 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.

4.2.2 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 converted autologous cells, 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, 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 allogeneic 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, Ilic *et al.* 2015 *Br Med Bull* 116:19-27) because of the complex safety considerations.

4.2.3 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.

4.2.4 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.

4.3 Regulatory Options

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. Autologous based-interventions, involving more than minimal manipulation and non-homologous practices, merit stringent regulation of their manufacturing and use commensurate with risk. **The only option that would provide the appropriate remit of the TGA in this important issue would be modification of the current Excluded Goods Order as detailed in Option 4, with the addition of "homologous" use in the definition of excluded autologous cells and tissues (4q of the Excluded Goods Order).** Provided these modifications are implemented the Academy would also support the broadening of the Excluded Goods Order to dental practitioners.

The other three options described in the Consultation Paper lack the necessary rigour and raise significant concerns regarding enforcement and in the base of Option 1 may even risk exacerbating the problem. While the Australian Academy of Science supports broadening item 4q of the Excluded Goods Order to dental practitioners supervising the manufacturing and administration of accepted dental procedures, this should only be considered in conjunction with Option 4. Any lesser regulation could foster a further expansion of non-evidence based autologous practices and further exploitation of Australian patients.

The Australian Academy of Science also acknowledges that while the **responsibility for this specific regulatory change rests with the TGA, allied agencies such as the Australian Health Practitioners' Regulation Agency and the Australian Competition and Consumer Commission share responsibility for the co-ordinated oversight of unethical medical and other practices** that have dominated the Australian cell therapy landscape and placed Australian patients and visitors at risk.

Such regulatory change may come at a cost to those currently profiting from the sale of unproven interventions. However, the Australian Academy of Science does not support the argument that the financial loss associated with increased regulation of the commercialisation of cell therapies justifies the continuing practice of charging hopeful clients large sums of money for ill-defined cellular products of unknown benefit and possible risk.

4.4 Clarification regarding terminology and scope

In addition to requesting feedback on the proposed regulatory models, the TGA consultation paper seeks feedback on several terms and concepts used throughout the Consultation Paper.

4.4.1 Human cell and tissue products for autologous use

The Australian Academy of Science supposes the clarification that the scope of the Consultation Paper and the regulatory framework under review is better addressed as "human cell and tissue products for autologous use" rather than "autologous stem cells".

4.4.2 Under the supervision of a medical/dental practitioner

As acknowledged above, provided Option 4 together with an amendment regarding homologous use is implemented, the Academy would also support the broadening of the Excluded Goods Order to under the supervision of dental practitioners in addition to medical practitioners. However the implementation of any other regulatory option currently under consideration is likely to further fuel entrepreneurial opportunities for products and services claiming to use 'stem cells' to enhance regenerative powers.

4.4.3 As part of a single course of treatment

The Academy is concerned about the current lack of regulations and TGA oversight associated with banking and storage of autologous cells and tissues. These concerns are particularly around issues of traceability, stability, integrity, identification and the management of risks given that many of the clinics and businesses involved in the provision of autologous cell therapies do so in private for-profit clinics with no recognised accreditation or requirement for suitably qualified staff. Provided Option 4 and the associated modification around homologous use is adopted, it is anticipated that these concerns would be addressed.

4.4.4 Minimal manipulation

As stated above, the Academy supports the revised definition of minimal manipulation. It is essential that TGA regulations be enforced for autologous cell-based interventions that involve more than minimal manipulation and non-homologous use.

4.4.5 Homologous use

The Academy remains concerned about the absence of "homologous use" in the Excluded Goods Order. Although the Consultation paper (page 29) clearly states that TGA intends to capture "stromal vascular fraction" under the revised definition of minimal manipulation, and therefore subjected to the standards required under the Biologicals Framework, concerns about the challenge of demonstrating "alterations of biological characteristics, physical function or structural properties" may lead to further uncertainty and a lack of regulatory oversight.

For example, it is envisaged that the Autologous Multi-lineage Potential Cells (AMPC) currently being marketed by a Queensland based clinic and associated companies, where cell-derivatives of autologous blood cells have been 'converted' to a more pluripotent state, would be rightly considered as "more than minimally manipulated" under the revised definition, but it is unclear how this would be established and by whom. There is no simple test, or even a combination of simple tests, to illustrate a change in biological characteristics, physical function or structural properties. Would the onus be on the provider to demonstrate that their product is minimally manipulated? Who would conduct such an evaluation? To avoid any further ambiguity, the addition of homologous use should be considered in addition to the change in the definition of minimal manipulation. Having observed the rampant growth of the unregulated 'stem cell' industry in

Australia, unambiguous parameters are essential.

4.4.6 Human cell and tissue products that form part of established medical practice

The Academy recognises that established medical practices may utilise autologous cells and tissues and that it would be inappropriate to subject these accepted practices to increased regulations as a consequence of adopting reforms counter the provision of unproven cell-based interventions. With the exception of cultured keratinocytes for the treatment of burns, and the infusion of pancreatic islets, the Academy is not aware of any other established medical practices that could be inadvertently affected. The Academy would of course encourage TGA to continue to consult broadly to ensure that regulatory reform does not impact on legitimate medical endeavours.

4.4.7 Mechanism for implementing options

The Australian Academy of Science would support changes to the mechanism to provide legal certainty whereby cells and tissues are excluded goods under section 7AA of the Therapeutic Goods Act by the Minister.

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 2016 ISSCR Guidelines on Stem Cell Research and Clinical Translation and the position statement of the 2015 International Cell Therapy Society, in particular their stance that it is unethical to market unproven cell-based interventions outside of clinical trials—even when the patient's own cells are used. We also echo the 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 Australian Health Practitioners' Regulation Agency and the Australian Competition and Consumer Commission who share responsibility for oversight of unethical medical and other practices.