Submission from the Australasian Society for Stem Cell Research to the TGA Consultation on Regulation of Autologous Cell Interventions.

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Executive Summary

The Australasian Society for Stem Cell Research (ASSCR) is the primary society for stem cell researchers and related professionals in Australia and New Zealand, with over 300 members. It is widely acknowledged that Australia has an established legacy in stem cell research and clinical translation, and as such, the TGA's stance on autologous therapies runs through the heart of our society's focus.

While some medical practitioners may turn to unproven stem cell procedure for compassionate care of refractory diseases and medical conditions, there are also those who are founding an industry outside of these ideals. Exemption of autologous stem cells from the current TGA regulatory framework has allowed exploitative stem cell clinics to advertise unproven autologous stem cell treatments as safe alternatives to conventional care

The ASSCR recommends that the Therapeutic Goods Administration (TGA) take a firm stance to ensure appropriate clinical translation of stem cell research in Australia by:
1) application of at least proposed regulatory Option 4 or higher
2) mandatory reporting of outcomes (including adverse events) from autologous cell interventions
3)requiring use of defined language relating to therapeutic safety, efficacy
4) providing mechanisms to support emerging autologous cell interventions
5) providing the TGA the ability to investigate and recommend prosecution for inappropriate claims and/or use of autologous stem cell interventions

These recommendations are consistent with the position statement from the International Society for Stem Cell Research (ISSCR) on delivery of unproven autologous cell-based interventions, where they "urge 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".

ASSCR Recommendations to TGA Consultation on Regulation of Autologous Cell Therapies:

The current Australian regulatory framework for autologous stem cell-based interventions assumes that any current or new intervention will be effective at best and benign at worst. Under this model no distinction is made between different autologous stem cell interventions based on whether or not the safety and efficacy of the intervention has been assessed through internationally-accepted clinical trials processes. However, this regulator model has become deeply flawed due to the recent and ongoing expansion of unproven, autologous stem cell interventions that are marketed directly to patients with little or no evidence of the intervention's safety and/or efficacy. As a result, this outdated regulatory framework is exposing Australian patients to the potential of losing much more than just their money.

Key risks of unregulated autologous cell interventions include transplantation of cells and cell-debris into inappropriate sites, introduction of infectious agents from stem cells isolated using uncertified processing facilities and non-validated protocols, financial and emotional exploitation of vulnerable patients, questionable consent processes, and propagation of unverified medical and/or scientific claims, including those which distract from rigorous and peer-reviewed medical research.

As a result of the increasing risks of the current regulatory model, Australians have been warned against the dangers inherent in overseas stem cell clinics offering unproven stem cell interventions. Yet worryingly, we are now seeing an increase in the numbers of unregulated private stem cell clinics on Australian soil. Unlike hospital-based clinical trials, the use of stem cells in private clinics is not subject to the scrutiny of an ethics committee, nor any oversight of the consent process. In the absence of evidence-based research patients are viewed as potential clients, and in

many cases are offered assurances that these expensive treatments are safe and efficacious. As the number of clinics touting these unproven cell interventions increases, there is a real and growing need for the TGA to ensure safe patient access to autologous cell interventions through closer regulation of these interventions including i) homologous vs non-homologous use, ii) manufacturing oversight, and iii) reporting of adverse events.

Under the current regulatory framework, there is no requirement for reporting on safety and efficacy of autologous stem cell procedures. Teamed with inappropriate advertising, there is a misrepresentation of the risks and potential dangers of unproven autologous stem cell interventions. The ASSCR views this arrangement as open to potential abuse at the expense of patient safety, and therefore is an unwanted development for vulnerable patients that will likely negatively impact the progress of true medical innovators performing robust clinical trials.

The diversity of avenues to bring medical innovations to patients is widely recognised and includes clinical practitioners, clinician-scientists and basic scientists Accordingly the ASSCR has actively engaged in consultation with its members who are representative of each of these professional groups. Through these consultations the ASSCR has observed a broad and robust consensus to change the current regulatory framework relating to the clinical use of autologous stem cells, in order to improve patient safety, improve patient outcomes, and improve progression of new interventions into clinical practice.

1. ***Recommendation for regulatory framework via Option 4or higher***

Under the current regulatory guidelines, autologous stem cells are not subject to scrutiny for safety prior to administration. Although the TGA has established a set of criteria for minimal manipulations, the processing of primary tissues or cells is not currently required to be performed under GMP conditions. The ASSCR acknowledges that the end products of manipulated cells must be safe for use, regardless of whether they are allogeneic or autologous. This is particularly important if the cells are to be used in a non-homologous context. This could be demonstrated by testing the final product for sterility and absence of animal-derived products. Should the autologous stem cells be serially passaged, there should be evidence obtained via standard tests to demonstrate there are no genomic or karyotypic abnormalities that can be introduced and/or selected for through culture manipulations. It is also important to ensure that adverse events using such cell products are reported in order to monitor the long-term safety of stem cells that are more than minimally manipulated and/or applied for non-homologous uses (see Recommendation 2).

The ASSCR recommends that requirements mandatory for allogeneic products, such as evidence of sterility and absence of endotoxins, should be applied to use of autologous stem cell products as well - given that these safety concerns apply to cell manufacturing processes regardless of whether the product is autologous or allogeneic. While some may argue that this is overkill for a minimally manipulated product, the current TGA definition includes exemption for processes such as trimming, cutting, flushing, washing and the addition of cryopreservatives. Any of these steps may inadvertently introduce substances that risk the health of the patient.

The ASSCR interprets the current section 7 declaration as meaning that both minimally and extensively manipulated autologous stem cells should not be advertised and applied in a non-homologous manner based on the assumption that such uses are not accepted medical practice. These practices are potentially unsafe and are often provided at great financial cost to the patient with no evidence of efficacy.

The ASSCR's position is the same as the ISSCR's position statement, which "condemns the administration of unproven stem cells or their direct derivatives to a large series of patients outside of clinical trials, particularly when patients are charged for such services."

[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]

The risks associated with autologous stem cell interventions are reduced by progressing from the proposed regulatory Option 1 through to Option 5. Also with this progression benefits to patients are most likely to increase, although arguably patient access to treatment decreases. While Option 2 significantly reduces the risk of non-homologous use and inappropriate advertising to consumers, it is not until Option 3 that Act Standards are imposed and adverse reporting is required. Option 3 is likely to provide simpler application of autologous cell therapies in isolate instances of compassionate care. Options 4 and 5 impose increased safety requirements. Given that patients typically pay a premium to access these treatments, safety requirements should be expected even if efficacy is not. Option 5 additionally imposes manufacturing requirements which can prove to be costly and may well out-price legitimate operations that already meet safety requirements.

Based on the above assessment, the ASSCR recommends that regulation of autologous cell-based interventions should include at least Option 4 or 5.

2. Recommendation for mandatory reporting of outcomes from autologous cell interventions

Patient safety should be a priority and this will involve a number of processes that will need to be put into place. Under the current TGA exemption, patient safety is left in the hands of the Australian Health Practitioners' Regulation Agency (AHPRA). The notion of self-regulation is based on the premise that the governing body has access to appropriately qualified advisors such as scientists and clinician-scientists specialising in the field of cell therapies. One mechanism to bridge this regulatory gap and ensure patient safety would be to require evidence of safety of the autologous cell products. In line with this, the ASSCR recommends that reporting of adverse events should be mandatory for autologous stem cell interventions. This reporting should be done in a specified but reasonable timeframe to an independent body, and the reporting outcomes should be transparent and accessible to enable monitoring and assessment by the medical community.

Inclusion of an autologous cell intervention in the Australian Register of Therapeutic Goods (ARTG) under Option 4 would enable simpler application of such interventions, for example on compassionate grounds. However, this could also imply an unintended indication of efficacy for the intervention. To address this, the ASSCR recommends mandatory reporting of all outcomes from autologous cell interventions under Option 4 to enable ongoing assessment of safety and efficacy for autologous cell interventions included on the ARTG.

3. Recommendation for defined advertising standards for autologous stem cell interventions

Under the proposed regulatory frameworks defined by Options 4 and 5, there is the ability to advertise autologous stem cell interventions to health practitioners. Currently, there are stem cell clinics in Australia that provide information on their websites which mislead both consumers and health practitioners as to the risks of stem cell injections, comparing them to that of vitamin D and cortisone. For example, the advertised stem cell isolation procedures involving stem cell selection from tissues such as lipoaspirates arguably breach the criteria of minimal manipulation and homologous use. Furthermore, suggested clinical applications include non-homologous applications via intra-articular injection for hip and knee complaints, and intravenous delivery for a wide range of conditions including multiple sclerosis, Parkinson's disease and spinal cord repair. The ASSCR therefore recommends the introduction of at least guidelines (if not specific codes or regulations)

for the accurate labelling and advertising of autologous cell-based interventions to health practitioners.

4. Recommendation for mechanisms to support emerging autologous stem cell interventions

It is clear that the Australian public is prepared to travel overseas in search of stem cell treatments regardless of the risk and lack of evidence. It is therefore important not to withhold potentially life-saving therapies to patients with diseases refractory to conventional treatments even if the stem cell therapy has no proven efficacy, for as long as the procedure is demonstrably safe. Also it could be argued that medical standards in Australia will be higher than in many places overseas where these interventions are being delivered. The ASSCR therefore recommends that legitimate clinical practices should be provided support to meet safety requirements and, where possible, encouraged and given support to work with public hospitals on clinical trials. This could include facilitating progress through ethics committees, particularly for interventions based on compassionate care. This will make potentially efficacious stem cell treatments more accessible to the public, and thus reach enough people to make clinical outcomes, and assessment of their efficacy, statistically useful.

5. Recommendation for investigative powers for the TGA relating to autologous cell interventions

The ASSCR recommends that the TGA should be empowered to investigate and recommend for prosecution inappropriate claims and/or use of autologous stem cell interventions. We believe that the TGA needs to be empowered with the authority to prosecute offenders in the manner described in subsection 19B(4), 19(D) and/or paragraph 42DL(1) of the Therapeutic Goods Act 1989. There should also be a mechanism through which whistle-blowers can work with the AHPRA and TGA to report breaches in regulation.

In summary, the ASSCR supports the move to reform current regulatory guidelines surrounding clinical use of autologous stem cells. We propose a number of mechanisms in which the TGA can improve the safety of autologous stem cell interventions in Australia. Our proposal is not targeted at inhibiting legitimate clinical practices based on evidence of safety. However, as with all clinical practice, we believe that advertising to patients must be stopped and mechanisms to support AHPRA must be put in place to ensure patient safety. Autologous stem cell interventions, as is the case for all clinical treatments and interventions, must be proven to be safe before widespread application. We believe that self-regulation can only be reliable when a regulatory body has suitable sets of guidelines by which to regulate and the necessary advisors and/or staff to aid implementation of the guidelines.