ASSCR Submission to 2016 TGA Consultation on Regulation of Autologous Cell and Tissue Products and Proposed Consequential Changes to the Classification of Biologicals

6 October 2016
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 Therapeutic Goods Administration’s (TGA’s) stance on autologous therapies runs through the heart of our society’s focus.

While some medical practitioners may turn to providing unproven stem cell procedures 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 procedures as safe alternatives to conventional care.

The ASSCR recommends the TGA take a firm stance to ensure appropriate clinical translation of stem cell research in Australia by adopting Option 4 and the new definition of minimal manipulation. The ASSCR also believes that the distinction between homologous and non-homologous use be included in the context of the exclusion criteria, and overseen by the TGA similar to allogeneic cell-based interventions. We believe this is the minimal standard required for better regulation of autologous cell and tissue interventions in Australia. The potential impacts on existing and well-established autologous cell and tissue therapies that are accepted as standard medical practice could be minimized by specifically excluding these practices as described in the consultation paper, (i.e., cultured keratinocytes for the treatment of burns and infusion of pancreatic islets following removal of the pancreas).

The ASSCR’s recommendation is consistent with maintaining the best interest of patients as well as public confidence in this emerging area of significant national and economic interest. It is also consistent with recently published guidelines from the International Society for Stem Cell Research (ISSCR) that state 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. Government authorities and professional organizations are strongly encouraged to establish and strictly enforce regulations governing the introduction of stem cell-based medical interventions into commercial use.”

We welcome this second consultation by the TGA and efforts to address the current regulatory exclusion.

Detailed discussion
Problems with current regulation:
The current exclusion of autologous cells and tissues from oversight by the TGA raises the following significant issues:

- There is no consideration given to autologous cell products despite the increased risks associated with more than minimal manipulation of the cells and whether “potency, purity, identity, traceability, safety, and product stability” standards are met.
- There is no consideration given to the risks associated with the route of administration – injection routes may cause increased risks of “infection, embolism and ectopic tissue formation”.
- The autologous interventions being sold in Australia are unproven and patients are being subjected to unnecessary and potentially risky procedures for which there is little reputable evidence of benefit.
- Direct-to-consumer advertising of unproven interventions not only exposes the patient to potential financial, psychological and physical harm but in some instances can also prevent patients from accessing more efficacious evidence-based treatments in a timely manner.
- There is currently no stipulation for providers of autologous interventions to meet TGA’s requirements for clinical trials.
- There is no requirement or system to report or capture adverse events related to unproven autologous interventions and as a result no consolidated knowledge of adverse effects, risks or safety of a particular autologous cell type.
- The current TGA exclusions are broader than those in Europe or US.

**Description of how Option 4 overcomes issues with the current regulation:**
The following detail outlines the ASSCR’s response to questions posed in the TGA consultation paper:

**Explanation of key terms:**
Under the supervision of medical/dental practitioner – We agree that dental practitioners should be added to the Exclusion but this needs to sit alongside the adoption of Option 4. Failure to do so could result in a further expansion of the Australian autologous ‘industry’ offering non-evidence-based dental care or other products and/or services by dentists.

As part of a single course of treatment (rather than single procedure) – We recognise that providing treatment over a period of time, which may include the storage of cells and tissues, introduces potential risks and that such risks warrant TGA oversight. For example, there needs to be oversight to ensure that:

- the end product is safe for use, especially if used in a non-homologous manner, e.g. testing the final product for sterility and absence of endotoxins;
- where the cells are serially passaged, there should be evidence obtained via standard tests to demonstrate there are no genomic or karyotypic abnormalities introduced and/or selected for through culture manipulations;
- adverse events using autologous 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, and
- groups conducting any ‘cell therapies’ need to demonstrate substantial data supportive of the application from a range of *in vitro* and *in vivo* pre-clinical testing prior to any infusion into a patient.

**Minimal manipulation** – We support the TGA’s change to the definition of minimal manipulation from a list of ‘actions’ (manipulations) to include any and all alterations in cell or tissue function that may impact on their intended use.
Homologous use – We consider it necessary for TGA to include this distinction in the context of the exclusion. Due to the greater risks to the patient associated with non-homologous use of autologous cells and tissues, we do not support the TGA’s position that the “decision on use of the product for each specific indication should rest with the medical or dental practitioners under whose supervision the treatment is occurring”. Autologous cell-based interventions should be overseen by the TGA in a similar way to similarly prepared/manufactured allogeneic cell-based interventions. Making a distinction between homologous and non-homologous use would be consistent with recent draft guidance provided by international regulatory bodies such as the US FDA.

Human cell and tissue products that form part of established medical practice – We believe clinicians still need to be held accountable and that their pre-clinical research/testing needs to meet acceptable standards (such as those outlined above) even when the cells or tissues are minimally manipulated. TGA must still have a role both setting and enforcing standards. It is noted that the TGA will publish guidance material about how to apply the definition of minimal manipulation and examples, but we remain concerned about enforcement and accountability.

Proposed options:

Option 1: No change from current regulation, but extends exemption to dental practitioners. Advertising allowed.

We do NOT support this option.

Option 2: Same as Option 1, but advertising is not allowed.

We do NOT support this option.

Option 3: Same as Option 2, but products that involve more than minimal manipulation are not excluded but still exempt from being included on ARTG or subject to GMP.

We do NOT support this option.

Option 4: Same as Option 2, but products that involve more than minimal manipulation are not excluded and are regulated as Class 3 or 4 biologicals.

We RECOMMEND that this option is the minimal standard required for better regulation of cell and tissue therapies with the addition of incorporating the term homologous into the exclusion.

Furthermore, that the classification of more than minimally manipulated autologous cells and tissue as Class 3 or 4 biologicals will ensure:

- increased safety, especially in relation to manufacturing standards;
- clinical trials that meet TGA’s requirements for approval, and
- enforced reporting of adverse events.

This will also provide Human Research Ethics committees with a set of clear guidelines to follow as they are a proxy of the TGA in assessing the suitability of projects to be conducted.