

## Submission to the TGA public consultation: Regulation of autologous stem cell therapies: Discussion paper for consultation

### Introduction

There is considerable confusion in the discussions around “stem cells”. Much of this relates to lack of clear definitions of what is being discussed. There are four products, three appear to be referred to in this discussion paper as ‘autologous stem cells’. It is clear that manipulation refines fat in a progressive manner. In this continuum we can define four separate products that are in use today. Increasing manipulation is seen to be associated with increasing risk and increasing benefits.

It would appear that the intention is to exclude **whole fat** from the discussion. Whole fat can be further manipulated to produce a more refined product by removing various components such as blood, debris, free oil, extra-cellular matrix and broken fat cells. These actions have the effect of changing the ratio of fat cells to stromal cells. Gentle handling of the fat tissue breaks fewer fat cells. It is possible to intentionally break more fat cells. As this ratio changes so the new product is referred to as **cell-enriched fat**.

Removing all of the fat cells, all the extra-cellular matrix and connective tissues leaves the product referred to as **stromal vascular fraction cells**.

Culturing allows the isolation of a single line of **stem cells** (also known as mesenchymal stem cells). The traditional manipulations available to change the composition of fat have been regarded as minimal manipulation as they are thought not to change the behavior of the constituent cells. Culturing to separate out the Mesenchymal Stem Cells is associated with changes to the cells and may be more than minimal manipulation and merit further regulation.

It would be more accurate to restrict the use of the phrase “Stem Cell Therapy” to those therapies that utilize purely stem cells and not a heterogeneous mix of stromal cells (containing stem cells) and fat cells.

With the introduction of the Excluded Goods order the TGA appeared to draw a line separating the use of fat, cell-enriched fat and stromal vascular fraction cells from single lines of mesenchymal stem cells and this indeed seems to remain valid.

This discussion paper seems to revolve around whether or not the separating line (excluded goods order) should be moved to regulate stromal vascular fraction cells as well as stem cells.

### Discussion questions

- What are the public health risks of ‘autologous stem cells’ in your view?

## 2. Safety of the product, including issues related to any processing of the product I will assume that the ‘product’ to be discussed is stromal vascular fraction’

The procedure clearly divides into three phases. 1. Harvesting of fat, 2. Separation of the components and 3. Administration of the tissue or cells

1. *Harvesting*

Harvesting of fat for stromal cell or stem cell preparation is the same as harvesting for fat transfer and can be described as a mini-liposuction. There are surgical risks such as bleeding and infection. This phase falls clearly into the realm of the practice of medicine. Adverse events from this phase are surgical and not caused by the product.

2. *Separation of the components*

Preparing fat for fat transfer demands the same care and attention to sterile technique and respect for tissues that occurs with the manipulation of fat to prepare stromal vascular fraction.

The use of enzymes such as collagenase is not novel in medicine as it is indicated for the treatment of Dupuytren's contractures and Peyronie's disease. Any *in vivo* changes to the cells caused by collagenase in the body are happening when collagenase is used to treat these two diseases. Thus any changes occurring when collagenase is mixed with tissue *in vitro* have already been seen to occur *in vivo*. The considerations for the supply and use of collagenase are present regardless of its intended end use. The use of collagenase does not create any more risk *in vitro* than is already created by collagenase used *in vivo*.

The variability of biological tissues combined with the short time frame from harvest to administration raises a significant challenge in that it is not possible to characterize the components of each sample before administration. It can be argued that it is also not necessary. Whilst my cells are different from everyone else's they are identical to the rest of me and are compatible with me. There is nothing to be gained by characterizing all the components of my tissues. My cells are safe for me. Clinical experience of the use of these cells in animals for 10 years and humans for more than 5 years supports this approach.

There is some concern for the training of staff who perform these tissue manipulations. The presence of standard operating procedures, quality control, audit and revision of protocols are addressed in accreditation processes, and in the proposed code of conduct. This does not merit further regulation by the TGA.

On page 31 of the discussion paper the final paragraph begins 'Before cells can be used, the cells need to be cultured *in vitro*.' This is untrue. A small number of clinics have used cultured cells but by far the majority use stromal cells and do not culture.

3. *Administration of cells or tissue*

This is the practice of medicine and not novel. Injecting into joints is associated with risks such as infection and reactive synovitis. Whole fat has been injected into joints and some would consider this to be homologous due to the presence of fat pads inside the knee joint (Hoffa's pad).

Injecting into a vein carries similar risk to the injection of platelets or whole blood. Transfusion reactions can be seen if the cells are administered too quickly. There is a theoretical risk of infection despite careful adherence to sterile techniques. Disseminated Intravascular Coagulation is a potential risk if the cells are not carefully prepared and administered. (See point 2 above 'processing of the product')

When reading reports of adverse events it is important to separate the procedural risks (Surgical and mode of administration) from the adverse events caused by the product, and to clearly identify the exact product that was used (Whole Fat, Cell-enriched fat, Stromal cells or cultured Stem Cells).

**Attachment 2 reviews the literature surrounding 'autologous adipose derived mesenchymal stem cell therapies'**

It is unfortunate that the review mixes adverse events associated with fat transfer, cell-enriched fat transfer; stromal vascular fraction and cultured stem cells.

*'Sporadic reports of adverse effects pertaining to adipose-derived stromal cells were identified. The effects were diverse in nature and ranged from cyst formation, fat necrosis, micro calcifications, pulmonary embolism, microthrombosis, bone formation, high blood pressure and fever, suggesting a context-dependent manifestation.'*

Cyst formation, fat necrosis and microcalcifications are seen in fat transfer. Pulmonary embolism is caused by the development of extrinsic factor when cells are cultured. It is not seen in uncultured cells. A single case of atopic bone formation was seen when cell-enriched fat transfer was mixed with the known powerful osteogenic inducer hydroxyapatite in the dermal filler used. Although this was cell-enriched fat transfer the same reaction most likely would have occurred had stromal vascular cells been used. High blood pressure and fever are transient effects that are seen with surgical trauma and with transfusion reactions. None of these adverse events were caused by the product 'stromal vascular fraction'

*Pulmonary embolism and infarction are theoretical risks of IV administration of mesenchymal stromal cells, and literature reports indicate that a large proportion of injected cells are detected in the lungs of humans upon first passage; however, only one human case report of pulmonary emboli after cell infusion was identified in the scientific-medical literature. This is in contrast to the situation in small animal species, where fatal pulmonary emboli after IV injection of mesenchymal stromal cells is commonly reported.*

'Mesenchymal Stromal Cells' defies definition. Stromal cells contain mesenchymal stem cells which can be isolated by culture. Pulmonary embolism is not a risk of 'mesenchymal stromal cell'. Once stromal cells are cultured there is then a risk of tissue factor production on the surface of the mesenchymal stem cells that have been isolated.

(Tatsumi et al. **Tissue factor triggers procoagulation in transplanted mesenchymal stem cells leading to thromboembolism.** [Cytotherapy](#). 2013 Jan 11. pii: S1465-3249(12)00039-4. doi: 10.1016/j.jcyt.2012.11.010.)

It is important to note the difference between 'stromal' and 'stem' cells.

Stem cells are a single cell line (100% stem cells) whilst stromal cells are a mixture of many cell types that include as few as 2% mesenchymal stem cells. Stromal cells are not cultured. Stem cells are cultured.

A large proportion of cultured stem cells are reported to be trapped in the lungs on first passage. This does not happen with stromal cells which are seen to pass through the lungs in large numbers.

*Additional risk factors that may affect clinical safety were also identified based on pre-clinical studies, both in vitro and in vivo. These risk factors included recruitment of adipose derived stromal cells into tumour propagation, bi-modal immunomodulatory response in vivo to high or low cytokine levels and potential to develop cytogenetic aberrations in vitro that may have tumorigenic potential in vivo.*

*A general lack of standardised cell characterisation and expansion protocols combined with paucity of knowledge with regards to biological context in which the cells operate in vivo are also confounding risk factors.*

These are interesting scientific questions that one day we may or may not be able to answer but they do not prevent us using the cells and finding out what the cells can do. We have used Panadol for more than 50 years. We know how to use it and how not to use it but we still don't know how it works. We understand that Panadol can cause liver failure and death. We have used stromal vascular fraction cells for more than 5 years in humans and can see some of the ways to use them and some of the ways not to use them. We don't understand all the components and it will be many, many years before we do. After 5 years of use stromal cells appear safer than Panadol.

After 150 years of fat transfer we still have not fully characterized fat, we do not have standardized lists of *in vitro* and *in vivo* characteristics, we do not even have standardized protocols for harvesting fat. Whilst these are undoubtedly admirable and important pursuits they have not stopped the use of fat transfer and need not stop the use of these stromal vascular fraction cells.

I totally agree that there may be under-reporting of adverse events and that a mechanism to facilitate reporting not only of adverse events but also number of procedures and results is desirable.

### **3. Lack of evidence to support the efficacy of the product and the large sums of money being charged for unproven treatments**

There is no medical treatment without cost. When a patient attends a public hospital he is paying for that treatment with the taxes collected every time he or she spends money. (GST). The hospital staff are paid. The treatment is not free. In a clinical trial the patient contributes with every dollar of government funding that is used. If industry pays then the patient may not be contributing and the cost of the treatment is not being carried by the patient. It is still not free.

Clinical trials are not cheap and neither are surgical procedures. We have in place other government departments that are better positioned to evaluate the fairness or otherwise of the cost of these procedures. I would suggest that this is not a matter for the TGA.

It is a fallacy to suggest that clinical trials discover new treatments. New treatments are discovered in the process of medical innovation. Once they have been optimized clinical trials are conducted to measure and validate the effect of the new treatment.

*'This means that treatments that might have a benefit are not being researched sufficiently and the public is missing out on the potential real benefits.'*

Under the present arrangement the public has access to treatments before they are measured in clinical trial. The public is not missing out.

Evidence continues to mount for the safety of adipose derived stromal cell therapy and for its efficacy in the treatment of Osteoarthritis. It is medical innovation has discovered these new treatments and elucidated protocols that appear to be effective. There is very strong incentive to undertake clinical trials that will help to validate the optimal treatment protocols and dosages needed to maximize treatments. It is important to remember that it is medical innovation, and not clinical trials that continues to discover these protocols. Medical innovation has brought us to the point we are at. It has taken a lot of personal money and continues to do so. Government funds have not been available and are unlikely to become available. It is no joy to have to tell patients that I don't know if they will be a responder or a non-responder. Research to answer questions like this and many others will not be funded by government in the present environment. Grants for funding through the NHMRC are extremely competitive with a success rate of around 18% for those with a proven track record of research. My research colleagues tell me that applications for trials that involve treatments that do not have a Medicare item number are even less likely to be funded.

Performing clinical trials is expensive and no government has enough money to pay for all the clinical trials that are needed. The government has already given hundreds of millions of dollars to stem cell research with very few clinical outcomes. This is a needs based problem that is being addressed by industry. All the research on the use of stromal vascular fraction cells to treat osteoarthritis to date has come from industry. None of it has been government funded. Changing the excluded goods order to regulate stromal vascular fraction cells would not increase research into stromal cells, it would decimate it.

I certainly do not believe that the government should invest more money into stem cell research. Industry funds for research are "needs based." This means that research will be funded only if it has very good prospects of providing a commercial return. I.E. it is cost effective. This was very eloquently expressed by Yock in his editorial *Needs-based innovation: the biodesign process* *BMJ Innov* 2015;1:3 doi:10.1136/bmjinnov-2014-000024 where he coins the phrase '*frugal innovation*'.

There is no doubt that Osteoarthritis is an extremely expensive disease and that many of the patients treated to date have achieved good improvement. How to maximize that improvement is of paramount importance and deserves data gathering such as could be achieved through a national registry such as that maintained for joint replacement (ACORN). Further clinical trials will be done.

#### 4. Lack of reporting adverse effects of the product

Australia does not have a central agency that is interested enough to collect adverse events. The TGA has been approached about this but as the product is not regulated by them they have no desire nor funding to collect the data. Individual companies have in-house data collection and one company sponsors a registry that has ethics committee approval. Industry is keen to have a central registry but there are obstacles. There is no government funding for such a registry so it would need to be user pays. There are problems of data ownership and lack of trust between competing commercial practices. This could be reduced if the registry were to be maintained by an independent facility. We have had consultations with the Ingham Institute who house the Arthroplasty Clinical Outcomes Registry NSW (ACORN) <http://www.biomedcentral.com/1472-6963/14/512> . This is a hospital based registry funded by the hospitals it serves. They have indicated a willingness to host a registry and clearly have the skill to do so. Their initial estimate was of a cost of \$200,000 to maintain. A registry such as this would also collect efficacy data.

## 5. Inappropriate advertising the product

The very small number of complaints from consumers vindicates the conduct of medical practitioners and emphasizes the relative safety of the procedure. Consumers are being correctly consented such that they are aware of what is known and what is not known about the procedure. They then have the opportunity to make up their own minds about the costs, risks and benefits. If the procedure was too expensive or the risks too great they can decide as best any person can whether they should invest their time and money.

Regulation of advertising is very clearly and adequately controlled by the Australian Health Practitioners' Regulation Agency (AHPRA.)

### Attachment 3 addresses the concepts of minimal manipulation and homologous use

#### a) Minimal manipulation

The descriptions of 'minimal manipulation' from each of the overseas jurisdictions mentioned are quite similar. Health Canada and the FDA seek to maintain the tissue or cell characteristics. The TGA and the EU are more descriptive with the major variant being for the EU 'cell separation, concentration or purification,' and for the TGA 'the use of additives such as cryopreservatives, anticoagulants, antimicrobial agents;'

Collagenase is used in vitro to treat Dupuytren's and Peyronie's. If there are any changes to cell characteristics caused by collagenase they are already happening in patients and have not caused any problems. Thus for the TGA to add collagenase to the list of additives seems entirely reasonable.

Concentration and purification are happening via the steps already mentioned. To add cell separation using mechanical, enzymatic or other means would align the TGA with the EU.

#### b) Homologous use

Homologous use revolves around having the same basic function. The function of Stromal cells in each of the tissues of the body is to repair, to maintain and to replace if necessary. Stromal cells from fat are not fat cells. Perivascular cells (Mesenchymal Stem Cells) reside on the outside of blood vessels. They are not vascular cells but can repair blood vessels. Regardless of where stromal cells are located the function of the stromal cells is not parenchymal. They do not function as fat cells and they do not function as vascular cells. Their basic function is repair, maintenance and replacement of cells and tissues all over the body.

In their recent review, Caplan's group have eloquently described the basic location and function of Mesenchymal Stem Cells (MSCs). *Experimental & Molecular Medicine* (2013) **45**, e54; doi:10.1038/emm.2013.94

*The relative abundance of MSCs throughout the body is understandable in light of recent findings that most, if not all, MSCs are of perivascular origin.*

*It is hypothesized that pericytes are the in vivo source of MSCs, with cellular components protruding into the endothelial lumen of blood vessels to monitor and react to systemic signals.*

It seems clear from this description that MSCs have a systemic function. Does it then follow that their homologous use is therefore systemic via intravenous delivery?



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

The public does deserve access to new and novel treatments. The risk/benefit analysis for stromal vascular fraction cells has proven to be extremely favorable in animals over the last 10 years of commercial use. In Australia we have a 5-year history of treating diseases with stromal vascular fraction cells. The few adverse events seen to date have related mainly to the surgical component. The cells appear extremely safe.

Australia spends two billion dollars per year on treating osteoarthritis. When fully implemented this treatment will cut that figure in half. Those saved funds will be well used to reduce suffering in other areas of health. Stromal cell treatment is a minor surgery with minimal recovery whilst joint replacement is major surgery with recovery over several months. The reduction in pain and suffering that stromal cells gives can be dramatic.

#### *Discussion question for Option 1*

- Is there an argument that autologous stem cells are not therapeutic goods and, therefore, should remain under the current Section 7 declaration?

Autologous stem cells by definition have been cultured and therefore should be regulated.

Stromal vascular fraction cells are not cultured. The preparation of stromal vascular fraction cells does not alter cell characteristics and therefore can be performed with minimal manipulation. The mix of cells in stromal vascular fraction all have systemic functions. (*Experimental & Molecular Medicine* (2013) **45**, e54; doi:10.1038/emm.2013.94) The homologous use of stromal vascular fraction cells is systemic. As their preparation is minimally manipulated and uses are homologous they are not therapeutic goods and should remain under the current Section 7 declaration.

#### *Discussion question for Option 2*

- Should autologous stem cells that are more than minimally manipulated and/or are not for homologous use continue to be excluded from regulation? Why or why not?

Autologous stem cells are cultured and merit regulation.

Stromal vascular fraction cells are minimally manipulated. Their homologous use is systemic. They do not need regulation.

## **Possible solutions**

This discussion paper suffers from lack of consultation with the doctors who understand this treatment best and to whom this consultation paper is directed. Many of the deficiencies of this paper could have been corrected prior to release for public comment had consultation occurred.

I assume that this lack of prior consultation has happened because the doctors practicing Stromal cell therapy are not organized into a group that can provide a contact point for government.

A group of stromal cell doctors and scientists has come together and over the last two years have written a voluntary code of conduct. The code will seek to bring together experienced doctors and scientists from a wide group of disciplines to educate and guide practitioners wishing to perform stromal cell therapies.

Self-regulation has been very successful for doctors practicing IVF therapy and appears to be an ideal model for doctors practicing stromal cell therapy.

With few exceptions doctors want what is best for their patients and are law abiding citizens. The popular press, medical newspapers and other public forums (*Concerns about these therapies that have been expressed to the TGA and in public forums include:....*) thrive on scandalous headlines, gossip and untruths fuelled by self interest groups who fear loss of prestige and government funding. There is little evidence reported from clinical trials of adverse events.

Formation of a professional group of stromal cell therapists with a code of conduct will address many of the issues raised in this discussion paper.

National Registry: The issue of a lack of reporting of adverse events arises because there is no mechanism available to collect this information. When a group is formed options for funding a national registry can be addressed in consultation with the TGA and experts such as those who run the ACORN registry. This will provide a focus for data collection and from this much needed national information.