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I am not a medical practitioner, and these following comments are my own personal view and do not represent those of Monash University but are based on extensive experience in this field.

In my capacity as a Professor in stem cells and immunobiology at Monash, and in particular in my former role as Director of Monash Stem Cells and Immunology Laboratories, I have had extensive exposure to the rapidly emerging field of stem cell research and its obvious translation to the clinic. It was clear to me from the outset that a major problem was managing public expectations relative to that of rigorous science and clinical realities. Accordingly in 2008 I instigated a public information initiative "Stem Cell Awareness Day" – bringing together stem cell researchers, clinicians, representatives of ethical and regulatory bodies and foremost the patients and general public. Stem Cell Awareness Day is now a global event, annually. Like many professionals in the field I am constantly receiving requests from patients and their carers as to whether there are any new stem cells (indeed any cell-based therapies) that can meet their unmet clinical needs – ranging from life threatening, to more commonly life debilitating, conditions through a broad clinical spectrum. It must also be remembered that it was the power of public pressure and patient need, which drove the successful launching of the Californian Institute for Regenerative Medicine and its $3billion budget, even in California's financially restrained conditions. Indeed the CIRM initiative has transformed the power base for stem cell research and has had a major impact globally. While Australia cannot expect to access this level of resource for research, I believe the TGA and its related parties should be congratulated in facilitating the status of Australia as a premier site for clinical treatments and their validation, through a rigorous chain of command that ensures only the very best of clinical practice.

Like the vast majority of medical researchers, it has always been my goal to develop new clinical approaches, which will hopefully bring a better, healthier society. I must also declare that given the parlous situation of funding for medical research and clinical translation in Australia, that I have formed strategic commercial partnerships to link in with our NHMRC/ARC platform funded research to develop new clinical programs. Indeed my own group was the first in the world to undertake a successful phase II trial on the rejuvenation of the immune system of cancer patients. This was funded by Norwood Immunology Pty Ltd. and performed at the Alfred Hospital and Peter MacCallum Cancer Institute in Melbourne. This then led us to explore the power of stem cells to successfully build a new thymus for the continual production of new T cells as a means of overcoming immune deficiency caused by common cancer treatments but also HIV and more commonly, the natural aging process. This is currently one of our most active research programs. It is with this background that I have become centrally involved in the usage of stem cells to treat other degenerative conditions.

The particular world of cell/stem cell therapies, because of their fundamental role in building and repairing all parts of the body has caused a well founded, yet unprecedented level of public expectation. This has unfortunately been aided by superfluous claims of miracle cures from disreputable commercial opportunists. However, the clinical urgency emanating from patients

requires strict attention to prevent them from travelling to very poorly regulated jurisdictions in search of unfounded therapies. Australia must set the appropriate regulatory landscape that pragmatically achieves the evolution of such treatments, but through worlds best clinical practice. Not an easy constellation to satisfy. The reality is that the era of stem cell therapies has started – even if so far mainly mesenchymal stem/stromal cells. The intent of the very innovative Therapeutic Goods (Excluded Goods) Order No. 1 of 2011 was to enable a regulatory framework in a world class environment that facilitated intelligent medical intervention by the practioner. In turn this would allow the exploration of potentially new clinical treatments that of course would ultimately see the need for appropriate randomiseed clinical trials.

Having appraised the clinical needs and hence opportunity, and the wealth of evolving stem cell research, it was apparent to me that the usage of mesenchymal stem/ stromal cells (MSC) would be a logical candidate to treat musculoskeletal disease. Accordingly, we were one of the first to have a PhD student research the relative properties of MSC derived from adipose tissue, bone marrow and umbilical cord. It became very apparent that while they shared many properties, there was extensive patient – patient variation. One generic property, however, was their potent anti-inflammatory properties and their ability to differentiate in to bone, cartilage, and fat. To take these findings to treating disease, we formed a partnership with Vet Stem (USA) and established a cross-licensing agreement for the establishment of Australian Veterinary Stem Cells, with the realisation that MSC treatment of large animals (dogs, horses and to a lesser extent cats, may not only improve animal health, but also serve as an unparalleled model for human conditions, given the musculoskeletal disease of these animals was occurring through natural wear and tear. As a collective we have now treated over 12,000 animals – such preclinical data has no precedence that I am aware of. While there are obvious restrictions on exploratory biopsies and efficacy tests, three findings became immediately apparent: no safety concerns; substantial relief from pain; obvious repair of damage (MRI on horse tendons) and increased freedom of movement.

With this remarkable data base, I met with clinicians at the Melbourne Stem Cell Centre and the (stem) cell production company Magellan – which I declare a minor financial interest in reflecting my role as a scientific advisor. We determined that MSC's should be trialled in humans. Accordingly MSCC and Magellan established an appropriate clinic and "clean room" (effectively to GMP standards but not yet accredited).
In specific reference to the current TGA Discussion Document, our fundamental *modus operandi* focussing on safety, efficacy and research, include:

1. Strong safety profile
2. Good evidence of likely efficacy determined in appropriate pre-clinical animal models – preferably larger animals with disease conditions more closely resembling the human disease
3. Ethics approval for clinical trials – where possible all patients to be subjected to the same safety, research and clinical follow-up
4. All patients to be referred by doctors
5. Clear patient consent forms with explanation than treatment is experimental
6. All form of advertising would conform to the current well established guidelines
7. The cells (eg MSC's) must be expanded under ultrasterile culture conditions reflective of current international "best practice"; this minimises the invasiveness of collection and allows generation of numerically sufficient therapeutic cells
8. The cells (eg MSC's) must be as uniform as possible for appropriate quality control of the injected product and thoroughly characterised prior to injection. Multiple cell mixes such as the stromal vascular fraction should be avoided. In our studies all MSC preparations are screened for sterility, chromosomal alterations, surface phenotype for MSC and non-MSC markers, and their released cytokine profiles. Through these sophisticated technologies, we

know what the cells are and what they produce. To our knowledge no-one else is doing this anywhere.

9. Understanding the impact of the environment on the MSC – eg where possible the synovial fluid from the knee joint is also subjected to cytokine array analysis – can this alter the function of the injected cells
10. Thorough follow-up of patients – safety, impact on pain, impact on tissue repair and disease progression; close monitoring and reporting of expected and unexpected events
11. Publication of data in peer reviewed journals
12. Costs kept to minimum

The above points are to be read in conjunction with the Code of Practice For Use of Autologous Cell-based Interventions, developed by the Australian Cell Therapy Society, of which I am a founding member. This hs already been submitted to the TGA.

In our group all therapies are conducted under the auspices of the TGA EGO No1 2011. If this is no longer going to be available, the above will fold costing patients access to important treatments and hence loss of clinical trial data and development of therapies, and the ~$1m invested by the entire clinical, research and commercial personnel.

However, it is very clear that some clinics in Australia are not applying the same level of diligence that the MSCC- Magellan team are. It is thus my contention that the TGA should retain the EGO but have increased powers to ensure an increase in the level of clinical rigour, compliance and transparency for all treatment regimes. While all the points listed above would fit into multiple Option candidates in the Discussion document, the major issue is the realism of costs. While no charges can be asked of patients on the trials, the dilemma arises for patients who miss the trial either because it is closed or more often because of the specific inclusion exclusion criteria. Appropriate financial remuneration thus needs to be sourced, ideally government supported.

By facilitating a greater role and responsibility for clinicians, the EGO thereby gave patients greater hope that maybe relief from their suffering was evolving. *We must never lose sight of this fundamental premise – this is all about better care for patients.* Not withstanding the need to realign the initial intent of the EGO to prevent its abuse, should the EGO now be revoked thereby triggering excessive financial demands on the therapy providers, the new treatments will stop, but the pain and suffering won't. There will no doubt be an exodus of such patients to alternative, poorly regulated, unsafe clinics in neighbouring countries. This must be avoided at all costs.

Sincerely

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