Murdoch Childrens Research Institute
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2 March 2015

To whom it may concern,

RE: Response to Therapeutic Goods Administration (TGA) options for regulating autologous stem cell therapies

We thank the TGA for the opportunity to make comment on the implications of the existing exempt position around autologous stem cells and provide our opinion on the appropriate course of action in the interests of the Australian community.
The Murdoch Children's Research Institute is an independent medical research institute integrated with the Royal Children's Hospital and Melbourne University. Our researchers work across the breadth of biomedical, clinical and public health research with a focus on patient outcomes. Researchers at the MCRI perform substantial research into stem cell biology, including work on autologous stem cells and on pluripotent stem cells with a focus on the long term development of cellular therapies. Within our stem cell research, we have laboratories active in cord blood stem cell and human pluripotent stem cell research. The Cord Blood Stem Cell Research Laboratory is exploring the use of cord blood for cellular therapies. Within the Cell Biology Theme, several laboratories work on programs for the directed differentiation of human pluripotent stem cells into a variety of tissues, including heart, pancreas, kidney and blood. Our researchers are world-class stem cell biologists with strong international reputations and represent the largest concentration of stem cell biologists in Australia focusing on the generation of differentiated cell types from human stem cells, the derivation of stem cells from patients and the gene editing of mutations within stem cell lines. As such, the promise of stem cells for cellular therapies is a key issue for our scientists. The prospect that the existing regulatory framework in this country is providing an opportunity for the exploitation of unproven stem cell treatments is of concern to us.

We are aware that a number of practices involving the use of material from the patient to be treated are specifically excluded from regulation under the Therapeutic Goods Act (1988) provided they are administered under the supervision of a medical practitioner and for a single indication in a single course of treatment. We accept that those examples provided in Attachment 1 of the consultation documentation, including skin grafts and autologous haematopoietic stem cell transplantation for leukaemia, are appropriate, efficacious and are appropriate to remain excluded from further regulation. Hence, our comments focus most specifically on developing products that fall under the description of autologous 'stem cell' therapies. At present, these are also excluded from regulation. It is our opinion that this exemption, while designed to prevent unnecessary obstacles to the use of the patients own cells, is too broad and insufficiently constrained, to be appropriate for these processes. As such, the scope and wording of the existing exemption provides an open-ended capacity for the delivery of a poorly defined, potentially dangerously manipulated products into patients in the absence of evidence for either safety or efficacy and in the absence of any oversight of adverse events or objective documentation of

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benefit. This is driven by the increasing 'hope' and 'hype' around the prospects of being able to treat disease with stem cells, with little definition of 'stem cell' or what is an acceptable level of 'minimal manipulation'.

While it is understood that this exemption results from a desire for proven autologous therapies to be able to proceed unhindered by regulation, any such exemption must continue to ensure that the balance point between patient access and patient safety is appropriately maintained (Lysaght et al. 2013, Cell Stem Cell 13:647). Even under circumstances where patient safety is not compromised, patients remain at risk of significant financial exploitation by providers of unproven therapies. While not abused in the majority of instances, this exclusion has allowed a small number of medical practitioners to provide unproven stem cell therapies to patients, a trend that appears to be on the rise. These products have been marketed in such a way as to suggest that they are appropriate for the treatment of a wide for range of severe chronic conditions, including multiple sclerosis, diabetes and Alzheimer's disease. There is no evidence base for such claims. By way of example, companies such as Autologous Stem Cell Technology (Probiotech Australia) are offering treatments based upon the conversion of peripheral blood into pluripotent stem cells (described as autologous multi-lineage potential cells). Depending upon the nature of the manipulation of the cells involved, we would regard such a reprogramming as exceeding the definition of minimal manipulation. Indeed, such a product should potentially fall under TGA Level 4 risk classification were it not for the fact that it involves the use of autologous cells. The delivery of this product without regulation by the TGA is highlighted in this website (http://asctech.com.au/index.html#services).

The exempt status of such activities has the following caveats, all of which represent a risk to the patient. In the first instance, Australian medical practitioners offering such therapies are not required to adhere to any standards with respect to product preparation or administration. As a result, such cell therapeutics are of unknown composition or quality control. This also provides no framework around which adverse events must be reported or efficacy data stringently evaluated. The implication is that this exemption exists because such treatments will involve minimal manipulation or modification of the cells involved and that the treatments involves the delivery of autologous cells. Unfortunately, there is evidence that the boundaries of what can reasonably described in this way have been breached. It is also evident that claims are being made, and products actively marketed to patients, suggesting efficacy around treatments for which there is no disclosure and no publicly available evidence base for efficacy or safety.

It would appear that one of the failures of this exemption has been a lack of clarification of the terms "minimal manipulation" and "homologous use". The reprogramming of cells involves the re-expression of specific transcription factor networks. This usually requires the overexpression of key genes delivered using a vector system that can result in permanent genetic change. Claims that this end result can be achieved via simple manipulation of pH or cell culture environment have been widely discredited (http://www.nature.com/news/stem-cell-scientist-found-guilty-of-misconduct-1.14974). This would suggest either that the providers of such 'treatments' are not reprogramming cells or

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they are delivering a product that cannot be regarded as having undergone minimal manipulation. Hence, allowing this to proceed without TGA regulation is a significant risk.

The presence of this exemption places Australia at odds with other international jurisdictions. The Public Health Safety Act in the US states that stem cell products comprised of cells cultured in the laboratory or processed in other ways (more than minimally manipulated) or used for other than their normal function (non-homologous use) 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). The NHMRC recognizes that the situation in Australia is not in line with other jurisdictions and has published advice to the public and medical practitioners of the risks of unproven stem cell therapies (NHMRC Media Release, Dec 19 2013). This is also the position of the National Stem Cell Foundation of Australia (*Australian Stem Cell Handbook*, 2013). We echo these concerns.

As an organisation at the forefront of the development of legitimate, safe and effective treatments employing stem cells, including stem cells derived from the receiving patient, we would flag the reputational risk to all potential stem cell therapies of the proliferation of unregulated, unproven and potentially unsafe practices. There is a substantial risk at present for the proliferation of opportunistic practices around the autologous cell space as a result of the intense media interest in the potential to treat disease using stem cells. The provision of an unregulated environment around this area will support the emotional and financial exploitation of vulnerable patients. While there remain many products available outside of the regulatory framework of the TGA that make unsubstantiated claims of efficacy, regulations around therapies have in large part prevented unsafe practices. It is imperative that this continue to be the case. The risk of a continued lack of regulation in the autologous stem cell space will not only place patients at risk of exploitation and harm, but adverse end results in this field will significantly undermine the appropriate development of genuine autologous therapies being developed under appropriate clinical trial environments.

In issuing its consultation documentation, the TGA acknowledges the need to review the situation. The TGA has proposed 5 potential recommendations, to which we will address specific comment.

1. Continue to exclude autologous cells from regulation under the Act

We strongly recommend against this course of action for autologous 'stem cell' therapies. Indeed, we would suggest the possibility that there be an immediate change to the Excluded Goods Order in order to prevent such activities until a decision is made on the basis of this consultation process. Our primary objections to the continuation of what is essentially the existing position rests with issues of safety. The current exemption makes it possible for the unregulated modification of patient cells, which provides the significant risk of doing harm.

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2. Exclude autologous stem cells from regulation under the Act in defined circumstances

We would not support this option for autologous 'stem cell' therapies as it creates an unworkable framework requiring constant re-evaluation of changes in evidence with no reporting or compliance requirements.

3. Regulate autologous stem cells under Act, but exempt from registration and manufacturing requirements

We do not support this option for autologous 'stem cell' therapies. The provision of an exemption from manufacturing requirements in the absence of clear definitions around minimal manipulation will provide no greater protection for patients from unproven and unethical practices.

4. Regulate under the Act as Class 1 biologicals

Our understanding of the definition within the Australian regulatory guidelines is that a Class 1 biological should demonstrate a low risk, involve minimal manipulation and the delivery of homologous cells and will not be subject to manufacturing oversight, however a statement of compliance is required. We would regard this as the minimal level of regulation for most of the practices currently of concern. The imposition of a reporting requirement is also seen positively. We would note, however, that without a clear definition of 'minimal manipulation' this level of classification would remain ambiguous. The requirement for a statement of compliance should at least ensure the full disclosure of the product, including the method of preparation. The TGA has identified the risk that the provision of a classification would imply a level of jurisdiction that is not present. We note that there is no requirement for evidence of efficacy associated with this regulation, or of quality or safety. We also remain concerned that this level of regulation is insufficient for some products being offered to patients at the present time.

5. Regulate under the Act as Class 2, Class 3 or Class 4 biologicals

We would suggest that this is an appropriate course of action. A blanket recommendation that all autologous stem cell therapies on offer will be suitably regulated at a Class 1 level is unlikely to be appropriate. We would accept that some existing 'stem cell' based biologicals might fit into a Class 2 category, and hence would require evaluation by the TGA, rather than a simple statement of compliance. However, there are already existing therapies classified under Class 3, including the non-autologous use of mesenchymal stem cells, where the manipulations required for production represent a much less risky process than 'reprogramming of patient cells to pluripotency'. Hence it is our opinion that, in some instances, autologous stem cell products now on offer represent a risk as high as that encompassed by existing Class 3 and 4 biologicals. For this reason, a level of oversight sufficient to evaluate the Class of biological suitable for any such product is should be required.

In conclusion, it is our recommendation that the TGA

i) immediately revoke the existing excluded goods order until the issue has been considered and

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ii) provide clear definitions of acceptable minimal manipulation and

iii) require a statement from all providers as to the nature of the product being provided so as to evaluate on a case by case basis the Class of Biologicals appropriate. This decision would need to be dependent upon the specific cell type, cell source and most importantly level of manipulation being proposed.

Our recommendations are in line with the international opinions of organisations such as the International Society for Stem Cell Research who released a statement to this effect in 2013 ((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). Our concerns are also consistent with those of the Australian Academy of Science, Australian Academy of Health and Medical Scientists, Australasian Society for Stem Cell Research and International Society for Cellular Therapy, all organisations with membership including MCRI researchers. MCRI stem cell researchers are also members

Kind regards,

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