

Please cite as:

Lysaght T, Kerridge I. Rhetoric, power and legitimacy: A critical analysis of the public policy disputes surrounding stem cell research in Australia (2005-6). *Public Understanding of Science*. 2012;21(2):195- 210.

Lysaght et al. (2013). *American Journal of Bioethics*. 126(11): 941-943.

## Global bionetworks and challenges in regulating autologous adult stem cells

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The research for this article was conducted as part of the 'Asian Biopoleis: Biotechnology and Biomedicine as emergent Forms of Life and Practice' Project, funded by the Ministry of Education, Singapore, and the Humanities and Social Sciences (HSS) Division of the Office of the Deputy President (Research and Technology) at the National University of Singapore (NUS).

The authors have no conflicts of interest to declare and all have played a substantive role in writing the manuscript.

Article type: Commentary

Key words: Cell therapy, regulation, bioethics, stem cell research

Running head: Challenges in regulating autologous adult stem cells

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Autologous adult stem cells (ASCs) are increasingly being administered to patients with limited evidence from clinical trials that they are safe and effective. The marketing of autologous ASCs predominantly over the Internet by companies based in low-to-middle income countries, such as the Bahamas, Mexico, India and China, is well documented.(1, 2) However, even in countries such as the United States, Japan, and Australia, physicians are prescribing autologous ASCs to patients outside the context of clinical trials. These doctors often form part of loose collaborative networks of clinicians, businesses, patients and researchers operating both domestically and across national boundaries. The emergence of these networks not only puts patients who seek out these interventions at risk: it threatens to undermine the very basis of 'good medical practice'.

### Bionetworks

The concept of bionetworks has been described in a study, funded by the Ethics & Social Science Research Council in the UK, which traces the relationships between physicians, science entrepreneurs, researchers, patients and healthcare providers that are offering ASCs outside clinical trials as 'experimental therapies' across Asia.(3) According to the authors, bionetworks operate mostly, although not exclusively, within the private healthcare sector, and work to exploit differences and similarities in the provision of healthcare, standards of evidence, and regulatory infrastructure across geographical contexts.(4) They may also work to shape healthcare policies and regulations across international borders.

One example of how global bionetworks may influence health-related policies recently emerged in the US following reports that Texas Governor Rick Perry had received a preparation of expanded autologous adipose-derived mesenchymal stem cells for back pain

in 2012. This procedure was administered by Houston orthopaedic surgeon, Dr. Stanley Jones, who himself had received a similar one for arthritic pain at a clinic in Japan that, at the time, was in a partnership with a South Korean-based company, RNL Bio – a company that has been previously been investigated following the deaths of two South Korean patients who had travelled to China and Japan for administration of autologous ASCs. Jones has since co-founded a company called Celltex Therapeutics, which secured an exclusive license in 2012 to market RNL Bio's cell processing technology from its American subsidiary. At the same time, the Texas Medical Board, whose members are appointed by the Governor, determined that the "use of investigational agents constitutes the practice of medicine" and adopted the *Standards for Use of Investigational Agents*, which allows physicians to use stem cells in certain clinical settings pending approval from an IRB.

This approach – which has yet to be replicated in other states – has been the subject of extensive criticism, principally because it appears to substitute formal regulatory oversight with IRB approval,(5) although the FDA has issued Celltex with a warning letter for non-compliance to federal manufacturing standards, which *supersede state laws*. The Texas case does, however, highlight a number of issues that have both domestic and international salience. These include the ways in which regulatory approaches to biomedical products may be translated across national borders, the impact that bionetworks are having in shaping global healthcare and challenging the sometimes uncertain distinction between clinical trials and 'innovative medicine', and the failure of regulators worldwide to adequately monitor and control the emergence and translation of cellular therapies. Examination of the regulatory context in Japan, the United Kingdom, and Australia make clear the difficulties in regulating these practices.

In Japan, which has a large domestic market for novel cell-based therapeutics, licensed practitioners and institutions are allowed to administer autologous ASCs under a regulatory framework that is very similar to that advanced in Texas. While manufacturers must seek approval from the Pharmaceuticals and Medical Devices Agency to market products, in a manner broadly similar to how the FDA approves biological drugs in the US, practitioners in Japan may also prescribe unapproved medicines outside the context of clinical trials. This act is considered to fall within the scope of 'physician discretion' in medical practice, and is permitted under the *Medical Practitioner's Law* (1948). In addition, the Ministry of Health, Labour and Welfare has issued the *Practice Notice: Regarding the Practice of Regenerative and Cell Therapy with Autologous Cells and Tissue in Medical Institutions* (2010), which only requires medical institutions intending to implement medicines using autologous stem cells or tissues to seek approval from an institutional ethics committee.

Many practitioners, clinics and bio-companies have taken advantage of this situation. Media outlets in Japan have reported that more than 20 clinics are offering unproven interventions with autologous ASCs outside clinical trials, which may increase once the government implements proposed changes to fast-track cell products through the regulatory approval process.<sup>(6)</sup> The situation is similar in Australia, where the manufacturing and therapeutic use of autologous cells is excluded from regulation under the *Therapeutic Goods (Excluded Goods) Order of the Therapeutic Goods Act* (1989). This exclusion means that ASCs can be administered to consenting patients by any registered medical practitioner without any form of external review. As a consequence, like Japan, the number of private clinics offering autologous ASCs has increased, with many being run by practitioners who are not specialists

in the management of the medical conditions experienced by the patients who seek their care.(7)

In contrast, the United Kingdom has been relatively successful in controlling the use of autologous cellular therapies. Even though practitioners may access unapproved medicinal products through the manufacturer's 'specials' licence program and the 'hospital use' exemption scheme, the administration of autologous ASCs outside the standard of care appears to have been restricted to use within clinical trials. This situation may, at least in part, have been influenced by actions taken by the British General Medical Council against Dr Robert Trossel, who was struck off the medical registry in 2010 for unjustifiably administering inappropriate stem cell-based interventions to patients affected by multiple sclerosis.(8) Although in this case, Trossel was administering an allogeneic preparation (found to also contain bovine neural cells) at a clinic in Rotterdam, it is likely that his deregistration would have sounded a stern warning to other British practitioners considering offering unproven interventions with any stem cell-based product outside clinical trials.

### Regulatory Challenges

The socio-political and regulatory contexts that enable the exploitation of cell therapies in some countries and not others are, of course, highly complex. The issues in play not only relate to the confounding of research and clinical practice, they reflect ongoing contestations over the standards of evidence that should be required before novel interventions are introduced into clinical settings. They also raise profound questions concerning professionalism, patient vulnerability, and professional and personal autonomy.

One of the greatest challenges in regulating autologous cell products will thus be finding a balance between protecting vulnerable patient populations while still allowing enough flexibility in the regulations for doctors to develop new and innovative cell-based therapies. There also needs to be recognition, that due to small market sizes, autologous cell-based therapies are unlikely to provide a viable business model if forced to follow the established drug pathway for all indications, particularly where regulators operate on a cost-recovery basis.<sup>(9)</sup> Repositioning the applicable frameworks to provide more flexible cost-effective pathways to market whilst establishing product safety and efficacy may be a better alternative than simply exempting entire classes of therapeutics from regulation. Professional medical bodies should also play a greater role in providing guidance that aligns doctors with international standards of clinical care and research ethics and, where necessary, enforce appropriate sanctions for breaches of unethical or unprofessional conduct. For these practices, whether conducted independently or as part of a bionetwork, are not only detrimental to the emerging field of stem cell medicine, they potentially undermine public trust in the medical profession and the agencies that regulate it.

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