

# The Present and Future of Stem Cell Therapy in Japan<sup>1</sup>

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## ABSTRACT

Stem cell therapy offers limitless possibilities. If human stem cells enable the creation of new cells and tissues, then treating diseases of the body by replacing cells and tissues as if they were mechanical parts becomes possible, thereby aiding in overcoming illnesses and extending life. Although stem cell therapy is regarded as a blessing, it is necessary to fully discuss its ethical, legal and social implications, given that these therapies can greatly change the concept of human life.

The 23rd November, 2010 issue of *Nature* reported the deaths of two South Korean patients, one of whom travelled to Japan and the other to China, to receive stem cell therapy. The patient who travelled to Japan was a 73-year-old male. Through a company based in South Korea, he received stem cell therapy at a co-operating Japanese hospital. However, he subsequently died of pulmonary embolism. According to the article, the company claimed that ‘only a very small number of patients have died, and the causal relationship with stem cell therapy is unclear’. According to a South Korean expert, however, ‘it is already known among scholars through preclinical trials using animals that side effects such as pulmonary embolism and lymphoma can occur’.

The death of the patient receiving stem cell therapy in Japan did not initially receive widespread domestic coverage. On 1 February, 2011, the Japanese Society for Regenerative Medicine, which had been discussing the issue, released a statement about unapproved regenerative and cellular medicines that do not conform to the

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Pharmaceutical Affairs Act or any research guidelines. In the statement, the Society urged its members not to participate in ‘unapproved’ regenerative cell therapy, advised patients and their families to avoid such procedures and asked the government to construct a new medical services framework that would include legal revision. According to the International Society of Stem Cell Research, however, stem cell therapy can be performed under rigorous conditions in exceptional cases, even if clinical trials or research studies have not been formally approved. If the appropriateness of stem cell therapy cannot simply be judged on the basis of approval or disapproval by law or administrative guidelines, then where does the problem actually reside?

To clarify the issues involved in stem cell research, which is now becoming a topic of discussion, this paper provides a brief introduction of the related trends in other countries and discusses the present situation and potentially relevant problems with the existing regulations in Japan. Furthermore, we propose two future directions (research or innovative therapy) along which the current trends can develop. Finally, we comment on the risks of maintaining the current regulations.



Stem cell therapy offers limitless possibilities. If human stem cells enable the creation of cells and tissues, then treating diseases of the body by replacing cells and tissues as if they were mechanical parts becomes possible, thereby aiding in overcoming illnesses and extending life. Although stem cell therapy is regarded as a blessing, it is necessary to fully discuss its ethical, legal and social implications, given that these treatments could greatly change the concept of human life.

The 23rd November 2010 issue of *Nature* reported the deaths of two South Korean patients who travelled abroad—one of them to Japan, the other to China—to undergo stem cell therapy (Cyranski 2010a). The patient who travelled to Japan was a 73-year-old male. Through the South Korean-based company RNL Bio, he received stem cell therapy at Kyoto Bethesda Clinic, a co-operating Japanese hospital. However, he subsequently died of pulmonary embolism (Dong-a Ilbo 2010). Because it is illegal to administer stem cells to patients outside the framework of clinical trials in South Korea, RNL Bio extracts mesenchymal stem cells from the patient’s fat and bone and injects these cells back into the patient at co-operating hospitals in other countries. According to the articles published thus far, RNL Bio, which has treated

over 10,000 patients, claims that ‘only a very small number of patients have died, and the causal relationship with stem cell therapy is unclear’. According to Oh Il-hwan, head of the functional cell treatment center at the School of Medicine of Catholic University of Korea, however, ‘it is already known among scholars through preclinical trials using animals that side effects such pulmonary embolism and lymphoma can occur’ (Dong-a Ilbo 2010).

Initially, the death of the patient treated in Japan was not widely reported in Japan. On 1st February, 2011, the Japanese Society for Regenerative Medicine, which had been discussing the issue, released through their website a statement about unapproved regenerative and cellular medicines that do not conform to the Pharmaceutical Affairs Act or any research guidelines (Asahi Shinbun 2011, Japanese Society for Regenerative Medicine 2011, Kyōdo News 2011). In the statement, the Society urged its members not to utilize unapproved regenerative cell therapies, advised patients and their families not to undergo such procedures and asked the government to construct a new medical services framework that would include legal revision. Around the time this statement was issued, scattered reports on the patient’s death appeared in the Japanese media, with the word ‘unapproved’ emphasized in the headlines (Asahi Shinbun 2011, Kyōdo News 2011, Science Portal 2011). Yet, as we discuss in this paper, regenerative cell therapy may not subject to the Pharmaceutical Affairs Act or research guidelines, and it is not clearly prohibited in Japan. Furthermore, according to the International Society of Stem Cell Research (ISSCR), stem cell therapy can be performed under rigorous conditions in exceptional cases, even if clinical trials or research studies have not been formally approved (International Society of Stem Cell Research 2008). If the appropriateness of stem cell therapy cannot simply be judged on the basis of approval or disapproval by law or administrative guidelines, then where does the problem actually reside?

To clarify the issues involved in stem cell research, which is increasingly becoming a topic of debate, this paper provides a brief introduction to related trends in other countries and discusses the present situation and potentially relevant problems with the existing regulations in Japan. Furthermore, we propose two future directions along which the current trends can develop. Finally, we comment on the risks of maintaining the current regulations.

PROBLEMATIC TRENDS RELATED TO STEM  
CELL THERAPY IN OTHER COUNTRIES

Induced pluripotent stem cells, embryonic stem (ES) cells and somatic stem cells carry the potential to treat a great number of conditions that are difficult to cure with contemporary medicine. However, with the exception of haematopoietic stem cell transplantation for leukaemia and lymphoma, the efficacy and safety of stem cell therapy have not been sufficiently proven to permit their widespread use in the clinical setting (Barclay 2009). However, patients with severe diseases that lack treatments, and their family members, place sincere hope in stem cell therapy. Countless patients worldwide undergo stem cell therapy in their own or other countries because they or their families cannot wait for clinical research to begin and do not want to simply wait for death without investigating other potential options. The existence of the Internet in particular has accelerated this trend. Stories of cures appearing on the blogs of affected individuals or clinic websites attract more patients and family members to stem cell therapy.

However, examination of these blogs and websites has revealed the true conditions and problems of stem cell therapy in various countries. For example, according to a fact-finding investigation of patient and family blogs, patients with a wide array of conditions—including spinal cord injury, optic nerve hypoplasia, motor disorders, brain injury, polio and multiple sclerosis—have received stem cell therapy (Ryan et al. 2010). The countries where the treatments were performed include China, India, the Dominican Republic, Costa Rica, Russia, Mexico, Germany and Turkey. Cord blood stem cells, autologous bone marrow stem cells and stem cells derived from human fetuses and embryos were administered by intravenous injection or lumbar puncture. Despite the lack of evidence, a significant number of clinics were very optimistic about efficacy and safety, and they downplayed the risks (Lau et al. 2008). The costs of therapeutic intervention ranged from US\$5,000 to \$39,500 (Regenberg et al. 2009).

Severe adverse effects on health and even deaths have been reported. In Russia, a man who received injections of human ES cells for cosmetic purposes developed multiple tumours on his face (Titova and Brown 2004). A British patient experienced a severe acute allergic reaction and required hospitalization immediately after receiving therapy in the Netherlands (Sheldon 2006). At a Chinese clinic, numerous complications, including cerebral meningitis, were confirmed in five of seven patients injected with foetus-derived cells (Dobkin et al. 2006). A Thai woman whose kidney

was injected with autologous stem cells experienced an increase in vascular and bone marrow cells in her kidneys, liver and adrenal gland 6 months later, and she eventually died (Cyranoski 2010b, Thirabanjasak et al. 2010); however, the causal relationship remains unclear in this case. Moreover, not all reported victims have been adults. A 9-year-old Israeli boy who was administered foetus-derived nerve cells in the cerebellum and spinal cord at a Russian facility developed a brain tumour 4 years later. The tumours were derived from the cells of at least two donors (Amariglio et al. 2009, Pownall 2010). In Germany, a 10-year-old patient from Azerbaijan who received stem cell injections in the brain became gravely ill, and an 18-month-old Romanian child who received the same treatment died (Mendick and Palmer 2010).

As described previously, many patients throughout the world seek these treatments even though their safety and efficacy are unproven, and they pay large sums of money for therapy and travel while exposing themselves to deadly risks. In relation to these events, the ISSCR created 'Guidelines for the Clinical Translation of Stem Cells' in 2008 (International Society of Stem Cell Research 2008). These guidelines clearly state the following: 'The ISSCR condemns the administration of unproven uses of stem cells or their direct derivatives to a large series of patients outside of a clinical trial, particularly when patients are charged for such service'.

National governments have continued to address this issue. The government of the Netherlands banned the clinical use of stem cells in 2007 (Sheldon 2007), whereas the Russian government closed approximately 37 clinics (Cohen and Cohen 2010a). In Germany, the relevant associations issued a statement, and 2 weeks later, the upper house of Parliament passed an amendment that more closely regulated stem cell therapy (Stafford 2009). Regulations enacted in China in 2009 introduced a licensing system for facilities offering unproven treatments such as stem cell therapy. Violations are now punished with fines or suspension of treatment licenses (Qiu 2009). India and Thailand are also moving towards tighter control (Cohen and Cohen 2010a, Qiu 2009). Throughout the world, concerned organizations are releasing critical statements and questioning the clinics involved (Pownall 2010, Qiu 2009). Against this backdrop, the US and UK have adopted a basic stance against the commercialization of stem cell therapies that lack official approval (Cohen and Cohen 2010b).

## CURRENT STATUS AND REGULATORY PROBLEMS IN JAPAN

In Japan, some stem cell therapies are promoted which, in other countries, are considered problematic and strictly regulated as a result. An Internet search provides easy access to clinics that offer stem cell therapy in private practice. The target conditions differ among clinics and range from cancer, cerebral infarction, myocardial infarction, Parkinson's disease, rheumatic conditions, paralysis after spinal cord injury, diabetes and kidney and liver impairment to chronic fatigue, stress relief, menopause, skin rejuvenation and breast augmentation. The stem cells used in these therapies are extracted from bone marrow, cord blood or fat cells and administered intravenously, intradurally, subcutaneously or intra-articularly. Some clinics clearly state that the efficacy is unknown, whereas others offer statements such as 'it is a safe treatment and significant results can be expected' (Kojima Regenerative Medicine Clinic, accessed 2013) or 'in some cases, patients experienced an improvement on the same day of the treatment' (Kanda Ishin Clinic, accessed 2013). Some statements by clinics include no mention of the risk of side effects. The therapies frequently cost several million yen, and treatment costs are not covered by insurance. Compared with international trends, Japan constitutes a distinct case; many Japanese clinics have escaped international criticism thus far because their websites are available only in Japanese. There are, however, clinics that communicate with patients in foreign languages, suggesting that patients do indeed come from other countries to receive treatment.

Relevant to the emergence of these circumstances in Japan is the issue of regulating medical care involving stem cells. In Japan, the administration of stem cell therapies that are still at the experimental stage can proceed along two paths. The therapies can be utilized in trials according to the Pharmaceutical Affairs Act or administered as part of research pursuant to the Ministry of Health, Labour and Welfare's Guidelines on clinical research using human stem cells (hereafter, Human Stem Cell Guidelines) (Ministry of Health, Labour and Welfare 2006). If a treatment is framed as a trial, then a proposal must be submitted to the Ministry's clinical trials review committee and the institution conducting the trial, and the plan must undergo a detailed audit. Therapies that are provided as part of research must be doubly reviewed by the Health Science Council and the research institution's ethics review committee. In both cases, clinics have an obligation to report any serious side effects to the national government. Therefore, irrespective of whether the therapy is administered as part of a trial or research, the national government has an opportunity to evaluate the clinic

administering the therapy, the patients receiving treatment and the extent of risks involved. It also ensures that mechanisms to oversee and manage such therapies are in place.

Another possibility is that stem cell therapy may be provided as practice. In 2010, the Ministry of Health, Labour and Welfare issued a notice on Conducting Regenerative and Cellular Medicine Using Autologous Cells and Tissues at Medical Institutions (Ministry of Health, Labour and Welfare 2010). This notice summarized the requirements that must be met while administering regenerative and cellular medicine using autologous cells prior to insurance listing or approval under the Pharmaceutical Affairs Act, or while offering regenerative and cellular medicine not subject to the Human Stem Cell Guidelines. This notice stated that such care must be provided as part of research, but it did not specifically prohibit the use of regenerative and cellular medicine as a preventive treatment or for cosmetic purposes at the patient's own expense. It did mandate review by the medical institution's ethics committee but not the participation of outside committee members, which would contribute to transparency of the review. Furthermore, it did not address the obligation to report serious conditions to the national government. In short, with respect to stem cell therapies using autologous cells that are not covered by the Pharmaceutical Affairs Act or research guidelines, an official notice has been issued but such therapies are not domestically prohibited. Consequently, much is left to voluntary regulation by the medical facility, thereby precluding third-party audits.

## TWO POSSIBLE DIRECTIONS: RESEARCH OR INNOVATIVE THERAPY

We present two viewpoints that could each serve as a path to improve this situation and regulate problematic stem cell therapy. The first method would define as research all forms of stem cell therapy, including those regarded as problematic, and regulate them uniformly using existing guidelines. Hypothetically, application of the Human Stem Cell Guidelines would enable the government to exercise some oversight and management of the institutions offering the treatment, the target conditions, expected benefits and risks, and details on serious consequences. This may also prevent patients from being overcharged for treatment. However, application of the Human Stem Cell Guidelines will require clarification of the definition of the scope of application: 'clinical research that transplants or administers human stem

cells or the like into the human body for the purpose of treating a malady' (Ministry of Health, Labour and Welfare 2006). Currently, this definition can have multiple interpretations, including the judgment of some in the field that stem cell therapy is practice that aims only at treatment and is not subject to any guidelines because it is not research.

It is not possible, of course, to equate stem cell therapy with routine medical care. It differs from standardized medical care in that aspects of its safety and efficacy cannot yet be verified. This sort of unproven medicine, which physicians administer either as part of pure practice or as part of varying degrees of mixed research and practice intent, is called innovative therapy (Levine 1978). It is a controversial field that lies at the border of research and practice, and it has been debated for over 30 years. It is worth emphasising that the fact that these therapies are unproven and exist in a grey area is not a sufficient reason to ban them. 80%–90% of surgical procedures develop from practice without ever being investigated in clinical trials (Cosgrove 2008). Therefore, the alternative approach is to regard stem cell therapy as an innovative therapy and establish strict requirements for its use.

Adoption of the ISSCR guidelines would truly fit this approach (Hyun 2010). Although these guidelines generally oppose the administration of stem cell therapy to large numbers of patients for profit, they allow the possibility of using cutting-edge medicine related to stem cells to treat a small number of patients with severe conditions. In addition, it is necessary to clarify the requirements that would be equivalent to those covering research (International Society of Stem Cell Research 2008). Two factors are of particular importance: first, a peer review process by an appropriate expert who has no vested interest; second, the existence of clinical quality control monitoring. A number of questions would have to be considered if similar regulations were adopted in Japan. Who (among, for example, the government, medical associations, academic societies, medical institutions) would perform the monitoring and management and at what level (e.g., law, guidelines, notification)? How should we establish the conditions with reference to which procedures qualify as innovative therapy? What types of penalties should be applied for guideline violations? In considering such questions, it should be noted that the ISSCR guidelines could also be criticized on the grounds that some countries do not legally recognize innovative therapies (Cohen and Cohen 2010b).



## CONCLUSION: THE RISKS OF MAINTAINING THE CURRENT REGULATIONS

It is highly likely that many of the stem cell therapies provided in Japan at the patient's own expense do not meet the criteria of research or innovative therapy. Although their safety and efficacy are unknown and they may even pose deadly risks at times, Japan currently does not have an independent body charged with identifying, monitoring and managing the providers and recipients of stem cell therapy, nor with identifying, monitoring and managing the extent of the risks involved. This represents a major problem. Fulfilling these functions would likely have resulted in the death of the Korean patient mentioned in the Introduction being reported more swiftly after the event. To protect future patients from grave consequences associated with advanced medicine, including death and severe side effects, such information should be widely disseminated throughout society.

With the aim of being the first country in the world to act on the development of therapeutic technologies using stem cells, Japan is promoting stem cell research as a national policy. The fear is that this widespread use of stem cell therapies, which are harshly criticized abroad, may jeopardize this aim. If this situation is left unresolved, then the relevant research and researchers in Japan who are involved in global competition may lose international trust. As mentioned previously, several issues relating to the regulation of stem cell therapy warrant discussion. The society must collectively recognize that maintaining the status quo and not implementing proper countermeasures could have dire consequences not only for patients and their families, but also for researchers and national policies.

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