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Production and Use of Cloned Human Embryos
— Status of Therapeutic Cloning —

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1 Introduction

Cloned human embryos are cells (embryos) produced by implanting the nuclei of human somatic cells into enucleated eggs. By purpose of use, human cloning can be classified into "reproductive cloning," which uses cloned embryos for producing cloned human individuals, and "therapeutic cloning," in which cloned embryos are used for medical treatment and research purposes.

International opinion is against the production of cloned human individuals (reproductive cloning), represented by an international treaty banning human cloning discussed in the United Nations. Over this issue, the United Nations has split into (1) those appealing for a complete ban on human cloning and (2) those accepting therapeutic cloning, claiming that banning should be limited to the production of cloned human individuals and that regulating production and using cloned human embryos should be the decision of individual governments. The discussion started in 2001, but no agreement has been reached, and it will continue until this December (2004).

In October 2003, the Inter Academy Panel (IAP), an international science academy forum with membership of over 80 academies from around the world including the Science Council of Japan and the U.S. National Academy of Sciences has issued a statement on human cloning regulation. In this statement, IAP urges the United Nations to ban cloned human individual production (reproductive cloning) but also claim that "therapeutic cloning" intended to establish ES cells for research and therapeutic use should not be banned, considering its potential contribution to medical and scientific progress.

While the application of cloning technology to human beings has become a controversial issue in many areas, in March 2004, Korean and U.S. researchers successfully established ES cells from cloned human embryos and published the results of their research in the American journal, Science[1]. ES cells derived from cloned embryos had already been established in experimental animals, but the report demonstrates that they can also be established in humans. At the same time, the low success rate of the reported method, i.e., merely a single ES cell line could be obtained from 242 eggs, suggests that, in addition to ethical issues, there are a number of scientific and technical barriers to overcome before applying similar methods in practice.

In Japan, the Bioethics Committee of the Council for Science and Technology Policy has been discussing whether or not to pave the way to the production and use of cloned human embryos (therapeutic cloning). This report overviews the status of cloned human embryos, both from a biological and a social point of view.

2 Laws and regulations concerning cloned human embryos

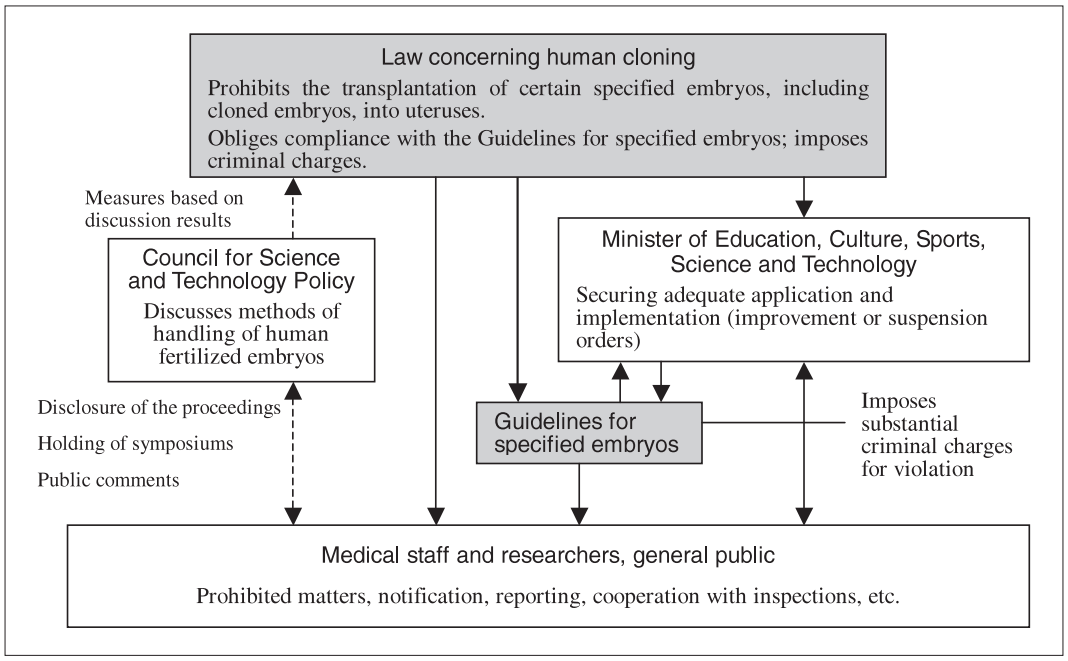
In Japan, any research concerning cloned human embryos must be conducted in compliance with the laws and regulations. Currently, governmental guidelines with de facto legal force prohibit research on the production and use of cloned human embryos. From an

international standpoint, some countries have laws concerning human cloning, while others do not, and some laws prohibit any human cloning at all, while others prohibit only reproductive cloning. In December 2000, Japan enacted the "Law concerning Regulation relating to Human Cloning Techniques and other Similar Techniques" (2000 law no. 146, hereafter referred to as the "Law concerning human cloning"), which legally prohibits the implantation of cloned human embryos into a uterus (prohibition of the creation of cloned human individuals) and imposes criminal charges (imprisonment of up to 10 years or a fine of up to 10 million yen) for any violation. Based on this law, the Minister of Education, Culture, Sports, Science and Technology has established "Guidelines on handling specified embryos" (hereafter referred to as the "Guidelines for specified embryos") that instruct users to follow the guidelines when handling specified embryos such as cloned human embryos and chimeric or hybrid embryos (mixtures or hybrids between human and other animals) and impose substantial criminal charges for any violation. In other words, anyone whose research has been judged to violate the guidelines by the Minister and who does not follow the Minister's improvement or suspension orders, etc., will face imprisonment of up to 1 year or a fine of up to 1 million yen.

Table 1 : Classification of specified embryos employed in laws and guidelines in Japan

Specified embryos (simplified forms of the definitions given in the Law concerning human cloning):
(1) Human somatic clone embryo : human enucleated unfertilized egg + human somatic nucleus (2) Human-animal chimeric embryo : human embryo + animal embryo (3) Human-animal amphimictic embryo : human gamete fertilized with an animal gamete (or a clone obtained using its nucleus) (4) Human-animal hybrid embryo : animal enucleated unfertilized egg + human cell nucleus (including the embryo) (5) Human split embryo : embryo produced by splitting the human early embryo (the developing embryo) (6) Human-human chimeric embryo : human embryo + human cell (including the embryo) (7) Human embryonic clone embryo : human enucleated unfertilized egg + human early embryo nucleus (8) Animal-human hybrid embryo : human enucleated unfertilized egg + animal cell nucleus (9) Animal-human chimeric embryo : animal embryo + human cell
Definitions of the terms used
Human : contains a human nucleus Animal : contains an animal nucleus Chimeric embryo : an embryo produced by mixing no fewer than two embryos. Chimaera embroyo Amphimictic embryo : a hybrid embryo produced through the fertilization of gametes, and a cloned embryo obtained using its nucleus Hybrid embryo : an embryo produced by transplanting a nucleus into an enucleated egg or a fertilized egg

Figure 1 : Structure of regulations concerning human cloned embryos



The Guidelines for specified embryos prohibit any production or use of specified embryos given in the list, except for the production of animal-human chimeric embryos. In other words, not only the implantation of cloned human embryos into uteruses but also their production is prohibited by the guidelines.

3 Significance of therapeutic cloning

The greatest value of therapeutic cloning is its potential to produce patients' own cell transplants, thus avoiding the immunological rejection that occurs in regenerative medicine. This section summarizes the situation surrounding this aspect of therapeutic cloning.

Regenerative medicine refers to technologies to regenerate functionally disturbed or incompetent tissues or organs through the active use of cells. Using various techniques, cells, tissues, etc., are artificially adapted to perform their intended functions and then implanted into dysfunctional organs or tissues so that their lost functions and health are restored.

In organ/tissue transplantation, immunological rejection occurs in individuals (recipients) whose cells, tissues, etc., have received implants. For successful results in regenerative medicine, this rejection must be adequately suppressed. Immunosuppressants are usually used, and the improvement in immunosuppressants (emergence of cyclosporin) has largely contributed to the establishment of the medical transplantation techniques used today for the heart, lungs, liver, kidneys and other organs.

The immunosuppressants used to prevent and suppress immunological rejection are accompanied by certain adverse effects listed in Table 2 (listing only drugs generally used in renal transplantation. Other immunosuppressants such as antilymphocyte antibodies and anti-IL2 receptor antibodies are not shown). After transplantation, patients usually receive two or more kinds of immunosuppressant in combination and must continue taking them for rest of their lives (as long as they have the implants within them).

The results of an investigation conducted in 1983 show that one-year graft survival rates after cadaveric transplantation were 72% and 52% when dosing with cyclosporin alone (117 cases) and dosing with other agents (steroids/azathioprine, 115 cases), respectively[5]. The graft survival rate after cadaveric transplantation has increased to 88.7% through combination therapy (calculated from 268 cases examined since 1983[6]).

As can be seen, eliminating immunological rejection is essential in medical transplantation as well as in the cell transplantation employed in regeneration medicine. Since rejection is due to variation in immune-related genes (differences in tissue antigens) observed among individuals, rejection is in theory suppressed by establishing ES cells derived from embryos (with the genomic genes of the patients) cloned from the patients themselves and by implanting cells appropriately differentiated from such ES cells.

In mice, the use of ES cells derived from cloned embryos has actually proved effective in avoiding rejection in regenerative medicine[7].

Table 2 : Immunosuppressants

Immunosuppressants	Adverse effects
common to all agents	reduced resistance to infectious diseases
cyclosporin	nephropathy, hepatopathy, encephalopathy symptoms, neuro-Behcet-like symptoms, acute pancreatitis, thrombotic microangiopathy, hemolytic anemia, rhabdomyolysis, lymphoma, lymphoproliferative tumor, malignant tumor, hirsutism, trembling of hands, etc.
tacrolimus	nephropathy, diabetes, trembling of hands, cardiopathy, etc.
steroids	peptic ulcer, diabetes, hypertension, glaucoma, cataract, obesity, moon face, etc.
mycophenolate mofetil	leukopenia, anemia, diarrhea, inappetence, etc.
azathioprine	leukopenia, inappetence, nausea, liver dysfunction, etc.
mizoribine	leukopenia, liver dysfunction, inappetence, nausea, stomatitis, pancreatitis, etc.

4 Status of cloning technology

This section overviews the technical aspects of the process of establishing ES cells from cloned embryos, from the perspective of applying cloned human embryos to regenerative medicine.

Cloned human embryo production involves techniques that take the nucleus of a somatic cell (containing genomic genes principally identical to the donor of the somatic cell) out of the target individual to be cloned, transfer it into an egg, and treat the egg appropriately to promote embryo development without the involvement of gametes (sperm and eggs) or fertilization. From the resulting early embryo (at the blastocyst stage), a specific group of cells (inner cell mass) is removed and used to establish ES cells. This is how ES cells are established from cloned human embryos. Achievements in bioresearch in this process are discussed in the following paragraphs.

To date, cloned individuals have been obtained in sheep, mice, cattle, goats, pigs, rabbits, cats, mules, horses and rats using cloning technology. Success in the production of cloned individuals depends on the type of abnormality observed, etc., and these are different among the above species. Mice in particular, which are generally used in animal experiments, have great physiological differences from other mammals.

Phenotypic abnormalities are believed to be caused by (1) technical factors such as artificial handling that may damage the eggs, (2) genetic factors, such as abnormalities in the genomes of the somatic cells used for nuclear transplantation, or the genetic variation observed in the differentiation or the aging process or (3) non-genetic factors (epigenetic factors are explained later) concerning reprogramming (to obtain a condition suitable for development) or egg activation.

4-1 Abnormalities observed in cloned individuals

The scientific and technical aspects of cloning technology have been developed by analyzing results obtained from experiments on the production of cloned individuals from cloned embryos using domestic or experimental animals. The findings from these cloned animal production experiments should help us understand the nature of cloned human embryos used for therapeutic cloning.

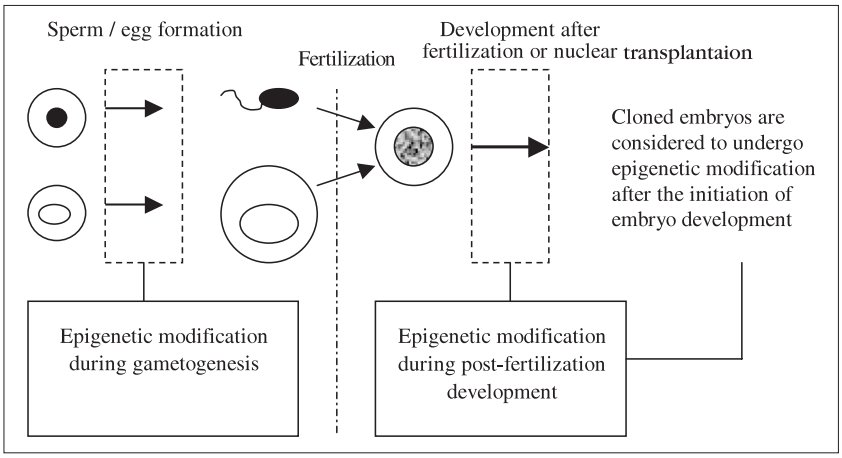
(1) In animal experiments, when embryos produced through cloning are implanted into the uterus, most early mouse embryos die immediately after their implantation, i.e., at the stage of placenta formation, while cattle and sheep embryos stop developing in late pregnancy, resulting in a high percentage of stillborn and abnormal babies. Moreover, the size of the newborn babies and their placentas is unusually large, and this commonly observed independent of species. After birth, a wide range of abnormalities is observed in respiratory function, kidneys, liver, heart, brain, etc., and obesity, oncogenesis and short life are observed after growth.

(2) The risk of inducing abnormal traits partially depends on the type of donor cell (fibroblasts, ES cells, etc.) used for nuclear transplantation. With ES cell nuclei, cloned embryo production is 10-20 times more efficient than production using other somatic cells.

(3) Abnormalities observed in cloned individuals are considered to be induced by abnormal reprogramming or egg inactivation, the use of abnormal donor cells or in vitro culture. For example, the efficiency of microfertilization can deteriorate due to technical factors, even in the absence of non-genetic abnormalities. However, in biological terms, epigenetic factors[*1] such as genome imprinting, rather than technical damage or genetic factors, seem to be the main cause of abnormal cloned individuals.

(4) Reprogramming is an epigenetic process required to achieve a state suitable for initiating embryo development. The process appears to have two stages, i.e., during the formation of the gametes (sperms or eggs) in the reproductive organs, and after the fertilized eggs and embryos have started

Figure 2 : Process involving epigenetic modification



developing. Since the nuclei of cloned embryos skip the process of gametogenesis, they cannot achieve a completely reprogrammed state (Figure 2).

Even in embryos derived through usual sexual intercourse, the absence of normal epigenetic reprogramming after fertilization results in abnormal development. For example, parthenogenesis of an egg results in the formation of teratoma, while an embryo with only a sperm-derived nucleus results in developing vesicular mole.

Furthermore, the epigenetic factors involved in gametogenesis include a mode of gene modification called imprinting (mechanism for regulating gene expression which leads to differential expression between paternal and maternal genes) and the modification of non-imprinted genes, and the factors involved after the initiation of development include X-inactivation and telomere length regulation. Cloned embryos undergo normal epigenetic processes after the initiation of development, i.e., X-inactivation and telomere length regulation.

(5) Cells consisting of various organs in cloned individuals differ greatly from those found in individuals produced through ordinary reproduction in terms of the kinds of gene expressed, DNA methylation patterns, expression levels of various substances, etc.

4-2 Procurement of eggs

The biological significance of using eggs to prepare cloned embryos is their capability of reprogramming the transplanted nuclei. Reprogramming is required to modify the cells, which have once experienced differentiation and are functioning as somatic cells, so that they can form early embryos again (initiate development).

(1) Eggs can be provided (i) by female volunteers or (ii) from eggs obtained for fertility treatment or through other medical procedures.

From the viewpoint of human rights and gender issues, there is a great fear that females may be treated as a means of supplying egg materials for human cloning. In the United Nations, African countries have expressed their concerns about “poor women in African countries becoming exploited as egg factories.” Moreover, egg retrieval imposes physical risks such as the use of ovulation-inducing agents, anesthesia and surgical operation. For instance, ovulation-inducing agents may induce severe symptoms such as ovarian hyperstimulation syndrome.

Meanwhile, eggs may be obtained through medical procedures other than fertility treatment, such as from ovaries removed in surgery.

(2) There is no established method for the cryopreservation of eggs. However, the use of frozen eggs has resulted in successful in vitro fertilization in a number of cases. Advances in cryopreservation technologies should enable the preservation of individual

eggs or of eggs as a part of the ovary tissues.

(3) Alternatives to using eggs collected or provided from living bodies to reprogram the somatic nuclei of donors are currently being developed, such as the use of eggs differentiated from human ES cells or eggs derived from other species. In 2003, Hü bner, et al. reported that egg cells could be differentiated from mouse ES cells[9]. This report suggests that, although less efficiently than egg cells derived from living bodies, a large number of egg cell-like cells can easily be obtained (from ES cells through only in vitro treatment) as a tool for reprogramming somatic nuclei and initiating the development of cloned embryos. This report implicates that cells required for medical cell transplantation can be supplied on an industrial basis.

(4) In the future, the development of new techniques for the reprogramming process, such as the direct reprogramming of somatic cells, may eliminate the necessity of eggs derived from living bodies to obtain rejection-free cells that inherit the immunological characteristics of the patients themselves. Unfortunately, much of the biological mechanism underlying the reprogramming process remains unexplained, even at the level of animal experiments.

4-3 Low success rate

With sufficient technical skill, ES cells can generally be established from blastocysts derived from fertilized embryos with a 100% success rate. In comparison, establishing ES cells from cloned human embryos has a low success rate. Hwang et al. collected 242 eggs from 16 females and used them for nuclear transplantation to achieve 30 blastocysts (12%). However, only one ES cell strain could be obtained, resulting in an extremely low success rate compared to the rate using fertilized embryos. The ultimate success rate was 0.4%, which is impractical considering the use of eggs derived from living bodies.

Nevertheless, their report is significant in that it demonstrates the possibility of establishing ES cells from cloned human embryos, and technical issues should be solved by future research and development. As discussed in the section on abnormalities observed in cloned individuals, cloned embryos skip the process of nuclear reprogramming in the gametogenesis process, and developing an alternative means to this natural process requires basic research using experimental animals. Currently, there is no clear vision concerning the development or the results of such basic research, and scientific and technical breakthroughs are awaited. Nevertheless, including the use of ES cell-derived eggs (or cells similar to these) in research, we must establish a system under which research involving cloned human embryo production can be conducted within an appropriate framework.

5 Status of regeneration medicine research using ES cells

To date, transplantation experiments with animals using cells differentiated from ES cells have been reported on hematopoietic cells, dopamine-producing nerve cells, motor cells and insulin-producing cells, which are applicable to hematopoietic diseases, Parkinson's disease, spinal cord injury and diabetes, respectively. Among these reports, an experiment using immunosuppressed mice simultaneously succeeded in differentiating ES cells derived from cloned embryos and using them in gene therapy through genetic recombination. The success of this experiment is based on the potential of cloned embryos in regenerative medicine and the technical advantage of using ES cells in genetic recombination.

In Japan, the Institute for Frontier Medical Science of Kyoto University has established the 3 human ES cell lines (KhES-1, 2 and 3) shown in Table 3 and has already begun distributing some of them (human ES cell project information disclosure website). Their nature as ES cells is currently being confirmed, such as whether they are capable of stable self-replication (the forms of cells and colonies), their pluripotency, normal chromosomes (karyotype) and the expression of markers for undifferentiation (ALP, SSEA-4, TRA-1-60/81, Oct-3/4, Rex-1, etc.). The nature

of ES cells is not fully understood, and therefore requires further research, e.g., to elucidate the molecular mechanism of self-replication.

In addition to the various abnormalities found at the level of the individual, animals derived from cloned embryos differ from normal at tissue level. This generates risks in the application of cloned embryos to regenerative medicine, i.e., the use of artificially generated (naturally non-existing) cloned embryos as cell transplants. These abnormalities are believed to depend on reprogramming, but as mentioned earlier, their mechanisms are not fully understood, even in experimental animals. Meanwhile, the difference between cloned embryos and normal cells may be significant in the process of ontogenesis, but as long as they retain the functions required for cell transplants to treat adults, their safety and benefits may not be considered as practical problems. Furthermore, ethical issues concerning the procurement of eggs may be solved by a new alternative means, such as the use of materials removed in surgical operations or eggs (or egg-like cells) prepared from ES cells as tools for reprogramming.

Based on these points, various patterns of ES cell establishment are shown in Figure 3. A number of attempts have been made to establish ES cells applicable to regenerative medicine, not only ES cells derived from fertilized or cloned embryos but also egg-like cells derived from ES cells or the application of cell fusion techniques. Moreover, the British scientific journal, Nature, has recently published a report[10] by Japanese and Korean researchers who generated eggs with a mutation in a gene (H19) potentially involved in epigenetic genome imprinting in mice, and who successfully initiated development without fertilization in individual reproductive mice. This study clearly demonstrates the involvement of epigenetic phenomena in reprogramming, and other studies are also being conducted to elucidate the reprogramming mechanism.

Table 3 : Examples of human ES cell strains established in various countries

U.S.	27
Sweden	25
India	10
South Korea	6
Australia	6
Israel	4
Total	78

Source: Prepared by the author based on the NIH Stem Cell Registry that presents the number of human ES cell lines approved by U.S. NIH by August 2001

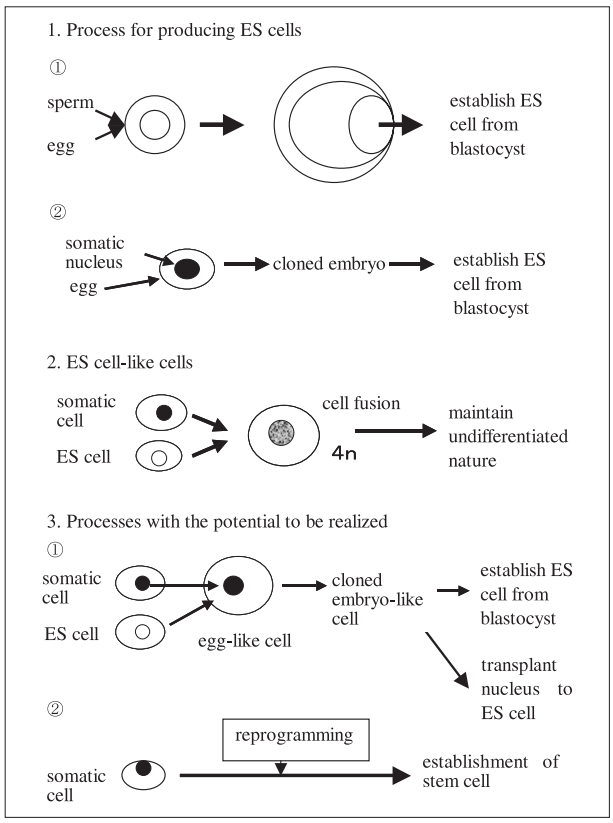
Japan	3

ES cell lines established in May and October 2003 by the Institute for Frontier Medical Sciences of Kyoto University

6 Somatic stem cells and ES cells

In contrast with ES cells, which are derived from cloned human embryos, somatic stem cells are obtained from the tissues of adult individuals. Although their biological properties differ from those of ES cells, somatic stem cells are also useful in regenerative medicine. Unlike human embryos or cloned human embryos, the use of somatic stem cells is free from ethical issues. Here are some important points concerning somatic stem cells compared with cells derived from

Figure 3 : Process for producing ES cells, etc.



cloned embryos or ES cells.

(1) Unlike cells artificially derived from cloned embryos, immature ES cells or cells derived from such cells, somatic stem cells are originally part of the body and can therefore be assumed to be safer when returned to the same body in medical transplantation.
(2) Somatic stem cells potentially have various differentiation potencies and practical uses, as demonstrated in an attempt to differentiate mouse bone-marrow cells into myocardial cells. Transplantation therapy against leukemia, etc., using cord blood cells is already equivalent to bone marrow transplantation in terms of the number of patients receiving this therapy (cord blood cell transplantation requires a long recovery period and has a high risk of bleeding and infection in adult recipients, but strategies to overcome these disadvantages, such as alleviating preoperative myelosuppression and using in vitro culture, have been discussed).
Stem cells have limited differentiation potency, but as an exception to this, Jiang et al. (2002) have reported the isolation of pluripotent somatic stem cells[11]. These stem cells have been isolated in mice, rats and humans, but their application has not yet been researched. Some reports doubt the pluripotency of somatic stem cells, and their potential for future application is unclear.
(3) Compared to ES cells, somatic stem cells are difficult to collect and propagate (ES cells can be propagated and maintained without limit over a long period of time).
(4) Some of the advantages of ES cells are that their genes can be modified, they can be supplied in large amounts with consistent quality, their sublines can be established, and their supply can be stabilized and standardized. On the other hand, such advantages are unknown or are hardly observed in somatic stem cells.

Mamoru Ito et al., Central Institute for Experimental Animals, have developed immunosuppressed mice (NOG mice: NOD/SCID/γ (gamma) C^{null}) intended for studying the clinical application of somatic stem cells and ES cells. They are expected to serve as a means of examining in vivo regeneration, and the differentiation and the safety of cell transplants.

As mentioned above, somatic stem cells and ES cells each have different advantages and disadvantages. If collected from the individual to be treated, somatic stem cells require neither the use of fertilized embryos nor the preparation of cloned embryos. However, they seem to have limited capacity for differentiation, propagation and retrieval from living bodies. Therefore, research must be promoted for both cell types.

According to the "Surveys on the clinical application of somatic stem cells in Japan" conducted by the Health Sciences Council in 2002, 90, 3 and 16 facilities were at the stages of research, pre-clinical research and clinical study, respectively (based on data from the references[3]). At least in these facilities, transplantation of the epidermis or bone, or transplantation therapy for vascular occlusion diseases, has already been performed on actual patients in clinical trials. Furthermore, a Japanese patient with a spinal cord injury has received spinal cord regenerative medicine using olfactory ensheathing cells in China. Establishing regulations and guidelines for regenerative medicine has become an urgent social issue for Japan.

7 Debates on therapeutic cloning

7-1 Debates in Japan

Article 2 in the Supplementary Provisions of the "Law concerning Regulation relating to Human Cloning Techniques and other Similar Techniques" (2000) states that "the Government shall, within three years of enforcement of this Law, take necessary measures in accordance with the results of its study and examination of the provisions under this law, based on the results of the examination by the Council for Science and Technology Policy concerning the method of handling of human fertilized embryos as the beginning of human life." The deadline

is June 2004, and the Expert Panel on Bioethics of the Council for Science and Technology has announced an interim report, "On basic concepts concerning the handling of human embryos." In response to comments by the public on the report, the committee is continuing discussion to reach a public decision on whether to permit therapeutic cloning and whether to pave the way to regenerative medicine research.

There are various arguments concerning therapeutic cloning. From the ethical viewpoint, arguments in favor of therapeutic cloning are based on medical, scientific and humane reasons. Meanwhile, those against therapeutic cloning are mostly based on religious and personal ethical convictions, or fear of scientific uncertainty, and some even claim that regenerative medicine itself is unnecessary or that the potential to increase exploitation of the human body is not acceptable. Complete agreement has not yet been reached through these arguments, and neither is it expected in the future. Therefore, we should return to the original purpose of achieving both respect of individual rights and public benefit. In other words, the government must establish a social system that approves the independence of individuals with various ethical values and that ensures social safety and peace of mind.

7-2 Trends in therapeutic cloning in the United Nations and other countries

As mentioned earlier, the United Nations has not reached an agreement between those in favor of and those against therapeutic cloning. Complete prohibition of human cloning, suggested by Costa Rica, is supported by more than 50 countries including the United States, African countries, the Vatican, Spain and Italy, while prohibition of only reproductive cloning is supported by more than 20 countries including Belgium, Germany, France and Japan. The United States, which supports complete prohibition, imposes regulations on NIH concerning the use of funds, but does not have any federal law that directly regulates the handling of human embryos including human clones. In other words, the country has no federal regulation on privately funded human embryo research, so human embryo technology has been developed in the private sector. The President's advisory council announced "Human Cloning and Human Dignity" concerning cloning, "Monitoring Stem Cell Research" concerning stem cell research and "Reproduction and Responsibility" concerning assisted reproduction technologies in July 2002, January 2004 and March 2004, respectively. In these reports, the Council only mentions the necessity of social debate, the fact that the Council has been divided over this issue, and that the bill prohibiting both reproductive and therapeutic cloning of human has passed the House but has not been approved in the Senate. Meanwhile, ES cell research has been supervised by NIH (encouraging studies using existing ES cells that have been registered) based on a presidential statement in 2001. At the individual state level, state laws concerning cloning vary greatly, but the law in California approves therapeutic cloning (production of cloned human embryos).

In "The Ethical Implications of Research Involving Human Embryos" and the "Commission Staff Working Paper: Report on Human Embryonic Stem Cell Research" in 2000 and 2003, respectively, the EU suggests establishing strict conditions on the production of human fertilized embryos for research purposes. However, the organization principally respects decisions made by individual governments concerning the production of human embryos for research purposes or therapeutic cloning. In 2001, the European Parliament rejected a bill prohibiting the contribution of public funds to human embryo research (CNN).

To the author's knowledge, countries prohibiting the establishment of ES cells from human embryos are Norway, Austria (imported ES cells are under discussion), Germany (imported ES cells are approved), France (under review), Spain (under review) and Ireland. Switzerland approves the establishment of ES cells but explicitly prohibits both reproductive and therapeutic cloning by law. On the other hand, in countries such as U.K., Belgium, South Korea, China, Israel, Luxembourg, Italy (under discussion) and Taiwan, therapeutic cloning is permitted either explicitly by law or substantially through freedom from legal restrictions. In

France, a revision of the Bioethics bill is currently under discussion in Parliament, and while moving toward an acceptance of research using human embryos for limited purposes, the Parliament is divided over therapeutic cloning. A public poll conducted in France revealed that 65% of people distinguish between reproductive and therapeutic cloning, while 31% make no distinction. The results also indicate that 45% are in favor of therapeutic cloning, while 20-30% are against it (the Science Generation Initiative). In Singapore, a bill that allows therapeutic cloning is currently under discussion and should be approved in the near future (ABC Online).

As in Japan, methods of handling of human embryos are controversial in many developed countries. Discussion concerning the acceptance of ES cells seems to be entering a new stage, while therapeutic cloning has already been socially accepted and researched in some countries.

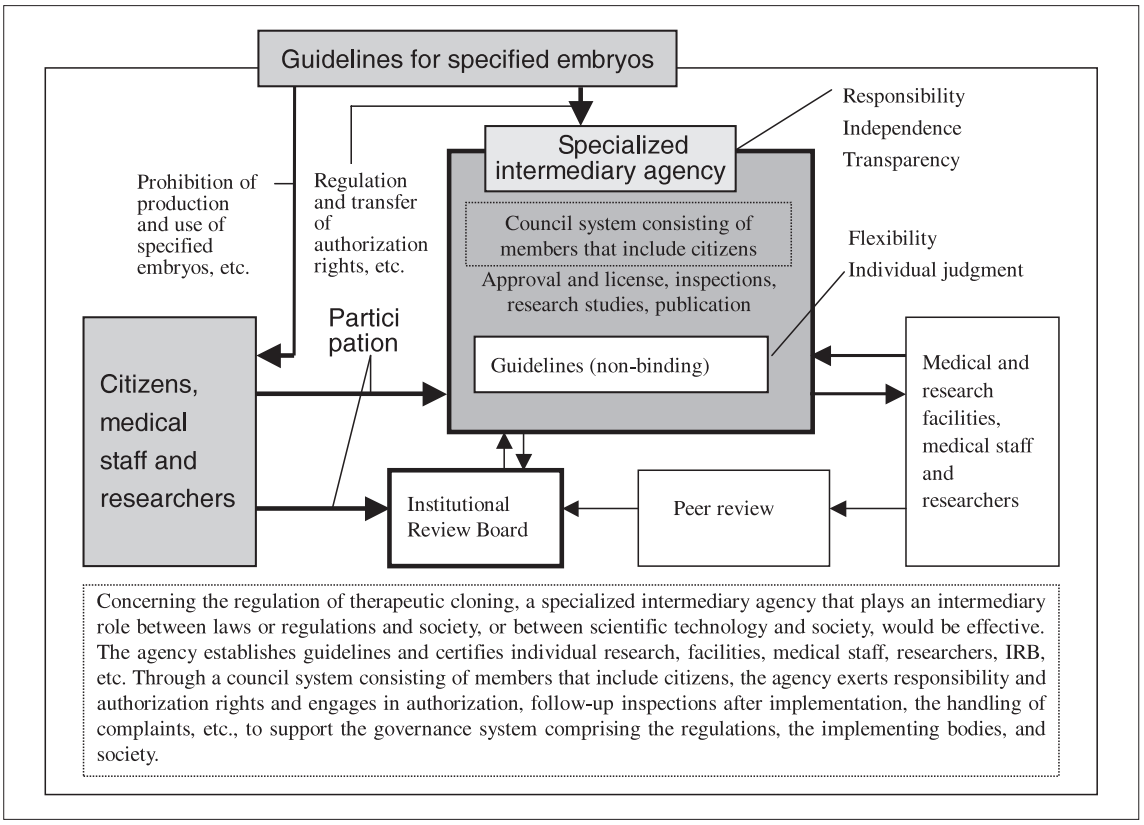
8 Conclusion

The pros and cons of therapeutic cloning have been socially discussed. As long as society demands and expects regenerative medicine and research in this area, protocols and systems for implementation that gain the acceptance and confidence of both sides must be established, based on social debate. As a candidate for such a system, the 2nd Policy-Oriented Research Group of the National Institute of Science and Technology Policy suggests a "social governance system of life science technology"[15], which comprehensively involves the participation of citizens and society, conducts risk management as well as the qualitative control of medical treatment and research, and protects subjects' rights, through a structure in which a specialized intermediary agency is the core. An intermediary agency is an organization that plays an intermediary role between scientific technology and society. As an example, the structure of a system for therapeutic cloning is depicted in Figure 4. Japan must consider the application of a governance system that secures confidence through the participation of citizens.

Acknowledgements

The author thanks Dr. Terutaka Kuwahara, Director of the Science and Technology Foresight

Figure 4 : Example of social governance system concerning the handling of therapeutic cloning



Center, for providing this opportunity to write this report. The author also thanks those who kindly advised me, especially Dr. Teruhiko Wakayama (RIKEN), Dr. Shinichi Nishikawa (RIKEN) and Dr. Satoshi Teraoka (Tokyo Women's Medical University).

Notes

*1 epigenetic: a mode of non-heritable modification involved in the regulation of gene expression, etc., without changing the gene. The modification involves DNA methylation, histone protein modification, the higher-order structure of chromosomes, etc[8].

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(Original Japanese version: published in May 2004)