

Fetal stem cell transplantation: Past, present, and future

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Abstract

Since 1928, human fetal tissues and stem cells have been used worldwide to treat various conditions. Although the transplantation of the fetal midbrain substantia nigra and dopaminergic neurons in patients suffering from Parkinson's disease is particularly noteworthy, the history of other types of grafts, such as those of the fetal liver, thymus, and pancreas, should be addressed as there are many lessons to be learnt for future stem cell transplantation. This report describes previous practices and complications that led to current clinical trials of isolated fetal stem cells and embryonic stem (ES) cells. Moreover, strategies for transplantation are considered, with a particular focus on donor cells, cell processing, and the therapeutic cell niche, in addition to ethical issues associated with fetal origin. With the advent of autologous induced pluripotent stem cells and ES cells, clinical dependence on fetal transplantation is expected to gradually decline due to lasting ethical controversies, despite landmark achievements.

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Key words: Fetal tissue; Fetal stem cells; Fetus, Embryonic stem cells; Transplantation; Clinical trials

Core tip: Based on the history of fetal stem cell transplantation since 1928, this article discusses strategies for transplantation, with a focus on donor cells, cell processing, and the therapeutic cell niche, in addition to ethical issues associated with fetal origin. We described the stream line to current clinical trials using fetal and embryonic stem cells based on Clinical. Trials. gov. Finally, we discussed the perspective of fetal stem cell transplantation.

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INTRODUCTION

In 1988, an article reported the hopeful results of a clinical trial in which the fetal mesencephalic substantia nigra was transplanted in patients with Parkinson's disease (PD)^[1]. In the preceding year, 1987, a Chinese team had reported similar findings of fetal tissue transplantation conducted in August 1985^[2]. Following the publication of these reports, similar neural tissue transplantation procedures became widespread. Most notably, a double-blind, sham surgery controlled study of transplantation of fetal dopaminergic neurons in PD patients was reported in 2001^[3], which provided convincing data regarding the efficacy of fetal tissue transplantation for treating this condition. Since then, fetal tissue transplantation has advanced to include the clinical development of isolated fetal cells, particularly neural stem cells in business entities.

Although many review articles have focused on the application of neural tissue and/or cells in fetal tissue transplantation^[4-14], the clinical use of fetal cells is not new or simply confined to the field of neurological field. The rationale of fetal tissue transplantation lies in the potential for fetal cell proliferation and differentiation,

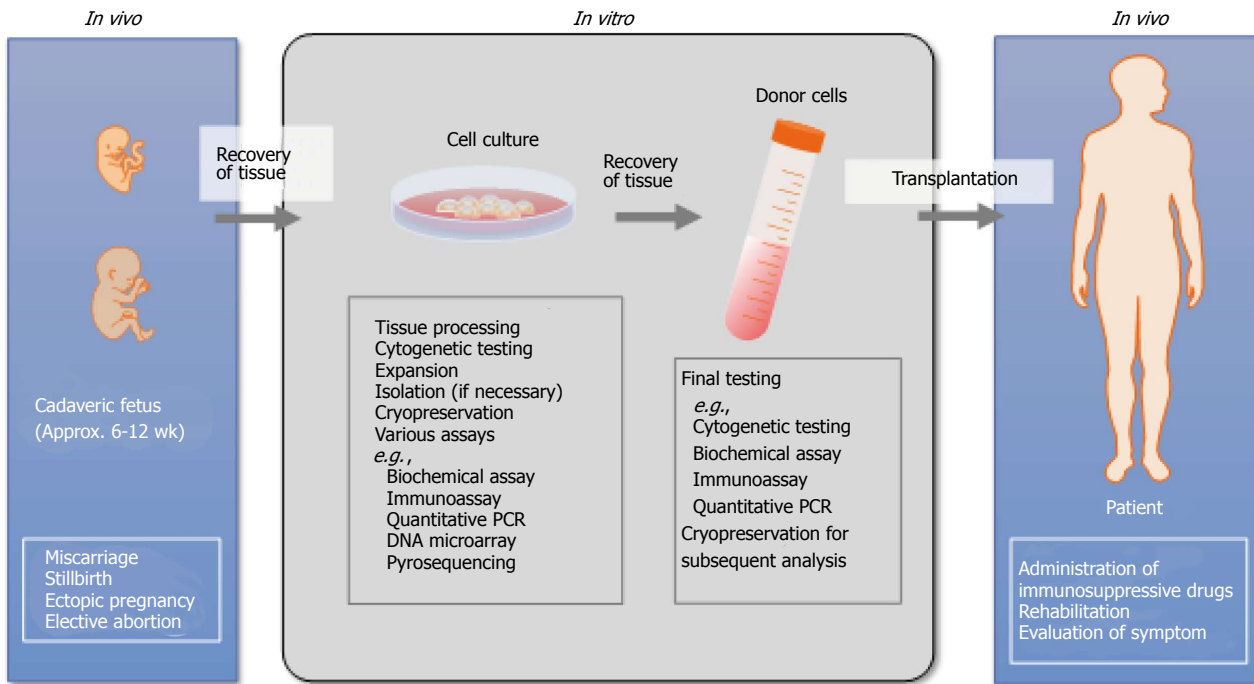


Figure 1 Fetal tissue transplantation procedures. Fetal tissue can be obtained from cadaveric fetuses for medical and non-medical reasons in obstetrics and gynecology hospitals. Procured fetal tissue, which was donated with consent for research, is processed *in vitro*, confirming cell function without contamination and genetic abnormality. After careful examination, donor cells are used for grafts primarily in the form of a cell suspension, which is usually intravenously or intraperitoneally injected or, otherwise, transplanted into predefined implant sites during surgery. Although fetal tissue cells are less likely to be rejected by transplant recipients, immunosuppressive drugs are administered in some cases. PCR: Polymerase chain reaction.

and fetal grafts may be integrated into the host without inducing immune rejection. These features of fetal tissue are well known, as is the established clinical use of transplants derived from cadaveric fetuses in the history of transplantation therapy. For example, early as 1928, a form of fetal tissue transplantation in Italy was documented in a medical journal as a treatment for diabetes mellitus^[15]. Subsequently, the indications for fetal tissue transplantation expanded to other subjects with therapeutic efficacy in conditions other than diabetes. Since the early 1960's, a tremendous number of fetal liver and thymus transplantations have been performed worldwide to treat immunodeficiency and hematological disorders.

In order to gain new perspectives on future clinical application of stem cells, it is worth considering the history of fetal tissue transplantation, taking into account an overview of current fetal stem cell research. In this report, the authors examine the history of fetal tissue transplantation, as well as many associated complications including procuring and processing fetal tissue, selecting appropriate diseases and subjects, developing new transplantation strategies, assessing graft survival and integrity *in vivo*, providing long-term monitoring of patients treated with fetal grafts for adverse events. Moreover, important ramifications of ES cell research are addressed and transplantation strategies are considered from the viewpoint of donor cells, cell processing and the therapeutic cell niche, in addition to ethical concerns. Finally, the authors provide future perspectives on fetal stem cell transplantation.

In this article, the authors offer a discussion of the progression from previous applications of fetal tissue transplantation to current uses of stem cell transplantation. In humans, the product of conception after implantation in the uterine wall through the eighth week of development is referred to as the embryo. From the ninth week to birth, the embryo is called a fetus. The authors largely follow this nomenclature.

FETAL TISSUE TRANSPLANTATION PROCEDURES

Fetal tissue contains a sufficient number of stem cells and progenitor cells for development, making it valuable for some treatments. Namely, fetal tissue cells are easier to culture and proliferate more readily than comparable adult tissue cells^[16-24], with the exception of pancreatic cells^[25,26]. Fetal tissue cells are also less likely to be rejected by transplant recipients, as these cells are less antigenic, expressing HLA-G for immune tolerance during pregnancy^[27]. This fact and the findings of animal experiments suggested a reduced need for an exact tissue match, which is frequently difficult to obtain^[28]. Collectively, the features of fetal tissue cells facilitate engraftment *in vivo* and may provide beneficial effects against diseases difficult to treat.

Fetal tissue can be obtained from cadaveric fetuses following spontaneous abortion, stillbirth, or surgery due to ectopic pregnancy in obstetrics and gynecology hospitals (Figure 1). In addition, such tissue may be derived

from elective abortions. The obtained fetal tissue is ordinarily processed and used for grafts in the form of a cell suspension, which is usually intravenously or intraperitoneally injected or, otherwise, transplanted into predefined implant sites during surgery.

PREVIOUS FETAL TISSUE TRANSPLANTATION PROCEDURES

Early attempts

A bibliographic survey revealed the use of fetal pancreatic transplantation to treat insulin-dependent diabetes mellitus, as well as an attempt to treat human cancer in Italy as early as 1928^[15]. The applied tissues were acquired from three human fetuses. Prior to this period, a diabetic dog experiment was conducted in Canada in 1921, the result of which suggested that injections of insulin, a hormone secreted from the pancreas may be used to treat diabetic patients. The following year, a clinical trial involving a 14-year-old boy with diabetes was performed; the boy recovered from his condition following insulin injections^[29]. This therapeutic achievement was awarded the Nobel Prize in Physiology or Medicine in 1923 and provided a background for the development of fetal pancreatic transplantation in Italy, as the fetal transplants may be used to circumvent the need of repeated insulin injections while offering the potential for curative therapy for diabetes. Nonetheless, this attempt eventually failed, due to a lack of treatment. Meanwhile, the first fetal pancreatic transplantation in the United States was carried out in 1939^[30]. In the clinical setting, pancreatic tissue removed from an aborted fetus was transplanted into a diabetic patient twice, albeit in vain. Subsequently, in 1959, two United States physicians reported the transplantation of fetal tissue derived from six stillborn fetuses into their diabetic mothers^[30]. However, only a transitory reduction in the need for insulin was observed in one case. Although fetal tissues are less likely to be rejected due to their reduced antigenicity, allotransplantation remained difficult until the availability of immunosuppressive drugs, such as azathioprine, in the early 1960's.

In contrast, fetal tissue was frequently used in biomedical research at that time. For instance, fetal kidney cell cultures were applied to produce large quantities of viruses, leading to the development of the polio vaccine, which was awarded the Nobel Prize in Physiology or Medicine in 1954. The application of fetal tissue cultures also contributed to the development of the rubella vaccine.

1960's to mid-1980's

The first bone marrow transplantation to treat fatal leukemia was reported by United States researchers in 1957^[31]. However, the results of marrow transplantation achieved in six patients, after first destroying their marrow with radiation, was disappointing; none of the patients survived beyond 100 d. It was not until the late 1970's when the marrow transplantation consistently resulted in success-

ful outcomes due to tissue matching, thus controlling both infectious complications and graft-*vs*-host disease (GvHD). These experiences in marrow transplantation simultaneously facilitated the development of fetal tissue transplantation, which ultimately became a frequently used therapeutic option in cases where no histocompatible donor was available for marrow transplantation.

In adult humans, hematopoiesis normally occurs in the bone marrow; however, a succession of organs sustains blood cell production during human embryogenesis^[32]. The process of hematopoiesis is initiated in the yolk sac during the third week of development, then subsequently relayed to the liver, thymus, and bone marrow at the 11th week, at which time stabilization of definitive post-natal hematopoiesis begins. Most elective abortions are performed during the first trimester. In this era, clinical availability of fetal liver and thymus tissue has encouraged researchers to performed transplantation to treat hematological disorders and cases of severe immunodeficiency.

In 1958, it was reported that a devastated immune system in rodents was restored by inoculating fetal hematopoietic tissue following lethal total body X-irradiation^[33]. In 1961, a United Kingdom group reported the results of transplantation of fresh or stored fetal liver cells ($1-20 \times 10^9$ /case, gestational age unknown) *via* intravenous injection to treat aplastic anemia, stating that remission was achieved in two of 14 patients (18 mo to 55 years of age)^[34]. Similar findings were subsequently reported from China^[35,36], Hungary^[37], India^[38-41], Italy^[42-44], and United States^[45,46].

In 1975, a United States group reported successful fetal liver transplantation in a male infant (3 mo of age) with adenosine-deaminase (ADA) deficiency, which causes severe combined immunodeficiency (SCID)^[47]. In that case, an 8.5-wk-old embryo was obtained, with permission from a mother undergoing termination of pregnancy and sterilization with hysterectomy. A suspension containing 2.5×10^8 liver cells was injected into the recipient intraperitoneally, who developed immunocompetent T and B cells in an orderly manner until one year after the procedure, when he died of fatal nephrotic disease. Soon after that case, a United States group reported the results of transplantation of fresh fetal liver cells (obtained from 8-, 9-, and 10-wk-old fetuses) in two infants with SCID in 1976^[48]. Although no functional immunological improvements were achieved in the first infant, both clinical and functional immunological improvements were noted in the other patient, who was monitored for 19 mo after transplantation. In that case, the engraftment of fetal cells, as confirmed by chimerism in the recipient's lymphocytes, reversed the patient's immunodeficiency. Similar treatment of ADA-SCID was also reported by a Japanese group in 1985^[49]. In addition, according to a case report published in 1985, a patient with X-linked SCID whose parents and siblings were not suitable HLA-compatible bone marrow donors underwent, embryonic liver cells were transplanted intravenously in 3 stages ($6 \times 10^6 - 9 \times 10^7$)^[50]. Although the procedure resulted in T-cell recon-

stitution in addition to the initiation of immune globulin production, the child died at five months of age due to respiratory failure. In another SCID case reported by a French group in 1979, an infant who received two separate grafts of both hepatic and thymus cells recovered from the same fetus exhibited a partially restored immune system^[51].

Fetal liver transplantation has also been attempted to treat leukemia. In 1982, an Italian group reported the use of fetal liver transplantation in two patients with acute leukemia following the administration of a conditioning regimen consisting of cyclophosphamide and total body irradiation^[52]. Although each patient achieved remission with a hematopoietic recovery, the survival time after transplantation was only 153 and 30 d, respectively. A similar transplantation procedure was subsequently conducted to treat acute myeloid leukemia in India^[53]. In 1986, a Chinese group reported the results of fetal liver transplantation in 10 patients with malignant tumors^[54]. The authors prepared fetal liver cells using 3.5-6-mo-old fetuses and observed 1.8×10^8 - 4×10^{12} fetal liver cells in a fetus over five mo of age, in which most of the cells were are CFU-Cs (granulocyte progenitor cells). These findings suggest that fetal liver transplantation improves the peripheral blood profile and stimulates the production of bone marrow.

In February 1986, a symposium on fetal liver transplantation was held in New-Delhi, India^[55]. A relevant review article critically analyzed progress in the field at that time and reported that over 300 individuals had received fetal liver transplants for a spectrum of disorders, including immunodeficiency, aplastic anemia, leukemia and genetic conditions. Additionally, in a review article published in 1987, a United States researcher, Gale, examined the results of fetal liver transplantation in patients with hematological disorders^[46]. With respect to aplastic anemia, 122 two patients received transplants, with engraftment reported in four patients and GvHD in no cases. Although complete and partial responses were reported in half of the patients, the majority displayed no evidence of engraftment. Meanwhile, 39 patients with leukemia received transplants; transient engraftment was reported in 40% of cases, and two patients developed GvHD. In that report, the survival was extended to more than two years. The relatively high rate of engraftment also suggested the efficacy of pretransplant immune suppression. Therefore, the risk of GvHD appears to be low, despite complete HLA-mismatching.

Regarding thymus transplantation, two cases were reported in 1968, in which fetal thymus tissue was transplanted into neonates suffering from DiGeorge syndrome, which is characterized by the absence or incomplete development of the thymus with varying degrees of T-cell immunodeficiency^[56]. In addition, August *et al*^[56] reported the case of a 21-mo-old male with DiGeorge syndrome who underwent transplantation of thymus fragments derived from a 16-wk-old female fetus. In that case, abnormalities in the patient's lymphocyte function

were promptly ameliorated. Cleveland *et al*^[57] also reported the implantation of three thymus fragments derived from a 13-wk fetus into a 7-mo-old male infant. Although no XX cells were identified in the host, the infant's immunological data and ability to resist infection suggested that his immunological function was reconstituted by the fetal transplants^[57]. Another article reported that the combined transplantation of the fetal thymus and liver resulted in effective immunological reconstitution in a presumed case of DiGeorge syndrome^[58]. Two similar thymus transplantation procedures were performed in Japan^[59,60].

During this period, various cases of fetal tissue transplantation were reported in medical journals. However, the clinical results and patient survival rates were largely dismal. At that time, most fetal tissue transplantations were conducted based on previous experience with bone marrow transplantation in which irradiation-based or chemical conditioning is performed prior to transplantation in order to facilitate post-transplantation engraftment following the administration of immunosuppressive drugs. However, cellular characteristics of fresh or preserved fetal tissue were insufficient in most cases, with total cell count usually being the only parameter reported, while the cell functions was not thoroughly assessed. Moreover, in general, precautionary measures to prevent infectious diseases were not taken. For example, fetal tissue donors were not carefully screened, and testing of fetal tissue prior to transplantation was largely insufficient. Despite clinical success in some cases, the use of fetal liver and/or thymus transplantation should have been based on sufficient data from preclinical research using disease model animals, as is common in current stem cell research.

Mid 1980's to early 2000's

Around the mid-1980's, the application of fetal neural transplantation to treat neurological diseases began to receive significant attention. In this era, clinical trials using fetal cerebral tissue were conducted worldwide primarily in patients with Parkinson's disease (PD), a progressive disorder of the central nervous system that affects movement. PD is characterized by the death of dopaminergic neurons, the substantia nigra in the brain for unknown reasons. Langston *et al*^[61] identified a chemical, MPTP (1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine), that selectively damages cells in the substantia nigra, resulting in the development of marked parkinsonism in monkeys and humans, and the injection of MPTP can be used to create an animal model of PD. Preclinical research using such animals has demonstrated that transplanting the fetal substantia nigra significantly improves motion symptoms^[62-65]. Although L-Dopa therapy has been applied to PD since the 1960's, this medication induce troublesome side effects, such hypotension and a variety of abnormal involuntary movements^[66]. Therefore, the transplantation of fetal neural tissue, including dopaminergic neurons, is thought to be an alternative treatment for PD.

In addition to preclinical research using animal dis-

ease models, fetal neural tissue transplantation was performed based on preclinical data, including the impact of cryopreservation^[67], and screening for infection and cytogenetic abnormalities^[68]. Regarding the *in vivo* survival of fetal tissues and cells, Freeman *et al.*^[69] reported the implantation of human mesencephalic dopaminergic neurons in a rat model and suggested that the upper age limit should be postconception (PC) day 56 for suspension grafts and PC day 65 for solid implants.

In September 1986, a Mexican group conducted a renowned clinical trial in which the fetal mesencephalic substantia nigra procured from a 13-wk-old fetus of spontaneous abortion, was transplanted in the caudate nucleus in two PD patients. The cases were subsequently reported in 1988^[1], and the results of monitoring at three months showed a dramatic improvement in symptoms; in particular both rigidity and dyskinesia disappeared^[70]. In the preceding year, 1987, however, a Chinese team had already reported the transplantation of similar fetal tissue in a PD patient in August 1985, the first clinical trial in which brain tissue was transplanted from one human being to another^[2]. In that case, a suspension containing substantia nigra fragments was implanted into the striatal caudate nucleus to which a collateral projection extends from the substantia nigra. The case involved a 54-year-old male patient whose HLA status was determined prior to transplantation, although the fetal HLA status was not tested. The transplanted tissue was obtained from a 5-mo-old fetus, as the authors considered the clinical use of the substantia nigra derived from fetuses of 4.5-5.5 mo of age to be appropriate based on the stage of tissue development at that age. However, this presumption was inaccurate compared to the evidence (in embryos up to nine weeks of age) provided by Freeman *et al.*^[69]. However, the Chinese team reported a reduction in limb tremors and rigidity on the third day after the surgery, with satisfactory control of parkinsonism confirmed after eight months of diagnostic monitoring. Moreover, a United Kingdom group published a case report of fetal tissue transplantation for PD in 1988^[71]. The authors stated that two patients (a 60-year-old female and 41-year-old male) with early and late parkinsonism, respectively, showed immediate improvements in motion symptoms following the administration of a mesencephalic cell suspension (fetal age unknown). These cases, with the exception of the China case, made worldwide headlines, commanding considerable attention from patients and their families. However, all three cases lacked comprehensive, long-term results, including the findings of behavioral, biochemical, psychological, physiological, and motor assessments.

Subsequently, a Swedish group demonstrated that deep brain transplantation of fetal brain tissue could be used to restore local dopamine production and relieve symptoms^[72]. According to their report published in 1990, mesencephalic dopamine neurons derived from embryos of eight to nine weeks of gestation exhibited survival in the recipient. The grafts, which were implanted unilaterally into the putamen *via* stereotactic surgery,

restored dopamine synthesis and storage in the grafted area, as assessed on positron emission tomography with 6-L[18F]fluorodopa. These neurochemical changes resulted in a significant reduction in severe rigidity and bradykinesia, with marked diminution of fluctuations in the patient's condition under optimal medication. Following this achievement, long-term (up to 46 mo) stable improvements and graft integrity were reported in various cases^[73-76]. Stable integration and the persistence of fetal grafts have also been confirmed on functional imaging as well as postmortem analyses^[77-79]. Such clinical results have encouraged many researchers worldwide to apply this therapeutic approach as a treatment for PD. Namely, fetal brain tissue transplantation, which began in China^[2,80], has been attempted in Canada^[81], Cuba^[82], the Czech Republic^[83], France^[84], Mexico^[1], Poland^[85], Slovakia^[86], Spain^[87,88], United Kingdom^[71,89], United States^[2,3,73,77,90,91], and USSR (currently Russia)^[92]. Moreover, the Network of European CNS Transplantation and Restoration (NECTAR) was founded in 1990 to bring together European groups who share the common goal of protecting, repairing and restoring the central nervous system damage resulting from degenerative diseases and/or injury^[93].

Fetal tissue transplantation for PD has also been conducted using fetal adrenal medullary tissue^[1,80] other than the substantia nigra, and several clinical trials have assessed the efficacy of fetal neural transplantation for neurological conditions other than PD. For instance, patients suffering from Huntington's disease (HD) have been evaluated in the United Kingdom^[94]. In the report, cell suspensions of fetal ganglionic eminence were transplanted unilaterally into the striatum in four patients with early to moderate HD, all of whom received immunotherapy with cyclosporin A, azathioprine, and prednisolone for at least six months postoperatively. During the six month post-transplantation period, the only adverse events related to the procedure were associated with the immunotherapy regimen. Magnetic resonance imaging demonstrated the presence of tissue at the implantation site, although no signs of tissue overgrowth were detected. The United Kingdom team concluded that the unilateral transplantation of fetal striatal tissue in patients with HD is safe and feasible. Meanwhile, an Indian group issued a report in which human fetal neuroretinal cells were transplanted in patients with advanced retinitis pigmentosa^[95]. The results of a long-term phase I safety study (12-40 mo) prompted the initiation of phase II trials.

Notably, in 2001, a United States group reported the results of a double-blind, sham surgery controlled-study of transplantation of fetal dopamine neurons in PD patients^[5]. The neural tissues were recovered from 7- to 8-wk-olds embryos, and the tissue cell culture, in which dopamine production was monitored according to homovanillic acid concentration in the medium, was transplanted up to four weeks after recovery. Consequently, a reduction in motor symptoms was observed in the patients 60 years of age or younger, but not in the older

patients. This study provided the first direct evidence that fetal grafts can be used to improve the condition of some PD patients, separate from the placebo effect. Another United States group reported the results of a similar double-blind controlled trial in which, approximately half of the patients treated with solid mesencephalic grafts derived from 6- to 9 wk-old embryos developed dyskinesia, with no significant overall treatment effect^[96]. Moreover, postmortem analyses revealed the subjects who displayed significant improvements had at least 100000 dopaminergic neurons per sides with organotypic reinnervation of the striatum^[97,98]. In these cases, four 6- to 9-wk-old fetuses were required to obtain the requisite number of cells for a graft. Therefore, some research groups have introduced a temporal moratorium on such procedures since 2003 owing to the uncertainty and difficulty in conducting clinical trials^[99].

ETHICAL ISSUES AND POLITICAL RESPONSES

As mentioned above, the results of fetal brain tissue transplantation for PD have received significant attention, making worldwide headlines in the news media since the late 1980's. Such advancements have simultaneously raised profound ethical concerns and objections against the medical use of cadaveric fetal tissue, which is frequently derived from cases of elective abortion. This report briefly addresses this issue and associated political responses. The ethical debate in the United States, which involves anti-abortion movement, led to a moratorium on federal funding (1987-1992) of fetal tissue transplantation research^[100-103]. There are five issues related to fetal tissue transplantation. First, females may be advised or persuaded to undergo induced abortion on the grounds that it may help others by donating fetal tissue. Second, the widespread use of fetal tissue transplantations may result in an increase in the number of abortions. Third, the successful use of fetal tissue may make such procedures more socially acceptable. Fourth, the abortion procedure may be changed based on medical needs. Most notably, the question as to whether rightful informed consent for the use of fetal tissue can be obtained in cases of induced abortion is the most controversial issue. Ideally, the decision to undergo induced abortion should be completely separate from the consent to fetal tissue donation (*i.e.*, the "principle of separation"^[104]).

In the United Kingdom, the Department of Health and Social Security issued a report by their advisory group (the Peel report) regarding the use of fetuses and fetal material for research in 1972. The Department subsequently reviewed their guidelines on the research and use of fetuses and fetal material in the Polkinghorne report in 1989^[105]. The main issue in that report was the consistent application of the "principle of separation"^[104]. In contrast, the British Medical Association (BMA) dissented from the Polkinghorne report in their guidelines on the use of fetal tissue^[106], and United Kingdom sociol-

ogists expressed concerns about the fetal tissue economy from the abortion clinic to the stem cell laboratory^[107, 108]. In 1994, NECTAR considered the ethical issues and published guidelines for the use of human embryonic or fetal tissue for research and clinical use^[109]. In Japan, discussions in the Ministry eventually resulted in the development of guidelines on clinical research using human stem cells, in which the clinical use of fetal cells is intentionally excluded due to potential, profound ethical issues^[110].

Thus, fetal tissue transplantation has raised ethical controversy worldwide. The "principle of separation" suggests fetal tissue can be procured if informed consent is separately obtained from females who underwent spontaneous abortion and still birth in Europe and the United States. It is also suggested that fetal tissues may be obtained if the induced abortion is conducted for a clear medical reason (*e.g.*, ectopic pregnancy). However, if the informed consent is obtained from females who will undergo induced abortion only for a social reason, some would query the validity of the informed consent^[107]. The difficulty in the 'principle of separation' in some cases is likely to lead to the exclusion of fetal cells in stem cell transplantation, as in Japan if future results of fetal tissue transplantation are overhyped.

CHANGES WITHIN THE LAST DECADE

Since 2000, fetal cell transplantation has advanced to the clinical development of isolated fetal stem cells. As mentioned above, there are hundreds of investigator-initiated clinical trials of fetal transplantation in the academic setting. In addition, several companies have developed or are developing fetal stem cell products *via* the use intracerebral or spinal transplantation^[111].

A wide variety of conditions have been assessed using fetal stem cell transplantation. Recently, evaluated conditions can be categorized into six groups: neurological diseases, central nervous system (CNS) injury, heart failure^[112], diabetes^[113], skin wounds^[114], and osteogenesis imperfecta^[115]. Neurological diseases include amyotrophic lateral sclerosis (ALS)^[116-118], cerebral palsy (CP)^[119,120], cerebral atrophy^[121], Huntington's Disease^[122,123], and PD^[124-126]. With respect to CNS injury, spinal cord injury (SCI)^[127] and traumatic brain injury^[128] have been recent topics in the setting of fetal cell transplantation. Some of these reports are described below.

Olfactory ensheathing cells (OECs) are radial glia with a variety of functions. These cells phagocytose axonal debris and dead cells in the olfactory system^[129]. OECs are also known to secrete many neurotrophic factors. A Chinese group, Chen *et al.*^[120] conducted a randomized controlled clinical trial among 33 patients in order to confirm the feasibility of OEC transplantation for treating CP in children and adolescents. In that report, OECs were isolated from aborted human fetal olfactory bulbs, cultured and propagated for two to three weeks and then characterized using immunostaining with Abs against p75. OECs derived from one to two fetuses, representing

two million cells, were transplanted in each patient, and HLA-DR-matching analyses ensured histocompatibility between the donors and recipients. The trial ultimately demonstrated that fetal OEC transplantation is effective for obtaining functional improvements in children and adolescents with CP, without obvious side effects. Another Chinese group, Wu *et al.*^[127] followed patients with complete chronic SCI for an average of 14 mo after OEC transplantation. Consequently, both sensation and spasticity improved moderately, whereas the recovery in locomotion recovery was minimal. In contrast, Piepers and den Berg asserted that there are no benefits from experimental treatment with fetal OECs in patients with ALS^[118]. The authors carried out a prospective study of seven patients who underwent fetal OEC treatment in China^[130], following the subjects for four months to one year after treatment, and found no objective improvements, while the outcome measurements gradually declined in all patients. Two patients experienced severe side effects. Therefore, although careful examination is needed, fetal OEC transplantation is likely to be effective against trauma-induced neurological conditions, but not ALS or the selective degeneration of motor neurons. These findings highlight the significance of selecting appropriate diseases and conditions for each type of stem cell transplantation.

Regarding fetal neural progenitor cells (NPCs) and neural stem cells (NSCs), a Chinese group, Luan *et al.*^[119] performed fetal NPC transplantation in 45 patients with severe CP by injecting NPCs derived from aborted fetal tissue into the lateral ventricle. The NPCs were isolated from aborted human fetal forebrain tissue and likewise propagated. The cells used for transplantation were characterized as nestin-positive and microbe-free with normal karyotype, viability of over 95%, and endotoxin level below 2 EU/mL. After one year, the developmental level for each functional sphere (gross motor, fine motor, and cognition) was significantly higher in the treatment group than in the control group, with no delayed complications. Therefore, both fetal NPC and OEC transplantation appear to be efficacious against CP^[119,120]. A United States group, Grass *et al.*^[117], consequently reported the results of a phase I trial of the intraspinal injection of fetal NSCs in patients with ALS. This study was a first-in-human clinical trial with the goal of assessing the safety and tolerability of introducing stem cells into the spinal cord, in association with the administration of immunosuppressants. Twelve patients received either five unilateral or five bilateral (10 total) injections into the lumbar spinal cord at a dose of 100000 cells per injection. Clinical assessments ranging from six to 18 mo after transplantation demonstrated no evidence of acceleration of disease progression due to the intervention; therefore, the goal of the clinical trial was attained. Hence, ALS may be treated with fetal NSC transplantation, but not fetal OEC transplantation^[117,118].

In addition to the above bibliographic survey, relevant trials were searched on ClinicalTrials.gov in order

to provide an overview of recent clinical trials of fetal transplants (Table 1). Consequently, 11 trials were identified, most of which (7/11) were sponsored by business entities. In addition, fetal neural stem cells were used in most trials (8/11), focusing on ischemic stroke, SCI, age-related macular degeneration, and neurological disorders, including ALS and Pelizaeus-Merzbacher disease (an inherited dysmyelination disorder). Meanwhile, fetal mesencephalic tissue or dopamine neuronal precursor cells were used for transplantation in PD patients in two trials and fetal liver cells were used in one trial. Most of these studies (7/11) were sponsored by private companies, including Stem Cell, Inc. (California, United States), Neuralstem Inc. (Maryland, United States), and ReNeuron Ltd. (United Kingdom). Stem Cell Inc. has developed a neural stem cell product for use in Batten's disease (neuronal ceroid lipofuscinosis) and obtained approval for a new investigational drug (IND) from the FDA, although a phase I trial was terminated due to difficulties in recruiting an adequate number of patients. Instead, the company opted to focus on thoracic SCI, age-related macular degeneration, congenital Pelizaeus-Merzbacher disease for clinical development. Other companies are currently developing neural stem cell products to treat stable ischemic stroke (ReNeuron) as well as ALS and chronic SCI (Neuralstem Inc.).

Among the above companies, Stem Cell, Inc. is the most active developer of fetal neural stem cells. For example, it has generated unique mAbs and isolated neural stem cells derived from fetal brain tissue using cell sorters. The company has identified and enriched CD133⁺ CD24^{-/lo} population cells using their unique mAbs against CD133 and CD24. The transplantation of CD133⁺ sorted/expanded neurosphere cells into the lateral ventricle in newborn NOD-SCID mouse brains has been shown to result in specific engraftment in numerous sites, according to the levels of brain markers. The researchers therefore concluded that human central nervous system (CNS) stem cells can be clonally isolated^[153]. Using CNS stem cells, the company is currently developing stem cell products for use in patients with SCI, macular degeneration, and Pelizaeus-Merzbacher disease. In most cases, de novo neurogenesis is not the goal, but rather the treatment of enzyme deficiencies, as well as remyelination, or the modulation of endogenous repair *via* neoangiogenesis and/or neuroprotection^[131-134]. Moreover, the company has isolated fetal liver progenitor cells and developed a unique co-culture system with endothelial cells in a three-dimensional matrix^[135]. These liver cells are studied for the future application of transplantation therapy and drug discovery assay systems.

Recent fetal stem cell transplantation procedures have used isolated and well-characterized fetal tissue cells designed in a sufficiently rational manner. Clinical trial results also allow researchers to be optimistic about the future of fetal stem cell transplantation. Nevertheless, uncertainties abound in the clinical settings. Amariglio *et al.*^[136] reported an adverse event following NSC trans-

Table 1 Ongoing clinical trials of fetal stem cell transplantation

Clinical Trials.gov	Start (yr)	Sponsor	Status	Title	Interventions	Cell source
NCT 01013194	2007	The Mediterranean Institute	Unknown	Human fetal liver cell Transplantation in chronic liver failure	Human fetal liver cell transplantation	Fetal liver cells derived from fetuses between the 16 th and 26 th week of gestation
NCT 01151124	2010	ReNeuron Limited.	Active, not recruiting	Pilot Investigation of Stem Cells in Stroke	Surgical delivery of a neural stem cell line to the damaged area of the brain	CTX0E03 neural stem cells ¹
NCT 01321333	2011	StemCells, Inc.	Active, not recruiting	Study of HuCNS-SC in patients with thoracic spinal cord injury	Intramedullary spinal cord transplantation of human CNS stem cells	HuCNS-SC cells (Human Central Nervous System Stem Cells) ²
NCT 01348451	2009	Neuralstem Inc.	Active, not recruiting	Human neural stem cell Transplantation for the Treatment of amyotrophic lateral sclerosis	Surgical implantation of human neural stem cells	Human spinal cord derived neural stem cells ³
NCT 01391637	2011	StemCells, Inc.	Active, not recruiting	Long-term follow-up study of human stem cells transplanted in subjects with pelizaeus-merzbacher disease	HuCNS-SC transplantation	HuCNS-SC cells (Human Central Nervous System Stem Cells) ²
NCT 01632527	2012	StemCells, Inc.	Recruiting	Study of HuCNS-SC in age-related macular degeneration	Transplanting HuCNS-SC cells directly into the subretinal space of one eye.	HuCNS-SC cells (Human Central Nervous System Stem Cells) ²
NCT 01640067	2011	Azienda Ospedaliera Santa Maria	Recruiting	Human neural stem cell Transplantation in Amyotrophic Lateral Sclerosis	Surgical microinjection of human neural stem cells	Human foetal neural stem cells suspension
NCT 01730716	2013	Neuralstem Inc.	Enrolling by invitation	Dose escalation and safety study of neural stem cell transplantation for the treatment of amyotrophic lateral sclerosis	Human spinal cord stem cell implantation	Human spinal cord derived neural stem cells ³
NCT 01772810	2014	Neuralstem Inc.	Not yet recruiting	Safety study of human spinal cord-derived neural stem cell transplantation for the treatment of Chronic SCI	Human Spinal Cord-derived Neural Stem Cell Transplantation	Human spinal cord derived neural stem cells ³
NCT 01860794	2013	Bundang CHA Hospital	Recruiting	Evaluation of safety and tolerability of fetal mesencephalic dopamine neuronal precursor cells for Parkinson's disease	Transplantation of fetal mesencephalic dopamine neuronal precursor cells	Fetal mesencephalic dopamine neuronal precursor cells
NCT01898390	2012	University of Cambridge	Enrolling by invitation	TRANSEURO open label transplant study in Parkinson's disease	Neural allo-transplantation with fetal ventral mesencephalic tissue	Fetal ventral mesencephalic tissue

The survey was conducted in ClinicalTrials.gov using key words "fetal + transplantation, or fetus + transplantation". The status is on June 24, 2014. The description of the table is based on the database. See also the details by entering the identifier No. into the database website. Additional investigation confirmed that the neural stem cells¹ are derived from first trimester human fetal cortical cells, the central nervous system stem cells² from fetal brain tissue, and the spiral cord derived neural stem cells³ from a single eight-week-old fetus.

plantation in a boy with ataxia telangiectasia treated with the intracerebellar and intrathecal injection of human fetal NSCs. Four years after the first injection, the patient was diagnosed with a multifocal brain tumor, a biopsy of which showed a glioneuronal neoplasm. In addition, molecular and cytogenetic studies demonstrated the tumor to be of nonhost origin and microsatellite and HLA analyses revealed that the tumor was derived from at least two donors. This is the first report of a human brain tumor complicating the outcome of NSC therapy. These findings suggest that neuronal stem/progenitor cells may induce gliomagenesis. Therefore, considerable caution is required when implementing NSC transplantation, although clinical trials of NSCs are proceeding worldwide.

RAMIFICATIONS OF EMBRYONIC STEM CELL RESEARCH

The results of previous fetal neural transplantation therapy for PD have indicated that the use of more biologically defined and clinically reliable sources of dopaminergic neurons is required in future clinical trials. For this reason, other stem cell sources are often investigated in parallel with clinical trials of fetal stem cell transplantation.

Pluripotent ES cells are established from preimplantation, not implantation, embryos. ES cells possess self-renewal properties and almost infinitely proliferate in petri dishes. In addition, under appropriate differentiation protocols, ES cells exhibiting pluripotency can be differ-

entiated into any lineages of the ectoderm, mesoderm, or endoderm. Therefore, ES cells can be used to obtain the number of cells required for transplantation therapy for various diseases.

Two reports regarding the establishment of mouse ES cell lines were published in 1981^[137,138]. The first derivation of human ES cell lines was based on knowledge obtained *via* the establishment of non-human primate ES cells, first attained in 1995^[139,140]. It took a considerable amount of time to transition from mouse to human ES cells due to differences in molecular and cellular mechanisms between mice and humans that hampered the technical establishment of the culture method. For instance, human ES cells, unlike their mouse counterparts, do not appear to require leukemia inhibitor factor (LIF) for propagation or the maintenance of pluripotency^[140,141]. Instead, fibroblast growth factor (FGF) signaling has a central role in the self-renewal of human ES cells. It has been previously demonstrated that basic FGF (bFGF) stimulates the clonal growth of human ES cells on fibroblasts in the presence of a commercially available serum replacement^[142]. In addition, while the expression of many of markers is similar in mouse and human ES cells, significant differences are noted in the expression levels of vimentin, β -III tubulin, alpha-fetoprotein, eomesodermin, HEB, ARNT, FoxD3, and the LIF receptor complex LIFR/IL6ST (gp130)^[143]. Furthermore, focused microarray analyses have identified significant differences in cell cycle and apoptosis regulation as well as cytokine expression^[143].

Human ES cells which were first reported in 1998 were established from surplus *in vitro* fertilization (IVF) embryos, a byproduct of assisted reproduction treatment. The creation of embryos for research purposes, which is associated with ethical issues and requires rigorous reviews in many countries even if legally permitted^[144], was not conducted to establish the ES cells. Nonetheless, an ethical debate ensued, as some regard preimplantation embryos to constitute the beginning of human life. Meanwhile, in 2009, the United States FDA approved an IND applied by the Geron Corporation (California, United States)^[111]. The biologics of human ES cell-derived cells was developed in the first clinical trial after the company verified that there were no problems with the cell product regarding the formation of micro-cysts in animal transplants. The approved phase I study was conducted to assess the safety of transplantation of human ES cell-derived oligodendrocyte precursor cells in patients with thoracic spinal cord injury. In that study, the subjects with functionally complete spinal cord injury at the T3 to T10 spinal segments underwent grafting of oligodendrocyte progenitors into the spinal cord at the site of injury under conditions of immunosuppression. Although Geron terminated the study for financial reasons in 2011, another company plans to restart the trial^[145].

Current clinical trials of ES cells (Table 2) include at least eight trials of ES cell-derived cells underway in France, South Korea, United Kingdom, and the United

States. Again, most of these studies are being sponsored by business entities (6/8). Namely, Advanced Cell Technology (ACT), Inc. (Massachusetts, United States) is currently developing ES cell-derived retinal pigment epithelium cells to treat conditions such as age-related macular degeneration and macular dystrophy using an orphan drug status to accelerate clinical trials. In addition, CHA Bio and Diostech (South Korea) is advancing two pipelines similar to that of ACT using the cell product developed by ACT. Pfizer is also currently developing a similar pipeline to that of ACT and CHA Bio and Diostech; however, Pfizer is using a different cell product. Hence, macular generation is the primary condition currently receiving attention with respect to the development of ES cells. The remaining two trials are being sponsored by French and United States universities. UCLA is attempting to initiate a clinical trial in which ACT's cell product applied to treat macular regeneration, while Assistance Publique - Hôpitaux de Paris is recruiting patients to develop a treatment for ischemic heart disease using ES cell-derived CD15⁺ Isl-1⁺ progenitors. All of these trials are open-label, not blind, studies. More recently, the use of autologous ES cells, which reduces the possibility of immune rejection, has recently become realistic based on somatic cell nuclear transfer^[146,147]. Clinical success rates of transplantation using autologous ES cell-derived cells would be expected to increase, although there is a potential ethical issue when procuring oocytes from females.

Another type of pluripotent stem cell, embryonic germ (EG) cells, can be established from cultured human primordial germ cells (PGCs) derived from early embryos. The first establishment of human EG cells from 5- to 9-wk-old embryos obtained as a result of the therapeutic termination of pregnancy, was reported in 1998^[148], followed by other reports^[149]. However, knowledge of human PGCs and EG cells is insufficient, as these cells are difficult to study in the gonadal ridge during the fifth and sixth week of development, with further PGCs often being detected in the gut mesentery, most likely during transit^[149]. To our knowledge, there have been no clinical trials of human EG cells.

FUTURE DIRECTIONS OF STEM CELL TRANSPLANTATION

In the 20th century, clinical issues abounded in the field of fetal tissue transplantation and many lessons were learned from such practices. After reflecting on the history of fetal tissue cell transplantation, this report will now consider the future direction of stem cell transplantation based on issues related to donor cells, cell processing, and therapeutic cell niche.

Donor cells

Earlier fetal tissue cell transplantation procedures required careful screening of maternal donors and testing of fetal tissues in order to prevent infectious diseases as well as match histocompatibility; however, such analyses

Table 2 Ongoing clinical trials of embryonic stem cell-derived cell transplantation

Clinical Trials.gov	Start (yr)	Sponsor	Status	Title	Condition	Intervention	Remarks
NCT01344993	2011	Advanced cell technology	Recruiting	Safety and tolerability of transplantation of MA09-hRPE cells in patients with advanced dry age related macular degeneration	Advanced dry age related macular degeneration	Sub-retinal transplantation of MA09-hRPE	A Phase I / II, open-label, multi-center, prospective study in United States. MA09-hRPE cells are human embryonic stem cell derived retinal Pigmented epithelial cells.
NCT01345006	2011	Advanced cell technology	Recruiting	Transplantation of MA09-hRPE cells in patients with stargardt's macular dystrophy	Stargardt's macular dystrophy	Sub-retinal transplantation of MA09-hRPE	A Phase I / II, open-label, multi-center, prospective study in United States
NCT01469832	2011	Advanced cell technology	Recruiting	Safety and tolerability of transplantation of hESC-RPE cells in patients with stargardt's macular dystrophy	Stargardt's macular dystrophy; fundus flavimaculatus; juvenile macular dystrophy	Sub-retinal transplantation of MA09-hRPE	A Phase I / II, open-label, multi-center, prospective study in the United States
NCT01625559	2012	CHA Bio and diostech	Recruiting	Safety and tolerability of MA09-hRPE cells in patients with stargardt's macular dystrophy	Stargardt's macular dystrophy	Sub-retinal transplantation of MA09-hRPE	A Phase I, open-label, prospective study in Korea
NCT01674829	2012	CHA Bio and diostech	Recruiting	Safety and tolerability of transplantation of MA09-hRPE cells in patients with advanced dry age-related macular degeneration (AMD)	Dry age Related macular degeneration	Sub-retinal transplantation of MA09-hRPE	A Phase I / II a, open-label, single-center, prospective study in Korea
NCT01691261	2014	Pfizer	Not yet recruiting	Implantation of human embryonic stem cell derived retinal pigment epithelium in subjects with acute wet age related macular degeneration and recent rapid vision decline	Age related macular degeneration	Implantation of human embryonic stem cell derived retinal pigment epithelium	Phase 1, open-label, safety and feasibility study in United Kingdom. PF-05206388 is human embryonic stem cell derived retinal pigment epithelium living tissue equivalent.
NCT02057900	2013	Assistance publique - hôpitaux de Paris	Recruiting	Transplantation of human embryonic stem cell-derived progenitors in severe heart failure (ESCORT)	Ischemic heart disease	Human embryonic stem cell-derived CD15+ Isl-1+ progenitors	Phase 1, open-label, feasibility and safety study in France
NCT02122159	2014	University of California, Los Angeles	Not yet recruiting	Research with retinal cells derived from embryonic stem cells for myopic macular degeneration	Myopic macular degeneration	MA09-hRPE cellular therapy	A Phase I / II, Open-label, prospective study to determine the safety and tolerability in United States

The survey was conducted in ClinicalTrials.gov using key words "Embryonic + Stem + Cells". The status of clinical trials listed is confirmed on June 19, 2014. The description of the table is based on the database. See the details by entering the identifier No. into the database website.

were often not conducted sufficiently. In addition, mouse transplantation experiments showed that the immunogenicity of first-trimester human fetal pancreatic grafts (6- and 9-wk-old embryos) is less than that of older, second-trimester human fetal pancreatic grafts^[28]. This reduced immunogenicity is insufficient to completely circumvent the need for immunosuppressive conditioning in the recipient^[150]. Such precautions are now common sense for assuring safety in present-day stem cell transplantation.

The authors emphasize the need for sufficient implementation of cytogenetic testing, such as karyotyping and CGH arrays, in order to attain the therapeutic goal (Figure 1). Fetal tissue can be obtained from cadaveric fetuses following spontaneous abortion, stillbirth, or surgery due to ectopic pregnancy, in addition to elective abortion. Among these types of cells, fetal tissues de-

rived from spontaneous abortion and stillbirth are more likely to induce adverse events after transplantation, and frequent chromosomal or genetic causes of spontaneous abortion and stillbirth are likely to affect the pre- and post-transplantation behavior of donor cells. In addition, genetic changes may occur during cell culture. Therefore, cytogenetic testing is required to confirm the therapeutic validity of stem cells for transplantation. From this viewpoint, fetal tissue derived from cases of elective abortion or ectopic pregnancy is more likely to be an appropriate source for transplantation. However, the use of such cells remains still ethically, and socially controversial, primarily mainly due to the difficulty in consistently applying the "principle of separation" in cases of elective abortion^[100-103,107,108]. For these reasons, the procuring of the required amount of fetal tissue for transplantation is

challenging.

In contrast, adult tissue stem or progenitor cells, or terminally differentiated cells derived from non-fetal, adult tissues are more likely to be candidates for transplantation. In addition, the clinical use of human pluripotent stem cells recently became realistic (Table 2). As mentioned above, ES cells have been established from a more ethical source, surplus IVF embryos^[144]. Compared with adult tissue stem cells, ES cells proliferate more readily *in vitro*, and the directed differentiation of human ES cells can be used to produce a desired lineage, with some types of differentiated cells currently being applied as grafts in clinical trials (Table 2). Furthermore, a far more ethical source, induced pluripotent stem (iPS) cells, which are established from reprogramming the patient's own somatic cells *via* ectopic expression of defined factors, is now available^[151]. Human iPS cells can be likewise differentiated and used for autologous transplantation. Recently, the Japanese Ministry of Health, Labour, and Welfare approved a clinical research application for the use of iPS cell-derived retinal pigment epithelium cells in patients with age-related macular degeneration^[152]. Therefore, with the exception of fetal stem cells, a variety of human pluripotent stem cells are available for study in clinical trials.

Cell processing

A few weeks of culture has frequently been applied to expand fetal cells prior to transplantation^[3,119,120,153]. Close monitoring during cell culture is needed to assess whether the culture changes the cell population and/or function. If a change in cell population is detected, the population intended for use in transplantation must be isolated *via* methods such as a cell sorting^[154], as the presence of a remaining unintentional cell population in the culture may cause side effects. Notably, the effects of intermingled serotonergic neurons in part explain the onset of graft-induced dyskinesia in the setting of fetal neural transplantation^[155]. Such caution should also be applied to cell cultures resulting from the directed differentiation of pluripotent stem cells. In addition, culture additives, such as serum replacement and bFGF, must be carefully tested to avoid contamination with viruses or other microorganisms as well as potential epigenetic effects. Therefore, cell processing requires sufficient optimization in preclinical research.

Again, cell-processing also requires cytogenetic testing to confirm that the absence of karyotype or genetic changes during cell culture. Regarding application of human pluripotent stem cells, there remain still technical obstacles. For example, human ES cells and iPS cells exhibit a progressive tendency to acquire genetic changes during prolonged culture^[156]. In addition, it is necessary to take precautions against genetic instability (in the nucleus and mitochondria) of iPS cells, which may occur regardless of the reprogramming method used^[157]. However, future advances in stem cell research would overcome such obstacles.

Therapeutic cell niche

The selection of appropriate diseases and symptoms largely constitutes successful transplantation therapy, subsequently requiring the systematic consideration of autonomous or non-autonomous cell pathology, the localization of the affected tissue, and the assessment of progressive *vs* chronic disease.

Although only cell transplantation is considered to be efficacious in the setting of autonomous pathology, non-autonomous conditions are more likely to require extrinsic cues (cytokines, growth factors, inflammatory mediators, *etc.*) for proper use in stem cell transplantation. Although the therapeutic intervention requires only NSCs in the two identified pipelines developed for a CNS injury, including SCI (Table 1), the application of extrinsic cues may facilitate graft integration at the site of implantation, thus maximizing the therapeutic efficacy. Hepatocyte growth factor (HGF), a mitogen for mature hepatocytes and mediator of the inflammatory responses to tissue injury, was recently highlighted as a potent neurotrophic factor in the CNS. In addition, the intrathecal administration of human HGF in non-human primates has been demonstrated to have therapeutic efficacy in cases of SCI^[158]. Therefore, combined treatment with HGF and NSCs may improve the outcomes of therapy for SCI.

The localization of affected tissue defines the required number of cells and transplantation methodology. A survey of current clinical trials indicated that macular degeneration is a major subject of current studies using ES cell-derived cells (Table 2). For instance, four cohorts, ranging from 50000 to 200000 MA09-RPE cells, were designed in the NCT01344993 trial. These numbers are relatively small, as the cells are confined to application at the affected site in patients with retinal disease. With respect to fetal neuronal transplantation for PD, significant motion improvements require the integration of at least 100000 dopaminergic neurons into the striatum^[97,98]. However, graft-induced dyskinesia may occur in the setting of cell transplantation in the striatum^[3,96]. The development of a new transplantation procedure to construct dopamine projections from the substantia nigra to the striatum may eliminate the occurrence of dyskinesia.

Presumed pathological changes must be sufficiently considered in patients undergoing stem cell transplantation for progressive diseases. Notably, fetal neural tissue transplantation for in cases of PD has been reported to be efficacious in young and earlier-phase patients, but not old or later-phase patients^[3]. This finding implies that the efficacy of cell transplantation depends on the condition of the recipient. Such indications are represented by a key concept, the therapeutic cell niche, the local environment surrounding the cell graft that makes the graft functional *in vivo*. The therapeutic cell niche may vary based on symptoms depending on the disease.

Currently, researchers are able to differentiate stem cells into the desired lineage *in vitro* to obtain highly specified, isolated differentiated cells. Many pipelines are

sponsored by business entities (Tables 1 and 2). However, current stem cell transplantation procedures may lack firm evidence regarding the therapeutic cell niche *in vivo*. Therefore, it is necessary to provide proof of the therapeutic concept in disease model animals and subsequently confirm the safety and efficacy of the treatment in clinical trials, consistently paying attention to the therapeutic cell niche. Otherwise, similar side effects to the adverse events caused by NSC transplantation^[136] may occur in clinical trials. It is thus vital to continue to take a cautious approach to designing stem cell transplantation protocols for various conditions.

CONCLUSION

This report considered perspectives on fetal stem cell transplantation. To date, hundreds of clinical trials using various types of fetal transplants have been performed worldwide. Although success has been observed in some cases, most cases of fetal tissue or cell transplantation have been hastily implemented, and research groups must share their knowledge and experience. Meanwhile, research communities have learned many important lessons through these experiences and continue to improve transplantation strategies, leading to clinical trials of isolated fetal stem cells and ES cell-derived cells (Tables 1 and 2).

Although there remain still ethical and social issues with respect to the clinical use of fetal tissue, ongoing clinical trials of fetal transplants should proceed as fetal transplantation may be currently the sole benchmark for other types of stem cell transplantation. Indeed, the decade-long moratorium on cell transplantation for PD was recently lifted^[99], and European, United States and Japanese research groups recently formed the Parkinson's Disease Global Force to assess fetal transplant protocols for ES and iPS cell-derived dopaminergic neurons. In this process, essential issues, including those associated with the therapeutic cell niche, donor cells, and cell processing, should be sufficiently considered in order to develop more successful transplantation therapies.

Finally, clinical dependence on fetal transplantation, despite its landmark achievements, is expected to gradually fade in the setting of stem cell research owing to lasting ethical controversies and the advent of autologous iPS cells and ES cells.

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