Presidency of the Council of Ministers

OPINION OF THE NATIONAL BIOETHICS COMMITTEE ON THE THERAPEUTIC USE OF STEM CELLS

27 October 2000

Introduction and definitions

1. Research on stem cells and their possible therapeutic applications did not begin yesterday. However, in recent times interest in them has increased, among other things as a result of the consulting committee set up on the topic by the British government, of the guidelines published by the US Health Ministry and of the resolution of the European Parliament. On several occasions, the National Bioethics Committee has expressed its opinion on problems related to human genetics in specific documents: Identity and status of the human embryo on 21 June 1996, Cloning on 17 October 1997, Declaration on the possibility of patenting cells of human embryonic origin of 25 February 2000 and Opinion on the project for a European protocol on the protection of the human embryo and foetus of 31 March 2000. Furthermore, within the National Bioethics Committee a working group was set up several months ago which has collected a large body of documentation and discussed the problem in detail in its various aspects. The following document is the collective expression of this work: it aims to make a timely contribution to the discussion of the scientific, ethical and political questions that the use of stem cells for therapeutic purposes raises for society and government. For the reader's convenience, several preliminary definitions are given, also for the purpose of correcting the ambiguities and distortions introduced into the debate by the association between the expression "stem cells" and the term "cloning", which refers to one of the techniques by which it is possible to produce them.

2. The expression "stem cell" is used to refer to a cell capable, in the course of the continuous process of its successive duplications, of differentiating until it becomes a "mature" cell of a specific tissue or generates other stem cells. It had been known for some time that certain bone marrow cells act as "progenitors", that is, as cells capable of differentiating into blood cells which are thus continuously replaced. As late as 1998 it was observed that stem cells extracted from a human embryo may be isolated, cultured in the laboratory and induced not only to differentiate into a single specific type of cell (such blood, muscle, or heart, etc.) but to differentiate into any type of cell whenever the culture conditions are suitable. Stem cells can multiply indefinitely, giving rise to both lines of new stem cells and to specialized "daughter" cells. This property could in future allow completely new forms of cell or tissue therapy to be performed, and allow the creation of both undifferentiated and differentiated cells and tissues. The therapy applied to a diseased or damaged cell or tissue could actually consist of transplanting new cells or tissues, which are added to the diseased or damaged ones and ultimately replace them. In recent research on mice, for example, it was found that embryonic stem cells injected into the heart of an adult mouse were incorporated perfectly into the heart muscle of the adult animal, that is, they differentiated into heart muscle cells and became perfectly synchronized with the beat of the host heart.

3. The capacity of the stem cells to differentiate into specific tissues changes according to the origin of the cells and to the development stage of the organism from which they have been extracted. "Multipotent" cells, socalled because of their capacity to multiply and remain in the culture but without the capacity to be renewed an unlimited number of times, have been identified in foetuses as well as in the adult human being, although in limited numbers.

4. By day 4-5 after zygote formation (fertilization) an embryo consists of identical cells (2 in number after about 30 hours, 4 after about 40 hours, 12-16 after about three days, etc.) that are called "totipotent" insofar as they are not specialized and thus have the property of differentiating into all the cell lines required to form the embryo, including those that will produce the placenta and the surrounding membranes. By day four or five after fertilization (morula stage), the embryo still consists of identical embryonic cells, although these cells can no longer form an embryo. From day five to day six after fertilization (blastocyst stage,

some hundred or more cells) a spherical cavity is formed in the morula from the external cell mass of which the cells that will ultimately make up the placenta begin to differentiate, together with the membranes surrounding the embryo, while from the internal cell mass (20-30 cells) the cells that will form the actual embryo itself start to differentiate. The latter cells, isolated from the cell mass of the internal cavity are "pluripotent" stem cells, in the sense that they have the potential to differentiate into any type of adult animal cell but not the property specific to totipotent cells of producing an embryo. Indeed if these cells were transferred into a uterus, they would not have the capacity to become implanted and develop because the development of the embryo cannot take place unless they are synchronized with that of the placenta from which the embryo draws its nourishment. Lastly, "germ" cells are defined as those pluripotent stem cells that have been isolated from the progenitor reproductive cells, those that will subsequently develop spermatozoa and egg cells.

5. In research on stem cells, the term cloning is often used ambiguously. In the first instance it is necessary to make a distinction between cloning by cell division and cloning by nuclear transplant. The former consists in producing several embryos by separating the cells during the early stages of division. It has been carried out successfully on human embryos for the purpose of increasing the effectiveness of in vitro fertilization methods and in pre-implantation diagnosis. The latter, associated with the highly-publicized generation of the sheep Dolly, is performed by removing the nucleus from an egg cell ("enucleated oocyte") and replacing it ("nuclear transplant") with the nucleus of a somatic cell from a patient ("somatic nuclear transplant"). If it were to prove possible to apply this technique to human beings, all the pluripotent stem cells cultured from the embryo formed by transferring the nucleus of a cell of any kind (for example, a blood cell) of a patient affected by any disease (for example, of the cardiac muscle), would be genetically identical to those of the patient him/herself and, if injected into the cardiac muscle, would probably not give rise to any rejection reaction. The production of these stem cells by means of this technique requires the formation of an embryo, the development of which is arrested at the blastocyst stage and from which the stem cells are isolated for the purpose of growing them indefinitely in vitro. It thus does not consist of the complete development of a embryo from which spare tissues or organs would be taken. If this technique were used in a treatment programme, the aim would be to accumulate an adequate source of cell supplies for the patient. It is still not understood how the material contained in the enucleated egg cell succeeds in reprogramming the activity of the transplanted adult nucleus, although it has been suggested that it may be possible to create pluripotent cell lines directly from the patients' transplanted cells, thus avoiding the step of the formation of an embryo by means of an actual auto-transplant: however, this option is not available at the present time. The somatic nuclear transplant defined above is also known as "therapeutic cloning", an ambiguous term as it suggests the duplication of completely formed individuals from which tissues or even spare organs are taken. They are instead actually stem cells deriving from the embryo that, when grown in the laboratory, can be induced to differentiate into cells and ultimately into tissues of therapeutic interest.

6. The sheep Dolly is genetically identical to the adult sheep whose mammary gland was extracted, and the nucleus of which was transplanted into the enucleated egg cell from which the animal was subsequently born. In this case we are dealing with cloning of an entire organism, not just of a cell, and the term "reproductive cloning" is used to distinguish this complete development process from the previous one, which is partial and not aimed at the reproduction of a human or animal organism which, after insertion in a host uterus, can develop until birth and ultimately evolve into an adult organism. Reproductive cloning applied to man is explicitly prohibited by art. 1 of the Additional Protocol to the Convention on Human Rights and Biomedicine of the Council of Europe. Reference is often made to

the latter by the National Bioethics Committee, which shares the same views on prohibition and so reproductive cloning will not be taken into consideration in the present document.

How stem cells are isolated

7. Stem cells may be obtained from tissues of different origin and, at the present state of our knowledge, may be distinguished by the greater or lesser facility with which they can be isolated, multiplied and grown in the laboratory and by the variety and types of mature tissue cells that they may be induced to produce. Hitherto stem cells have been isolated in the tissues of adult individuals, foetuses, umbilical cord blood, embryos in the early stages of development and, for the time being, only as a potential possibility, as a conceivable "reprogramming" of the adult cells which are thus already differentiated and specialized into the desired cell type.

8. It has so far been possible to isolate and grow in the laboratory stem cells derived from the cells of adult individuals for the following tissue types: bone marrow, blood, endothelium, nervous system, muscle. Table I shows the results of the most recent results, from which it may be seen that, so far, no stem cells have been found in other adult individual tissues. The use of stem cells derived from the above-mentioned tissues is subject to two main constraints: the difficulty of isolating them, expanding them and maintaining them in an undifferentiated state in the laboratory (a difficulty that for the time being it seems possible to solve only in the case of bone marrow) and, once they have been isolated, the difficulty of inducing them to specialize over a wide range of tissues that are different from the one from which they were isolated. So far in man only bone marrow stem cells have successfully been induced to differentiate into other types of cells (see Table I). In rat, one research group has succeeded in getting nervous system stem cells to differentiate into blood cells . The potential offered by this research, which is of vital interest as it would allow genetically compatible cell transplants, will certainly be developed over the long term. This explains why research into embryonic stem cells, which are much easier to isolate, expand, maintain and differentiate, is considered by many researchers as a necessary preliminary to the identification of the potential of stem cells derived from adult individual tissues, i.e. that which will most likely be used for therapeutic applications.

9. Stem cells can be isolated also from human foetal tissue derived from the reproductive cells of foetuses resulting from spontaneous abortions or voluntary interruption of pregnancy, or else from the blood of the umbilical cord removed at birth. At present it is not known what potential they have for differentiation into different tissues. For example, stem cells from umbilical cord blood currently have the potential to develop certain tissues (bone marrow and blood) but not others, which indicates that the differentiation of these cells into tissues different from those in which they were isolated still has a limited outcome, although mesenchymal progenitor cells have recently been identified in umbilical cord blood . In Italy research in this area is fairly well advanced, although the determination of the degree of multipotentiality of stem cells obtained by this procedure still requires much verification before they can be considered as an alternative to embryonic cell use.

10. The source of pluripotent stem cells that are easy to isolate and culture in vitro in the laboratory is currently the embryo at day five or six after fertilization (at the blastocyst stage). The empirical demonstration of the truth of this claim is obtained by examining the results of numerous experiments carried out animals, in the first place the mouse , but also in guinea pigs, chickens, pigs, primates, etc. In late 1998 a group of US researchers published a preliminary report describing the cultivation of human stem cells derived from 14 blastocysts successfully developed from 36 embryos donated by women who had undergone medically assisted procreation . This result was confirmed by other researchers who succeeded in isolating and then in maintaining in culture human stem cells derived from four blastocysts, which were then induced to differentiate into progenitor cells of

many different types of tissue. However, only in mouse has it so far been possible to transplant these progenitor cells into host mouse tissues and to induce them to differentiate and be integrated. For example, hemopoietic stem cells from mouse bone marrow were transplanted into rats affected by the human equivalent of type I hereditary tyrosinemia, a fatal metabolic disease, the target of which is mainly liver hepatocytes: the transplanted stem cells induced regeneration of the liver cells of the diseased mice and thus repaired their genetic defect.

11. The nuclear transplant technique described in section 5 above and tested in sheep, cattle, goats, pigs and mice has shown that it is possible to generate embryos without using spermatozoa. In the case of certain animals (the sheep Dolly, for example), the process was carried out before birth. If however, in the case of man, the process is halted after five or six days (at the blastocyst stage), the stem cells derived from the blastocysts not only behave like the stem cells derived from an embryo generated by the union of sperm and egg, but could also afford the substantial advantage of being genetically identical to the cells of the person from which the nucleus was extracted, thus avoiding all problems of rejection of the cell transplant in the case in which the nucleus donor is a patient and the cell transplant is aimed at repairing damage to diseased tissue in him (auto-transplant). It should be noted however that animals born as a result of the nuclear transplant technique are not exactly identical to the animals whose cell nucleus was used to generate them. Indeed they inherit the mitochondrial DNA contained in the cytoplasm of the enucleated cell egg and the effects of this mitochondrial inheritance on the immunological compatibility between donor cell and receiving egg cell are still unknown. Another problem that renders nuclear transplantation a therapeutic option of difficult clinical generalization is the finite number of human egg cells available, which cannot be increased at will. However, somatic nuclear transplant may be said to represent a very promising research avenue (although by no means yet of treatment) regarding the possibility of "reprogramming" adult human cells (see following section), which is the most ambitious cell transplantation treatment project.

12. There is no doubt that the long-term aim of research on stem cells for therapeutic purposes is to "reprogramme" a mature cell of an adult individual in such a way as to convert it back to its undifferentiated state and then to induce it to differentiate into a specific type of cell different from the type to which it belonged prior to "reprogramming". Once it is understood how the human egg cell, after removal of its nucleus, is capable of controlling the conversion of a differentiated cell into a stem cell not only will it no longer be necessary to form an embryo but also nuclear transplantation will probably not be accompanied by the problem of tissue incompatibility and subsequent rejection of the tissues introduced into the individual hosting the transplant. This long-term objective nevertheless means that experiments must be performed on embryonic stem cells, the only ones that are available today at a pluripotent stage. Obviously this experimentation must be performed in animals in the initial stages.

Possible therapeutic uses of stem cells and nuclear transplants

13. Tissues and organs damaged by traumas or disease can recover spontaneously. In some cases, however, treatment consists of repair or even of replacement. For example, the transplanting of bone marrow cells has been used with varying degrees of success in the treatment of certain forms of leukaemia and certain genetic diseases. The biological mechanisms underlying their repair would be able to act much more effectively if an adequate supply of undamaged cells was available to colonize the organ or the damaged tissue in such as way as to speed up the repair action and the normal physiological mechanisms. This is the direction currently being followed by research into the therapeutic use of stem cell lines: the laboratory reconstruction of entire organs, such as kidneys or

the heart, with their lymphatic and blood vessel systems and their complex tissue architecture or even their parts is still considered too remote a goal for therapeutic applications realistically to be expected in the short term. Available scientific evidence points rather to the possibility that laboratory culture of cells capable of repairing the damage suffered by certain organs may become possible quite rapidly. The following table lists the diseases that could represent a possible target for the specialized cells generated by inducing the differentiation of stem cells.

Cell type	Disease
Nervous system cells	Cerebral infarctus, Parkinson's, Alzheimer's, Spinal cord damage, Multiple sclerosis
Heart muscle cells	Infarctus of the myocardium
Insulin-synthetizing cells	Diabetes
Cartilage cells	Osteoarthritis
Blood cells	Cancer, immunodeficiencies, diseases of the hemopoietic system, leukaemia
Liver cells	Hepatis, cirrhosis
Epithelial cells	Burns, wounds
Skeletal muscle cells	Muscular dystrophy
Bone cells	Traumas, osteoporosis

One of the socially more significant applications of this innovative therapeutic technology could well prove to be the treatment of diabetes, a multifactorial disease of genetic origin that affects about 3% of the Italian population . In this way it would be possible to inject patients with stem cells instead of the current practice of injecting large quantities of pure insulin; with the same end in view, stem cell lines induced to produce human insulin on a permanent basis could conceivably be prepared in the laboratory.

14. The nuclear transplant technique could be used for purposes other than the production of stem cells, for instance, for the correction of genetic defects during the early stages of embryonic development or to treat diseases caused by alteration of the mitochondrial DNA. Furthermore, progress in our knowledge of human cell differentiation would allow animal experimentation to be progressively reduced. These arguments nevertheless lie beyond the scope of the present document and will be further investigated by the Committee.

Technical problems and risks

15. The use of stem cells to produce tissues for treatment purposes raises a number of technical issues, including: how "normal" is the resulting tissue in terms of rate of ageing, effects of harmful mutations, contamination of different tissues, immunological tolerance; b) if the stem cells produced by nuclear transplant from adult tissues give rise to as broad a range of differentiated tissues as that derived from the stem cells of an embryo produced by the fusion of sperm and egg cell; c) if it is possible to general the number of cells required for treatment purposes; d) to what extent and in what dosage is the incorporation of health tissue derived from stem cells effective in repairing damaged tissue. Obviously research will be able to provide answers to these fundamental questions only after a large quantity of experimental work has been done initially using animal models, as is customary in all experimentation performed for therapeutic purposes.

16. It may be anticipated that the two greatest risks involved in the use of stem cells are: immunological rejection of the nuclear transplant (mentioned above), which is common to all transplants and with respect to which the simplest theoretical solution would be to derive stem cells from the patients themselves, a process that could be defined as cellular auto-transplantation; and the risk of tumour formation due to the transplantation of incompletely or anomalously developed stem cells. Also in the latter case only experimentation, in the first instance on animal models, will allow us to understand the probable behaviour of laboratory-cultivated cells after transplantation into an organism, their capacity to perform normal functions, to integrate with existing cells, and the factors that may induce them to develop tumours.

Ethical problems

17. The use of human stem cells raises important ethical issues that essentially concern the origin of the cells and the way in which they are derived. The fact that these cells are currently isolated from human embryos at the blastocyst stage (about day 5 or 6) or from tissues obtained from spontaneous abortions or from voluntary interruptions of pregnancy implies that the ethical problems should be treated very carefully prior to any scientific discussion of the therapeutic potential or research in this sector. Considering the matter in the light of the origin of the stem cells, it would be preferable to divide the arguments according to whether these cells derive: from embryos created ad hoc for the purposes of scientific research; from tissues of foetuses obtained from spontaneous abortions or from voluntary interruptions of pregnancy; from tissues obtained by means of somatic nuclear transplant; from embryos not used in medically assisted fertilization.

18. The illegitimacy of creating an embryo in vivo or in vitro for the sole purpose of research is a principle on which a strong consensus exists at both the national and the European level. More specifically, the Council of Europe has explicitly banned it in art. 18, paragraph 2 of the Convention of Human Rights and Biomedicine. Also the National Bioethics Committee has expressed an opinion in this sense and reiterates this position on the previously stated grounds. What remains to be debated are the various ethical issues raised by the other procedures for obtaining stem cells.

19. Although there is no specific legislation in Italy regulating the use of foetal cells, tissues and organs, it is quite easy to derive norms in this field from international conventions and other laws or regulations. Ethically speaking, the use of tissues from aborted foetuses has already been taken into consideration by the National Bioethics Committee in one of its previous documents and deemed legitimate in principle whenever warranted by exclusive study, research or treatment purposes. Conversely, the National Bioethics Committee is of the opinion that the decision to interrupt pregnancy must be conditioned by the expectation of possible economic and therapeutic benefits deriving from the use of cells, tissues or organs from the foetus. Likewise, the marketability and patentability of the latter must be excluded. The National Bioethics Committee deems that the use for therapeutic purposes of stem cells deriving from foetal tissues must be subject to the informed consent of the aborting woman, that it must consist of a free, gratuitous and unconditioned act of disposition and that the physicians performing the abortion must be different from those performing removal of the organs.

20. It is considered that the possibility of deriving pluripotent stem cells from the somatic cells of a patient with a damaged tissue or organ would not raise any particular ethical problem, except for those commonly related to human experimentation, which include the need for adequate preliminary testing on animal models. If such stem cells were found to have the potential to differentiate into the damaged tissue and to integrate with it, they would be able to begin or accelerate the repair process. It would represent an actual autologous cell or tissue transplant, or auto-transplant, that would have the fundamental advantage from the therapeutic standpoint of not causing any rejection reactions. The

problem consists in the fact that, at the present state of research, human stem cells in optimal conditions of pluripotency, stability (when cultivated in the laboratory) and of indefinite growth, can be obtained only from embryos in the early stages of development.

21. Under what conditions and with what limitations is it possible to allow the formation of embryos specifically intended to be a source of material to prepare pluripotent cell lines for treatment purposes? In this connection, several different positions are represented on the National Bioethics Committee. Several members identify the formation of the zygote as the beginning of an individual human being that must be guaranteed the same protection as a person. Other members of the National Bioethics Committee consider that the status of person is acquired at a later stage, and that the degree of protection due to the embryo must be offset by an at least equivalent concern for the treatment of the sick person. This concern, together with that for the progress of scientific knowledge, would, after rigorous investigation and scrutiny, justify the creation of embryos for therapeutic purposes. As stated earlier, art. 18, paragraph 2 of the Convention on Human Rights and Biomedicine, awaiting ratification by the Italian parliament, is significant in this connection. Lastly, some members consider as compatible with their ethical values only the use of embryonic cells for therapeutic purposes, but not their creation. These different positions are represented within the Committee, which acknowledges their respective ethical legitimacy.

22. However, there is a de facto situation with which the Committee cannot come to terms, namely the existence in Italy of embryos not used for implantation and cryoconserved in the various centres in which medically assisted fertilization is carried out. The substantial lack of control over these centres means that the number of these socalled "supernumerary" embryos cannot be assessed, although by extrapolating the data from other countries and from personal knowledge, it is believed to be very high. This is not the proper place to discuss the reasons for these large numbers, or even to express the obvious desire that they should decrease or disappear, but rather to show how these embryos, owing to the fact that they were not implanted within a period of time compatible with an acceptable biological risk, are today doomed to be destroyed. The likelihood of some of them being donated by married couples to other couples in any case currently involves only a small number of cases. Part of the Committee believe that removal and laboratory culture of stem cells taken from an embryo that cannot be implanted does not signify lack of respect for it, but if anything may be considered a contribution by the donor couple to research into possible treatment of diseases that are hard to treat and often incurable which stems from an act of solidarity. The same part of the National Bioethics Committee are aware that any use for research purposes of cells derived from supernumerary embryos must be measured against the constitutional principles which include the protection of the life of the conceived being, the right to health and the freedom of scientific research. They in any case call for a regulatory mechanism coordinated with the more general and now urgent regulation of medically assisted fertilization techniques, without prejudice to the fact that it should in any case consist of regulations based on transitory criteria. Another part of the Committee expressed the opinion that the respect due to human beings prevents the instrumental use of embryos leading to their destruction which - at the time of thawing for the purpose of removing pluripotent stem cells - must necessarily be still alive in order to be used as a source of stem cells. This direct and intentional destruction of "supernumerary" embryos, even though performed for research or therapeutic purposes, is in contrast with the duty to respect human life from the time of conception on. The supporters of this opinion also criticize the practice of freezing and storing human embryos in the socalled embryo banks as this could encourage also other instrumental uses of them.

23. The National Bioethics Committee has not neglected reflection on the ethical significance that in research on stem cells is acquired not only by the embryo's ontological

status, not only the health that it is hoped to restore to sick persons by applying this research, but also the autonomy of women in deciding to donate their egg cells to make somatic transplantation possible (socalled "therapeutic cloning") and the freedom of women and couples to decide on the fate of non implanted embryos. For that part of the Committee who consider it acceptable to remove and culture in the laboratory the stem cells of an embryo that cannot be implanted, two factors thus become particularly important: the quality of the information available to the woman and the couple concerning the use of their donation, which may involve research in the field of medically assisted procreation or else therapeutic purposes; and the imperative need for consent to the donation, in full respect of privacy and of the principles governing the treatment of sensitive data, as is in any case provided for by the laws of those European countries that have legislated on the issue of research performed on the embryo.

24. Several members of the Committee have expressed the opinion that, for the time being, the right conditions do not exist to commence experimentation on human beings and that a lot more information must be gathered in the field of animal experimentation.

Conclusions and recommendations

The National Bioethics Committee:

25. deems that the possibility of cultivating in the laboratory stem cells having the capacity to reproduce indefinitely and to specialize in the formation of any tissue of the human body represents a line of research of particular interest as regards therapeutic applications. The use of these cells to repair damaged tissues and, in future, also damaged organs, by means of cell transplantation opens up new prospects of treatment for a wide range of frequently occurring human diseases that are today difficult to treat and often incurable.

26. expresses the hope that such a line of research will pursue the optimal objective of succeeding in "reprogramming" mature cells, that is, of deriving stem cells capable of differentiating into the desired tissues directly from the already differentiated cells of the patient whose tissue it is intended to regenerate. This would represent a cellular auto-transplant that had the substantial advantage of tissue compatibility and would thus presumably be used for important therapeutic applications.

27. is fully aware that the pluripotent stem cells with the greatest potential for differentiating into the widest range of tissues (in animal models and in observed cases also in man) are the stem cells derived from the embryo at the blastocyst stage even when they are derived from the somatic nuclear transplant process. The alternative attempts to derive stem cells from umbilical cord blood or from other tissues that are capable of expanding and differentiating into cells of tissues other than the original ones are still at the early experimental stage.

28. deems it to be ethically legitimate to derive stem cells from the cells of spontaneously aborted foetuses or those produced by voluntary interruption of pregnancy provided suitable steps are taken to exclude both causal relations between abortion and stem cell derivation and any collaboration among corresponding operators and marketability. Some members of the Committee have nevertheless expressed reservations concerning the possibility of distinguishing de facto collaboration among those performing the abortion and the team using the foetuses derived from the voluntary interruption of pregnancy even when suitable formal procedures are adopted to distinguish the relationship of causality between abortion and stem cell derivation.

29. points out that several of its members acknowledge and agree with the ban on creating human embryos for the sole purpose of using them for scientific research, as provided for in art. 18, paragraph 2, of the Convention on Human Rights and Biomedicine. A thorough evaluation of the experimental results of somatic nuclear transplantation suggests, according to other members of the Committee, that this new line of research could produce therapeutic results of great significance and for the time being without any

alternative such as to suggest evaluating the ethical aspects of future applications on a case by case basis.

30. reiterates the illegitimacy of using the somatic nuclear transplant technique for reproductive purposes ("reproductive cloning").

31. points out that part of the Committee consider it ethically legitimate to derive stem cells for therapeutic purposes from embryos that it is no longer possible to implant, again on condition that they are wittingly donated by the women or the couples concerned. They nevertheless recommend performing investigations and rigorous verifications on a case by case basis concerning the suitability for implantation, the consent to donate and the therapeutic purpose of the experimentation. These should be carried out by applying ad hoc indicators of a reasonable degree of impossibility of implantation, as well as the relative guidelines, ensuring that a preventive evaluation is made by the ethical committees. Other members are in any case against using supernumerary embryos even when cryopreserved and not required for transfer to the uterus, as they consider such practices to entail the direct and deliberate suppression of the embryos and thus an instrumental use of human beings and an offence to their dignity.

32. expresses the hope that a topic of such importance for biological and medical research and so significant as regards the possible treatment of diseases of great social impact and today difficult to treat will be the object of accurate information and wide debate. This should be the case not only within the scientific community but also in civil society, so that the latter can be made aware of and responsibly address the problems of a chapter of medicine that, while certainly new, it is hoped will also be effective, and to which the name of "regenerative medicine" has been given.

adult	tissue/original cells	tissue/final cells	Authors	Year
from cadaver	progenitor cells of hippocampus neurons	neurons	Eriksson P.S. et al., Nature Medicine 1998, 4:1313-1317	1998
	mesenchymal cells of bone marrow	adipocytes, chondrocytes, osteocytes	Pittinger M.F. et al., Science 1999, 284: 143-147	1999
umbilical cord	progenitor hemopoietic cells	erythrocytes, granulocytes, megakaryocytes, monocytes	Fasouliotis S.J., Schenker J.G., Obstetrics & Gynecology 2000, 90: 13-25	2000
	bone marrow	cells expressing neural proteins (neuron-like and glial cells)	Sanchez-Ramos J et al., Exp. Neur. 2000, 164: 247-256	2000
neuron progenitor pool	progenitor cells of hippocampus neurons	neurons	Neeta Singh Roy et al., Nature Medicine 2000, 6: 271-277	2000
	olfactory bulb	neurons, astrocytes, oligodendrocytes	Pagano S.F. et al., Stem Cells 2000, 18: 295-300	2000
healthy adult volunteers	stromal cells of bone marrow (mesenchymal derivation)	(non mesenchymal) neuronal cells	Woodbury D. et al., Journal of Neuroscience Research 2000, 61:	2000

			364-370	
	stem cells from bone marrow	hepatocytes	Alison M.R. et al., Nature 2000, 406: 257	2000
tissues from autopsies and biopsies	stem cells from bone marrow	hepatocytes and cholangiocytes	Theise N.D. et al., Hepatology 2000, 32: 11-16	2000
case report and review	progenitor cells from umbilical cord	"hemopoietic and immunological reconstitution" in acute leukaemia patient	Elhasid R. et al., Leukemia 2000, 14: 931-934	2000