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Ethical and legal frameworks for embryonic stem-cell based research in France and in Europe: a challenge for biotechnology.

Anne-Marie Duguet*, Emmanuelle Rial-Sebbag*, Aurelie Mahalachtimy**, Mou Li*, Anne Cambon-Thomsen*

*UMR 1027 Inserm / Paul Sabatier University TOULOUSE France; ** Centre for Global Health Policy School of Global Studies University of Sussex

Abstract

Developing research based on the use of biological material raises the question of the sources of the cells. Should we use human stem cells or embryonic stem cells? For human stem cells, since 1994, the French law considers the human body is inviolable and cannot be subject of property (Art 16-1 of the Civil Code) that means no trade and no patent. Focusing on embryos, the Oviedo convention (Council of Europe) on Human rights and biomedicine (1997) says in Art 18: it is up to each country to authorize or not the embryo research. There are differences among countries in Europe, from a total ban to an approval of the research with nuclear transfer. In France, several opinions of the French National Ethics committee (CCNE) claimed for the protection of the embryo. Regarding commercialization of cells and patentability, the European Directive 98/44.CE on legal protection of biological inventions says: Biotechnology inventions are essential for the development of the community; only adequate protection can make them profitable and facilitate trade. The national patent law remains the reference. In France, in 2006 research on embryo and embryonic stem cells was organized by the decree of April 27th, 2006 under the control of the French National biomedicine Agency. Even if the research on embryo was not permitted it could have been conducted under exceptions. . In 2010 the French National Ethics committee changed his position in the opinion 112 and the Act 2013-715 of August 6, 2013 is now allowing research on embryo and on embryonic Stem cells under conditions.

Key words: Embryo – embryonic stem cells – ethics – regulatory framework – France and Europe.

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Introduction

The use of biological material for biotechnology applications and research raises the question of sources. Should we use human stem cells or embryonic stem cells?

For human stem cells, since 1994, the French law considers the human body is inviolable and cannot be subject of property (Art 16-1 of the Civil Code) that means no trade and no patent.

Regarding the use of embryonic stem cells in research, one of the major ethical issues is relying to the destruction of the embryo, the impossibility to ensure its development, and the ethical consequences regarding the principle of respect for the beginning of life.

In France (A), several opinions of the French National Ethics committee (CCNE) claim for the protection of the embryo. From a formal opposition to use embryonic stem cells for research, to an authorization under specific conditions.

In the meanwhile, research on embryo and stem cells was organized by the decree of April 27th, 2006 under the control of the French National biomedicine Agency. Even if the research on embryo was not allowed it could have been conducted under exceptions. The regime has been modified since the adoption of the Act 2013-715 of August 6, 2013 allowing human embryonic stem-cells (hESC) research under conditions.

A quite different evolution can be seen at the European level (B) where the institutions were less keen to frame this issue on research on embryo through hard law instruments.

A- Evolution of the ethical and legal frameworks in France for using human embryonic stem cells in research.

For a long time the ethical issues dominated the debate on the authorization of research on embryos and since 1984, the National Consultative Ethics Committee (CCNE) has produced 8 opinions. The last one in 2010, opinion 112 synthesizes the previous reflection. Meanwhile the legislator in various laws and regulations organized the conditions of access and use of embryonic cells, ending by a change of legal regime in 2013 after deep discussions occurred in the CCNE.

1) The ethical values at a glance: the opinions of the National Consultative Ethics Committee CCNE

The first opinion adopted by the CCNE in 1984 was on "sampling of dead human embryonic and fetal tissue for therapeutic, diagnostic, and scientific purposes". [1] In this opinion the embryo was considered as a potential human being. The opinion followed the first in vitro fertilization carried out in France. The development of these new techniques questioned the new possibilities to separate reproduction from sexuality while also posing challenges to the legislative ability to use tissues that were not previously available for research (in particular for technical reasons).

In Opinion No. 8 (1986) [2] on research on supernumerary embryos, there were large discrepancies among the members of the Committee on the statute of the embryo and on the moral ability to use them (or their cells) for research. Following the progresses on IVF and on the technical possibilities to extract and to store hESC, the Committee supported the possibility to make some research on supernumerary embryos in opinion 53 (1997) [3] and 67 (2001) [4] but only under restricted conditions. Regarding reproductive cloning, in its opinion 54 (1997) [5] the CCNE was clearly against and this position was comforted by the adoption of the Law: Art 16-4 al. 3 of the Civil Code stating "Any intervention seeking to raise a child genetically identical to another, living or deceased, is prohibited."

So, two reactions have developed in parallel, on the one hand the doctrine of the National Ethics Committee on Ethics regarding the possibility of using embryos and embryonic stem cells in research, and secondly a legislative framework to strictly regulate these practices.

The ethical questions which came out from the committee were relating to the nature of the embryo and the cells: [6] [7] Is the embryo a person? A bundle of cells ? The opinion No. 93 of the Committee adopted on the 13 December 2006 on the Commercialization of human cell lines and stem cells [8], questioned mainly the ethical values that can be balanced as to the distribution of cells. Two principles were identified and used as a framework for the analysis made by the committee: "the nature and the limits of acceptable commercialization of human cell" and "the parents 'consent" to research. Even this opinion is not only covering embryonic stem cells but all types of cells on; the embryo had been largely targeted because of its ontological nature.

After noticing that the majority of the States in the world was considering the human body "out of market", the CCNE admitted, however, that this issue should be reconsidered in light of new practices that tended to develop. Indeed, the human body elements which can currently be completely detached from the body, can also be submitted to large transformations and therefore can potentially be turned into products that could be freely commercialized on national territories as goods. At the same time, the French bioethics law applies a common principle to all elements of the body in article 16-1 of the Civil Code: "The human body, its elements and products cannot be the subject of proprietary law ". This provision totally banned the cells and stem cells from being commercialized in France. Nevertheless, the CCNE applied this principle according a certain degree of flexibility. It insisted on the fact that this principle of non-commercialization should fully apply to the links between the donor and the researcher (no remuneration of the donor, no commercialization), whereas compensation of costs or commercial uses could apply to "sufficiently" or "radically" transformed elements of the body. These exemptions could also be applicable in case of transformation of embryonic stem cells. The criterion of "transformation" has been discussed in the 93 opinion and has been defined as human manipulations leading to the change of the ontological status of the cells, in other words transform human cell to a cell product. This argument has not been shared by all the members of the Committee as some of them provided divergent thoughts. Indeed, some members argued that the representation of the embryo as laboratory material, underlying the possible commercialization of cell lines, could lead to "crossing a very important line into a trivialization of embryo research". The other issue raised by the commercialization of stem cells, including embryonic stem cells, was relating to patents [9]. The question posed was linked to the nature of the cells which are coming from the human body: should these natural elements be patentable?

2) Research on embryo and on embryonic stem cells: legal overview

In France, research on embryos and hESC is organized by the Decree 2006-121[10]. The embryos that may be devoted to research are supernumerary embryos that are no longer subject to a parental project, or embryos not subject to transfer. At the end of the parental project, a prior informed consent specific for embryo research is necessary before starting the research. The written consent of the couple (or of the surviving member), is compulsory after informing on the other possibilities either to destroy the embryo or to make it available for a transfer for another couple. The embryos which are not subject to transfer in utero because of their quality (developmental abnormalities) rejected after preimplantation diagnosis when an

abnormality is detected, may be used for research. In all cases, the consent is revocable at any time.

The authorization for conducting research on embryo and embryonic stem cells is delivered by the Biomedicine Agency for 5 years to the establishments holding an authorization for conservation (L.2151-3-1 CSP). The biomedicine Agency verifies the feasibility of the protocol, the sustainability of the organization and the research team; the conditions of premises and equipment; the means to ensure the quality, the safety, the traceability of embryonic cells. The Agency holds a national register of embryos and cells (coded).

When research is performed on embryo and embryonic stem cells without respecting the law, punitive sanctions are defined by the criminal code. Sanction for cloning is five years in prison and 7 500 000 euros fine (Article 214-2 of the Penal Code). The article 511-1 PC punishes anyone who lends itself to gamete donation for cloning, even abroad. Regarding embryo research, the Article 511-19 PC punishes research without consent and without authorization of seven years' imprisonment.

Until today, there is no jurisprudence of criminal courts for violating the law. Nevertheless there is a decision against an authorization to import stem cells. In 2003 the "Tribunal Administratif "of Paris has received a request from an association defending the 'Right to live" for cancellation of the authorization to import stem cells. The association argued that the research on stem cells is a destruction of the embryo. The Tribunal considered that these stem cells could not be regarded as embryos. The decision was confirmed on appeal by the Administrative Court of appeal [11].

3/ Latest evolution of the ethical and legal frameworks in France.

France has undergone profound changes in recent years at the ethical and the legal level. While research on stem cells advances, including embryonic stem cell research, the CCNE doctrine and the legal framework had to evolve to frame the new practices. French law has modified the legal regime for embryonic stem cells research in 2013 as a result of a dual influence: on one hand the ethical assessment made by CCNE in 2012 on research on the embryo (12) and the other hand one court decision.

As for the opinion, the committee starts its argumentation by emphasizing on where the majority of States have agreed "There is one true interdict, shared by everyone: the integrity of embryos in vitro cannot be jeopardized as long as they are included in the concerned couple's plans to-have a child.". Insisting, therefore, on parental project as the foundation for the embryo integrity protection (this excludes *de facto* Human Dignity as a principle to ensure embryo protection), the Committee draws consequences to legitimate research on embryos, even though in 2012 we were still under a legal regime of prohibition of research with exceptions. CCNE admitted, according to his previous doctrine, that the "issue of the exact nature of the embryo" is an enigma which cannot be resolved by consensus. The only consensus which can be reached is on the need of a parental project as a source of protection of the embryo, the end of the parental project is considered the only moral condition to make the embryo available for research. Thus, the first condition to be fulfilled to morally allow

research on embryos is the expression of consent from the couple to waive their parental project on their spare embryos. This condition obviously assumes that the embryos were originally designed as part of a medically assisted procreation project which thereby prohibits creating embryos for research directly. Thus, as already stated in previous opinions, the Committee legitimates the use of embryos for research purposes in the framework set by the law and since the parental project (which only establishes the link "potential human being") no longer exists. Recall that in 2012 the legal regime prevailing in France was a ban of the research on embryos and embryonic stem cells with exemptions.

This framework has been also modified on a different basis with the adoption of a court decision in 2012. [13] In this case a Foundation was appealing against a decision of the Biomedicine Agency which was authorizing research using embryonic stem cells. Interpreting the 2011 bioethics law [14] and the requirements for research posed by the law, the Court has considered that two of the conditions required by law were not fulfilled: research should allow "major therapeutic progress" and cannot be carried out "by an alternative method of comparable effectiveness ". The Foundation formed an appeal arguing the authorization adopted by the Biomedecine Agency respects neither the one nor the other of these conditions. The Foundation was successful since the Court noted that "the Biomedicine Agency, by merely opposing defense to the lack of scientific consensus on the substitutability of the two techniques, does not establish that an alternative method did not exist at the date of the contested decision." Thus, the judge clearly places the burden of the proof concerning the lack of comparable methods, on the Agency. Indeed, secondly, the lack of demonstration, created ambiguity about the possible "major therapeutic progress", making, therefore, the second condition of the law inoperative.

Since that decision other appeals have been formed but with a limited impact because of the adoption of the law in 2013 [15] which now defines new conditions for research in France.

Since 2013 the legal balance has changed in France. Now, research on embryos and human embryonic stem cells is no longer subject to a prohibition regime with exemption but an authorized activity under conditions. One could interpret this legal regime as a move towards liberalization of research [16] but it can also be felt as a response to a future market [17].

This change in the regulation framing the research on embryos was also the occasion for the French legislator to soften the legal requirements to realize a research protocol [16]. Since the 2013 law the following conditions have to be demonstrated prior the commencement of the research: the scientific relevance of the research project as well as the medical purpose (this condition is interpreted largely as it includes basic research) ; the law maintains the principle of subsidiarity but in a flexible formulation; ethical principles should be respected but the incentive to promote alternative research is deleted; the consent of the partners is required in the same manner as under the 2011 law, but now parents will not be informed of the nature of the research that will be considered. From this last provision one can say that the law is validating a form of blanked consent from the parents. In fact, as parents are no longer informed on the nature of the future research on the embryos, their consent could be considered valid for any research protocol. This position could have been problematic as it is the first time in the French law where a legal provision legitimates blanked consent. This issue has been partially solved by the adoption of the implementing decree in 2015 [18] where

it is required from the practitioner to deliver any available information on the research to be conducted in the future. In addition, the new law and implementing decree further specifies procedural requirements for the evaluation, approval and implementation of research protocols.

B - European dimension: ethics and law

For a long time in Europe, ethics committees focused their reflection on embryo research, taking into account the different historical and cultural sensitivities.

1) The European Group on Ethics

The European Group on Ethics in Science and New Technologies (EGE) [19] is a neutral forum, independent, pluralist and multidisciplinary; it is composed of fifteen experts appointed by the European Commission for their expertise and personal qualities. The Group's mission is to examine the ethical issues related to Science and New Technologies and on the basis of their work, to submit opinions to the European Commission as part of the development of legislation and the establishment of Community policies

The opinion 9 (1997) [20] focuses on the ethical aspects of cloning and opposes reimplantation into the uterus. Opinion 12 (1998) [21] allows research on embryos within a maximum period of 14 days after fertilization, with parental consent, but forbids the human / animal hybrids. In 2000 an opinion on stem cell specifies that the egg donation should not increase the constraints on women (Opinion 15, 22).

In 2002, an opinion was issued on the patentability of stem cells. Indeed in 2002 over 2000 patent applications were filed worldwide for human and non-human stem cells among them, 25% for embryonic cells. The patent may cover either process: isolation, enrichment, culture, genetic differentiation modification processing of somatic cells into stem cells; either product: the cells themselves, the lines, the genetically modified cells. The EGE concludes with the need not to ban patent on cells or cell lines that would be contrary to the public interest and in the interest of patients. The EGE distinguished according to the nature of stem cell, the lines that have not undergone any changes that do not meet the conditions for patentability, and cells modified by treatment in vitro or by genetic engineering which can fulfill the conditions for patentability (opinion 16, 23).

2- The Council of Europe : The Oviedo Convention

The member States of the Council of Europe, have signed on April 4 1997 the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine, so called the Oviedo Convention [24]. The convention takes into account all the previous declarations or conventions on human rights (WHO, European social charter, Convention for data protection, rights of the child.....).

The preamble recalls the following points. The aim of the Council of Europe is the achievement of a greater unity between its members and that one of the methods by which that aim is to be pursued is the maintenance and further realization of human rights and

fundamental freedoms. The accelerating developments in biology and medicine needs international co-operation so that all humanity may enjoy the benefits of biology and medicine. The Council is conscious that the misuse of biology and medicine may lead to acts endangering human dignity and affirms that progress in biology and medicine should be used for the benefit of present and future generations. The Council considers that measures as are necessary to safeguard human dignity and the fundamental rights and freedoms of the individual with regard to the application of biology and medicine.

The general provisions of the convention are the protection of dignity rights and fundamental freedoms. In article 1, parties to this Convention shall protect the dignity and identity of all human beings and guarantee everyone, without discrimination, respect for their integrity and other rights and fundamental freedoms with regard to the application of biology and medicine. Each Party shall take in its internal law the necessary measures to give effect to the provisions of this Convention. The primacy of the human being is recalled in article 2 : the interests and welfare of the human being shall prevail over the sole interest of society or science.

Regarding the research on embryos *in vitro*, the convention says in article 18 : Where the law allows research on embryos *in vitro*, it shall ensure adequate protection of the embryo. The creation of human embryos for research purposes is prohibited. We can conclude from this analysis that there is no consensus at the Council of Europe level on the research on embryo. This question is still regulated under national laws and no European framework have been proposed and adopted as a common rule. This position is demonstrating the impossibility, for some very few area, to reach a European position due to cultural and legal traditions.

3) The legal framework in Europe for research and patent

There are major differences regarding research on the embryo among the EU member states and foreign countries, from a ban in Italy and Germany, to an approval of the research and nuclear transfer in UK, Belgium, Sweden, Canada, USA, Japan, China, Singapore, South Korea. Some countries authorize research, but prohibit the nuclear transfer: Brazil, Australia, France, Denmark, Greece, Finland, Estonia, Latvia, Slovenia and Switzerland.

In the EU each country defines the organization of research as the EU is claiming not to have competency in that field. However, the UE has funded research on stem cells in the 6th and 7th framework research and development program, under the condition of compliance with ethical and legal framework of the country. The EU recognizes the great economic potential of new technologies that is necessary to promote and protect.

Through the Directive 98/44/EC, on biotechnology inventions [25], we can find arguments on the position of the EU on the status of the human body and its elements. The preamble of the Directive states that biotechnology inventions are essential for the development of community. Only adequate protection can make them profitable and facilitate trade. The national patent law remains the reference. The patent is an industrial property that allows especially the limits of use by third parties of the patented invention. To be patentable an invention must: being new, Have an inventive step and industrial application

Regarding the patentability of human body elements, the European Directive 98/44.CE says in Article 5: *“The human body ... Including the partial sequence of a gene, cannot constitute patentable inventions ...An element isolated from the human body or otherwise, produced by a technical process ,may constitute a patentable invention ... the partial application of a sequence or partial sequence of a gene must be described in the patent application”*.

Inventions shall be considered non patentable where their commercial exploitation would be contrary to public order or morality; however, exploitation shall not be deemed to be so contrary merely because it is prohibited by law or regulation (article 6). The following, in particular, shall be considered non patentable: processes for cloning human beings; for modifying the germ line genetic identity of human beings; the uses of human embryos for industrial or commercial purposes and processes for modifying the genetic identity of animals which are likely to cause them suffering without any substantial medical benefit to man or animal, and also animals resulting from such processes.

Considering 16 asserts the principle that the human body, at any stage in its formation or development, including germ cells, and the simple discovery of one of its elements or one of its products, including the sequence or partial sequence of a human gene, cannot be patented.

There is a European consensus that says: the person to whom the item is taken must have given consent under national law.

In France, transposition of the Directive was delayed because of a degree of reluctance. The matter was referred to the European Court of Justice in the course of an action for failure to fulfil obligations, which led to the ECJ's ruling against France on July 1, 2004, (Aff. C-448/03).*“By not adopting the laws, regulations and administrative provisions necessary to comply with the Directive 98/44 / EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions the French Republic has failed to fulfill its obligations under Article 15 of that Directive. The French Republic shall pay the costs”*.

The provisions of the Law on Bioethics voted on August 6, 2004 as a result of the transposition of Directive 98/44 were a compromise solution and attempted to temper the scope of patents. CPI Article L. 611-18 transposes differently Article 5 of the Directive by stipulating that "only an invention constituting the technical application of a function of an element of the human body can be patent-protected". Nevertheless, significant divergence between the formulation of the above text (and that of CPI Article L. 613-2-1) and Article 5 of the Directive dated July 6, 1998, is problematic.

In conclusion, the French law has evolved in a sense to open the conditions for conducting research on embryos and stem cells in France. This position was the one claimed by the French researchers notably because of their willing to contribute to the international “race” which the previous legislation was impairing. However, even though we can support this vision, the French law and its interpretation will have to ensure a high level of protection of the parents and of the embryo, opening the research should not have to be detrimental to the respect of fundamental rights. At the European level, we can conclude that the European institutions do not want to go further on solving the issue from a regulatory point of view. As it is considered as a very problematic issue, only the European Group on Ethics has decided to

propose some values and rules about embryo research. In a sense, these values can be considered as common roots for considering embryo research acceptable in Europe.

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[2] CCNE, Opinion n° 8 on research and use of in vitro human embryos for scientific and medical purposes, (15/12/86), <http://www.ccne-ethique.fr/en/publications/opinion-research-and-use-vitro-human-embryos-scientific-and-medical-purposes#.WAYehSRnBek>

[3] CCNE, Opinion n°53 on the establishment of collections of human embryo cells and their use for therapeutic or scientific purposes (11/03/97), <http://www.ccne-ethique.fr/en/publications/opinion-establishment-collections-human-embryo-cells-and-their-use-therapeutic-or#.WAYftiRnBek>

[4] CCNE, Opinion n° 67 on the preliminary draft revision of the laws on bioethics (18/01/01), <http://www.ccne-ethique.fr/en/publications/opinion-preliminary-draft-revision-laws-bioethics#.WAYgECRnBek>

[5] CCNE, Opinion n° 54 Reply to the President of the French Republic on the subject of reproductive cloning (22/04/97), <http://www.ccne-ethique.fr/en/publications/reply-president-french-republic-subject-reproductive-cloning#.WAYg8CRnBek>

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[8] CCNE, Opinion n° 93 on the Commercialisation of human stem cells and other cell lines (22/06/06), <http://www.ccne-ethique.fr/en/publications/commercialisation-human-stem-cells-and-other-cell-lines#.WAIROSRnBek>

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[10] Decree 2006-121 of 27 April 2006 JORF n°32 du 7 février 2006

[11] CAA Paris 9 mai 2005 (No. 03PA00950).

[12] CCNE, Opinion 112, Ethical reflection concerning research on human embryonic cells and on human embryos in vitro, 21/10/10, http://www.ccne-ethique.fr/sites/default/files/publications/avis_112eng_0.pdf

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- [14] Act 2011-814 of 7 July 2011 on Bioethics
- [15] Act 2013-715 of August 6, 2013
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