Chapter I. European pluralism and the regulation of research on Human Embryonic Stem cells in Spain: too far from nowhere[4]

I.1. Premise and starting point: a variable geometrical context in Europe of research on Human Embryonic Stem cells

There is a constant in any approach from Juridical Sciences to medical advances and no matter how obvious it can be it must always be recalled as a premise: "Science moves faster than Law which is always lagging behind the facts". Consequently, as a caution, we must advert that juridical answers don't come fast and in any case, they are not immutable for a long time.

Having assumed the previous premise, as a starting point in our analysis we must comment the variable geometrical context in Europe as regards regulation in human embryonic stem cells (hESC)

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research[5]. Geometrical, on the one hand, because it is possible to recognise four different approaches among European Union Member States on hESC research[6]:

Permissive position (A few Member States have specific legislation for hESC research, covering the procurement of stem cells and their use for research. In Belgium, Spain, Sweden and the United Kingdom, for example, embryo creation is allowed for research purposes.

Permissive position with restrictions (In other European Union Member States as the Czech Republic, Denmark, Finland, France, Greece, Netherlands and Portugal, regulations allow the derivation of new hESCs from embryos created as a result of assisted reproduction technology (ART) and in vitro fertilisation to induce pregnancy, but only when they can no longer be used for that purpose.

Restrictive position (Germany and Italy have stricter hESC research regulations. Scientists in these countries cannot derive new hESC cell lines, but can import them. In Germany, a new discussion

[5] The European Group on Ethics in Science and New Technologies to the European Commission, in its Opinion No 22 (Recommendations on the ethical review of hESC FP7 research projects) of 20 June 2007, evidenced a situation, normatively speaking, of "variable geometrical" among European Union Member States' regulation on human embryonic stem cells (from now on "hESC")

[6] Recommendations on the ethical review of hESC FP7 research projects, Opinion N° 22, 2007, pp. 29 and ff., in http://europa.eu/european_group_ethics/publications/docs/opinion_22_final_follow_up_en.pdf

has arisen as to whether the 2002 Stem Cell Act regulating the importation of hESC lines should be revised, but no legal proposal has been forthcoming by the date of these Recommendations. The Italian legislation covers Artificial Reproduction Technology and the production of new hESC (research involving the destruction of embryo is not allowed). Italy has therefore no legal provision as regards to the use of imported hESC or existing hESC).

No specific legislation or indirect legislation only (In many Member States, hESC research has still no specific legislation (Bulgaria, Cyprus, Estonia, Ireland, Luxemburg, Latvia and Romania). Ireland, for instance, currently has no specific legislation dealing with embryonic stem cell research and furthermore does not have a legislative basis for the practice of in vitro fertilization. Some other European Union Member States have no 'specific' regulation on hESC research, but explicitly indicated that they are against it (Austria, Lithuania, Malta, Poland and Slovakia) by voting against hESC research during the Council decision for FP7. Lastly, in some countries hESC is at present regulated only by indirect legislation for embryo research (Hungary, Slovenia), but without specific references to hESCs.

Variable geometrical context also, because it seems evident that Science moves faster than Law and this situation described by the European Group on Ethics in Science and New Technologies to

the European Commission, in its Opinion No 22, should to be updated today, for example in the case of Germany[7].

Such a variable geometrical context in Europe as regards regulation of research on embryonic stem cells may have important effects and juridical consequences[8], particularly as far as commercialisation and patenting in Europe is concerned[9]. The European Groups on Ethics in Science and New Technologies evaluated it so in its Opinion No 16 "Ethical aspects involving the patenting of human stem cells", and furthermore, the Main Board of Appellation ("EBoA") in the European Patent Office showed

[7] In 2008 Germany changed its legislation and since then scientists there can do research on stem embryo cells imported into Germany provided they had been created before the 1st May 2007 (and not only those created before 1st January 2002). Notwithstanding, big changes are not expected any time soon and lack of harmonization still keeps on as the major challenge for Europe: "how to respect diversity while unifying the different systems in order to foster advances in European research for the benefits of all", DRUML, Ch.: "Stem Cell Research: Towards Greater Unity in Europe?", Cell, No. 139, 2009, p. 651.

[8] See: NIPPERT, I.: "The pros and cons of human therapeutic cloning in the public debate", Journal of Biotechnology 98 (2002), pp. 53-60. PLOMER, A.: "The European Group on Ethics: Law; politics and the limits of moral integration in Europe", European Law Journal, 14 (2008) 6, p. 859.

[9] A debate on patenting hESCs was ongoing at both institutional (European Patent Office, the European Commission) and academic level. And although the Directive on the legal protection of biotechnological inventions (98/44/EC, Official Journal L213, 30/07/1998, pp. 13-21) regulates patentability of biological material, including hESCs, it is also true that there is no European Union consensus on the moral status of embryo and its products. Consequently, reflecting this wide diversity of moral cultures, there are different policies for patenting among national patent offices which may difficult to achieve a European patent consensus at this regards.

coincidence in this point it in its decision of 25 November 2008 in the so called WARF case.[10] Under the situation above describes there is a fact which could help to explain it: we miss in Europe a common understanding of human beings, of the beginning of human life and, consequently, of status and rights of embryo as far as its human dignity.

I.2. Waiting for Godot: a different understanding of the beginning of human life and, consequently, of status and rights of Human embryo as regards dignity

It is not a novelty to reads The European Group on Ethics in Science and New Technologies' Opinion No 22, on the ethical review of the hESC FP7 research projects, when it seriously concludes that:

> "As far as human embryo stem cells research is concerned, there is no consensus on its social acceptability in the European Union, and divergent views co-exist. A debate on the best model (e.g. "minimal consensus" or "subsidiary"

[10] It was a ruling in an appeal connected to the so-called WARF/Thomson stem cell application describing a method for obtaining embryonic stem cell cultures from primates, including humans, and was filed by the Wisconsin Alumni Research Foundation (WARF) in 1995. In 2006, the Technical Board competent for the case referred it to the EBoA whose final decision was a refusal to grant a patent for an invention which necessarily involves the use and destruction of human embryos since it would be contrary to public order or morality in Europe, which was prohibited in the European Patent Convention and on the EU Biotechnology Directive (98/44/EC). Decision can be obtained in http://www.epo.org/topics/news/2008/20081127.html

model) to regulate hESCs research at European Union level is therefore taking place within and across several European Union Member States."[11]

The European Court of Human Rights, ruling as a Grand Chamber, said previously the same with different words in 2004 in the case of VO v. France[12]. Then, the European Court considered that the issue of when the right to life begins is a question to be decided at national level: firstly, because the issue has not been decided within the majority of the States which had ratified the Convention, in particular in France, where this question has been the subject of public debate; and, secondly, because there is no European consensus on the scientific and legal definition of the beginning of life. It also established that:

> "At European level, there is no consensus on the nature and status of the embryo and/or foetus. At best, it can be regarded as common ground between States that the

[11] Op. cit., p. 38.

[12] Judgment of 8 July, 2004. The case concerned an application brought by a French national, Mrs Thi-Nho Vo, who attended on 27 November 1991 the Lyons general Hospital for a medical examination scheduled during the six month of pregnancy. On the same day another woman, Mrs Thi Thanh Van Vo, was due to have a coil removed at the same hospital. Owing to a mix-up caused by the fact that both women shared the same surname, the doctor who examined the applicant pierced her amniotic sac, making a therapeutic abortion necessary. Having exhausted local remedies, Mrs Thi-Nho VO lodged an application before the European Court complaining of the authorities' refusal to classify the unintentional killing of her unborn child as involuntary homicide, relying on Article 2 of the European Convention on Human Rights.

> embryo/foetus belonged to the human race, its potential and capacity to become a person requires protection in the name of human dignity, without making it a person with the right to life for the purpose of Article 2."[13]

The same conclusion was achieved two years later in the case Evans v. United Kingdom, judgments of 7 March, 2006 (Chamber) and of 10 April, 2007 (Grand Chamber)[14]. In both judgments the European Court of Human Rights refused to recognise eventually the right to life under Article 2 of the European Convention of Human Rights to human embryos. Furthermore, this Court even self-restrained of willing to judge at European level on the question concerning the beginning of human life, considering the wide margin of appreciation any European country has been recognized on the matter.

So, the next and envisaged question we need to pose is the following one: at which extent and how this lack of consensus at European level (Council of Europe and European Union) on the nature and status of the embryo may influence in countries like Spain or United Kingdom leading research in hESCs? The answer is that at a large state such lack of consensus may negatively influence in the economy and development of European Societies, like Spanish one,

[13] Paragraphs 82 and ff. of the Judgment. The European Court of Human Rights also remembered that not even the Convention on Human Rights and Biomedicine of 1997 (Oviedo Convention) nor its Additional Protocol of 2005 concerning Biomedical Research include a definition of human being or of a person.

[14] See paragraphs 45 to 47 in the former and paragraphs 54 to 56 in the latter.

which freely have decided to bet for innovation and hedge technologies as a better way for surmounting the current economic crisis.

I.3. Research on human cloning and cells reprogramming exclusively for therapeutic reasons: the example of Andalusia and Spain

The Autonomous Community of Andalusia (a region of Spain like Catalonia or Basque Country) has been pioneer in Spain enacting a legal framework for research on cloning for therapeutic purposes[15] and particularly, concerning research on cellular reprogramming exclusively for therapeutic purposes with the already cited Law 1/2007 of 16 March, 2007[16]. Such a legislative path has to be understood considering several provisions in the Andalusian Statute de Autonomy[17]. Contrary to the option assumed at national level[18],

[15] See Law 7/2003 of 20 October, 2003, by which was regulated Research in Andalusia with human pre-embryos non valid for IVF. BOJA (Official Journal of Andalusia) No. 210, 21 October, 2003.

[16] That is, very soon after 2006 when cells reprogramming was a success. See TAKAHASI, K. and YAMANAKA, S.: "Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors", Cell, 126 (2006), pp. 663-667) up to present with third generation of protein-induced pluripotent stem cells, also called piPS. See a general overview in: STEIN, R.: "Researchers May Have Found Equivalent to Embryonic Stem Cells", The Washington Post, 24 July 2009.

[17] It is a kind of Regional Government's Constitution which was newly approved by Organic Law 2/2007 of 19 March, 2007.

the Autonomic Authorities in Andalusia preferred a concise Law which would be ready to provide immediately legal cover to the research on human cell reprogramming exclusively for therapeutic reasons.

We have already had the opportunity to express our concern that Andalusian Law 1/2007 of 16 March, 2007 of Research on Cellular Reprogramming exclusively for therapeutic reasons would run the risk of being perceived as a potentially illegal Act in comparison to Spanish Law on Biomedical Research and considering international obligations assumed by Spain under the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine (the Oviedo Convention)[19]. In my opinion, such a risk derives from the ambiguity in expressing the object of the Andalusian Law 1/2007.

Article 1 of Law 1/2007 explains which is the purpose of this Act: Besides the creation of the Committee of Research on Cellular Reprogramming, it is aimed "To regulate the research in the Autonomous Community of Andalusia through the use of techniques of cellular reprogramming in human somatic cells, in order to change

[18] Law 14/2007 of 3 July, 2007, of Biomedical Research in Spain was approved only three months latter that the Andalusian Law 1/2007 and it is more perfect, legally speaking. Not only for its length, 90 Articles in comparison with 9 in the Andalusian Law, but also for it having been conceived as a norm of reference in this field, and so, covering as much present and envisaged questions as possible.

[19] Signed in Oviedo the 4th April, 1997. BOE No. 251 of 20th October, 1999. i.e. my work: Bioderecho en Andalucía, Centro de Estudios Andaluces, 2009.

them into pluripotent stem cells with exclusive therapeutic purposes." The risk pointed out emerges of reading this provision together with Article 2 "Definitions", namely, letters d)[20] and f) (providing the definition of somatic pre-embryo)[21] to the light of Par II of the Preamble of this Law[22].

In view of Preamble of Law 1/2007, namely, its third paragraph beginning from the end[23], definitions of cell nuclear transfer and of

[20] According to this Article 2.d) cellular reprogramming is a technique by which a differentiated adult cell is forced to go back in its evolutionary process up to change into a pluripotent cell which can later change into different kinds of cells, tissues or even organs;

[21] By which "Somatic pre-embryo" is considered a group o cells resulting from successive division of the cellular form created throughout techniques of cellular reprogramming, like the nuclear transfer or other similar techniques, from the moment such a technique is applied and up to fourteen days after.

[22] "Among the techniques of cellular reprogramming it has achieved a notable development for its feasibility and reproductive capacity the so called nuclear transfer. This technique consists of the transfer of the nucleus of a somatic cell to the cytoplasm of an oocyte previously enucleated. The process generates, under some circumstances, a reprogramming of the nucleus of the somatic cell which assumes the features of a pluripotent cell and its immediate division in successive stages, similarly to a pre-embryo in stage of blastocyst. From that point on, it is possible to get stem cells with the genetic features of the somatic cells whose nucleus was inserted into the oocyte. The differentiation of these stem cells in different cellular lines could allow in future, just in case research progresses duly, to using these cells or tissues for replacing those ones irreversibly damaged by a degenerative illness by working with a cell from the same person."

[23] "The Autonomic Commission on Ethic and Medical Research in Andalusia redacted an opinion favourable to the biomedical research by way of nuclear transfer with therapeutic purposes, where it was asked from the Andalusian Government for the development of the regulatory normatively for being possible these techniques of researching."

somatic pre-embryo in letters e) and f), respectively, of Article 2 of this Law, seems to be confusing. According to this later provision, cell nuclear transfer is a technique of cellular reprogramming consisting of the transfer of the nucleus of a somatic cell to the cytoplasm of an oocyte previously enucleated. Similarly, a somatic pre-embryo would be a group of cells resulting from successive division of the cellular form created throughout techniques of cellular reprogramming, like the nuclear transfer or other similar techniques, from the moment such a technique is applied and up to fourteen days after. In my opinion, letter e) read together with Preamble could be easily misunderstood as if it was considering human cloning for therapeutic purpose and, given the fact that creation of pre-embryos and embryos for research purposes is prohibited in Spain, the cell nuclear transfer technique would had been mixed up with reprogramming techniques in order to use the concept of somatic pre-embryo instead of human pre-embryo. So, it would not be formally illegal such techniques although they will be in other context!.

It is easy to find reasons for someone making such mistake of interpretation Law 1/2007: reprogrammed cells were not just functionally identical to embryonic stem cells (at least this was true in 2007) and although future was blooming considering advances in research on induced pluripotent stem cells (iPSCs) any scientist in the world would agree in the necessity of keeping on working on embryonic stem cells –no matter they are ethically sensible- as well as adult stem cells and reprogrammed adult cells because it still remains unclear which of them will eventually prove most effective. Maybe all of them would be required depending on the therapy and

patient targeted. Obviously, Andalusian Legislator has no intention of making anything illegal. The Law 14/2007 of 3 July, 2007 of Biomedical Research in Spain, remembers in paragraph 3 of it Preamble that:

> "The Law expressly prohibits the creation of human pre-embryos and embryos exclusively for the purpose of experimentation, in accordance with the gradualist perspective on the protection of human life set out by our Constitutional Court in rulings such as 53/1985, 212/1996 and 116/1999, but allows the use of any technique for the obtaining of embryonic stem cells for therapeutic or research purposes that does not entail the creation of a pre-embryo or of an embryo exclusively for this purpose and in the terms provided in this Laws".

Such a prohibition is included in Article 33, in Title IV "On the obtaining and use of cells and tissues of human embryonic origin and other similar cells" when it says:

> "1. The creation of human pre-embryos and embryos exclusively for experimentation purposes is prohibited. 2. The use of any technique for obtaining human stem cells for therapeutic or research purposes is allowed, always when it does not entail the creation of a pre-embryo or an embryo exclusively for this purpose, in the terms provided in this Law, including the activation of oocyte, through nuclear transfer".

Furthermore, Law 14/2007 is being consistent with the Convention for the protection of Human Rights and dignity of the human being with regard to the application of biology and medicine: Convention on Human Rights and Biomedicine (Oviedo

Convention), which Article 18.2 stipulates: "The creation of human embryos for research purposes is prohibited". Nevertheless, in the already mentioned Opinion No. 22 of the European Group on Ethics in Sciences and New Technologies, it could be read in page 32 that Spain allowed the creation for human embryos for research purposes. Are we facing a contradiction with Andalusian and Spanish Laws on biomedical research? It rather seems a case of confusion.

I.4. Human embryos facing somatic embryos: a case of Mr. Jekyll and Mr. Hide?

The case of confusion we have pointed out might be due to the unfortunate wording of Article 33 of Law 14/2007, of Biomedical Research in Spain[24] and according the object of the Andalusian Law 1/2007 how it is prescribed in its Article 1 as allowing to do research on cellular reprogramming exclusively for therapeutic purposes.

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[24] This provision arises doubts as regard if it is allowed any technique of obtaining human stem cells, including the activation of oocyte by way of nuclear transfer for therapeutic and research purposes or if, on the contrary, the right meaning of such provision is to allow the obtaining of human stem cells providing no pre-embryo or embryo is created, including in such prohibition the activation of ovocite by way of nuclear transfer of somatic cells. To be honest, such confusion should not take place considering the mention made in Article 4 of the Law 1/2007 to Additional protocol to the Oviedo Convention, concerning prohibition of cloning of human beings: "According to Additional Protocol to the Convention of 4 April, 1997 for the protection of human rights and dignity of the human being with respect to applications of biology and medicine, by which it is forbidden cloning human beings, this Law forbids researching with techniques of cellular reprogramming with somatic cells to generate pre-embryos with reproductive purposes. It is also forbidden researching with these techniques for any other purpose apart from that authorised in this Law."

Reading this provision, one may wonder which are those other purposes referred in Article 4 of Law 1/2007? As far as reaches our knowledge, human cloning may be reproductive or for therapeutic purposes, so hardly can we understand Article 4 in fine since it could imply that it is also forbidding techniques of cellular reprogramming with somatic cells to generate pre-embryos for research purposes, which in fact could be thought to be authorised according to Article 2 and Preamble of the same Law!

Spearing some light into darkness it is necessary to remember that commonly is assumed as the aim of activating oocyte with nuclear transfer of adult somatic reprogrammed cells, not to create human embryos but embryonic bodies. They are things quite different[25] for most of authors[26] although it is not unanimously

[25] HESCs naturally reside within the inner cell mass (embryoblast) of blastocysts, and in the embryoblast, differentiate into the embryo while the blastocyst's shell (trophoblast) differentiates into extra embryonic tissues. The hollow trophoblast is unable to form a living embryo and thus it is necessary for the embryonic stem cells within the embryoblast to differentiate and form the embryo. IPSCs were injected by micropipette into a trophoblast and the blastocyst was transferred to recipient females. Chimeric living mouse pups were created: mice with iPSCs derivatives incorporated all across their bodies with 10%-90% chimerism. See http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell visited on 3/2/2010

[26] See, for instance: LÓPEZ MORATALLA, N.: "Clonación terapéutica", Persona y Bioética, 8 (2004) 22, in http://biblioteca.unisabana.edu.co/revistas/index.php/personaybioetica/article

accepted[27]. If Science keeps advancing at present rate making possible to create human pre-embryos and embryos with the technique of nuclear transfer of adult reprogrammed cells which would be totipotent and not only pluripotent[28], then a dilemma would rise in the Autonomous Community of Andalusia –indirectly also in Spain- since, scientifically speaking, no difference would be pertinent to distinguish a reprogrammed cell to be totipotent which is transferred to a human egg to generate a whole individual. In Science Daily[29], last February 12, 2008 it could be read: "University of California –Los Angeles Stem Cell Scientists have reprogrammed human skin cells into cells with the same unlimited properties as embryonic stem cells without using embryos or eggs[30]. Recent works published in 2009 would confirm this point[31].

[27] See as this regards: ZNIDARSIC, V.: "Biomedical research in Andalusia: a critical approach from Slovenia", Régimen Jurídico de la Investigación Biomédica en Andalucia (Daniel García San José coord.), Laborum, Murcia, 2009, pp. 205-206.

[28] We consider here the general sense of totipotency, that is, the ability of a single cell to generate an entire individual. See TESTA, G., BORGHESE, L., STEINBECK, J. A. and BRÜSTLE, O.: "Breakdown of the Potentiality Principle and Its Impact on Global Stem Cell Research", Cell Stem Cell (2007) 1, pp. 153-156.

[29] http://www.sciencedaily.com/releases/2008/02/080211172631.htm

[30] As it can be read in this piece of news, the UCLA study confirms the work first reported in late November 2008 of researcher Shinya Yamanaka at Kyoto University and James Thomson at the University of Wisconsin. Taken together, the three studies demonstrate that human iPS cells can be easily created by different laboratories and are likely to mark a milestone in stem cell-based regenerative medicine. Besides these new techniques to develop stem cells could potentially replace a controversial method used to reprogram cells, somatic cell nuclear transfer (SCNT), sometimes referred to as therapeutic cloning. (Cursive is ...

It is needless to say that the results of such research techniques foster those in Europe who make opposition to any kind of human stem cell research and defeats Andalusian scientists to see recognised a patent by the European Patent Office. This is so according to the ruling of its Enlarged Board of Appeal in the so called WARF case in 25 November 2008. Such a refusal for granting the European patent would be based on being morally unacceptable in some European societies and, specially, due to the fact that there no exists other means of obtaining similar results but being ethically less

added). To further reading on ethics opposition to using human eggs: DICKENSON, D.: "Good Science and good ethics: why we should discourage payment for eggs for stem cell research", Nature Review Genetics, 10 (2009) 11, p. 743.

[31] See, e.g. the work of Honguan ZHOU, Shili WU, Jin Young JOO, and others, published in Cell Stem Cell (2009) 4, pp. 381-384 (http://www.cell.com/cell-stem-cell/supplemental/S1934-5909(09)00159-3 In this study scientists have demonstrated that somatic cells (in the case, murine fibroblasts) can be fully reprogrammed into pluripotent stem cells by direct delivery of recombinant reprogramming proteins. This protein transduction method represent –in the words of its authors- a significant advance in generating iPSCs in comparison with previous iPSCs methods: "First, it effectively eliminates any risk of modifying the target cell genome by exogenous genetic sequence, which are associated with all previous iPSCs methods, and consequently offers a method for generating safer iPSCs. Second, the protein transduction method provides a substantially simpler and faster approach than the currently most advanced genetic method, which requires time-consuming sequential selection of potentially integration-free iPSCs. And finally, given the robustness and wide availability of large-scale recombinant protein production, this demonstrated completely chemically defined reprogramming regime could potentially enable broader and more economical application of reprogramming methodology."

controversial[32] as LÓPEZ MORATALLA has recently analysed in Spain[33].

We face a European context of incertitude as regards ethical implications of patenting biotechnological inventions implying the use of human embryos[34] and those more suffering it are scientists[35].

[32] It is publicly advertised by private enterprises (for instance www.advancedcell.com) some of the technologies that support their research on cellular reprogramming: somatic cell nuclear transfer, chromatin transfer and fusion technologies. From the three techniques seems to be particularly interesting the third one. In their own words: "Our fusion technologies involve the fusion of the cytoplasm of one cell into another. In the same manner that the cytoplasm of an egg cell is capable of transforming any cell back to an embryonic state, the fusion of the cytoplasm of other cell types, including differentiated cell types (such as blood cells) is capable of reprogramming another cell type (such as a skin cell)... They also have the potential to fuse the cytoplasm of undifferentiated cells, such as embryonic stem cells, with somatic cells to transport the somatic cell DNA back to pluripotency. We believe that the fusion technology we are developing can be developed into as broad and powerful a technique as SCNT, producing histocompatible, youthful stem cells that are multy and potentially even pluripotent. If successfully developed, this technology may also provide a pathway that does not utilize human egg cells which would reduce the cost of the procedure, increase the number of patients that could benefit from its implementation and bypass many of the ethical issues associated with technologies based upon or using eggs and embryos, because it does not require the creation or destruction of embryos."

[33] LÓPEZ MORATALLA, N.: "¿Resucitan al inicio de 2009 las células troncales procedentes de embriones? (Does 2009 mark a revival of embryonic stem cells?)" Cuadernos de Bioética, XX (2009) 3, pp. 471-485.

[34] It is relevant at this point to pay attention to the fact that even inside the European Group of Ethics for Sciences and New Technologies to the European Commission was impossible to reach a consensus on this topic when Opinion No. 16 on the ethical aspects of patenting inventions involving human stem cells was redacted. It was needed to include the dissident opinion of Professor Günter Virt: "Human embryonic stem cells are excluded

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It may be clarifying in this sense to evoke those informing principles which, according to the European Group of Ethics in Science and New Technologies to European Commission, would help to competent authorities of European Union countries in order to grant or to refuse granting authorisation for such kind of patents. To be as clear as possible these principles are pre-grouped in four items: Firstly, concerning the content of patents and regarding patentability of processes which imply human stem cells notwithstanding its source[36]; Secondly, as regards different origins of human stem cells[37];

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from patentability because we cannot get embryonic stem cell lines without destroying an embryo and that means without use of embryos. This use as material contradicts the dignity of an embryo as a human being with the derived right to life. If the condition for patentability is the industrial and commercial use and if the use of human embryos for industrial and commercial purposes is not patentable, then every exception, which cannot exclude industrial and commercial purposes, is against the ethical sense of the directive. Patenting is an incentive. Patentability of human embryonic stem cells and stem cell lines would push research towards embryonic stem cells and thus undermine the priority of research using non embryonic stem cells. Despite the relatively clear regulations in the directive this incentive for research will lead to forms of "bypasses" which makes it impossible to guarantee an ethically tolerable situation in the field of patentability."

[35] Just to mention some recent articles as this regard: MCLAREN, A.: "A Scientists's View of the Ethics of Human Embryonic Stem Cell Research", Cell Stem Cell (2007) 1, pp. 23-26. SUGARMAN, J. and SIEGEL, A.: "How to Determine Whether Existing Human Embryonic Stem Cell Lines Can be Used Ethically", Cell Stem Cell (2008) 3, pp. 238-239. LO, B. and PARHAM, L.: "Ethical Issues in Stem Cell Research", Endocrine Reviews 30 (2009) 3, pp. 204-213.

[36] "Isolated stem cells which have not been modified do not, as product, fulfil the legal requirements, especially with regards to industrial applications, to be seen as patentable. In addition, such isolated cells are so close to the human body, to the foetus or to the embryo they have been isolated from, that their patenting may be considered as a form of commercialisation of the human body. When unmodified stem cell lines are established,

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Thirdly, as far as methods for obtaining stem cells are concerned[38]; Finally, regarding the protection of donors, the eventual economic and social consequences and the philosophical implications of the system of patents when it is applied to stem cells[39]. This set of informing principles surrounding the patentability of biotechnological inventions implying the use of human embryos may

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they can hardly be considered as a patentable product. Such unmodified stem cell lines do not have indeed a specific use but a very large range of potential not yet described uses. Therefore, to patent such unmodified stem cell lines would also lead to too broad patents. Thus, only stem cell lines which have been modified by in vitro treatments or genetically modified so that they have acquired characteristics for specific industrial applications, fulfil the legal requirements for patentability."

[37] "Application for a patent involving human stem cells should declare which is the source of the stem cells and, considering the strong ethical concerns about the use of human embryos, processes which would lead to uses of human embryos for industrial or commercial purposes are contrary to "ordre public" and morality and not patentable."

[38] "When the donated cells may become part of a patent application, donors should be informed of the possibility of patenting and they are entitled to refuse such use. Apart from justified compensation, donors ought not to get a reward which could infringe the principle of non-commercialisation of the human body. These ethical requirements should apply as far as possible to imported stem cells."

[39] "Concerning ethical aspects of patents involving human embryonic stem cells, political and legal decisions may change the self understanding of what it means to be a human being in a given epoch and society. Furthermore, the questions of the dignity and the moral status of the embryo remain indeed highly controversial in a pluralistic society as the European Union. Those who are opposed to human embryo research, cannot, a fortiori, consider any patenting in that field. Among those who consider research on embryos ethically acceptable, some may feel great reluctance towards patenting the resulting inventions, while others consider patenting inventions derived from embryo research as acceptable, especially given the potential medical benefits."

be translated into a golden rule: it should be advisable not to authorise patents in processes implying techniques of nuclear transfer (human cloning) which are ethically controverted for a part of the European society if they entail the destruction of the human embryo. This golden rule was fully assumed by the European Patent Office in 2008 in the so called WARF case and nothing suggests a change in future.

So the question to be finally resolved concerns to the risks surrounding human reprogramming research currently in process in Andalusia (as in other parts of Spain). There is a clear difference (at least in order to future patenting) between processes for inducing adult stem cells to undergo 'retro differentiation' or 'trans differentiation'[40] from processes to create embryos by transfer of a somatic cell nucleus to an enucleated egg (cloning technique) for derivation of stem cells. Nevertheless, the Andalusian Act seems to allow firstly, the reprogramming of mature somatic adult cells to pluripotent form -and in case Science make it possible, to totipotent form- (Induced Pluripotent Cell or iPS) and secondly, using somatic cell nucleus transfer (SCNT) and cell fusion to cultivate embryonic stem cells (ESC). These adult cells reprogrammed and transferred harder and harder can be distinguished from embryonic stem cells so controversial. This is so at present more than never. As it has been

[40] Trans differentiation is the induction of adult stem cells to differentiate into cells of a tissue type different from that normally associated with the particular stem cells. Op. cit., p. 11.

commented worldwide[41], Chinese scientists published last summer two works in the journals Nature[42] and Cell Stem Cell[43] where they asserted to have created live mice from mature skin cells that had reverted to an embryonic-like state. No doubt that such scientific success could overlap controversy surrounding embryonic stem cells, and although in Andalusia the clause "exclusively for therapeutic purposes" could seem a limit for scientific research, there is a fear that it also raises new ethical issues[44]. Particularly worrying is the possibility of making clones selected for specific traits with or without individuals' consent[45]. In any case, many scientists in ant

[41] See, i.e. The Washington Post, July 24, 2009.

[42] The work of the team of scientists led by Qi ZHOU of the Chinese Academy of Sciences was published in Nature 460 (2009) 7254: 37 iPS cell lines created, three of which produced 27 live offspring, the first of which they named Tiny. One of the offspring, a 7-week-old male, went on to impregnate a female and produced young of its own.

[43] The work of the team of researchers led by Shaorong GAO of the National Institute of Biological Sciences in Beijing appeared published in Cell Stem Cell, 5 (2009) 2, 135-138: five iPS cell lines, one of which was able to produce embryos that survived until birth. Four animals were born but only one lived to adulthood.

[44] See: HENDERSON, M.: "New artificial stem cells have their own ethical issues", The Times on line, July 24 2009. http://wwwtimesonline.co.uk/tol/news/science/article6725335.ece

[45] In words of Robert LANZA, a stem cell researcher at Advanced Cell Technology in Worcester (United States): "With just a little piece of your skin, or some blood from the hospital, anyone could have your child –even an ex-girlfriend or neighbour... This isn't rocket science; with a little practice, any IVF clinic in the world could probably figure out how to get it to work. In addition, researchers could genetically engineer traits into the cells before using them to create embryos for designer babies. For instance, the technology already exists to genetically increase the muscle mass in animals by knocking out a gene ...

outside Andalusia could still consider necessary –as it is indeed- to evaluate iPS with embryonic stem cells so, controversy would remain for a while[46].

I.5. Conclusion

The nature of the topic dealt with in this Chapter prevents us from presenting definitive concluding remarks. In the way of provisional ideas, summing up the questions analysed above, we can put forward the following:

First. The situation of variable geometrical regulation in Europe as regards research on human embryonic stem cells is a reality with unknown consequences in future for human cellular reprogramming. Although doing research on induced pluripotent stem cells (IPSCs) it seem to have overcome moral objections to nuclear transfer techniques which imply destroying early-stage embryos, the key stone of the matter is the lack of a European common conception of human life and concerning the beginning of human life.

Second. It is reasonable to think that there is a risk that the distinction between somatic embryos and human embryos, in cellular

known as mystain, and could be used by a couple who wants a great child athlete." Interviewed by STEIN, R.: "Researchers May Have Found Equivalent of Embryonic Stem Cells", The Washington Post, July 24 2009.

[46] LÓPEZ MORATALLA, N.: "¿Resucitan al inicio del 2009 las células troncales procedentes de embriones?", op. cit., pp. 482-483.

reprogramming or in human cloning for therapeutic purposes respectively, will be weaker and weaker in next future. Furthermore, even though what it is at stake in the case of research in Andalusia and Spain is a somatic embryo and not properly a human embryo, as it had been normally considered up to now, science makes possible cellular reprogramming techniques without being necessary the method of somatic nuclear transfer. Consequently, situation in next future might be particularly worrying in the case of trying to patent at European level the results of research at present done in Andalusia considering the guidelines provided by the European Group of Ethics in Science and New Technologies to the European Commission and the ruling of the Enlarged Board of Appeal of the European Patent Office is the so called WARF case concerning patentability of biotechnological inventions implying the use of human embryos. That is, refusing to grant European patent for any controverted technique considered contrary to public morals and human dignity of any European society were to be proved the existence of less controverted techniques.

Third. In order to propose solutions to the problem identified in previous pages any jurist interested in Sciences of Life and, in particular, on embryo research advances, should focus its attention in identifying a common normative framework (a corpus iuris) not as far as the conception of human life or the status of embryo, but better as regards biomedical research; namely, human cloning and cell transfer and reprogramming exclusively for therapeutic purposes

on a basis of fairness[47]. That is, assuming justice as fairness in the distribution of the benefits and burdens of public policy in a pluralistic society (in this case, the European society). Four questions would implement the requirements of fairness: 1. what is the nature of the burden of those who object to a public policy supporting biomedical research? 2. What is the burden of mortality, morbidity, lost functional status, and care giving of the current standard of medical care that might be reduced by the research? 3. What is the opportunity for those who will be burdened to have access to the clinical benefits of the research? 4. When different groups are significantly burdened but in different ways, whose burden should be judged as more serious, far-reaching, and irreversible? [48]

Fourth. Juridical research on the existence of such a corpus iuris –were to exist- should pay attention to a couple of questions. Firstly, as far as regulation on what can or cannot be object of research and by which means and procedures. Secondly, as far as

[47] This is the approach suggested by authors like CHEVERNAK, F. A. and MCCULLOUGH, L. B.: "How physicians and scientists can respond responsibly and effectively to religiously based opposition to human embryonic stem cell research", Fertility and Sterility, 90 (2008) 6, pp. 2056-2059. In the same sense: SCLAEGER, Th. M. and other in the editorial of Drug Discovery Today, 12 (2007) 7/8, pp. 269-271.

[48] Ibidem, p.2057. Thus, in opinion of these authors, "Fairness does not oblige physicians and scientists to agree with the judgment that hESC research is morally burdensome, but does oblige them to take this moral burden very seriously. Physicians and scientists should not express disrespect, or worse, contempt, for opponents or attempt to define their objection away. Physicians and scientists should, however, insist that other, clinically relevant, burdens must be identified, and the opportunity for offsetting or compensating benefits must be addressed."

legal protection of results of such research techniques by way of patents. Once we have identified this European corpus iuris concerning biomedical research it will be useful to establish confining parameters (like a frame) of any national legislation in Europe in this field, by fixing the margin of how much discretional can be national authorities and private entities as well. It will also help for guaranteeing rights and freedoms of citizens and for providing security for those who do research on human embryos. To sum up, the result of this juridical work would provide security of the legality of human cloning research and cell reprogramming techniques with nuclear transfer in Europe.