

Research on Human Cells Reprogramming in Andalusia (Spain): *Quo vadis* Europe?

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Resumen / Abstract: Andalucía ostenta una especial posición dentro de España, entre el grupo de países que lideran, a nivel mundial, la investigación sobre reprogramación celular embrionaria. Las nuevas técnicas de investigación sobre reprogramación celular parecen haber superado la controversia moral y ética que rodea a otras técnicas de investigación que implican la creación/destrucción de embriones humanos en la medida en que en la reprogramación celular se estaría trabajando con embriones somáticos. Sin embargo, se advierte en estas páginas que no existiendo una común concepción de la vida humana en Europa, pueden surgir en un futuro próximo problemas de índole ético a la hora de patentar, a nivel europeo, los resultados de estas técnicas de reprogramación celular embrionaria. En este sentido, el caso WARF, resuelto el pasado 25 de noviembre de 2008, por el Órgano Colegiado de Apelaciones de la Oficina Europea de Patentes, ha suscitado cuestiones que deben ser consideradas por las autoridades andaluzas y españolas, más aún, si cabe, ahora que hemos conocido del logro de la creación de ratones en China, en 2009, mediante estas mismas técnicas de reprogramación celular.

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Andalusia has a special situation within Spain¹, among the group of countries that lead biomedical research on embryonic cell reprogramming at a global level, research which seems to have overcome the moral and ethical controversy surrounding other research techniques involving the creation-destruction of human embryos. Nevertheless, as there is no common European conception of human life, some ethical problems could emerge in the near future when it comes to patenting the results of these cell-reprogramming techniques at a European level.

Palabras clave / Keywords:

Bioderecho Internacional / Protección de la patente Europea / Convergencia de la normativa de los Estados miembros de la Unión Europea / Moralidad pública y concepción de la vida humana

International Biolaw / European patent protection / Convergence of European Union Member States' regulations / Public morality and conception of human life

1. Background and state of the problem: a *variable geometry* in Europe as regards the regulation of research using human embryonic stem cells

The *European Group on Ethics in Science and New Technologies to the European Commission* (hereinafter "EGE"), 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 geometry" among European Union Member States' regulations on human embryonic stem cells (from now on "hESC"). **Geometrical**, firstly, because it is possible to recognise four different approaches from European Union Member States on hESC research²:

— *Permissive position*: A few Member States have specific legislation for hESC research, covering the procurement of stem cells and their use

¹ Special, I mean, by taking into consideration that the Autonomous Community of Andalusia has competence under the Spanish Constitution and its *Statute* to carry out research on human cells. *Vide* the Andalusian Law 1/2007, of 16 March, governing research on cellular reprogramming exclusively for therapeutic purposes in Andalusia (BOE, Official State Gazette, No. 89, 13 April 2007, pp. 16299 to 16302). It can be consulted in English at <http://www.grupo.us.es/biodeinter>

At national level, biomedical research is regulated by the Spanish Law 14/2007, of 3 July, on Biomedical Research (BOE No. 159, 4 July 2007). It can be consulted in English at: <http://www.catedraderechoygenomahumano.es/images/novedades/Spanish%20Law%20on%20Biomedical%20Research.pdf>

² Recommendations on the ethical review of hESC FP7 research projects, Opinion No. 22, 2007, pp. 29ff. Available at: http://ec.europa.eu/european_group_ethics/publications/docs/opinion_22_final_follow_up_en.pdf

- 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 EU Member States such as the Czech Republic, Denmark, Finland, France, Greece, the Netherlands and Portugal, regulations allow the derivation of new hESCs from embryos created as a result of Assisted Reproductive 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 debate has arisen as to whether the 2002 Stem Cell Act regulating the importation of hESC lines should be revised, but no legal proposal had been forthcoming by the time of these Recommendations. Italian legislation covers Artificial Reproductive Technology and the production of new hESC (research involving the destruction of embryos is not allowed). Italy has therefore no legal provision as regards the use of imported hESC or existing hESC.
 - *No specific legislation or indirect legislation only*: In many Member States, hESC research still has no specific legislation (Bulgaria, Cyprus, Estonia, Ireland, Luxembourg, 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* fertilisation. Some other European Union Member States have no 'specific' regulation on hESC research, but have explicitly indicated that they are against it (Austria, Lithuania, Malta, Poland and Slovakia) by voting against hESC research during the Council decision on FP7. Finally, in some countries hESC is at present regulated only by indirect legislation on embryo research (Hungary and Slovenia) but without specific references to hESCs.

Variable, secondly, because it is evident that Science moves faster than Law and this situation (described by the EGE in its Opinion No. 22) should be updated today, for example in the case of Germany³.

³ 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 1 May 2007 (and not only those created before 1 January 2002). Notwithstanding, big changes are not expected in the near future and the lack of harmonisation still continues 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"; DRUMML, Christiane, "Stem Cell Research: Toward Greater Unity in Europe?", in *Cell*, Volume 139, Issue 4, 2009, p. 651.

The situation outlined above has important effects⁴ and juridical consequences as far as commercialisation and patenting in Europe is concerned. A debate on patenting hESCs has been ongoing at both institutional (European Patent Office, the European Commission) and academic levels. And although the Directive on the legal protection of biotechnological inventions (98/44/EC⁵) regulates the patentability of biological material, including hESCs, it is also true that there is no European Union consensus on the moral status of embryos and their products. Consequently, reflecting this wide diversity of moral cultures, there are different policies for patenting among national patent offices which may make it difficult to achieve a European patent consensus in this respect. The *EGE* evaluated it so in its Opinion No. 16 "Ethical aspects involving the patenting of human stem cells", and the Enlarged Board of Appeal ("EBoA") at the European Patent Office coincided on this point in its Decision of 25 November 2008 in the so-called *WARF* case. This was the 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 in 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, and it was prohibited by the European Patent Convention and by the EU Biotechnology Directive (98/44/EC)⁶.

2. The key issue: the lack of a common European conception of human life and of the beginning of human life

In its Opinion No. 22, the *EGE* expressed the view, in the ethical review of hESC FP7 research projects, that "as far as human embryonic stem cell 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 "subsidi-

ary" model) to regulate hESC research at European Union level is therefore taking place within and across several European Union Member States."⁷ *Nihil nobis sub sole*. The European Court of Human Rights, ruling as a Grand Chamber, said something very similar in the case of *VO v. France* some years before⁸. 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 asserted 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 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."⁹ It is a case-law confirmed in the case *Evans v. United Kingdom*, judgments of 7 March 2006 (Chamber) and of 10 April 2007 (Grand Chamber)¹⁰. In both judgments the European Court of Human Rights eventually refused to recognise the right to life of human embryos under Article 2 of the European Convention of Human Rights. Furthermore, this Court even practised self-restraint and proved unwilling to pass judgment, at European level, on the question concerning the beginning of human life, taking into consideration the wide margin of appreciation that European countries have been recognized on the matter.

⁷ *Op. cit.*, p. 38.

⁸ Judgment of 8 July, 2004. The case concerned an application brought by a French national, Mrs Thi-Nho VO who, on 27 November 1991, attended 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 about 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.

⁹ Paragraphs 82ff. of the Judgment. The European Court of Human Rights also recalled that not even the Convention on Human Rights and Biomedicine of 1997 (the Oviedo Convention) nor its Additional Protocol of 2005 concerning Biomedical Research include a definition of a human being or of a person.

¹⁰ See Paragraphs 45 to 47 of the former and Paragraphs 54 to 56 of the latter.

⁴ See: NIPPERT, Irmgard, "The pros and cons of human therapeutic cloning in the public debate", in *Journal of Biotechnology*, Volume 98, Issue 1, 2002, pp. 53-60. See also: PLOMER, Aurora, "The European Group on Ethics: law, politics and the limits of moral integration in Europe", in *European Law Journal*, Volume 14, Issue 6, 2008, p. 859.

⁵ Official Journal L213, 30/07/1998, pp. 13-21.

⁶ Decision available at: <http://www.epo.org/topics/news/2008/20081127.html>

3. Biomedical research in Andalusia: human cloning and cell reprogramming exclusively for therapeutic reasons

The Autonomous Community of Andalusia has been a pioneer in Spain by enacting a legal framework for research on cloning for therapeutic purposes¹¹ and, in particular, with regard to research on cellular reprogramming exclusively for therapeutic purposes with the above-cited Law 1/2007 of 16 March 2007¹². To understand such a legislative path, we have to take into consideration several provisions in the *Andalusian Statute of Autonomy*, a kind of Regional Government's Constitution¹³. It was precisely according to these provisions concerning research in the *Andalusian Statute of Autonomy*¹⁴ that Law 16/2007, of 3 December 2007, concerning Science and Knowledge in Andalusia, was passed¹⁵. As regards specific biomedical research in Andalusia, these legal initiatives, though recent ones, are nevertheless old fashioned. It is true that Science moves faster than Law, which is always lagging behind the facts. In the case of Andalusia, this is especially true due to the specific intention of Regional Legislators to provide a legal framework mainly for the research already started in Andalusia by Dr. Bernat Soria with three germinal cell lines brought to him from the Karolinska Institute of Sweden in 2003.

¹¹ See Law 7/2003 of 20 October 2003, by which research in Andalusia with human pre-embryos non valid for IVF was regulated. (BOJA, Official Journal of Andalusia, No. 210, 21 October, 2003).

¹² From 2006 (See: TAKAHASHI, Kazutoshi and YAMANAKA, Shinya, "Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors", in *Cell*, No. 126, 2006, pp. 663-667.) up to the present with third generation of protein-induced pluripotent stem cells, also called piPS. For a general overview, see: STEIN, Rob, "Researchers May Have Found Equivalent to Embryonic Stem Cells", in *The Washington Post*, July 24, 2009.

¹³ Provisions approved by Organic Law 2/2007 of 19 March 2007.

¹⁴ Article 10.3.11 of the *Andalusian Statute of Autonomy* states that one of the main basic objectives of this Autonomous Community is industrial and technological development based on innovation, scientific research, public and private initiatives, energy sufficiency and quality assessment as the basis for the harmonious development of Andalusia. Art. 37.1.13 of the Statute also envisages the encouragement of the capacity to foster star projects, research and innovation as one of the guiding principles of public policy in Andalusia. Articles 54 and 55 are also relevant. The former stipulates that the autonomous competences of Andalusia cover up to "a) fixing proper lines of research and the control and evaluation of projects; b) the organisation, functioning, control, monitoring and accreditation of research centres in Andalusia (...)". The latter provision asserts that the Autonomous Community of Andalusia is competent to do research for therapeutic purposes, notwithstanding general coordination at state level by the Central Government of Spain.

¹⁵ BOE No. 20, 23 January, 2008, pp. 4455-4467.

Thus, contrary to the option assumed at national level¹⁶, the Autonomous Authorities in Andalusia preferred a concise law ready to provide legal cover for research on human cell reprogramming exclusively for therapeutic reasons immediately. To mention only some examples to support this assessment, Law 14/2007 on Biomedical Research in Spain regulates vital aspects of research in this field, such as compensation for damages and its assurance to persons as a consequence of their participation in this kind of research (Article 18); it contemplates specific situations such as research during pregnancy and lactation or as regards protection of persons without the capacity to provide their consent (Articles 19 to 21); Law 14/2007 also regulates the creation of a Guarantees Commission for the creation of Biobanks (Articles 63 to 71); it stipulates in detail a regime of infractions, sanctions and compensations for damages in Title IV (Articles 72 to 76). It is also remarkable for Law 14/2007 to have included a clause in Article 89 which, in my opinion, is unduly absent in Andalusian Law 1/2007, which considers that concern for knowledge transfer and, thus, for patenting the results of biomedical research is shared at national and regional level¹⁷.

The comparison between both laws on human cell research at national and regional level shows how Legislators adopted such a different approach in the case of the Andalusian Autonomous Community. This would normally have no major consequences, but in this case it definitely can since some questions not covered in the Andalusian Law, which has been dealt with in the national legislation, may have a negative influence on biomedical research in Andalusia. To give an example, Article 78.1.d) of Law 14/2007 provides as competence of the *Spanish Committee on Bioethics* to: "(...) d) Represent Spain in the supranational and international forums and organisations that deal with Bioethics." As is evident, there is no mention of the possibility of Autonomous Communities like Andalusia to express their opinion – if only indirectly – or their right to be informed of issues discussed at international level by the Spanish Government, even though these issues may include some matters of

¹⁶ Law 14/2007 of 3 July 2007 on Biomedical Research in Spain was passed only three months later than 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 having been conceived as a norm of reference in this field, and so, covering as many present and envisaged questions as possible.

¹⁷ Pursuant to Art. 89 "(...) 4. Likewise, measures shall be taken that contribute to promote adequate returns to the National Health System in relation to the investments undertaken in the ambit of biomedical research."

their exclusive competence¹⁸. Further evidence of eventual negative implications for biomedical research in Andalusia is the risk of intrusion of Central Authorities into the competences of Regional Government by way of the previous and favourable report of the *Guarantees Commission for the Donation and Use of Human Cells and Tissues* for those research projects which deal, in whole or in part, with matters listed in Law 14/2007 (practically all possible matters concerning human stem cells). Article 37 of Law 14/2007 is clear when it establishes a relation of hierarchy of the *Guarantees Commission for the Donation and Use of Human Cells and Tissues* over any other commission which could be created in the Autonomous Communities of Spain¹⁹. Furthermore, Article 17 of this Law includes a specific mandate to competent Autonomic Commissions to temporarily suspend authorised research in cases where the requirements provided by this Law are not met and when it is necessary to protect the rights of citizens. Temporary suspension of a research project authorised in Andalusia under Law 1/2007, which regulates research on cellular reprogramming for therapeutic purposes, could be ordered, for instance, when the undertaking of such research would entail an invasive procedure in human beings and there was no assurance of the general and special damages that could be derived for the person who the research had been carried out on. Andalusian Law 1/2007 does not require such assurance but Article 18 of Law 14/2007 does.

Moreover and importantly, we have already had the opportunity to express our concern that Andalusian Law 1/2007 of 16 March 2007 regulating Research on Cellular Reprogramming exclusively for therapeutic reasons would run the risk of being perceived as a potentially illegal law in comparison to the Spanish Law on Biomedical Research, taking

into consideration 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)²⁰. In my opinion, such a risk derives from the ambiguity in expressing the object of Andalusian Law 1/2007.

Article 1 of Law 1/2007 explains what the purpose of this Law is: Besides the creation of the Committee for Research on Cellular Reprogramming, it is intended "To regulate research in the Autonomous Community of Andalusia through the use of cellular reprogramming techniques in human somatic cells, in order to change them into pluripotent stem cells with exclusive therapeutic purposes." The risk pointed out emerges from reading this provision together with Article 2 "Definitions", namely, letters d)²¹ and f) (providing the definition of somatic pre-embryo)²² in the light of Part II of the Preamble of this Law²³.

In view of the Preamble of Law 1/2007, namely, the third paragraph from the end²⁴, definitions of cell nuclear transfer and of a somatic pre-embryo in letters e) and f), respectively, of Article 2 of this Law, seem to be confusing. According to this latter provision, cell nuclear transfer is a

²⁰ Signed in Oviedo the 4th April, 1997 (BOE No. 251 of 20 October 1999). For further development, see my work: GARCÍA SAN JOSÉ, Daniel, *Bioderecho en Andalucía*, Centro de Estudios Andaluces, Consejería de la Presidencia, Junta de Andalucía, Sevilla, 2009.

²¹ 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 the point of changing into a pluripotent cell which can later change into different kinds of cells, tissues or even organs.

²² By which "Somatic pre-embryo" is considered to be a group of cells resulting from successive division of the cellular form created through cellular reprogramming techniques, such as nuclear transfer or other similar techniques, from the moment such a technique is applied and up to fourteen days after.

²³ "So-called nuclear transfer has achieved notable development among cellular reprogramming techniques for its feasibility and reproductive capacity. This technique consists of the transfer of the nucleus of a somatic cell to the cytoplasm of a previously enucleated oocyte. 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 the 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, given the case that research progresses duly, these cells or tissues to be used in the future to replace those irreversibly damaged by a degenerative illness, by working with a cell from the same person."

²⁴ "The Autonomic Commission on Ethics and Medical Research in Andalusia emitted an opinion favourable to Biomedical Research by way of nuclear transfer with therapeutic purposes, when it was asked by the Andalusian Government to develop the regulatory guidelines to make these research techniques possible."

¹⁸ The belief of a long-term "political marriage" between Central and Regional Governments in more recent years might explain why the Andalusian Authorities do not seem to be worried at this point. In my opinion, in case political change should occur, Law 1/2007 should have included – on the basis of Articles 54.3 and 45.3 of the Andalusian *Statute of Autonomy* – that "Andalusia expresses its will and determination to participate, in collaboration with the *Spanish Committee on Bioethics*, in the supranational and international forums and organisations that deal with Bioethics."

¹⁹ Pursuant to Article 37: Creation of the Commission. 1. A Guarantees Commission for the Donation and Use of Human Cells and Tissues is created as the association composed of several persons, assigned to the Institute of Health Carlos III, of a permanent and consultative nature, aimed at providing counsel and guidance on the research and experimentation with human embryonic biological samples and to contribute to the updating and dissemination of the scientific and technical knowledge in this matter. 2. *The counterpart commissions that are created in the Autonomous Communities shall be considered as commissions to provide support and reference to the Guarantees Commission for the Donation and Use of Human Cells and Tissues and shall collaborate with it in the exercise of its functions.* (Italics added)

cellular reprogramming technique consisting of the transfer of the nucleus of a somatic cell to the cytoplasm of a previously enucleated oocyte. Similarly, a somatic pre-embryo would be a group of cells resulting from successive division of the cellular form created through cellular reprogramming techniques, such as 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 the Preamble could easily be misunderstood, as if it were considering human cloning for therapeutic purposes and, given the fact that the creation of pre-embryos and embryos for research purposes is prohibited in Spain, the cell nuclear transfer technique would have been mixed up with reprogramming techniques in order to use the concept of somatic pre-embryo instead of human pre-embryo. So, such techniques would not be formally illegal although they would be in another context. It is easy to find reasons for someone making such a mistake of interpretation of Law 1/2007: reprogrammed cells were not just functionally identical to embryonic stem cells (at least this was true in 2007) and although the future was promising in terms of advances in research on induced pluripotent stem cells (iPSCs), any scientist in the world would agree on the necessity of keeping on working on embryonic stem cells – regardless of the fact that they are ethically sensitive – 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 Legislators have no intention of doing anything illegal. Law 14/2007 of 3 July 2007 on Biomedical Research in Spain, recalls in paragraph 3 of its 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 under the terms provided by this law”.

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, under the terms provided by this law, including the activation of oocytes through nuclear transfer”.

Furthermore, Law 14/2007 is 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 (the Oviedo Convention), whose Article 18.2 stipulates: “The creation of human embryos for research purposes is prohibited”.

Moreover, the risk of confusion we have pointed out might be due to the unfortunate wording of Article 33 of Law 14/2007 on Biomedical Research in Spain. This provision raises doubts as to whether any technique of obtaining human stem cells is allowed, including the activation of oocytes by way of nuclear transfer for therapeutic and research purposes or if, on the contrary, the correct meaning of such a provision is to allow human stem cells to be obtained providing no pre-embryo or embryo is created, including in such prohibition the activation of oocytes by way of nuclear transfer of somatic cells²⁵. To be honest, such confusion should not occur if we take into consideration the mention made in Article 4 of Law 1/2007 to an Additional Protocol to the Oviedo Convention, concerning the prohibition of cloning of human beings²⁶:

“According to the Additional Protocol to the Convention of 4 April 1997 for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine, by which the cloning of human beings is forbidden, this Law forbids undertaking research with cellular reprogramming techniques with somatic cells to generate pre-embryos for reproductive purposes. It is also forbidden to carry out research with these techniques for any other purpose apart from that authorised in this Law.”

Risk of confusion, however, is still present because if the object of Andalusian Law 1/2007 is prescribed in Article 1 as allowing to do research on cellular reprogramming exclusively for therapeutic purposes, one may wonder what those other purposes referred to in Article 4 of Law 1/2007 are. As far as our knowledge is concerned, human cloning

²⁵ In my opinion, this is a real risk. In this sense, it is only necessary to recall Opinion No. 22 of the EGE, where Spain was referred to as a country allowing the creation of human embryos exclusively for research purposes, like the United Kingdom and Sweden. *Recommendations on the Ethical Review of hESC FP7 Research projects, op. cit., p. 32.*

²⁶ Some authors also consider the prohibition of creating human pre-embryos is not only for reproductive purposes but also for therapeutic purposes. See: ZNIDARSIĆ, Viktorija, “Biomedical research in Andalusia: a critical approach from Slovenia”, in *Régimen Jurídico de la investigación biomédica en Andalucía*, Daniel GARCÍA SAN JOSÉ (Coord.), Editorial Laborum, Murcia, 2009, p. 206

may be reproductive or for therapeutic purposes, so we can hardly 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 the Preamble of the same Law.

It is true that the aim of activating oocytes with nuclear transfer of reprogrammed adult somatic cells is not to create human embryos but an embryoid body, something different²⁷ for most authors²⁸ but not unanimously²⁹. However, if Science keeps advancing at the present rate, making it possible to create human pre-embryos and embryos with the technique of nuclear transfer of reprogrammed adult cells which would be *totipotent* and not only *pluripotent*³⁰, then a dilemma would rise in the Autonomous Community of Andalusia – and indirectly also in Spain. In such a case, Autonomic commissions and committees with competence in this field, namely, the Committee for Research on Cellular Reprogramming, could make a literal interpretation of Law 1/2007 and consider that nuclear transfer of reprogrammed adult somatic cells is authorised even in the case of a human pre-embryo (still called somatic pre-embryo) being created exclusively for therapeutic purposes³¹. When this happens, a situation of illegality would arise in relation to Law 14/2007 on Biomedical Research in Spain (Preamble and Article 33) and it would generate the international responsibility of Spain for the violation of obligations assumed under Article 18 of the Oviedo Convention. Needless to say that the results of such re-

search techniques could hardly be recognised through a patent issued by the European Patent Office, according to the ruling of its Enlarged Board of Appeal in the so-called *WARF* case on 25 November 2008. Such a refusal to grant a European patent would be based on being morally unacceptable in some European societies and, especially, due to the fact that there now exist other means of obtaining similar results while being ethically less controversial³², as LÓPEZ MORATALLA has recently analysed³³.

In *Science Daily*³⁴, on February 12, 2008, the following 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 eggs³⁵. Recent works published in 2009 would confirm this issue³⁶."

³² Some private enterprises, for instance, Advanced Cell Technology (for further development: <http://www.advancedcell.com/>) publicly advertise some of the technologies that support their research on cellular reprogramming: somatic cell nuclear transfer, chromatin transfer and fusion technologies. Among these three techniques, the third one seems to be particularly interesting. 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 multi 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, Natalia, "¿Resucitan al inicio del 2009 las células troncales procedentes de embriones? Does 2009 mark a revival of embryonic stem cells?", in *Cuadernos de Bioética (Ejemplar dedicado a: «Bioética y Con-ciencia»)*, Vol. 20, No. 70, 2009, pp. 471-486.

³⁴ Available at: <http://www.sciencedaily.com/releases/2008/02/080211172631.htm>

³⁵ As it can be read in this news item, 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, SCNT, sometimes referred to as therapeutic cloning.* (Italics added). For further reading on ethical opposition to using human eggs, see: DICKENSON, Donna, "Good Science and good ethics: why we should discourage payment for eggs for stem cell research", in *Nature Review Genetics*, Volume 10, Issue 11, 2009, p. 743.

³⁶ See, for example, the work of ZHOU, Honguan, WU, Shili, *et al.*, "Generation of Induced Pluripotent Stem Cells Using Recombinant Proteins", in *Cell Stem Cell*, Volume 4, Issue 5, 2009, pp. 381-384 (Available at: <http://www.cell.com/cell-stem-cell/supplemental/>

²⁷ 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 iPSC derivatives incorporated all across their bodies with 10-90% chimerism. Available at: http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell

²⁸ See, for instance: LÓPEZ MORATALLA, Natalia, "Clonación terapéutica", in *Persona y Bioética*, No. 22, 2004. Available at: <http://palabraclave.unisabana.edu.co/index.php/personaybioetica/article/view/893>

²⁹ See, in this respect: ZNIDARSIC, Viktorija, "Biomedical research in Andalusia: a critical approach from Slovenia", *op. cit.*, pp. 205-206.

³⁰ We consider here the general sense of totipotency, that is to say, the ability of a single cell to generate an entire individual. See: TESTA, Giuseppe, BORGHESE, Lodovica, STEINBECK, Julius A. and BRUSTLE, Oliver, "Breakdown of the Potentiality Principle and Its Impact on Global Stem Cell Research", in *Cell Stem Cell*, Volume 1, Issue 2, 2007, pp. 153-156.

³¹ That is, not just to germinate specific lines of stem cells but any human body cell and thus, ready to derive in chimeric embryos, as was already successfully achieved in China in 2009 with chimeric mice.

We face a European context of uncertainty as regards the ethical implications of patenting biotechnological inventions involving the use of human embryos³⁷ and those who are suffering most from this are our scientists³⁸. It may be clarifying, in this sense, to evoke those *informing principles* which, according to the *EGE* would be of help to the competent authorities of European Union countries when it comes to granting or refusing to grant authorisation for such kinds of patents³⁹:

S1934-5909(09)00159-3). In this study scientists have demonstrated that somatic cells (in this case, murine fibroblasts) can be fully reprogrammed into pluripotent stem cells by direct delivery of recombinant reprogramming proteins. This protein transduction method represents – in the words of its authors - a significant advance in generating iPSCs in comparison with previous iPSC methods: "First, it effectively eliminates any risk of modifying the target cell genome by exogenous genetic sequence, which is associated with all previous iPSC 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."

³⁷ It is relevant at this point to pay attention to the fact that even inside the *EGE* it 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 written. It was necessary to include the dissident opinion of Professor Günter Virt: "Human embryonic stem cells are excluded 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."

³⁸ Just to mention some recent articles in this respect: MCLAREN, Anne, "A Scientist's View of the Ethics of Human Embryonic Stem Cell Research", in *Cell Stem Cell*, Volume 1, Issue 1, 2007, pp. 23-26. SUGARMAN, Jeremy and SIEGEL, Andrew, "How to Determine Whether Existing Human Embryonic Stem Cell Lines Can be Used Ethically", in *Cell Stem Cell*, Volume 3, Issue 3, 2008, pp. 238-239. LO, Bernard and PARHAM, Lindsay, "Ethical Issues in Stem Cell Research", in *Endocrine Reviews*, Volume 30, Issue 3, 2009, pp. 204-213.

³⁹ In order to be as clear as possible, these principles are pre-grouped in four items: First, concerning the content of patents and regarding the patentability of processes which involve human stem cells notwithstanding their source; second, as regards different origins of human stem cells; third, concerning methods for obtaining stem cells; and finally, with regard to 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.

1. Isolated stem cells which have not been modified do not, as products, fulfill 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, they can hardly be considered as a patentable product. Such unmodified stem cell lines do not in fact have a specific use but rather a very large range of potential, but not yet described, uses. Therefore, to patent such unmodified stem cell lines would also lead to too broad claims. 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, fulfill the legal requirements for patentability.

2. Application for a patent involving human stem cells should declare what the source of the stem cells was 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 "public order" and morality and not patentable.

3. When 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 cells⁴⁰.

4. With regard to 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 era and society. Furthermore, questions of the dignity and the moral status of the embryo remain indeed highly controversial in such 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 benefits⁴¹.

⁴⁰ *Ibid.*, p. 17.

⁴¹ *Ibid.*, p. 13.

This set of *informing principles* surrounding the patentability of biotechnological inventions involving the use of human embryos may be translated into a golden rule: it would be advisable not to authorise patents in processes involving techniques of nuclear transfer (human cloning) which are ethically controversial for part of 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 the future.

So the question that remains to be resolved concerns what is authorised under the Andalusian Law⁴². As a jurist, I recognise my lack of in-depth knowledge in this scientific field but, as the *EGE* has commented in its Opinion No. 16 of 7 May 2002 on ethical aspects of patenting inventions involving human stem cells, there is a clear difference (at least with regard to future patenting) between processes for inducing adult stem cells to undergo 'retro-differentiation' or 'transdifferentiation'⁴³ and processes to create embryos by transfer of a somatic cell nucleus to an enucleated egg (cloning technique) for the derivation of stem cells. Thus, according to the Andalusian Law, it seems to be allowed to reprogram mature somatic adult cells to pluripotent form (Induced Pluripotent Cell or iPS) and then, using SCNT and cell fusion to cultivate embryonic stem cells (ESC). These reprogrammed and transferred adult cells can hardly be distinguished from the embryonic stem cells which are so controversial. The truth of previous statement seems more evident at present than it was ever before. In effect, as it has been commented worldwide⁴⁴, Chinese scientists published two works last summer in the journals *Nature*⁴⁵ and

*Cell Stem Cell*⁴⁶ where they claimed to have created live mice from mature skin cells that had reverted to an embryonic-like state. No doubt that such scientific success could affect the controversy surrounding embryonic stem cells, and although in Andalusia the clause "exclusively for therapeutic purposes" would seem to impose a limit for scientific research, there is a fear that it also raises new ethical issues⁴⁷. What is particularly worrying is the possibility of making clones selected for specific traits with or without individuals' consent⁴⁸. In any case, many scientists inside and outside Andalusia could still consider it necessary – as indeed it is – to equate iPS with embryonic stem cells, so controversy would remain for a while⁴⁹.

In terms of proposing solutions to the problem identified above, any jurist interested in Life Sciences and, in particular, in advances in embryo research, should focus his or her attention on identifying a common normative framework (*a corpus iuris*), not to the extent of defining the conception of human life or the status of an embryo, but rather as regards biomedical research; namely, human cloning and cell transfer and reprogramming exclusively for therapeutic purposes on a basis of fairness⁵⁰.

⁴⁶ The work of the team of researchers led by Shaorong GAO of the National Institute of Biological Sciences in Beijing: "iPS Cells can Support Full-Term Development of Tetraploid Blastocyst-Complemented Embryos", appeared published in *Cell Stem Cell*, Volume 5, Issue 2, 2009, pp. 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.

⁴⁷ See: HENDERSON, Mark, "New artificial stem cells have their own ethical issues", in *The Times* (Online version), July 24, 2009. Available at: <http://www.timesonline.co.uk/tol/news/science/article6725335.ece>

⁴⁸ In words of Dr. 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 known as myostatin, and could be used by a couple who wants a great child athlete." Interviewed by STEIN, Rob, "Researchers May Have Found Equivalent to Embryonic Stem Cells", in *The Washington Post*, July 24, 2009.

⁴⁹ LÓPEZ MORATALLA, Natalia, "¿Resucitan al inicio del 2009 las células troncales procedentes de embriones? Does 2009 mark a revival of embryonic stem cells?", *Op. cit.*, pp. 482-483.

⁵⁰ This is the approach suggested by authors such as: CHERVENAK, Frank A and McCULLOUGH, Laurence B, "How physicians and scientists can respond responsibly and effectively to religiously based opposition to human embryonic stem cell research", in *Fertility and Sterility*, Volume 90, Issue 6, 2008, pp. 2056-2059. In the same sense: SCHLAEGER, Thorsten M, LENSCH, M William and TAYLOR, Patrick L, "Science aside: the trajectory of embryonic stem cell research in the USA", in *Drug Discovery Today*, Volume 12, Issue 7-8, 2007, pp. 269-271.

⁴² It is a serious question and, because of this, somehow inconvenient at present. As it was referred to, in a regional newspaper "*El Correo de Andalucía*", last 17 February 2010, the Andalusian Department of Health has signed a contract with the University of Michigan to create induced pluripotent cells in Andalusia, under the direction of Dr. José Cibelli. Nevertheless, the first lines of this piece of news suggest the answer: "Andalucía contará desde este año con un laboratorio destinado a la producción de células clonadas" (italics from the original) ("From 2010 Andalusia will have a laboratory for producing cloned cells").

⁴³ Transdifferentiation 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.

⁴⁴ See, for example, *The Washington Post*, July 24, 2009.

⁴⁵ The work of the team of scientists led by Qi ZHOU of the Chinese Academy of Sciences: "iPS cells procedure viable mice through tetraploid complementation", was published in *Nature* No. 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.

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 measure and help 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 in different ways, whose burden should be judged as more serious, far-reaching, and irreversible?⁵¹

Juridical research on the existence of such a *corpus iuris* should pay attention to a couple of questions. Firstly, regarding the regulation of what can or cannot be the object of research, and by which means and procedures. Secondly, with respect to the legal protection of the results of such research techniques by way of patents. Once we have identified this European *corpus iuris* concerning biomedical research, it would be useful to establish confining parameters (like a framework) of any national legislation in Europe in this field, by fixing the margin of how much discretion can be given to national authorities and also to private entities. It would also help in guaranteeing the rights and freedoms of citizens and for providing security for those carrying out 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 Andalusia and Spain.

4. Concluding remarks

The nature of the topic dealt with in this article 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:

⁵¹ *Ibid.*, 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."

- a. The situation of *variable geometry* in Europe, at national and supranational level, as regards the regulation of research using human embryonic stem cells, is a reality with unknown consequences for future research on cellular reprogramming. Although research with induced pluripotent stem cells (iPSCs) seems to overcome moral objections to nuclear transfer techniques which involve destroying early-stage embryos, the cornerstone of the matter is the lack of a common European conception of human life and of determining when human life begins.
- b. Bearing in mind that Science advances faster than Law, which is always lagging behind the facts, it is reasonable to think that there is a risk that the distinction between somatic embryos and human embryos, in cellular reprogramming or in human cloning for therapeutic purposes respectively, will be weaker and weaker in the near future. The recent works of two Chinese teams of scientists, published in *Nature* and in *Cell Stem Cell* in 2009, informing that they have created live mice from mature skin cells that they had reverted to an embryonic-like state, should be seen as evidence of such a risk.
- c. The situation we envisage in the near future is particularly worrying in the case of research currently being carried out in Andalusia, because we have tried to prove the inconsistency of the wording of Andalusian Law 1/2007 governing research on cellular reprogramming exclusively for therapeutic purposes. In addition, this is especially so considering the guidelines provided by the EGE and the ruling of the *Enlarged Board of Appeal of the European Patent Office* in the so-called *WARF case* concerning the patentability of biotechnological inventions involving the use of human embryos.
- d. Jurists interested in Life Sciences and, in particular, concerned by embryo research advances, should focus their attention on identifying a common European normative framework (a *corpus iuris*) on the basis of fairness, not to the extent of defining the conception of human life or the status of an embryo, but rather as regards biomedical research on human cloning and on cellular transfer and reprogramming exclusively for therapeutic purposes. That is, assuming justice as fairness in the distribution of the benefits and burdens of public policy in a pluralistic society like European society.
- e. According to Article 2 of Law 1/2007, cellular reprogramming techniques in Andalusia involve the nuclear transfer of reprogrammed somatic cells. That is, the same technique used in clon-

ing the sheep Dolly and the one for which a European patent was not granted in 2008 in the so-called *WARF* case, although what it is at stake is a somatic embryo and not really a proper human embryo, as had normally been considered to be the case up to now. Science makes cellular reprogramming techniques possible without the necessity of using the somatic nuclear transfer method. From a scientific point of view, there is no problem in assuming the need to keep on working on embryonic stem cells – even if it is an ethically sensitive issue – as well as on adult stem cells and on reprogrammed adult cells, because it still remains unclear which of them will eventually prove most effective. Unfortunately or not, it is not only the concern of scientists alone but also of society at large. Then, Law makes its appearance, even with the best of intentions, to provide further complexity to the matter. In the end, it could turn into a question of political choice, where Law does not reach and where the only thing we can do is to wonder: *Quo vadis* Europe?

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