ARTIGO

LEGAL STATUS OF EMBRYO GENE-EDITING IN SPAIN IN THE LIGHT OF CONTROVERSIAL PRACTICES INVOLVING HUMAN GERMLINE

STATUS LEGAL DA EDIÇÃO DE GENES DE EMBRIÕES NA ESPANHA À LUZ DE PRÁTICAS CONTROVERSAS ENVOLVENDO A LINHA GERMINAL HUMANA

SITUACIÓN JURÍDICA DE LA EDICIÓN GENÉTICA DE EMBRIONES EN ESPAÑA A LA LUZ DE LAS CONTROVERTIDAS PRÁCTICAS RELACIONADAS CON LA LÍNEA GERMINAL HUMANA

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ABSTRACT:
This article examines the controversial insertion of primate DNA into human embryos at a Chinese research center, led by scientist Juan Carlos Izpisua. The creation of a human-monkey "chimera" for studying early embryonic development raises significant ethical and bioethical questions, particularly regarding gene editing technologies such as CRISPR. The article explores the impact of these techniques on precise genome modification, considering their ethical and regulatory implications. It suggests a

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discussion on the potential for a moratorium on experiments altering the human germline, especially in light of contentious events such as the birth of genetically edited twins in China. Legal challenges, Spanish and EU legislation, and issues related to donor anonymity and privacy are also analyzed. The conclusion emphasizes the urgent need for more robust regulations in response to the rapid advancement of gene editing.

KEYWORDS: Gene editing. Germline modification. Bioethics

RESUMO:
Este artigo examina a controversa inserção de DNA de primatas em embriões humanos no centro de pesquisa chinês liderado pelo cientista Juan Carlos Izpisua. A criação de uma "quimera" humano-macaco, destinada a estudar estágios iniciais do desenvolvimento embrionário, levanta importantes questões éticas e bioéticas, especialmente em relação às tecnologias de edição genética, como CRISPR. O impacto dessas técnicas na modificação precisa de genomas é abordado, considerando suas implicações éticas e regulatórias. O artigo propõe a discussão sobre a possibilidade de um moratório em experimentos que alteram o germline humano, em meio a eventos controversos, como o nascimento de gêmeas chinesas com embriões geneticamente editados. Além disso, são analisados desafios legais, legislação espanhola e da UE, bem como questões relacionadas à proteção da privacidade e ao anonimato do doador. A conclusão destaca a necessidade urgente de regulamentações mais robustas diante do rápido avanço da edição genética.

PALAVRAS-CHAVE: Edição de genes. Modificação do germline. Bioética

RESUMEN
Este artículo examina la polémica inserción de ADN de primate en embriones humanos en el centro de investigación chino dirigido por el científico Juan Carlos Izpisua. La creación de una "quimera" humano-simio, concebida para estudiar las primeras etapas del desarrollo embrionario, plantea importantes cuestiones éticas y bioéticas, especialmente en relación con tecnologías de edición genética como CRISPR. Se aborda el impacto de estas técnicas en la modificación precisa de genomas, considerando sus implicaciones éticas y normativas. El artículo propone un debate sobre la posibilidad de una moratoria de los experimentos que alteran la línea germinal humana, en medio de acontecimientos controvertidos como el nacimiento de gemelos chinos con embriones editados genéticamente. Además, se analizan los desafíos legales, la legislación española y comunitaria, así como cuestiones relacionadas con la protección de la privacidad y el anonimato de los donantes. La conclusión subraya la urgente necesidad de una normativa más sólida ante el rápido avance de la edición genética.

PALABRAS CLAVES: Edición de genes. Modificación del germline. Bioética

1. INTRODUCTION

At the time of writing this paper, the insertion of primates´ DNA in human embryos in China research centre, as announced by an international researcher team

led by the Spanish scientist Juan Carlos Izpisua[2] , has proven to be highly controversial. As a result, a human-monkey "chimera" viable for 20 days was developed with the aim of studying critical early stages of embryonic development. The term "chimera" describes in genetics "*an organism or tissue that contains at least two different sets of DNA, most often originating from the fusion of as many different zygotes (fertilized eggs)"*[3].

The use of gene editing technologies, as an example of "disruptive technology", raises serious doubts about the real capacity of regulators for guaranteeing its use in accordance with well-established scientific and bioethics principles. The Tsunami of gene editing, as the 2020 Nobel Prize Professor Jennifer Doudna deliberately defined in a classic article published in Nature in 2015[4], has thus become a matter of growing concern about the unwanted consequences that may derive from the uncontrolled use of new technologies such as CRISPR and has bring again into discussion the imperative need of halting the irrepressible race to obtain mutants, or even worse "chimerae". In a sharp contrast, the fact that we know the technology for making H-bombs do not imply that we shall actually built such kind of devices.

Other related aspect is the development of gene-engineering Genetically Modified Organisms by gene-editing techniques. Following the judgment of the European Court of Justice of 25 June 2018, the European Union applies the full alignment of new mutagenic organisms within the general framework of GMOs. This fact obliges to adapt Directive 98/44/EC of 6 July 1998 on the legal protection of biotechnological inventions to include mutagenesis techniques affecting human germline.

In Spain, there are currently tens of thousands of human embryos donated for research that are not used due to the scarcity of suitable scientific projects. On

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[2] A. PARK. "Scientists Report Creating the First Embryo with Human and Non-Human Primate Cells", *Time*, April, 15, 2021: "In a ground-breaking experiment, researchers have successfully created the first human-monkey chimera. The work, published in the journal Cell, describes the first embryo containing both human and monkey cells that was cultured for 20 days. Led by Juan Carlos Izpisua Belmonte, the study represents the culmination of decades of work in understanding early embryo development in non-human species, which Belmonte hopes will now apply to humans. But it is bound to raise serious ethical questions about the implications of combining human cells with those from a different species (even if it is a closely related one), and the report was accompanied by commentary from ethicists on how the work should be interpreted and what the careful next steps should be in pursuing this line of study." at *https://time.com/5954818/first-human-monkey-chimera-embryo/*

[3] *https://britannica.es/*

[4] J. DOUDNA. "My whirlwind year with CRISPR", *Nature*, Vol 528. 24-31 December 2015, p. 469.

December 31, 2017, there were 545.333 cryopreserved embryos in Spain[5]. Two are the main issues at stake identified by this "embryos´ surplus": the ethical issues arising of protection of human germline through the entire research and the protection of fundamental rights of anonymous donors and recipients.

In spite of the advanced legislative framework provided by the Spanish Law 14/2006, of May 26 on *Técnicas de reproducción humana asistida*, the fact that any ongoing experiments involving human embryos need to follow the international agreed rules[6] and namely the WHO guidelines, must not be neglected.

2. USE OF GENETIC ENGINEERING TECHNIQUES FOR EDITING HUMAN EMBRYOS

The impact analysis of new gene editing techniques[7]. and their enormous potential for modelling natural processes and especially those influencing the ways human genes are expressed, have been highlighted by the work of Jennifer Doudna following the pioneering efforts of Professor Francisco Juan Martínez Mojica[8]. and others on CRISPR molecular mechanisms the awarding last November of the Nobel Prize in Chemistry 2020 to Doudna and Charpentier only underlines the major role that gene editing techniques will play in the future of biochemistry and genomics research.

The first CRISPR repeat sequences were originally observed in *Escherichia coli* and *Haloferax mediterranei* (Archaea) as an adaptive microbial immune system against bacteria or viruses[9]. The introduction of gene editing tools allows accurate

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[5] J. CORBELLA. "Lack of suitable scientific projects prevents the use of donated embryos for research purposes", *Vanguardia*, February 11, 2020 at *https://www.lavanguardia.com/ciencia/20200211/473429546045/embriones-congelados-espana-medio-millon.html*

[6] C. LINDMIER. "Statement on governance and oversight of human genome editing", *World Health Organization*, July 2019 at *https://www.who.int/news/item/26-07-2019-statement-on-governance-and-oversight-of-human-genome-editing*

[7] Among the mutagenesis techniques, those that have been tested most effective to obtain gene-edited organisms are those using site-specific bacterial DNA cutting enzymes (site-specific nucleases), which include: meganucleases (MNs), zinc-finger nucleases (ZFs), transcription activator-like effector nucleases (TALEN), and clustered regularly interspaced short palindromic repeats-CRISPR (as CRISPR/Cas9). Q. U. ZAMAN et al. "Genome editing opens a new era of genetic improvement in polyploid crops", *The Crop Journal*, Volume 7, Issue 2, 2019, Pages 141-150, at *https://doi.org/10.1016/j.cj.2018.07.004*

[8] K. W. MAKAROVA et al. "An updated evolutionary classification of CRISPR–Cas systems" *Nature Reviews Microbiology*, Vol. 13, 2019, pp. 722–736.

[9] Y. ISHINO et al. "History of CRISPR-Cas from Encounter with a Mysterious Repeated Sequence to Genome Editing Technology", *Journal of Bacteriology*, Vol. 200, No. 7, 1 April 2018 at *https://doi.org/10.1128/JB.00580-17* and F.J.M. MOJICA et al. "Transcription at different salinities of

manipulation of plant genomes, thus replacing established methods of random mutagenesis such as and gamma-irradiation sequencing, reducing laborious screening of huge populations for mutants[10].

By mutagenesis we mean[11] the direct intervention in the original genome of the individual without introducing foreign genetic material into the process, leading to a mutation with the potential to self-perpetuate in future generations.

Additionally, the awarding of the Nobel Prize to this pioneering line of research makes it necessary to review the global regulatory framework for GMOs obtained by mutagenesis or autogenesis (editing or "rewriting" of one's own genetic material), in parallel to those currently authorized, And this distinction is not an innocent one, since it opens the regulatory debate on forced mutations in animal and plant varieties, which are considered products of nature and equivalent to the natural species, but not autogenic or mutagenic ones, as opposed to these same varieties and their hybrids.

3. IMPACT OF GENE-EDITING

On a more concrete level, mutagenesis within modern biotechnology is defined as the process by which the genetic information of an organism is modified with the consequent mutation. This mutation can occur spontaneously in nature or by exposure to mutagens. It can also be achieved experimentally using laboratory procedures. In nature, naturally occurring mutagenesis is often an evolutionary disadvantage in many cases, leading to degenerations, tumours and hereditary diseases; it is also undoubtedly a driving force of evolution[12].

In any case, the definition of modern biotechnology requires appropriate modifications because the introduction of gene editing techniques with the potential to modify the germline for all live species, including the humans. Genome editing, with predetermined and precise changes, has revolutionized the reproduction of crop species. The identification and characterization of gene editing nucleases has also increased the possibilities for intervention. Such mutations occur routinely - and on a

Haloferax mediterranei sequences adjacent to partially modified PstI sites", *Mol. Microbiol.,* Vol. 9, 1993, pp. 613-621.

[10] P. SIKORA et al. "Mutagenesis as a Tool in Plant Genetics, Functional Genomics, and Breeding", *International Journal of Plant Genomics*, January 2011 at *https://doi.org/10.1155/2011/314829*

[11] C. AUERBACH; J. M. ROBSON, "Production of mutations by allyl isothiocyanate", *Nature* 154, 1944, p. 81.

[12] Q. U. ZAMAN et al, *Op. Cit*, 2019.

large scale - without human intervention, so expert geneticists argue that there is no logical reason to treat them differently[13]. Unlike what happens with targeted selection (conventional mutagenesis), which is complex, imprecise and time-consuming, genomic editing carried out by CRISPR has the potential to accelerate mutations in a targeted and precise way[14].

However, the future ramifications of advances on gene editing directly affecting the human germline in the current state of science may lead to other unexpected consequences. In February 2018, the UK Parliament voted to approve regulations permitting the clinical use of mitochondrial replacement techniques. While mitochondrial gene transfer does not *sensu stricto* involve gene editing techniques, approval of any form of human germline genetic modification poses a regulatory challenge. There has been a rapid development of gene editing technologies in the last five years following the announcement in April 2015 of genomic editing of non-viable human embryos using CRISPR-Cas9, thus demonstrating that germline genetic modification and clinical applications are feasible. This ease of use poses a real danger of deregulation in the current international regulatory landscape that constrains modification of human cells in the short and medium term[15] (Le Page, 2018).

Is not surprise therefore that recent developments in the field of biomedicine and biotechnology have provoked intense debate on the variety of ways in which parts of human tissues and human cells can be used, modified, donated or sold, thus leading to a public debate on crucial issues in the interaction of bioethics and biotechnology, influencing policy initiatives and the decision-making process with the real risk of a global commodification of human beings.

In addition, the rapid changes in scientific knowledge of the bases of gene editing have generated, at the end of this process, a formidable challenge: the use of genetics to directly modify human embryos for clinical (and non-clinical). The issue opens also a new dimension with the generation of genetically modified organisms capable of perpetuating their genome with the subsequent threat to biodiversity.

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[13] As an example, spontaneous mutations occur in conventional livestock breeding that can lead to hundreds of unpredictable changes in an animal's DNA. One of these natural changes is the birth of young cattle without horns, which are easier to handle when they reach adulthood. Selective crossbreeding between breeders is enough to pass this trait permanently into a given population. M. LE PAGE. “The second great food war”, *New Scientist*, July 7, 2018, at *https://doi.org/10.1016/S0262-4079(18)31203-X*.

[14] P. A. C. HUNDLEBY; W. A. HARWOOD. “Impacts of the EU GMO regulatory framework for plant genome editing”, *Wiley Online Library*, Volume8, Issue2, May 2019 at *https://doi.org/10.1002/fes3.161*

[15] M. LE PAGE, *Op. cit*., 2018.

4. TOWARDS AN ABSOLUTE MORATORIUM ON EXPERIMENTS ALTERING THE HUMAN GERMLINE

The Tsunami of gene editing, in the words of Professor Jennifer Doudna, focus in the potential use of genetics to directly modify human embryos with the real possibility of perpetuating these mutations through mutagenic processes (such as CRISPR-Cas9[16]). In the months leading up to the Nobel Prize award, Jennifer Doudna did not hesitate to voice her strong objections to the course that the systematic use of genetic engineering was taking.

At the end of 2019 and just before a real biological tsunami occurred, the coronavirus, SARS cov 2, the news on the birth of twin girls in China fathered from gene-edited embryos was a “rude awakening to the almost idyllic panorama”[17].

Putting her well-known Tsunami definition of gene editing before the more obscure reality of its use by third parties outside the norms of self-control and, of course, the obligatory control of high-level bioethics committees, Dr. Doudna issued a stern warning that only reflected the unanimous feeling of the international scientific community. In Doudna's words: "... the temptation to tinker with the human germ line is not going away (…) There are key moments in the history of every disruptive technology that can make or break its public perception and acceptance. For CRISPR-based genome editing, such a moment occurred 1 year ago—an unsettling push into an era that will test how society decides to use this revolutionary technology. In November 2018, at the Second International Summit on Human Genome Editing in Hong Kong, scientist He Jiankui announced that he had broken the basic medical mantra of “do no harm” by using CRISPR-Cas9 to edit the genomes of two human embryos in the hope of protecting the twin girls from HIV. His risky and medically unnecessary work stunned the world and defied prior calls by my colleagues and me, and by the U.S. National Academies of Sciences and of Medicine, for an effective moratorium on human germline editing[18].

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[16] CRISPR is Clustered Regularly Interspaced Short Palindromic Repeats / CRISPR-Cas9: CRISPR associated proteins from *Streptococcus pyogenes.*

[17] J. DOUDNA. “CRISPR’s unwanted anniversary”, *Science*, Vol 366 Issue 6467, November 15, 2019, p. 777 at *https://doi.org/10.1126/science.aba1751*

[18] J. DOUDNA. *Op. cit*., 2019, p. 779.

Previously, in July 2019, WHO issued a statement requesting that regulatory agencies ban experiments involving human germline editing and announced the first steps to establish a registry for future such studies[19].

This was the position previously shared by Sheila Jasanoff[20] and David Baltimore in the Second International Summit on Human Gene Editing, held in November, 2018. Immediately thereafter, an International Commission on the Clinical Use of Human Germline Genome Editing convened its first meeting to set the scientific, medical and ethical requirements necessary for the evaluation of clinical guidelines that would avoid potential editing of human germline. The U.S. National Academy of Medicine and the U.K. Royal Society spearheaded this commission, which had the participation of the world's leading academies of science and medicine, reflecting the urgent nature of its mission.

Returning to the case of the Chinese twins, a paradigm of technical misuse in therapeutic applications, experts have also pointed out an additional challenge: the measure of genetic efficiency of direct interventions on the human genome, which is far from being absolute from a strict "zero risk" policy[21]. It is therefore necessary, in our own interest and in the interest of our descendants, to establish the adequate legal mechanisms to limit access to the scientific knowledge necessary to develop mutagenesis processes, including patent law mechanisms and regulatory barriers, if necessary. It has not taken long to obtain an international response to infringements of ethical and scientific guidelines[22].

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[19] "The WHO expert advisory committee on governance and oversight of human genome editing convened on 18-19 March 2019. At this meeting the Committee in an interim recommendation to the WHO Director-general stated that "it would be irresponsible at this time for anyone to proceed with clinical applications of human germline genome editing." WHO supports this interim recommendation and advises regulatory or ethics authorities to refrain from issuing approvals concerning requests for clinical applications for work that involves human germline genome editing. "Human germline genome editing poses unique and unprecedented ethical and technical challenges," said WHO Director-General Dr Tedros Adhanom Ghebreyesus. "I have accepted the interim recommendations of WHO's Expert Advisory Committee those regulatory authorities in all countries should not allow any further work in this area until its implications have been properly considered." C. LINDMIER, *Op. Cit.,* 2019.

[20] N. DELANEY. "Sheila Jasanoff wants society to reclaim the meaning of life", *Harvard Kennedy School*, Summer 2019 at *https://www.hks.harvard.edu/faculty-research/policy-topics/science-technology-data/democracy-science-sheila-jasanoff-wants*

[21] A. RICROCH et al. "The ethical concerns about transgenic crops". *Biochemical Journal*, Vol 475, 2018, pp. 803– 811 at *https://doi.org/10.1042/BCJ20170794*

[22] J. DOUDNA. "The promise and challenge of therapeutic genome editing", *Nature*, Vol 578, February 13, 2020, p. 229. *https://doi.org/10.1038/s41586-020-1978-5*

5. ASILOMAR REVISITED. THE PANIC BUTTON

A return to the bioethical principles of the Asilomar Conference held in California (USA)[23] and the scientific consensus that led to the 1975 moratorium, which proved to be an excellent instrument of self-regulation to avoid undue results. After 45 years, a dark cloud now appears on the horizon.

As the first initiative aimed at specifically limiting the potential harms that could result from the inappropriate use of biotechnology, the 1975 Asilomar Conference followed to the moratorium imposed by the Committee on Recombinant DNA Molecules of the US National Academy of Sciences. A series of scientific principles were adopted to guide the experiments to be carried out with agents potentially pathogenic for humans and, in general, those that could lead to an intentional or unintentional release of modified organisms into the environment, reinforcing the protocols for the safe confinement of the cell lines under study. From another point of view, the work of this conference and its proposals for self-regulation have been considered as the first practical application of the precautionary principle in the area of biotechnology[24].

Since then, the technology has undergone a formidable ethical, regulatory, technical and social challenge, scientists have gained a better understanding of the processes by which the genetic material of microorganisms, plants and animals can be modified and it is now possible to precisely insert or delete the DNA sequences of interest through gene-editing. The global consensus, which has allowed a de facto moratorium for forty years on genome studies that could affect the human germ line, has recently come under significant pressure from the advance of gene editing techniques, with the competing interests of emerging powers. In parallel, somatic cell gene editing is currently in the clinical development phase due to a few conditions.

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[23] "An important milestone was the International Summit on Human Gene Editing, held in Washington DC in December 2015. (…) Nobel laureate David Baltimore began the summit by invoking the 1975 Asilomar meeting on recombinant DNA research: "In 1975, as today, we believed it was prudent to consider the implications of a remarkable achievement in science. And then, as now, we recognized we had a responsibility to include a broad community in our discussions." Asilomar is often remembered as a model of successful self-regulation that affirmed science's autonomy and the principle of responsible research. (…)" S. Jasanoff; B. Hurlbut. "A global observatory for gene editing*", Nature,* Vol 455, March 2018, p. 435.

[24] J. LARRION. "La resistencia a las razones de Pusztai. El conocimiento y la incertidumbre en la polémica sobre los organismos modificados genéticamente", *Política y Sociedad*, Vol. 47 Núm. 1, 2010, pp. 215-230 at *https://revistas.ucm.es/index.php/POSO/article/view/POSO1010130215A*.

Certainly, genome editing in human somatic cells raises ethical questions, but it is distinct from germline genetic modification.

And with that we enter the thorny field of eugenics; Eugenics is the discipline that seeks to apply the biological laws of heredity to perfect the human species[25].

In general, the progress of the "OMIC" techniques (genomics, proteomics, etc.)[26]. and the wide availability of low-cost interventions on gene expression have given rise to efficient gene-editing techniques with sufficient potential to ultimately alter the germline of living beings and in particular humans. And not only the human germline. Biosafety issues are also reaching a unknown level of concern[27]. In the short term, this concern shall force a detailed assessment of the key safety elements that will be essential to evaluate the use of CRISPR/Cas in future developments[28].

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[25] American Medical Association adverted "On July 17, 2018, the UK-based Nuffield Council on Bioethics released its long-awaited report on the social and ethical issues raised by heritable genome editing. The significance of the report has only been heightened by unconfirmed news from China of the birth of twins whose genomes are said to have been edited before implantation. Heritable genome editing denotes the modification of the DNA of an embryo, sperm, or egg to alter the characteristics of future generations. Unlike earlier reports, this report rejects drawing a distinction between therapeutic heritable genome editing (eg, corrects disease-causing genes) and heritable genome editing intended for cognitive or physical enhancement (eg, augments stature or other attributes). (…) Editing the genome of human gametes or embryos is a disruptive unactualized technology and continues to be the subject of a wide range of concerns. (…) A key argument against heritable genome editing intended for enhancement draws on the notion of genomic essentialism, according to which genetics is the foundation of human nature. This school of thought asserts that genes comprise the essential self and thereby the essence of human identity. Facetiously referred to as Genes "R" Us, this reductionist outlook views a person as the sum of his or her genes or the nucleotide components of those genes. This conception is hardly insignificant, in that the equation of genes with destiny may raise the spectre of state-sanctioned eugenics. A related objection to heritable enhancement upholds the genome as the embodiment of humanity's common heritage, dignity, and diversity, and, thus, as being unalterable. Enshrined in Article 1 of the Universal Declaration on the Human Genome and Human Rights, which is a key position statement of the United Nations Educational, Scientific, and Cultural Organization, concerns are raised about heritable genome editing in general, and, particularly, the prospect of enhancement". E. Y. ADASHI; I. GLENN COHEN. "The Ethics of Heritable Genome Editing New Considerations in a Controversial Area", *JAMA*, Vol 320, Number 24, December 25, 2018 at *https://doi.org/10.1001/jama.2018.18270*

[26] C. MANZONI et al. "Genome, transcriptome and proteome: the rise of omics data and their integration in biomedical sciences". *Brief Bioinform*, Vol 19 Number 2, 2018, pp. 286–302 at *https ://doi.org/10.1093/bib/bbw11 4*

[27] K. M. WHITWORTH et al. "Resistance to coronavirus infection in amino peptidase N-deficient pigs", *Transgenic Res,* Vol. 28, Issue 1, 2019, pp. 21–32 at *https://doi.org/10.1007/s1124 8-018-0100-3*

[28] "In recognition of the potential risk/threat posed by genetic modification, we strongly support the involvement of the Biological Toxins and Weapons Convention (BTWC) to ensure the inclusion of the biosafety and biosecurity communities in any deliberations and standard setting (...). The potential for CRISPR to be used to create or manipulate more viruses, bacteria, and bacteria-produced toxins (i.e., select agents) has been discussed (Clapper, 2016). Previous bioweapons programs focused on molecular experimentation with select agents to make them more effective. Now, techniques such as CRISPR may enable an improved ability to manipulate pathogens for this purpose and may make such manipulations easier and faster to achieve". D. DIEULIIS; J. GIORDANO, "Gene editing using CRISPR/Cas9: implications for dual-use and biosecurity", *Protein Cell* Vol. 9 Number 3, 2018, pp. 239–240 at *https ://doi.org/10.1007/s13238-017-0493-4.*

6. OVERVIEW OF SPANISH AND EU LEGISLATION

As said before, in Spain there are tens of thousands of human embryos donated for research that are not used due to the scarcity of suitable scientific projects. According to the most recent data from the Spanish Fertility Society, on December 31, 2017, there were 545,333 cryopreserved embryos in Spain. The number of embryos that are frozen (about 87,000 per year in 2016 and 2017) far exceeds the number that are thawed yearly for implantation (4,500 per year), so the total number of stored embryos must currently be (at the end of 2020) around 700,000.

The rapid development of reproductive techniques and the need to respond to the problem of the fate of supernumerary pre-embryos led in the past to a revision of Law 35/1988, which was successively repealed and ultimately by Law 14/2006, of May 26, on Assisted Human Reproduction Techniques[29].

According to article 11 of the current Law 14/2006, the pre-embryos left over from in vitro fertilization treatments which are not implanted in a reproductive cycle can be cryopreserved in banks authorized for this purpose and can be prolonged until the doctors in charge, with the favourable opinion of outside independent specialists, consider that the recipient does not meet the clinically adequate requirements for the practice of the assisted reproduction technique.

Ignoring redundant questions as the definition of “preembrion” currently hold in article 1. 2. *“*pre-embryo means the in vitro embryo consisting of the group of cells resulting from the progressive division of the oocyte from fertilization to 14 days later”, this Law has been deemed as one of more progressive pieces of legislation regulating in vitro fertilization

Relevant provisions of Law 14/2006 on Article 3. “Personal conditions for the application of the techniques. 1. Assisted reproductive techniques shall be performed only when there is a reasonable chance of success, do not pose a serious risk to the health, physical or psychological, of the woman or the possible offspring, and after free and conscious acceptance of their application by the woman, who must have been previously and duly informed of their chances of success, as well as their risks and the conditions of such application. 2. In the case of in vitro fertilization and related

[29] *https://www.boe.es/eli/es/l/2006/05/26/14/con*

techniques, only the transfer of a maximum of three pre-embryos in each woman in each reproductive cycle is authorized. 3. The information and advice on these techniques, which must be given both to those who wish to use them and to those who, if applicable, are to act as donors, shall cover the biological, legal and ethical aspects of the techniques, and shall also include information on the economic conditions of the treatment. It shall be mandatory for this information to be provided in appropriate conditions that facilitate its understanding to those responsible for the medical teams that carry out its application in the centers and services authorized for its practice. (...) 6. All data relating to the use of these techniques should be recorded in individual clinical records, which should be treated with due guarantees of confidentiality with respect to the identity of the donors, the data and conditions of the users and the circumstances surrounding the origin of the children thus born. Nevertheless, an attempt will be made to maintain the maximum possible integration of the clinical documentation of the person using the techniques".

On the same law, on Article 11. "Cryopreservation of gametes and pre-embryos. 1. The semen may be cryopreserved in authorized gamete banks during the life of the male from whom it originates. 2. The use of cryopreserved oocytes and ovarian tissue shall require prior authorization from the corresponding health authority. 3. The pre-embryos left over from the application of in vitro fertilization techniques which are not transferred to the woman in a reproductive cycle may be cryopreserved in banks authorized for this purpose. The cryopreservation of the oocytes, ovarian tissue and surplus pre-embryos may be prolonged until such time as it is considered by the medical authorities, with the favourable opinion of independent specialists from outside the corresponding center, that the recipient does not meet the clinically adequate requirements for the practice of the assisted reproduction technique. 4. The different possible destinations that can be given to the cryopreserved pre-embryos, as well as, in the appropriate cases, to the cryopreserved semen, oocytes and ovarian tissue, are: (a) Their use by the woman herself or her spouse. b) Donation for reproductive purposes. c) Donation for research purposes. d) The cessation of their conservation without any other use. In the case of cryopreserved pre-embryos and oocytes, this last option will only be applicable once the maximum period of conservation established in this Law has expired without having opted for any of the destinations mentioned in the previous paragraphs. (...) 6. The consent to give the cryopreserved pre-embryos or

gametes any of the above-mentioned destinations may be modified at any time prior to its application.

In the case of the pre-embryos, at least every two years, the woman or the progenitor couple will be asked to renew or modify the previously signed consent. If during two consecutive renewals it is impossible to obtain from the woman or the progenitor couple the signature of the corresponding consent, and the actions carried out for the purpose of obtaining said renewal without obtaining the required response can be reliably demonstrated, the pre-embryos will remain at the disposal of the centers in which they are cryopreserved, which may use them according to their criteria for any of the aforementioned purposes, maintaining the established requirements of confidentiality and anonymity, and free of charge and not for profit.

Other legislative references:

A) Law 14/2007, of July 3, 2007, on Biomedical Research[30]: Relevant provisions on Article 28. “Donation of human embryos and foetuses. 1. The human embryos that have lost their capacity for biological development, as well as the dead human embryos or foetuses, can be donated for biomedical research purposes or other diagnostic, therapeutic, pharmacological, clinical or surgical purposes. 2. The termination of pregnancy shall never have as its purpose the donation and subsequent use of the embryos or foetuses or their biological structures. The procedure and manner of performing the termination of pregnancy shall be subject only to the legal requirements and limitations and to the characteristics and circumstances of the pregnancy. The professionals who are members of the medical team performing the termination of pregnancy shall not intervene in the use of the aborted embryos or foetuses or their biological structures. To this effect, the members of the research team shall leave a written record of this circumstance, as well as of the absence of conflict of interest with the medical team. 3. Foetuses expelled prematurely and spontaneously will be treated clinically as long as they maintain their biological viability, with the sole purpose of favouring their development and vital autonomy. 4. Before proceeding with any intervention on human embryos that have lost their capacity for biological development or on dead embryos or foetuses, a record shall be made by the corresponding medical personnel that such circumstances have occurred”.

[30] https://www.boe.es/eli/es/l/2007/07/03/14/con

B) Law 41/2002, of November 14, 2002, basic law regulating patient autonomy and the rights and obligations regarding clinical information and documentation.[31]

C) Organic Law 3/2018 of December 5, 2018, on the Protection of Personal Data and guarantee of digital rights.[32]

D) Law 24/2015, of July 24, 2015, on Patents[33]. Relevant provisions on Article 5. “Exceptions to patentability. They may not be the object of patent: 1. Inventions whose commercial exploitation is contrary to public order or morality, without the exploitation of an invention being considered as such by the mere fact that it is prohibited by a legal or regulatory provision. In particular, the following shall not be considered patentable by virtue of the provisions of the preceding paragraph: a) The processes of cloning human beings. b) The processes of modification of the germinal genetic identity of the human being. c) The use of human embryos for industrial or commercial purposes. 5. The human body in the different stages of its constitution and development, as well as the simple discovery of one of its elements, including the total or partial sequence of a gene. However, an element isolated from the human body or otherwise obtained by a technical process, including the sequence or partial sequence of a gene, may be considered as a patentable invention, even if the structure of said element is identical to that of a natural element. The industrial application of a total or partial sequence of a gene must be explicitly stated in the patent application. 6. A mere sequence of deoxyribonucleic acid (DNA) without indication of any biological function.”

E) Oviedo Convention, European Convention on Human Rights and Biomedicine. 1997.

F) Universal Declaration on the Genome and Human Rights of UNESCO, November 11, 1997.

G) Universal Declaration on Bioethics and Human Rights of October 19, 2005.

7. NEW CHALLENGES TO PRIVACY: PERSONAL DATA PROTECCION AND DONOR ANONYMITY

[31] https://www.boe.es/eli/es/l/2002/11/14/41/con
[32] *https://www.boe.es/eli/es/lo/2018/12/05/3*
[33] *https://www.boe.es/eli/es/l/2015/07/24/24/con*

An additional question is the protection of the anonymity of the donor in Spain[34], in contrast with the situation in Portugal where anonymity has been repealed by a ruling of the Constitutional Court, significantly reducing the number of gamete donors.

The Constitutional Court of Portugal declared, through its 2018 Judgment (*Acórdäo do Tribunal Constitucional, no. 225/2018, of April 24),* the unconstitutionality of "absolute secrecy with respect to persons born as a result of a process of medically assisted procreation having resorted to gamete or embryo donation, even in situations of surrogate gestation", on the grounds that it violated the rights to personal identity and to the development of the personality of the children.

Article 15 of the Portuguese Law on assisted reproduction (Law No. 32/2006, of July, on medically assisted procreation), contrary to what happens in Spain, did not provide for any exception to the rule of anonymity on the grounds of danger to the life or health of the child (it was only admitted by judicial decision). Following this annulment, a law was issued to amend the Portuguese assisted reproduction regulation (Law No. 48/2019, of July 8), which has amended the aforementioned art. 15, to include that "persons born as a result of medically assisted procreation procedures, resorting to gamete or embryo donation, may obtain, together with the competent health services, the genetic information concerning them, as well as, provided they are 18 years of age or older, they have the right to obtain, at the National Council of Medically Assisted Procreation, information on the civil identification of the donor".

The right to know the biological origin is not an absolute right. European Court of Human Rights, following the Gaskin v. United Kingdom case (Judgment of 7 July 1989).

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[34] "European countries of our environment, highlight the leadership of Spain in the performance of assisted reproduction treatments with gamete and embryo donation, which allows to meet the clinical needs of the Spanish population that needs them to have offspring. 2. It is an objective fact that in the countries where the rule of anonymity of the donors has been suppressed, the donations have decreased in a very sensitive way. In Spain, 20% of gamete donation treatments are performed on foreign patients, which is directly related, among other things, to the anonymity rule. The final conclusion of the group is that a hypothetical elimination of the rule of anonymity in gamete donation would not be justified, among other reasons, because it would be notably detrimental to care in Spain for the population that needs donor gametes for reproduction" - Positioning of the Spanish Fertility Society Regarding the Rule of Anonymity in Gamete Donations at *https://www.sefertilidad.net/docs/posicionamientoAnonimato.pdf*

8. FINAL REMARKS

Improved knowledge of the human genome and the universalization of genetic testing now allow access to extensive information on the genetic profile of human beings, which opens up the real possibility of providing patients with solutions a la carte, as in the case of the twins born after Dr. He Jiankiu's genetic intervention. The collection of this big data poses a challenge to the identity and integrity of human beings with the protection of personal data, privacy and intimacy seriously compromised for the sake of "precision medicine".

At the same time, the improvement of human genome knowledge and the universalization of genetic testing makes possible access to wide information of the genetic profile of human beings. A logical step from this Big Data realm is offering A la carte solutions for patients. The collection of this big data poses a challenge to the identity and integrity of human beings with the protection of personal data and privacy on the grounds of “precision medicine”.

The experts also have pointed out an additional challenge: the measure of genetic efficiency of the interventions of human germline, where the strict zero-risk policy applies in our own most essential interest and in the interest of our descendants.

The general claims for remedial measures against undesirable effects of genetics technology, which has now come to stay, are:

A) Introduction of effective and enforceable ethics codes such as United Nations Educational, Scientific and Cultural Organization (UNESCO) Universal Declaration on Bioethics and Human Rights, which is not realistic given “the widespread accessibility and ease of use” of the genome intervention techniques;

B) Monopolising the so-called self-limiting genes or killer genes (as a last-resource panic button);

C) Limiting the editing to Ribonucleic acid (RNA) codes (which modifies the expression of proteins but not the human germline itself); and

D) Establishing the legal mechanisms for auto limiting the access to the scientific knowledge necessary for developing those process, through intellectual property law mechanisms or directly.

As a corollary, 545,333 cryopreserved embryos in Spain potentially provide for thousands and thousands of chimers.

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