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José Rafael Blesa, Julio Tudela & Justo Aznar

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Article

Ethical aspects of nuclear and mitochondrial DNA transfer

José Rafael Blesa, Julio Tudela, and Justo Aznar

Catholic University of Valencia, Spain

Somatic cell nuclear transfer (SCNT) (cloning), as a reproductive or therapeutic method, and mitochondrial DNA transfer, as a method to prevent the transmission of mitochondrial diseases, are analyzed in this paper from a bioethics perspective. The licit purpose of being able to treat certain diseases, as in the case of SCNT, cannot justify, in any case, resorting to illicit means such as the manipulation, selection, and elimination of human embryos in the blastocyst phase, by using cell lines obtained from them. Crossing this line paves the way (as utilitarian ethics advocates) to assuming any cost in scientific experimentation so long as satisfactory results are obtained. With mitochondrial replacement, either human embryos are directly manipulated (pronuclear transfer) or germline cells are manipulated (maternal spindle transfer); changes in these could be transmitted to the offspring.

Lay Summary: This article analyzes somatic cell nuclear transfer (cloning) and mitochondrial DNA transfer techniques, in both reproductive and therapeutic applications, and preventive methods in the transmission of mitochondrial diseases, from a bioethical perspective. The manipulation, selection, and elimination of human embryos delimits the ethical acceptability of these promising techniques.

Keywords: Nuclear DNA transfer, Mitochondrial DNA transfer, Mitochondrial diseases, Mitochondrial replacement, Cloning, Somatic cell nuclear transfer, SCNT

Background

Cloning is a term that has been widely used in the media and in everyday language to refer in general to the production of organisms with an identical genome using laboratory techniques. The method essentially consists of transferring the nucleus from a cell of the organism to be cloned to an enucleated oocyte, which is then stimulated to continue its biological development. Due to its mechanism of action, this process is called somatic cell nuclear transfer (SCNT).

As the term "cloning" is already very widespread, the terminology to be used and the biotechnology processes to which they refer must first be clarified. The concept of cloning, in the field of animal and biomedical research, can refer to: a) the production of DNA fragments with a sequence identical to an original DNA fragment using recombinant DNA techniques; b) the production of a cell or cell population genetically identical to another cell; c) the artificial division of early embryos; and d) the generation of an organism (biological being) genetically

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identical to another organism from the genetic material of a cell from the person or animal to be cloned by means of asexual reproduction. The latter definition is the one to which the term "cloning" usually refers, although as we have already mentioned, hereinafter the term "cloning" shall be replaced with "SCNT."

Depending on its purpose, SCNT can be reproductive or therapeutic, although the methodology used is the same. Reproductive SCNT refers to SCNT aimed at the production of an individual. This has been achieved in animals, but not in humans, in which experiments have not advanced beyond the blastocyst phase, to a certain extent because it is legally prohibited in most countries. Therapeutic SCNT is aimed at the production of embryonic stem-cell lines for possible use in biomedicine. The lines are grown from cells obtained from the granular inner cell mass of the blastocyst. Cells of all types of tissues can be derived from these, except for extra-embryonic tissues, such as the amnion and the chorion.

Nucleic acids from the mitochondria, instead of the cell nucleus, can also be transferred. This is the case in mitochondrial transfer or mitochondrial replacement.

The methodology, purpose, and bioethical challenge posed by the different types of nucleic acids transfer (nuclear and mitochondrial) in the case of the human species have both technical and ethical aspects in common, so we shall assess them jointly. In both cases, the germ cells or embryos (zygotes) are manipulated (even destroyed), thereby instrumentalizing the produced persons; moreover, in this case, any abnormalities produced can be passed on to the offspring.

Methods

A literature review has been performed, in related journals subjected to peer review and electronic databases, of published articles on somatic nuclear transfer, mitochondrial DNA transfer, mitochondrial replacement mitochondrial diseases and therapeutic proposals related, focusing on the bioethical analysis of the different procedures included.

History of Human SCNT

What we could call "pioneer" human cloning is an attractive process of experimental research that appears to be more a product of the imagination of some researchers than an objective scientific reality.

Early research in this field was conducted by Cibelli's team (Cibelli et al. 2001); a Chinese team later announced that they too had managed to produce human blastocysts (Chen et al. 2003).

Subsequent experiments on human SCNT were those of Woo Suk Hwang (Hwang et al. 2004), who, in 2004, published in *Science* preliminary research related with the production of human blastocysts by SCNT. In May 2005, another team led by Hwang published an article (also in *Science*) in which they stated that, for the first time in the world, they had cloned human embryos, developing them to the blastocyst phase, from which they were able to derive human embryonic stem cell (ESC) lines (Hwang et al. 2005). The study almost immediately aroused controversy, when it was denounced that it could be fraudulent; this was later confirmed, and the article was retracted by *Science* (Kennedy 2006).

Around the same time, Stojkovic et al. (2005) also published a study in which they too stated that they had cloned human embryos to the blastocyst phase, and so they were considered to be the first to accomplish this technological feat. However, they were unable to derive ESC

lines from the biological entities produced by them, so this work could not be considered as an objective demonstration of human SCNT either.

In 2006, Zavos and Illmensee (Zavos and Illmensee 2006) likewise reported that not only had they managed to clone human embryos to the blastocyst phase, but they had also implanted them in several women and had achieved pregnancies that at that time were ongoing, but this was never corroborated in scientific journals.

Given the above, we believe that we can state that until 2007, there was no scientific evidence that human embryos could be cloned to the blastocyst phase, from which human ESC lines could have been derived (Hanna et al. 2007; Takahashi et al. 2007; Yang et al. 2007; Yu et al. 2007)

However, in 2008, a team from the Stemagen Corporation in La Jolla, California, reported that they had been able to obtain human blastocysts by SCNT, using adult skin cells as nuclear DNA donors and twenty-nine oocytes from three young women (20–24 years old) that were left over from *in vitro* fertilization (IVF) (French et al. 2008). They managed to produce twenty-one embryos from these, five of which evolved to blastocyst stage. Despite this, true SCNT could only be demonstrated in one of them although, as had hitherto happened in all the previous experiments, they were also unable to derive human ESC, which called into question whether human embryos had really been cloned in these experiments.

As far as we are aware, no further human SCNT experiments were published until 2011, when three related studies were presented. The first (Egli et al. 2011) stated that they had managed to produce human embryos by SCNT, but that these had not progressed beyond eight-cell embryos; The second (Noggle et al. 2011) reported similar findings. However, the third (Fan et al. 2011), did manage to obtain human embryos that evolved to the blastocyst phase, although they too were unable to derive ESC lines. Thus, up to 2011, it could not be said that cloning of human individuals had been achieved.

One of the aforementioned research lines was to produce human embryos by SCNT from the cells of donors with various diseases, with the intention of deriving (from the blastocysts obtained by SCNT) cell lines of individual patients that could be used to better understand the disease pathogenesis, or to evaluate drugs that could be used in their treatment (Noggle et al. 2011). However, Noggle et al. stated that after 270 attempts at SCNT, they were unable to derive cell lines with the genotype or phenotype typical of these diseases. Nevertheless, they did manage to obtain human blastocysts if the nucleus was not removed from the oocytes used, but the nucleus of the adult somatic cell of the patient in question was transferred to them. Using this technique, they were able to produce zygotes that developed to the blastocyst stage, and to obtain ESC lines from these blastocysts. These cells were cultured for six months, completing more than thirty passages, without undergoing a replicative crisis, which is common in cultures of these types of cells after seventy to one hundred passages (Ma et al. 2014). This paved the way for the possibility of achieving the proposed objectives (obtaining human blastocysts by SCNT for clinical use). However, this technique presented a major difficulty for use in human medicine, as the zygotes were triploid.

In May 2013, Mitalipov's group in Oregon published a study in which they claimed to have produced human blastocysts using SCNT and, from these, human ESC lines (Tachibana et al. 2013a). After making a modification to SCNT that increased the efficiency in the production of ESC lines, they used eight enucleated oocytes from the

same donor to which nuclei from fetal skin somatic cells were transferred; from these, they obtained five blastocysts that gave rise to four human ESC lines, which is an efficiency of 62.5 percent. In addition, in order to generate patient-specific pluripotent stem cells, they used skin fibroblasts from a patient with Leigh syndrome. Fifteen and five oocytes were retrieved from two separate donors and subjected to SCNT with the fibroblasts, obtaining seven blastocysts (4 out of 15, and 3 out of 5) from which two human ESC lines were eventually derived, one from each oocyte cohort.

The success of Mitalipov's work lay in identifying the critical steps in cell reprogramming and development of SCNT blastocysts: elimination of mitotic use, fusion of donor cells, and cytoplast activation. Specific aspects were the use of oocytes from young women, and the use of caffeine to inhibit some enzymes that mediated the process.

After the text had been published online, an anonymous reader stated that he had found four errors in the aforementioned study, mainly the duplication of images or parts of figures (Cyranoski and Hayden 2013). Mitalipov acknowledged these errors, stressing that three of them were "innocent mistakes" that had occurred while assembling the paper (Tachibana et al. 2013b); the fourth was not a major problem in his opinion either, blaming the errors on the first author, Masahito Tachibana, who compiled the data. Nonetheless, regardless of how it happened, the existence of these errors fostered extensive ethical discussion on Mitalipov's work, especially about the haste in its acceptance by medical journal *Cell*, without adequate peer review (the timeline of the manuscript according to the journal was: "Received: April 30, 2013; Received in revised form: May 3, 2013; Accepted: May 3, 2013; Published Online: May 15, 2013").

In any case, aside from the aforementioned errors, the study by Mitalipov et al. can be considered as the first in which human embryos were cloned to the blastocyst stage, from which human ESC lines could be derived.

In summary, the study by the Oregon investigators (Tachibana et al. 2013a) is undoubtedly a major technical breakthrough, with as yet unproven clinical applicability and, as we shall later see, objective ethical difficulties.

Subsequent studies on SCNT

In 2014, an article was published by Egli's group, in which they used skin cells from a newborn and a woman with type 1 diabetes to produce human embryos using SCNT (Yamada et al. 2014). Four ESC lines were obtained from the embryo produced, from which different cell types could then be derived, among them insulin-producing pancreatic beta cells. This could certainly be major step towards treating patients with type 1 diabetes by cell therapy in the more or less near future.

Also in 2014, an article was published in *Cell Stem Cell*, in which skin cells from two adult males (one aged 35 and the other 75) were used as nucleus donor cells (Young et al. 2014). The authors stated that their study showed, for the first time, the possibility of cloning using human adult cells as donors of the nucleus transferred to the enucleated oocyte, although as previously reported, somatic cells from an adult female with type 1 diabetes were also used in Egli's study (Yamada et al. 2014).

Regardless of the method, we believe that we can state that to date, only human blastocysts have been produced. Whether or not these will be viable is as yet unknown, so it seems rather risky to state

that cloning of human beings capable of developing to birth has been achieved.

Mitochondrial DNA Transfer: Mitochondrial Replacement

Mitochondrial diseases and mitochondrial DNA

Mitochondrial diseases are a group of rare diseases (1 case per 5,000–10,000 individuals) that present in both children and adults, and which are associated with mitochondrial dysfunction. They can affect any organ, at any age. They are incurable, degenerative, and usually have a fatal outcome.

Mitochondria, which the body uses for many biochemical and metabolic processes, are responsible for ATP synthesis. These organelles contain their own DNA, mitochondrial DNA (mtDNA). Indeed, not all cellular DNA is in the nucleus. Mitochondria contain a 16,569-base pair circular DNA that codes for thirty-seven genes, thirteen of which correspond to key proteins in cell metabolism, as they are partly responsible for energy production in the cell. The proportion of mtDNA in the cell with respect to nuclear DNA (nDNA) is around 0.0005 percent. However, bearing in mind that there are between 100 and 100,000 mtDNA copies per cell, it represents 0.026 to 26 percent of the total cellular DNA. (Approximately 3,200 million base pairs reside in the nucleus [nDNA], of which there are only two copies per cell.) As regards genes coded, mtDNA accounts for approximately 0.06 percent of the total number of human genes, if we consider only different genes. However, if we look at mitochondrial proteins expressed in a cell from mtDNA compared to proteins expressed from nDNA, the calculation differs notably, since the number of mitochondrial proteins varies between 1,300 and 1,300,000. The variation in the number of copies of mtDNA depends on the tissue to which it belongs. The composition of each mtDNA, i.e., the genome sequence of these copies, may be identical (a state known as homoplasmy), or there may be differences due to changes in the sequences (different alleles and haplogroups) (a state known as heteroplasmy). Mitochondrial DNA is inherited exclusively from the mother.

Mutations in mtDNA that were the molecular basis of mitochondrial diseases were first identified in 1988 (Holt, Harding, and Morgan Hughes 1988; Wallace et al. 1988).

Prevention of mitochondrial disease transmission

Research in this field has been conducted for a decade or so, trying to correct the transmission of mitochondrial disease (Roberts 1999).

In 2010, a group from Newcastle (England) published a study which proposed a solution to prevent the transmission of mitochondrial diseases, a technique consisting of pronuclear transfer (PNT) following IVF, or previous PNT between oocytes (Craven et al. 2010). In the first, nDNA from a fertilized ovum with abnormal mitochondria is transferred to a donor zygote with normal mitochondria that has also been enucleated, consequently a healthy embryo should develop, which is a carrier of the prospective mother's nDNA (PNT). In the second, the nucleus from the "sick" oocyte is transferred to the healthy donor enucleated oocyte before being fertilized, and the resulting hybrid is then fertilized with the father's sperm (maternal spindle transfer [MST]).

However, it is interesting to highlight the inappropriate use of terminology when

it comes to referring to these techniques, aimed at eliminating abnormal mitochondria, in order to prevent the inheritance of certain diseases. We are referring here to so-called "mitochondrial replacement," a term that refers to the replacement of "sick" mitochondria with "healthy" ones. Instead, the techniques that supposedly achieve this "replacement" (PNT and maternal spindle transfer) completely substitute the cell except for the nDNA, i.e., nuclear transfer, as the names of these methodologies suggest.

Ethical Reflection on nDNA and mtDNA Transfer

When discussing the ethical aspects of SCNT, we believe it interesting to address reproductive and so-called therapeutic SCNT separately.

Reproductive SCNT

If we start from the actual fact that reproductive SCNT is legally prohibited worldwide, we can infer that it has serious ethical difficulties. Be that as it may, the ethicality of human reproductive SCNT has been raised in the bioethics field.

The main arguments in favor of the procedure maintain that people have a right to reproductive freedom, as opposed to the right of the cloned child to be him- or herself, for his or her genetic identity is what makes him or her a unique individual, and not to be predetermined (Havstad 2010); or put another way, reproductive SCNT seems to be contrary to the cloned child's right to self-determination (Feinberg 1980).

It also violates what Hans Jonas (Jonas 1974) calls the right to ignorance, which considers that producing a child with a predetermined genome deprives him of the right to be unaware of how he will evolve in the future, i.e., he is denied the right to ignorance, because we are designing his genome, which is predetermined from this time. However, one counter argument to that proposed by Jonas is that there are increasingly more studies confirming that an individual cannot be identified exclusively by their genome, as their phenotypic personality is also determined by epigenetic mechanisms derived from their relationship with the environment.

Another ethical problem relative to human reproductive SCNT is the large number of oocytes required for the procedure (Ikemoto 2014). Obtaining them thus violates the dignity of the woman, not only by instrumentalizing her, that is, using her as a source of oocytes, but also because the ovarian hyperstimulation required to obtain the oocytes can have objective negative effects on her health, particularly renal problems, subsequent infertility, and even occasionally (although rare), death (Georges 2007).

It also seems contrary to the ethical permissibility of human SCNT that the child produced could have psychological problems as he develops (Matoba et al. 2014).

Unquestionably however, the main argument that definitively precludes the ethical permissibility of this technique is that it objectifies human beings, it instrumentalizes human beings. This goes against the dignity that by their nature they intrinsically possess and so does not support designing or processing human genetic identity.

Nevertheless, counter to these arguments against human reproductive SCNT there are authors who defend it, among them Dworkin (1993), who justifies it as a manifestation of the reproductive freedom of the individual, a specific expression of individual liberty and personal autonomy.

Similarly, other authors conclude that, "because most moral reasons against doing

human cloning remain speculative, they seem insufficient to warrant at this time a complete legal prohibition of either research on or later use of human cloning" (Brock 2003, 594), or

> when Dolly's birth was reported in Nature on February 27, 1997, amazement at the achievement and celebration of the science was overwhelmed by the comprehensively hostile reaction to the very idea of cloning. This hostility has lead to what is effectively a worldwide ban on reproductive cloning. Is such a ban justified? I do not believe so. (Harris 2005, 145)

Moreover, others consider that the ethical assessment of human reproductive SCNT could be positive if improving the technique were to constitute a real alternative to some of the current assisted procreation techniques (Simpson 2007; Strong 2005); and others, from a more eclectic position, think that on assessing the ethicality of human reproductive SCNT, the right of the individual to reproductive freedom must be reconciled with the right of the child born to be himself (Havstad 2010).

In our opinion, however, human reproductive SCNT is not ethically acceptable because: (a) it goes against the dignity of the human individual produced; (b) it infringes personal individuality by producing genetically identical human beings; (c) it is contrary to the right to ignorance of the child produced; (d) there are negative side effects in children born using this technique; (e) it goes against the dignity of the egg donor; and finally (f) there are human embryos lost as a consequence of the still low efficacy of the technique. Fundamentally, we believe its wrongfulness lies in the instrumentalization of the human being produced.

The Catholic Church has categorically expressed its opposition to human cloning experiments, calling it "a grave offense to the dignity of that person as well as to the fundamental equality of all people" (Congregation for the Doctrine of the Faith 2008, n. 29).

Therapeutic SCNT

There are several arguments against the ethicality of this technique, but the main argument is undoubtedly the instrumentalization of the human embryo produced, which is objectified, since it is generated for purposes other than its own good. The unavoidable destruction of human embryos entailed in the technique must also be considered. Reasons considered as favorable by some are that cell lines can be obtained from the human embryo produced that could be used for experimental and medical purposes, in accordance with a utilitarian interpretation of the process, that is, the essential purposes justify the means which include the destruction of a human embryo.

Once again, as in the case of SCNT, one cannot justify, in any case, resorting to illicit means such as the manipulation, selection and elimination of human embryos in the blastocyst phase, by using cell lines obtained from them.

Crossing this line, that means to violate the integrity of the new human embryo, paves the way (as utilitarian ethics advocates) to assuming any cost in scientific experimentation so long as satisfactory results are obtained. Bioethics seeks specifically to preserve respect for human dignity in all research and therapeutic processes, with no exceptions.

Ethical Reflection on Mitochondrial Replacement

The alternatives for couples in order to prevent disease transmission presently

range from not having children, adopting them, using donor eggs or selecting healthy embryos using preimplantation genetic diagnosis (although this is rather unreliable for mtDNA-linked diseases), or selecting fetuses using prenatal diagnosis. However, the vast majority of couples want children who are genetically related to them, which not all of the aforementioned techniques offer.

This parental desire raises an objective ethical issue, which could be avoided if a consequentialist or utilitarian ethical principle, so that the good of the end sought would justify the means used, were *not* applied. However, objections could be raised to this approach: even though the purpose of these experiments is good (since families with a high risk of having sick children could have healthy ones), the means used to achieve it, which involves the manipulation and even destruction of embryos is not. Therefore the overall assessment of mitochondrial replacement, even though the results obtained are good, must be considered in principle ethically very questionable. Moreover, the first principle of practical reasoning states that "good is to be done and pursued; evil is to be avoided." However, the issue that can be raised in this case is whether the "good" is to have children at any cost. In other words, if there are diseases present in the aspiring mother that can cause problems, should one do everything to have healthy children? In relation to this, Doug Turnbull, states that "it is important that we do all we can to help these families and give them the chance to have healthy children, something most of us take for granted" (Muscular Dystrophy UK 2016).

But what is this "all" that we can do? This is the ethical issue that must be clarified.

It should be added that, as can occur in any biomedical research, the use of a technical means for a purpose considered ethically acceptable can also encourage its use for other purposes which are not ethically acceptable. In this respect, the Nuffield Council on Bioethics suggests that we could be looking at a "slippery slope," although they themselves refute this by arguing that it could be resolved by establishing appropriate legal regulations that would prevent it (Nuffield Council on Bioethics 2012). Another ethical difficulty is that with mitochondrial replacement, either human embryos are directly manipulated (PNT) or germline cells are manipulated (MST); changes in these could be transmitted to the offspring (Bredenoord et al. 2011).

That is to say, it could be unequivocally stated that this is germline therapy, with the ethical difficulties that this entails, namely altering the principle of

> intangibility of the subject's genetic inheritance, which in turn is based on the respect of the physical integrity of the person. This principle is compatible (and in our opinion even required) with the sick subject's right to maintain or recover the integrity and efficiency of their own genetic endowment according to the therapeutic principle. (Sgreccia 2007, 420–22)

Germline gene therapy can only be considered ethically acceptable when its purpose and objectives are therapeutic. Furthermore, there are aspects of mitochondrial replacement that are unresolved, such as the existence of mitochondrial myopathies due to mutations in the mtDNA, but which only present if the haplotype (a set of genetic information in mtDNA that varies according to geographical area) is a particular one, i.e., not all mutations will result in disease, so therapeutic intervention would not be justified in all cases.

The ethical question of determining whether the children (or their

descendants) born after mitochondrial replacement could suffer some type of medical problem must also be considered, so the ethical issue of this transfer cannot be assumed to be resolved until these difficulties have been overcome, which could take decades. In relation to this, and from an ethical perspective, the question arises as to whether it would be correct to subject children born using this technique to decades-long evaluation, as their consent would not have been sought, and especially, whether it is ethical to subject a certain population group to a possible health risk in order to determine whether this will or will not occur.

One possible, although utopian solution to alleviate this difficulty would be to use mitochondrial replacement so that only boys (males) are born. Thus, if there were any problems, the possibility of generational transmission would be limited, since it is girls that transmit mtDNA; in this case however, selecting individuals according to their sex introduces a new ethical issue that is difficult to justify.

Still another fact: the embryos produced after mitochondrial DNA transfer have three genetic parents, due to the presence of identifiable genetic material from someone other than the two individuals identified as genetic parents (Baylis 2013), which involves crossing a line towards the construction of "designer babies," whose genome can be composed with genetic contributions beyond their parents.

From a general bioethical point of view, mitochondrial replacement could be assessed from the perspective of a principalist bioethics, although in relation to this, there is the difficulty that there is no patient, but a future person programmed not to be ill. The patient does not heal, but rather is not born ill and/or does not become ill, so beneficence does not apply (although it might for the family and species). Considering non-maleficence, the same problem arises, since there is no patient. The same argument can be applied to the principles of autonomy and justice, they may not apply to the person who does not yet exist. Finally, it does not seem justifiable that in order for a child to be born healthy, the natural process of conception must be by-passed and laboratory reproductive techniques used, leaving few options to the wisdom of nature. In summary, this is therefore an attempt to justify these techniques from a utilitarian bioethical perspective, in which the interests related to the end pursued take precedence over the interests of those affected in the process, or which at least would justify it by assuming a good considered greater than the bad that could be derived from it, whatever it was.

From an ethical point of view, the long-term social consequences of using these techniques must also be considered. Accepting manipulations in embryos that affect the germline to prevent sick children being born could lead to a "slippery slope," which will justify germline manipulation, with the uncontrollable consequences that this could have. In any case, it is argued that as all technology can be used for good or bad, it is merely about adopting social norms and legal regulations. Another major ethical issue is to determine where the limit is between healthy and sick subjects when we talk about genetic characteristics. There are characteristics that contribute to a higher likelihood of suffering certain diseases, so to avoid them would focus on selection of "perfect" DNAs for eggs that would give rise to a perfect race, free from all mutations and defects that could cause illnesses throughout life. Who does not have a disease or genetic peculiarity that they would like to avoid? Even something non-pathological, like height, skin or hair color, facial features, that we would like to change. In short, if mitochondrial replacement is put

into practice, it could be a further step towards "enhancement," an ethical problem with unpredictable consequences.

Finally, we would like to refer to the comment made by the Human Fertilization and Embryology Authority (HFEA), which seeks to downplay the fact of manipulating the genetic information that will be inherited with these techniques: "We are not changing characteristics, we are not changing those things that make you, 'you'. What we are changing is energy metabolism" (HFEA 2013). It should be refuted in this respect: there are many nDNA regions that code mitochondrial proteins, specifically around 1,100 genes. As stated above, these genes (DNA) would not make us who we are either. Many other genes in the nDNA participate in metabolic processes that "only affect" specific basic reactions and do not make us who we are either. What part of DNA makes us who we are? The part that codes for visible external characteristics, for a certain phenotype? DNA, considered overall, is the heritage of man that defines him biologically as a unique, inimitable individual. It is reductionism to consider that mtDNA does not alter, or cannot not result in manipulation of offspring (Bredenoord et al. 2011). It is also a contradiction, the alteration in that DNA is what is causing the devastating mitochondrial disease, which shows its importance as an integral part of that human genetic heritage.

In relation to this, in 2012, the British Nuffield Council on Bioethics issued a report in which it stated:

> Due to the health and social benefits to individuals and families of living free from mitochondrial disorders, and where potential parents express a preference to have genetically related children, on balance we believe that if these novel techniques are adequately proven to be acceptably safe and effective as treatments, it would be ethical for families to use them, if they wish to do so and have been offered an appropriate level of information and support. Given the above and subject to the appropriate oversight, we believe that as a research objective it is ethical to gather further information about pronuclear transfer and maternal spindle transfer in order that they can be considered for treatment use. (Nuffield Council on Bioethics 2012)

Legalization of Mitochondrial Replacement in the United Kingdom

Regarding mitochondrial replacement, very recently, on February 3, 2015, the British parliament voted in favor of amending the law that prevented carrying out the technique of mitochondrial replacement (UK Legislation 2015), and it has also been approved by the House of Lords, on February 24 in a vote of 280 in favor and 40 against, so the UK is the first country in the world where this technique can be applied (UK House of Lords 2015).

Regarding mitochondrial transfer, in 2012, the British government promoted a public consultation through the HFEA, in order to drive a change in the laws that would permit these types of experiments, which were prohibited in the United Kingdom until their recent legalization, since they involve a process of nuclear transfer in human embryos and gene therapy in germ cells (HFEA 2013). Accordingly, on June 27, 2013, the British Department of Health approved a bill to legalize the technique of mitochondrial replacement, a bill which has just been debated and approved in the British Parliament, making the United Kingdom the first country in the world to legalize mitochondrial transfer (UK Department of Health Human Fertilisation and Embryology Authority 2013).

Conclusion

SCNT is not ethically acceptable because it infringes on the dignity and individuality of the individual produced, affects the right of the child produced to ignorance, treats the oocyte donor as an object, and may have adverse effects in the children born.

In mitochondrial transfer, as in SCNT, the main ethical difficulty is that germ cells or embryos (zygotes) are manipulated (even destroyed), so that the produced persons are being instrumentalized; moreover, in this case, any abnormalities produced can be passed on to the offspring.

The licit purpose of being able to treat certain diseases, as in the case of SCNT, cannot justify, in any case, resorting to illicit means such as the manipulation, selection, and elimination of human embryos in the blastocyst phase, by using cell lines obtained from them. Crossing this line paves the way (as utilitarian ethics advocates) to assuming any cost in scientific experimentation so long as satisfactory results are obtained. Bioethics seeks specifically to preserve respect for human dignity in all research and therapeutic processes, with no exceptions.

With mitochondrial replacement, either human embryos are directly manipulated (PNT) or germline cells are manipulated (MST); changes in these could be transmitted to the offspring. That is to say, it could be unequivocally stated that this is germline therapy, with the ethical difficulties that this entails.

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Biographical Note

José Rafael Blesa, Ph.D., is associate professor of genetics, cell biology, gene therapy and bioethics, and chairman of the Department of Basic Medical Sciences, Catholic University of Valencia, Spain.

Julio Tudela, Pharm, Ph.D., is a member of the Life Sciences Institute and the Centre for Bioethics at the Catholic University of Valencia; and is associate professor of bioethics, Catholic University of Valencia, Spain.

Justo Aznar, M.D., Ph.D., is former head of the Department of Clinical Pathology at the University Hospital La Fe; and is director of the Life Sciences Institute at the Catholic University of Valencia, Spain. Corresponding author, justo.aznar@ucv.es.