



BIOETHICS NEWS



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Reports

Is progress being made towards the creation of artificial life?

Recent press reports have highlighted what appears to be a major advance towards the creation of artificial life, when they reported the total synthesis of the first chromosome of an organism, a yeast, that is biologically more similar to humans than to bacteria. The study was conducted by researchers at the Johns Hopkins and New York universities in the United States, in what was an interesting innovation in the approach to this type of research. The new chromosome has substantial differences with respect to the original model. These modifications, which result in it being roughly 14% shorter, were introduced in order to make it more stable and flexible from a genetic point of view. According to the authors, this flexibility will enable it to be modified in vivo to change a specific property aimed at, for example, the production of antibiotics or biofuels. Although the synthetic chromosome has several differences with respect to the original, the yeasts that contain it are biologically indistinguishable from natural yeasts.

This is one further step in the field of Synthetic Biology, which already had huge media coverage in 2010, with the synthesis of the first whole genome. At that time it was Craig Venter's group who made a copy of a bacterial chromosome that was shown to be perfectly functional, as in the case of the yeast. Interestingly, the size of the bacterial molecule was four times larger than the one synthesised now and essentially identical to the original, unlike the yeast chromosome, which is significantly different. After this breakthrough, which already foreshadowed the current one, a couple of years later (in 2012) Profes-

or Eduardo Moreno produced a new species of fly, synthetic *Drosophila*, using an essentially different approach based on genetic modification.

The synthesis of the yeast chromosome was without question a major step for Synthetic Biology, an area of research with a novel focus on biotechnological research, using advances in biological techniques and knowledge towards bioengineering, the synthetic genome, synthesis of protocells and finally,

towards artificial molecular biology. The tools used in Synthetic Biology are basically Molecular Biology techniques developed in the later decades of the last century that have enabled advances to be made in fields like gene therapy and the production of genetically modified organisms.

This latter discovery shows that it is only a question of time and effort, since the technology has already been available for some time. This will probably be the start of a race in two directions: on one hand, the synthesis of genomes of increasingly complex organisms (including humans) and, on the other, the production of completely synthetic cells, in what would be the closest thing to artificial life.

Following on from this news, statements from expert researchers in this field have been published, such as that of Harvard University professor George Church, indicating the possibility of generating a "healthy" whole human genome. According to this investigator, the only limitation for Synthetic Biology is imagination. This field has been advancing extraordinarily quickly, since on one hand technical tools are already available and, on the other, the



concept is relatively simple: use the “parts” that nature gives us to construct a new “whole”.

However, this new technology raises major bioethical issues, such as risks for the environment, biosafety, distribution of resources, long-term impact of the sudden alteration of the evolutionary process or the manipulation of human genetic patrimony with the ever closer possibility of producing human

beings on demand from zero. Hence, the establishment of an ethical framework based on respect for the human person is urgent.



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New steps towards the production of human cell lines

In 2013, Mitalipov’s group published an impressive study (*Cell* 153; 1228-1238, 2013) in which they reported the production of human blastocysts, and how embryonic cell lines could be derived from them, and from these, cells of various tissues.

Regardless of the ethical difficulties of these experiments, since obtaining cell lines inevitably entails the destruction of the human blastocysts obtained, it has also been revealed that Mitalipov’s study apparently contained some errors. Thus reports an anonymous author on PubPeer, an online site in which readers can leave comments on published scientific papers (Cyranski D and Hayden EC *Nature/News* 23-05-2013). In this case, the writer highlighted the existence of four errors in the Oregon authors’ study. In defence, Mitalipov stated, in the same *Nature* article, that it was true, but that three of the four errors were “innocent mistakes” that occurred on putting the paper together and that the fourth was not an objective problem, adding that he did not consider it to be fully substantiated.

However, apart from these errors, the study by Mitalipov et al. can be considered as the first in which a human blastocyst was cloned, and from which human embryonic cell lines could be derived.

To obtain these blastocysts, human oocytes, apparently from young women, and somatic cell donor nuclei, obtained from fetuses and infants, were used.

That same year (2014) another article was published by Egli’s group (*Nature*, doi: 10.1038/natureA3287) in which skin cells from a newborn and a woman with type 1 diabetes were used to produce the cloned human embryo. Four embryonic stem cell lines were obtained from the embryo produced, which were then able to be derived into different cell types, among them pancreatic beta cells. These are insulin-producing cells, which could certainly be an important step in the treatment of patients with type 1 diabetes in the more or less near future.

However it has even gone one step further towards the production of human embryos, and specifically blastocysts, from which human embryonic stem cells can be derived. For this they used skin cells from two adult males (a 35-year-old and a 75-year-old) as nucleus donor cells (*Cell Stem Cell* 14; 1-4, 2014). The



Shoukhrat Mitalipov

authors remarked that their study showed, for the first time, the possibility of using adult human cells as nucleus donors for transfer into the enucleated oocyte, for somatic cell nuclear transfer. However, also in the aforementioned paper by Egli’s group, somatic cells from a woman with type 1 diabetes were used, i.e. somatic cells from an adult.

Nevertheless, be it one way or another, it should not be forgotten that to date, only human blastocysts have been produced. It remains unknown whether or not these will be viable, so it seems rather auda-

cious to state that human cloning has been achieved. Certainly human blastocysts have been produced, but there is a long way from that to the production of living human beings, and right now, we do not know if this distance can be overcome.

One final consideration is that, regardless of the technical importance that these advances may have in relation to regenerative and reparatory medicine, they have an insurmountable ethical difficulty, which is that all the experiments require the production of human blastocysts that must be destroyed af-

ter being produced, something that ethically seems difficult to justify. Would it not be better therefore, to direct research efforts towards the use of adult stem cells, iPS cells (Cell 126; 663-676, 2006) or STAP cells (Nature 505, 641-647, 2014.)?



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News

The ethical legal tangle of assisted reproduction

In mid-June, the European Court of Human Rights will be hearing the case of Adelina Parrillo versus Italy. The case goes back to 2002, when Adelina and her husband froze five embryos for future transfer. However, her husband died one year later. Adelina lost her dream of becoming a mother and requested that the embryos be destroyed. Right at the end of 2003, Italy approved a law prohibiting experimentation with embryos and their destruction. In 2011, Adelina decided to sue the Italian state before the Strasbourg court for violating her property rights over the frozen embryos. The NGO European Centre for Law and Justice will present its opinion before the Strasbourg Court. One of their arguments is that embryos cannot be objects of property, as they are subjects of law according to Italian legislation.

This is one of many unique and eccentric cases that have arisen since assisted reproduction practices began 25 years ago. The early ethical debates have given way to social and legislative resignation caused by the inertia of the facts, emotional appeals, chrematistic impulses and biological and semantic claudications.

However, this apparent factual normality hides numerous frustrations, future threats and unresolved problems. At the centre of this prickly issue stands the ethical status of the human embryo, by-passed

lazily and selfishly by scientists, bioethicists and legislators.

“Those who practice assisted reproduction or experiment with embryos, as with those who recommend certain contraceptive methods, are not unaware that, to a greater or lesser extent, these procedures imply the loss or destruction of human embryos”. Thus says pathologist and bioethicist Gonzalo Herranz in the preface of his new book “El embrión ficticio” (The fictitious embryo), in which, after extensive research, he takes apart the main biological

arguments used to justify the ethical irrelevance of assisted reproduction and embryo experimentation processes, “a paradigmatic example of how a weak biology necessarily leads to misleading bioethics”.

Hailed in its beginning as a system for repairing infertility, the assisted reproduction debate now is on whether it is ethical to choose the sex of an embryo or to discard it due to a risk of strabismus. It has

become consumer medicine aimed at satisfying preferences. As well as the legal tangle that has arisen with disputes that are difficult to resolve fairly, artificial fertilisation sometimes detracts from the sense of maternity and paternity, by putting them in a context where the contractual character prevails. And in its uncritical progress leaving thousands of “fateless” frozen embryos, an increase in the num-



ber of twins, growing eugenic temptations, surrogate mothers and mothers desperate after several fruitless cycles. Rethinking this reproductive iner-

tia is a bioethical challenge (Diario Médico, 28-IV-2014 to 4-V-2014).

New technology is leading to better knowledge of embryo implantation in the maternal uterus

Better knowledge of the mechanisms that govern embryo implantation in the uterus, besides being of great biomedical interest, also has unquestionable ethical interest. We must not forget the widespread controversy about when human life begins, as one group of experts in this field maintain that it starts when implantation of the embryo is consolidated, towards the 14th day of life (having begun roughly around the 7th day), while others contend that it begins with fertilisation.

The biological mechanisms related with embryo implantation are fairly unknown. Now however, a major step has been taken in relation to this, following the publication of an article in *Cell* (156; 1032-1044, 2014) by Ivan Bedzhov and Magdalena Zernicka-Goetz.

Interestingly, it was Zernicka-Goetz's team who, in 2001, demonstrated with a simple but clear ex-

periment that human life begins with the first division of the zygote.

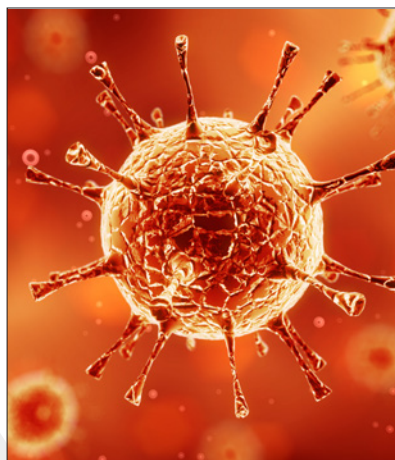
Bedzhov and Zernicka-Goetz have now provided new information on embryo implantation, showing that the blastocyst (the 60-200 cell embryo) that implants in the uterus is transformed from a small ball of cells to a more complex structure. The experiments were conducted in mice. Using a particular technique, they were able to record the entire implantation process, observing how the blastocyst is transformed into a kind of cellular rosette immediately before implanting in the uterus, which occurs on the 4th day of murine (mouse) embryo life. According to Zernicka-Goetz herself, "It's a beautiful structure. It's fascinating how beautiful we are then, and how these small cells organise so perfectly to allow us to develop".

New dilemmas in AIDS treatment

There is no doubt that HIV antiviral treatment is one of the major advances in medicine in the last 25 years. However, despite its prolonged use, the medication does not cure the infection. This is demonstrated by several facts: the detection of viral DNA and RNA in the cells of the huge majority of patients treated; the possibility of rescuing virus with replication capacity after *ex vivo* stimulation of lymphocytes in their blood; the persistence of residual viraemia (fewer than 50 copies of viral RNA per millilitre of blood) in most patients; the presence of the microorganism in secondary lymphatic tissues despite the medication; and the almost universal reappearance of the virus in the blood of those who abandon treatment.

Therefore, although antiretrovirals stop HIV replicating, they do not cure the infection, leading to an increase in the number of persons living with

the virus. This poses new challenges regarding the long-term clinical effects of treatment. Although the mortality in HIV positive individuals continues



to fall as treatments become better, there are still negative side effects. For example, the incidence of neoplasia, liver, cardiovascular and neurocognitive diseases and loss of bone mass in patients treated with antiretrovirals is higher than that in the general population, especially when the CD4+ T lymphocyte count is low.

Moreover, new infections need to be curbed urgently, since for every infected person who starts treatment, there are two new HIV infections. Stigma and discrimination, which remain despite access to therapy, must also be prevented. There is however, another even more important aspect: As the treatment is lifelong, patient compliance is not easy. Added to this are possible

toxicity and a high long-term economic cost, which limits universal access to therapy. Consequently, the development of strategies that seek sustained viral remission after a period of treatment would pro-

vide major individual, global and economic benefits (Javier Martínez-Picado, *Investigación y Ciencia*, July 2013; Fragment).

In Brief

01 The number of children per woman of reproductive age in Spain has fallen from 3.01 in 1964 to 1.32 in 2012. These rates per year were: 3.01 in 1964; 2.84 in 1970; 2.89 in 1974; 2.20 in 1980; 1.36 in 1990; 1.23 in 2000; 1.39 in 2007; 1.46 in 2008; 1.39 in 2009; 1.38 in 2010; 1.36 in 2011 and 1.32 in 2012 (Source: Spanish National Institute of Statistics).

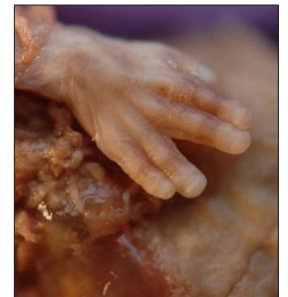
02 What are the views of the Christian Orthodox church on experiments with human embryos? In the opinion of Mark Hodges, of St. Stephen's Church in Lima, Ohio (Orthodox Research Institute; www.orthodoxresearchinstitute.org), the opinion is clear: they defend the life of the unborn, from the first, smallest and most fragile stages of development. They are opposed to ending the life of innocent human beings for any reason. This opinion coincides with that of the Synod of Bishops of the Orthodox Church in America (17 October 2001).



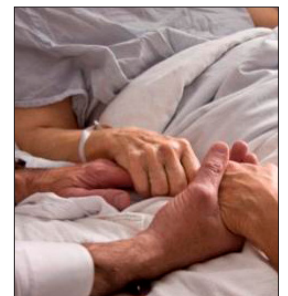
03 There is a passionate medical and ethical debate about whether genetic testing should be carried out on all women to detect whether they are carriers of BRCA genes, as carriers are known to have a much higher likelihood of developing breast cancer in adulthood. The topic was debated in a recent article in *Annals of Internal Medicine* (*Ann Intern Med* 160(4); 271-281, 2014), concluding that it should only be recommended in women with "family members who have breast, ovarian, tubal or peritoneal cancer"; however the aforementioned genetic test is not recommended in women with no family members with these types of cancers or mutations in the BRCA1 or BRCA2 genes.

04 The remains of more than 15,000 babies were incinerated as "clinical waste"

in British hospitals, with some even used to heat the hospitals themselves. Ten NHS (UK National Health Service) trusts have admitted that the foetal remains were burned together with other rubbish for incineration, while another two hospitals used the bodies in "waste to energy" plants to feed the heating system. One of the leading UK hospitals, Addenbrooke's in Cambridge, incinerated 797 babies below 13th weeks of gestation in their "waste to energy" plant. The mothers were told that the remains had been "cremated". Ipswich hospital, operated by a private company, incinerated 1,101 foetal remains between 2011 and 2013 (Sarah Knapton, Science Correspondent. "The Telegraph", 24 March 2014).



05 Since its introduction in the 1980s, palliative care has been developing little by little in Latin America. There are currently 922 services in 19 countries. This corresponds to 1.63 services per million inhabitants, so most patients in the region who require this treatment do not have access to it. The Atlas of Palliative Care in Latin America stresses that the development of palliative care in Latin America has been very slow and fragmented. Thus, it ranges from 16.06 services per million inhabitants in Costa Rica down to 0.24 in Honduras. Chile has the highest absolute number of services (277), while 46% are located in Argentina and Chile, accounting for 10% of the entire Latin American population. This confirms that governments must adopt the public policies and measures necessary to guarantee that the needs of the entire population are met (Vida Universitaria. University of Navarra. 21-III-2014).



06 Malaga-born Pablo Pineda, the first European with Down's Syndrome to obtain a university degree, has called for this disability to be considered normal, and asks that we respect the right to life of those who have it. This is in relation to the proposed reforms in abortion legislation in Spain, which is considering the possibility of aborting in the case of foetal problems, if this would result in demonstrable psychological damage for the mother. "It makes me sad that a person is denied the right to life because they have Down's syndrome, because we have a lot to contribute to society: happiness, optimism, tenderness and endless positive values. I can assure you that Down's syndrome is not suffered but enjoyed" states Pineda, at an event to commemorate World Down Syndrome Day on 21 March (Europa Press. Madrid. 19-III-2014).

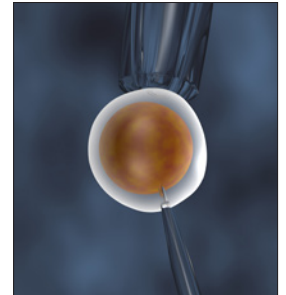


07 Three strange cases have been described of patients infected with HIV in whom the virus has not continued to replicate after stopping treatment. The first was described in 1999, and is known as the "Berlin patient". Now, a further two cases have been reported, the "Mississippi baby" and another in Massachusetts, also called the "Berlin patient". The latter was described in 2008 and unlike the "first Berlin patient", whose identity remains unknown, this patient's is known (New England Journal of Medicine 370; 682-683, 2014).



08 Between 1995 and 2012, antiretroviral treatments prevented 5.4 million deaths due to AIDS in under- and moderately developed countries, and averted the death of more than one million children by impeding mother-child transmission (New England Journal of Medicine 370; 495-498, 2014).

09 After several decades of in-vitro fertilisation and intra cytoplasmic sperm injection (ICSI), the pregnancy and birth rate has often been mentioned. While these rates have apparently not been well determined in the United States or England (Reproductive Biomedicine. Online 27; 1-3, 2013), figures are available for Australia and New Zealand for the period 2009-2011. The pregnancy rate for women commencing this treatment is 54% and for live births is 40%, after five cycles. These rates do not improve when the number of cycles exceeds five (Reproductive Biomedicine. Online 28; 405, 2014).



10 Do children born as a result of in-vitro fertilisation or ICSI have medical problems? A recent review on the subject (Reproductive Biomedicine online 28; 162-182, 2014) concluded that: "IVF-conceived children have lower birthweights and higher peripheral fat, blood pressure and fasting glucose concentrations than controls". The risk of imprinting disorders is less than 1%. It was not possible to establish whether some of the problems are due to the older age at which women undergo these procedures, or to the assisted reproduction techniques themselves. It concluded therefore that further studies are required to be able to confirm whether there are long-term health problems in assisted conception children.