Taylor & Francis
Taylor & Francis Group

Accountability in Research

Policies and Quality Assurance

ISSN: 0898-9621 (Print) 1545-5815 (Online) Journal homepage: https://www.tandfonline.com/loi/gacr20

Breaking the germline barrier in a moral vacuum

Sheldon Krimsky

To cite this article: Sheldon Krimsky (2019): Breaking the germline barrier in a moral vacuum, Accountability in Research, DOI: 10.1080/08989621.2019.1644171

To link to this article: https://doi.org/10.1080/08989621.2019.1644171

Accepted author version posted online: 15 Jul 2019.
Published online: 26 Jul 2019.

ACCOUNTABILITY IN RESEARCH
https://doi.org/10.1080/08989621.2019.1644171

Taylor & Francis
Taylor & Francis Group

Breaking the germline barrier in a moral vacuum

Sheldon Krimsky

Department of Urban & Environmental Policy & Planning, Tufts University, Medford, MA, USA

ABSTRACT

In November 2018 a Chinese scientist claimed to have used CRISPR/Cas 9 technology to genetically modify two human embryos that were then gestated in one adult woman through an IVF pregnancy and brought to term. The twin girls are allegedly the first babies born with their prenatal genomes edited. Using both English language and Chinese supporting documents, this paper discusses the background of this human experiment, the social context of Chinese science, and the alleged ethical transgressions of its principal scientist.

KEYWORDS

CRISPR/Cas9; gene editing; human embryos; AIDS; CCR5; HIV

Introduction

The international science community was caught off guard in late November 2018 when Chinese scientist Dr. He Jiankui announced through the media that he had used CRISPR/Cas9 editing technology to modify the genes of two human embryos, which were subsequently implanted in a Chinese woman by IVF techniques and brought to term as fraternal twin girls. The world press announced this report as the first genetically edited babies. *New York Times* journalist Pam Belluck wrote that Dr. He's announcement (on a video posted November 25) "sent a thunderbolt through the scientific world" (Belluck 2018). An initial investigation by Chinese state authorities confirmed in late January 2019 that human embryos were genetically altered by Dr. He and his collaborators, implanted in a woman, and brought to term (Ramzy and Wee 2019) .

Dr. He is an associate professor at Southern University of Science and Technology in Shenzhen, China. He has been on unpaid leave since February 2018, according to a report in the *New York Times* (Kolata, Wee, and Belluck 2018), and is expected to be on leave until 2021 (Harney and Kelland 2018). Dr. He reported his results at the Second International Summit on Human Genome Editing, held in Hong Kong November 27–29, 2018 (Second International Summit on Human Genome Editing 2018). Dr. He also spoke about his work on editing a gene in human embryos a year earlier at a conference at the Cold Spring Harbor Laboratory in

CONTACT Sheldon Krimsky sheldon.krimsky@tufts.edu Department of Urban & Environmental Policy & Planning, Tufts University, Medford, MA 02155, USA

New York, held on July 21–23, 2017 (He 2017). In his Power Point presentation, Dr. He cited his 2009 co-authored paper on CRISPR (He and Deem 2009). This paper was at the very early stages of CRISPR's discovery as it addressed bacterial and archaeal DNA, which had been shown to possess a new type of antiviral immune system and had not yet been applied to eukaryotic (i.e., human) cells.

Dr. He also discussed off-target effects and the efficiency of embryo editing of mice, monkeys and humans. According to Dr. He, most of the embryos he edited resulted in mosaics, some with the edits and some without. Dr. He suggested methods for getting higher efficiency and minimizing off-target effects. At the end of his talk he referred to the fatal gene therapy experiment on Jesse Gelsinger as a note of caution. But Dr. He never mentioned that his edited embryos were going to be implanted in women. That final step is what shocked the scientific community.

Dr. He's intention was not to cure a disease in the embryos, but rather to instill a trait that would endow the embryo and the adult child resistance to HIV infection. In his Informed Consent statement he referred to his research as an "AIDS vaccine development project." His approach was theoretically possible because it is believed that the HIV virus can only enter the cell when a certain co-receptor protein known as CCR5 is present in the cell's surface. If CCR5 is absent by a genetic mutation or deletion, then it is presumed the individual would be resistant to the HIV infection. However, it is known that not all HIV variants need CCR5 for infection although it is considered the main receptor involved in the virus entry into cells and has been the principal target for drug discovery (Lopalco 2010). Dr. He claimed that by using CRISPR/Cas9 gene editing technology he knocked out the gene that codes for the co-receptor protein thus making the embryo resistant to HIV. As the embryo develops into the billions of cells that make up a person, if the CRISPR deletion is stable, every cell in the body will have the deletion. If it is not stable, some cells will retain the deletion while others will retain the gene for the receptor protein, an outcome known as mosaicism.

While these may be the first CRISPR generated babies, it is not the first genetically modified baby if we count non-nuclear, mitochondrial DNA. Several experiments in embryo modification by ooplasmic transfer from donated eggs represent the first known genetic modification of embryos with foreign mitochondrial DNA. These experiments on embryos brought to term were carried out at the Saint Barnabas Medical Center in West Orange New Jersey by Jacques Cohen (Krimsky 2015). Subsequent to Cohen's experiments in the United States, Dr. John Zhang, an infertility expert at the New Hope Fertility Center in New York City, conducted a mitochondrial transfer in Mexico (Zhang et al. 2012).

CRISPR/Cas 9 has also been applied to non-viable human embryos where Chinese scientists used tripronuclear (3PN) zygotes to investigate gene editing

of human cells (Liang et al. 2015). If Dr. He's claims and data are validated then his team has produced the first CRISPR-modified babies. Doubts have been raised, however, about whether Dr. He has achieved what he has alleged. Ethical concerns have also been raised about his clinical trials on embryos.

Dr. He's background

According to his publicized resume, Dr. He acquired a Bachelor of Science in Modern Physics at University of Science and Technology of China (2002–2006). He attended Rice University between 2007–10 and was awarded a PhD in Biophysics. Following Rice, he attended Stanford University in a Postdoctoral position from 2011–12. One statement of Dr. He's credentials also states that he was awarded a AAAS-SWARM prize for his doctoral thesis in 2010. A Pub Med search using "He, Jiankui" revealed 19 articles under "He, J." that he coauthored (his website listed 13 articles), some on sequencing viral DNA and only one published article involving CRISPR techniques. There were no citations under his name in Web of Science and 4 citations in Science Direct, none involving CRISPR.

Dr. He reported that he had visited one of the AIDS villages in China, where nearly 30% of the population was infected with HIV. AIDS spread like wildfire in China when blood-selling became an established enterprise. Several hundred blood markets were licensed but there were many illegal ones. Dozens of villages had AIDS epidemics especially in Henan and Wenlou (Siling 2016). According to He, the villagers wanted to send their children to healthy relatives, so they could raise them and avoid their risk of AIDS infection (Wang 2018).

Donated embryos for the CRISPR procedure

It has been reported that the men participating in the embryo experiment, whose sperm fertilized their wives' eggs, had previously contracted AIDS. The disease is highly feared in China and those who have contracted AIDS are stigmatized by others in the Chinese population. Initially, the state had declared AIDS a Western disease resulting from drug use and homosexuality. There were social incentives for families affected by AIDS to protect their newborns against the virus. Also, some families feared the father's infected sperm could transfer AIDS to the embryo. There were reasonably inexpensive ways of protecting such an outcome including sperm washing of a father's infected sperm (McLaughlin 2018). In sperm washing, individual sperms are separated from the semen preceding artificial insemination. The process removes chemicals from the semen and significantly reduces the risk of HIV infection when the sperm donor is HIV positive but does not completely eliminate the risk (WHO semen washing).

This was not the first time that scientists used CRISPR to alter the genes of human embryos. As previously noted, Chinese scientists altered non-viable human embryos using CRISPR/Cas9 in April 2015 (Liang et al. 2015). Those scientists had no intention of implanting the embryos.

Dr. He's CRISPR process and results

Speaking at an international meeting in Hong Kong in late November 2018, Dr. He described his process for editing the embryos. "The gene editing occurred during IVF, or lab dish fertilization … a single sperm was placed into a single egg to create an embryo. The gene editing tool was added. When the embryos were 3 to 5 days old, a few cells were removed and checked for editing. Couples could choose whether to use edited or unedited embryos for pregnancy attempts. In all, 16 of 22 embryos were edited, and 11 embryos were used in six implant attempts before the twin pregnancy was achieved" (Marchione 2018). Dr. He used multiple microinjections of the CRISPR editing molecule to enhance the results of the gene edits. He found one off-target edit in an embryo before it was implanted but considered it unlikely to affect the biological function of the baby. Having sequenced DNA after the birth of the twins, Dr. He reported that he did not detect any off-target effects (Begley 2018).

Dr. He issued a YouTube video on his embryo edits and gave a slide presentation at the Hong Kong international conference on gene editing. In his video report Dr. He wrote:

> Two Chinese girls, who we'll call Lulu and Nana to protect their privacy, were born healthy a few weeks ago. Their mother Grace started her pregnancy by regular IVF with one difference: right after sending her husband's sperm into her eggs, an embryologist also sent in CRISPR/Cas9 protein and instructions to perform a gene surgery intended to protect the girls from future HIV infection. The surgery reproduces a natural genetic variation shared by more than 100 million people of primarily European origin that confers strong resistance to initial HIV-1 infection and disease progression. While CRISPR/Cas9 has been studied in human cells and in early clinical trials, gene surgery in embryos intended for pregnancy has not previously been reported. Safety remains a key concern, particularly for unintended changes to the genome. To assess the girls' genomes for safety after the surgery, multiple whole genome and targeted deep sequencing techniques were used before implantation, during the pregnancy, and now after birth. These data indicate the girls' genomes were changed as intended by the gene surgery, but no off-target edits or large deletions occurred. Further assessments to confirm these findings will be conducted over the next year. We will publish our full data soon (He Jiankui YouTube).

While his work has thus far not been published or independently evaluated, some scientists have seen some of his data from a slide presentation he gave at the international conference in Hong Kong. According to a report in *The*

Scientist based on the data Dr. He presented, several scientists were skeptical that he was successful in disabling the ideal DNA sequence (32-base pair deletion) to create the resistance to HIV. He's data showed that one of the embryos had a 15-base pair deletion, while the other embryo had a four-base pair deletion suggesting that He did not excise the full DNA sequences (Zimmer 2018).

At the Hong Kong meeting, Dr. He reported that only one allele was edited in one of the twin-sister embryos, making HIV immunity impossible even if it were the correct DNA deletion. Also, he said that all of the embryo's cells were not successfully edited resulting in mosaicism (Dyer 2018). His talk included some comments about off-target effects. He said: "Another safety concern is off-target effects. [For] embryo targeting of a few cell stages of life, any off-target [effects] would pose very serious consequences and extend potentially through the whole body" (He 2018).

The method and results of the embryo editing were not published. There is no evidence that the methods were peer reviewed and the data independently evaluated. China's National Health Commission ordered provincial health officials to investigate the experiment. Both Shenzhen's Medical Ethics Committee and the Guangdong Provincial Health Commission announced they were investigating Dr. He's activities (Harney and Kelland 2018).

Social context of Chinese science

What do we know about the structure of Chinese science, particularly in biomedicine, that would help us understand the behavior of Dr. He? As we shall see in a following section, there have been international scientific meetings held as far back as 1988 continuing through 2017 advocating that there should be a moratorium on genome editing. Was Chinese science lax in supporting these international norms? Or was Dr. He a renegade scientist neglecting current national and international standards?

According to Dickenson and Darnovsky (2019) Dr. He's choice to undertake embryo editing came about from an international climate of permissiveness. They site the Neufield Council (UK) report on germline editing calling it permissible and even "ethically obligatory" if done under certain circumstances. The authors argue that "without a robust and meaningful airing of the perils of human germline modification, these views are likely to encourage additional, more mainstream moves in the same dangerous direction" (Dickenson and Darnovsky 2019).

No one in the United Kingdom or the United States breached the norm that was widely embraced in 2018, namely that human genome editing was not ready for clinical trials. But since the world scientific community had not established an absolute prohibition against it, that might have played a role in Dr. He's decision as suggested by Dickenson and Darnovsky.

In my view, the conditions in his country were more important. And while no single factor may offer a sufficient cause of Dr. He's decision, the totality of conditions do help us understand how the scientific culture affected his decision. According to a preliminary investigation by Chinese officials released in late February 2019, Dr. He was described as a renegade scientist. "He deliberately sidestepped regulations, dodged oversight, and used fake ethical review documents" (Normile 2019). By itself, this statement suggests that Chinese science was not permissive of such experiments. However, Chinese ethicists and researchers reportedly claimed that the relevant regulations date back to 2003 and pre-dated CRISPR. A biologist at Peking University in Beijing said that Dr. He was functioning under a "chaotic situation," suggesting that he was able to exploit the outdated rules to undertake his embryo experiments (Normile 2019). After its investigation of Dr. He China tightened its regulations.

Other than the lax regulations, there is evidence and corroboration of intense competition among Chinese scientists to succeed, which provides an additional context for Dr. He's decision to produce the first CRISPR babies. A dramatic rise in the scientific publications among Chinese scientists has been observed over the last ten years, including highly cited publications. The Chinese government has also increased investment into science and technology and introduced incentives to turn discovery into commercial products.

Beginning with the reform policy in 1978, Chinese universities expanded from teaching and conducting research to supporting technological development. The state developed a legal framework for establishing ties between universities and business enterprises, somewhat analogous to the Bayh-Dole Act in the United States (Wang et al. 2013). Between 1991–2002 there was a sizable expansion in the collaborations between Chinese universities and Chinese enterprises based on co-patenting activities. That resulted in co-publishing between university and company scientists. Studies showed that these partnerships influenced the firms' innovation performance.

Universities have become a key component in China's national innovation initiative. The country has turned from a centrally planned system of resource allocation to one that utilizes principles of the free market. For several decades China has created incentives through the passage of hundreds of laws to foster the collaboration between business-style enterprises, universities and research institutes (Gao, Guo, and Guan 2014).

In 2006 the development of a bioindustry became one of the top priorities of the new Chinese economy. Six years later biomedicine was one of the seven major field in the biotechnology sector. Since 2006, China has acquired 21 percent of the global biotechnology patents, ranking second in the world behind the United States. In 2018 *Nature* reported that China overtook the United States in the total number of publications, based on statistics from the

National Science Foundation, with 426,000 Chinese studies in 2016 (18% of the total) versus 409,000 U.S. studies (Tollefson 2018).

The pressure to publish and to achieve major breakthroughs among Chinese scientists has been recognized as intense. It has been reported that retracted scientific papers from Chinese authors are disproportionately higher than authors from other countries (Jia 2017). The heightened pressure to publish high ranking articles has also resulted in unprecedented cases of research misconduct. *Science Magazine* reported in 2006: "An unprecedented number of researchers stand accused of cheating – from fudging results to fabricating data – to gain fame or plum positions" (Marshall 2006, 1464).

A scientist from the Chinese Academy of Sciences was quoted as saying: "The combination of pressure and incentives has nurtured an environment that's rife with simultaneous or serial duplicate manuscript submissions, self-plagiarized cookie-cutter papers, individual and institutional honorary authorship, and outright plagiarism" (Marshall 2006, 1465). China has been found to be the 7th highest retraction nation (based on papers published) behind Iran, Romania, India and South Korea (Science Magazine News 2018). Schmitz reported for NPR that "scientists and legal experts say China's economic, social and political environment helped create him" (Schmitz 2019).

The three-part incentive system in Chinese science includes: international recognition, commercial application of research, and business partnerships including the acquisition of intellectual property. Jiankui He was immersed in this social system, embedded in scientific culture that was supposed to take risks in order to gain international prestige. He was part of a biological and medical community that was at least indefinite about gene editing embryos. While there were rules for human experiments, they were outdated and not considered inviolable for achieving success.

Without strict international rules, and operating under lenient Chinese guidelines with powerful national incentives for risk taking, Dr. He could well have seen his role as the vanguard in an ethical frontier. By March 2019, after world scientific opinion was heavily weighted against Dr. He's experiment, the Chinese health ministry released draft guidelines that requires human gene editing be approved by the ministry (Nature editorial 2019).

Moral issues

In this section I shall examine the moral conduct of Dr. He's experiments on editing embryos, based on his interviews with the media, the informed consent document for his clinical trial, comments and a slide presentations at a national conference, statements he made on his website, and news stories in English and Chinese. Based on this body of evidence, there appear to be a number of serious violations of responsible conduct of research and

contemporary scientific norms in his experiments on the genetic editing of human embryos and the creation of CRISPR babies. I previously classified these infractions in another publication (Krimsky 2019). I shall begin by situating Dr. He's experiment within the context of consensus positions taken at international science meetings.

International consensus statements on genome editing

Various sectors of the international scientific community have supported either a moratorium or a ban on editing human germ cells or embryos prior to Dr. He's work. At a workshop on International Cooperation for the Human Genome Project in Valencia, Spain in October 1988 a French researcher proposed a moratorium on the manipulation of gametes and embryos (Elias and Annas 1992). The Council for International Organizations of Medical Sciences, under the auspices of the Science Council of Japan and co-sponsored by the World Health Organization, issued the Declaration of Inuyama in 1990, which stated that the alteration of germ cells is not at present a prospect and continued discussion of its ethical and technical aspects is essential. Participants numbered 102 from 24 countries representing all continents. At the final session the conference agreed on the Declaration (CIOMS 1991).

The Convention of Human Rights and Biomedicine within the Council of Europe passed Article 13 that came into force 12 January 1999, which states: "An intervention seeking to modify the human genome may only be undertaken for preventative, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants. It was ratified by 29 countries by 2018 (Council of Europe Convention on Biomedicine 1997). In 2003, the International Bioethics Committee of UNESCO stated: "Because of the many technical problems and uncertainties about possible harmful effects on future generations, germ-line intervention has been strongly discouraged or legally banned" (Galjaard and International Bioethics Committee, UNESCO 2003). The International Summit on Human Gene Editing, 2015 Washington D.C. Organizing Committee Statement supported a moratorium on gene editing embryos until certain conditions could be met. The 12-member organizing committee stated that it would be irresponsible to proceed with any clinical use of germline editing unless and until (i) the relevant safety and efficacy issues have been resolved, based on appropriate understanding and balancing of risks, potential benefits, and alternatives, and (ii) there is broad societal consensus about the appropriateness of the proposed application. Moreover, any clinical use should proceed only under appropriate regulatory oversight. At present, these criteria have not been met for any proposed clinical use: the safety issues have not yet been adequately explored; the cases of most compelling benefit are limited;

and many nations have legislative or regulatory bans on germline modification (International Summit on Human Gene Editing: A Global Discussion. First International Summit 2015). The American Society of Human Genetics. On 3 August 2017 issued a statement that "Future clinical application of human germline gene editing should not proceed unless, at a minimum, there is (a) a compelling medical rationale, (b) an evidence base that supports its clinical use, (c) an ethical justification, and (d) a transparent public process to solicit and incorporate stakeholder input" (Ormond et al. 2017). These international declarations speak to the scientific consensus that researchers were not to move precipitously into human germ line editing.

Dr. He produced his own list of ethical issues on his website titled "Ethical Principles of Therapeutic Assisted Reproductive Technology." Included among his list of five principles he wrote: "Gene surgery is a serious medical procedure that should never be used to design a child for aesthetics, enhancement, or sex selection purposes or in any way that would compromise a child's welfare, joy, or free will. No one has the right to determine a child's genetics except to prevent a disease" (Weibo 2018). There was no reference in his ethical guidelines to Chinese regulations or international consensus guidelines. Nor were such references cited in his paper on the ethical principles published in *The CRISPR Journal* (He et al. 2018).

By the time Dr. He had completed his embryo editing experiments, the Organizing Committee of the Second International Summit in Gene Editing in Hong Kong wrote that "it would be irresponsible to proceed with any clinical use of heritable 'germline' editing at this time … and that heritable genome editing of either embryos or gametes poses risks that remain difficult to evaluate" (Second International Summit on Human Genome Editing. Statement by the Organizing Committee 2018). The international scientific community seemed to be in unanimous agreement that Dr. He's human experiment was outside the boundaries of scientific consensus and should not have been done.

Failure to report studies on CRISPR edits of primate and human embryos

There have been recent studies warning about the dangers of editing embryos with CRISPR/Cas9. For example, So et al. writing in *Frontiers in Genetics* discussed the risks of CRISPR. "Given our lack of experience with these technologies, the use of CRISPR in a human embryo at this stage would be more likely to produce mosaicism and off-target effects than the desired enhancement. Modifications capable of being inherited by future generations must also be held to especially rigorous safety standards. The risk of introducing disorders into the germline of a healthy embryo, or of providing RCD to some diseases at the cost of increased vulnerability to others, ought to be taken into account in the calculus of labeling interventions as enhancement" (So et al.

2017). It is universally acknowledged that invasive therapies on human subjects must be preceded by approved and successful animal experiments before these subjects are subjected to risks. There is no evidence that this was accomplished prior to Dr. He's human experiment by his research team.

Dr. He reported that he has spent three years editing of embryos of mice, primates and humans (Belluck 2018). Yet, there are no publications in English language journals of these experiments and the risks of off-target effects. Understanding these effects is one of the most important preconditions of engaging in either somatic cell or embryo editing with CRISPR.

Responding to his experiments, a group of Chinese scientists wrote "Jiankui He acknowledged that his sequencing work could only cover 80% of the genome at best. This means that he does not have the ability to comprehensively examine whether the off-target phenomenon in the research is really absent as he said before … . even with such incomplete data, Jiankui He had actually observed off-target effects in one of the implanted embryos" (Weibo 2018).

Scientific criticism of Dr. He's genome edits

Much of the criticism against Dr. He was not against the idea behind gene editing embryos per se, but rather that he disregarded the current consensus across the scientific community, particularly that the risks were not sufficiently understood and public acceptance was still in doubt. Leading scientists and bioethicists throughout the world concur that Dr. He's experiments violated ethical standards. Some examples from this group are: Josephine Johnston, a lawyer and bioethicist at the Hastings Center said that Dr. He violated research ethics and acted ahead of national and international consensus on whether and under what conditions it is appropriate to edit an embryo's genes (Saey 2018). G. Own Schaefer, research assistant professor in biomedical ethics at the National University of Singapore cited "serious risks and lack of necessity" of the embryo experiments. "He's recklessness, then, was not limited to risk but also to failing to earn public trust and buy-in before proceeding" (Schaefer 2018). Eric Topol, professor of molecular medicine at the Scripps Research Institute wrote that Dr. He's experiments were "unethical when balanced against the known and unknown risks … a misguided, reckless demonstration of using powerful gene-editing tools to create edited human beings" (Topol 2018). NIH Director Francis Collins said that Dr. He "flaunted international ethical norms" (Belluck 2018). The National Academies of Sciences, Engineering and Medicine stated a consensus view that gene-edited babies would be acceptable but only if they could be created safely and over strict oversight (Regalado 2018).

In an open letter listing ten questions directed at Dr. He, scientists wrote: "the CCR5 gene is known to have important biological functions, such as immune

system function and neurodevelopmental function. Even if He Jiankui only destroys the CCR5 gene, it can still cause serious diseases." The scientists who signed the letter questioned how Dr. He can prove the safety of the research (Xiansheng 2018). Dr. He did report that he had a plan to monitor the children for the next 18 years, a claim not made in the informed consent statement.

Non-compliance with Chinese ethical guidelines

In an interview, Dr. He claimed to have reviewed the Chinese authoritative ethical guidelines on embryo editing but did not abide by them (Guokr.com 2018). China does not explicitly ban human embryo research including the use of CRISPR editing but does prohibit the implantation of embryos used in research under a 2003 ministerial guidance to IVF clinics (Regalado 2018). Dr. He listed his embryo research on China's Clinical Trial Registry. The registry noted: "[Dr. He's trial has] been withdrawn for the reason that the original applicants cannot provide the individual participants' data for reviewing safety and validity evaluation of HIV immune gene CCR5 gene editing in human embryos" (Clinical Trial Registry). His research was condemned by more than 300 international Chinese scientists, 140 Chinese HIV and AIDS researchers and over 100 independent groups worldwide (Dyer 2018). In a joint letter, the signatories wrote "The technology for genome-wide sequencing of individual cells is not mature. He Jiankui also acknowledges that his sequencing work can only cover about 80% of the genome at best. This means that he does not have the ability to comprehensively examine whether the off-target phenomenon in the study is really absent as he said" (Xiansheng 2018). Kang et al. (2016) wrote: "We advocate preventing any application of genome editing on the human germline until after a rigorous and thorough evaluation and discussion are undertaken by the global research and ethics communities" (Kang et al. 2016). According to the initial state investigation into Dr. He's embryo editing, he was accused of violating state rules on gene editing, evaded supervision of his clinical trial, used unsafe and ineffective methods, and forged the ethics approval form (Zhang 2019).

Dr. He claimed to have received approval from a bioethics committee. Harmonicare Hospital in Shenzhen, the hospital to which he was associated, issued a clarification statement on 27 November 2018. "Upon preliminary investigations by the company, the signatures of the application for review by the Medical Ethics Committee of the Shenzhen Harmonicare Hospital circulated on the internet are suspected to have been forged, and no relevant meeting at the Medical Ethics Committee of the hospital in fact took place" (Harmonicare Hospital 2018).

Violated university norms

Dr. He's university, The Southern University of Science and Technology, disavowed any knowledge, funding, or involvement in his embryo experiments. This is highly unusual, even for someone who has an unpaid leave. Dr. He, who admitted not informing his university of his embryo experiment, stated that he had gotten ethics approval from Shenzhen Harmonicare Women's and Children's Hospital for the trial. As stated previously, hospital officials claimed to have no knowledge of the births. However, one Harmonicare administrator who heads the hospital's ethics panel was quoted as saying that the editing and implantation of the embryos was ethical (Marchione 2018). There has yet to be a full accounting of the role the hospital played in Dr. He's clinical trial (Sohu News 2018).

Choosing to enhance an embryo/person

The widely accepted consensus position among scientists is that if CRISPR were ever to be approved as safe and effective enough to be used on embryos that would be brought to term, the goal should be to cure a life threatening or debilitating disease for which alternative methods of cure or treatment are not possible. Dr. He chose as a goal to make the baby resistant to HIV, for which there are preventative measures and, should they fail, successful treatment. The spread of HIV is clearly a global public health problem. However, no responsible public health authorities consider gene editing of embryos as a sound approach for preventing infection from this virus. From his personal ethical guidelines, it appears that Dr. He does not view his approach to gene editing HIV resistance into the genome as enhancement.

Financial inducements of parents

The consent form described the payments to the parents involved in the embryo editing. The treatments covered in the payments included IVF, supportive care for the IVF pregnancy, and a daily allowance added up to about US$ 40,000. This represents over four times the annual average wage of an urban Chinese family (Schaefer 2018). Paying parents such excessive fees to participate in a trial can influence and distort the way the parents view the benefits and risks. The inducement rather than the potential outcome becomes the benefit. In an interview with Hua Bai, Dr. He claimed his research was funded by the government and treatment and participation was free for parents seeking a pregnancy. The state's interim investigation makes no mention of government involvement, but claims

Dr. He acted on his own (Zhang 2019). Hua Bai noted: "it seemed like Jiankui He didn't have any interpersonal relationships in the area of AIDS treatments. He just wanted to apply the technology to this area" (Wang 2018).

Informed consent process

Parents participating in Dr. He's embryo experiments were given a 23-page informed consent document in Chinese. The risks from the use of CRISPR/Cas9 listed in the Informed Consent form were downplayed. There is no discussion about what off-target effects can do to a child, although Dr. He had acknowledged the seriousness of those effects. He also did not discuss how the deletion of CCR5 can make a person more vulnerable to other diseases, which is part of explaining all the risks to the parents. The language and concepts in the Informed Consent form use terms that ordinary individuals, even those with a college education, would find difficult to understand. For example, "this technique can cause nonspecific cleavage resulting in mutations in non-targeted genome sites" (Informed Consent Form 2018). Under the method section, the document looks more like a grant proposal than an informed consent statement delivered to people without a scientific and medical background.

> Method: Based on the human assisted reproductive technology, early embryos were infected with trace amounts of Cas9 RNP after intracytoplasmic sperm infection (ICSI) during normal IVF treatment. Cas 9 RNP (Cas9 protein and optimized optical sgRNA) can act on the CCR5 gene, so as to prevent the newborn from the AIDS by editing the CCR5 gene and hindering the HIV-1 virus from invading the (CD4+) T cell" (Informed Consent Form).

The terminology is so far from what a general audience could grasp. It would never meet the U.S. standards for communicating with patients. During a question and answer period at the Hong Kong meeting, Dr, He was asked about the parents given the informed consent form.

(Q) "Could they read [the informed consent form] and understand it?"

(A) "Yes, they were very well education (He Transcript).

Also, the consent form states: "this project team is not responsible for the risk of off-target which is beyond the risk consequences of the existing medical science and technology." In other words, if the investigators cannot detect the off-target effects, then they are not responsible for them. The document does state that the parents can ask questions to the investigators who will explain anything to them in the consent form they do not understand. Members of the Chinese scientific community raised

questions about Dr. He's informed consent process. "Jiankui He repeatedly emphasized that he prepared detailed informed consent [for the parents] and spent 10 minutes (later said 1 hour and 10 minutes) in discussing all details with every subject. But we noticed that the 20-page informed consent form was full of scientific terminology. How did they make the subjects truly understand the intrinsic risks of the research in just 10 minutes or 1 hour and 10 minutes?" (Weibo 2018). Further in-depth studies can reveal whether the language in the document was satisfactorily understood by the parents and whether all their questions about risks and benefits were adequately answered.

Conflicts of interest

While it is not a universal practice in science to disclose potential conflicts of interests of principal investigators in a clinical trial, it has become a widely adopted norm after the Jesse Gelsinger case at the University of Pennsylvania (Krimsky 2003).

Dr. He has roles in four companies in Guangdong Province and another company in Beijing. He is an investor in eight companies. One of his principal companies is Genomics Biotechnology, a DNA sequencing company that markets smaller and cheaper DNA sequencing devices (Coleman 2018). No mention is made of any of these affiliations nor of any affiliated companies that could benefit from the genetic modification of human embryos in the informed consent form. Omission of any disclosure of financial affiliations by a principal investigator in a clinical trial can tarnish the trust relationship between the researcher and the clinical participant.

Conclusion

From the list of ethical violations and the condemnation of Dr. He's embryo trial across the global scientific community, it can be reasonably concluded that the gene-edited babies he created will stand as one of the most controversial human experiments in post-World War II science. This will be true even if the experiment as a whole or in part is deemed scientifically successful, which is still uncertain but unlikely. The paper describing this experiment has not yet been published and it is not certain that it will. The world is now awaiting a full and transparent investigation of Dr. He's CRISPR embryo experiment as well as international criteria on whether and to what extent human embryos should ever be genetically modified prior to implantation. In the middle of March 2019, 18 prominent scientists signed a commentary in *Nature* calling for a moratorium on heritable genome editing until an

international governance framework could be established. Among them Paul Berg who was supportive of the moratorium on certain recombinant DNA experiments in the early 1970s and a leader of the Asilomar meeting in 1975 (Lander et al. 2019). Soon thereafter, the World Health Organization called for a global registry of studies that involve editing the human genome (Reardon 2019).

Disclosure statement

No potential conflict of interest was reported by the author.

References

Begley, S. 2018. "Amid Uproar, Chinese Scientist Defends Creating Gene-Edited Babies." STAT, November 28. https://www.statnews.com/2018/11/28/chinese-scientist-defends-creating-gene-edited-babies/

Belluck, P. 2018. "Gene-editing Scientist Defends His Work, but Others Call It Irresponsible." *New York Times*, November 29.

CIOMS (Council for International Organizations of Medical Scientists). 1991. "The Declaration of Inuyama and Reports of the Working Groups." *Human Gene Therapy* 2 (2): 123–129.

Clinical Trial Registry. China. Accessed 8 December 2018. http://www.chictr.org.cn/showprojen.aspx?proj=32758

Coleman, Z. 2018. "The Business behind the Doctor Who Manipulated Baby DNA." *Nikkei Asian Review*, November 27.

Council of Europe Convention on Biomedicine. 1997. "The Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine." *Human Reproduction*. 12 (9): 2076–2080. September. doi:10.1093/humrep/12.3.503.

Dickenson, D., and M. Darnovsky. 2019. "Did a Permissible Scientific Culture Encourage the 'CRISPR Babies' Experiment?" *Nature Biotechnology* March. doi:10.1038/s41587-019-0077-3.

Dyer, O. 2018. "Researcher Who Edited Babies' Genome Retreats from View as Criticism Mounts." *BMJ News*. 363 (8179): k5113. 30 November.

Elias, S., and G. J. Annas. 1992. "Somatic and Germline Gene Therapy." In *Gene Mapping: Using Law and Ethics as Guides*, edited by G. J. Annas and S. Elias, 142–154. Oxford, UK: Oxford University Press.

Galjaard, H., and International Bioethics Committee, (UNESCO) United Nations Educational, Scientific and Cultural Organization). 2003. *Report of the IBC on Pre-Implantation Genetic Diagnosis And Germline Intervention*. Paris. April 24. 1–27. http://unesdoc.unesco.org/images/0013/001302/130248e.pdf

Gao, X., X. Guo, and J. Guan. 2014. "An Analysis of the Patenting Activities and Collaboration among Industry-university-research Institutes in the Chinese ICT Sector." *Scientometrics* 98: 247–263.

Guokr.com. 2018. November 30. https://mp.weixin.qq.com/s?__biz=MTg1MjI3MzY2MQ==&mid=2651703619&idx=1&sn=9a57dfdb9e0e6e7ecc3b6f19bff3e74f&chksm=5da1edd16ad664c7fcae77

Harmonicare Hospital. 2018. File:///E:/PAPERS%202018/GE%20BABIES/GE%20BABIES/CLARIFICATION%20ANNOUNCEMENT%20REGARDING%20Dr.%20He PDF

Opening page in the statement by Harmonicare Hospital, Shenzhen related to the claims by He Jiankui

Harney, A., and K. Kelland. 2018. "China Orders Investigation after Scientist Claims First Gene-edited Babies." *Reuters*, November 26. Accessed 23 March 2019. https://www.reuters.com/article/health-china-babies-genes/chinese-university-to-investigate-after-academic-claims-to-have-edited-twins-genes-idUSL4N1Y12P6

He, J. 2017. "Cold Spring Harbor Lecture Titled: Evaluating the Safety of Germline Genome Editing in Human, Monkey and Mouse Embryos." Conference Titled: Genome Engineering: The CRISPR-Cas Revolution, July 21–23. https://www.youtube.com/watch?V=llxNRGMxyCc

He, J., and M. W. Deem. 2009. "Heterogeneous Diversity of Spaces within CRISPR (clustered Regulatory Interspaced Short Palindromic Repeats)." *Physical Review Letters* 17 September. https://www.youtube.com/watch?V=llxNRGMxyCc

He, J., R. Ferrell, Y. Chen, J. Qin, and Y. Chen. 2018. "Draft Ethical Principles for Therapeutic Assisted Reproductive Technologies." *The CRISPR Journal* 1 (6): 1–3. doi:10.1089/crispr.2017.29000.rba.

He, J. T. 2018. *Talk at the Human-Genome Editing Summit, Hong Kong*, November 27–29. Accessed 8 March 2019. https://divhpl.us/wiki/transcripts/human-genome-editing-summit/2018-hong-kong/jiankui-he-human-genome-editing

He Jiankui YouTube. Accessed January 12, 2019 https://www.youtube.com/watch?v=th0vnOmFltc

Informed Consent Form. 2018. "For CRISPR/Cas9 Human Embryo Editing by Scientist Dr." *He Jiankui Carried out in China. The Form was Translated into English from the Original Chinese*. https://web.archive.org/web/20181128061149/http:/www.sustc-genome.org.cn/source/pdf/Informed-consent-women-English.pdf

International Summit on Human Gene Editing: A Global Discussion. First International Summit. 2015. Washington, D.C. Accessed 7 December 2018. https://www.nap.edu/catalog/21913/international-summit-on-human-gene-editing-a-global-discussion

Jia, H. 2017. "Retractions Pulling China Back." *Nature Index*, November 17. Accessed 8 December 2018. https://www.natureindex.com/news-blog/call-for-tougher-sanctions-in-response-to-growth-in-papers-recalled-for-misconduct

Kang, X., W. He, Y. Huang, Q. Yu, Y. Chen, X. Gao, X. Sun, and Y. Fan. 2016. "Introducing Precise Genetic Modifications into Human 3PN Embryos by CRISPR/Cas-mediated Genome Editing." *Journal of Assisted Reproduction and Genetics* 33 (5, May): 581–588. doi:10.1007/s10815-016-0710-8.

Kolata, G., S.-L. Wee, and P. Belluck. 2018. "Chinese Scientist Claims to Use CRISPR to Make First Genetically Engineered Babies." *New York Times*, November 26.

Krimsky, S. 2003. *Science in the Private Interest*. Lanham, MD: Rowman & Littlefield.

Krimsky, S. 2015. "Crossing the Germline Barrier: The Three-genome Baby." *Ethics in Biology, Engineering and Medicine* 6 (3–4): 237–261. doi:10.1615/EthicsBiologyEngMed.2016016331.

Krimsky, S. 2019. "Ten Ways in Which He Jiankui Violated Ethics." *Nature Biotechnology* 37 (1, January): 19–20. doi:10.1038/nbt.4337.

Lander, E. S., F. Baylis, F. Zhang, E. Charpentier, P. Berg, C. Bourgain, B. Friedrich, et al. 2019. "Adopt a Moratorium on Heritable Genome Editing." *Nature* 567: 165–166. March 14.

Liang, P., Y. Xu, X. Zhang, C. Ding, R. Huang, Z. Zhang, J. Lv, et al. 2015. "CRISPR/Cas9-mediated Gene Editing in Human Tripronuclear Zygotes." *Protein & Cell* 6 (5): 363–372.

Lopalco, L. 2010. "CCR5: From Natural Resistance to a New Anti-HIV Strategy." *Viruses* 2 (2): 547–600. doi:10.3390/v2020547.

Marchione, M. 2018. "Chinese Researcher Claims First Gene-edited Babies." *Associated Press*, November 26. Accessed 8 December 2018. https://www.wkyc.com/article/news/nation-world/chinese-scientist-claims-he-helped-make-worlds-first-genetically-edited-babies/507-617600124

Marshall, E. 2006. "Scandals Shake Chinese Science." *Science* 312: 1464–1465. 9 June. at p.1464. doi:10.1126/science.312.5779.1464.

McLaughlin, K. 2018. "China's History with AIDS Explains a Puzzling Aspect of the 'CRISPR Babies' Story." *STAT*, December 14.

Nature editorial. 2019. "Set Rules for Germline Gene Editing."*Nature* 567. 145. 14 March.

Normile, D. 2019. "China Tightens Its Regulations of Some Human Gene Editing, Labeling It 'high-risk'." *Science Magazine*, February 28. https://www.sciencemag.org/news/2019/02/china-tightens-its-regulations-some-human-gene-cutting-labeling-it-high-risk

Ormond, K. E., D. P. Mortlock, D. T. Scholes, Y. Bombard, L. C. Brody, W. A. Faucett, N. A. Garrison, et al. 2017. "Human Germline Genome Editing." *American Journal of Human Genetics* 101 (Aug. 3): 167–176. doi:10.1016/j.ajhg.2017.06.012.

Ramzy, A., and S.-L. Wee. 2019. "Scientist Who Edited Babies' Genes Is Likely to Face Charges in China." *New York Times*, January 21.

Reardon, S. 2019. "World Health Organization Panel Weigh in on CRISPR-babies Debate." *Nature News*, March 20.

Regalado, A. 2018. "Chinese Scientists are Creating CRISPR Babies." *Technology Review*, November 25.

Saey, T. H. 2018. "Chinese Scientists Raise Ethical Questions with First Gene-edited Babies." *Science News*, November 27. https://www.sciencenews.org/article/chinese-scientists-raise-ethical-questions-first-crispr-gene-edited-babies

Schaefer, G. O. 2018. "Rogue Science Strikes Again: The Case of the First Gene-edited Babies." *The Conversation*, November 27.

Schmitz, R. 2019. "Gene-editing Scientist's Actions are a Product of Modern China." NPR/Asia, February 5. https://www.npr.org/2019/02/05/690828991/gene-editing-scientist's-actions-are-a-product-of-modern-china

Science Magazine News. 2018. Accessed 23 March 2019. https://www.sciencemag.org/news/2018/10/what-massive-database-retracted-papers-reveals-about-science-publishing-s-death-penalty

Second International Summit on Human Genome Editing. 2018. November 27–29. http://www.nationalacademies.org/hk

Second International Summit on Human Genome Editing. Statement by the Organizing Committee. 2018. November 29. Accessed 7 December 2018. http://www.nationalacademies.org/hk

Siling, L. 2016. "Whistle-blowing AIDS Doctor Reflects on Roots of Epidemic in China." *New York* Times, December 1.

So, D., E. Kleiderman, S. B. Touré, and Y. Joly. 2017. "Disease Resistance and the Definition of Genetic Enhancement." *Frontiers in Genetics* 8 (40, April): 1–6. doi:10.3389/fgene.2017.00001.

Sohu News. 2018. "Rasman Gate of Immunization AIDS Gene Editing Baby: Is the Ethics Review Application Forgery?" November 26. Accessed 7 December 2018. http://www.sohu.com/a/277913742_260616

Tollefson, J. 2018. "China Declared Largest Source of Research Articles." *Nature* 553:390. 25 January. doi:10.1016/j.ijpharm.2018.10.032.

Topol, E. 2018. "Editing Babies? We Need to Learn a Lot More." *New York Times*, November 27.

Wang, S. 2018. "Investigation: Crazy He Jiankui and Retired Subjects." *San Lian Life Week Magazine*, November 29. Translated from Chinese by Minyu Situ. https://baijiahao.baidu.com/s?id=1618471475417466286&wfr=spider&for=pc

Wang, Y., J. Huang, Y. Chen, and X. Pan. 2013. "Have Chinese Universities Embraced Their Third Mission? New Insight from a Business Perspective." *Scientometrics* 97: 207–222. doi:10.1007/s11192-013-1055-z.

Weibo. 2018. *Translated from the Chinese text by Minyu Situ*, December 14. https://www.weibo.com/5705191799/44Us3ydE8?type=comment

WHO. No date. How effective and safe is semen washing for HIV-serodiscordant couples. http://www.euro.who.int/en/data-and-evidence/evidence-informed-policy-making/publications/hen-summaries-of-network-members-reports/how-effective-and-safe-is-semen-washing-for-hiv-serodiscordant-couples.

Xiansheng, S. 2018. "More than 300 Scholars Jointly Named: Ten Questions He Jankui Should Answer." November 29. Chinese document translated by Minyu Situ. https://www.weibo.com/5705191799/H4Us3ydE8?type=comment#_rnd1547324366576

Zhang, J., H. Liu, S. Luo, Z. Lu, A. Chávez-Badiola, Z. Liu, M. Yang, et al. 2012. "Live Birth Derived from Oocyte Spindle Transfer to Prevent Mitochondrial Disease". *Reproductive Biomedicine* 34(4): 301–368. April.

Zhang, P. 2019. "China Confirms Birth of Gene-edited Babies, Blames Scientist He Jiankui for Breaking Rules." *South China Morning Post*, January 22.

Zimmer, K. 2018. "Since He Jiankui Presented His Results at Last Week's Gene Editing Summit, Researchers Have Raised Concerns about His Protocol, Calling the Procedure "Amateurish" and "Unconscionable." *The Scientist*, December 4. Accessed 8 December 2018. https://www.the-scientist.com/news-opinion/crispr-scientists-slam-methods-used-on-gene-edited-babies–65167