HE JIANKUI, GENE *RESEARCH*, AND GENE *THERAPY*

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ABSTRACT

The international reaction to the human germline editing undertaken in China by Dr. He Jiankui is morally warranted by standards of research ethics and biomedical ethics generally. Here the distinction of gene *research* and gene *therapy* is taken into account to argue that Dr. He and his research associates failed in their expected research integrity, violating both Chinese and international best practice standards. He himself was not a trained and licensed allopathic physician, in which case the goals of medical research and medical practice were unacceptably conflated in the experimental setting that combined CRISPR/Cas9 gene editing with *in-vitro* fertilization (IVF) treatment. Further, *ex post facto* effort to provide clinical registration of the experiment violated normal procedures for ethical clearance of such a protocol. The case presents a manifest need for heightened bioethics training for researchers so that they understand the priority of doing no harm (non-maleficence) over providing benefit according to ability (beneficence).

Keywords: He Jiankui; genomics; China; human germline editing; gene therapy

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"A suite of experiments that use the gene-editing tool CRISPR-Cas9 to modify human embryos have revealed how the process can make large, unwanted changes to the genome at or near the target site."[1] Such is the report on recent studies, which returns to the fore the question concerning the ethics of any experiment designed to introduce germ-line editing into the human genome, whether for genetic enhancement or ostensible gene therapy. The distinction of *somatic* genomics in the context of human gene *therapy* or gene *correction*, on the one hand, and human *germ-line* genomics related to *genetic enhancement*, on the other hand, is well known among geneticists. The former is more or less settled as scientifically acceptable with appropriate scientific merit review and ethics committee approvals.[2] The latter is not acceptable under current standards, except for germ-line editing that is performed *ex vivo* (in culture, *in vitro*) and not translated (i.e., moved to *in vivo* clinical application, e.g., for human reproduction)—especially given that "pre-implantation genetic diagnosis or somatic gene editing after birth would be preferable to genome editing of germ-line cells."[3] Objections to translational research in clinical trial of this type include the major problem that, "first-in-human trials often have little or no human experience on which to draw in performing a risk-benefit analysis," in which case in this kind of research it is difficult to design protocols that effectively "minimize or manage the unusually high levels of indeterminacy."[4] For example, since 2015, there has been common agreement among the "US National Academies of Sciences, Engineering, and Medicine (NASEM), the Chinese Academy of Sciences, and the UK's Royal Society…that human germline editing would be 'irresponsible' until more was known about the risks and benefits, and a 'broad societal consensus' could be reached."[5] This was underscored in a NASEM "consensus study report" published in 2017[6] and in a further

1 Heidi Ledford, "CRISPR Gene Editing in Human Embryos Wreaks Chromosomal Mayhem," *Nature*, 25 June 2020, https://www.nature.com/articles/d41586-020-01906-4, accessed 13 July 2020.

2 For a general overview, see Norman K. Swazo, 'Gene Therapy', in *Encyclopedia of Global Bioethics* (Dordrecht: Springer, 2014), 1-9, DOI: 10.1007/978-3-319-05544-2_213-1.

3 National Academies of Science, Engineering, and Medicine, 'Proceedings of a Workshop: In Brief—Second International Summit on Human Genome Editing: Continuing the Global Discussion', January 2019, (Washington D.C.: NASEM), Online at DOI: https://doi.org/10.17226/25343 (accessed 2019-03-27)

4 Jonathan Kimmelman, Gene Transfer and the Ethics of First-in-Human Research: Lost in Translation, (Cambridge: Cambridge University Press, 2010), 3.

5 Stephen Buranyi, 'What Is the World to Do About Gene-Editing?' *The New York Review of Books Daily*, 21 March 2019, Online at https://www.nybooks.com/daily/2019/03/21/what-is-the-world-to-do-about-gene-editing/ (accessed 2019-03-27).

6 See here National Academies of Science, Engineering, and Medicine, *Human Genome Editing: Science, Ethics, and Governance*, (Washington D.C.: The National Academies Press, 2017), https://doi.org/10.17226/24623.

commentary in January 2019.[7] In 2018, the Nuffield Council on Bioethics similarly concluded that the global community is not yet adequately prepared for germ-line genome editing.[8] That said, however, internationally the scientific community remains, as Stephen Buranyi put it, in a "vacuum of indecision" that nonetheless moves ambiguously beyond a "yellow light" of caution.[9]

The distinction of gene therapy and germ-line editing is likely less well understood in settings of public discourse where the desideratum of public trust in the research integrity of scientists is paramount. The technical features of the scientific concepts and associated practices are confounding enough even for dedicated undergraduate students studying molecular biology, biochemistry, and human genetics that the lay public cannot be expected reasonably and adequately to comprehend the complexities of the science or the diverse moral dilemmas that are part of current research in human genomics and medical genetics. Yet, efforts to clarify the ethical, legal, and social implications (ELSI) of such research remain central to public discourse and to the national governmental and international inter-governmental approaches to regulatory oversight. This is consistent with principle-based ethical obligations researchers have of non-maleficence, optimization of risk/benefit ratio, respect for individual autonomy, and judiciously applied prior, explicit, informed consent when individuals are recruited as participants ("human subjects") in such research.

I. THE CASE OF HE *JIANKUI* IN CHINA: BASIC QUESTIONS

The recent international expressions of dismay and condemnation of the "research" performed by Dr. He Jiankui in China[10] to produce the world's first "gene-edited babies" have

7 NASEM, Proceedings of a Workshop.

8 Nuffield Council on Bioethics, *Genome Editing and Human Reproduction: Social and Ethical Issues*. 2018, Online at http://nuffieldbioethics.org/wp-content/uploads/Genome-editing-and-human-reproduction-FINAL-website.pdf (accessed 2019-03-27).

9 See footnote 2 above.

10 For an excellent overview summary with a view to a lay audience readership, see Ed Yong, 'The CRISPR Baby Scandal Gets Worse by the Day', *The Atlantic*, 03 December 2018, Online at https://www.theatlantic.com/science/archive/2018/12/15-worrying-things-about-crispr-babies-scandal/577234/science (accessed 2019-03-21). Dr. He's presentation at the Second International Summit on Human Genome Editing, held in Hong Kong, 27-29 November 2018, is available on YouTube at https://youtu.be/cH57-YO9Eso.

led to proposals for a *moratorium* on germ-line editing[11] as well as proposals for *registering*[12] all such research in the interest of self-regulatory transparency within the international scientific community involved in human germ-line genomics. Chinese professional scientists condemned He's research immediately for not having appropriate scientific validation or ethics approval for clinical application of the biotechnology used.[13] There is no manifest consensus internationally among researchers, ethicists, or policy analysts as to which regulatory approach is correct. Yet, in the case of He's specific research activities, at least as they have been reported without official verification by governmental authorities in China,[14] there is the more basic question to be clarified concerning the fuzzy line between gene research and gene therapy—no different from the usual distinctions made between public health research and public health practice or medical research and medical practice. What precisely was Dr. He doing? Was he (a) *functioning as a research scientist* per se, doing basic gene "research," or was he (b) *practicing medicine*, doing gene "therapy," albeit a hitherto unapproved form of such therapy insofar as it involves the germ-line? With what *authority*[15] did he perform the scientific work that he did?

11 Karen Weintraub, (2019). 'Scientists Call for a Moratorium on Editing Inherited Genes?', *Scientific American*, 13 March 2019, Online at https://www.scientificamerican.com/article/scientists-call-for-a-moratorium-on-editing-inherited-genes/ (accessed 2019-03-21).

12 Sarah Reardon, 'World Health Organization Panel Weighs in on CRISPR-babies Debate', *Nature*, 19/20 March 2019, Online at https://www.nature.com/articles/d41586-019-00942-z?utm_source=Nature+Briefing&utm_campaign=1c4f037965-briefing-dy-20190320&utm_medium=email&utm_term=0_c9dfd39373-1c4f037965-43974801 (accessed 2019-03-21).

13 See here *The Lancet*, Vol. 393, Correspondence, 05 January 2019, Online at http://dx.doi.org/10.1016/ S0140-6736(18)33082-4 (accessed 2019-06-11).

14 Several professional associations in China (Chinese Academy of Medical Sciences, Chinese Academy of Engineering) issued their official responses, although there are other reports that governmental officials may have known of the research and did not prohibit it. It was reported that, "Heads of the State Health and Health Commission, the Ministry of Science and Technology, and China Association for Science and Technology said the incident was "extremely abominable" and the relevant units had been asked to suspend their scientific research activities." See here Jack Kilbride, and Bang Xiao, 'Chinese scientist who edited twin girls' genes He Jiankui missing for over a week. *ABC News*, 07 December 2018, Online at https://www.abc.net.au/news/2018-12-07/chinese-scientist-who-edited-twins-genes-he-jiankui-missing/10588528 (accessed 2019-03-21). Yet, the fact is that, 'China has invested heavily in gene-editing technology, with the government bankrolling research into a number of world "firsts," including the first use of the gene-editing tool CRISPR-Cas9 in humans in 2016 and the first reported use of gene editing technology to modify nonviable human embryos in 2015.' See here Oscar Holland and Serenitie Wang, 'Chinese scientist claims world's first gene-edited babies, amid denial from hospital and international outcry', *CNN International Edition*, 27 November 2018, Online at https://edition.cnn.com/2018/11/26/health/china-crispr-gene-editing-twin-babies-first-intl/index.html (accessed 2019-03-21).

15 The question of authority here concerns not only He's professional training (he is trained as a biophysicist) but also whether he remained within the boundaries of research or confounded the role of a bench scientist with that of medical practice, in spite of the fact that he is not a qualified physician.

Or, did he fail to satisfy standards of authority normally to be expected in the case of someone doing either gene research or gene therapy? These are important questions to have answered, since both scientific and public media commentaries do not for the most part account for the basic question.[16] Clarification of these issues will help genomic scientists, ethicists, and policy analysts to think more clearly about the regulatory framework required. One cannot assume that a scientist's claims as to scientific merit review or ethics approval are credible even in informal communications. Stephen Quake, a former postdoctoral mentor of He when the latter was at Stanford University, was aware of He's experiment long before it was announced in Hong Kong in November 2018. Quake assumed He *would* have (and *did* have) proper ethics oversight, accepting He's claims he had received institutional committee approvals from two hospitals.[17]

Although a Stanford University investigation found Quake was not involved in the conception or conduct of He's research,[18] problematic is that Quake seemingly encouraged He's research endeavor despite considering it "a bad idea" at one point and as "legitimate scientific research" at another time, thus adding to the scientific perspective of providing a yellow light of caution rather than pointing out the red light of current international scientific and ethical consensus against such research.[19] Quake deferred to the authority of the local

16 See, e.g., Jing-Bao Nie and Alexander T.M. Cheung, 'He Jiankui's Genetic Misadventure, Part 3: What Are the Major Ethical Issues?', *The Hastings Center Bioethics Forum Essay*, 10 January 2019, Online at https://www.thehastingscenter.org/jiankuis-genetic-misadventure-part-3-major-ethical-issues/ (accessed 2019-03-24). The authors here, e.g., identify four categories—"typical problems related to research ethics; broader political, socio-cultural, and trans-cultural issues; fundamental ethical questions on the use of gene editing in human reproduction itself; and even more fundamental matters on the moral goals of science and technology."

17 See here Pam Belluck, 'Gene-Edited Babies: What a Chinese Scientist Told an American Mentor', *The New York Times*, 14 April 2019, Online at https://www.nytimes.com/2019/04/14/health/gene-editing-babies.html?utm_source=Nature+Briefing&utm_campaign=c221afff49-briefing-dy-20190415&utm_medium=email&utm_term=0_c9dfd39373-c221afff49-43974801 (accessed 2019-04-16). According to Chinese clinical registry information the ethics approval from the Medical Ethics Committee of Shenzhen HOME Women's and Children's Hospital was given 07 March 2017.

18 See here Pam Belluck, 'Stanford Clears Professor of Helping With Gene-Edited Babies Experiment', *The New York Times*, 16 April 2019, Online at https://www.nytimes.com/2019/04/16/health/stanford-gene-editing-babies.html?utm_source=Nature+Briefing&utm_campaign=982440ab43-briefing-dy-20190417&utm_medium=email&utm_term=0_c9dfd39373-982440ab43-43974801 (accessed 2019-04-18). Also see Stanford University, 'Stanford Statement on Fact-Finding Review Related to Dr. Jiankui He', 16 April 2019, from Online at https://news.stanford.edu/2019/04/16/stanford-statement-fact-finding-review-related-dr-jiankui/ (accessed 2019-04-19).

19 Belluck (above note) reports that the president of He's former university has leveled serious charges against Quake: "Prof. Stephen Quake provided instructions to the preparation and implementation of the experiment, the publication of papers, the promotion and news release, and the strategies to react after the news release." Quake has denied these allegations, although his comments and cited emails present a record of support for

ethics committee as sufficient for He to proceed, even as some colleagues he informed had an "unruffled response" to the news of the experimental outcome.

II. AUTHORITY FOR GENE EDITING RESEARCH?

At issue in human embryo research that was precursor to He's gene editing was the question whether what was being done remained at the level of *basic research* or whether *clinical applications* were intended in the medium-term (despite their apparent illegality in China). Of course, the fact is that all such research is intended eventually to have clinical application. The only question has been *when* those applications would be ethically, legally, and socially permissible within both national and international regulatory contexts, within what Margaret Hamburg calls a framework of responsible stewardship.[20] He obviously leaped ahead based entirely on his own scientific judgment, prematurely (in the uniform judgment of many) for not complying with all four categories of permissibility—scientific, ethical, legal, and social.[21] Granted, China's official governmental stance on gene editing

He's research agenda so long as He obtained relevant ethics approvals, despite international consensus against such human embryo germ-line editing research.

20 Reardon, see footnote 3.

21 For an exception of sort, see Jon Cohen's report of the view of Harvard biologist George Church, '"I feel an obligation to be balanced." Noted biologist comes to defense of gene editing babies', *Science*, 28 November 2018, Online at https://www.sciencemag.org/news/2018/11/i-feel-obligation-be-balanced-noted-biologist-comes-defense-gene-editing-babies (accessed 2019-03-24). Church minimizes the ELSI of He's research in stating, "The most serious thing I've heard is that he didn't do the paperwork right." He then refers to a contrast of events to categorize He's work: "But is this a Jesse Gelsinger or a Louise Brown [the first baby born through in vitro fertilization] event?" Church takes a problematic utilitarian/consequentialist approach here: "…I'm hoping it doesn't work out badly. As long as these are normal, healthy kids it's going to be fine for the field [of genomic research] and the family." Church apparently would accept a finding of "detectable" off target effects in the girls who were born, as long as the effects were not "clinical" in manifestation. Yet, Church is reported also to have opined, in one of the two girls born, "there really was almost nothing to be gained in terms of protection against HIV and yet you're exposing that child to all the unknown safety risks,"…which "suggests that the researchers' 'main emphasis was on testing editing rather than avoiding this disease.'" See here AP Exclusive, 'First gene-edited babies claimed in China', *Loop News*, 26 November 2018, Online at http://www.looptt.com/content/ap-exclusive-first-gene-edited-babies-claimed-china (accessed 2019-03-24).

is ambiguous,[22] and research involving embryo gene editing is supported,[23] even though a government investigation reportedly found He violated Chinese standards—"The government investigation found that starting in 2016, Dr. He had deliberately evaded supervision, used unsafe and ineffective methods, and forged ethical review materials."[24] "High-risk" germ-line editing procedures involving clinical application are soon to be more strictly regulated consequent to the international outcry over He's work.[25] It is especially problematic as a point of research misconduct that He's actions apparently included an unprecedented fabrication of ethics approvals for the research he did, since the hospital having the ethics review committee claimed not to have approved the research protocol.[26]

Yet, there is still no clear settlement on what precisely He's authority was. His professional training is apparently in "biophysics" (sometimes characterized as "bioengineering"), hence his affiliation with the Department of Biology at the Southern University of Science and Technology (SUST) in Shenzhen, Guangdong Province, China. While he held a postdoctoral appointment in the Department of Bioengineering at the Stanford University School of Medicine, He has no allopathic medical training and no license to practice medicine as such. Hence, He can claim no authority as a medical practitioner authorized to perform gene *therapy* in a clinical setting.

22 It was reported that there are documents attesting to Chinese governmental support (including here China's clinical trial registry) for He's research: "If the documents are correct, they would suggest China is supporting research that the U.S. and other countries consider unethical, and raise doubts about the preliminary conclusion of a government investigation that He acted mostly on his own." See Jane Qui, 'Chinese government funding may have been used for "CRISPR babies" project, documents suggest', *STAT*. 25 February 2019, from Online at https://www.statnews.com/2019/02/25/crispr-babies-study-china-government-funding/ (accessed 2019-03-21).

23 Steven Jiang, Helen Regan, Joshua Berlinger, 'China suspends scientists who claim to have produced first gene-edited babies', *CNN News*, 29 November 2019, Online at https://edition.cnn.com/2018/11/29/health/china-gene-editing-he-jiankui-intl/index.html, (accessed 2019-03-21). The authors here cite Xu Nanpang, vice minister of the Ministry of Science and Technology, to say, 'The gene-edited twins matter reported by the media has brazenly violated Chinese laws and regulations and breached the science ethics bottom line, which is both shocking and unacceptable.'

24 Austin Ramzy and Sui-Lee Wee, 'Scientist Who Edited Babies' Genes Is Likely to Face Charges in China', *The New York Times*, 21 January 2019, Online at https://www.nytimes.com/2019/01/21/world/asia/china-gene-editing-babies-he-jiankui.html?module=inline (accessed 2019-04-16).

25 See here David Cyranoski, 'The CRISPR-baby scandal: what's next for human gene-editing?' *Nature*, 26 February 2019 (Clarification 11 March 2019), Online at https://www.nature.com/articles/d41586-019-00673-1, (accessed 2019-03-21). Also see David Cyranoski, 'China to tighten rules on gene editing in humans', *Nature*, 06 March 2019, Online at https://www.nature.com/articles/d41586-019-00773-y (accessed 2019-03-06).

26 See Xiao Sisi Li Xiongying, 'Guangdong initially identified 'gene editing baby events', *Xinhua News Agency*, 21 January 2019, Online at http://www.xinhuanet.com/local/2019-01/21/c_1124020517.htm (accessed 2019-03-21). Notably, the ethics approval document manifests the standard "stamp" of approval from the hospital that authenticates the document.

As a researcher He summarizes his primary research focus to be "to develop early diagnostic protocols for diseases such as cancer based on DNA sequencing technology and to develop genome editing methods to treat diseases."[27] This focus is clearly that of basic research with applied science elements. As such it is unproblematic. Since joining SUST, He identified a specific research interest in "improving the safety of germline editing in human, monkey and mouse embryos," specifically with editing involving the CRISPR/Cas9 system. This research interest is unproblematic under current international guidelines in the case of the animal models involved (monkey and mouse zygotes), and even what He's research team describes as "waste" human embryos. But, it is problematic if the human germ-line editing moves to gene modification in a human embryo with the intent to implant *in utero* and gestate the fetus to full-term live birth. By comparison, there is ongoing research similar to that undertaken by He that is not ethically problematic precisely because it is not designed to proceed to implantation.[28]

Based on his team's research experience in the animal models and "waste" human embryos, He premised it scientifically and morally acceptable to proceed with germ-line editing in viable human embryos. The result is the two gene-edited infants born through IVF. Thereafter, He asserted that his team had "sequenced the genome of parents and the embryos" with a view to "detecting off-target [events]," and concluded that, hence, in his scientific judgment, "the CRISPR-cas9 genome editing has no more off-target events than control samples." He takes this as *sufficient evidence* of both safety and efficacy in a human clinical trial (as he seems to have concluded, given his shift to the clinical application that he reported at the summit held in Hong Kong). Despite seemingly valid results in animal models, however, there is no evident justification for *clinical* application of the method, even given He's desire to "treat diseases" this way.

Further, this raises the key question of He's confused authority (i.e., to do gene research and to do gene therapy) and his confusion of right and wrong in the Chinese sense of "*hunxiao shifei*," as bioethicists Jing-Bao Nie and Alexander T.M. Cheung have opined, reminding that Chinese regulations have "*unequivocally prohibited* any research beyond the first 14 days of an embryo creation as well as any implantation of a genetically modified embryo into the

27 He Jiankui *Linked In*, Online at https://www.linkedin.com/in/jiankui-he-a1917517/ (accessed 2019-03-24).

28 See, e.g., Rob Stein, 'New U.S. Experiments Aim to Create Gene-Edited Human Embryos', *NPR Health News*, 01 February 2019, Online at https://www.npr.org/sections/health-shots/2019/02/01/689623550/new-u-s-experiments-aim-to-create-gene-edited-human-embryos (accessed 2019-03-24).

human reproductive system."[29] For his "experiment" He recruited "eight couples whose males have HIV/AIDS," selected "*because of the offer of IVF treatment* (which would be otherwise prohibitively expensive) and *other medical and financial inducement*," but with inadequate informed consent as to "the nature of the medical trial." The clinical registry application states that He was recruiting "HIV-positive patients with infertility;" yet, there was no public information that either the father or the mother was infertile. Rather, the claim has been that the father was hesitant to procreate given his HIV+ status, He therefore providing the option of IVF with CCR5 gene editing to prevent the infant having HIV. Hence, one concludes He failed in the ethical integrity of the project in introducing unfair inducement and in the inadequacy of the informed consent process.

III. IVF THERAPY OR GENE THERAPY?

Here we have an important conceptual qualifier, however, that is pertinent to moral evaluation of He's "research" endeavor. The parents of the twin girls born as gene-edited babies were recruited into a *medical trial* in the context of a proposed *IVF treatment* they may not have wanted *per se* except for the financial inducements.[30] It is unclear that the HIV+ status of the father was really prohibitive to the couple proceeding with a pregnancy, even under IVF treatment that could have included pre-implantation genetic diagnosis (PGD) rather than gene-editing. In the normal course of medical care, IVF treatment is unproblematic as a recognized and approved process of technologically assisted human reproduction offered in fertility clinics. To link the IVF treatment—assuming it was clinically indicated[31]—to a clinical

29 See footnote 5 above; italics added.

30 It is reported that He disclosed a "clinical trial registration" for his work. See LeMieux, footnote 17 below. The inducements clearly stated in the consent form included: payment of IVF outpatient costs, COH costs, embryo laboratory culture costs; round-trip transportation costs; pregnancy detection and monitor costs; payment of rent and work-related expenses for the pregnant women; one nursing staff person daily; daily nutrition costs; abortion costs in a failed IVF cycle; expenses during prenatal care one month prior to delivery; post-natal care up to 28 days; payment of "the worker's mistress and one of the nursing workers' (at 200 yuan/day), until the completion of a variety of examinations for newborns;" health insurance for the baby. The research team's estimate and committed cost to be covered was 280,000RMB per couple. Any medical expenses related to research-related injury would be compensated at a limit of 50,000RMB.

31 That IVF treatment was clinically indicated is doubtful given that the clinical registry application states among the trial's inclusion criteria that, "Both subjects [HIV+ male and HIV- female] are willing to commit to *using preventive contraception* or *maintaining abstinence* for at least two months before egg collection and within one month after birth." (italics added) Further, He's explanation was that the principal "fear" of procreation

trial involving CRISPR-Cas9 germ-line editing, however, is *not normal clinical practice*, even as it is unclear who (among He's "research" team) has the *medical* authority to conduct such a clinical trial. As noted, He himself is not a licensed medical practitioner on staff in a research hospital where such a trial might be performed in the context of standard medical care after appropriate scientific merit review and ethics approval.

He undoubtedly conceived of his work as a case involving "therapeutic assisted reproductive technology," warranted (i.e., permissible, so He believed) "when the risks of the procedure are outweighed by a serious medical need."[32] It was by no means demonstrated, as many commentators have already stated, that this was a case of serious medical need, even as there was no clarity about the risks of the germ-line editing procedure involved. Even so, it was reported that, "China's Clinical Trial Registry rejected the experiment's application due to holes in the informed-consent process and research design, as well as questions over trial implementation and funding"—despite claim (valid or fabricated) of ethics approval by a medical ethics committee at the affiliated hospital.[33] It was, furthermore, ethically problematic that He sought clinical trial registration *after the fact* (apparently on 08 November 2018, with his research implemented as of the date of supposed ethics approval, given in March 2017, the infant girls reportedly born prematurely in October 2018). The clinical trial application was clear that He intended the "outcome" of "pregnancy and one or more live births"—an outcome clearly contravening Chinese scientific regulations at the time, hence the challenge

in this particular couple was the sociocultural situation of discrimination that occurs in China. See here The He Lab, 'About Lulu and Nana: Twin Girls Born Healthy After Gene Surgery as Single-Cell Embryos', 25 November 2018, Online at https://www.youtube.com/watch?v=th0vnOmFltc (accessed 2019-04-17).

32 *The CRISPR Journal* in which He's article (entitled "Draft Ethical Principles for Therapeutic Assisted Reproductive Technologies,") was published (on 26 November 2018) has been retracted (on 21 February) by the editors on grounds of He's "failure to disclose conflicts of interest," the editors adding that when the article was published they "had absolutely no idea the authors were actively conducting clinical studies or had engineered and implanted human embryos." See here, Julianna LeMieux, 'He Jiankui's Germline Editing Ethics Article Retracted by *The CRISPR Journal*', *Genetic Engineering & Biotechnology News*, 20 February 2019, Online at https://www.genengnews.com/insights/he-jiankuis-germline-editing-ethics-article-retracted-by-the-crispr-journal/ (accessed 2019-03-24).

33 Sixth Tone Ciaxin, 'Scientist Dodged Questions on Ethics of Gene-Editing Experiment. 20 December 2018, Online at https://www.sixthtone.com/news/1003359/scientist-dodged-questions-on-ethics-of-gene-editing-experiment (accessed 2019-03-24). The application was entitled, 'Evaluation of the Safety and Efficacy of Gene Editing with Human Embryo CCR5 Gene,' Registration Number ChiCTR1800019378 and listed as a "retrospective registration," the application under the name of Qin Jinzhou and He Jiankui as "study leader," research to have been implemented as of 17 March 2017 and continuing to 07 March 2019, with institutional affiliation including SUST and the Shenzhen HarMoniCare Women and Children's Hospital. The application included a claim that the research had been approved by ethics committee (Approval No. 20170307, Medical Ethics Committee of Shenzhen HOME Women's and Children's Hospital, on 07 March 2017.)

to the veracity of the ethics approval document. It seems entirely implausible that a hospital ethics committee aware of Chinese regulations would permit such an outcome and thereby authorize the clinical trial as designed.

He's associate on the clinical registry application is Qin Jinzhou of SUST, who is reported to be a fully trained embryologist "who conducted the actual gene surgery and in-vitro fertilization."[34] Yet, the Harmonicare hospital authority has denied that the gene-edited girls were delivered there or that the hospital was involved in the research.[35] In contrast, it is reported that Lin Zhitong, "a Harmonicare administrator who heads the ethics panel" at the hospital, asserted: "We think this is ethical."[36] That statement, if reliably true, questions the honesty of the Harmonicare statement of having no involvement in the research, meaning here (at minimum) that of the hospital ethics committee having reviewed the proposed research for an ethics approval, even though the infant girls were delivered at a second hospital involved. Clearly, without a valid approved clinical registration, however, He and Qin violated normal expectations (best practices) in ethics approval of clinical protocols. This is so even if it is granted, as the clinical trial application asserted, that the proposed trial was "based on preclinical research of cell lines, animal models, and human waste embryos." There has been no publication of He's preclinical research (at least not authenticated and peer-reviewed in English-medium publication except for conference presentations) to suggest He and Qin were ready for a clinical application such as we now have in result that He announced in November 2018.[37] Hence, both He (as study leader *qua* "research scientist") and Qin (*qua* "research embryologist" and not as clinical medical practitioner) performed research that violated norms of research integrity in human germ-line genomics.

The main point here is that He was not himself a qualified medical practitioner or medical genetics specialist to be leading this clinical trial,[38] even as his associate Qin was not authorized

34 See here Qin's video presentation on the topic, at https://youtu.be/-1mivZUXgNI (accessed 2019-03024).

35 The National, 'China scientist who pushed ethical limits is gene-editing rookie', 27 November 2018, Online at https://www.thenational.ae/world/asia/china-scientist-who-pushed-ethical-limits-is-gene-editing-rookie-1.796495 (accessed 2019-03-24).

36 'AP Exclusive…' see footnote 8 above.

37 He initially reported his work at the Second International Summit on Human Genome Editing in Hong Kong in November 2018.

38 He did present at a conference in Cold Spring Harbor Laboratory, 'Evaluating the Safety of Germline Genome Editing in Human, Monkey, and Mouse Embryos,' as published on 29 July 2017, commenting then that gene editing for CCR5 Delta 32 provides protection against HIV. See here, 'He Jiankui talking about human genome editing', Retrieved April 17, 2019, from Online at https://www.youtube.com/watch?v=llxNRGMxyCc (accessed 2019-04-17). In this presentation, He remarked that in the mouse, monkey, and human embryo gene editing performed they detected no off-target effects ("Sanger sequencing validation"), but this was with

to perform the actual gene surgery in a clinical setting, and especially not in the absence of a *bona fide* approved clinical registration. According to the Chinese registration authority, we are informed that the application was "withdrawn with the reason of [*sic*] 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."[39] What is to be concluded is that both He and Qin seem to have ignored the important distinction between medical research (gene research) and medical practice (gene therapy). They linked the CRISPR-Cas9 "research technique" to the IVF "treatment" intending a corrective/preventive "gene therapy" (i.e., preventing transmission of HIV to the intended newborns) without adequate prior, explicit, informed consent of the recruited parents, especially given that the consent forms—at least in English translation—apparently referred to the actual "research"/"therapy" being performed as "AIDS vaccine development." It is not correct, as He stated, that gene surgery is "another IVF advancement." Both claims are patently false.

IV. FAILURE OF NON-MALEFICENCE

Ethically knotty also is that He and his team were inclined to proceed on grounds of *beneficence* without prior due attention to their professional duty of *non-maleficence*. In Article 5 of the woman participant's consent form, the research team stated the "possible benefits of participating in the research" to be: "likely help you to produce HIV-resistant infants," although they asserted, "HIV resistance in infants is based on a health certificate issued by a post-natal medical institution obstetric." Robin Lovell-Badge of the UK's Francis Crick Institute has opined that he considered He "a rich scientist *who knew little biology*, with a huge ego, someone who wants to be the first to do something he believes will change the world, *irrespective of any guidelines*…The scientist consistently believed that he was doing good…but

only "45% effective genome coverage." Further, for N=8 human embryos, there was confirmation of off-target effects ("Embryos Off-target confirmed for 'bad' gRNA"). Of n=16 human embryos injected with Cas9 protein, the efficiency ranged between 11.1% and 60%, the average editing efficiency reported to be 32.14% --much lower than 94.1% in mice and 73.21% in monkey. The majority (70%) of the monkey embryos were mosaic in result.

39 Chinese Clinical Trial Registry, Registration Number ChiCTR1800019378, Scientific Title: 'Evaluation of the safety and efficacy of gene editing with human embryo CCR5 gene', Date of Registration 08 November 2018, applicant: Qin Jinzhou, Applicant Institution: Southern University of Science and Technology, Shenzhen, Guangdong, China.

the science and his ethics were flawed."[40] It is patently contrary to proper professional ethics in the use of biotechnology to privilege beneficence over non-maleficence—even on the basis of a claim (such as He advanced) that medical need outweighs medical risk—a fundamental of research ethics that both He and Qin should have understood and practiced. Qin claimed that the shift to clinical application was based on three years of animal model studies and that he is "an embryo's doctor." But, He's and Qin's inclination to beneficence and an apparent commitment to "patient benefit" without both (a) adequate attention to degree of risk and (b) patient autonomy involving prior, explicit, informed consent, clearly violated conventional standards of research integrity. A reasonably defensible rule utilitarian assessment would have made this clear.

One wonders: Where was the scientific and ethical reservation Qin, as research embryologist with the actual proficiency to perform the gene surgery, ought to have manifest in the research process, given that, as Lovell-Badge observed, "He [Jiankui] *did not know enough* about the mutation he was trying to introduce into the babies—known as Delta 32—which was intended to protect the girls from HIV but could also risk the West Nile virus and influenza, previous research had shown."[41] Hence, one concludes here that Qin, as research embryologist, is more morally culpable for failures in research integrity than He insofar as Qin proceeded with the gene surgery in the absence of validated ethics committee approval and clinical registry approval prior to implementation of the research protocol.

To the extent the researchers used obstetricians/gynecologists at a hospital (according to the consent form, "tentatively designated as Shenzhen Luohu Medical Institution") for Controlled Ovarian Hyper-stimulation (COH) and post-implant prenatal medical care, clearly the involvement of the IVF facility and medical staff is also morally disturbing insofar as they, too, ought to have declined to support the so-called research in the clinical setting of IVF treatment precisely because the process involved legally prohibited human embryonic germ-line editing. According to the female consent form (Version: Female 3.0), He informed the women participants that, "1-2 blastocysts will be transferred to uterus at the appropriate time according to the woman's physiological cycle with the clinic doctor's advice." One infers that He had arranged for a fertility clinic and licensed medical practitioners to provide the medical care to women participants before, during, and after embryo transfer; yet, there has been no

40 Meera Senthilingam, 'Chinese scientist was told not to create world's first gene-edited babies', *CNN News Edition*, 07 January 2019, from Online at https://edition.cnn.com/2019/01/07/health/robin-lovell-badge-gene-edited-babies-intl/index.html (accessed 2019-03-25). Italics added.

41 Senthilingam, as cited in footnote 23. Italics added.

indication in public media or official news releases that any licensed medical practitioner raised objections or declined to provide medical care as part of the clinical trial. Nor has there been any report of any medical practitioner being held accountable by Chinese authorities for the illegal and unethical experimental procedure, even though licensed physicians would have had to authorize amniocentesis and peripheral blood testing (as the consent form stated) "in different stages of pregnancy after transplantation…" While the Harmonicare hospital authority has claimed the babies were not delivered there, it is to be noted that since the consent form specified the Shenzhen Luohu Medical Institution as the clinic for delivery of the babies (the mother having to report there one month before delivery date), it is probable this was the unnamed institution where the twin girls were in fact delivered. To date there has been no reference in the literature to this facility's role and responsibility in the clinical trial.

The He experiment points to what is problematic in general in this kind of research, where the assumption is that the researchers *qua* clinicians are involved in gene therapy and are, therefore, doing something good, as He asserted. But, as J. Benjamin Hurlburt and Jason Scott Robert have correctly opined, "passing ethical review doesn't mean it's ethical."[42] What kind of ethical oversight there was or was not is especially important "in the case of germ-line editing," the authors clarify,

> because it's so unlike most conventional therapies. As the U.K. Nuffield Council has pointed out, it is incorrect to call it therapy. If one were undertaking gene therapy in a baby, or even a fetus, to address a life-threatening genetic disease, it would be appropriate to accept a certain amount of risk, because the alternative is much worse: living with a life-threatening disease. But in the case of embryo editing, there is not yet a child that is sick and needs to be healed. Because the genome editing molecules are delivered into the egg at the same time as the sperm, one brings the 'patient' into being in the same moment as one undertakes the 'therapy.' So, when the experiment is being contemplated, there is no child to heal.[43]

42 Benjamin Hurlburt, J. Banjamin, Jason Scott Robert, 'CRISPR babies raise an uncomfortable reality—abiding by scientific standards doesn't guarantee ethical research', *The Conversation*, 03 December 2018, Online at https://theconversation.com/crispr-babies-raise-an-uncomfortable-reality-abiding-by-scientific-standards-doesnt-guarantee-ethical-research-108008 (accessed 2019-04-15).

43 Ibid.

What this fact means, Hurlburt *et al*. remind, is that, "There is something missing in a process [of ethical or scientific merit review] that fails to prioritize the interests of the resulting child(ren). Yet since bringing them into being would involve risks that are significantly higher than normal reproduction, taking their interests into account may mean that the experiment simply should not be done." One infers in the case of He's experiment that, accounting for the *intrinsic* interest of the two twin girls who were born, in contrast to the *entirely contingent* interest of the parents and the researchers, this particular research *ought not* to have been done.

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