An Actor Network Theory and Virtue Ethics Analysis of He Jiankui's CRISPR-Cas9 Experiments on Human Embryos

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On my honor as a University Student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments

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Introduction

On November 25, 2018, the world's first babies with CRISPR-Cas9 (Clustered Regularly Interspaced Short Palindromic Repeats) genome modifications, twin girls Lulu and Nana were born in China. They were the results of Professor He Jiankui's (Southern University of Science and Technology, SUST) CRISPR-Cas9 experiments on embryos. He applied this technology to create genetic mutations that lead to the production of HIV-resistant immune cells. The goal of He Jiankui's experiments was to create embryos that are resistant to HIV, given that one or both parents are infected by HIV (Rose & Brown, 2019).

He Jiankui's CRISPR-Cas9 experiments sparked international criticism as he announced the deliveries of Lulu and Nana at a conference in Hong Kong. The current understanding characterizes He Jiankui's experiments as morally wrong and illegal, because applying CRISPR-Cas9 on embryos are prohibited by regulations. Moreover, mutations introduced by CRISPR-Cas9 might bring unknown risks to children. However, there exists little discussion on the morality of He Jiankui and other human and non-human actors. Refusing to reflect the morality of He Jiankui and other actors will lead to an insufficient understanding on the driving force behind these immoral experiments, which is crucial to prevent the same mistakes in the future.

He Jiankui was not the only actor responsible for the immoral experiments. Other actors such as Lulu and Nana's parents, He Jiankui's institution, colleagues, and funders, carry some moral responsibility. I will first use Actor Network Theory (ANT) to characterize the actors around He Jiankui's experiments and their contributions, then I will use virtue ethics to analyze the morality of human actors in this network. ANT is a conceptual framework that defines an event as a network of actors influencing each other, while virtue ethics is a moral standard that

judges morality based on intentions. He Jiankui could conduct these immoral experiments without hindrance because the adversaries in this network failed to function, and He Jiankui was overpowering other actors. Evidence from press releases, ethical reports, and He Jiankui's own account will be utilized to perform this analysis.

Background

CRISPR-Cas9 is a well-known genome editing technology that could add, remove, or alter specific sections of the DNA. The CRISPR-Cas9 technique generally involves three steps: a guide RNA locates the complementary DNA, Cas9 enzyme makes a cut across the marked part of the DNA, then mutations are introduced. However, the Cas9 enzyme might cut some unmarked parts of the DNA, creating off-target mutations. This technique is currently being explored in research and clinical trials as a treatment of various genetic diseases such as cystic fibrosis and hemophilia (Redman et al., 2022). In He Jiankui's case, this technique was applied to embryos, trying to delete a gene responsible for producing CCR5, a protein on immune cells that HIV uses to enter the cells. Mutations introduced in embryos could be passed down to future generations. (Cohen, 2019).

Literature Review

Plenty of research efforts have been devoted to analyze the ethics of He Jiankui's application of CRISPR-Cas9 on embryos. Marcos Alonso and Julian Savulescu proposed a few perspectives on He Jiankui's experiments (Alonso & Savulescu, 2020). The first perspective is based on consequentialism, a philosophical theory that focuses on maximizing happiness, well-being, and other forms of good. The consequences of an action determine its morality. Alonso and Savulescu pointed out that He Jiankui failed to maximize well-being, because he did not

"select embryo that would have developed into a child that would have benefited more (such as embryo with Tay-Sachs disease) from the experiment." Therefore, He Jiankui's experiments were morally wrong. However, Lulu and Nana were born as a result of the experiments. This helped to create life that is worth living, which should be a fundamentally good thing. Consequentialism is unable to clearly judge the morality of He Jiankui's experiments. The second perspective is based on "rights." Alonso and Savulescu presented the following definition of right: "rights do not attach to people's numerical identities, but rather to the kinds of creatures they are, and the positions they occupy in relation to others." He Jiankui's experiments undermined Lulu and Nana's rights by not respecting their genome integrity, damaging Lulu and Nana's future autonomy and their right to have a free and unfettered life. Therefore, He Jiankui's experiments were morally wrong. However, the rights-based analysis is too restrictive, because it indicates the damages right violations always overwhelm the possible goods. Damage is so strong that Lulu and Nana will never enjoy the goods in their future.

Alonso and Savulescu provided analysis based on different ethical theories. On the other hand, Erika Kleiderman and Ubaka Ogbogu gave some insights to He Jiankui's case through the lens of clinical regulations and guidelines (Kleiderman & Ogbogu, 2019). China adopted the Ethical Review Guidelines on Biomedical Research Involving Human Subjects in 2016, requiring all institutions and hospitals to address informed consent, voluntary participation, risk-benefit assessment, and other matters in research. There are also two specific ethical guidelines for embryo research: the Ethics Guiding Principles for hESC Research, and the Technical Norms on Human Assisted Reproductive Technologies. They prohibit the manipulation of human gametes, zygotes, and embryos for the purpose of reproduction. He Jiankui's embryo experiments clearly violated the above clinical regulations and guidelines. Moreover, his

experiments also had problems in transparency, formal ethical review, and obtaining informed consent. Therefore, He Jiankui's experiments were morally wrong and illegal.

Both analyses shown above discussed the morality of He Jiankui's embryo CRISPR-Cas9 experiments. Nevertheless, they did not directly address the morality of He Jiankui himself, namely the nature of the acting person. The two analyses also did not address whether other actors, such as He Jiankui's institution and colleagues, parents, contemporary Chinese regulations, and the technology itself, had contributed to or had moral responsibility. This paper will not only examine the morality of He Jiankui by investigating the nature and intentions of his actions, but also examine the morality of other actors and their contributions to this case.

Conceptual Framework

Analysis in this paper relies on two conceptual frameworks: Actor Network Theory (ANT) and virtue ethics. ANT provides an effective framework to identify different actors in a sociotechnical network, and analyze the interactions among actors and their contribution to the network. ANT defines a sociotechnical network as a system of diverse actors organized by a network builder to achieve a goal. Actors in a network are heterogeneous, meaning they can be human or non-human. They can be allies that work for the interest of the network or adversaries that try to interrupt the network. All actors in a network should have equal amounts of power. Privileged actors will cause an imbalance of power in a network, which might lead to undesirable results (Cressman, 2009). Translation is the process that a single entity forms and maintains a functioning network. It includes the following steps: problematization, interessement, enrollment, mobilization, and black-box (Callon, 1986). The network builder first identifies a problem in the problematization step, then actively recruits other actors to address the problem in the interessment step. Roles and positions in the network will be assigned in the enrollment step.

Finally, the network starts to function under the lead of the network builder in the mobilization step. The Black-box step will not be discussed because it is not applicable to the network of interest. In this paper, I will first use ANT to identify the human and non-human actors around He Jiankui's CRISPR-Cas9 experiments on embryos. Then I will discuss how the adversaries in this network, such as He Jiankui's institution and concurrent Chinese regulations, failed to stop He Jiankui's experiment. He Jiankui himself was a privileged actor in this network, which was able to dominate other actors such as the parents, facilitating the success of the experiments.

On the other hand, virtue ethics provides a powerful framework to analyze the morality of the human actors. Virtue ethics is an ethical theory that focuses on the nature of the acting person. The central theme of virtue ethics is that human should strive to develop good intellectual and personal character traits in order to be morally good and responsible individuals. This ethical theory was first developed by Aristotle, stating that each moral virtue stands in the middle of two extreme evils (the middle course). For example, courage is in the middle of cowardice and recklessness, while pride is between subservience and arrogance. Thomas Aquinas defined four cardinal virtues: prudence, temperance, justice, and fortitude. Some other basic virtues include reliability, honesty, and responsibility (van de Poel & Royakkers, 2011). Pritchard proposed a list of virtues for morally responsible engineers:

- Expertise
- Clear and informative communication
- Cooperation
- Willingness to make compromises
- Objectivity
- Being open to criticism

- Stamina
- Creativity
- Striving for quality
- Having and eye for detail; and
- Being in the habit of reporting on your work carefully. (Pritchard, 2001)

Satisfying all the virtues on this list is not sufficient to prove an engineer is morally responsible, but any violations will indicate an engineer is morally wrong. In this paper, I will first examine the morality of the parents by investigating their intentions and whether they sought the "middle course." Then I will examine the morality of He Jiankui and his colleagues by investigating their intentions and whether they violated any of the virtues on Pritchard's list.

CRISPR-Cas9 Embryo Experiment Network

Reconstructing the network around the CRISPR-Cas9 embryo experiments is necessary to understand the connections among actors, the contribution of each actor, and the power distribution in this network. In the problematization phase, He Jiankui determined medical assistance was needed to protect embryos from HIV carried by one or both parents. Based on this problem definition, he identified CRISPR-Cas9, which could create genetic mutations that lead to the production of HIV resistant immune cells, was the medical technology needed. In the intersessment phase, He Jiankui recruited other human and non-human actors to solve the problem. I define the actors that participated in the design or implementation of the clinical stage experiments to be direct contributors, while actors that provide supports to the direct contributors are supporters. Direct contributors and supporters are both allies to the CRISPR-Cas9 embryo experiment network, because they want the experiments to be successful.

Zhang Renli and Qin Jinzhou were recruited as He Jiankui's collaborators to provide additional technical support, directly contributing to the success of the clinical stage experiments. Zhang Renli is an expert in obstetrics and gynecology, affiliated with the Guangdong Academy of Medical Science and Guangdong General Hospital. Zhang performed human embryo microinjections, introducing the mutations to embryos with CRISPR-Cas9. Qin Jinzhou is an embryologist at Southern University of Science and Technology, providing the theoretical basis for clinical stage experiments, also named as an applicant on the experiments (Cyranoski, 2020). Zhang and Qin are classified as direct contributors because they, along with He Jiankui, designed and implemented the clinical stage experiments.

Rice bioengineering and physics professor Michael Deem was also recruited as a collaborator, but his role is to provide credibility rather than technical supports. According to Jane Qiu's STAT article, Deem was listed as the last author in He Jiankui's research paper "Birth of twins after genome editing for HIV resistance," a typical way to credit the contribution of an overseer in life sciences. This evidence confirmed that Deem was aware of and might provide advices to He Jiankui's experiments, but it did not suggest that Deem designed or participated in the clinical stage experiments. Qiu's article also stated that Deem participated in a meeting with several volunteers (the parents) in 2017 to go through the informed consent process, and he helped to obtain the informed consent by speaking (through a translator) with the volunteers (Qiu, 2019). Deem is a professor from a prominent U.S. university, persuasion from him would be particularly powerful. Even though Deem might not directly contribute to the implementation of the experiments, his credibility and persuasion enabled He Jiankui's research group to recruit volunteers, therefore Deem is classified as a supporter.

He Jiankui's research required a significant amount of funding support. A major source of funding was his institution. According to Ouagrham-Gormley and Vogel's article, SUST offered He Jiankui an associate professor position and a brand-new research laboratory in 2012, and he was able to hire research assistants and carry out the safety evaluation for germline editing. He Jiankui received Another sizable funding source in 2017 as the recipient of a sub-program of the Thousand Talents Plan, a prestigious Chinese research initiative. This program provided He Jiankui a $76,000 living subsidy and a $150,000 to $500,000 research subsidy (Ouagrham-Gormley & Vogel, 2020). This budget, combined with the research fund provided by SUST, allowed He Jiankui to perform preliminary research on non-human and human embryos, paving the way for clinical stage research, therefore the funders are classified as supporters.

In order to recruit subjects for the clinical stage research, He Jiankui cooperated with a Beijing based HIV advocacy group to find couples with a healthy female and an HIV positive male. Ultimately, seven couples agreed to participate in the clinical research. The CRISPR-Cas9 editing took place during in vitro fertilization (IVF). Only two couples were implanted with the edited embryos, and one of them gave birth to Lulu and Nana (Ouagrham-Gormley & Vogel, 2020). The couples are classified as direct contributors, because they want the experiments to be successful to have healthy children.

Required by the contemporary Chinese regulation, He Jiankui had to recruit an ethics committee of a hospital to evaluate his clinical stage research. When He Jiankui was ready for clinical stage research, HarMoniCare Women and Children's Hospital in Shenzhen granted the ethics review (Ouagrham-Gormley & Vogel, 2020). The contemporary Chinese regulation and the ethics committee are classified as adversaries, because these actors have an opposite interest: the CRISPR-Cas9 experiments should not be conducted.

In the above analysis, I have shown that He Jiankui's embryo experiments were supported by a network of human and non-human actors, containing both allies and adversaries. It is very tempting to attribute all faults to the insufficient implementation of contemporary Chinese regulation and negligence of the ethics committee. However, this view fails to consider the weight of He Jiankui in this network. He Jiankui is a privileged actor in this network, exerting influence to affect the performance of other actors. According to Henry Greely, a law professor at Stanford University, He Jiankui was "a darling of China's current system of sciences" and "a smart and ambitious young scientist." Greely also gave the following remarks, "in 2018, he was nominated for the China Youth Science and Technology Award of the Central Government and the Chinese Association of Science and Technology. More importantly, He was selected to the Central Government's top science program, Qianren Jihua (Thousand Talents Plan). The plan claims to be 'world's most prestigious and influential state science program', involving almost every department of the government. The program's overall goal is to advance a number of specific scientific and financial areas, such as gene technologies and genetics industry, that the state deems to be of primary strategic importance" (Greely, 2019). Even though regulation states that manipulation of human gametes, zygotes, and embryos for the purpose of reproduction is prohibited, He Jiankui was slightly out of the jurisdiction before he sparked international criticisms by publishing the experiment. Selected by the Thousand Talents Plan indicated China recognized He Jiankui as a rising star in the biotechnology field, and the government expected him to lead this field in the future. Moreover, his research has "strategic importance" for the Chinese government, indicating any agencies or entities that tried to strictly enforce the regulation might face consequences from the government for impeding this important research. The pressure from the above would be overwhelming for a local hospital if an ethics review was

not granted to He Jiankui. Even though the experiments are immoral, He Jiankui's credentials are too strong for a hospital to stop his research. As a result, the adversaries failed to break this network and stop the experiments.

Virtue Ethics Moral Analysis of the Human Actors

The following analysis will focus on the morality of He Jiankui and his colleagues (Zhang Renli, Qin Jinzhou, and Michael Deem) and the parents. Pritchard's virtues for morally responsible engineers are applicable on He Jiankui and his colleagues since they are scientists. He Jiankui received his Ph.D in biophysics at Rice University under the guidance of Professor Michael Deem. Greely gave the following remarks to He Jiankui's expertise, "He is not a physician, let alone a reproductive endocrinologist or an obstetrician/gynecologist, the clinical specialties with expertise in assisted reproduction. He had no expertise in using CRISPR in embryos, human or non-human, and absolutely no expertise in assisted reproduction" (Greely, 2019). He Jiankui's expertise was on biophysics, not gene editing or embryo. He was not qualified to conduct CRISPR-Cas9 experiments on embryos, and this was a violation of expertise/professionalism in Pritchard's virtues for morally responsible engineers. He Jiankui posted a video named "About Lulu and Nana: Twin Girls Born Healthy After Gene Surgery as Single-Cell Embryos" on YouTube to explain his research and his motivation. He described his CRISPR-Cas9 experiments as "a gene surgery that could save a child from a lethal genetic disease like cystic fibrosis or from a life-threatening infection like HIV. It doesn't just give that little girl or boy an equal chance at a healthy life, we heal a whole family" (He, 2018). However, both Lulu and Nana had immune cells that exhibited the desired mutations while some remained unchanged, and geneticists call this "mosaic" (Greely, 2019). Lulu and Nana would not have natural protection against HIV, and the mutations might lead to the production of proteins with

unpredictable functions. (Cohen, 2019) He Jiankui was making inaccurate claims in a field that he had no expertise in, which was another violation of expertise/professionalism. This was also a violation of responsibility, because he introduced unnecessary risks to Lulu and Nana. He Jiankui also stated: "I understand my work will be controversial, but I believe families need this technology, and I am willing to take the criticism for them" (He, 2018). CRISPR-Cas9 was not yet a stable technology, since it could create off-target mutations that lead to cancer or other problems, but He Jiankui still believed he made the right decision, and he could carry all responsibility. This was a violation of objectivity and a display of arrogance.

I have shown that He Jiankui's was not a morally responsible engineer because he violated multiple virtues in Pritchard's list. Some might stop their analysis here, thinking the scientists who participated in this research should carry all the guilt. Yet it should be noted that other human actors, such as the parents, might carry some responsibility. Pritchard's virtues for morally responsible engineers are not applicable to the parents since they are not scientists. Instead, I will use Aristotle's definition of virtue to evaluate the morality of the parents. The parents had to sign an informed consent form before the experiments. The third paragraph of Article 3 contained a discussion of the risks to children that would born after the experiments, "The primary risk of gene editing (DNA-targeted CRISPR-Cas9 endonuclease) is the off-target effect of generating extra DNA mutations at sites other than the intended target" (Greely, 2019). However, the informed consent form did not include the consequences of off-target mutations. On one hand, He Jiankui violated honesty by not including the potential consequences of off-target mutations. On the other hand, the parents recognized that the gene editing procedures might bring unknown risks to the children, but they did not question the consequences, which

violated the cardinal virtue prudence. Therefore, the parents should also carry some moral responsibility.

Conclusion

Using the ANT, I identified He Jiankui as a privileged actor that had overwhelming power. The immoral CRISPR-Cas9 experiments could proceed without impediment was a result of He Jiankui's influence undermining the performance of contemporary Chinese regulation and hospital's ethics committee. Under the framework of virtue ethics, He Jiankui had violated expertise/professionalism, responsibility, objectivity, honesty, and displayed arrogance, while the parents violated prudence. This had shown that He Jiankui was not the only actor that carried moral responsibility. Readers will have a better understanding on why the immoral experiments were carried out without impediment. This knowledge could be translated to prevent future occurrences of similar events.

Word Count: 3386

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