Comments on Gene-editing Baby Case

1. Various responses to this continuing matter

On 26 November 2018, the day before the Second International Summit on Human Genome Editing convened, news of the ‘CRISPR babies’ broke. Twin girls, Lulu and Nana, had been born in China after their parents had received *in vitro* fertilisation (IVF) treatment in combination with CRISPR-Cas9 genome editing which altered their *CCR5* genes (Marchione, 2018). Mr. He Jiankui, a biophysicist of University X in south of China, announced his experiment. It surprised, shocked, and startled the world.

The case involves HIV and resulted from deficient MOH regulations issued in 2001. Under those regulations, the HIV positive husband was ineligible for Assisted Reproductive Technology treatment. But the concern caused more from the case is on the use of the CRISPR-Cas9 to do germline editing. Gene editing is a powerful new tool for making precise additions, deletions, and alterations to the genome. CRISPR/Cas9 has made genome editing cheaper, much more precise, efficient, and flexible. Many junior researchers are embracing this technology which is why it has raised such large concerns.

In the PRC, the news was first reported by People’s Net, Shenzhen Channel, after it had been released to the international media a day earlier. It was later reported by other networks, such as Guangming Net, Xinhua News Agency and web portals such as Sina, and Sohu, which brought the story to a wider audience.

Soon after the story broke, the University X, where Mr. He was employed, announced that his employment was terminated as of 1 February 2018. University X stated that his actions were unrelated to university. The Shenzhen Hemei Women and Children’s Hospital and other related organizations also declared their lack of involvement.

The media contacted several scholars for their opinions. Chinese scientists and regulators soon responded by condemning Mr. He’s experiment (CSCB and GSC, 2018; Zhishifengzi, 2018; Yicai, 2018; Xinhua, 2018). A large number of academic associations, including the China Reproduction Association (a branch of the China Medical Association), the Stem Cell Sub-association of Biology Associations, the Ethics Committee of the China Genetic Association, the China Medical Ethics Association, and some other institutions, including the Chinese Academy of Medical Sciences also released opinions to the public via websites or in journals. More than 120 scientists in issued a joint declaration condemning his behavior.

Their main points were similar and focused on the technology’s inherent uncertainty, gene pool risk, that there was no need to use the technology, and that any results, either experimental or clinical, should have been published in peer-reviewed journals before public release. They noted that his research and practices had violated national regulations and had done so secretively during his annual leave from University X (Shepherd and Ruwitch, 2018).

Whether it was unlawful, or criminal, remained unclear due to ambiguous regulations.

This was the first time in China that so many scientists and institutions had voiced opinions on a specific case. They all did not agree with regard to his behavior. They thought that Chinese science and scientists had lost face. They had no answer to the question “Why was it always Chinese scientists that broke international guidelines?”

The PRC’s Ministry of Science and Technology (MOST) and its National Health Commission (NHC) have both held several meetings since 27 November 2018 to deal with the situation. They invited scholars in the field to help to clarify the situation, analyze the impact of the event and establish an investigatory group, and gave them the assignment to go to Shenzhen to investigate.

The Ministry of Education (MOE) responded in December 2018 by requiring universities and institutions to initiate self-checks and report to MOE as to whether they have approved such kind of research, and what their plans are for those who have supported such research and how to supervise its process.

Government agencies hope to improve their management of biotechnology research using this case and the lessons learned from it to revise regulations and require institutions to strengthen their management.

The National Science Foundation Commission released an open letter on its website stating concern about the case and insisting that research related to genetic editing must be done in a legal and ethical manner. It must also be supervised and follow research ethics guidelines (NSF, 2019). The National Natural Science Foundation (NSF) of China has funded 31 CRISPR technology-related projects in 2014 valued at 13 million RMB. In 2015, the NSF funded 57 CRISPR technology-related projects at a significantly higher rate than in 2014. The funding exceeded 31 million RMB (Fan Yuelei, 2018).

In sum, two types of responses have been seen: 1. institutions connected to Mr. He denied any relationship with him and his actions; and, 2. more and more scientists, associations, and institutions are condemning his actions. There is almost no support for him or his actions.

1. Initial investigation results

On January 21, 2019, the provincial (Guangdong Province where the case happened) investigation committee released its preliminary findings in the He case (Xinhua, 2019). It reports that Mr. He had assembled a research team consisting of foreign and domestic researchers and started the project no later than June 2016. The investigation stressed that Mr. He’s experiment using human genome editing to edit to-be-implemented human embryos violated national regulations. It also revealed that Mr. He had forged the ethics review approval. Inclusion criteria for the test specified that the to-be-enrolled husbands test HIV-positive, and that the wives must be HIV-negative. Eight couples were recruited for treatment between March 2017 and November 2018. Genome editing was conducted in combination with IVF treatment. During the research one couple withdrew. Of the remaining seven couples, two female participants became pregnant. One gave birth to Lulu and Nana. As of this writing the other is expecting. The investigation concluded that Mr. He’s research violated scientific integrity and research ethics, broke applicable regulations, and had far-reaching adverse effects on science and society in, and outside of, China.

Personnel and institutions involved with him are now the subject of a criminal investigation. The provincial government also announced it would conduct observational studies and follow-up examinations of Lulu, and Nana, and the other pregnant female participant. These studies will be guided by applicable national regulatory agencies and coordinated among interested parties.

The primary investigation result is very simple. the further investigation is still on going.

1. Basic analysis and update
   1. Medical community perspectives

Mr. He claimed he had edited the CCR5 gene to prevent HIV infection in the babies when the father was a HIV carrier. The mothers were not infected. HIV-positive males can father non-HIV babies using established Assisted Reproductive Technology (ART) which has a very high success rate. Scientists in the gene editing area commonly regard such gene editing embryos is completely unnecessary to prevent HIV transmission to the fetus. In considering possible future immunity to HIV, simply avoiding potential risk of HIV exposure is sufficient for most people. Therefore, editing early embryos will not benefit the babies, while it does pose potentially serious risks on multiple fronts, which we will discuss next. (Wang H, 2019)

* 1. Gaps between local regulations and international guidelines

Science is a global community. Many scientists outside China have expressed deep concerns. One scientist called him “rogue”: “Some U.S. researchers knew of a Chinese scientist’s intentions to implant edited embryos but were unable to stop him. Now scientific institutions are trying to devise global safeguards.” (Pam Belluck, 2019).

The universities where Mr. He studied abroad, Stanford and Rice, responded by stating that they are investigating. Stanford said: “We have a review under way of the circumstances around Mr. He’s interactions with researchers at the university,” said spokesperson Ernest Miranda” ([Antonio Regalado](https://www.technologyreview.com/profile/antonio-regalado/), 2019). Recently, Stanford clears its researchers in CRISPR-baby scandal, and University says its scientists did not aid controversial research in China.

No other new investigation results are available at the time of this writing.

Behind the gene-editing case, there is a hidden issue not discussed widely. It is whether Lulu and Nana’s parents had right to make the decision to remove CCR5 to avoid HIV infection? Parents should and need make decisions for children. The point is that if the parents did not act in the best interest of child, then the government is usually reluctant to involve itself, especially in a medical context. Though this phenomenon is not limited in China, some cases have revealed its problems and its disadvantage, and this debate has not aroused the sense among society in China.

Nationally, the most recent call is for suggestions and recommendations for a “Regulation on clinical uses of new biomedical technologies” issued by the National Health Commission on 26 February 2019. This updated regulation has 63 parts. A two layer-management mechanism is proposed. For high risk biomedical technology, which includes gene-editing, the research must be reviewed first at the provincial level and then submitted to the national health agency for review. If the new biomedical technology is safe and effective, a local institution that has implemented the research can apply to the provincial government for clinical applications of tested technologies. Additionally, it clearly indicate that the legal responsibilities are now shouldered on institutions if they break it.

What the international audience can learn from this is that international guidelines should be followed if local level guidelines are lacking. *The* [*Human Genome Editing: Science, Ethics, and Governance*](https://www.nap.edu/catalog/24623/human-genome-editing-science-ethics-and-governance) clearly indicates so in RECOMMENDATION 5-1 which states:

Clinical trials using heritable genome editing should be permitted only within a robust and effective regulatory framework that encompasses:

* the absence of reasonable alternatives;
* restriction to preventing a serious disease or condition;
* restriction to editing genes that have been convincingly demonstrated to cause or to strongly predispose to that disease or condition;
* restriction to converting such genes to versions that are prevalent in the population and are known to be associated with ordinary health with little or no evidence of adverse effects;
* the availability of credible preclinical and/or clinical data on risks and potential health benefits of the procedures; ...... (the National Academies of Sciences, Engineering, and Medicine, 2017)

One point needs addressing, the NHC regulation only covers healthcare institutions and hospitals, and it has no legal authority over non-health institutions. Many biology departments in non-medical universities and many biotechnology companies are not regulated by the NHC. It was not a mere serendipity that the Mr. He gene-editing case happened at University X. He was faculty in the biology department and University X is responsible to Ministry of Education, rather than NHC.

Another gap in the new regulations is that they might trigger more administrative procedures and might decrease efficacy. The Central Office of the Communist Party of China, Office of the Central Government co-issued a document: On deepening the reform of examination and approval system, and on encouraging innovation on drug and medical devices, on 8 October 2017. This document was addressed to the efficiency of ethical review. So, the potential inconsistency remains unclear among the government agency level, and how to make balance of quality and efficiency remains an important issue.

1. Reflections and the future

How this case happened is still being widely discussed in the biomedical areas, bio-technology fields, and scientist communities. Among the discussions, the issue of conflict of interest, financial and non-financial, are raised more and more.

Mr. He was encouraged by University X’s policy on translating knowledge into industrial use or for production and patenting. On February 26, 2016, the Central Government once issued a notice on Promoting the Transformation of Scientific and Technological Achievements (Guo Fa [2016] No. 16). The Ministry of Education and the Ministry of Science and Technology also issued similar documents (Teaching Technology [2016] No. 3). It encourages colleges and universities to take measures for transfer and transformation of scientific and technological…”, if the transformation is successful, obtaining patent, or getting licensing, then not less than 50 percent of the net income from the technology transfer or licensing can be rewarded to individuals who complete this translation...".

The national and university levels policies about encouraging the transformation is good for social development, but policy of conflict of interest policies should be developed in parallel to guide the researcher into not having conflicts of interest. In 2016, University X reported that Mr. He was part of the effort to in “encouraging faculty to start up business”, and setting up companies. Mr. He had a focus on gene sequencing in support of clinical diagnosis. It was named “Hao Hai Gene”. Mr. He was the company CEO. Though there is no investigation result from these possible conflicts of interest, it is a potentially a very serious issue related to the case and related motivations behind decisions made.

This “conflict of interest” issue is more and more being noticed and reminds many institutions that they must think about how to develop the management mechanisms towards the translation from bench to bedside.

Another reflection is about the values of moral judgment towards the biomedical innovation. It seems that there is consensus in the gene-editing area that there was necessity to use CRISPR-Cas9, however heritable genome editing might affect human kind. On this issue, Mr. He’s answers to questions at the press conference were that “I know my research has caused big debate, but I believe this can help those families in need. I’d like to face the problems and take responsibility.”

Many bioethicsts think that it is impossible to predict either benefits, or harm, and that is a sufficient reason for not allowing the practice. (Antonio Regalado, 2019). But the question of who is qualified to make such judgment about benefit and risk remains? It seems, the parents of twin babies strongly requested the research team to do this, is it sufficient for researcher or doctor to follow? We have to admit that many doctors are following unreasonable requests from families, instead of best interest of patients. (don't account whether Mr. He had some undue information or not). Currently, there is consensus about germline gene-editing and it is not yet time to apply this to medical treatment. Just suppose: if some years later, the follow up data of the twin girls provides evidence to show Mr. He’s research and application were successful, what would be the response to today’s condemnation? Good outcome, but breaking the rules, or following the rules, but bad result for the babies, which is more acceptable? Is a result-based judgment mechanism tenable, or the rule itself is sufficient? Moreover, does there exist differences of risk-benefit ratio judgment for a specific region compared to a different region? If the local ethics committee approves the study, it is legal to proceed, or it is not ethical?

What should be the fundamental values behind?

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