A Case of Human Genetic Engineering

LAI525

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People expect medical science research to proceed at an orderly pace and in an ethical manner. In order to avoid the mistakes of the past, there are government agencies, university ethics boards, and personal responsibility codes to prevent investigators from acting inadvisably and taking unnecessary risks. Occasionally, however, an individual or individuals will decide to push against those boundaries and proceed in a manner that seems to run counter to these ethical constructs in order to further their research. The most recent of example of this behavior was announced to the world on November 28, 2018.

On November 28, 2018, He Jiankui announced to the world that he has used CRISPR-Cas9 technology to genetically modify to human embryos. These embryos were successfully transplanted into a womb and has resulted in the birth of twin girls (Botting, 2018) (Marchione, 2018) (Stein, 2018) (Zimmer, 2018). If true, this represents the first instance of CRISPR technology use to produce genetically modified human beings.

Prior to this action, modification of human germlines has been discouraged by the majority of scientific bodies with over forty countries having a ban on such research in place (Lanphier et al., 2015). It is, perhaps, significant to consider that the announcement was made at the Second International Summit on Human Genome Editing, a conference with the express purpose of exploring the questions related to the *possibility* of human germline editing. As Dr. He has jumped the scientific gun, as it were, the questions of the safety, ethics, and governance of these procedure take on even more importance and urgency.

- Is CRISPR-Cas9 a safe technology for human germline editing?
- Did Dr. He act in an ethical manner by proceeding with this study?
- Is this work an example of unregulated human experimentation?

- How should this type of work be regulated in the future?
- How might this work affect the rights of the newborn children?

Background

Dr. He has a faculty position at the Southern University of Science and Technology in Shenzhen, China and owns two companies dealing with genetic engineering (Stein, 2018). While on leave from the University, He began a project to knock out the CCR5 gene. This gene produces a protein critical to the HIV infection pathway, and it has been shown in models that knockout of the CCR5 gene can prevent HIV infection (Baba, 1999) (Elsa et al., 2018). In this specific case, the embryos were created with invitro fertilization. The egg was provided by the HIV^- mother and the sperm provided by the HIV^+ father. The hope of the work was to offer HIV protection to the resulting offspring.

Poll: Do you believe this particular work is ethical?

The above question is rather broad. Therefore, before considering the ramifications of this situation, it would be helpful to examine a case study of another instance of researchers rushing ahead. A recent example is provided by the work on H5N1 virus modification.

Case Study: H5N1 Modification

In late 2011 two groups, working independently, announced that they had created strains of the H5N1 virus that were transmissible in ferrets, the preferred model for studying airborne disease transmission (Evans, 2012). As they prepared to publish, the National Science Advisory Board for Biosecurity (NSABB) and recommended partial censorship of the articles. In

response, conferences were convened in the USA and Geneva in order to discuss the issue in greater detail.

At the heart of the question was the idea of Dual Use Research of Concern (DURC) (NIH, 2014). According to the NIH,

> *Dual Use Research of Concern (DURC) is life sciences research that, based on current understanding, can be reasonably anticipated to provide knowledge, information, products, or technologies that could be directly misapplied to pose a significant threat with broad potential consequences to public health and safety, agricultural crops and other plants, animals, the environment, materiel, or national security* (NIH, p. 7).

In the work by Ron Fouchier of the Erasmus Medical Center and Yoshihiro Kawaoka of the University of Wisconsin, genetic engineering was used to introduce mutations into separate strains of the H5N1 virus in order to make them transmissible between humans (Resnik, 2013). Previously, the only known strains of H5N1 virus were incapable of direct human to human transmission.

Publication of the two articles would confirm the possibility of creating such an H5N1 virus, and in the hands of an unscrupulous actor, the methodological insights provided could lead to the production of a new bioweapon. This forced the NSABB to make their initial recommendation for censoring the articles.

The H5N1 work highlighted two key ethical issues: the value/risk ratio of performing the work and the decision whether to publish or censor the work. Dealing first with the issue of censorship, it is, of course, not uncommon for research to be carried out under the cover of secrecy and the results censored. The Manhattan Project is one such example.

However, in this case, due to the multiple projects coming to fruition within the same time frame, it is clear that the work on the flu virus was being carried on in multiple locations. What value, then, is there to be gained by censoring the papers? Is it not better to report the work in order to prevent unnecessary duplication and research missteps? Clearly the genie is out of the bottle and won't be put back in.

Is there value to this type of research though? Clearly in the case of the H5N1 work, the investigators were able to gain a better understanding of the virus function. In addition, it may enhance global monitoring programs by indicating key mutations for which to watch, though Bennett (2013) argues that such results are of limited utility as they may not represent the only mutations which could cause pandemic conditions. Carrying out the work in the light of day, allows for open discussion of regulatory and ethical issues related to viral research. Finally, advancement of vaccine work was also possible, though in this specific case, David Relman, MD., had this to say:

> *We already know enough to push full out for a broadly protective H5 vaccine. What more do we need? Do we really want to wait for a mammalian respiratory transmissible H5 to show up in nature? The general public appears to be largely opposed or at least highly concerned. A real moratorium should continue for the foreseeable future* (Roos, 2012).

This highlights the need to balance actual research benefit against risks.

What then of the risks? Careful consideration of the risk is key to the decision to carry out any DURC work. In our case study, the work carried a number of significant risks. First was the possibility of accidental release of a replication-competent mammalian virus into the environment. Though the researchers attempted to mitigate release risks via use of an ABSL3+

environment and prophylactic vaccination (Roos, 2012), a negative outcome was still a distinct possibility. As mentioned above once the work became known, it is possible that a bad actor would have staged a non-accidental release of the virus in order to create a pandemic situation. Publication of the work also carries the risk of advancing the research of other labs that are well-meaning but are not truly prepared to carry on research at this high a risk level.

How then is the community to proceed? In the words of Evans

> *This is a distinctly ethical decision-making process. Moreover, it is unlikely that such a process is one that should be governed exclusively by scientists. There are detailed technical issues involved in dual-use dilemmas that those scientists in the field (in the H5N1 studies, influenza research) can and should bring their expertise to. But considerations of value will require other expert (eg, public health, ethics and economics) and community participation. Scientists may approach their research with the best of intentions and the good of society in mind, but it would be a mistake to assume that they could know what is best for the world - and a tragedy to foist that burden on them* (Evans, p. 212).

In response to the NSABB recommendation, Fouchier and Kawaoka along with other researchers in the field voluntarily instituted a temporary moratorium on such research so that the scientific community and appropriate governing bodies could catch up with and develop the appropriate guidelines for carrying out such work (Keuhn, 2012). During this moratorium, scientific bodies and governmental organizations were able to meet to discuss the path forward. In the case of the United States, the Policy for Oversight of Life Sciences dual-use research of concern (NIH, 2014) was developed and put into place. This policy did not ban such work or call for its outright censorship. Rather, it called for institutions receiving federal funding to

institute internal review and risk assessment boards to approve and monitor any such work. Many other countries used the opportunity to institute similar policies (Fouchier et al., 2012). In addition, the virus has been reclassified as Risk Group 4 due to potential induced transmission which carries significant environmental and handling restrictions.

Once these safeguards were put into place and the appropriate guidelines were disseminated, the original papers were published in full, and the moratorium was lifted.

Poll: Do you believe the H5N1 publishing moratorium was justified?

Finally, what light can this case study shed on the ethical and regulatory issues associated with the human germline issue?

Genetic Engineering: Ethical Concerns

Returning to our consideration of the genetically modified twins, one must have a framework in which to consider the ethical questions. In the United States, research involving human subjects falls under the governance of Health and Human Services regulation 45 CFR part 46. However, though a member of the research team is a faculty member at Rice University, the work was carried outside the United States and not subject to the restrictions that come with US federal funding.

There are international guidelines we can consider, however, that began with the 1947 Nuremberg Code and is now represented by the Declaration of Helsinki and its revisions. Much of these guidelines deal with informed consent. As Dr. He's work remains unpublished and unreviewed, however, there is little for us to comment upon. Two key guidelines which we can focus on, however, are that the research participants should be put at no greater risk than were

they to receive conventional treatment and that the anticipated results are not already obtainable by conventional methods.

In China, the incidence of HIV infection is on the rise. In 2017, it was reported that incidence of HIV in the Chinese population was 4.2 in every 100,000 individuals (Zheng, 2018). As such methods of curbing the growth of HIV is a significant public health concern in China. Dr. He's work, similar to vaccination, was designed to protect individuals from the risk of HIV infection.

Subjects were recruited through a Beijing-based AIDS advocacy group and were all couples seeking in-vitro fertilization where the mother was HIV^- and the father HIV^+ (Marchione, 2018). The couples were offered in-vitro services and medical insurance for any resulting offspring. The male subjects were all under well-controlled anti-viral treatment and were not considered a risk of transmission of the virus. The male sperm was washed, the standard procedure for preventing HIV transmission to the embryo, and introduced into the ovum producing embryos that were then given CRISPR-Cas9 treatment. Of the sixteen embryos created, eleven were implanted in numerous subjects finally resulting in the birth of the twins in November.

One immediate consideration is that this CRISPR project offers no value from the perspective of delivering babies free of HIV. The sperm washing technique is the standard procedure and is considered effective in removing any HIV in the sample prior to fertilization. As such, even without the genetic engineering, the twin girls would have been born HIV-free.

What of the risk of contracting HIV from the male parent after birth? As stated, all male subjects in the study were well-controlled and not considered a risk for transmission (Stein,

2018). They present little or no risk to any offspring. However, with the incidence of HIV growing in China, perhaps a general immunity to HIV infection is a goal worth the risk? Are there any risks to the two girls? Initial genetic testing shows that in one girl, both copies of the CCR5 gene have been modified. However, in the other girl, only one copy has been modified leaving her open to possible HIV infection. Even had the procedure been completely successful for both twins, knockout of the CCR5 gene carries a higher risk of contracting other viruses, including the rapidly spreading West Nile virus and increases the chance of morbidity from contracting the flu (Stein, 2018) (Marchione, 2018). How does potential HIV protection in one or both twins balance against increased susceptibility to other diseases?

While CRISP-Cas9 technology is utilized for its specificity, off-target effects are not unknown (Kim et al, 2015) (Cho et al., 2014). Such effects can be reduced by choosing unique sequences for nucleic acid cleavage. At birth, both twins appeared healthy and have gone home with their parents. With the details of the work unpublished, there is no way to determine whether the cleavage target chosen displayed a sufficient level of specificity. As He states he acted outside the umbrella of a review committee for the work, we are left to trust his judgement and await full genetic testing to determine what additional risks to which the children may be subjected.

Stepping back from the particulars of this case, this work was not created in a vacuum. Genetic manipulation using CRISPR systems is a common technique in research, and the question of whether it should be applied to human research has been asked before. In 2015, Baltimore et al. offered the following guidelines (pg. 37)

1. Strongly Discourage any clinical attempts at germline modifications until scientific and governmental agencies have developed concrete guidelines.

2. Create forums for dissemination of scientific and bioethical information.
3. Encourage *transparent* research into CRISPR-Cas9 genetic engineering in human and non-human *model* systems.
4. Convene global representatives to draft appropriate guidelines.

These sentiments are echoed by Lanphier et al. (2015) who suggested a voluntary moratorium on human germline modification while the ethical and regulatory bodies came to terms with the potentials of easy genetic manipulation presented by CRISPR. Chan et al. (2015) offer fourteen recommendations regarding research involving modification of the human germline. One recommendation that seems particularly appropriate to our consideration of He's work is as follows:

> *Decisions about research and clinical uses of genome editing technologies should be made through inclusive, deliberative processes that will make engagement*
>
> *with the public and policymakers substantive, and should aim to strike the best possible balance between free scientific inquiry and social values. Further, best methods for integrating the outputs of public engagement into the policymaking process should be identified and utilized* (p. 45).

What then can we take from Dr. He's work? Does it fall within accepted ethical guidelines? Is it a case of an individual's arrogance causing him to rush ahead in spite of global norms in research? Where do you stand?

Poll: Can Dr. He's work be considered Ethical?

Poll: Should a temporary moratorium on clinical germline modification be enacted?

In my own case, I work at the University of Michigan and deal with stem cell and CRISPR products daily. The fallout from Dr. He's actions are far from clear. At this point to little is known about what went into the project, and what the final results will be for these children. However, it has already begun to reinvigorate the global conversation around human genetic engineering, and that, at least, is a positive result. This story serves as a reminder that all research decisions come with consequences, and hopefully this is a decision that the two girls will not come to regret.

In research, we are required to push the boundaries of current knowledge, but always with the protection of human research participants as a primary guiding principle. While all the information is not yet available, I do not believe that Dr. He adhered to these principles regardless of the outcome. As I work, and as I teach new investigators, this will be a used as a teachable moment in the ongoing consideration of our ethical responsibilities in science.

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