What Happened with the Chinese Gene-Edited Babies?

• He Jiankui, Assistant Professor South University of Science and Technology (China)
• Use of CRISPR/Cas9 technology to edit genes for the HIV co-receptor CCR5 in human embryos for implementation
• Public announcement at the Start of the Second International summit on Human Genome Editing (Hong Kong, November 2018)
• Male partner HIV-positive → HIV-negative offspring
• Led to birth of twins who were mutated for CCR5 genes
Why Was This Event So Controversial?

**SOMATIC**
- Therapy
  - Medicine & research

**GERMLINE**
- He Jiankui’s experiments

**ENHANCEMENT**
- Plastic surgery

- Designer babies
How Did Our Community React?

“TAG joins with the scientists and the ethicists who are condemning the work as unethical, unjustified, and potentially dangerous”

– Richard Jefferys

http://www.treatmentactiongroup.org/content/treatment-action-group-statement-reported-birth-twins-edited-ccr5-genes
How Did the Risks **Outweigh** the Benefits?

- There are **safe, effective and easier options** to prevent mother-to-child transmission and treat HIV
- Alteration of **germ line**
- **Incomplete ability** of CCR5 gene deletion to prevent HIV acquisition
- Safety of experimenting with CRISPR/Cas-9 in human embryos **not well-established**
- Informed consent process **questionable**
  - *Was there exploitation/coercion?*
- Did robust **regulatory/ethics review** occur?
- Secretive experiment followed with **public announcement before carefully peer-reviewed data** undermined credibility

[Source](http://www.treatmentactiongroup.org/content/treatment-action-group-statement-reported-birth-twins-edited-ccr5-genes)
What Are Some Other Ethical Issues?

- Failure to determine appropriate study participants (‘subject selection’)
- At least one of the twins was a mosaic – nothing gained but exposed to risks
  - Editing took place after embryo started cell divisions
  - Patch work of edited and unedited cells
- What happened to the other embryos generated through IVF that were gene-edited?
- He claimed another woman is pregnant who received embryos created the same way
- Slippery slope for enhancements, designer babies, eugenics
- Deletion of CCR5 gene could increase risk for other viruses, such as West Nile (risk exchange)
- Could a single experiment put an entire field in danger?

http://www.treatmentactiongroup.org/content/treatment-action-group-statement-reported-birth-twins-edited-ccr5-genes
The research team is launching an AIDS vaccine development project. As the volunteer, your partner is diagnosed to have Acquired Immunodeficiency Syndrome (ADIS) or has been infected with Human Immunodeficiency Virus (HIV). Your health and other conditions are in line with the research's enrollment conditions. Therefore, the research team would like to invite you to participate in the research.
• “The research team is launching an AIDS vaccine development project.”
• “Gene editing in the embryo would knock out the CCR5 gene. It would help these CCR5 editing babies to obtain the genotype of the Northern European to naturally immunize against HIV-1 virus”
• “…decrease the risk of off-target issues and other risks”
• “This technique may be able to produce IVF baby naturally immunized against AIDS”
• “There is a possibility that some embryos do not have anti-AIDS ability”
• “The project team is not responsible for the risk of off-target which is beyond the risk consequences of the existing medical science and technology”
• “Neonatal malformations, congenitally [sic] deficiency, suffering from common genetic diseases belong to the scope of natural risk of natural reproduction, the project team does not assume legal responsibility”

• Possible benefit: “This research project will likely help you produce HIV-resistant infants” [rest of the consent form explains how infant could still have HIV]

• “If you decide to leave the study due to other reasons (…), you will need to pay back all the costs that the project team has paid for you. If the payment is not received within 10 calendar days from the issuance of the notification of violation by the project team, another 100,000 RMB of fine will be charged”

• “Baby’s photo on the day of birth will be kept by the project team. The project team has the portrait right of the infant and can make it open to the public”
Ethical Considerations for Cell and Gene Therapy

Favorable Risks and Benefits Balance

• Risk/benefit assessment is one of the fundamental requirements in ethical review of research involving human participants (Aarons)
• Research must have higher chance of doing good, overall, than doing harm*
• Researchers should minimize risks and maximize benefits
• Need to protect participants from excessive risks
• Difficult to evaluate because there can be asymmetries
Ethical Considerations for Cell and Gene Therapy

Other Things to Consider in Evaluating Risks

- Innovativeness of interventions
- Modes of actions
- Nature of the target
- Relevance of animal models (pre-clinical evidence)
  - Stronger evidentiary justification needed for specific groups
- Uncertainty (major hallmark of FIH studies)
Gene Modification
- Zinc finger
- TAL Effector Nuclease
- CRISPR/Cas9
- MegaTals
Assessing Risks and Perceptions of Gene Therapy

- International survey to investigate gene therapy researchers’ perceptions and assessments of risks in clinical trials (n = 156)
- Strength of pre-clinical evidence strongly influenced risk disease severity, assessments, judgements of acceptable risk levels, perceptions of uncertainty, adverse events and perceived patient needs, and perceived validity/utility of pre-clinical models
- Differences between stakeholder types
- We have not yet done this research of gene therapy related to HIV cure
### Table 2. Framework for risk-benefit analysis for HIV-1-infected patient populations that could be targeted with HSPC-based gene therapy.

<table>
<thead>
<tr>
<th>No.</th>
<th>HIV/AIDS Subpopulation</th>
<th>Current Rx Options for HIV-1 infection</th>
<th>Aspects of SOC Rx for HIV-1 infection</th>
<th>Potential Benefit of Research Rx</th>
<th>Real or Potential Risks of Research Rx</th>
<th>Risk/Benefit Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HIV/AIDS pts on eART (controlled viremia and CD4 counts &gt;500/μL)</td>
<td>cART</td>
<td>&lt;10% treatment failure Outcome expectations excellent</td>
<td>Minimal to no potential benefit since virus control and CD4 counts are adequate</td>
<td>Transient myeloid dysfunction Unknown effects of genetic modification &amp; HSPC mobilization</td>
<td>Unfavorable; first in human trial cannot be justified in this group</td>
</tr>
<tr>
<td>2</td>
<td>AIDS pts off eART (side effects to eART or eART “fatigue”)</td>
<td>Symptomatic Rx if eART not tolerable</td>
<td>Heightened potential for AIDS progression</td>
<td>Improved control of HIV-1</td>
<td>Transient myeloid dysfunction Unknown effects of genetic modification &amp; HSPC mobilization</td>
<td>Favorable but conditioning adds unnecessary risk in these patients who are already drug adverse</td>
</tr>
<tr>
<td>3</td>
<td>AIDS pts on eART, with incomplete immune recovery with suboptimal CD4 levels</td>
<td>Treatment as indicated for infections</td>
<td>Poor expected outcome</td>
<td>Expansion of CD4 count Potential for improved control of HIV-1</td>
<td>Transient myeloid dysfunction Unknown effects of genetic modification &amp; HSPC mobilization</td>
<td>Favorable</td>
</tr>
<tr>
<td>4</td>
<td>AIDS pts who do not respond to eART</td>
<td>Research therapy with new antivirals</td>
<td>Poor expected outcome</td>
<td>Improved control of HIV-1</td>
<td>Transient myeloid dysfunction Unknown effects of genetic modification &amp; HSPC mobilization</td>
<td>Favorable but limitation of subject availability</td>
</tr>
<tr>
<td>5</td>
<td>ARL pts in remission following frontline Rx</td>
<td>cART Treatment as indicated for infections</td>
<td>Remission stable Outcome expectations very good; concern for risk of myelodysplasia</td>
<td>Minimal to no potential benefit if virus control and CD4 counts are adequate</td>
<td>Transient myeloid dysfunction Unknown effects of genetic modification</td>
<td>Less favorable due to potential for myelo-dysplasia post-chemotherapy and conditioning</td>
</tr>
<tr>
<td>6</td>
<td>ARL pts on salvage therapy (transplant)</td>
<td>cART Treatment as indicated for infections</td>
<td>Outcome expectations good; concern for myelodysplasia risk</td>
<td>Minimal to no potential benefit if virus control and CD4 counts are adequate</td>
<td>Transient myeloid dysfunction Unknown effects of genetic modification</td>
<td>Less favorable due to 10%–20% potential for myelodysplasia post-transplant and conditioning</td>
</tr>
</tbody>
</table>

Abbreviations: Rx = treatment; eART = combination antiretroviral therapy; SOC = standard of care; ARL = AIDS-related lymphoma.
### Table 1. A Regulatory Perspective on Feasibility to Surmount Genome-Editing Safety and Efficacy Challenges

<table>
<thead>
<tr>
<th>Challenges</th>
<th>Regulatory Feasibility to Overcome</th>
<th>Approaches to Address Challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Off-target activity, resulting in insertion or deletion mutations and/or chromosomal translocations</td>
<td>moderate</td>
<td>• assays to predict and identify off-target activity and/or translocations in place</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• biological assays to evaluate functional consequences of off-target activity still in development</td>
</tr>
<tr>
<td>Necessity to maximize efficiency of designer nuclease delivery and to control nuclease expression level and duration</td>
<td>moderate to high</td>
<td>• <em>in vivo</em> CRISPR-Cas delivery (mRNA, protein) via lipid nanoparticles may help to fine-tune level and duration of nuclease expression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• <em>ex vivo</em> delivery of nuclease encoding mRNA by electroporation allows fine-tuning level and duration of nuclease expression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• <em>ex vivo</em> delivery of nucleases in the form of DNA can be inefficient and induce high cytotoxicity</td>
</tr>
<tr>
<td>Inaccurate or random donor DNA (AAV or IDLVs, oligodeoxynucleotide donors) integration in the genome</td>
<td>moderate to high</td>
<td>• assays to detect random integration of AAV and IDLVs in place</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• randomly integrated oligodeoxynucleotides are difficult to detect</td>
</tr>
<tr>
<td>Highly variable tissue distribution of desired <em>in vivo</em> genome-editing event</td>
<td>moderate</td>
<td>• collection and assessment of a diverse panel of all major organs and tissues</td>
</tr>
<tr>
<td>Potential of immune reaction to nuclease components of current gene-editing systems</td>
<td>moderate</td>
<td>• use of immune suppression may be required</td>
</tr>
</tbody>
</table>

U.S. Attitudes of Human Genome Editing

Acceptance of gene editing
A majority finds use of human genome editing for therapeutic purposes acceptable, including somatic and germline edits. Public opposition increases for applications aimed at enhancement.

- Somatic therapy
- Germline therapy
- Somatic enhancement
- Germline enhancement

Percent of respondents

Prevailing Public Perceptions Matter

The FDA is witnessing **a surge of C&GT products** entering early development.”
“We anticipate that by 2020 we will be receiving **more than 200 INDs per year**”
“By 2025, we predict that the FDA will be approving **10 to 20 C&GT products a year**”
“We’re working to expand our review group dedicated to the evaluation of these applications to **keep pace with the rapid expansion** in new product development”
“The FDA plans to introduce additional new policy guidance and other advances in our drug development framework in 2019”
“Though we are very encouraged by the advances in science and clinical development in this field, we remain concerned at the FDA that a number of individuals (...) are working **outside of regulatory compliance**”
“We plan additional enforcement actions in 2019 to address products that pose a significant risk of potential harm to patients”

https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm629493.htm
Safeguards in Place

• FDA Investigational New Drug (IND) application process

• NIH Recombinant DNA Advisory Committee (RAC) (established in 1974)
  • Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into One or More Human Research Participants

• Good Manufacturing Practices (GMP) (ensures safety, purity and potency)

• FDA Guidance documents
WHO Forms Committee to Guide Editing of Human Genes

https://www.who.int/ethics/topics/human-genome-editing/committee-members/en/
Experiments on Gene-Edited Embryos on U.S. Soil

• Team at Columbia University examining newly fertilized eggs injected with CRISPR editing tools
• Goal is to prevent inherited diseases, such as Tay-Sachs, cystic fibrosis, Huntington’s disease, retinitis pigmentosa (blindness)
• Developmental biologist Dieter Egli conducting experiments ‘for research purposes’
• Egli stops modified embryos from development beyond Day 1

• What is our obligation to respond as a community?
• Should the use technology like CRISPR/Cas-9 be controlled?
• How do we prevent scientists like He from going rogue?
• What about assessing risks for combination gene therapy approaches?
• What about fetal cell and gene therapy or cell and gene therapy in pediatric populations?
• Is there a fine line between therapeutic/preventive warrant and research purposes?
• Should we consider unmet needs of study participants in ethical decision-making?
OUR COLLABOARTIVE MANUSCRIPT IS IN

• “ACCEPTABILITY OF CELL AND GENE THERAPY FOR CURING HIV INFECTION AMONG PEOPLE LIVING WITH HIV IN THE PACIFIC NORTHWEST UNITED STATES: A QUALITATIVE FOCUS GROUP STUDY” – SUBMITTED TO AIDS RESEARCH & HUMAN RETROVIRUSES ON JAN 21, 2019

• We wish to thank the defeatHIV Community Advisory Board and its coordinator, Michael Louella, for their role in our investigation. The impetus for this qualitative research is the direct result of their engaging communities affected by HIV in the cure-related research enterprise. It is solely due to their steadfast advocacy for more focus on people’s perceptions of cell and gene therapy as a potential HIV cure strategy that this research was conducted; and for their efforts and their willingness to work as equal partners with our research staff, they are to be commended.

SPECIAL THANKS TO KARINE DUBÉ
References