HIV Cure Research Ethics Update
Considerations for Cell and Gene Therapies

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2019 Pre-CROI Community HIV Cure Research Workshop
Sunday, March 3, 2019

defeatHIV

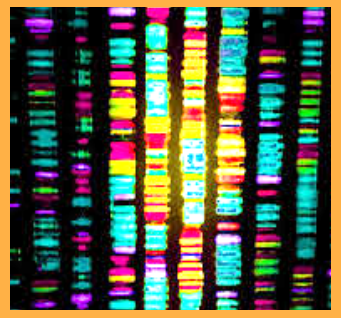
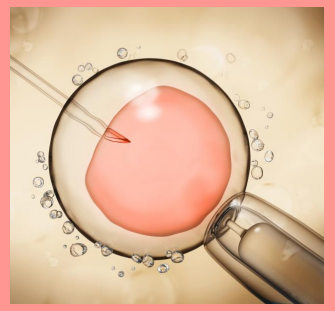
UNC GILLINGS SCHOOL OF GLOBAL PUBLIC HEALTH

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

He Jiankui

Why Was This Event So Controversial?

	SOMATIC	GERMLINE
THERAPY	medicine & research 	 He Jiankui's experiments
ENHANCEMENT	Plastic surgery 	 Designer babies

How Did Our Community React?

TAG

Treatment Action Group

Help us continue our work in 2019

MAKE A DONATION

HOME HIV CURE HCV TB BASIC SCIENCE POLICY PIPELINE REPORT TAGLINE EtE

LIMITED ART EDITIONS

WATCH THE VIDEO! TAG RESEARCH IN ACTION AWARDS

DONATE

Treatment Action Group Statement on the Reported Birth of Twins with Edited CCR5 Genes

New York, November 26, 2018 – Treatment Action Group (TAG) decries the claimed use of CRISPR technology to edit genes for the HIV co-receptor CCR5 in human embryos for implantation.

Yesterday, He Jiankui, an Associate Professor at the South University of Science and Technology of China, posted a video to YouTube claiming to have employed CRISPR/Cas9 technology to edit the genetic code of embryos, leading to the birth of twins with mutated genes for the HIV co-receptor CCR5.[1] The announcement has triggered extensive media coverage and ignited a firestorm of controversy.

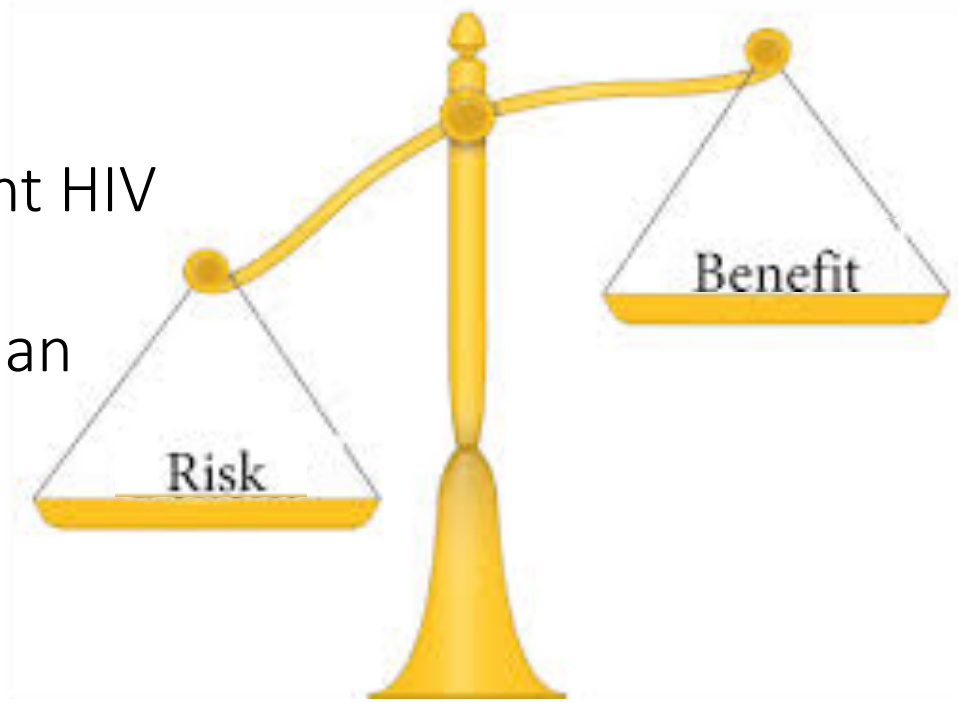
"TAG joins with the scientists and the ethicists who are condemning the work as unethical, unjustified, and potentially dangerous"

– 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



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?

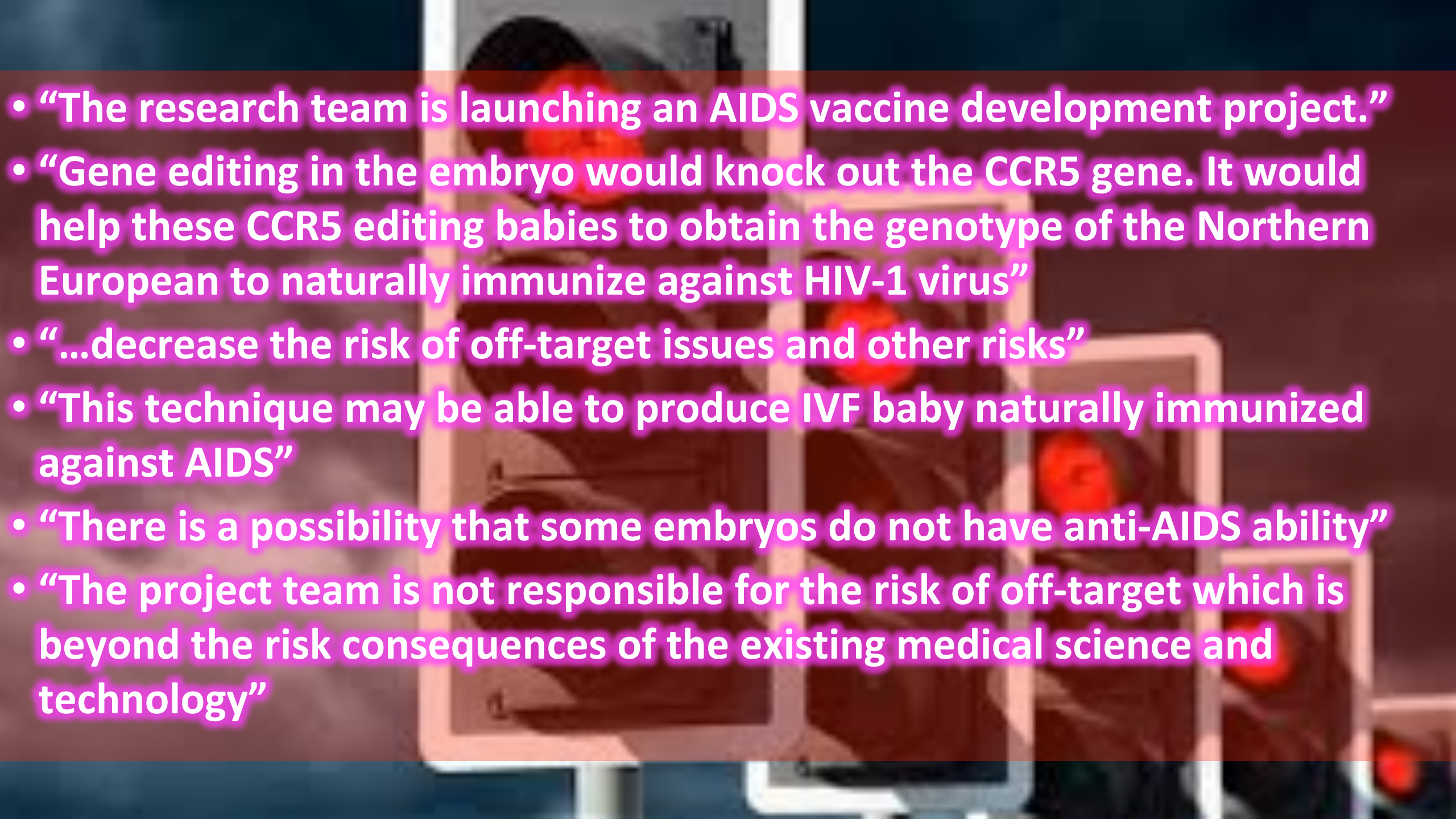
http://www.treatmentactiongroup.org/content/treatment-action-group-statement-reported-birth-twins-edited-ccr5-genes

Informed Consent Issues

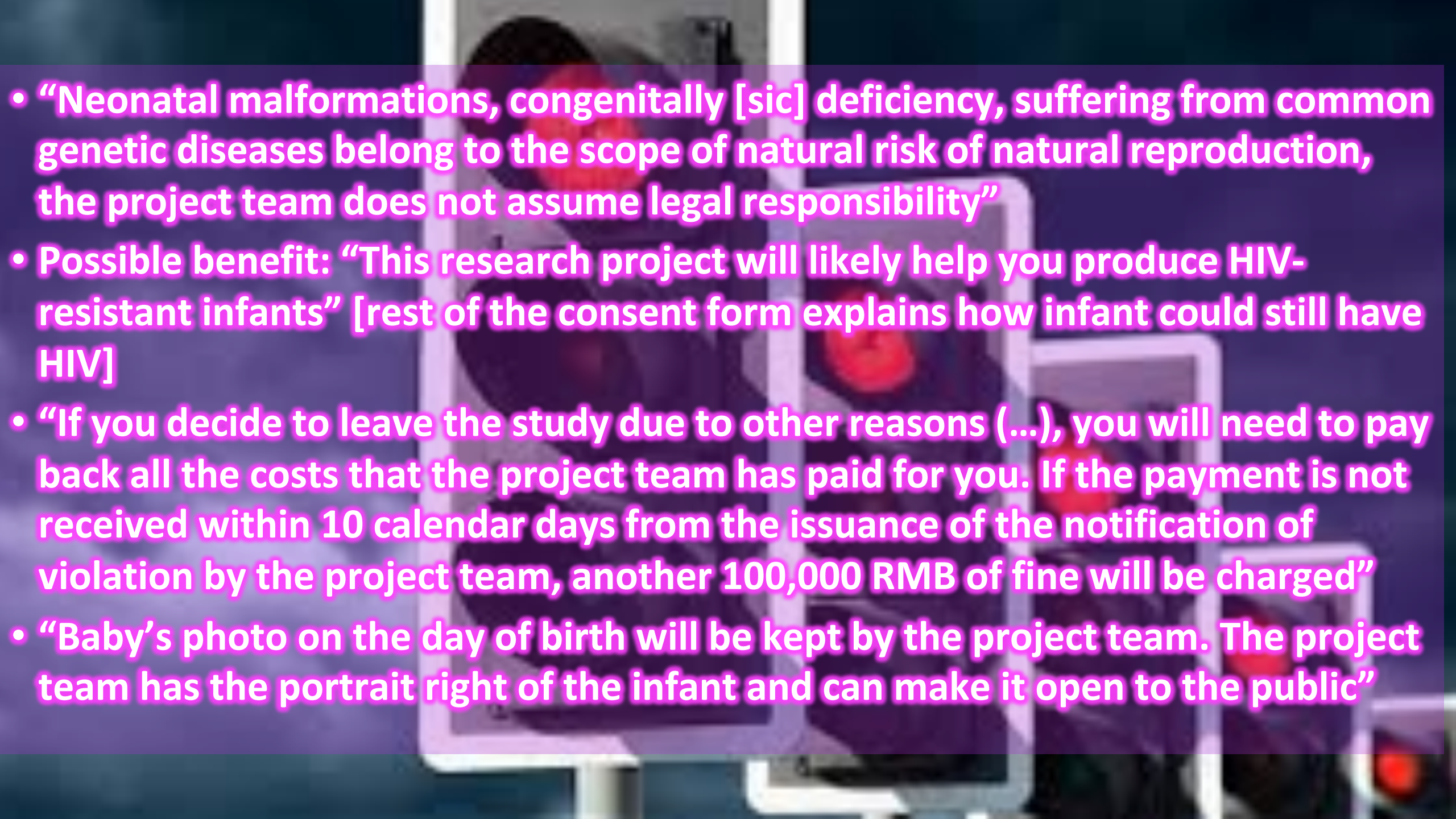
Version: Female 3.0

INFORMED CONSENT

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”

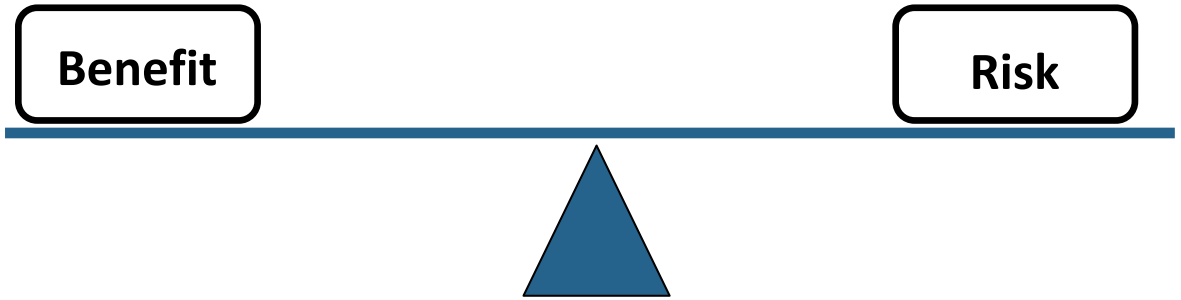


- “Neonatal malformations, congenitally [sic] deficiency, suffering from common genetic diseases belong to the scope of natural risk of natural reproduction, the project team does not assume legal responsibility”
- Possible benefit: “This research project will likely help you produce HIV-resistant infants” [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

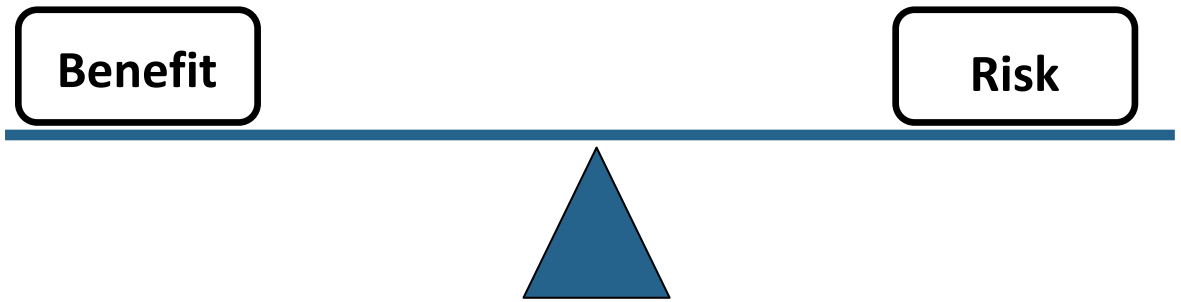
- Risk/benefit assessment is one of the fundamental requirements in ethical review of research involving human participants (Aarons)
- Research must have higher chance of doing good, overall, than doing harm*
- Researchers should minimize risks and maximize benefits
- Need to protect participants from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



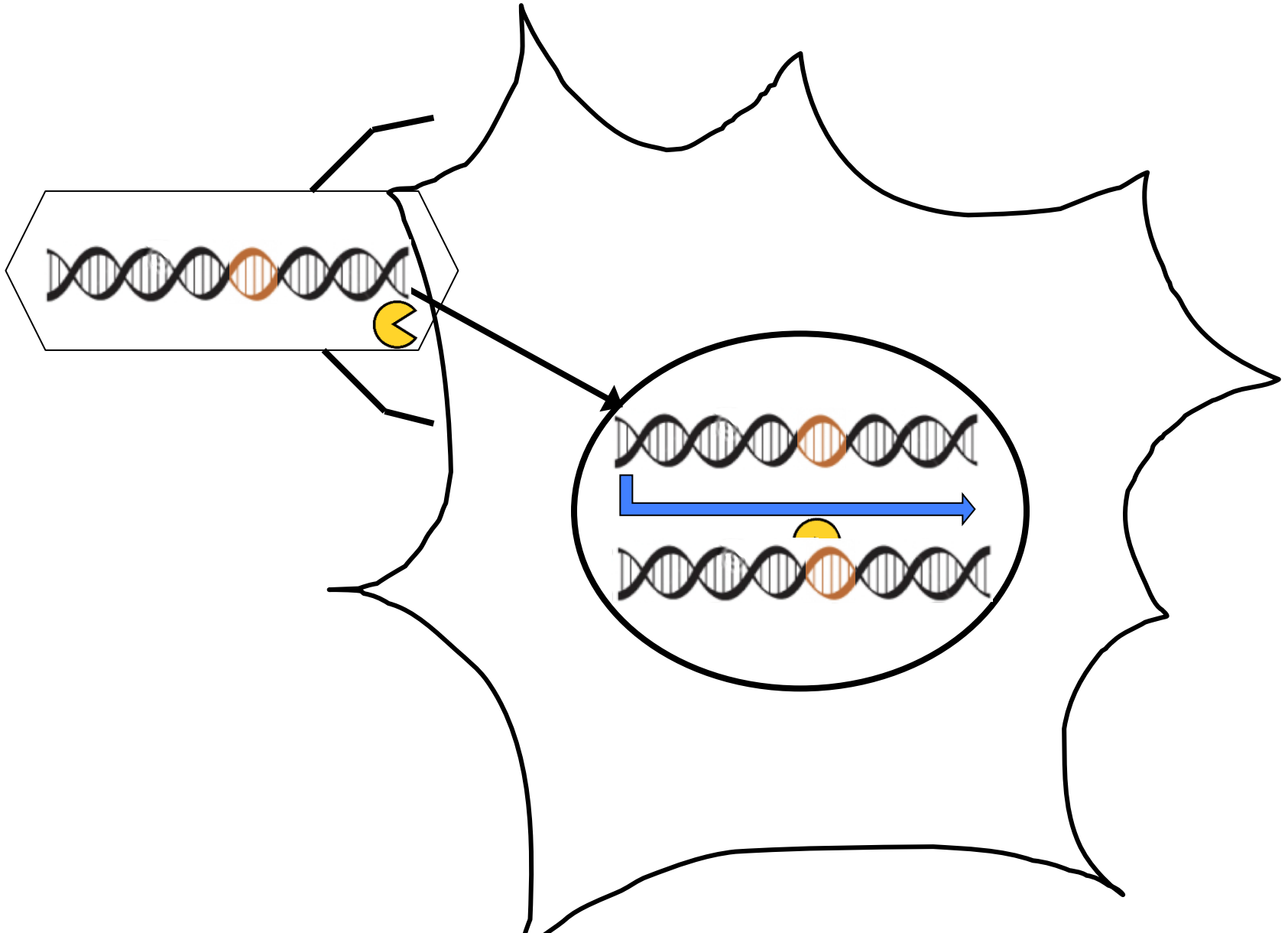
Ethical Considerations for Cell and Gene Therapy

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)

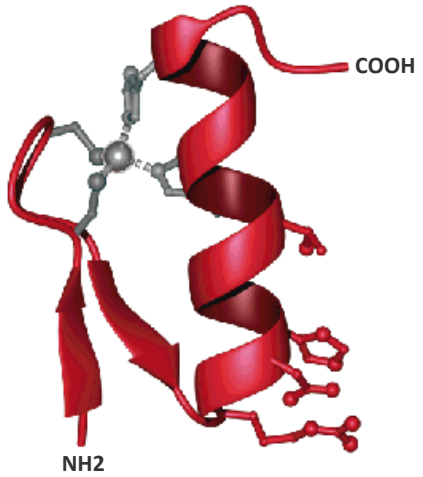


Gene Modification

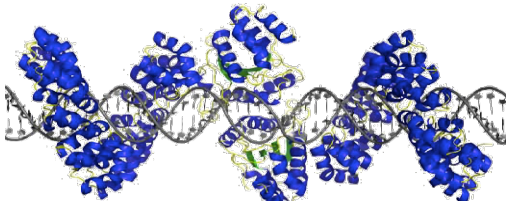


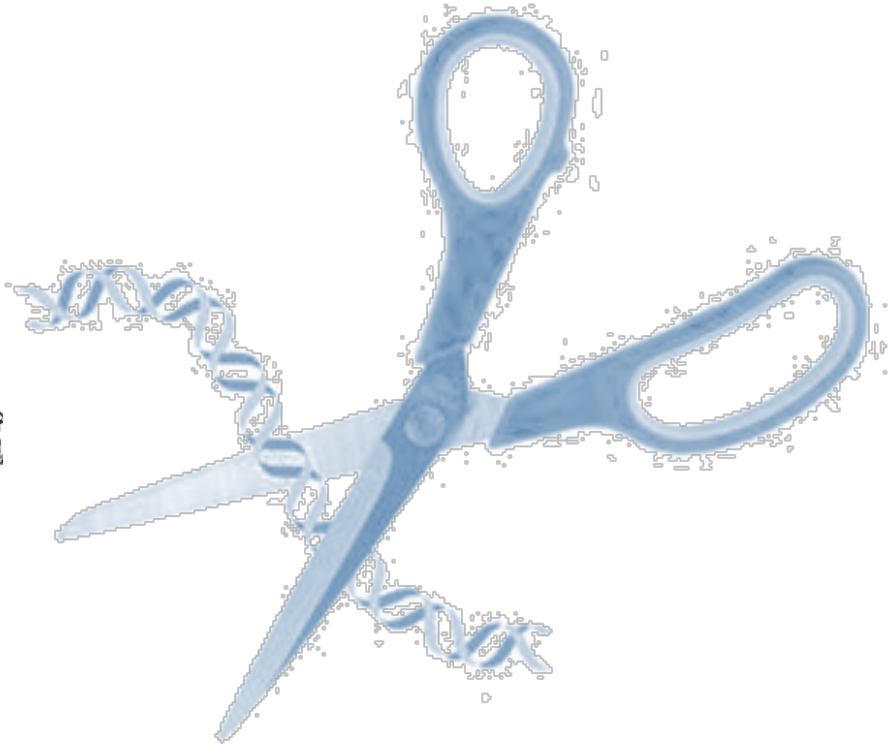
Nucleases

- Zinc finger

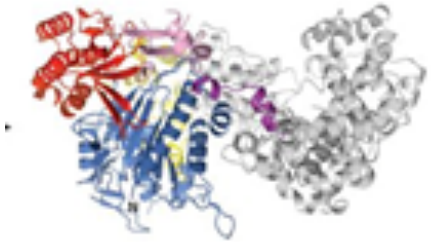


- TAL Effector Nuclease

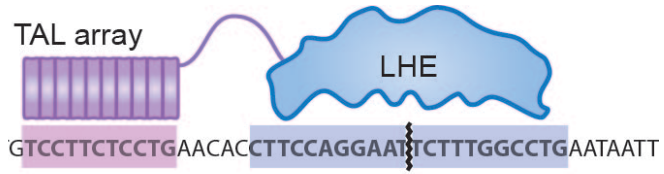




- CRISPR/Cas9



- MegaTals



Assessing Risks and Perceptions of Gene Therapy

original article

Gene Therapy Researchers' Assessments Of Risks And Perceptions Of Risk Acceptability In Clinical Trials

Claire T. Deakin[1,2], Ian E. Alexander[1,3], Cliff A. Hooker[2,4] and Ian H. Kerridge[2,5]

[1]Gene Therapy Research Unit, Children's Medical Research Institute and The Children's Hospital at Westmead, New South Wales, Australia; [2]Centre for Values, Ethics and the Law in Medicine, School of Public Health, Sydney Medical School, The University of Sydney, New South Wales, Australia; [3]Discipline of Paediatrics and Child Health, Sydney Medical School, The University of Sydney, New South Wales, Australia; [4]Faculty of Education and Arts, University of Newcastle, New South Wales, Australia; [5]Department of Hematology, Royal North Shore Hospital, New South Wales, Australia.

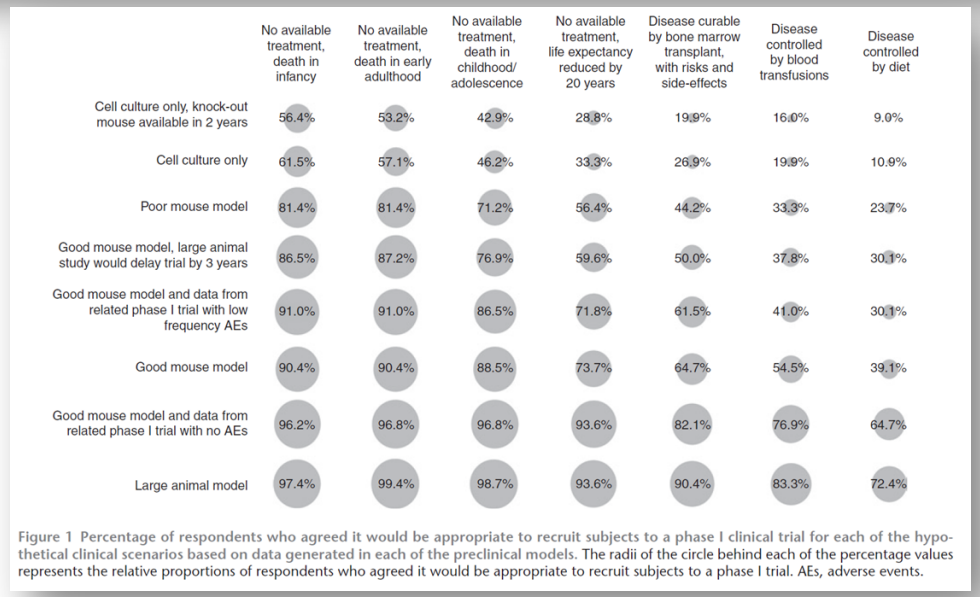


Figure 1 Percentage of respondents who agreed it would be appropriate to recruit subjects to a phase I clinical trial for each of the hypothetical clinical scenarios based on data generated in each of the preclinical models. The radii of the circle behind each of the percentage values represents the relative proportions of respondents who agreed it would be appropriate to recruit subjects to a phase I trial. AEs, adverse events.

- 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

Choice of Study Population Matters Greatly

Table 2. Framework for risk-benefit analysis for HIV-1-infected patient populations that could be targeted with HSPC-based gene therapy.

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

Abbreviations: Rx = treatment; cART = combination antiretroviral therapy; SOC—standard of care; ARL = AIDS-related lymphoma.

DiGiusto DL et al. Development of Hematopoietic Stem Cell Based Gene Therapy for HIV-1 Infection: Considerations for Proof-of-Concept Studies and Translation to Standard Medical Practice. *Viruses* 2013; 5, 2998 – 2919.

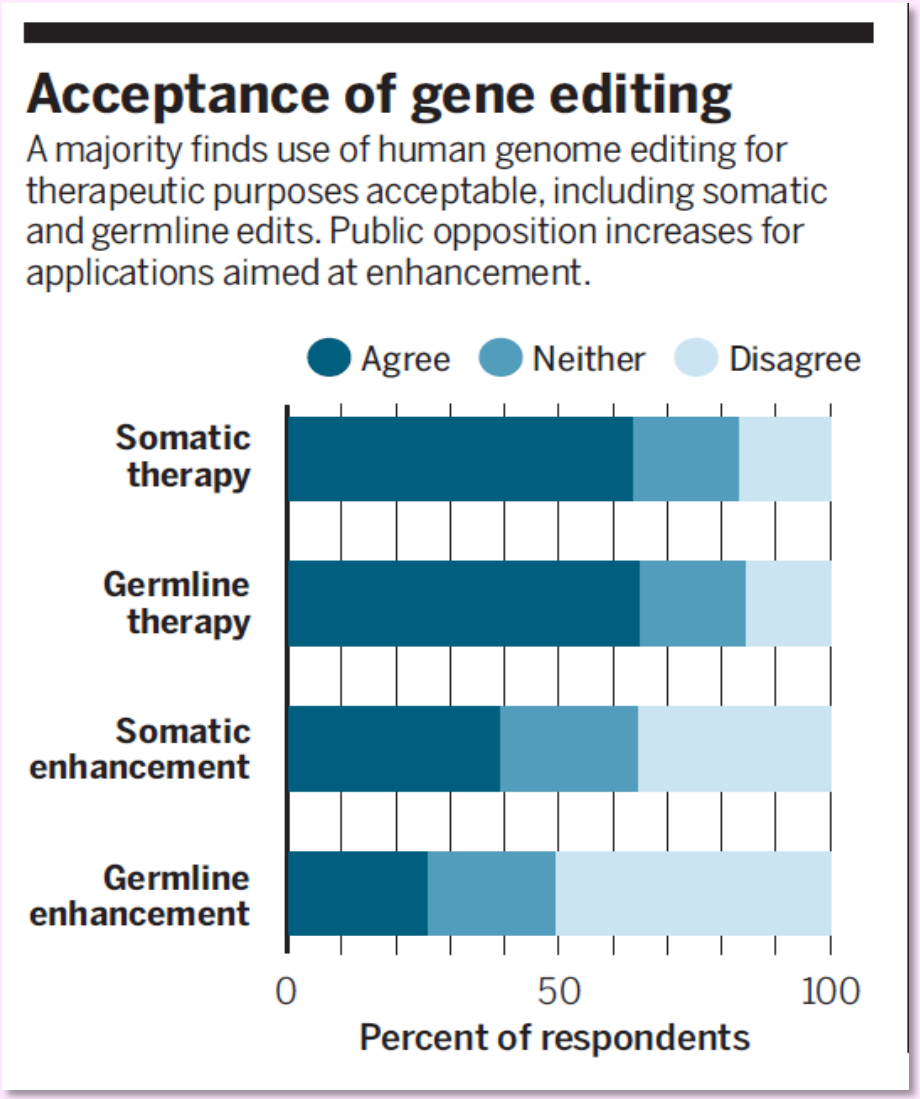
Regulatory Perspectives

Table 1. A Regulatory Perspective on Feasibility to Surmount Genome-Editing Safety and Efficacy Challenges

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

Abou-El-Enein M, Cathomen T, Ivics Z, June CH, Renner M, Schneider CK, Bauer G. Human Genome Editing in the Clinic: New Challenges in Regulatory Benefit-Risk Assessment. Cell Stem Cell 2017; 21: 427 – 30.

U.S. Attitudes of Human Genome Editing



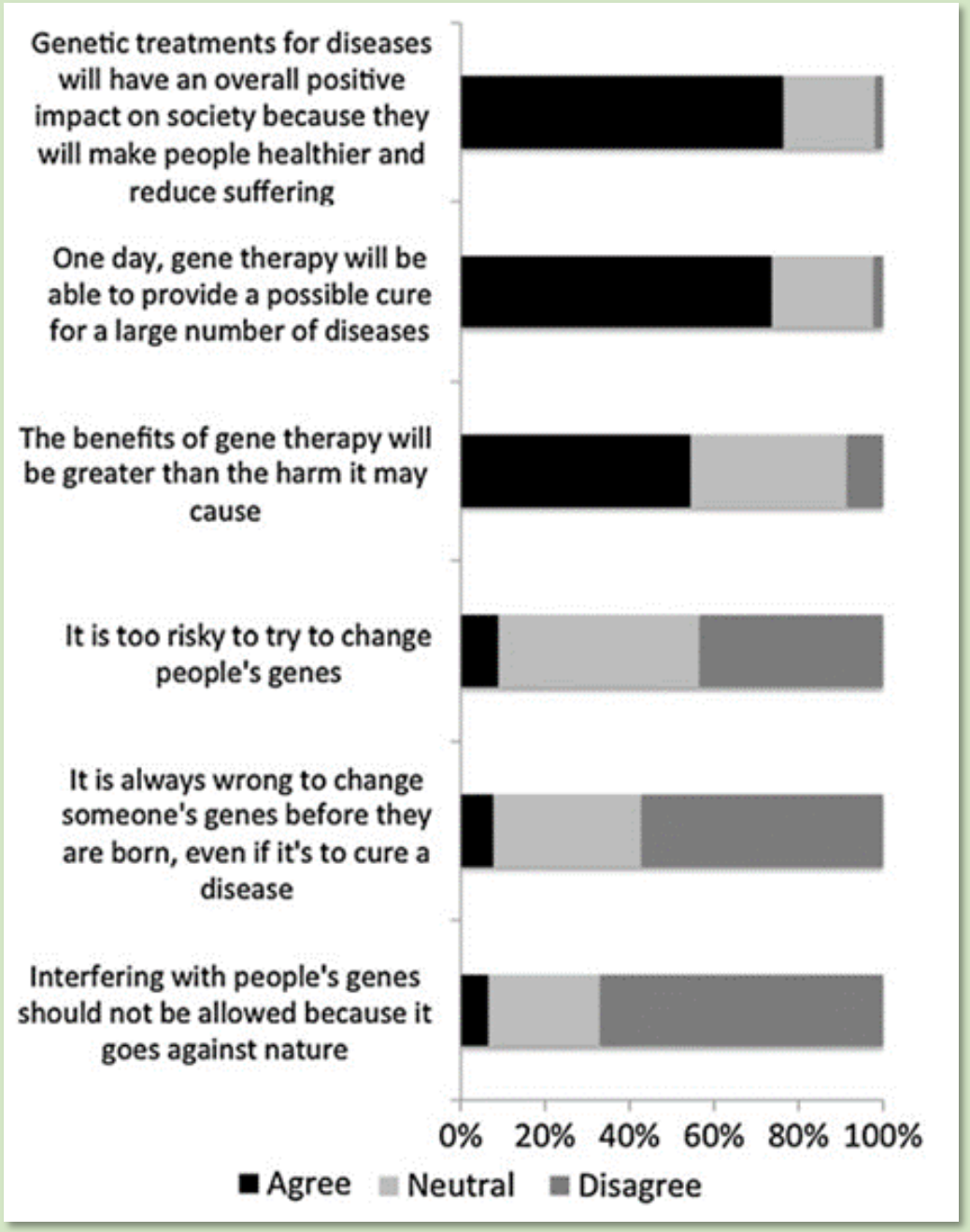
Scheufele DA, Xenos MA, Howell EL, Rose KM, Brossard D, Hardy BW. U.S. Attitudes on Human Genome Editing. Science 2011; 357(6351): 553 – 4.

Prevailing Public Perceptions Matter

HUMAN GENE THERAPY 25:740–746 (August 2014)

DOI: 10.1089/hum.2014.030

Prevailing Public Perceptions of the Ethics of Gene Therapy



Robillard JM, Roskam-Edris D, Kuzeljevic B, Illes J. Prevailing Public Perceptions of the Ethics of Gene Therapy. Human Gene Therapy 2014; 25: 740 – 6.

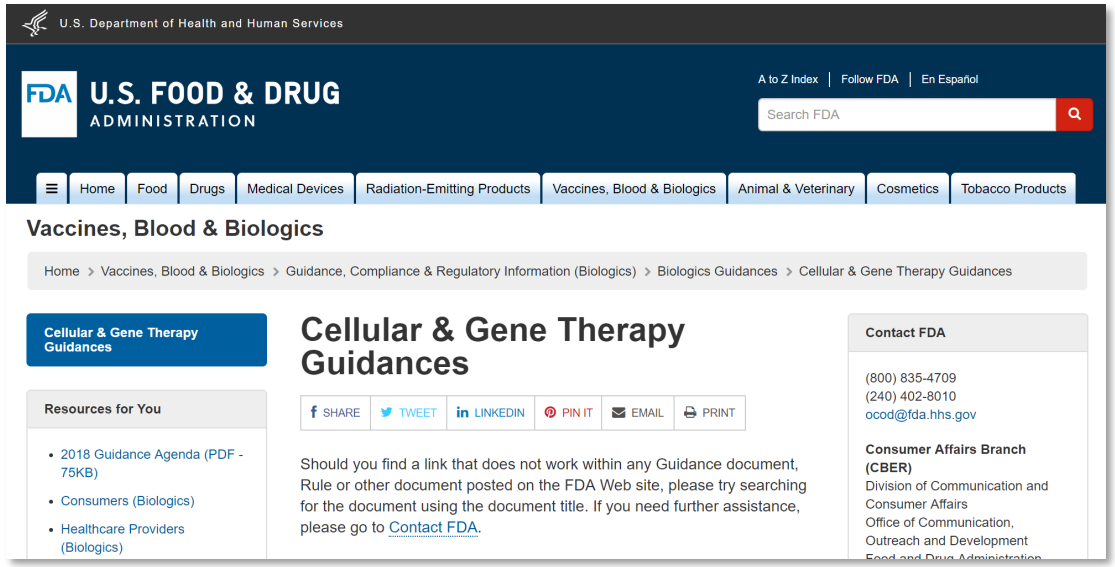
FDA Statement **January 2019**

Statement from FDA Commissioner Scott Gottlieb, M.D. and Peter Marks, M.D., Ph.D., Director of the Center for Biologics Evaluation and Research on new policies to advance development of safe and effective cell and gene therapies

- "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

World Health Organization

TREATMENTS

World Health Organization Forms Committee To Guide Editing Of Human Genes

February 14, 2019 · 3:02 PM ET

ROB STEIN

WHO expert advisory committee on Developing global standards for governance and oversight of Human Genome editing

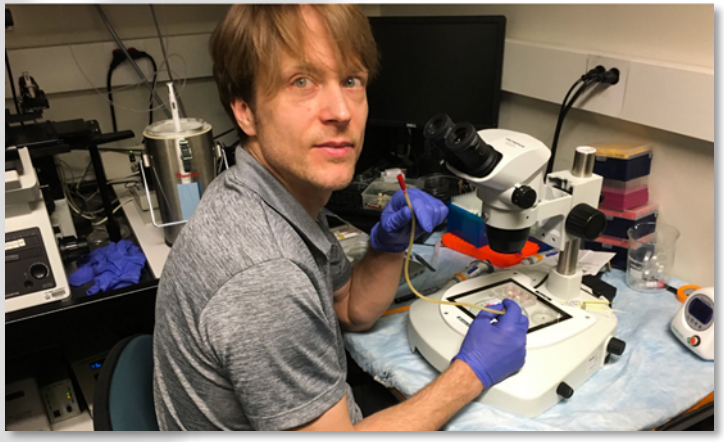
Membership

The World Health Organization is pleased to announce the membership of the WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome editing.

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



https://www.npr.org/sections/health-shots/2019/02/01/689623550/new-u-s-experiments-aim-to-create-gene-edited-human-embryos

Discussion Points for the Community

- 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**

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