

Ethics and Genome Editing

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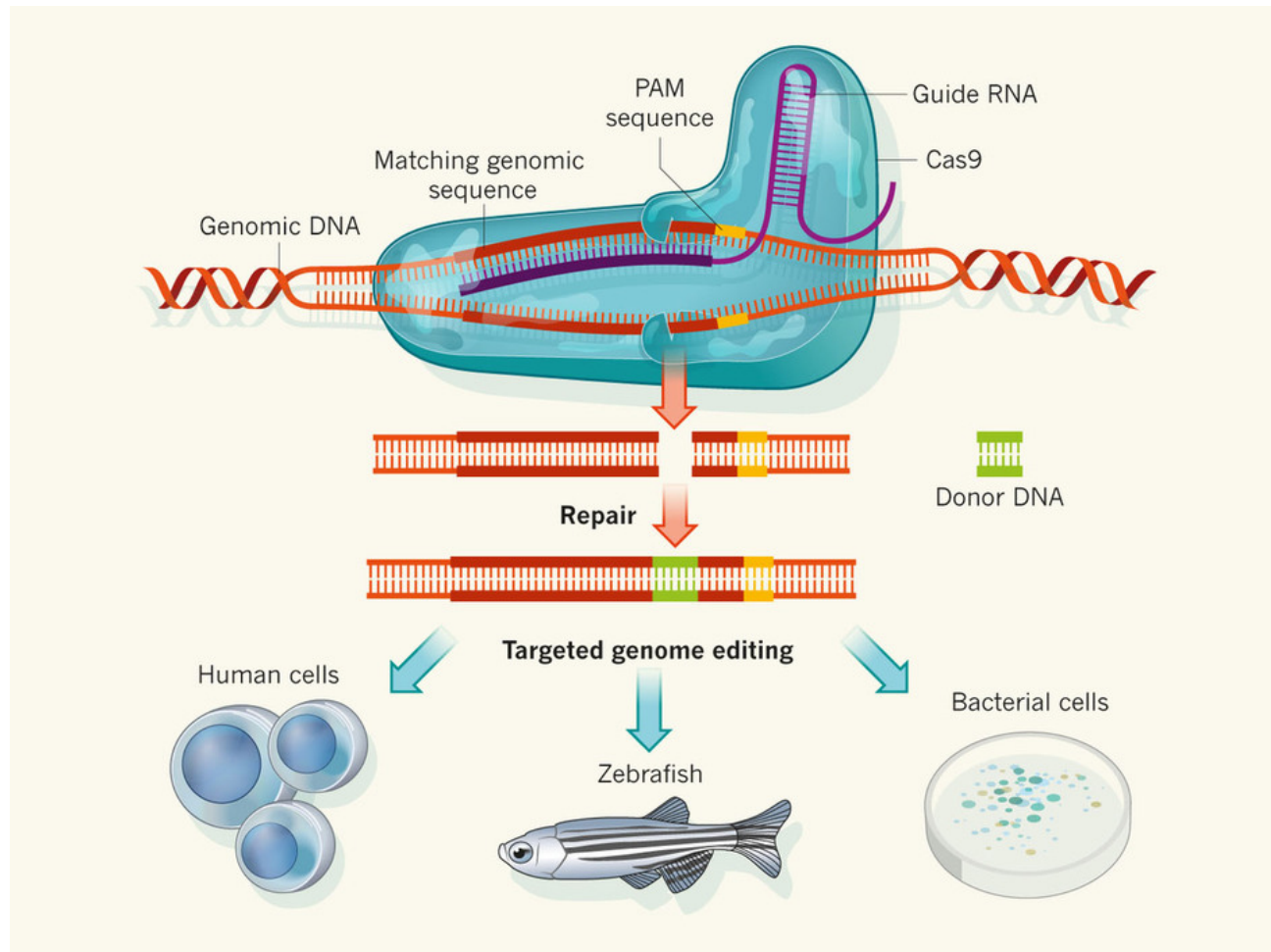


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Gene Editing Technologies

- **Zinc Finger Nucleases (ZFN)**
- **TALEN** (transcription activator-like effector nucleases)
- **CRISPR** (clustered regularly interspaced short palindromic repeat)- **Cas9** (CRISPR associated protein 9)

CRISPR-Cas9



Basic Idea

Cas=Universal scissor

gRNA=Homing device

Why the excitement?

- Precise (especially for knock-outs)
- Easy
- Inexpensive



Gene Editing:

Potential Research and Applications

- Pathogens
- Nonhuman animals
- Somatic
- Germline

Somatic

- Aimed at treating diseases by correcting genetic defects at the level of individual nucleotides
 - *Ex vivo* (e.g., CCR5 receptor)
 - *In vivo*
- Concerns
 - Possibility of inadvertent germline effects
 - Enhancements

Sugarman J. *EMBO Rep* 2015;16(8):879-80.

Germline

- Changing DNA in human germ cells and progenitors
- Hope for correcting genetic disorders that are fatal in utero (e.g., alpha-thalassemia)
- Supplant the need for certain assisted reproductive technologies
 - Correct a faulty gene in embryos or gametes
 - Decrease need for oocyte stimulation and selective abortion following prenatal genetic diagnosis
- Derivation of gametes with iPSCs
- “Permanently” correct disorders so they are not transmitted (e.g., Tay-Sachs)

BIOTECHNOLOGY

A prudent path forward for genomic engineering and germline gene modification

A framework for open discourse on the use of CRISPR-Cas9 technology to manipulate the human genome is urgently needed

By David Baltimore,¹ Paul Berg,²
Michael Botchan,^{3,4} Dana Carroll,⁵
R. Alta Charo,⁶ George Church,⁷
Jacob E. Corn,⁴ George Q. Daley,^{8,9}
Jennifer A. Doudna,^{4,10*} Marsha Fenner,⁴
Henry T. Greely,¹¹ Martin Jinek,¹²
G. Steven Martin,¹³ Edward Penhoet,¹⁴
Jennifer Puck,¹⁵ Samuel H. Sternberg,¹⁶
Jonathan S. Weissman,^{4,17}
Keith R. Yamamoto^{4,18}

Science 2015 Apr 3;348(6230):36-8.



RESEARCH ARTICLE

CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes

Puping Liang, Yanwen Xu, Xiya Zhang, Chenhui Ding, Rui Huang, Zhen Zhang, Jie Lv, Xiaowei Xie, Yuxi Chen, Yujing Li, Ying Sun, Yaofu Bai, Zhou Songyang, Wenbin Ma, Canquan Zhou[✉], Junjiu Huang[✉]

NATURE | NEWS

Chinese scientists genetically modify human embryos

Rumours of germline modification prove true — and look set to reignite an ethical debate.

David Cyranoski & Sara Reardon

22 April 2015

SECTIONS

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SEARCH

The New York Times

1 of 10 articles read

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In Miami, Facing Risk of Zika With Resolve but Limited Resources



WELL
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MISCONCEPTIONS
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HEALTH

Chinese Scientists Edit Genes of Human Embryos, Raising Concerns

By GINA KOLATA APRIL 23, 2015



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Selected Proclamations

- American Society for Gene and Cellular Therapy
- Hinxton Group
- International Society for Stem Cell Research
- National Institutes of Health
- Society for Developmental Biology
- UNESCO International Bioethics Committee
- Wellcome Trust

Adashi EY, Cohen IG. *Am J Bioeth* 2015;15(12):40-2.

International Summit on Human Gene Editing A Global Discussion



The New York Times



Even in a Warming World,
It Will Still Snow
Somewhere



MISCONCEPTIONS
Don't Let Them Tell You
You're Not at the Center
of the Universe



View From Space Hints at
a New Viking Site in North
America



SCIENCE

Scientists Seek Moratorium on Edits to Human Genome That Could Be Inherited

By NICHOLAS WADE DEC. 3, 2015

Ethical Worries

- Mis-targeting causes uncertain and unwanted problems
- Specter of eugenics
- Slippery slope to enhancement
- Once introduced it may not be possible to reverse alterations
- Alterations may exacerbate inequalities
- Manipulating the germline has long been viewed as morally unacceptable to many

Sugarman J. *EMBO Rep* 2015;16(8):879-80.

Prior Debates about Ethics and Germline Manipulation

- Recombinant DNA technology
- Assisted reproductive technologies
- Gene-transfer research
- Human cloning
- Embryonic stem cell research
- Mitochondrial replacement therapy



Sugarman J. *EMBO Rep* 2015;16(8):879-80.

Selected Arguments Against Germline Manipulation

- Intergenerational consent infeasible
- Impossible to predict consequences
- Threat to human dignity

UNESCO Declaration 1997, Article 24

Sugarman J. *EMBO Rep* 2015;16(8):879-80.

Counterarguments

- Intergenerational consent is not considered relevant for multiple other decisions regarding future generations
- It is impossible to predict consequences for other well-intentioned efforts to improve the human condition and this doesn't generally preclude attempts to do so
- There is not a shared conception regarding the notion of dignity

Sugarman J. *EMBO Rep* 2015;16(8):879-80.

Arguments for Permitting Germline Modification

- Clinicians' professional responsibility to choose the optimal treatment for their patients
- Right of individuals to have their reproductive autonomy respected

Sugarman J. *EMBO Rep* 2015;16(8):879-80.

Variable Oversight

- Research on and clinical uses of reproductive technologies has variable oversight
 - HFEA
 - “Octomom”
- This opens the door to shoddy science the possibility of rogue clinical practice akin to stem cell ‘tourism’



Charo RA. *N Engl J Med* 2016;374(10):901-3.

ISSCR 

INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

GUIDELINES FOR STEM CELL SCIENCE AND CLINICAL TRANSLATION



12 MAY, 2016
WWW.ISSCR.ORG

Overview

- Ethical principles
- Lab-based research
- Clinical translation
- Communications
- Standards

<http://www.isscr.org/professional-resources/policy/2016-guidelines/guidelines-for-stem-cell-research-and-clinical-translation>

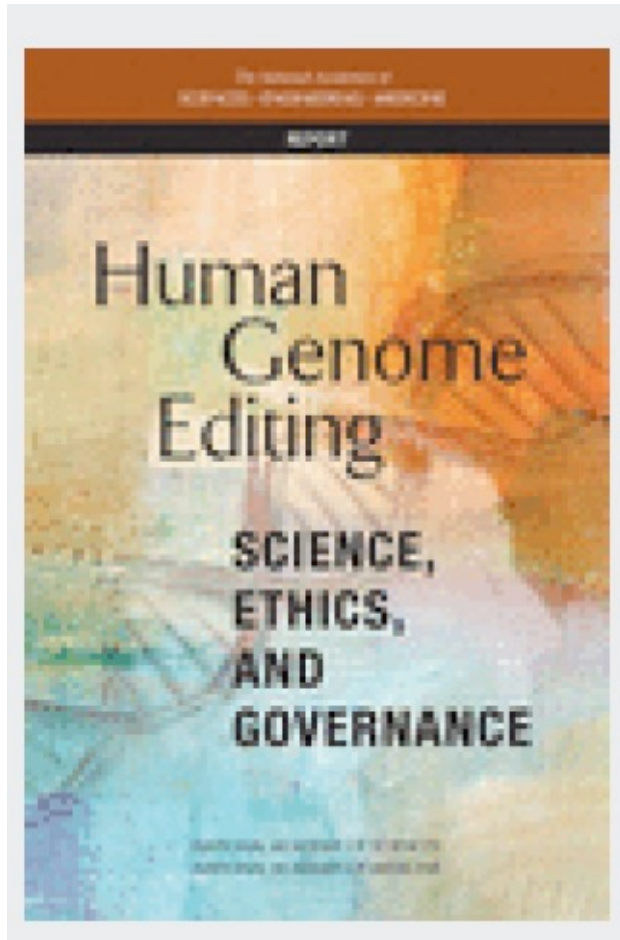
ISSCR Permissible Activities

“The ISSCR holds that scientific research on preimplantation-stage embryos is ethically permissible when performed under rigorous scientific and ethical oversight, especially in the area of human development, genetic and chromosomal disorders, human reproduction, and new disease therapies.”

ISSCR Modified Germline Restrictions

“Research in which human embryos that have undergone modification of their nuclear genome are implanted into or gestated in a human or animal uterus.”

NAM/NAS Report (2/14/2017)



- Global principles
- Basic laboratory research
- Somatic genome editing
- Germline genome editing
- Enhancement
- Public engagement

Basic Laboratory Research

- Use existing regulatory processes to oversee human genome editing laboratory research
(3.1)

Somatic Genome Editing

- Use existing regulatory processes for human gene therapy to oversee somatic human genome editing research and uses (4.1)
- Limit clinical trials or therapies to treatment and prevention of disease or disability at this time (4.2)
- Evaluate safety and efficacy in the context of risks and benefits of intended use (4.3)
- Require broad public input prior to extending uses (4.4)

Germline (Heritable) Genome Editing

- Permit clinical research trials only for compelling purposes of treating or preventing serious disease or disabilities, and only if there is a stringent oversight system able to limit uses to specified criteria (5.1)

Enhancement

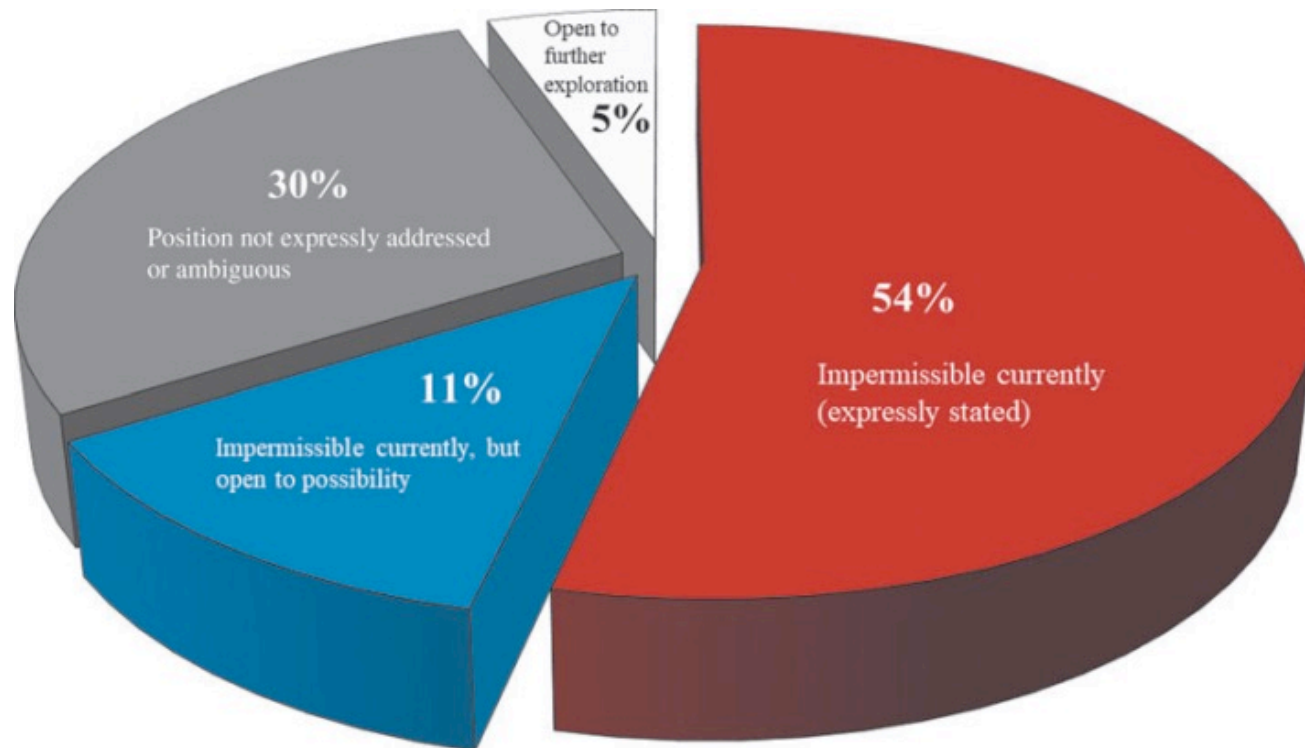
- Do not proceed at this time with human genome editing for purposes other than treatment or prevention of disease and disability (6.1)
- Encourage public discussion and policy debate with respect to somatic human genome editing for uses other than treatment or prevention of disease and disability (6.2)

“At least 61 ethics reports and statements have been crafted by more than 50 countries and organizations over the past 3 years”



Carolyn Brokowski, *The CRISPR Journal* 2018; 1 (2).
DOI: 10.1089/crispr.2017.0024

Heritable Genome Editing



Carolyn Brokowski, *The CRISPR Journal* 2018; 1 (2).
DOI: 10.1089/crispr.2017.0024

The Story Breaks

He Jankui told The Associated Press that he carried out his experiment to protect the twin sisters from HIV infection later in life. MARK SCHIEFELBEIN/AP PHOTO

- November 25, 2018 – MIT Technology Review posted a story: “EXCLUSIVE: Chinese Scientists Are Creating CRISPR Babies”
 - Based on online documents posted earlier that month
 - Efforts by He Jiankui’s team to create the first gene-edited baby
- He posted a 5 minute video on YouTube, “About Lulu and Nana: Twin Girls Born Healthy After Gene Surgery As Single-Cell Embryos” – and 4 additional brief videos describing the work
- Intense media coverage follows...

Second International Summit on Human Genome Editing

- November 27 – 29, 2018
- Sponsored by
 - The Academy of Sciences of Hong Kong
 - The Royal Society
 - US National Academy of Sciences
 - US National Academy of Medicine



Selected Problems

- The consent form mentions gene editing, but initially describes the research as an “AIDS vaccine development project”
- He appears not to have sought approval from Chinese regulators and waited months to list his research in a Chinese clinical trial registry (in November)
- AP reports that some of the medical staff assisting with the project were allowed to believe that they were involved in conventional IVF efforts that also included mapping genomes
- Questions raised about “ethics dumping” to overcome barriers to such research in the US

Lingering Questions

- Were warning signs missed?
- If others knew, what could or should they have done?
- Does this make similar efforts more or less likely in the future?
- Applicability for related science?

Human Genome editing



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WHO establishing expert panel to develop global standards for governance and oversight of human genome editing

14 December 2018 -- WHO is establishing a global multi-disciplinary expert panel to examine the scientific, ethical, social and legal challenges associated with human genome editing (both somatic and germ cell). The panel will review the current literature on the state of the research and its applications, and societal attitudes towards the different uses of this technology. WHO will then receive advice from the panel on appropriate oversight and governance mechanisms, both at the national and global level. Core to this work will be understanding how to promote

transparency and trustworthy practices and how to ensure appropriate risk/benefit assessments are performed prior to any decision on authorization.

14 MARCH 2019 | VOL 567 | NATURE | 165

Adopt a moratorium on heritable genome editing

Concluding Comments

- Continued deliberation among a broad range of stakeholders regarding the range of appropriate uses of gene editing technologies is clearly necessary

THANK YOU!!!



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