

# Harnessing the Power of the Genomic Revolution: Ethical Considerations

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John B. Francis Chair

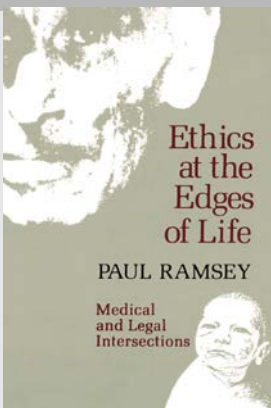
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# A Perspective on Bioethics History

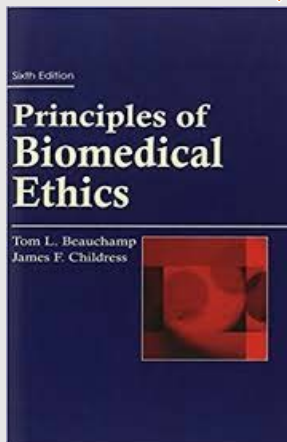
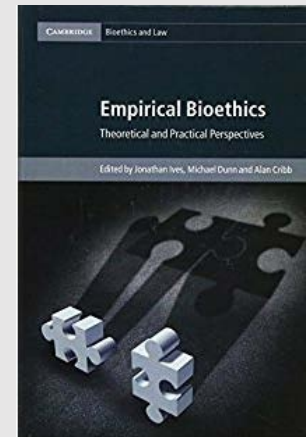


Religious perspectives

1950's-60's

Political-Empirical perspectives

1990's & beyond



1970's-80's

Philosophical perspectives

21<sup>st</sup> century

??????



Bioethics  
Future--  
Pressing  
Moral  
Questions



- Are there limits to scientific “advances”?
- Are there lines that the scientist-creator should not cross?

A Few Pressing  
Moral  
Questions  
Raised by  
Genome  
Manipulation



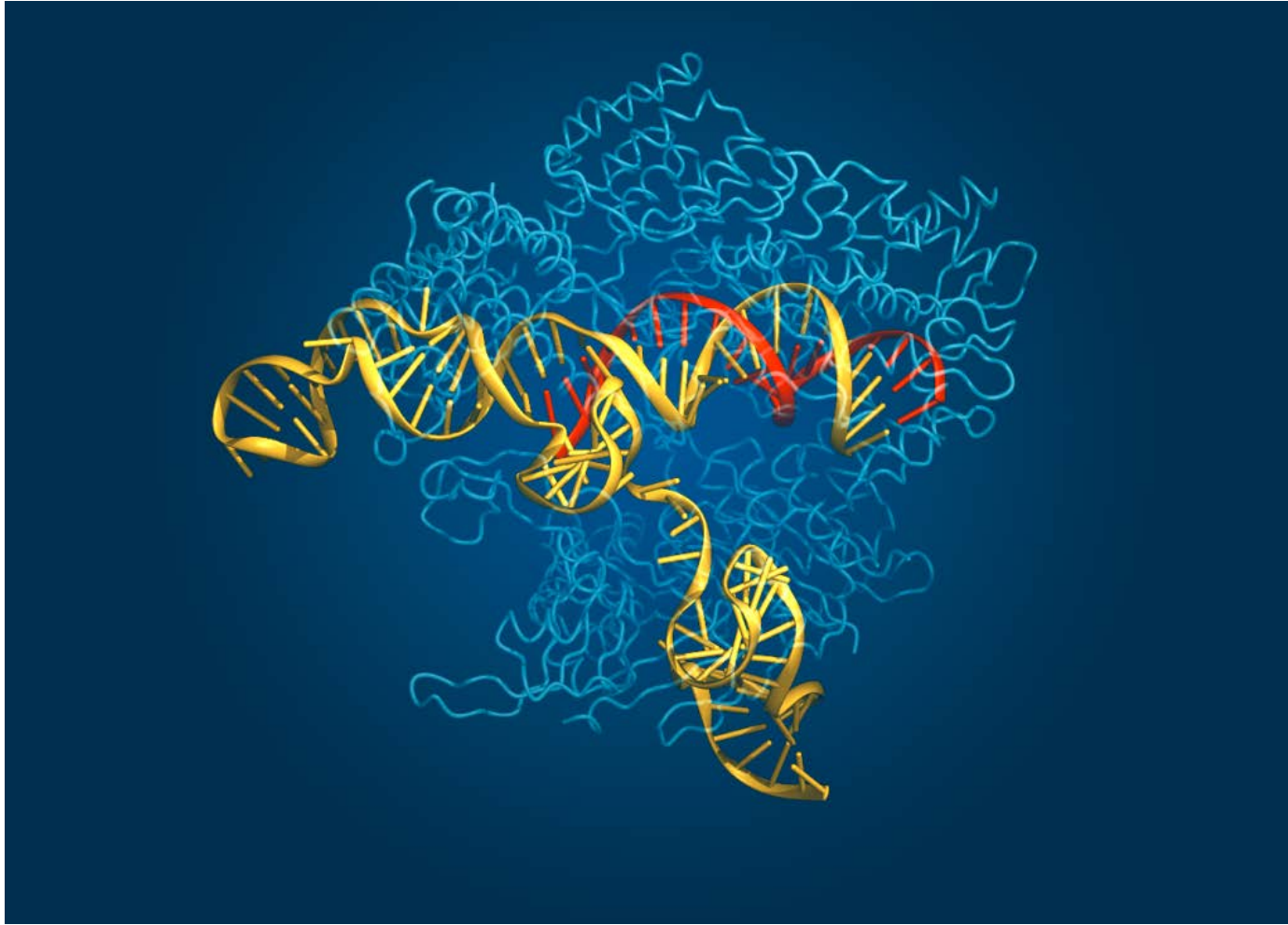
- Ethics of human “enhancements” — cognitive and otherwise
- Creation of human-nonhuman species
- Re-defining what “should be “normal” in preventing genetic disorders

# A Few Pressing Moral Questions Raised by Genome Manipulation



- What does it mean to be human?
  - Existence of human-non-human hybrid species
  - Moral and ethical acceptability of concept of “transhumanism”
    - Artificial Intelligence and bio-cyber interfaces
- Questions of justice
  - Promotion of the common good
  - Equitable access—current and future

A computerized rendering shows the Cas9 gene-editing enzyme (in light blue) interacting with an RNA guide (red) and its target DNA (yellow).



From, BANG WONG, BROAD INSTITUTE OF HARVARD AND MIT

Growing two-dimensional boron pp. 1409 & 1513

Managing biological risk p. 1473

Algal toxin alters spatial memory p. 1545

# Science

\$10  
18 DECEMBER 2015  
science.org

AAAS



# A CRACK IN CREATION

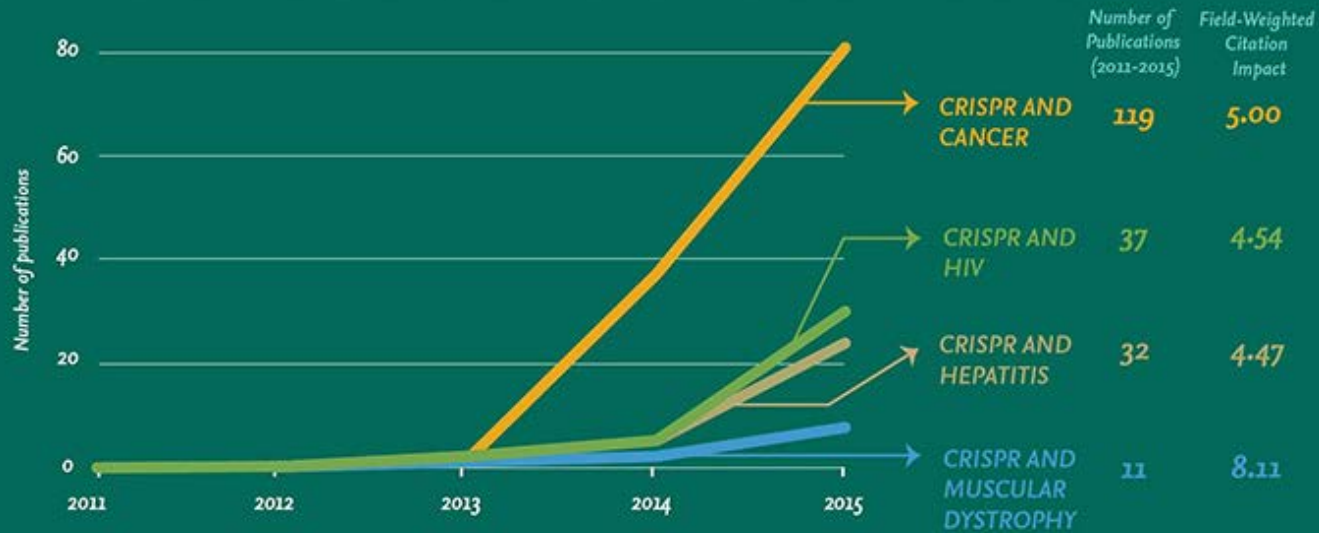
GENE EDITING AND  
THE UNTHINKABLE  
POWER TO CONTROL  
EVOLUTION

JENNIFER A. DOUDNA  
SAMUEL H. STERNBERG





# CRISPR and Disease



Using Scopus data, analyzed in SciVal (2011-2015)

## Applications of CRISPR Pros and Cons

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Don Pinker



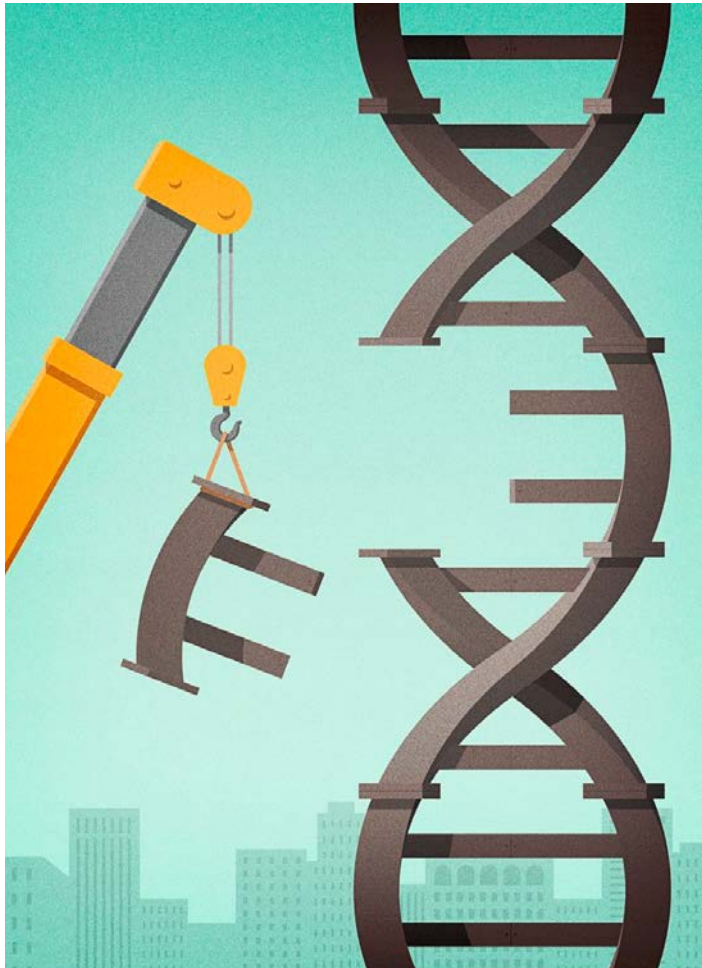
The Hastings Center



## Gene Editing & Human Flourishing

A summer bioethics workshop for secondary school teachers

CRISPR's unprecedented ability to edit genetic code will make possible a new generation of medical treatments.



## Correction of a pathogenic gene mutation in human embryos

Hong Ma<sup>1\*</sup>, Nuria Marti-Gutierrez<sup>1\*</sup>, Sang-Wook Park<sup>2\*</sup>, Jun Wu<sup>3\*</sup>, Yeonmi Lee<sup>1</sup>, Keiichiro Suzuki<sup>3</sup>, Amy Koski<sup>1</sup>, Dongmei Ji<sup>1</sup>, Tomonari Hayama<sup>1</sup>, Riffat Ahmed<sup>1</sup>, Hayley Darby<sup>1</sup>, Crystal Van Dyken<sup>1</sup>, Ying Li<sup>1</sup>, Eunju Kang<sup>1</sup>, A.-Reum Park<sup>2</sup>, Daesik Kim<sup>4</sup>, Sang-Tae Kim<sup>2</sup>, Jianhui Gong<sup>5,6,7,8</sup>, Ying Gu<sup>5,6,7</sup>, Xun Xu<sup>5,6,7</sup>, David Battaglia<sup>1,9</sup>, Sacha A. Krieg<sup>9</sup>, David M. Lee<sup>9</sup>, Diana H. Wu<sup>9</sup>, Don P. Wolf<sup>1</sup>, Stephen B. Heitner<sup>10</sup>, Juan Carlos Izpisua Belmonte<sup>3</sup>§, Paula Amato<sup>1,9</sup>§, Jin-Soo Kim<sup>2,4</sup>§, Sanjiv Kaul<sup>10</sup>§ & Shoukhrat Mitalipov<sup>1,10</sup>§

Genome editing has potential for the targeted correction of germline mutations. Here we describe the correction of the heterozygous *MYBPC3* mutation in human preimplantation embryos with precise CRISPR-Cas9-based targeting accuracy and high homology-directed repair efficiency by activating an endogenous, germline-specific DNA repair response. Induced double-strand breaks (DSBs) at the mutant paternal allele were predominantly repaired using the homologous wild-type maternal gene instead of a synthetic DNA template. By modulating the cell cycle stage at which the DSB was induced, we were able to avoid mosaicism in cleaving embryos and achieve a high yield of homozygous embryos carrying the wild-type *MYBPC3* gene without evidence of off-target mutations. The efficiency, accuracy and safety of the approach presented suggest that it has potential to be used for the correction of heritable mutations in human embryos by complementing preimplantation genetic diagnosis. However, much remains to be considered before clinical applications, including the reproducibility of the technique with other heterozygous mutations.



The New York Times

## ***Rhino Embryos Made in Lab to Save Nearly Extinct Subspecies***

The development is an early step toward the much more distant goal of resurrecting the northern white rhinoceros, whose last male died this year.



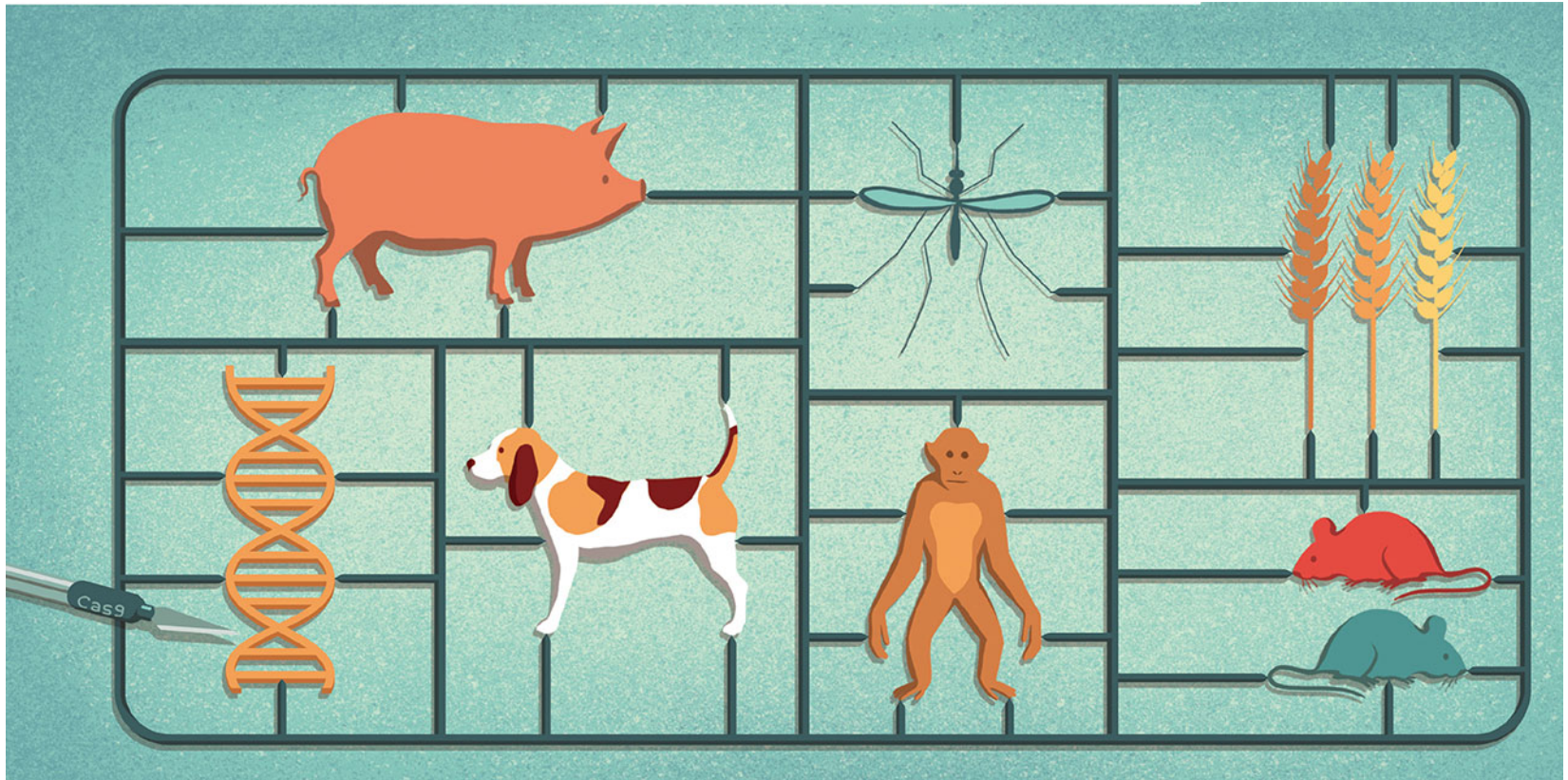
## ***Scientists See Promise in Resurrecting These Rhinos That Are Nearly Extinct***

Even if the technology can bring back the northern white rhinoceros, should we do it?





**CRISPR's ability to edit DNA has helped scientists create a menagerie of genetically new organisms.**

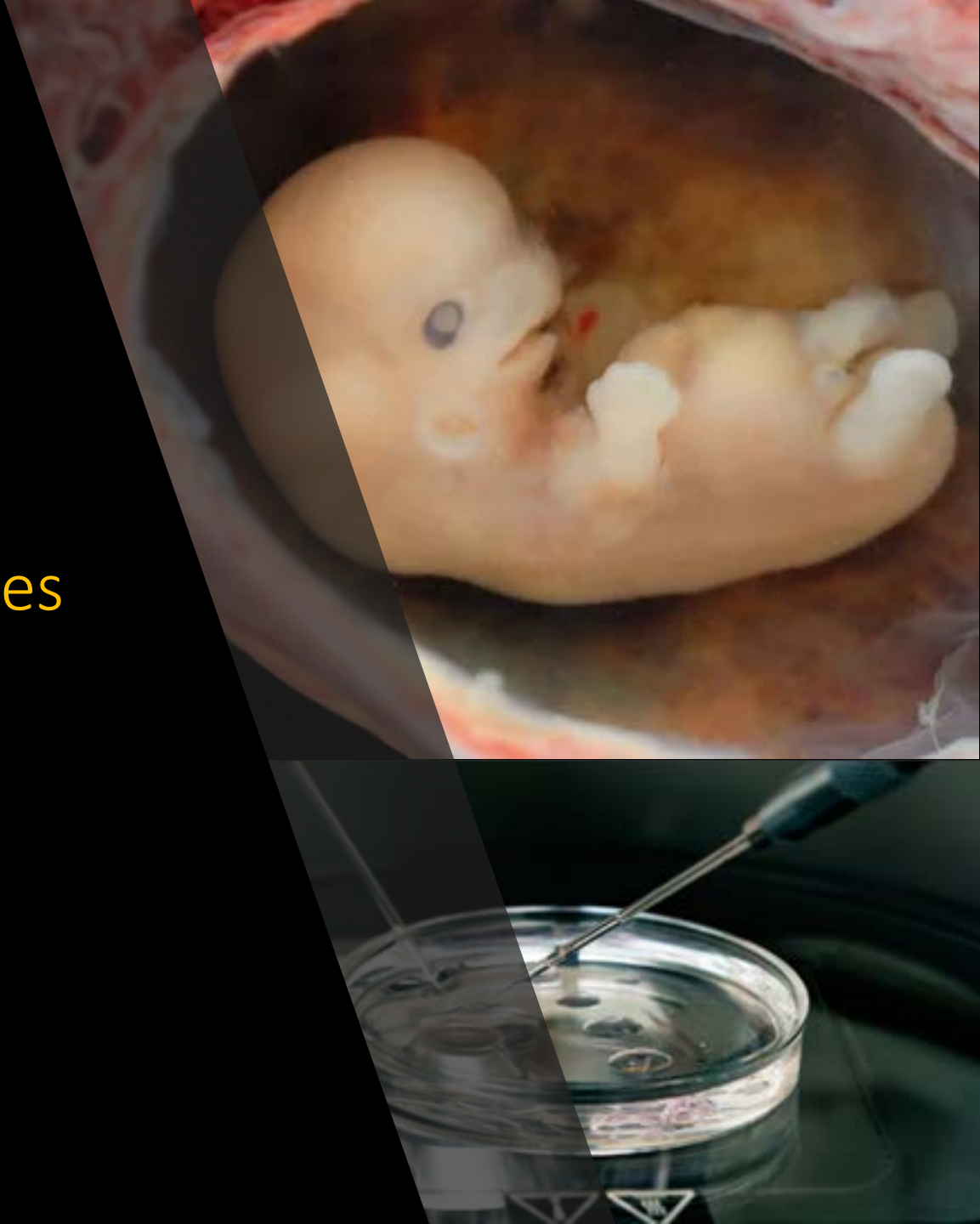


John Travis Science 2015;350:1456-1457



Synthetic Human  
Embryo-Like Entities

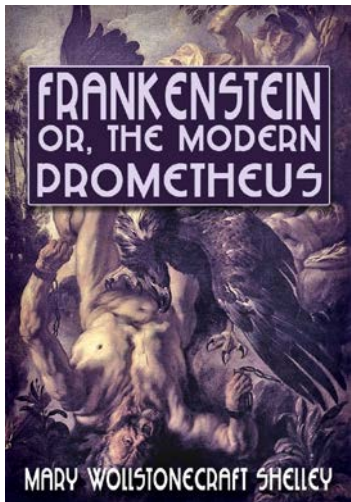
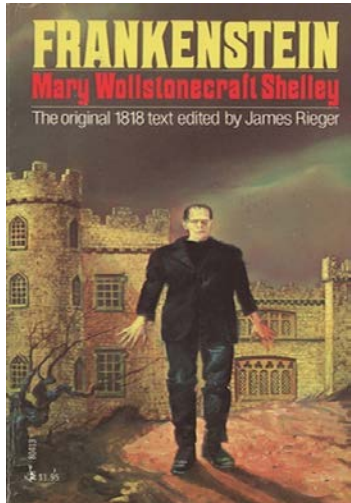
Need New Ethical  
Guidance





Playing  
God-  
when is  
“the line”  
crossed?

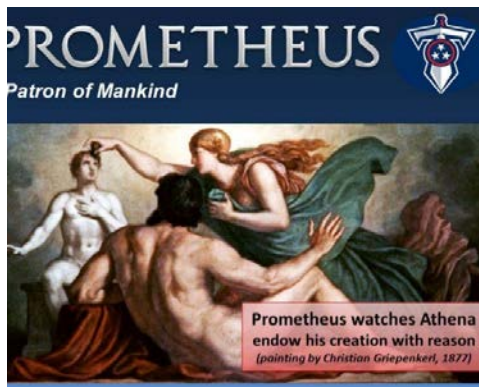
# Humans as Creators- Are there moral limits?



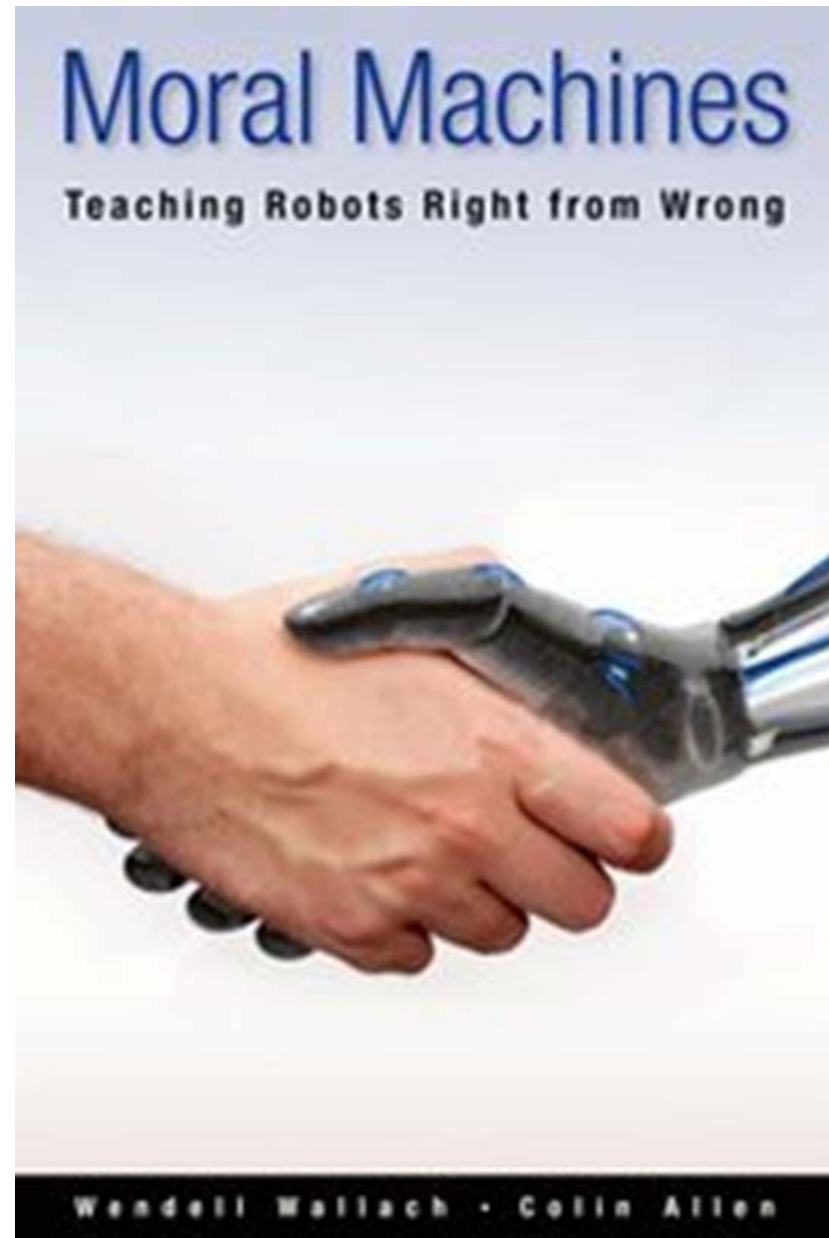
Creator "Man"  
Crosses a Line...  
Disaster occurs  
as the Creator (is  
destroyed and  
most of those  
around him or her)  
by his creation...



# Modern Telling of Prometheus/FrankensteIn Narratives



What Does  
It Mean to  
Be  
Human?



Real-World  
Premature Use  
of  
Biotechnology?

## Jesse Gelsinger

June 18, 1981 – September 17, 1999

- He suffered from a rare metabolic disorder, BUT he was not sick – his condition was under control.
- He signed up for a gene therapy trial at University of Pennsylvania to help test the safety of a treatment for babies.
- A few days after receiving the injection, Jesse experienced organ failure and passed away at 18 years old.





Playing  
God-  
when is  
“the line”  
crossed?



How much  
“abnormality” will be  
deem acceptable?

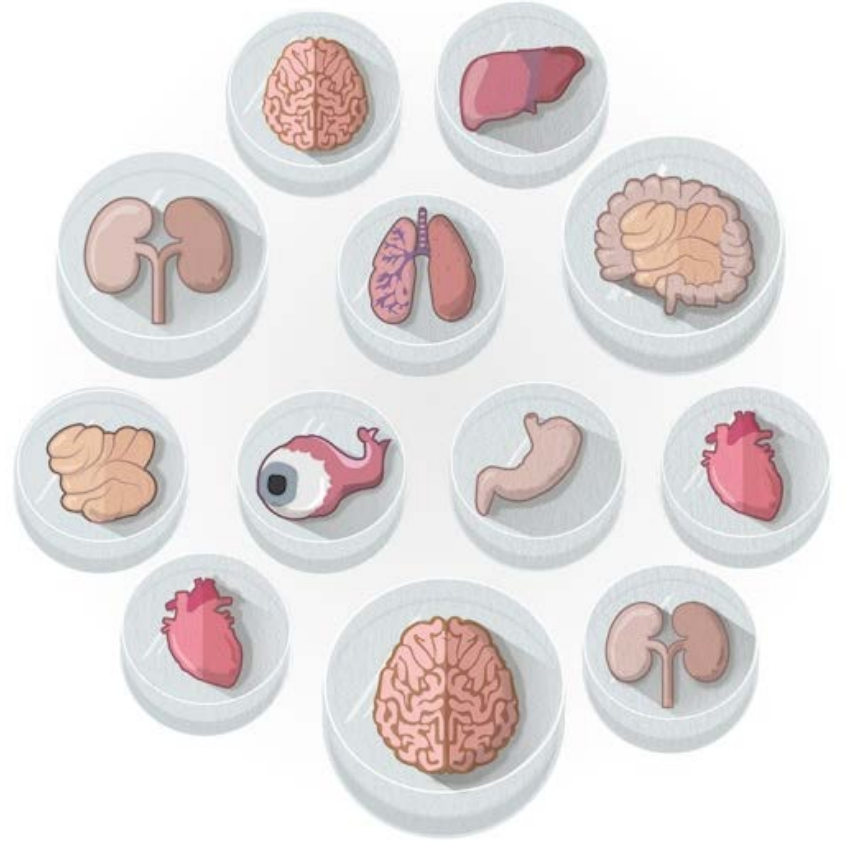
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## The ethics of experimenting with human brain tissue

*Difficult questions will be raised as models of the human brain progress to replicating its functions, explain Nita A. Farahany, Henry T. Greely and Jill Colclough.*



# Building Organoids- The Concept of “Brain Surrogates”



Important: Brain organoids are grown in laboratory conditions and are not cells in the starting material.

The ethics of experimenting  
with human brain tissue

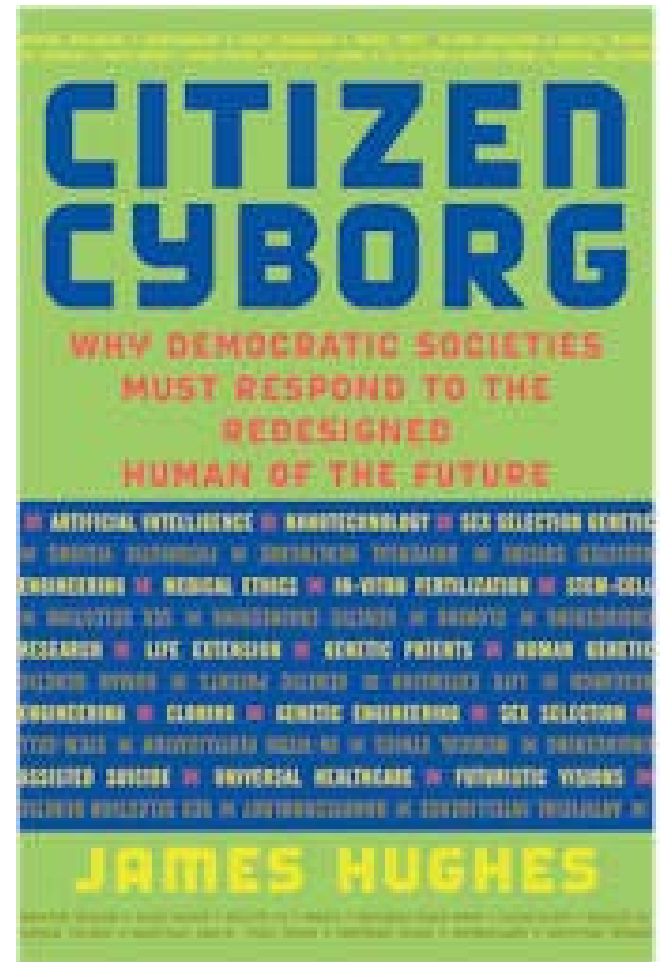
## Ethical issues raised:

- Morality of “organoids” have capabilities akin to human sentience
- ability to perceive pleasure, pain, distress
- ability to store and retrieve memories
- ability to have some perception of agency or awareness

Experimentation on Brain  
“Surrogates”



Democratic Societies  
should embrace  
science, technology and  
“transhumanism”



# When is a moral line crossed?



**Jurassic Park scientist:  
“We simply deny...”  
“I could not imagine...”**



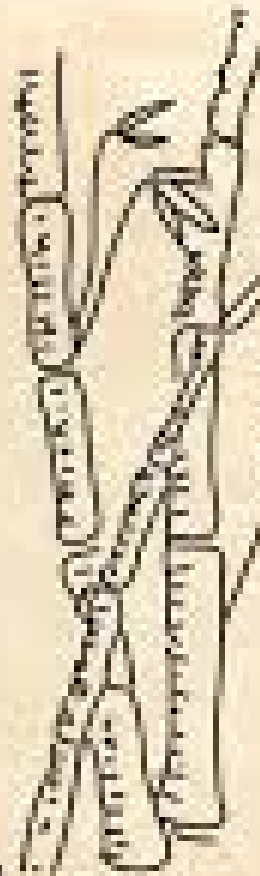
**Does the lack of  
epistemic humility  
“cross the line”?**

HUMILITY

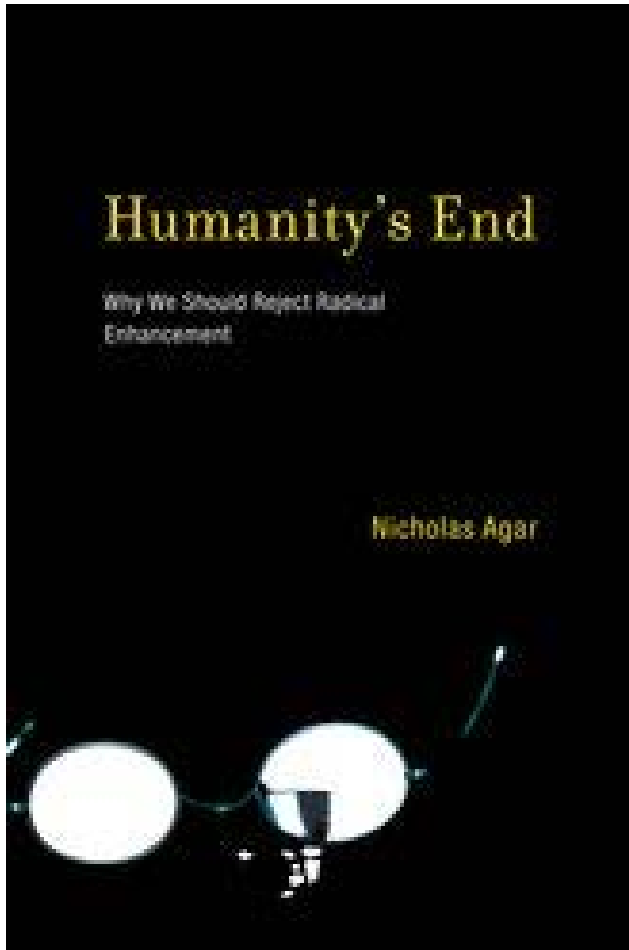
謙遜

"BE LIKE THE BAMBOO  
THE HIGHER YOU GROW  
THE DEEPER YOU BOW"

CHINESE PROVERB

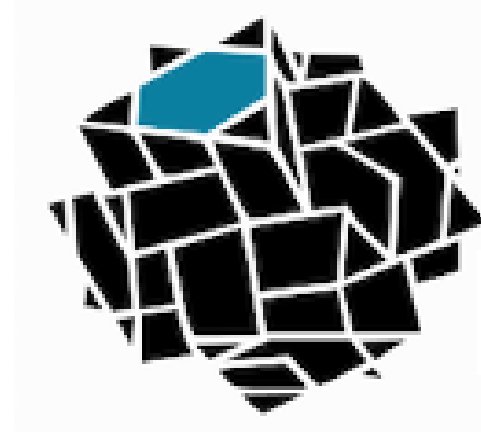


Humility

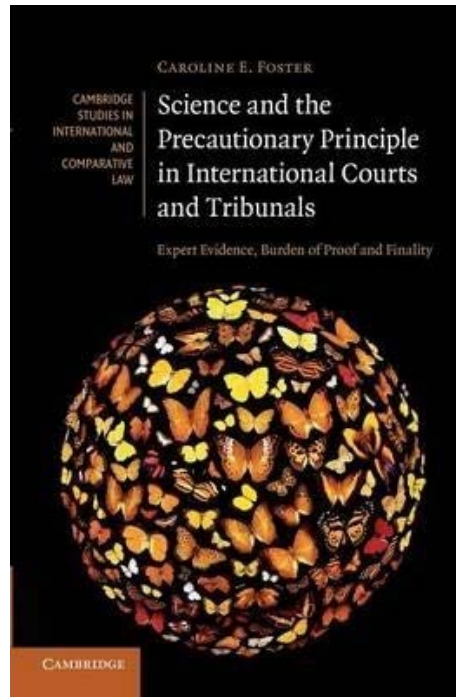
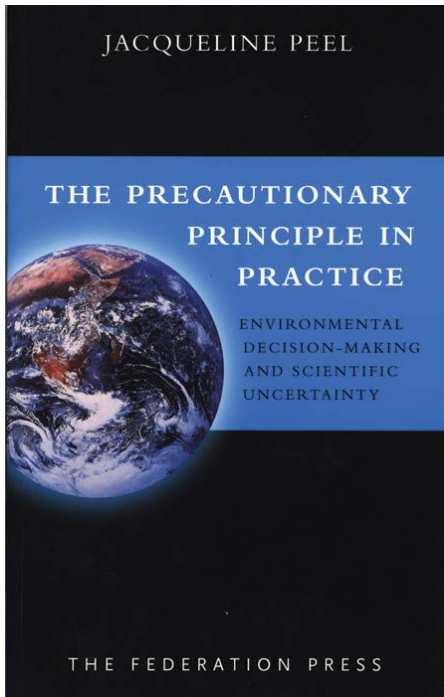


Major point of book:  
The outcomes of  
radical enhancement  
could be darker than  
the rosy futures  
described

**Existential Risk  
&  
Science/Technological  
Advancement**



**CENTRE FOR THE STUDY  
OF EXISTENTIAL RISK**  
UNIVERSITY OF CAMBRIDGE



# The Precautionary Principle

*Precaution and  
governance  
of emerging  
technologies*

Precaution can  
be consistent  
with support of  
science



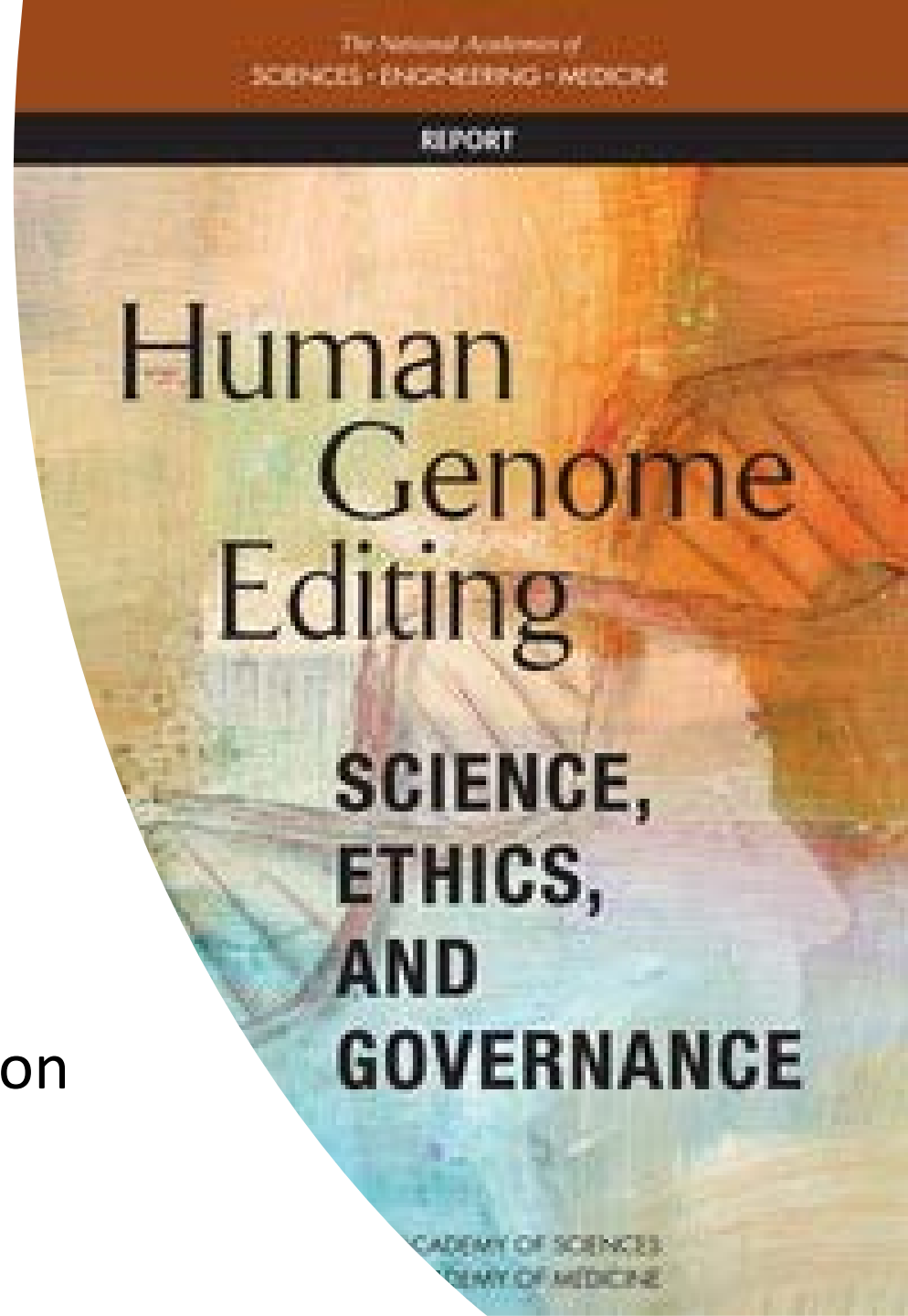
Kaebneck et al. SCIENCE 11 NOVEMBER 2016 • VOL  
354 ISSUE 6313 711 sciencemag.org



# Overarching Principles for Research on and Clinical Applications of Human Gene

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1. Promoting well-being
2. Transparency
3. Due care
4. Responsible science
5. Respect for persons
6. Fairness
7. Transnational cooperation



# Ethics Oversight of Gene Editing

## MEETING IN BRIEF

COMMITTEE ON SCIENCE, TECHNOLOGY, AND LAW  
POLICY AND GLOBAL AFFAIRS

December 1-3, 2015

### International Summit on Human Gene Editing A Global Discussion

New biochemical tools have made it possible to change the DNA sequences of living organisms with unprecedented ease and precision. These new tools have generated great excitement in the scientific and medical communities because of their potential to advance biological understanding, alter the genomes of microbes, plants, and animals, and treat human diseases. They also have raised profound questions about how people may choose to alter not only their own DNA but the genomes of future generations.

To explore the many questions surrounding the use of gene editing tools in humans, the U.S. National Academy of Sciences, the U.S. National Academy of Medicine, the Royal Society, and the Chinese Academy of Sciences hosted a three-day international summit on December 1-3, 2015, in Washington, DC. The summit brought together more than 500 people from around the world for three days of presentations and deliberations on the scientific, ethical, legal, social, and governance issues associated with human gene editing, while an additional 3,000 people watched the summit online.

"We could be on the cusp of a new era in human history," said David Baltimore (California Institute of Technology), chair of the summit organizing committee, in his opening remarks.

"Today, we sense that we are close to being able to alter human heredity. Now we must face the questions that arise. How, if at all, do we as a society want to use this capability? This is the question that has motivated this meeting."

This brief summary should not be seen as representing the conclusions of the summit as a whole. Rather, it highlights some of the observations made during the event in order to provide background for the statement issued by the organizing committee in the summit's final session.

#### Rapidly Improving Tools

As Klaus Rajewsky (Max Delbrück Center for Molecular Medicine) pointed out, the new gene editing tools are the product of more than 60 years of fundamental research into the

molecular nature of DNA molecules. Previous technologies using molecules known as zinc finger nucleases and TALENs had made it possible to alter DNA at targeted locations. While these technologies are currently being used in clinical trials, they are cumbersome and difficult to use. A new technique using a molecular assemblage known as CRISPR-Cas9, which arose out of research into how bacteria protect themselves from viral infection, is simple, inexpensive, and can target DNA sequences with great specificity. "The system is so overwhelmingly efficient and specific that it is changing our entire outlook for future gene editing," said Rajewsky.

Despite its capabilities, CRISPR-Cas9 still has deficiencies, observed Jin-Soo Kim (Seoul National University/Institute for Basic Science). It can alter DNA at locations other than the target, which could inactivate essential genes, activate cancer-causing genes, or cause chromosomal rearrangements. It can change the DNA in some cells but not all, resulting in a mosaic of altered and unaltered cells, it can generate immune responses if introduced into the body. Many drugs cause off-target effects but are still effective, Kim added. Nevertheless, the CRISPR-Cas9 system is still undergoing development to reach the level of safety where it could be used in clinical applications.

Methods to identify genome-wide off-target effects could help assess the safety and efficacy of these new tools, said J. Keith Joung (Massachusetts General Hospital and Harvard Medical School). Also, as Jennifer Doudna (University of California, Berkeley) and Emmanuelle Charpentier (Max Planck Institute

"...we are here as part of a historical process that dates from Darwin and Mendel's work in the 19th century. We are taking on a heavy responsibility for our society because we understand that we could be on the cusp of a new era in human history."

David Baltimore, Caltech

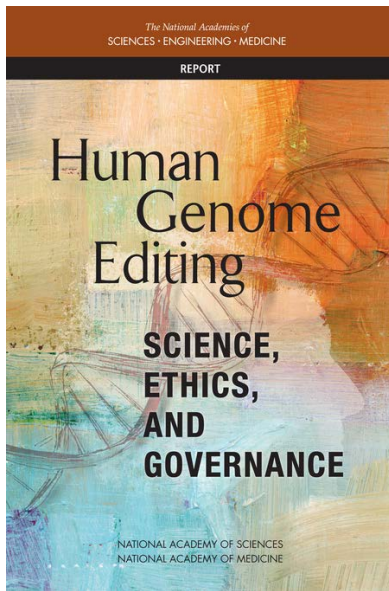
The National Academies of  
SCIENCES • ENGINEERING • MEDICINE



## INTERNATIONAL SUMMIT ON HUMAN GENE EDITING

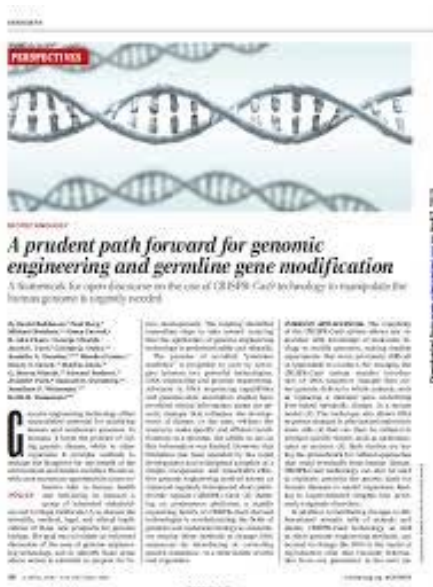
### A GLOBAL DISCUSSION

December 1-3, 2015 Washington, D.C.



# Ethics Oversight of Gene Editing

“Germline genome-editing research trials might be permitted, but only following much more research aimed at meeting existing risk/benefit standards for authorizing clinical trials and even then, only for compelling reasons and under strict oversight.”



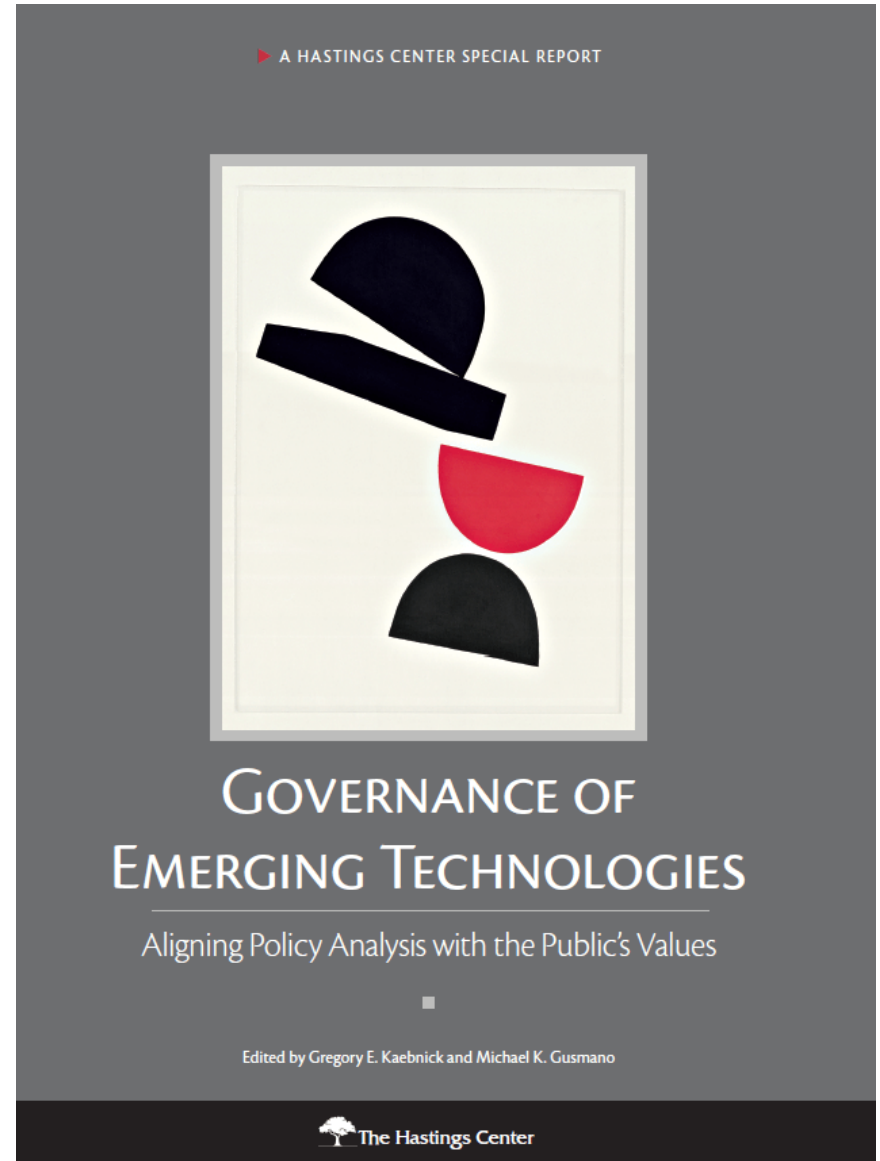
# Playing God as “God plays God”

## Theological Perspectives

- Humans created in the “image of God” are meant to understand the natural world and provide stewardship
- Intention to promote human flourishing
  - No malevolent intent
- Equality in access to all benefits



# Governance of Emerging Technologies: Aligning Policy Analysis with the Public's Values



Thank you

