Editing the genome: Opportunities and challenges for Christians

Jeff Hardin
The Bioethics Challenge
(since Hardin graduated from high school)

- 1978: Louise Brown, first “test tube” (IVF) baby
- **Surrogate motherhood** (1980s)
- Other *reproductive technologies* (embryo freezing, GIFT, ZIFT, ICSI, oocyte cytoplasm transfer)
Human blastomeres separated, 1993
Dolly the sheep cloned, 1997
2001: The Stem Cell Debate
2001: The Stem Cell Debate
Induced Pluripotency - 2006

Shinya Yamanaka
Primate Cloning - Nov. 2007

Semos
Cloning Technology: Clones from the Frozen

Mouse frozen for 16 years

Clone

Use of CRISPR/Cas9 in gene editing in eukaryotic cells - Feb. 2013

Feng Zang

George Church


Human Therapeutic Cloning - May, 2013

Seeing double: human embryonic stem cells have finally been made using cloning techniques.

REGENERATIVE MEDICINE

Human stem cells created by cloning

Breakthrough sets up showdown with induced adult lines.
Why Should a Christian Respond?

G.K. Chesterton
“If the ordinary [person] may not discuss existence, why should [he/she] be asked to conduct it?” (George Bernard Shaw)

http://mum6kids.files.wordpress.com/2011/06/chesterton.jpg
Why Should a Christian Respond?

• The 21st century is the “Century of Biology”.

• It is very likely that many people here or their loved ones will need to decide about ethically challenging therapies.
Why Should a Christian Respond?

Matthew 5:13: “You are the salt of the earth. But if the salt loses its saltiness, how can it be made salty again? It is no longer good for anything, except to be thrown out and trampled by people.”
The Central Dogma

This means that we can study a protein by working with the DNA that encodes it. DNA is far easier to work with than RNA or proteins. Editing DNA also allows for heritable transmission of changes that are made.

Campbell, 6e, Fig. 17.3
Intentionally altering the genome ("genetic engineering")

• We can **add** genetic material to make **transgenics**.

• We can **remove** genetic material by targeted deletion of a gene to make a "knockout". In mice, this can be accomplished via **homologous recombination** using engineered ES cells.

• In other animals we can use **genome editing**.
Transgenic mice

Campbell 5e, p.364

GFP mice
Transgenic marmosets (2009)

Making “knockout” or “knock-in” mice by homologous recombination

Insert DNA into ES cells; sometimes it inserts by replacing a normal copy of the gene (homologous recombination)

Select for right cells

Breed to obtain genetically altered mice

Insert into host embryo

Hardin and Bertoni 9e, Fig. 21-31
Making “knockout” mice: Nobel in 2007

Mario Capecchi  Martin Evans  Oliver Smithies

Making “knockout” human ES cells by homologous recombination

Making targeted deletions/replacements by homologous recombination: downsides

- Recombination only occurs very rarely
- Labor-intensive
- Breeding the mice takes a long time
- Can’t use on human germline (mosaicism, breeding, etc.)
- Genome editing is an alternative
Methods of Genome Editing
What is genome editing?

- An enzyme (an endonuclease) is targeted to a specific site in the genome to make cuts in DNA at a specific site.
- The cell’s DNA repair machinery tries to repair the break.
- If there is no repair template (a piece of added DNA) the cell will fill the gap (a process called nonhomologous end joining - NHEJ), “breaking” the gene.
- If a piece of DNA is provided, the cell will use it (a process called homology-directed repair - HDR).

http://www.yourgenome.org/facts/what-is-genome-editing
ZFNs and TALENs

TALEN - Transcription activator-like effector nucleases

A non-specific cutting enzyme (endonuclease) is fused to a protein that binds a specific DNA sequence.
CRISPR/Cas9

**CRISPR** = clustered regularly interspaced short palindromic repeats are DNA elements (see next slide)

**Cas** = CRISPR-associated genes

**Cas9, Csn1** = CRISPR-associated protein with two nuclease domains, that is programmed by small RNAs to cut DNA

Thomas Splettstoesser (www.scistyle.com)
Bacteria use CRISPR/Cas9 to protect against viral infection

When infected again, CRISPR/Cas9 system activated

PAM = Protospacer-Adjacent Motif
tracrRNA = trans-activating crRNA

Genome editing using the CRISPR/Cas9 system

- Almost **any gene** can be targeted by scanning for PAM sites and designing a **guide RNA**
- Providing a **repair template** allows insertion of designed sequences

Pros/Cons of CRISPR/Cas9

**Pros**
- Almost *any gene* can be targeted
- **Rapid and cheap** compared to other approaches

**Cons**
- **Off-target effects** (other sites in the genome might be cut by mistake)
- “Biohackers”: so easy that it can be done in a garage
Genome editing using CRISPR/Cas9

McGovern Institute
https://www.youtube.com/watch?v=2pp17E4E-O8
Applications of Genome Editing: Non-Human
Genome editing in the lab

fluorescently engineered version of the protein $\beta$-catenin expressed in a living *C. elegans* embryo (Xiangqiang Shao; Hardin lab)
“Open season” on genome editing in agriculture

Normal juvenile  Genome edited - no horns

CRISPR: Epic Patent Fight

Feng Zhang and Broad Institute (Harvard/MIT)

Emanuelle Charpentier (Max Planck Institute for Infection Biology, Berlin) & Jennifer Doudna (UC-Berkeley)


https://www.nytimes.com/2015/05/12/science/jennifer-doudna-crispr-cas9-genetic-engineering.html?_r=0
CRISPR: Epic Patent Fight

University of California attorney Todd Walters addresses the three judges presiding over the CRISPR patent hearing.

Round one of CRISPR patent legal battle goes to the Broad Institute

By Jon Cohen | Feb. 15, 2017, 2:30 PM
Gene drives: intentionally altering populations of organisms

Gene drives: intentionally altering populations of organisms

Wyss Institute
https://www.youtube.com/watch?v=cy69C6vnFCQ
Gene drives: big supporters

Bill Gates Doubles His Bet on Wiping Out Mosquitoes with Gene Editing

But the technology for extinguishing species is dividing conservationists.

by Antonio Regalado  September 6, 2016
Gene drives: potential problems

- **Law of unintended consequences**: many are uneasy that we cannot fully anticipate the unintended consequences of ecosystem engineering (the “Jeff Goldblum” problem)

- **Can a drive be reversed?** While there are proposals that seem to work that reverse the effects of drives (“safety drives”), they are unlikely to be 100% effective

- **Regulatory confusion**: US regulation is a tangle of inconsistency and can involve several agencies (FDA, USDA, EPA).
Applications of Genome Editing: Human
Induced Pluripotency - 2006

Shinya Yamanaka
Induced Pluripotent Stem (iPS) Cells

“Yamanaka factors”

Gilbert & Barresi 11e, 
Developmental Biology, 
Fig. 3.14
Using CRISPR to engineer iPS cells is a rapid way to repair specific genes.
CRISPRd iPS Cells and Therapy:
Retinitis pigmentosa (2015)

CRISPR Used To Repair Blindness-Causing Gene Defect

Emily Mullin, SUBSCRIBER
I write about the intersection of health and humanity. FULL BIO

Opinions expressed by Forbes Contributors are their own.

Forbes, Jan. 29, 2016

Retinitis pigmentosa by Christian Hamel (Licensed under CC BY 2.0 via Commons)
CRISPRd iPS Cells and Therapy: Muscular dystrophy (2017)

Muscle-specific CRISPR/Cas9 dystrophin gene editing ameliorates pathophysiology in a mouse model for Duchenne muscular dystrophy


Received: 03 April 2016
Accepted: 30 December 2016
Published online: 14 February 2017

Nature Communications, Feb. 2017
CRISPRd Pigs and Organ Farming

http://www.timeslive.co.za/thetimes/2016/06/07/Modified-pigs-save-patients-bacon
Genome Editing and the Human Germline
First CRISPR-Tinkered Primates Born

Twin macaques are the first primates born whose genomes were edited using CRISPR technology.

By Kerry Grens | February 3, 2014

Sister macaques Ningning and Mingming are the first born of a cohort of 10 primates whose genomes have been monkeyed with using CRISPR/Cas9 technology. The other eight macaques are still in utero. Although scientists have successfully edited the genomes of rats, mice, and other animals using CRISPR, this is the first demonstration of the technique in primates.

"People have been looking for primate models for a whole list of diseases, but in the past it's been either completely undeasible, or incredibly expensive. This is saying we can do this relatively inexpensively and quickly, and that is a major advance," Nelson Freimer of the University of...
Genome editing in primates

Feb. 13, 2014

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
“The concept of altering the human germline in embryos for clinical purposes has been debated over many years from many different perspectives, and has been viewed almost universally as a line that should not be crossed.”
Genome editing in humans - caution

• Gene-editing technology **should not be used to modify human embryos intended for use in establishing a pregnancy**

• “It would be irresponsible to proceed with any clinical use of germline editing unless and until (i) the relevant safety and efficacy issues have been resolved … and (ii) there is broad societal consensus…”

• Called for **cautious development of medical applications that cannot be passed on to offspring** (e.g. sickle-cell disease, or modification of immune cells to target cancer).

December, 2015

UK scientists get green light to genetically modify human embryos

The technique could help explain and ultimately eradicate many diseases in humans - but it is not without controversy

Adam Withnall | @adamwithnall | Monday 1 February 2016 | 79 comments
Genome editing in humans - Sweden

Where might the first CRISPR baby be born?

13 October 2015

NAS: Germline genome editing in humans?

- **Called for prohibiting any alterations resembling “enhancement”**

- Clinical trials of germline alteration “might be permitted, but only following much more research” on risks and benefits, and “only for compelling reasons and under strict oversight.” Those situations could be limited to couples who both have a serious genetic disease and for whom embryo editing is “really the last reasonable option” if they want to have a healthy biological child, says committee co-chair Alta Charo, a bioethicist at the University of Wisconsin in Madison.
NAS: Germline genome editing in humans?

“It is essential for public discussions to precede any decisions about whether or how to pursue clinical trials of such applications...And we need to have them now.”

http://news.wisc.edu/content/uploads/2017/02/Alta-Charo.jpg

Just a little “fixer upper”?

“If these fixes for severe diseases are shown to be safe and effective, why would small or large enhancements accompanying the fixes be unacceptable?”

George Church

February, 2017

Public perception - Pew

% of U.S. adults in each religious commitment group who say gene editing is meddling with nature and crosses a line we should not cross

Gene editing giving babies a much reduced disease risk

- High commitment: 64%
- Medium commitment: 48%
- Low commitment: 28%

Pew Research, July 26, 2016
Public perception and the “one-gene-wonder” problem

**Pleiotropy**

- Gene
  - Trait #1
  - Trait #2
  - Trait #3
  - Trait #4

**Multigenic trait**

- Gene #1
- Gene #2
- Gene #3
- Gene #4
- Trait
Autism: an example of a multigenic trait
A Personal Example

Christopher Hardin, February 9, 2014
Genome Editing and the Christian
A key issue: what does it mean to be human?

One woman, the mother of a child with Down syndrome, explained: “I love my child and wouldn’t change him. There’s something about him that’s so special…”

The scientist tears up telling this story. “It makes you think hard about what it means to be human, doesn’t it?” she says.
The Nature of Humans: Good

- **Image bearers** (Gen. 1:26-27; 9:6)
- That act as **stewards** (Gen. 1:28, 2:15)
- That procreate in **“one-flesh” relationships** (Gen. 2:23-24)
- Whose children are **“begotten gifts”** (Ps. 127:3-5)
- The **weak** deserve special protection (Ex. 22:22; Deut. 10:18,; Isa. 1:17, etc.)
The Nature of Humans: Broken

- **Require restraint** (Genesis 2:16-17)
- **Fallen** (Genesis 3)
- Life-taking only under divinely mandated circumstances (Gen. 9:6; Ex. 23:7)
- **Christ died for us** (Rom 5:6-8)
- **Suffering**, shared by Christ (Rom 5:3)
- Jesus: the **pattern** of restoration (Rom. 8:29)
Scientism not an option

James Watson (Nobel Laureate)

“The belief that surrogate mothers and clonal babies are inevitable because science always moves forward…”

http://www.foxnews.com/images/315962/0_61_watson_james.jpg
Scientism not an option

...represents a form of laissez-faire nonsense dismally reminiscent of the creed that American business, if left to itself, will solve everybody’s problems.” Moving Towards the Clonal Man: Is This What We Want in Pence and Pence, Flesh of My Flesh, p. 7)
The Human Difference?

“In this respect, experimenting on a human embryo is not to be compared in significance with experimenting on a living, sentient mouse...

(reprinted in Kuhse, H. and Singer, P., eds, Bioethics: An Anthology, p. 99)
Biblical Passages

• The human biblical authors don’t know about blastocysts! *The Bible is pre-scientific.*

• Its language doesn’t resolve this issue with *the certainty we would like.*

• As a result, *sincere Christians disagree.*

• “Such passages [may] not establish when human life begins, but *they establish God's care and involvement from the very beginning.*” (In Walters and Cole-Turner, p. 192)
Gilbert Meilaender (Christian Bioethicist) “If we are genuinely baffled about how best to describe the moral status of that human subject who is the unimplanted embryo,

we should not go 
forward in a way that 
peculiarly combines 
metaphysical 
bewilderment with 
practical certitude by 
approving even limited [use] for experimental purposes.”

(Begetting and Cloning, reprinted in Pence 
and Pence, p. 43-44)
Balancing Act

• We should seek to protect human beings at all stages of their development.
• We should desire to prevent disease (beneficence).
• Both are Christian obligations in tension!
• We should recognize the tendency of humans for sinful behavior.
Commodification

“[T]he application of germline manipulation would change our view of the value of human life. *If genomes are being altered to suit parents’ preferences, do children become more like commodities than precious gifts?*”

Francis Collins (Director, NIH)

http://images.politico.com/global/2013/01/15/francis_collins_ap_605.jpg

https://www.statnews.com/2015/11/30/gene-editing-crispr-germline/
“Humility would be a very good principle to attach to any such discussion.”
Next Steps

• Be *informed*.
• Be *critical thinkers*.
• Be *loving advocates*.
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Jeff Hardin