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Ethical concerns related to genome editing in human embryos

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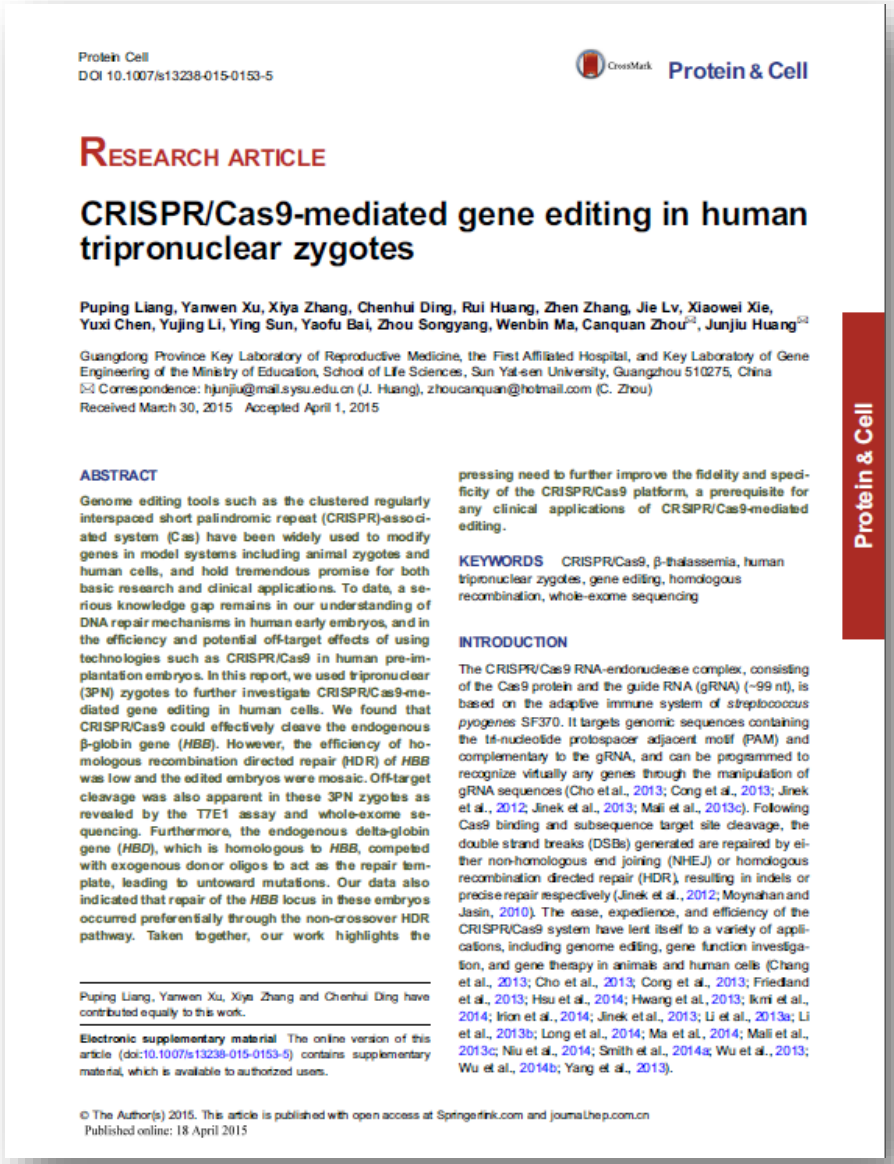
Symposium CFE-FCE, 25 November 2016

April 2015:
First publication of CRISPR/Cas9 gene editing in human embryos



Protein Cell
DOI 10.1007/s13238-015-0153-5

Protein & Cell

RESEARCH ARTICLE

CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes

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Received March 30, 2015 Accepted April 1, 2015

ABSTRACT

Genome editing tools such as the clustered regularly interspaced short palindromic repeat (CRISPR)-associated system (Cas) have been widely used to modify genes in model systems including animal zygotes and human cells, and hold tremendous promise for both basic research and clinical applications. To date, a serious knowledge gap remains in our understanding of DNA repair mechanisms in human early embryos, and in the efficiency and potential off-target effects of using technologies such as CRISPR/Cas9 in human pre-implantation embryos. In this report, we used tripronuclear (3PN) zygotes to further investigate CRISPR/Cas9-mediated gene editing in human cells. We found that CRISPR/Cas9 could effectively cleave the endogenous β-globin gene (*HBB*). However, the efficiency of homologous recombination directed repair (HDR) of *HBB* was low and the edited embryos were mosaic. Off-target cleavage was also apparent in these 3PN zygotes as revealed by the T7E1 assay and whole-exome sequencing. Furthermore, the endogenous delta-globin gene (*HBD*), which is homologous to *HBB*, competed with exogenous donor oligos to act as the repair template, leading to untoward mutations. Our data also indicated that repair of the *HBB* locus in these embryos occurred preferentially through the non-crossover HDR pathway. Taken together, our work highlights the pressing need to further improve the fidelity and specificity of the CRISPR/Cas9 platform, a prerequisite for any clinical applications of CRSIPR/Cas9-mediated editing.

KEYWORDS CRISPR/Cas9, β-thalassemia, human tripronuclear zygotes, gene editing, homologous recombination, whole-exome sequencing

INTRODUCTION

The CRISPR/Cas9 RNA-endonuclease complex, consisting of the Cas9 protein and the guide RNA (gRNA) (~99 nt), is based on the adaptive immune system of *streptococcus pyogenes* SF370. It targets genomic sequences containing the tri-nucleotide protospacer adjacent motif (PAM) and complementary to the gRNA, and can be programmed to recognize virtually any genes through the manipulation of gRNA sequences (Cho et al., 2013; Cong et al., 2013; Jinek et al., 2012; Jinek et al., 2013; Mali et al., 2013c). Following Cas9 binding and subsequence target site cleavage, the double strand breaks (DSBs) generated are repaired by either non-homologous end joining (NHEJ) or homologous recombination directed repair (HDR), resulting in indels or precise repair respectively (Jinek et al., 2012; Moynahan and Jasin, 2010). The ease, expedience, and efficiency of the CRISPR/Cas9 system have lent itself to a variety of applications, including genome editing, gene function investigation, and gene therapy in animals and human cells (Chang et al., 2013; Cho et al., 2013; Cong et al., 2013; Friedland et al., 2013; Hsu et al., 2014; Hwang et al., 2013; Ikmi et al., 2014; Irion et al., 2014; Jinek et al., 2013; Li et al., 2013a; Li et al., 2013b; Long et al., 2014; Ma et al., 2014; Mali et al., 2013c; Niu et al., 2014; Smith et al., 2014a; Wu et al., 2013; Wu et al., 2014b; Yang et al., 2013).

Puping Liang, Yanwen Xu, Xiya Zhang and Chenhui Ding have contributed equally to this work.

Electronic supplementary material The online version of this article (doi:10.1007/s13238-015-0153-5) contains supplementary material, which is available to authorized users.

Published online: 18 April 2015

COMMENT

Don't edit the human germ line

Heritable human genetic modifications pose serious risks, and the therapeutic benefits are tenuous, warn **Edward Lanphier**, **Fyodor Urnov** and colleagues.

It is thought that studies involving the use of genome-editing tools to modify the DNA of human embryos will be published shortly[1].

There are grave concerns regarding the ethical and safety implications of this research. There is also fear of the negative impact it could have on important work involving the use of genome-editing techniques in somatic (non-reproductive) cells.

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Genome-editing technologies may offer a powerful approach to treat many human diseases, including HIV/AIDS, haemophilia, sickle-cell anaemia and several forms of cancer[3]. All techniques currently in various stages of clinical development focus on modifying the genetic material of somatic cells, such as T cells (a type of white blood cell). These are not designed to affect sperm or eggs.

of germline modification, we encourage an open discussion around the appropriate course of action.

EDITING TOOLS

Genome editing of human somatic cells aims to repair or eliminate a mutation that could cause disease. The premise is that corrective changes to a sufficient number of cells carrying the mutation — in which the

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Key to all discussion and future research is making a clear distinction between genome editing in somatic cells and in germ cells. A voluntary moratorium in the scientific community could be an effective way to discourage human germline modification and raise public awareness of the difference between

INSIGHTS

PERSPECTIVES

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,[8] George Q. Daley,[9,10] Jennifer A. Doudna,[4,11]* Marsha Fenner,[8] Henry T. Greely,[12] Martin Jinek,[13] G. Steven Martin,[14] Edward Penhoet,[15] Jennifer Puck,[16] Samuel H. Sternberg,[10] Jonathan S. Weissman,[4,17] Keith R. Yamamoto[4,18]**

ture developments. The meeting identified immediate steps to take toward ensuring that the application of genome engineering technology is performed safely and ethically.

The promise of so-called "precision medicine" is propelled in part by synergies between two powerful technologies: DNA sequencing and genome engineering. Advances in DNA sequencing capabilities and genome-wide association studies have

CURRENT APPLICATIONS. The simplicity of the CRISPR-Cas9 system allows any researcher with knowledge of molecular biology to modify genomes, making feasible experiments that were previously difficult or impossible to conduct. For example, the CRISPR-Cas9 system enables introduction of DNA sequence changes that correct genetic defects in whole animals, such as replacing a mutated gene underlying

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In the near term, we recommend that steps be taken to:

1) Strongly discourage, even in those countries with lax jurisdictions where it might be permitted, any attempts at germline genome modification for clinical application in humans, while societal, environmental, and ethical implications of such activity are discussed among scientific and

A moratorium?

- Is this kind of research allowed in Belgium?
- Why a moratorium?
- Which are the relevant ethical concerns?
- Do these concerns legitimise a moratorium on clinical applications?
- Do these concerns legitimise a moratorium on research applications?

What does Belgian legislation say?

SERVICE PUBLIC FEDERAL SANTE PUBLIQUE,
SECURITE DE LA CHAINE ALIMENTAIRE
ET ENVIRONNEMENT

F. 2003 — 2156 [C − 2003/22592]

11 MAI 2003. — Loi relative à la recherche sur les embryons in vitro (1)

FEDERALE OVERHEIDSDIENST VOLKSGEZONDHEID,
VEILIGHEID VAN DE VOEDSELKETEN
EN LEEFMILIEU

N. 2003 — 2156 [C − 2003/22592]

11 MEI 2003. — Wet betreffende het onderzoek op embryo's in vitro (1)

Art. 3. La recherche sur les embryons in vitro est autorisée si toutes les conditions de la présente loi sont remplies et notamment si :	**Art. 3.** Onderzoek op embryo's in vitro is toegelaten indien aan al de voorwaarden van deze wet voldaan wordt en meer bepaald indien :
1° elle a un objectif thérapeutique ou vise l'avancement des connaissances en matière de fertilité, de stérilité, de greffes d'organe ou de tissus, de prévention ou de traitement de maladies.	1° het een therapeutisch doel heeft of bijdraagt tot een betere kennis inzake vruchtbaarheid, onvruchtbaarheid, transplantatie van organen of weefsels, het voorkomen of behandelen van ziekten.

Art. 4. § 1er. La constitution des embryons in vitro à des fins de recherche est interdite, sauf si l'objectif de la recherche ne peut être atteint par la recherche sur les embryons surnuméraires et pour autant que les conditions de la présente loi soient remplies.	**Art. 4.** § 1. Het aanmaken van embryo's in vitro voor onderzoeksdoeleinden is verboden, behalve indien het doel van het onderzoek niet kan worden bereikt door onderzoek op overtallige embryo's en voorzover voldaan is aan de voorwaarden van deze wet.

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11 MAI 2003. — Loi relative à la recherche sur les embryons in vitro (1)

Art. 5. Il est interdit :

1° d'implanter des embryons humains chez les animaux ou de créer des chimères ou des êtres hybrides;

2° d'implanter des embryons soumis à des recherches chez les humains, sauf si les recherches ont été menées dans un objectif thérapeutique pour l'embryon lui-même ou lorsqu'il s'agit d'une recherche d'observation ne portant pas atteinte à l'intégrité de l'embryon;

3° d'utiliser des embryons, des gamètes et des cellules souches embryonnaires à des fins commerciales;

4° d'accomplir des recherches ou des traitements à caractère eugénique, c'est-à-dire axés sur la sélection ou l'amplification de caractéristiques génétiques non pathologiques de l'espèce humaine;

5° d'accomplir des recherches ou des traitements axés sur la sélection du sexe, à l'exception de la sélection qui permet d'écarter les embryons atteints de maladies liées au sexe.

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2° embryo's waarop onderzoek is verricht in te planten bij mensen, behalve indien het onderzoek uitgevoerd is met een voor het embryo zelf therapeutisch doel of wanneer het gaat om een observatiemethode die de integriteit van het embryo niet schaadt;

3° embryo's, gameten en embryonale stamcellen te gebruiken voor commerciële doeleinden;

4° onderzoek of behandelingen met een eugenetisch oogmerk uit te voeren, dit wil zeggen gericht op de selectie of de verbetering van niet-pathologische genetische kenmerken van de menselijke soort;

5° onderzoek of behandelingen uit te voeren die gericht zijn op geslachtsselectie, met uitzondering van de selectie ter voorkoming van geslachtsgebonden ziekten.

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What does Belgian legislation say?

In a nutshell:

- **Embryo research** to gain better knowledge aimed at the treatment or prevention of diseases **using the technique of genome editing is allowed** (when it conforms to the other requirements of the law).
- **Clinical applications** using the technique of genome editing **with a 'therapeutic goal for the embryo itself' are allowed** (under conditions of good clinical practice).
- Research and clinical applications aimed at interfering with non-pathogenic genetic characteristics (so-called '**designer babies**') **are forbidden**.

Does the legislation sufficiently take ethical concerns into account?

Concerns linked to genome editing in human embryos for:

- Research
  - basic research (research using genome editing)
  - preclinical research (research into genome editing for reproductive purposes)
- Clinical applications
  - diseases
  - ‘designer babies’

Does the legislation sufficiently take ethical concerns into account?

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- **Research**
  - **basic research (research using genome editing)**
  - preclinical research (research into genome editing for reproductive purposes)
- Clinical applications
  - diseases
  - 'designer babies'

Basic research

Why would we want to use genome editing in embryos in basic research?

- Disease modeling
- Investigating effect of a particular mutation (on, for example, embryogenesis)
- …

Basic research

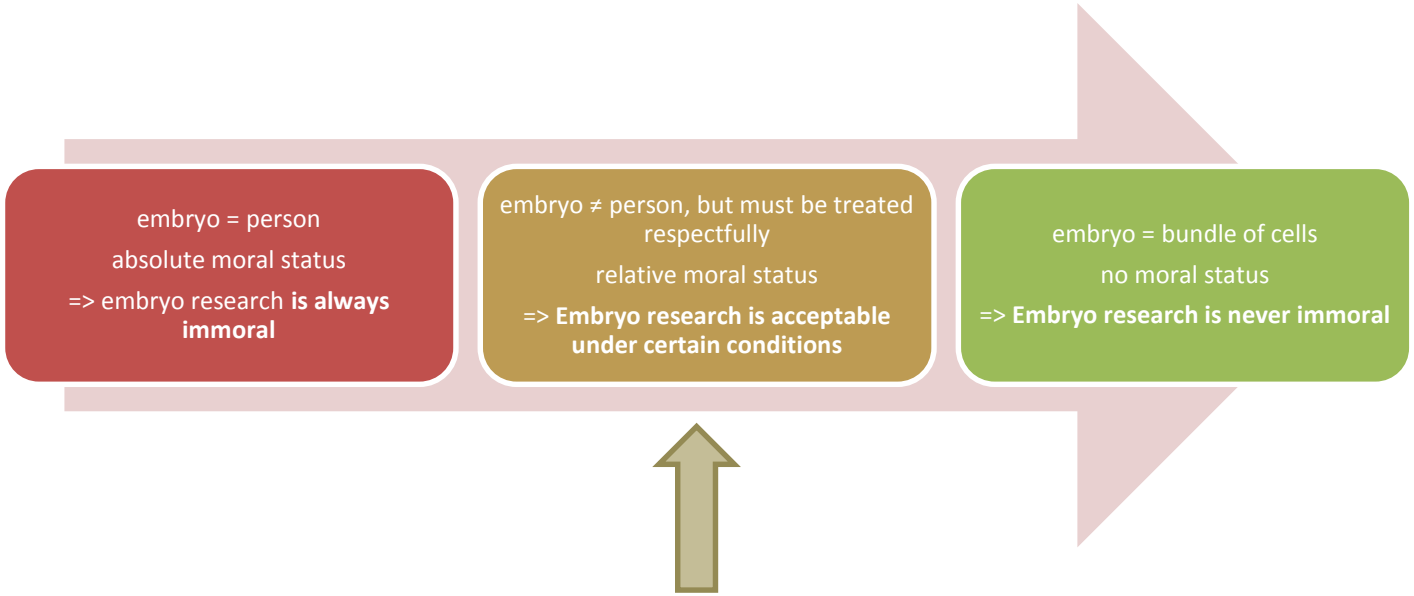
Moral concerns similar to any type of embryo research (e.g. human embryonic stem cell derivation and research)

- Should human embryos be used as tools in research?
- If so, under which conditions?

Basic research

Should human embryos be used as tools in research?

- Very diverse legislations reflect very diverse opinions about the moral status of the early human embryo



Basic research

Under which conditions can human embryos be used in research?

- Scientific goals are important, research protocol is sound, certified lab
- 14 day limit
- No alternatives with equal efficiency
- Oversight & transparency: local ethics committee + Federal Commission for Medical and Scientific Research on Embryos in vitro

In the context of genome editing research, special attention for:

- **consent of donors**
- **issues regarding the creation of embryos (vs use of 'spare' IVF embryos)**

Basic research

Consent of donors

- Preliminary remark: many Belgian patients decide to donate their spare IVF embryos to research!

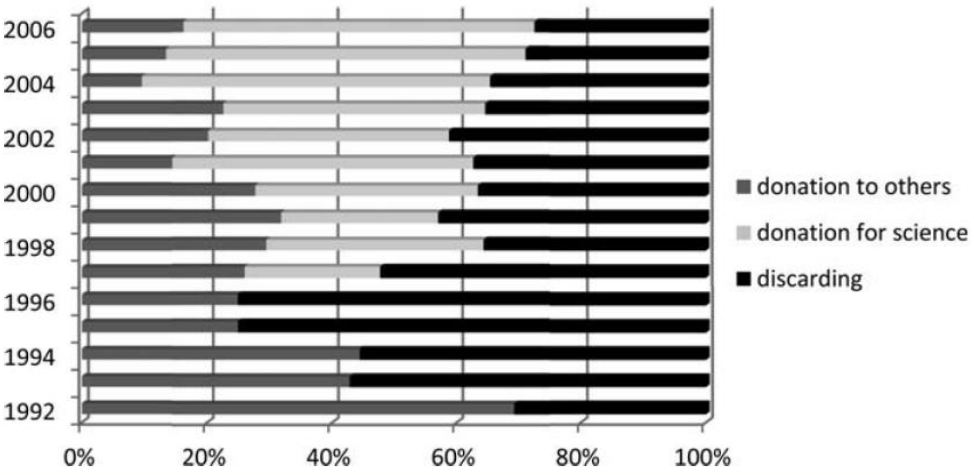


Figure 1 Proportion of final EDDs chosen over the years (1992–2006; *N*=1504).

Destination of spare IVF embryos at UZ Gent 1992-2006.
Provoost et al., Hum Reprod 2012;27:506-514.

Basic research

Consent of donors

- Decision whether or not to donate embryos for research is not only based on the attributed **moral status**, but also on the **instrumental value** attributed to the embryo, on **knowledge** about the research and on **trust** in the scientific community (Samorinha et al, 2014; Provoost et al, 2009).

- As genetic manipulation is a sensitive issue for many people (cf GMO-debates), an **explicit consent** should be sought of the embryo donors, not a generic consent. Donors should have a clear understanding of what will be done with the embryos and for which purpose this will be done.

- NB: currently donors give consent for a specific project for fresh embryo donation, for a category of projects for frozen embryo donation.

Basic research

Spare IVF embryos versus research embryos

- If genome editing needs to be performed in a very early stage (e.g. zygote stage), spare IVF embryos (day 3 - day 5) cannot be used.
- Belgium: no other option => embryos can be created for research
- Europe (Oviedo convention): Oviedo convention, art. 18: “The creation of human embryos for research purposes is prohibited.”
- Why?

Basic research

Spare IVF embryos versus research embryos

What might be the morally relevant differences between spare IVF embryos that are donated to research and embryos created for research purposes?

- Increase of total amount of wrongdoing
  - doomed embryo rule or nothing-is-lost-principle
- Intention
  - rule of double effect
- Complicity of the researcher
  - separation principle

Basic research

Spare IVF embryos versus research embryos

It is more consistent to:

either avoid the creation of spare IVF embryos all together

or allow the creation of both spare IVF embryos and research embryos

than to allow the creation of spare IVF embryos but not the creation of research embryos… which is why the Belgian initiators of the bill on embryo research denied a moral distinction between both.

Does the legislation sufficiently take ethical concerns into account?

Concerns linked to genome editing in human embryos for:

- **Research**
  - **basic research (research using genome editing)**
  - **preclinical research (research into genome editing for reproductive purposes)**
- Clinical applications
  - diseases
  - 'designer babies'

Preclinical research

Do we need genome editing in embryos in preclinical research?

YES!

- To ensure **responsible innovation** in the clinic.
- Investigate, for example, the chances of off-target mutations when trying to correct a particular disease-causing mutation.

Preclinical research

Do we need genome editing in embryos in preclinical research?

NO!

- We do not need it, we have **PGD** for most conditions (+ donor conception, adoption and childlessness are valid alternatives).
- This is a **bad allocation of research funds**, there are more urgent healthcare needs.
- This research may have a **negative effect on the regulation of non-reproductive applications of genome editing**.

  Lanphier et al.: *"We are concerned that a public outcry about such an ethical breach could hinder a promising area of therapeutic development, namely making genetic changes that cannot be inherited."*

Outline

Concerns linked to genome editing in human embryos for:

- Research
  - basic research (research using genome editing)
  - preclinical research (research into genome editing for reproductive purposes)
- **Clinical applications**
  - **diseases**
  - 'designer babies'

Clinical applications - diseases

avoiding transmission of diseases to future generation(s)

Main ethical objections:

- "We do not need this technology."
- "It's not safe."
- "There is no informed consent."
- "Germline gene modification is unethical."
- "It's elite medicine."

Clinical applications - diseases

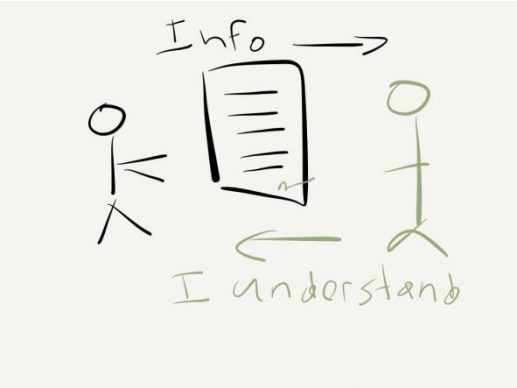
"It's not safe."

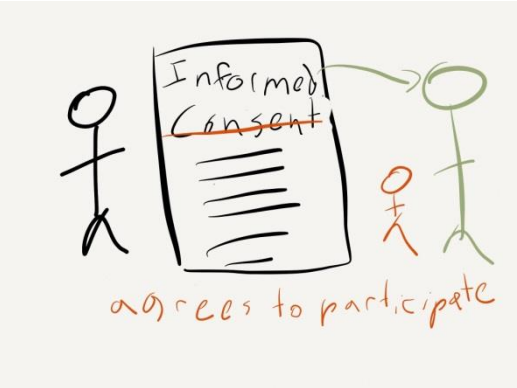
- Off-target mutations
- On-target mutations with unforeseen effects (possibly in later generations)
- Mosaïcism?
- Long-term follow-up in experimental phase is problematic, the ideal clinical trial should run over several generations.
- For most applications, PGD is a safer alternative.

Clinical applications - diseases

"There is no informed consent."

- Do we ever consent to our genetic make-up?
- We do allow therapeutic interventions on people incapable to consent, under the provisions that the best interest of the 'patient' is served and that the risk of harm is minimal.
- From the point of view of the future person, *not* intervening and letting them be born with a serious disability is also a choice for which consent of the person involved is not obtained.





Clinical applications - diseases

"Germline gene modification is unethical."

- The mutations (on-target or off-target) would not be limited to one individual, but would also be present in his/her descendants.

- BUT:
  - Also the beneficial alteration would be inherited, offspring ought to be 'better off'.
  - Edits are not necessarily irrevocable, could be re-edited in future generations.
  - Cf. situation in which people carry natural pathogenic mutations: reproductive decision-making (PGD, donor conception, childlessness)
  - Mutations in the germline are common:
    - Random, naturally occurring mutations
    - Due to our behavior (smoking, food intake, sports,…) we also induce epigenetic (uncontrolled!) changes in our offspring

  At least in this case, the edits are aimed at a clinical benefit.

Clinical applications - diseases

"It's elite medicine."

- Distributive justice: only the happy few will be able to afford genome editing
- This will lead to an increase in the disparity between the welfare of the rich and the poor.
- Rather than investing in this kind of personalized medicine, we should be investing in interventions aimed at improving the lives of a greater number of patients.
- Remember: new medical technology is the dominant driver of increases in healthcare costs!
- On the other hand: once the technique exists and is safe, can we prohibit rich people from using it if it leads to a better overall health?

Outline

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- Research
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- Clinical applications
  - diseases
  - **'designer babies'**

Clinical applications – designer babies

editing ‘healthy’ embryos in order to obtain desired characteristics

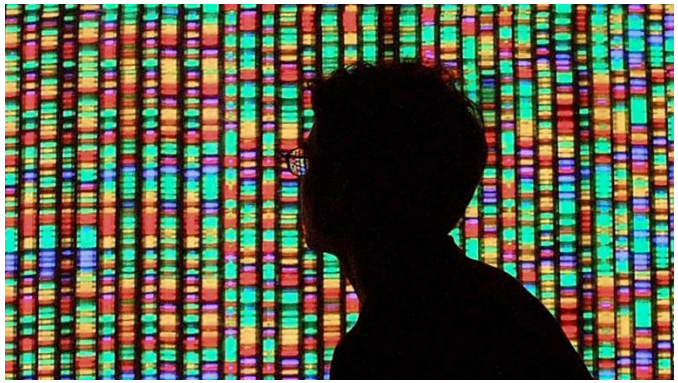
Main ethical objections (besides the ones mentioned before):

- “We should not change the human genome / alter the nature of the human species.”
- “This would have a negative impact on the gene pool.”
- “That’s eugenics. Eugenics is unethical.”
- “Designer babies are an insult to human dignity.”

Clinical applications – designer babies

"We should not change 'the' human genome."

- "*The implementation of heritable human genetic modification could irrevocably alter the nature of the human species and society*." (Open letter Center for Genetics and Society, 2015)
- What is 'the human genome'? What is 'the nature of the human species and society'?
- This objection only seems to make sense if someone were to try to change fundamental human characteristics / create chimeras / …
- If only known mutations are induced, this argument does not apply.



Clinical applications – designer babies

"This would have a negative impact on the gene pool."

- A number of presuppositions:
  - Everybody would want to have the same mutations.
  - Many people would want designer babies.
  - People will massively forego natural conception.

- Are these plausible?
- How does this risk compare to natural selection and genetic drift?

Clinical applications – designer babies

"That's eugenics. Eugenics is unethical."

- UNESCO's International Bioethics Committee: "*Interventions on the human genome should be admitted only for preventive, diagnostic or therapeutic reasons and without enacting modifications for descendants*." The alternative would "*jeopardize the inherent and therefore equal dignity of all human beings and* ***renew eugenics***."
- Historically, eugenics is associated with genocide, human rights violations (e.g. forced sterilization), racism, infractions against reproductive liberty,...
- However, that would not be the case for this type of eugenics.
- Procreative beneficence -> moral argument *for* the 'new eugenics'.

Clinical applications – designer babies

"Designer babies are an insult to human dignity."

- UNESCO's International Bioethics Committee: "Interventions on the human genome should be admitted only for preventive, diagnostic or therapeutic reasons and without enacting modifications for descendants." The alternative would "jeopardize the **inherent and therefore equal dignity of all human beings** and renew eugenics."
- Cf **disability critique**: by selecting against certain traits, we are labeling the people who have those traits as inferior, unwelcome.
- Idea that children should be accepted by their parents unconditionally. Demanding certain characteristics points at very high expectations towards the children and possible infractions against their right to an open future.
- What about enhancement during life? Education, plastic surgery, …

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Should we really be worried about designer babies (yet)?

Scientific obstacles:

- **Genotype-phenotype-correlation** is still poorly understood
- It's complicated! There is no gene for intelligence, gene for blue eyes,…
- **Healthcare-related edits will always be preferred** over trivial edits.

Legal obstacles:

- Also for PGD, there are **limitations** to what is permitted (only for serious diseases), why would this suddenly be different for genome editing?
- Remember: in Belgium, we already have a **prohibition** on editing non-disease related traits in clinical applications.

Conclusion

Research

- As Belgium allows embryo creation and destruction for **basic research**, there is no obvious reason why genome editing in embryos would not be allowed in a basic research context. In many other countries it will not be possible due to a prohibition on the creation of embryos for research.
- For **preclinical research** the main question is whether or not the allocation of research funds, effort and embryos is warranted at present, especially as for many applications PGD is an established alternative.

Conclusion

Clinical applications

- The main concern is safety. At present, it would be **irresponsible to bring genome editing to the clinic**, especially given the alternative of PGD (for most applications) => moratorium on clinical applications
- However, if the technique of genome editing of embryos is perfected and becomes safe, for the rare cases in which PGD is not possible, it is difficult to provide a well-founded reason to oppose reproduction with genome editing to avoid the transmission of serious diseases.
- The slippery-slope towards **designer babies** is something to be considered, but at the same time rather unlikely. It should therefore not stifle debate. This application is not allowed in Belgium.

Questions?

Vragen?

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