EDB Talk Series on Emerging Technologies - Science, Opportunities and Challenges

Nature's Red Pencil: Writing and Rewriting Genomes

The applications and ethics of genome editing

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<u>Your thoughts:</u> Is it ethically acceptable to use genome editing on plants/crops? What about animals? Or humans?

Types of genome editing

Editing in Non-Human Species

Editing in lab animals to study health and disease

Getty Images

Image from Salk Institute

Editing in microbes for production

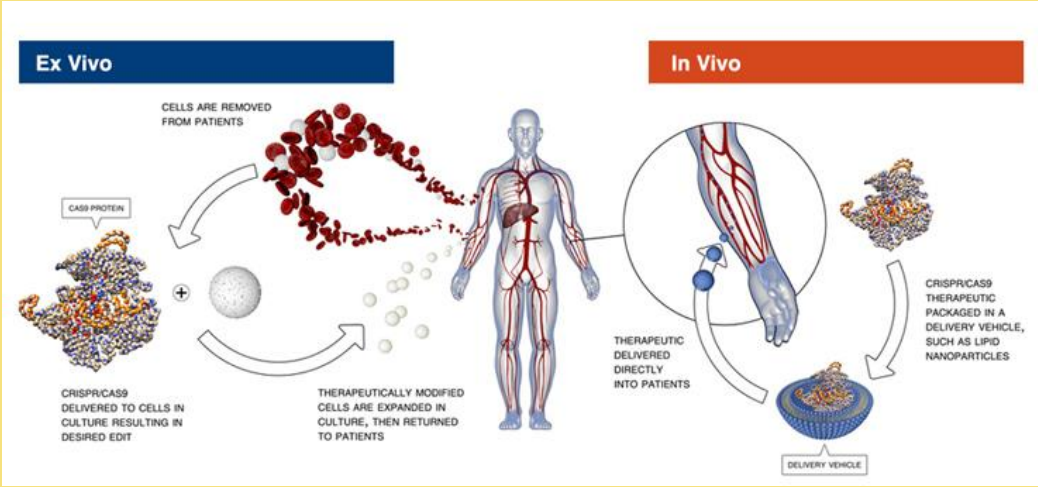
Rainis Venta Wikipedia (CC BY-SA 3.0)

Edited animals or plants to be released to the biosphere

Inari Agriculture

Jim Gathany - Wikimedia

Editing in Human or Human Tissue

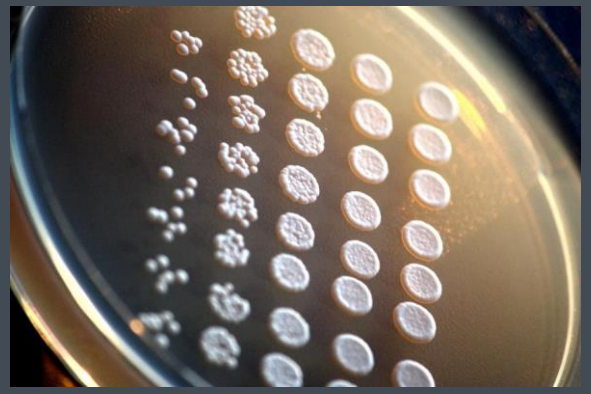


- Outside the body, or inside the body?
- Germ-line cells (eggs and sperm), or other somatic cells?

Non-human genome editing should be discussed more

Getty Images

A Macaque monkey with human genes that inflict brain changes and cause psychiatric disease: Is it humane? What can we learn?



Rainis Venta
Wikipedia (CC BY-SA 3.0)

Engineered yeast that can produce anti-malarial drugs and painkillers: How can we regulate this to prevent abuse?

Soybean with higher yield and more climate resistant: How to promote equitable access? Does it pose danger to the ecosystem?

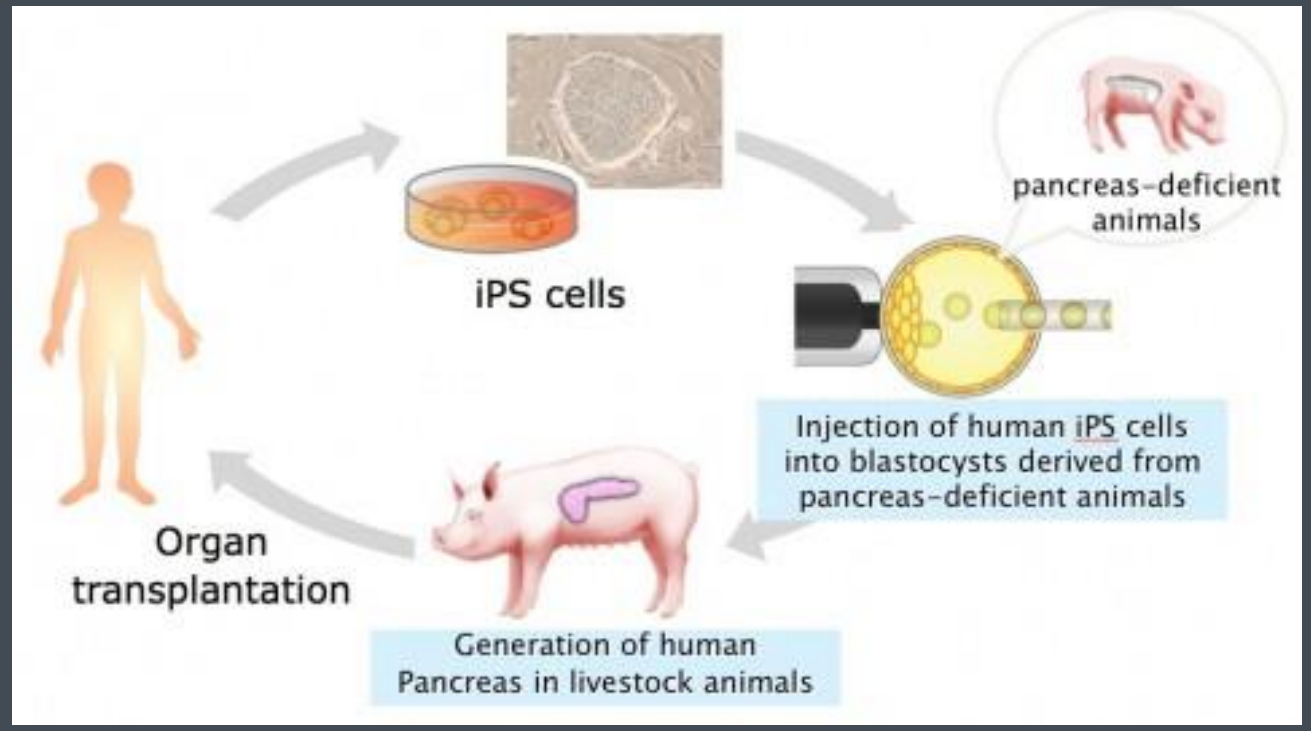
Inari Agriculture

Mosquitoes that kill other mosquitoes to reduce the spread of infectious diseases: Does it pose danger to the ecosystem? Is it practical?

Jim Gathany - Wikimedia

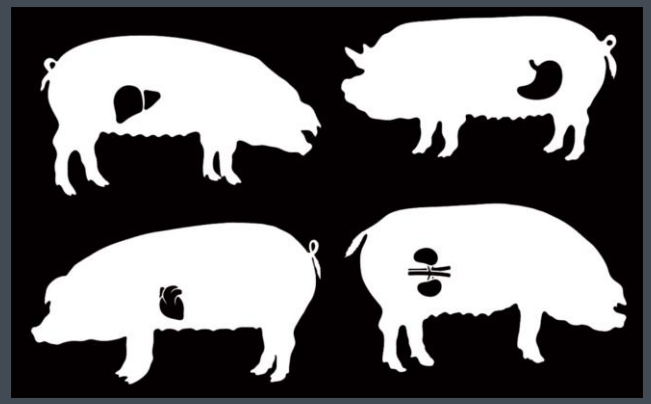
Another non-human genome editing example: chimeras

- E.g. chimeric pigs with human organs for organ transplantation
- “personalized animal” for organ transplantation – not only an issue of animal rights!



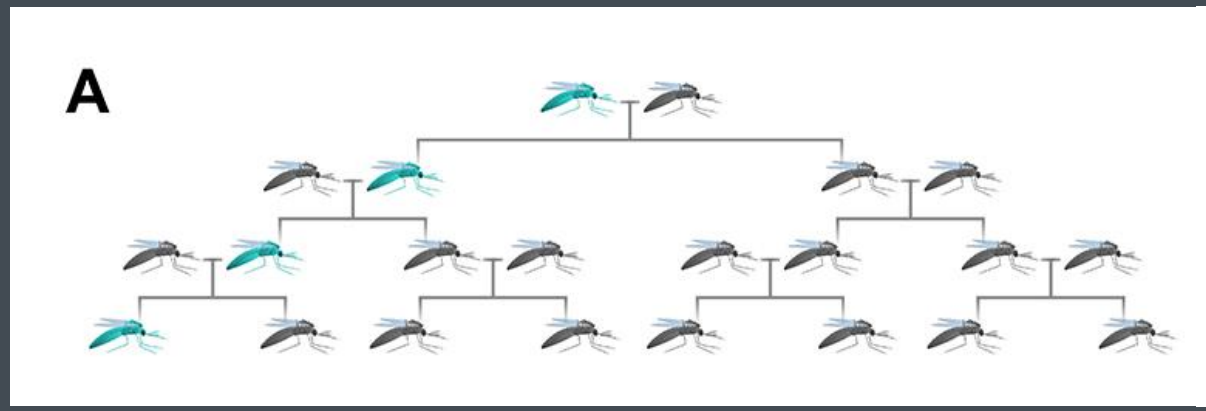
If a pig has a humanized brain, is it still a pig?

What if 50% of the chimeric pig is human organs? 60%? 70%?

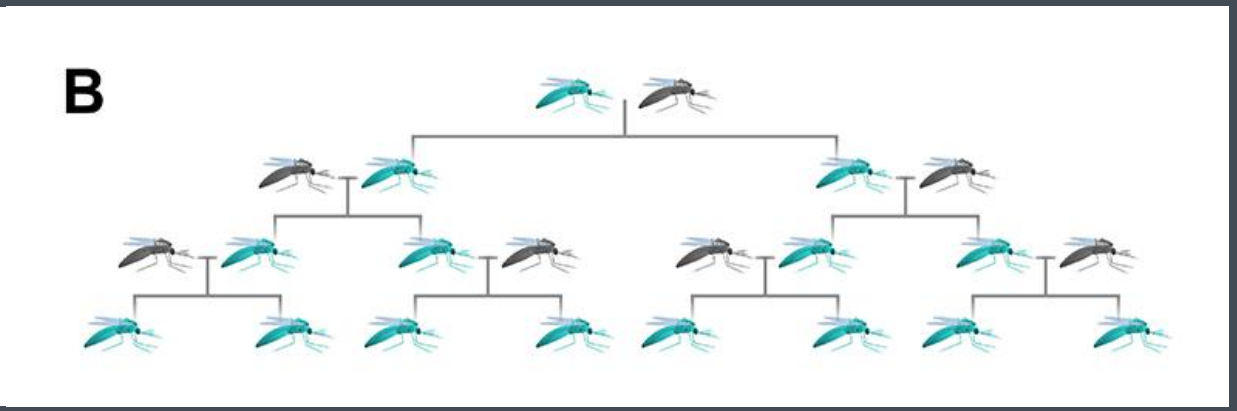


Non-human genome editing example: gene drives

- Gene drive:
  - Normally, each gene has a **50% chance of being inherited** by children
  - Genetic systems that violate these rules and increase the probability that a particular gene will be passed to offspring is a gene drive
  - **Increased % of inheritance means the gene can be spread to entire population**, even if it reduces chance of reproduction (e.g. a gene that makes a mosquito killing toxin)



normal



with gene drive

https://wyss.harvard.edu/staticfiles/newsroom/pressreleases/Gene%20drives%20FAQ%20FINAL.pdf

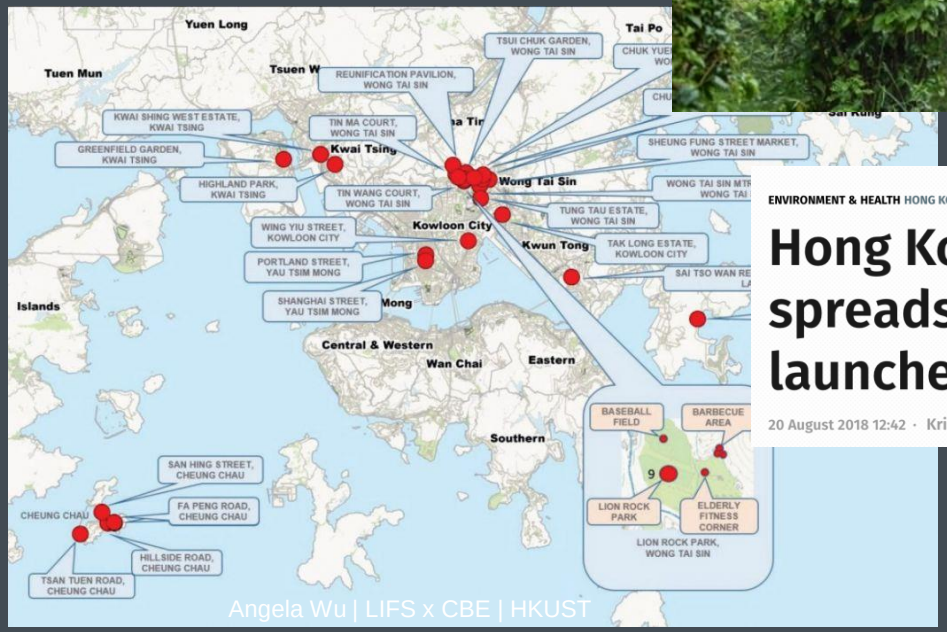
Gene drives: A Case Study for Hong Kong

In 2018, around 20 cases of dengue fever were confirmed locally in Hong Kong, causing alarm to locals and health authorities

Similar to malaria, dengue is spread by mosquitoes but it is a virus rather than a parasite, and severe cases can cause death

There was some talk of using gene drive to eradicate the dengue-carrying mosquitoes

Is this a good idea?

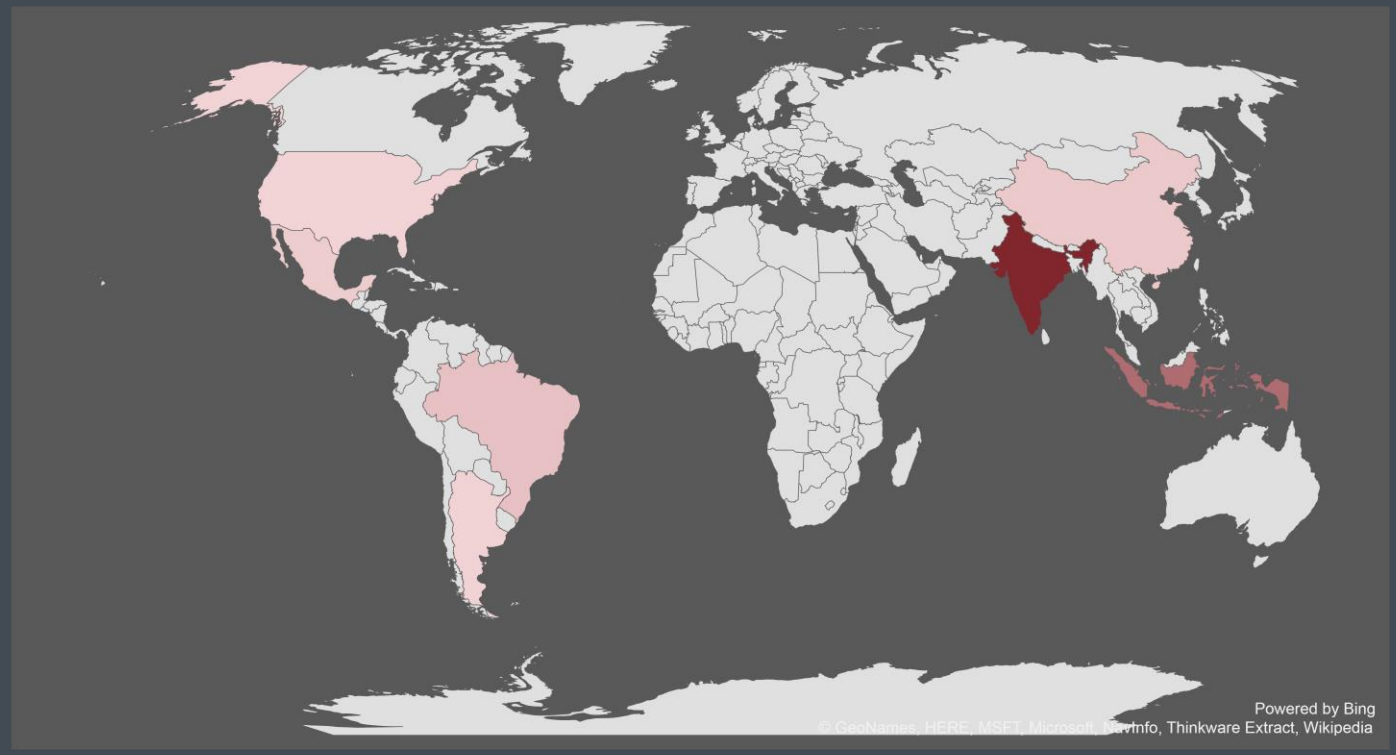


ENVIRONMENT & HEALTH HONG KONG

Hong Kong dengue fever outbreak spreads as anti-mosquito operation launched on Cheung Chau island

20 August 2018 12:42 · Kris Cheng · 3 min read

Gene drives: A Case Study for Hong Kong



	Dengue Cases in 2013 (thousands)
United States	51.0
Mexico	663.2
Brazil	1,907.9
Argentina	151.2
China	1,076.4
India	18,617.1
Singapore	15.0
Indonesia	11,101.2
Phillippines	39,000.0
Hong Kong*	0.1

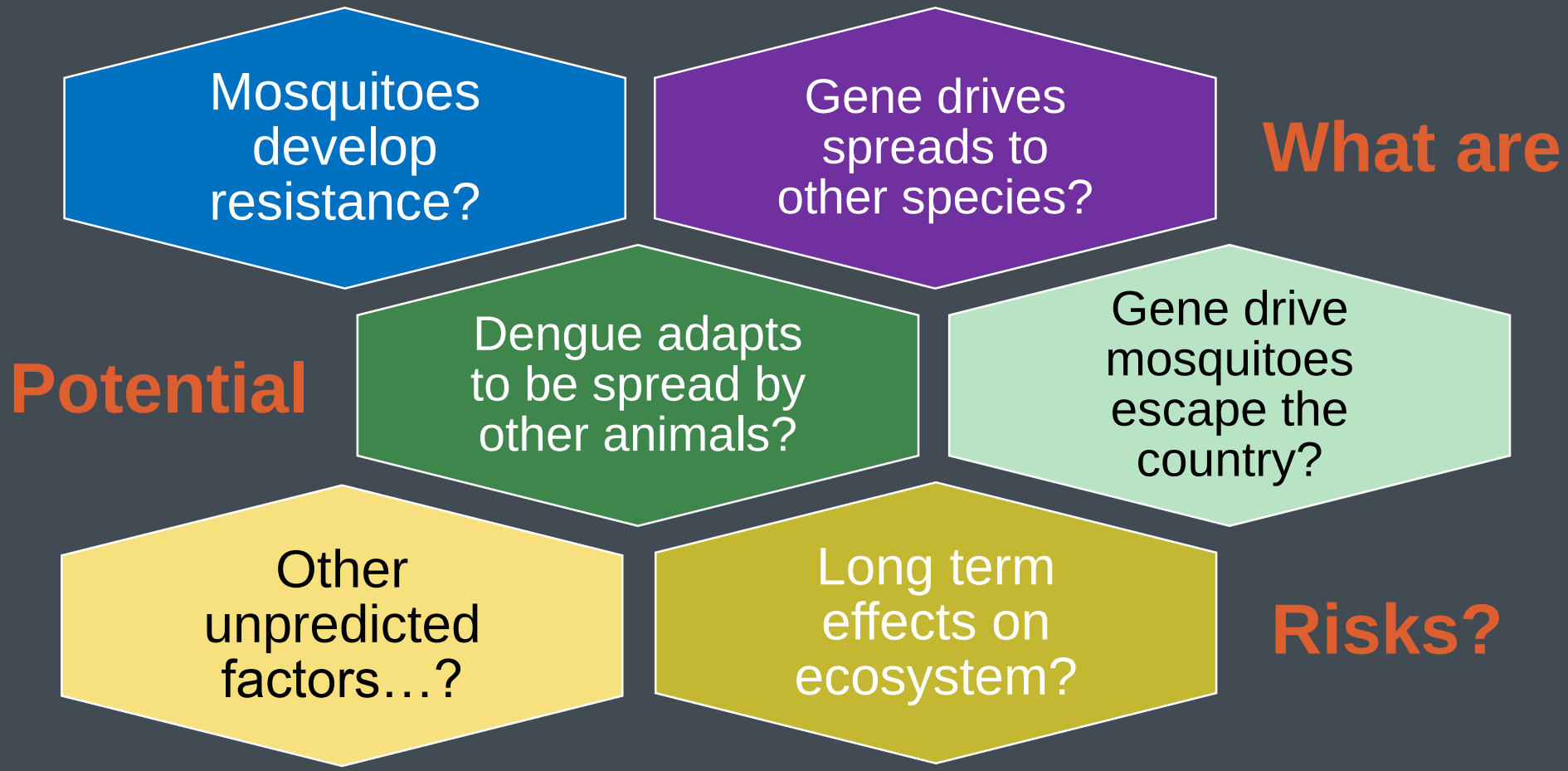
**Total 103 cases reported in Hong Kong in 2013)*

In Brazil gene drives were tested in a few cities in 2016

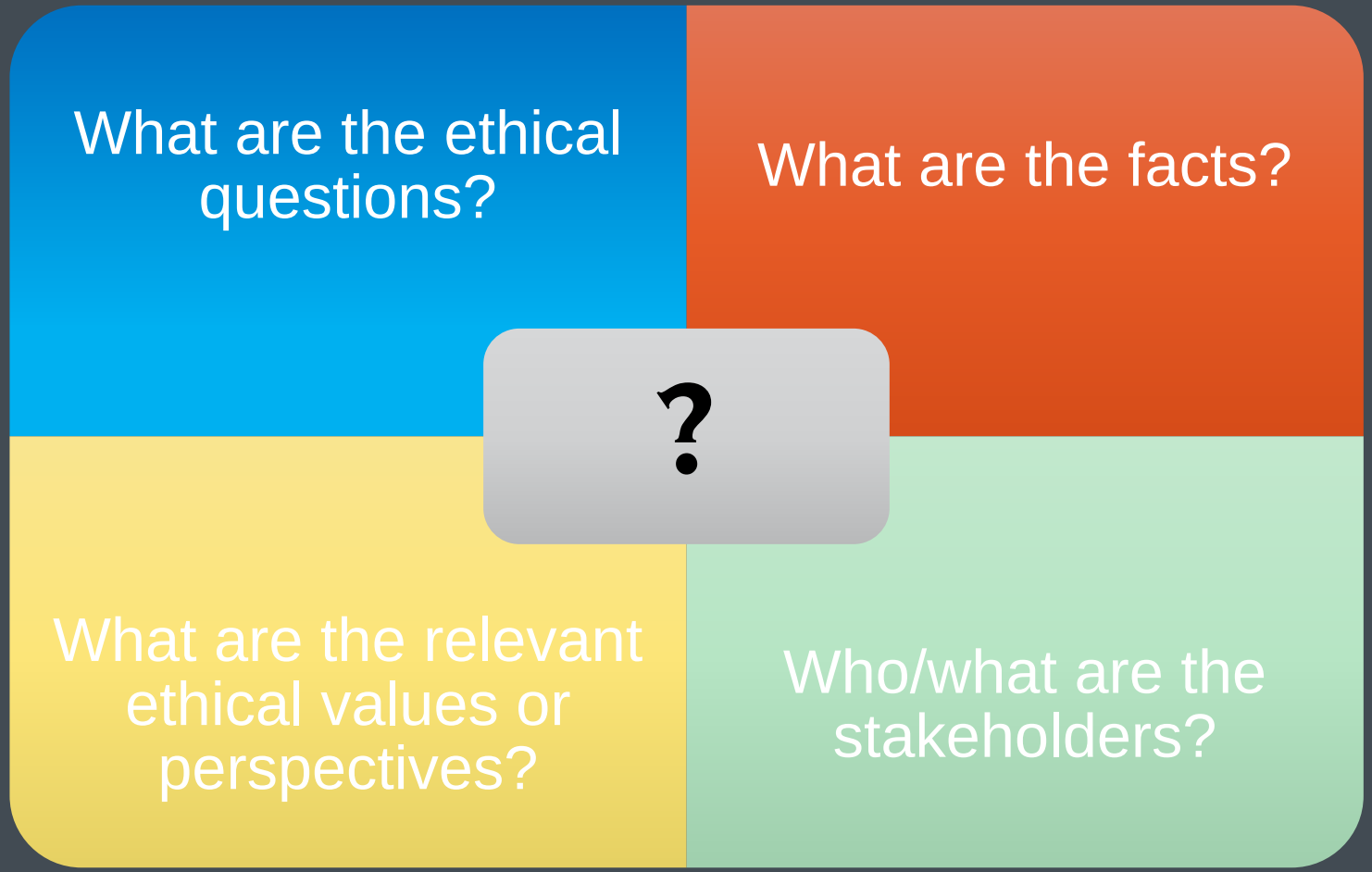
Cost: **> 8 million HKD for two years** of mosquito deployment in one city

Effects: No severe ecological effects have been observed so far. The mosquito population in the cities was reduced by over 60%; number of dengue cases were also reduced ~50%.

Gene drives: A Case Study for Hong Kong



How we can think about the ethics



We need to balance the risk and benefit

We cannot sacrifice a small group against their wish/without their knowledge, even for "greater good"

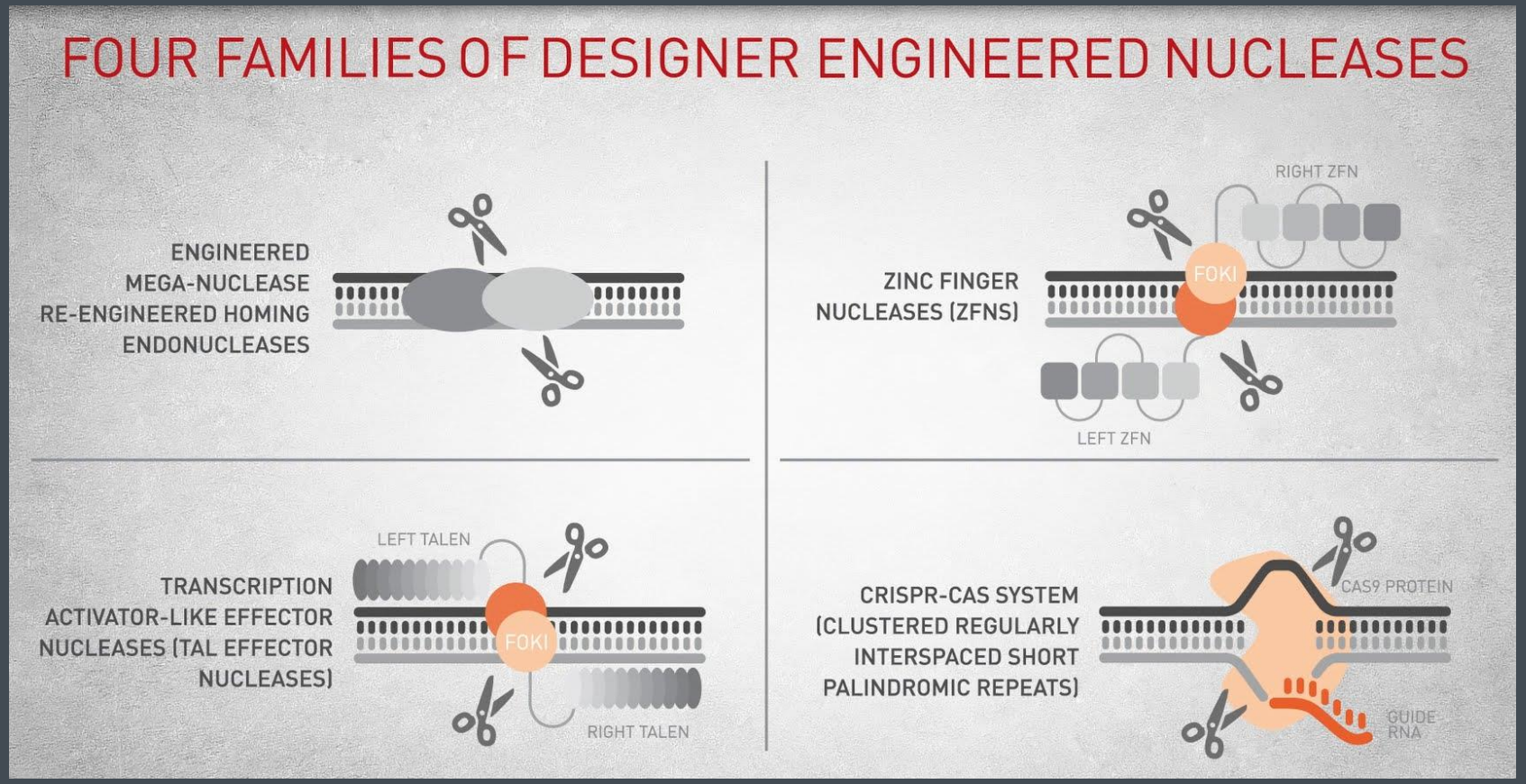
We need to consult key stakeholders

NIH Dept. of Bioethics: Exploring Bioethics, https://science.education.nih.gov/supplements/nih9/bioethics/guide/introduction.html

Human genome editing: Some key clarifications

1

Genome and gene editing itself is not new!

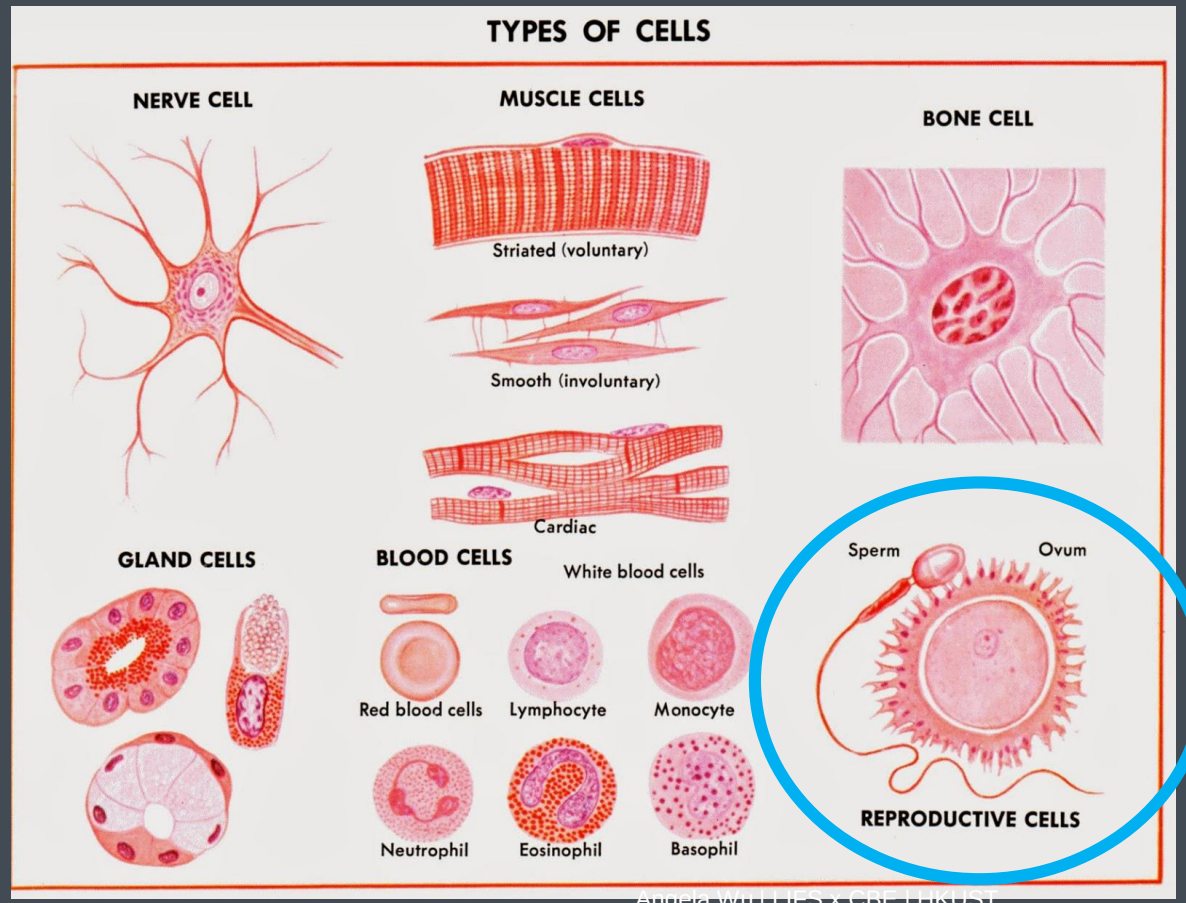


From ThermoFisherScientific: https://i.ytimg.com/vi/VvwKubUgwDQ/maxresdefault.jpg

Human genome editing: Some key clarifications

2

There is a major difference between talking about genome editing that is **HERITABLE vs. NON-HERITABLE!**



SOMATIC CELLS:
The rest

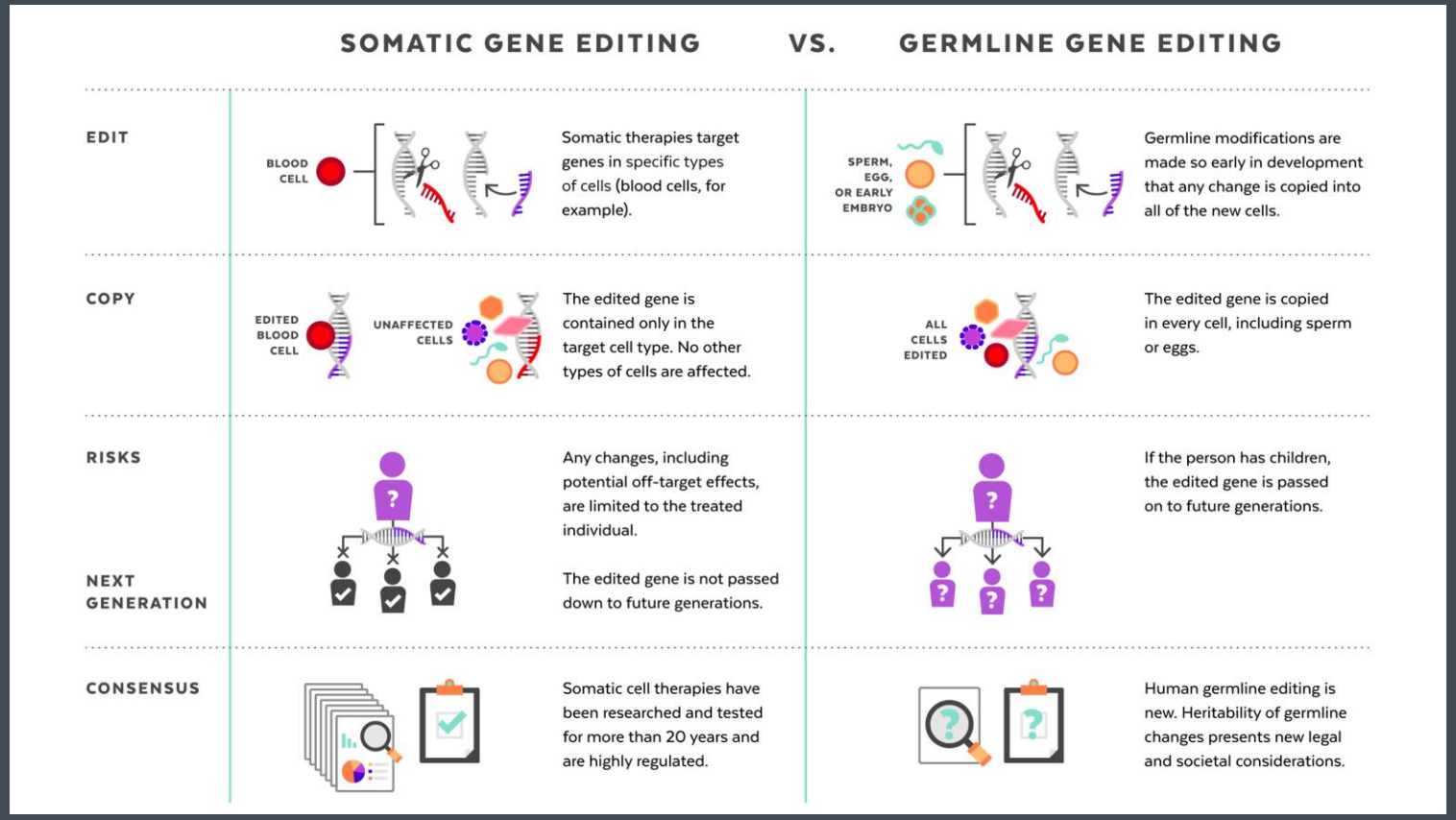
GERMLINE CELLS:
Egg, Sperm

https://wikis.engrade.com/a6thgradescience2/body

Human genome editing: Some key clarifications

2

There is a major difference between talking about genome editing that is **HERITABLE vs. NON-HERITABLE!**



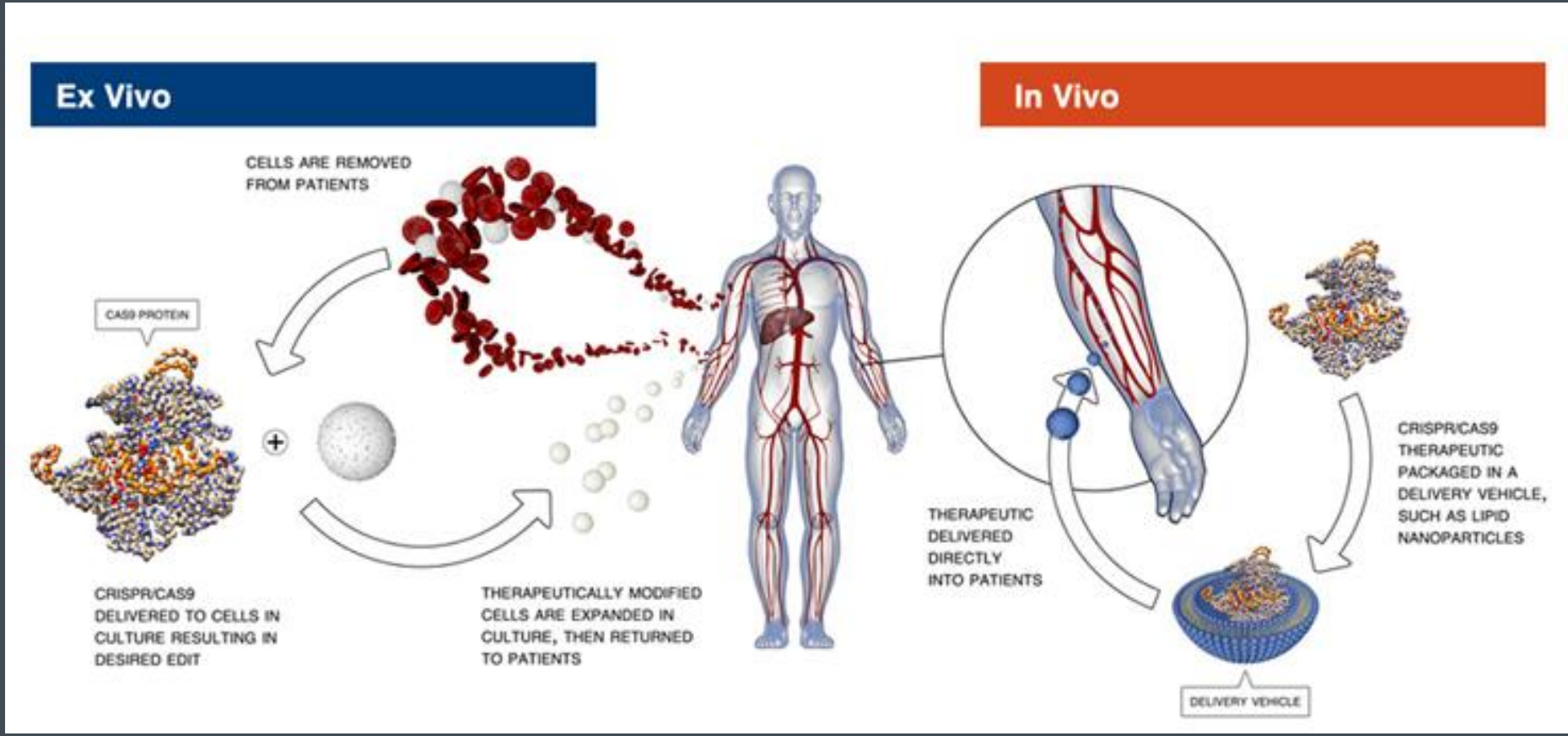
MOST applications we hear about today being commercialized use NON-HERITABLE genome editing to address a disease

https://news.harvard.edu/gazette/story/2019/01/perspectives-on-gene-editing/

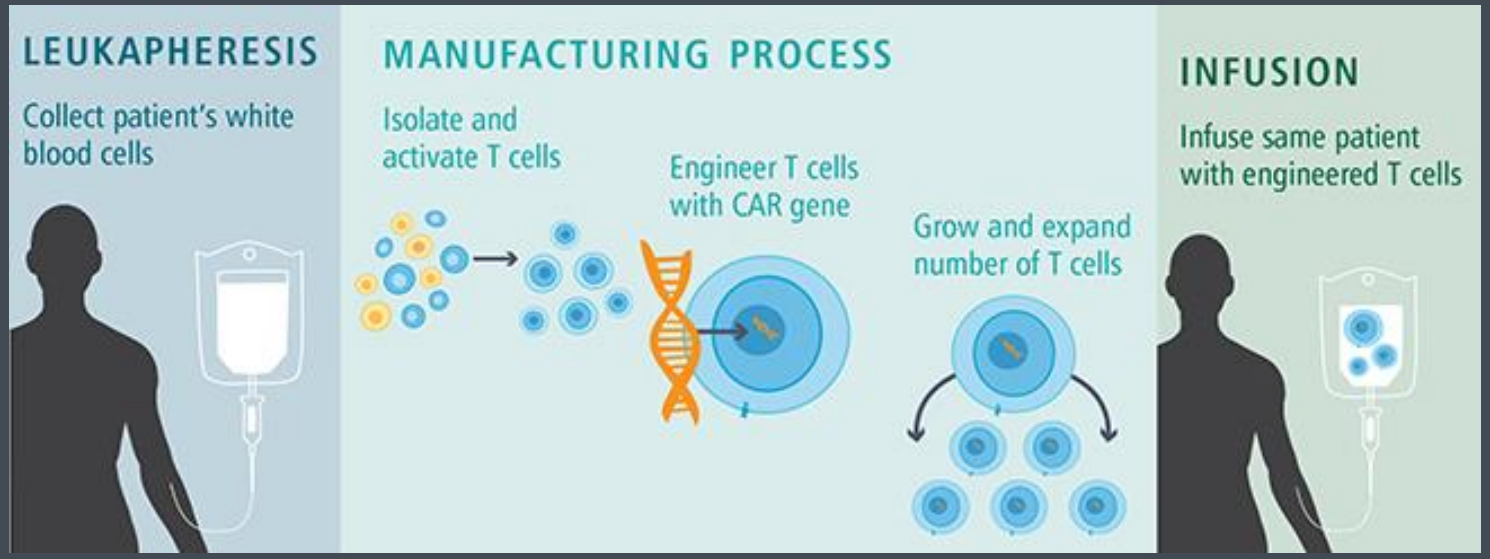
Human genome editing: Some key clarifications

3

The risk of editing human cells varies greatly depending on the application!



Non-heritable human genome editing example: CAR-T



- Multiple clinical trials on-going around the world against multiple types of cancer
- Despite side effects and some mortality due to host immune system responses, the potential benefit is greater than the risk for most cancer patients

https://www.dana-farber.org/cellular-therapies-program/car-t-cell-therapy/how-car-t-cell-therapy-works/

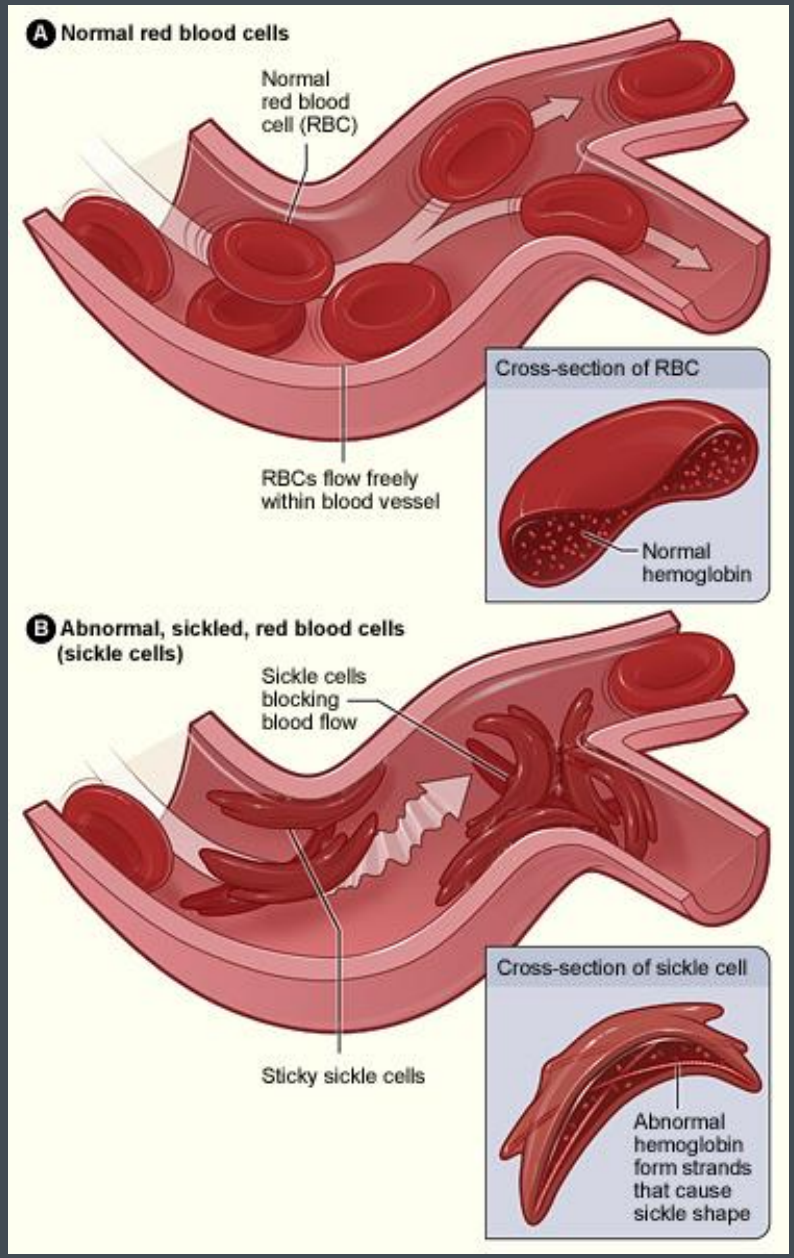
CAR-T trials ongoing; early success

- “Kite Pharma, a US pharmaceutical company, just released the groundbreaking results of their six-month gene therapy trial: terminal cancer patients in complete remission after just a single round.”
- “Patients who participated in the trial had one of three types of non-Hodgkin lymphoma. Patients were all given only a few months to live. However, following the first round of gene therapy, which took place nine months after the trial began, half the patients are not only still alive, but a third of them appear to be cured.”

https://futurism.com/4-gene-therapy-treatment-can-bring-terminal-cancer-patients-to-complete-remission/
http://ir.kitepharma.com/releasedetail.cfm?ReleaseID=1014817

Treating sickle cell anaemia

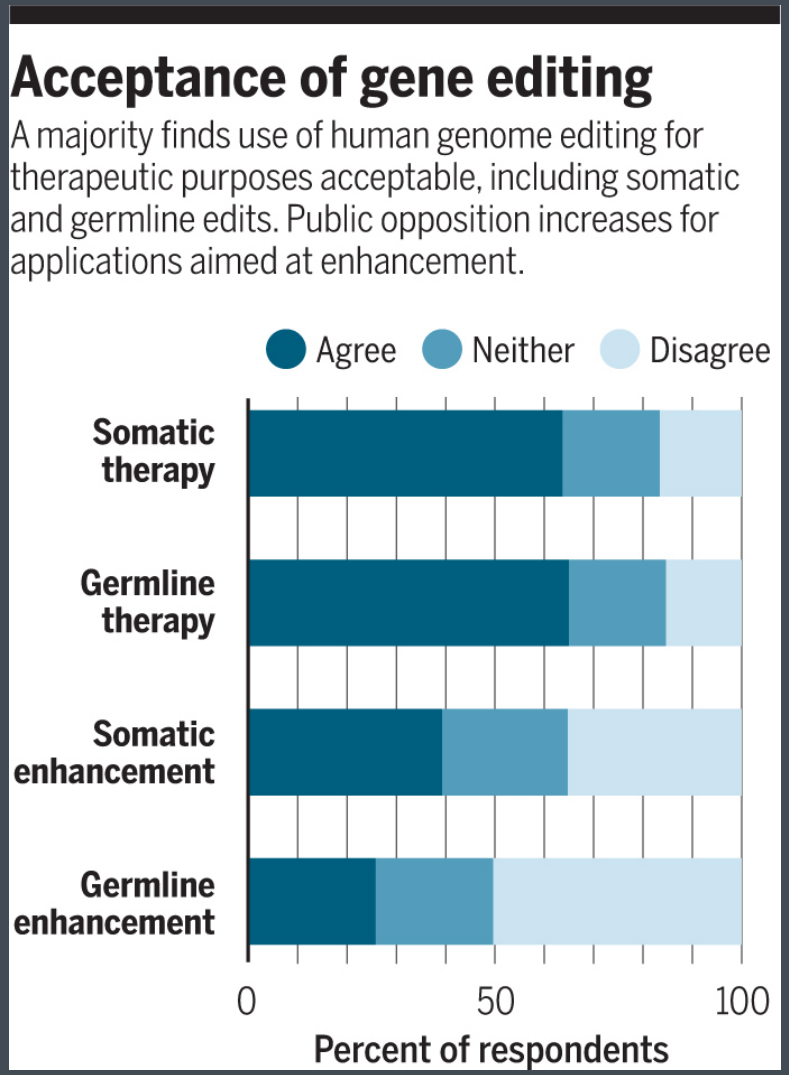
- Stanford University, used CRISPR to repair the single mutation in beta-globin gene that causes sickle cell
- Blood taken from sickle cell patients were corrected
- 30-50% of cells were repaired
- Upon injection into mice, healthy cells were able to survive in the bone marrow at least up to 16 weeks
- Autologous transplant trial requested for 2018 and on-going



https://en.wikipedia.org/wiki/Sickle-cell_disease

Ethics of human genome editing

- **Weighing benefit vs risk/harm**
- For cancer, what are the patients' alternatives, compared to their risk of trying a new non-heritable treatment?
- **Germ-line editing – will it ever become mainstream? Do we even need it?**
- Disease vs enhancement

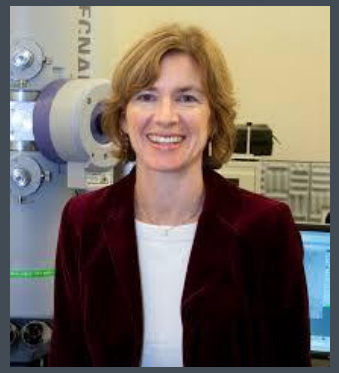


From Science: U.S. attitudes on human genome editing

https://science.sciencemag.org/content/357/6351/553/tab-figures-data

Commercialization of genome editing technologies

- UC Berkeley vs MIT BROAD

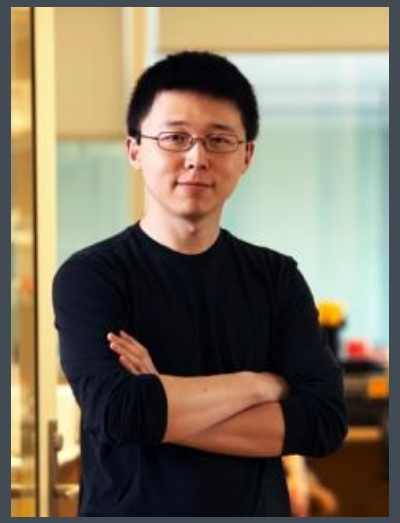


Intellia THERAPEUTICS

Already IPO

CRISPR THERAPEUTICS

Already IPO



editas MEDICINE

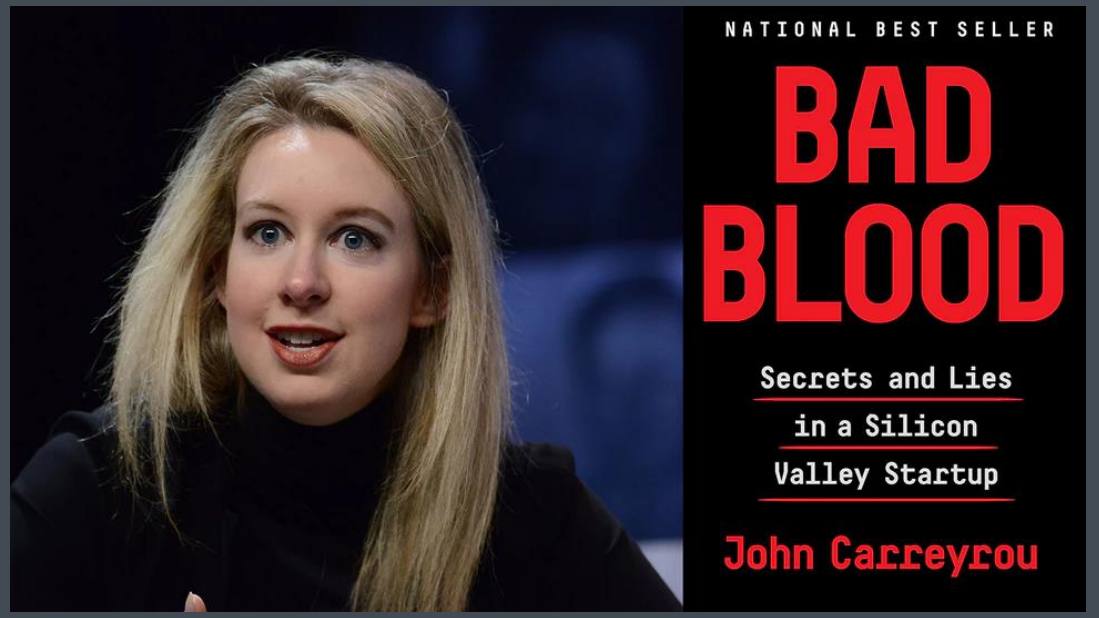
Already IPO

CARIBOU BIOSCIENCES™

Lots of intellectual property lawsuits…

Commercialization of genome editing technologies

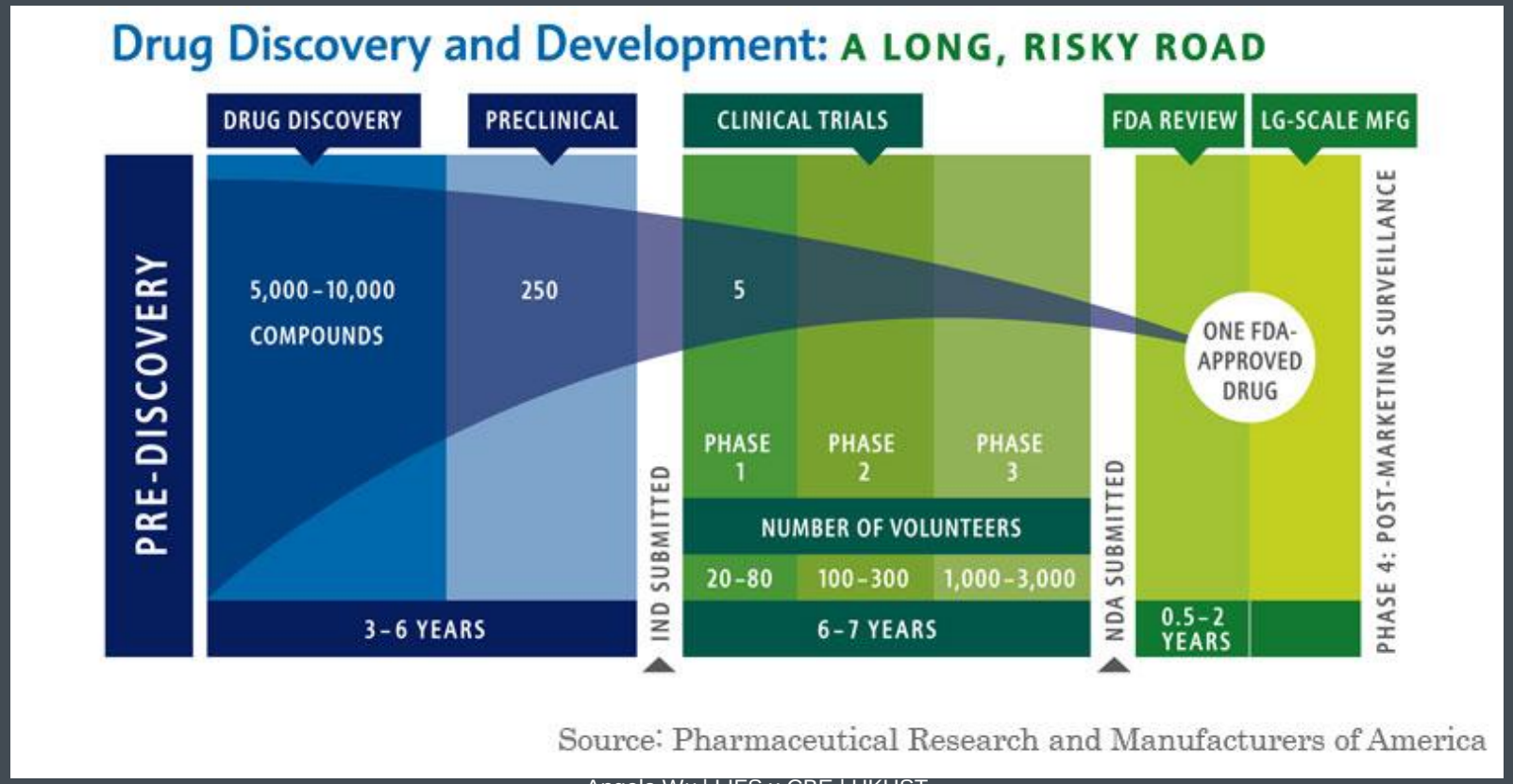
- **SAFETY: In the USA, FDA trials for a new therapeutic can up to take 10-20 years!**
- Biotech entrepreneurship is fundamentally different from other tech!!!
  - Longer timelines, much higher cost



A lack of recognition of the unique challenges and requirements and stakes/risks in medical therapeutics entrepreneurship can lead to big problems in terms of expectations on outcomes and returns, and result in ethical disasters (e.g. Theranos)

Commercialization of genome editing technologies

Although new pathways are being explored by the FDA for life-saving therapies that may take less time, it is nonetheless a long development cycle



Commercialization of genome editing technologies

	Software Startup	Medical Therapeutics Startup
Typical first VC raise	1 million to 10 million HKD	20 million to 100 million HKD
Timeline for milestones and product deliverables	Months to 1-2 years for launcheable product	1-2 years for first milestone (e.g. animal safety, non-human safety studies); could be 10 years for complete clinical trials and sales
Talent/Personnel	Can be young freshly graduated professionals (typical CEO/CTO/CSO age: 20-30 y.o.)	Needs at least 1-2 experts in medicine/science with deep experience (typical CEO/CTO/CSO age: ~40 y.o.)

Examples comparing biotech and tech

*Dollar amounts here are USD

BIOTECH

CRISPR Therapeutics
(200 Sidney St.)
VENTURE FUNDING: $154 million
PARTNERING CASH: $75 million
IPO SIZE: Unknown

$590 million at IPO

Series A: 25 million

Editas Medicine (300 Third St.)
VENTURE FUNDING: $163 million
PARTNERING CASH: $25 million
IPO SIZE: $94 million

Series A: $43 million

Intellia Therapeutics
(130 Brookline St.)
VENTURE FUNDING: $85 million
PARTNERING CASH: $94 million
IPO SIZE: $108 million

Series A: $15 million

TECH/E-COMMERCE

Whatsapp

Seed round: $250k
Series A: $8 million

Dropbox

Seed round: $15k
Series A: $6 million

Gogovan

Seed round: $41.3k
Series A: $6.5 million

15 July 2019

https://www.statnews.com/2016/05/12/crispr-therapeutics/

Summary

- **Extreme positions** that reject or accept new technology that has potential to change our lives are dangerous
- **Exchange of thoughts** between different roles in society is important to reach well-informed policy making: **scientists, physicians, law-makers, and advocates.**
- Ethics could be specific to different cultures, and could even require **multi-national discussions/cooperation**
- What we know about safety, and **what is ethically acceptable may evolve** over time. This doesn't mean it is OK to rush.

- **Be open-minded to new technologies**
- **Use evidence and critical thinking**
- **Consult key stakeholders and be collaborative**

<u>Your thoughts:</u> Has this talk changed your mind about genome editing and whether it should be acceptable?

Thank you

Happy to take questions!

What are the ethical questions?

- Is it ethical to privatize genome editing for reduction of disease?
  - Perpetuation of wealth gap; loss of empathy; informing policy
- Is it ethical to perform genome editing for non-therapeutic purposes?
  - For cosmetic, performance purposes? Can people who are not enhanced compete with those who are? Should govt pay?
- Is it ethical to risk the life of the fetus by performing genome editing in utero (which has a non-zero risk)?
  - Alternative could be baby survives but with some “undesirable” trait
- Is it ethical to edit the human germ line to cure genetically inherited diseases?
  - In the situation that it is known parents have chance to pass down some genetic disease
- Is it ethical for parents to make the decision for the unborn baby to perform genome editing?
- Is it ethical to use gene editing to eliminate genetic diversity?
  - How is diversity defined, vs. disability/disease?
- Is it ethical to approve a risky policy related to public health?
  - Because there are still unknown risks to genome editing
- What is the ethically acceptable risk for performing genome editing?
  - Weighing risk and benefit in specific context/diseases
- Is it ethical to perform genetic screening?
- Is it ethical to eliminate harmful species in the environment for the benefit of humans?
  - E.g. insects, super bacteria. Selection by human or nature? “Playing God” for the ecosystem
- Is it ethical to create chimeras for non-therapeutic use?
- Is it ethical to create chimeras for therapeutic use?

The twins with edited genomes:

NIH Dept. of Bioethics: Exploring Bioethics, https://science.education.nih.gov/supplements/nih9/bioethics/guide/introduction.html

The facts

- CCR5-delta32 is a mutation found in a small population of Caucasians that, when homozygous, makes the carrier immune to HIV infection
  - The heterozygous mutation seems to have no such protective effect
  - CCR5 is a surface co-receptor that some strains of HIV (and also smallpox) uses to enter the CD4 T-cell
  - CXCR4 is another surface receptor used by some strains of HIV to enter the cell; There have been cases of homozygous CCR5-delta32 carriers being infected with HIV
  - This mutation is not found in individuals of other ethnicities, such as Asian or African
  - Other mutations of CCR5 have been found in some other populations (e.g. CCR5-m303) to be associated with HIV-resistance, but they are not prevalent and very few of these examples have been discovered so far
  - This mutation results in severe response to influenze (death), and increased risk of West Nile virus infection

The facts

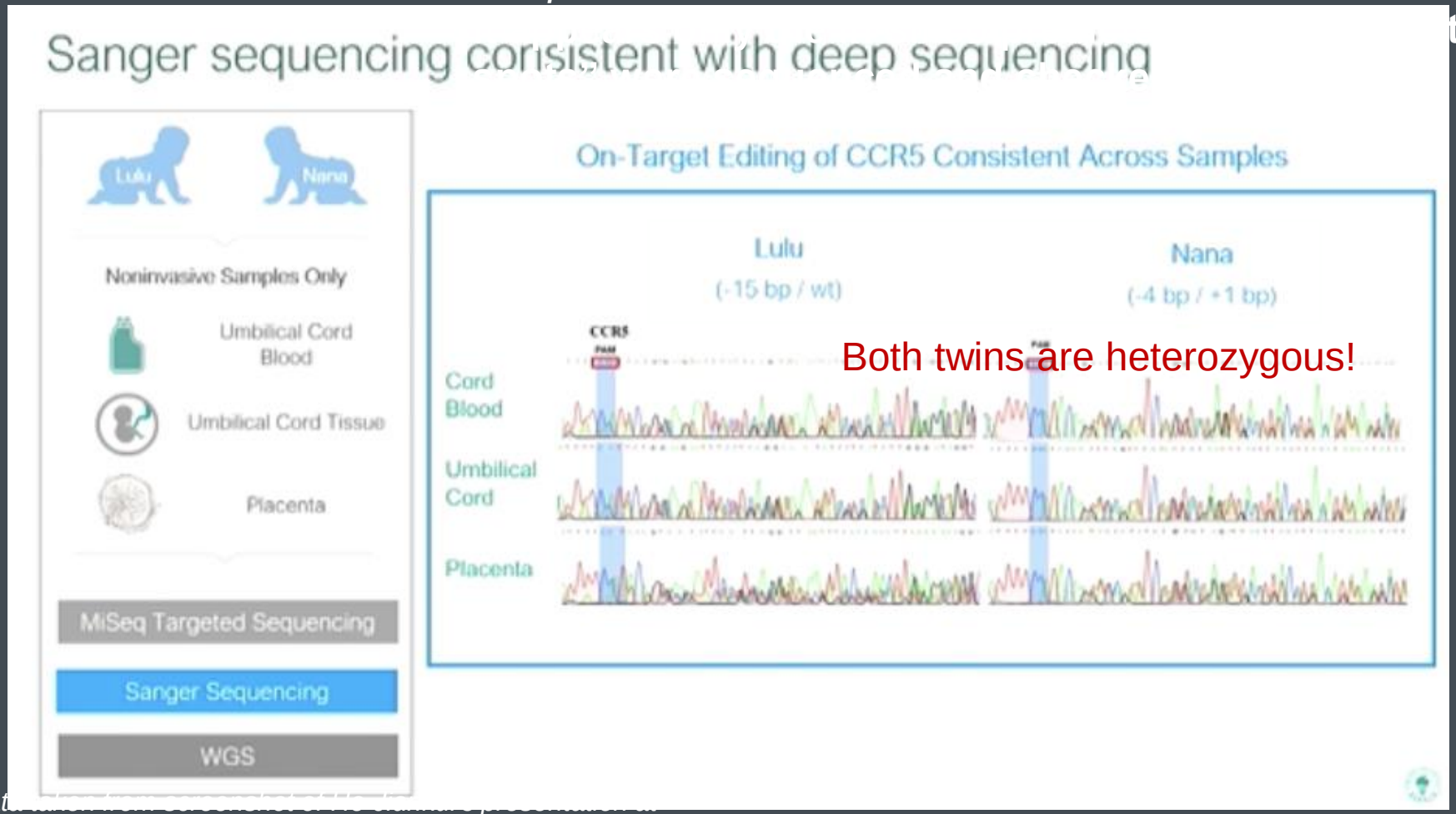
- There are other solutions for mixed HIV status couples who wish to conceive, such as ART, retroviral drug prophylaxis
- The risks of genome editing using CRISPR are not well understood
  - The extent and outcomes of CRISPR off-target effects are still being investigated
  - There is no good way to evaluate efficacy in the embryo and degree of mosaicism
  - Other unintended consequences are complete unknown!
- Which medical problems can only be addressed by germline editing? Which can be addressed by somatic editing?
  - Editing CCR5-delta32 could be accomplished by somatic HSC editing
- It is illegal for HIV-positive individuals to use ART in China
- The patients were informed of the procedures that they would undergo, and were told there are risks

The facts

- The approach for editing CCR5 was tested in cell lines, mice, and monkeys before performing in human
  - Tested efficiency of CRISPR system in cell lines and embryos (highest achieved in human embryos was ~50%, with sample sizes less than 30. In animals, highest was ~80% CCR5-null; some were mosaic; efficacy varied greatly depending on parent; sample sizes were usually less than 10)
  - Checking hESC for totipotency
  - Sequencing of edited animals to check for off-target
- In human embryos, efficiency and off-target effects were assessed:
  - Algorithm was used to predict CRISPR off-target sites *in-silico*, and targeted sequencing was performed to screen out mutated embryos and to ascertain no mutations in those sites for implanted embryos
  - Used embryos to establish hESC cell line, and assessed off-target by WGS in cell line – found a new indel, but couldn't confirm source because parental genomes were not available for comparison!
- None of the prior work was peer-reviewed/published

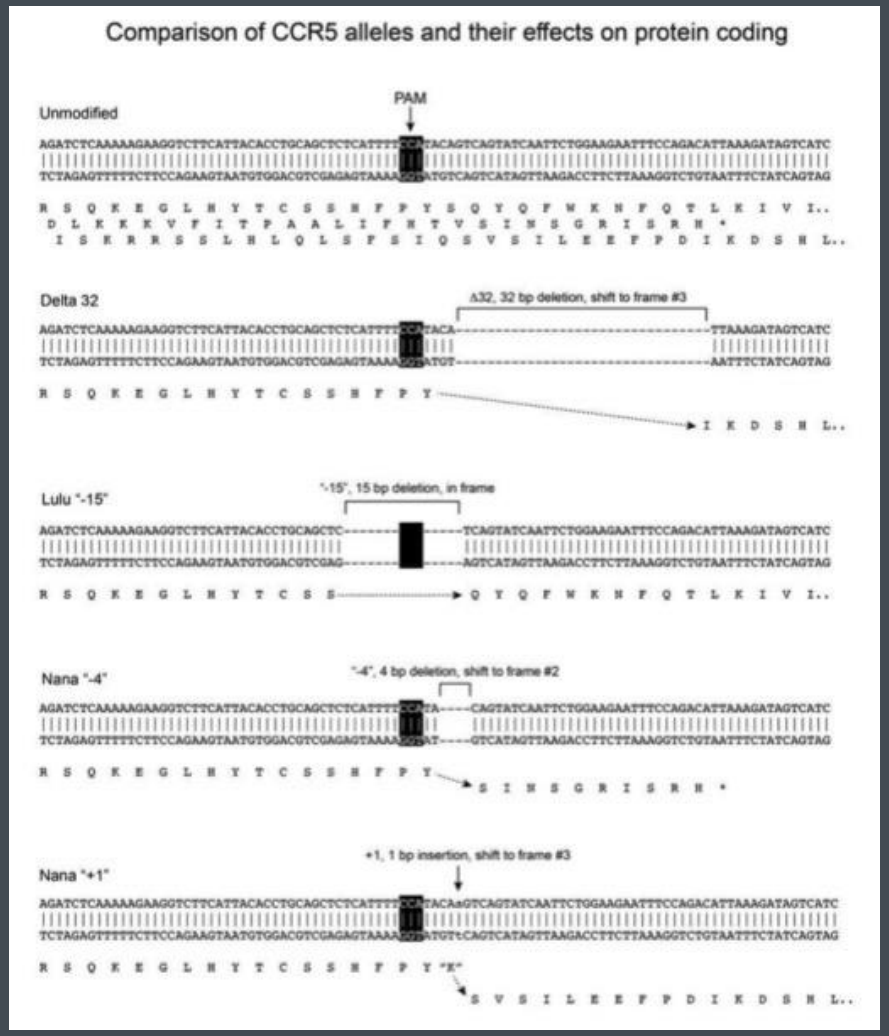
The facts

"Previously observed intergenic off-target in Lulu's PGD trophoblast samples was not observed in cord blood or placenta"
"No off-targets observed in Cord Blood and Placental samples"



Second International Summit on Human Genome Editing (Hong Kong)

The facts



Lulu (-15 bp/wt):

- one allele has a 15bp deletion upstream of the classic delta32 mutation
- the other allele is wild-type (i.e. no change to the CCR5 gene)

Nana (-4 bp/ +1 bp):

- One allele has a 4bp deletion that slightly overlaps with delta-32 region
- Other allele has a frame-shift insertion

We don't know if these have any protective effect against HIV

Figure taken from K. Zimmer, "CRISPR Scientists Slam Methods Used on Gene-Edited Babies", The Scientist, 2018

The stakeholders

- Parents
- Lulu and Nana
- Lulu and Nana’s future children, potentially
- Implications for public health – both practically and in regulatory contexts
- He and his team of researchers – also, who recruited the patients?
- The hospital where this took place – forgery? Blame game? What is the role of IRB?
- The University where this took place
- The government – U.S.-China relations? Blame game?
- Other genome editing researchers (remember Gelsinger?)

The stakeholders

- Were parents fully informed? Could they ever be sufficiently informed? How could the researchers have done better?

The stakeholders

- Were conflicts of interest clearly disclosed?
- Who recruited the patients and how? Were they qualified to recruit and inform patients?
- Was the ethics approval compliant with the Nuremberg Code?

The Nuremberg Code

1. Required is the voluntary, well-informed, understanding consent of the human subject in a full legal capacity.
2. The experiment should aim at positive results for society that cannot be procured in some other way.
3. It should be based on previous knowledge (like, an expectation derived from animal experiments) that justifies the experiment.
4. The experiment should be set up in a way that avoids unnecessary physical and mental suffering and injuries.
5. It should not be conducted when there is any reason to believe that it implies a risk of death or disabling injury.
6. The risks of the experiment should be in proportion to (that is, not exceed) the expected humanitarian benefits.
7. Preparations and facilities must be provided that adequately protect the subjects against the experiment's risks.
8. The staff who conduct or take part in the experiment must be fully trained and scientifically qualified.
9. The human subjects must be free to immediately quit the experiment at any point when they feel physically or mentally unable to go on.
10. Likewise, the medical staff must stop the experiment at any point when they observe that continuation would be dangerous.

Some ethical questions in this case

- Was it ethical to perform genome editing on humans, given what we know about the technology?
- Was it acceptable to use germline genome editing for mutating CCR5 with the aim of preventing HIV infection?
- Agree or disagree: This research is ethically acceptable today because the risks of genome editing will be eventually resolved/minimized, and human genome editing one day become routine/accepted
- Agree or disagree: The research is ethically acceptable because the patients have consented
- What responsibility do researchers, scientists, or clinicians have in terms of informing patients and/or making decisions on their behalf surrounding trials that involve very new technology?
- How should governments regulate genome editing in humans?

Example: Is it ethical for parents to modify genome of their unborn baby?

- Ethical perspectives:
  - Autonomy – who makes the decision? How do you consider the autonomy of the future child/generations? Age of consent?
  - Fairness – cost of procedure, underprivileged without resources
  - Benefit/harm? What is the benefit? Therapeutic vs non-therapeutic? Risk (technical risk)? Unintended consequences of editing/changing the genome
  - Disagreement between the stakeholders – how do you resolve?
    - Potentially irreversible; different from other decisions made by parents
- Stakeholders: parents; child; pharma companies; hospitals; future unborn generations; society; US - payers

Consequences

- Moratorium on CRISPR genome editing: https://www.forbes.com/sites/greglicholai/2019/03/14/call-for-crispr-moratorium-echoes-early-days-of-gene-therapy/
- https://www.nature.com/magazine-assets/d41586-019-00726-5/d41586-019-00726-5.pdf

COMMENT · 13 MARCH 2019

Adopt a moratorium on heritable genome editing

Eric Lander, Françoise Baylis, Feng Zhang, Emmanuelle Charpentier, Paul Berg and specialists from seven countries call for an international governance framework.

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Excerpts from the article:

We call for a global moratorium on all clinical uses of human germline editing — that is, changing heritable DNA (in sperm, eggs or embryos) to make genetically modified children.

By 'global moratorium', we do not mean a permanent ban. Rather, we call for the establishment of an international framework in which nations, while retaining the right to make their own decisions, voluntarily commit to not approve any use of clinical germline editing unless certain conditions are met.

To be clear, our proposed moratorium does not apply to germline editing for research uses, provided that these studies do not involve the transfer of an embryo to a person's uterus. It also does not apply to genome editing in human somatic (non-reproductive) cells to treat diseases, for which patients can provide informed consent and the DNA modifications are not heritable.

We recognize that a moratorium is not without cost. Although each nation might decide to proceed with any particular application, the obligation to explain to the world why it thinks its decision is appropriate will take time and effort.

Certainly, the framework we are calling for will place major speed bumps in front of the most adventurous plans to re-engineer the human species. But the risks of the alternative — which include harming patients and eroding public trust — are much worse. ■

Consequences

Early January - He Jiankui appears to be under heavy guard at his home

The New York Times

Chinese Scientist Who Claimed to Make Genetically Edited Babies Is Kept Under Guard

He Jiankui, the scientist who says he created the world's first genetically edited babies, on an apartment balcony in Shenzhen, China. A colleague confirmed his identity when shown video. Elsie Chen

https://www.nytimes.com/2018/12/28/world/asia/he-jiankui-china-scientist-gene-editing.html

Consequences

Late January - He Jiankui is fired

In the Focus

Southern University of Science and Technology Public Statement

Jan 21, 2019 Latest News

The Guangdong Province Investigation Task Force has completed a preliminary investigation of the gene-edited baby incident. Based on the conclusion of the task force and after deliberation, Southern University of Science and Technology (SUSTech) hereby makes the following statement:

Effective immediately, SUSTech will rescind the work contract with Dr. Jiankui He and terminate any of his teaching and research activities at SUSTech.

http://sustc.edu.cn/en/info_focus/3056