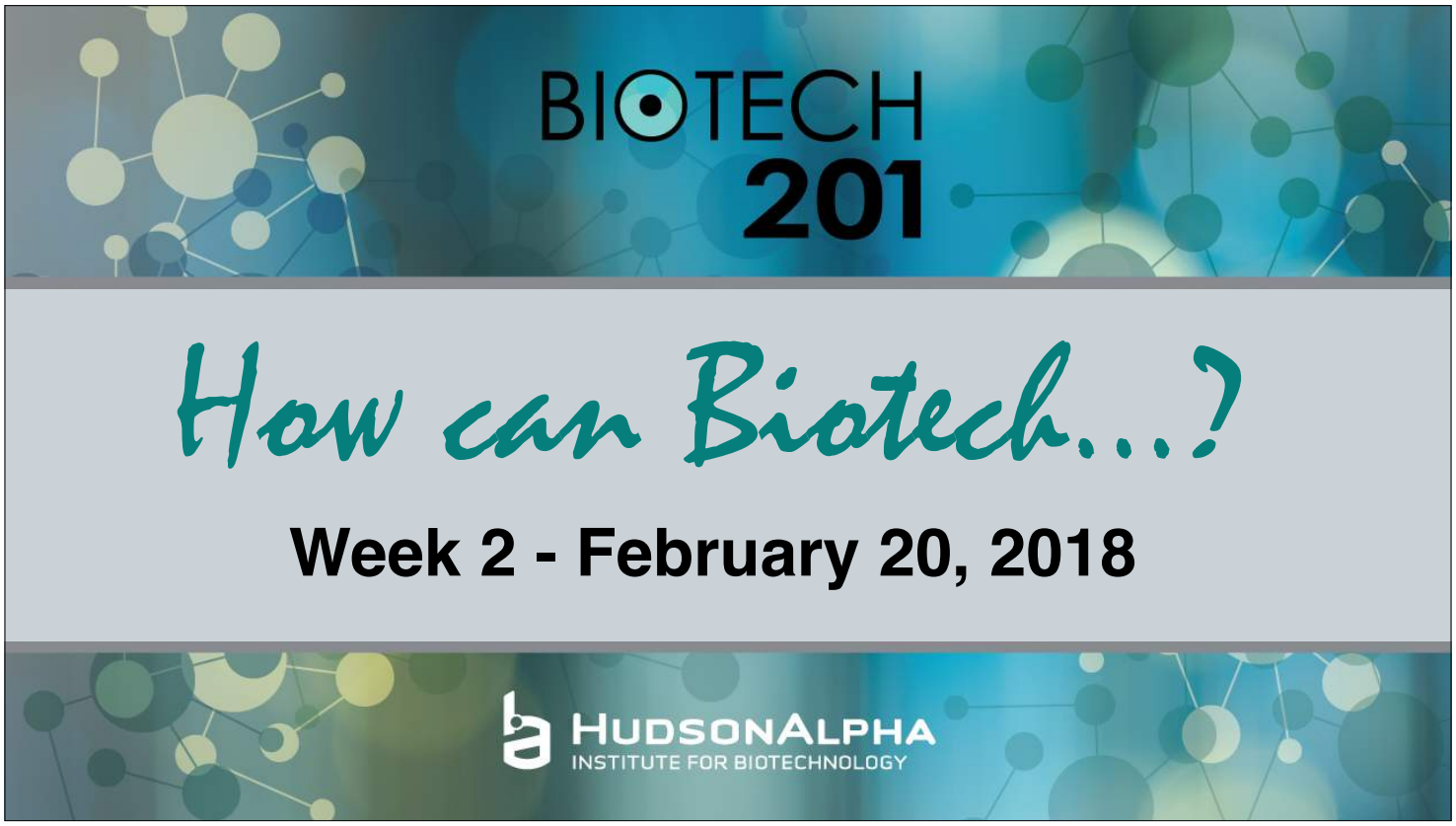


How can Biotech...

change my DNA?

How can Biotech...change my DNA?

Gene Therapy

transfer of additional DNA or RNA into a target tissue to correct/restore the function of a protein

Gene Editing

correcting the existing DNA mutation using a combination of molecular scissors and a repair template

How can Biotech...change my DNA?

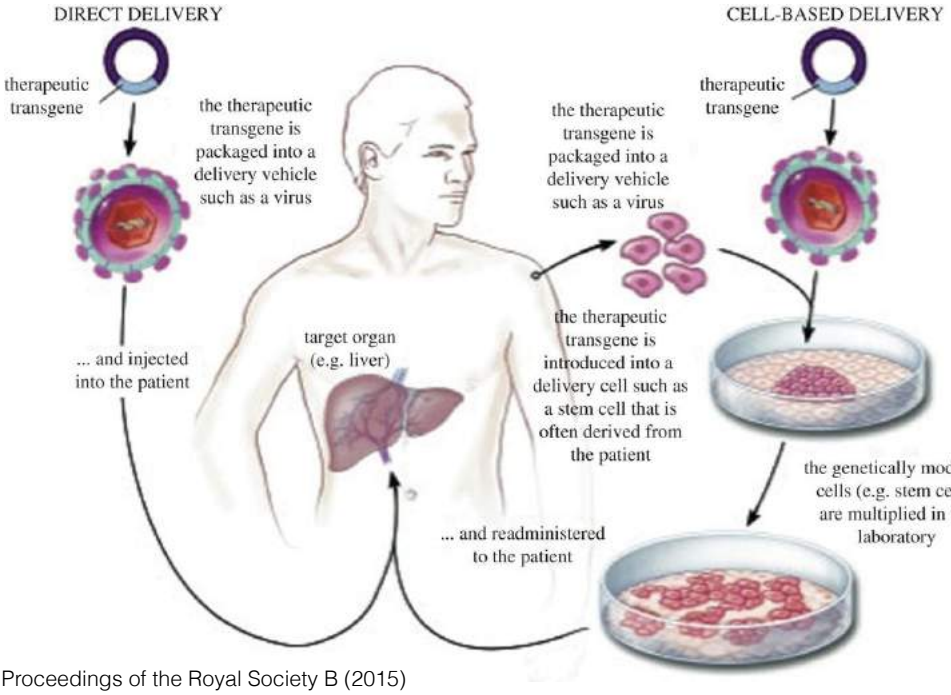
Gene Therapy

transfer of additional DNA or RNA into a target tissue to correct/restore the function of a protein

- *the right piece of genetic information*
- *in the right cells*
- *that follows typical activation/silencing signals*
- *maintains activity over time*
- *without disrupting other genes*
- *without overwhelming the immune system*

Gene Therapy - 2 categories

***In vivo* - direct introduction of the DNA into the patient**

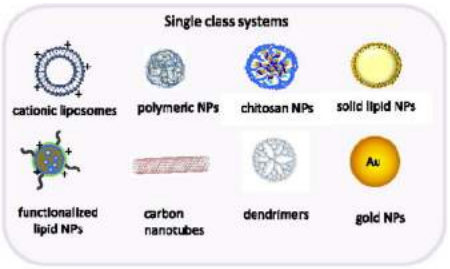


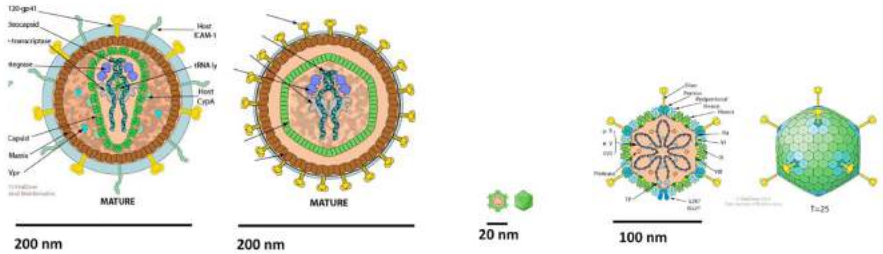
Ex *vivo* - patient's cells removed from the body, DNA is incorporated, and the cells are transplanted back to the patient

Collins and Thrasher, Proceedings of the Royal Society B (2015)

how the DNA is packaged

- **non-viral**
  - **naked plasmids**
  - **liposomes**
- **viral** — *most viral genes are replaced with the therapeutic DNA*
  - **integrating**
    - **Lenti**
    - **Retro**
  - **non-integrating**
    - **AAV**
    - **Adeno**





Korpisalo, Integrative Biology (2010); Foldavari, Journal of Controlled Release (2016); Dang et al. Experimental Eye Research (2017)

Gene Therapy Challenges

Gene delivery & activation

- getting the gene to the right cells
- activating the gene correctly

Avoiding immune response

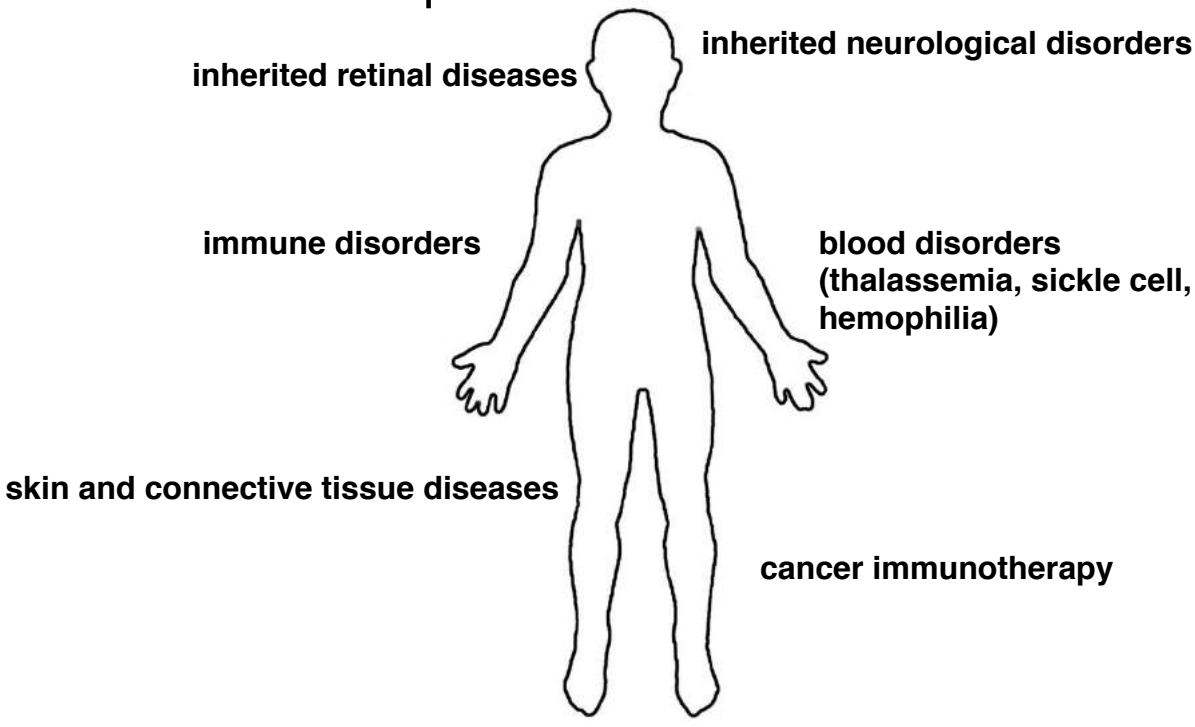
- viral vectors trigger an immune reaction

Long term integration/activity

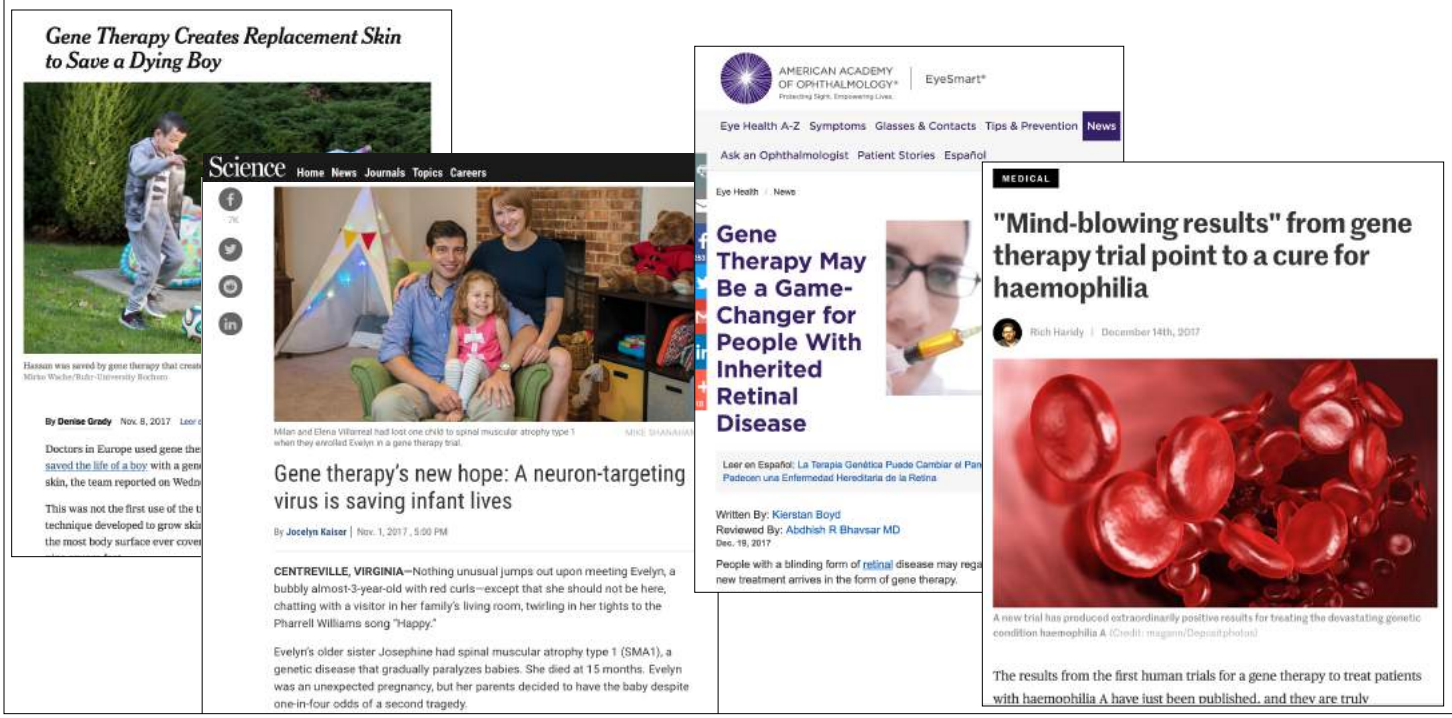
- maintaining gene activity over time
- integrating into the genome without disrupting other genes

Economics and Access

Gene Therapy Successes



Gene Therapy Successes



How can Biotech...change my DNA?

Gene Therapy

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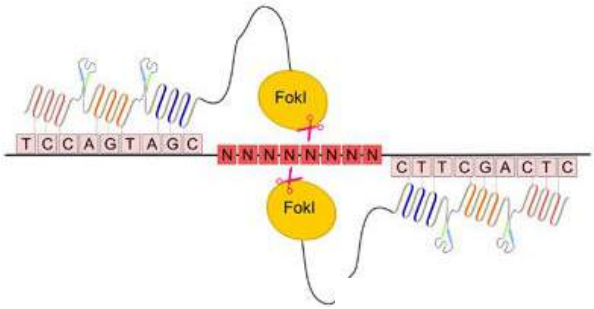
Gene Editing

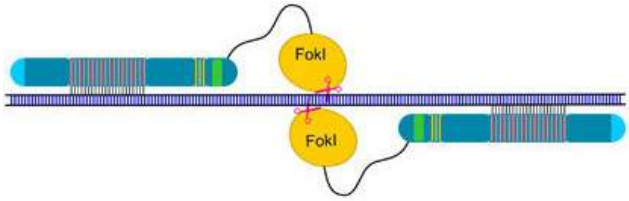
correcting the existing DNA mutation using a combination of molecular scissors and a repair template

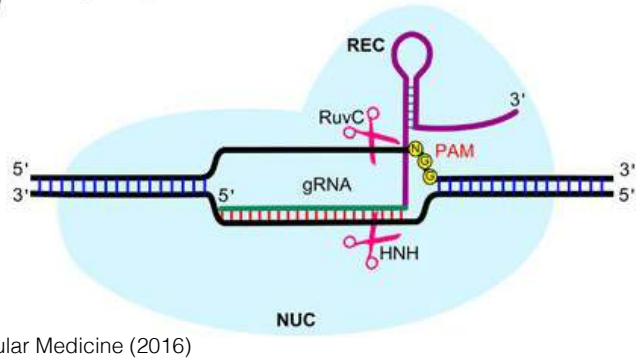
Gene Editing - various molecular scissors

zinc finger nuclease



transcription activator-like effector nuclease



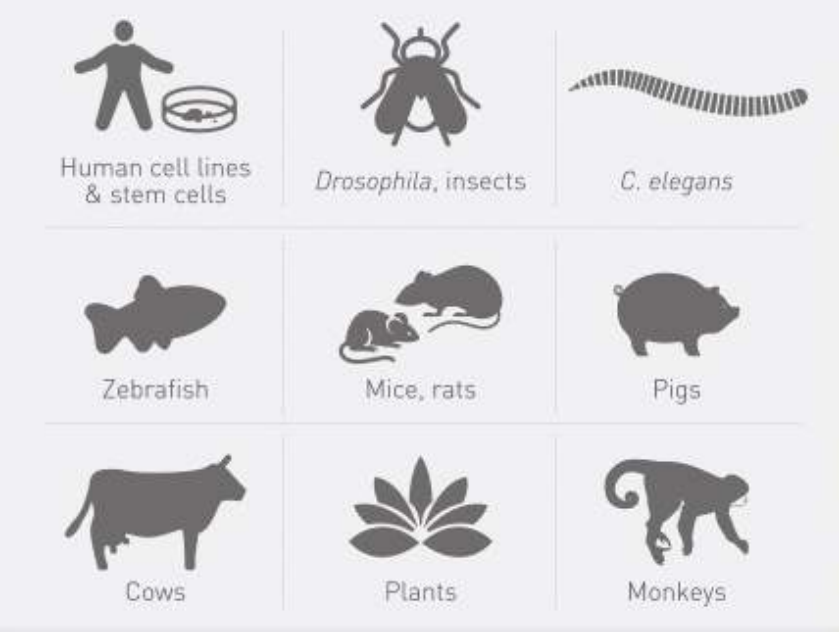


clustered regularly interspaced palindromic repeats (CRISPR) + CRISPR associated protein 9 (Cas9)

Eid and Mahfouz, Experimental and Molecular Medicine (2016)

Gene Editing - CRISPR-Cas9

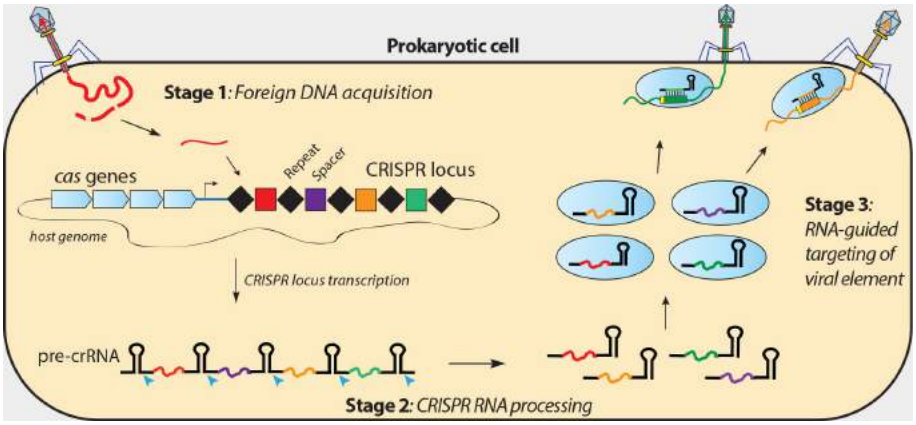
- easier/cheaper to develop than other molecular scissors
- successful across a number of species
- Applications:
  - identify function of genes
  - animal models of human disease
  - agriculturally important modifications
  - disease therapy



ThermoFisher

CRISPR-Cas origins in bacterial immunity

1. when bacteria are infected by viruses, they incorporate a tiny piece of the viral DNA into their genome as a record of the infection.

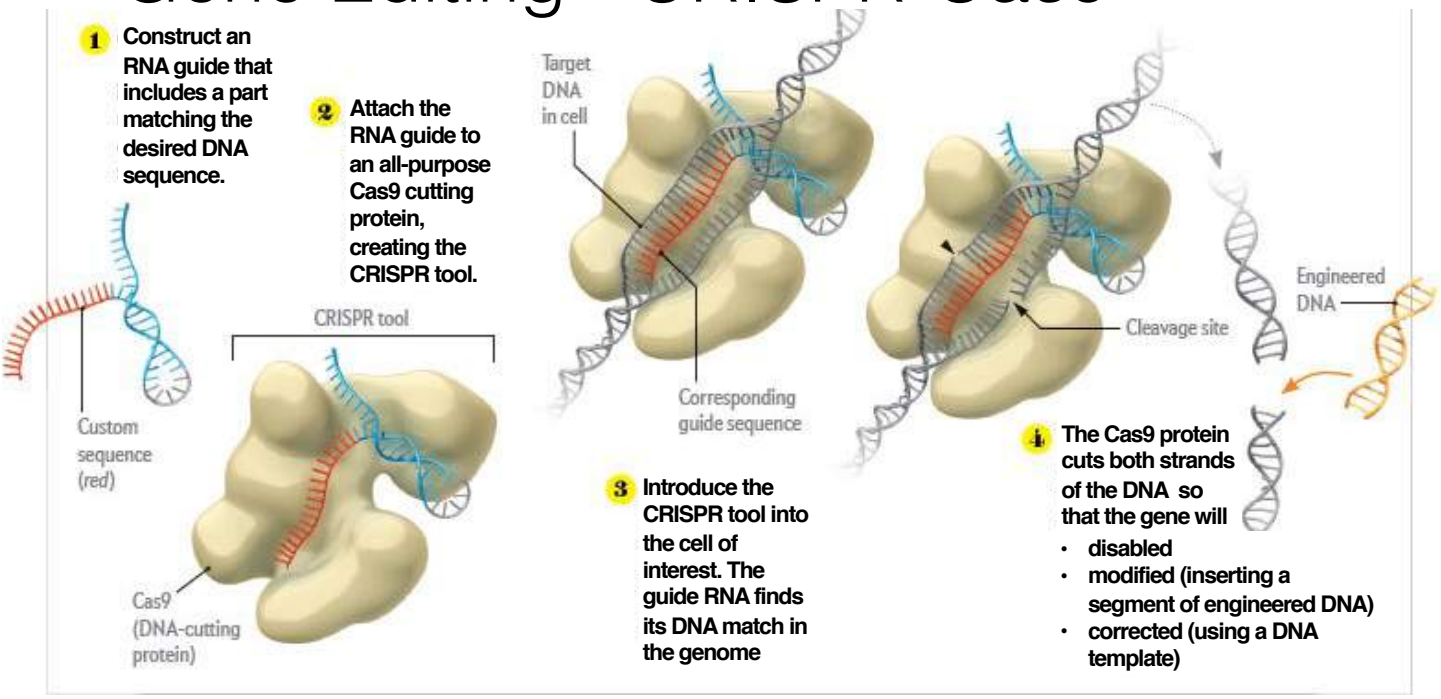


2. these pieces of DNA are copied into small RNA fragments that associate with the Cas protein

3. if the bacteria is infected with the same type of virus as before, the RNA/Cas complex detects, targets and destroys the viral DNA

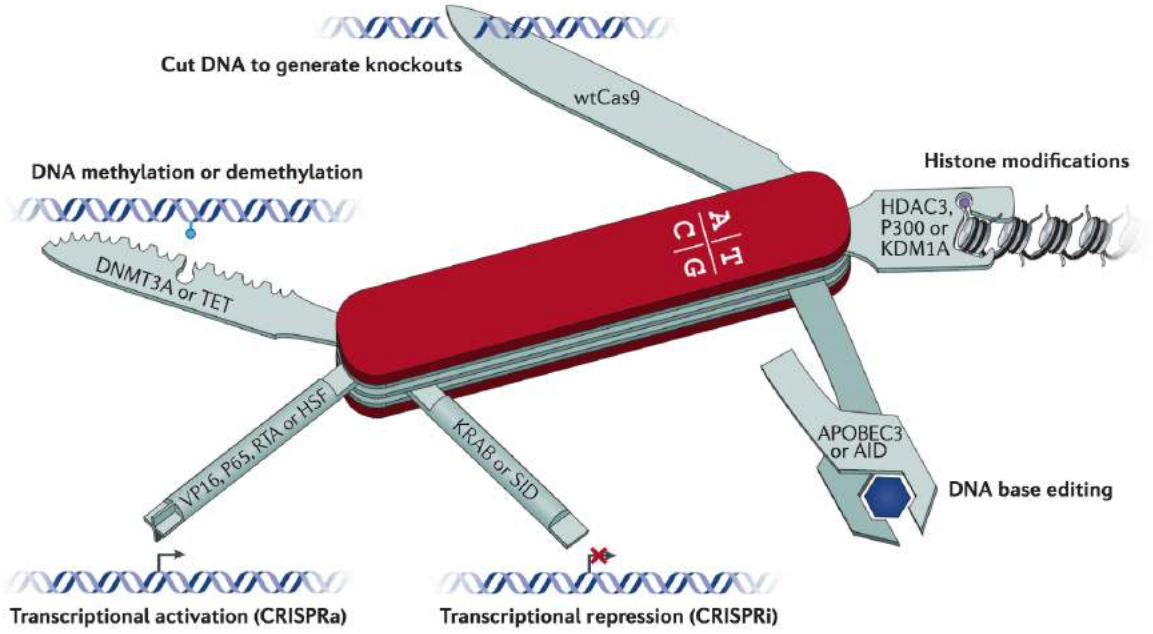
The Doudna Lab http://rna.berkeley.edu/crispr.html

Gene Editing - CRISPR-Cas9



Knox, Scientific American (2014)

Gene Editing - CRISPR-Cas9



Doench, Nature Genetics (2018)

CRISPR - Therapeutic potential

repairing genetic defects

work in animal models & human cells has corrected genetic mutations associated with:

- cataracts
- hearing loss
- duchenne muscular dystrophy
- beta-thalassemia
- hemophilia
- fanconi anemia
- sickle cell anemia
- cystic fibrosis

treating cancer

first U.S. human CRISPR clinical trials (starting this year) will treat pts. with myeloma, sarcoma & melanoma who are unresponsive to existing therapies

treating viral infections

- mimic naturally occurring mutations that confer resistance to HIV-1
- target viral DNA for destruction - eradicates latent infection for HIV-1 and HBV

CRISPR - Hope & Hype

STAT

Newsletters | Try STAT Plus

IN THE LAB

A CRISPR trick in blind mice points the way to possible treatments for inherited diseases

By SHARON BEGLEY @sxbegle
FEBRUARY 2, 2018

genomeweb

DNA Methylation Editing Rescues Neurons in Fragile X Syndrome

Feb 15, 2018 | staff reporter

NEW YORK (GenomeWeb) – Methylation editing targeting the fragile X syndrome gene can rescue neurons affected by the condition, according to a new paper.

Fragile X syndrome, which is caused by the mutations within the FMR1 gene on the X chromosome that lead it to be silenced, is the most common genetic form of intellectual disability among boys, affecting 1 in 3,600.

In a study appearing today in *Cell*, researchers described their use of a CRISPR/Cas9-based DNA methylation editing tool to switch FMR1 back on. Within neuronal and mouse models, they

ScienceDaily

Your source for the latest research news

Science News — *from research organizations*

New CRISPR method efficiently corrects Duchenne muscular dystrophy defect in heart tissue

Date: February 6, 2018

Source: UT Southwestern Medical Center

MIT Technology Review

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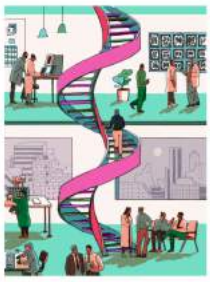
Rewriting Life

CRISPR in 2018: Coming to a Human Near You

The first clinical trials are slated to begin in the U.S. and Europe while others are stalled.

by Emily Mullin December 18, 2017



JOSH COCHRAN

No hunger.
No pollution.
No disease.

WIRED

And the end of life as we know it.

The Genesis Engine.

Editing DNA is now as easy as cut and paste. Welcome to the post-natural world.

Cell Stem Cell

Volume 21, Issue 2, 3 August 2017, Pages 153-155

CellPress

Preview

Engineering Skin with Skinny Genes

Anika Böttcher [1], Heiko Lickert [1, 2], Matthias Tschöp [3, 4]

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Refers to Jiping Yue, Xuewen Gou, Yuanyuan Li, Barton Wicksteed, Xiaoyang Wu
Engineered Epidermal Progenitor Cells Can Correct Diet-Induced Obe...
Cell Stem Cell, Volume 21, Issue 2, 3 August 2017, Pages 256-263.e4

Download PDF

The increasing prevalence of obesity and diabetes is an urgent worldwide health challenge. Now in Cell *Stem Cell*, Yue et al. (2017) report a proof-of-concept study using genetically engineered skin transplants that produce the incretin GLP-1 to prevent diet-induced obesity, suggesting a powerful

agricultural uses

nature — International weekly journal of science

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Archive > Volume 545 > Issue 7655 > News > Article

NATURE | NEWS

Fixing the tomato: CRISPR edits correct plant-breeding snafu

Geneticists harness two mutations — each cherished by breeders, but detrimental when combined — to improve on 10,000 years of tomato domestication.

Heidi Ledford

18 May 2017

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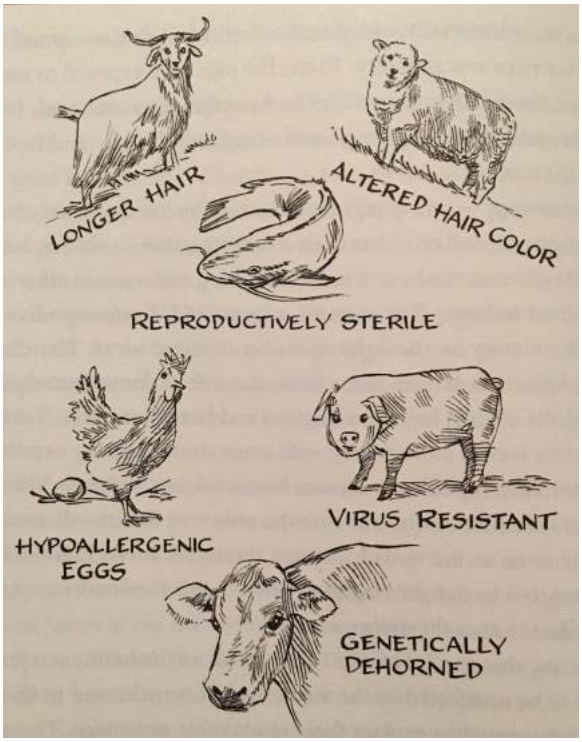


Doudna and Sternberg - A Crack in Creation (2017)

CRISPR - Limitations

- identifying optimal target sequences
- off target effects - DNA is cut at sequences that are ***nearly identical*** to the guide RNA sequence
  - reduce concentration of guide RNA:Cas9 complex
  - modify the Cas9 enzyme

    activate/silence rather than cut

    on/off switch
  - identify new classes of Cas enzymes
  - alter the structure of the guide RNA sequence
- challenge of delivering to the right cell type

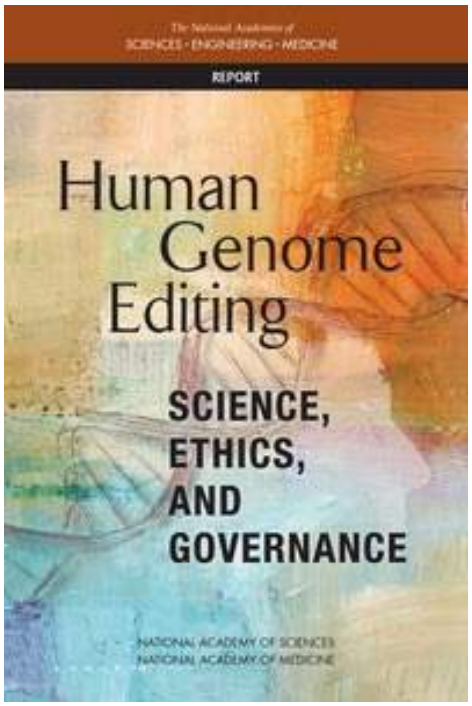
CRISPR - regulations

US National Academies of Science, Engineering and Medicine

- Feb 2017 Report - recommends permitting human germline genome editing under strict regulations/oversight to eliminate severe genetic diseases that have no other treatment options
- human enhancements not permitted

US FDA will not allow public funding for germline editing studies - but there are no outright genome editing bans

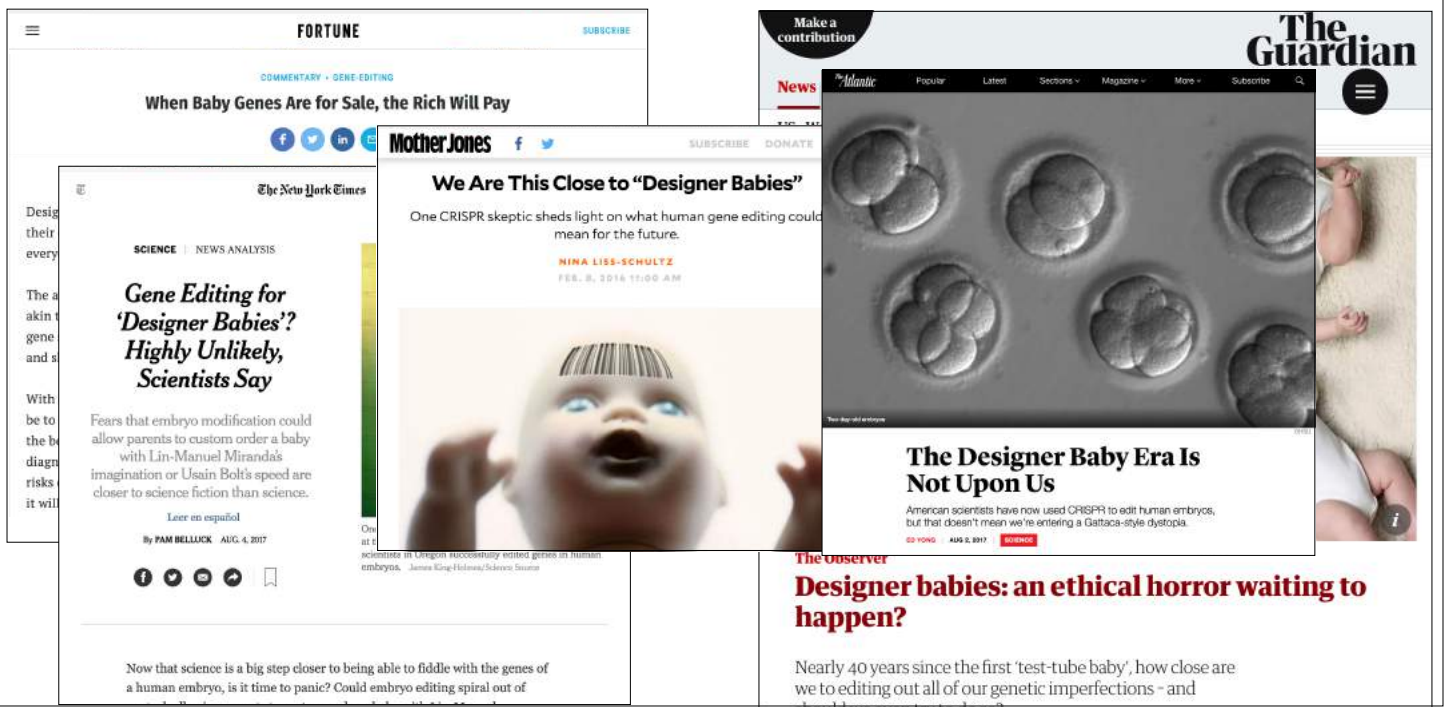
In Canada, germline editing = criminal offense



How can Biotech...

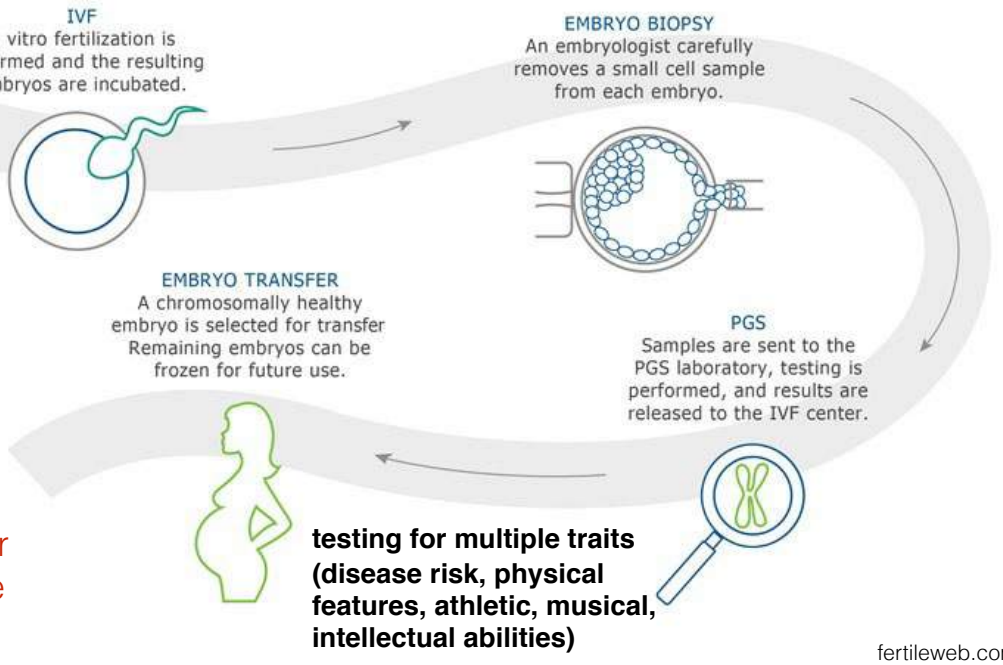
create designer babies?

Designer Babies in the popular press



How the “designer” scenario plays out

gene editing of egg & sperm or early embryos for desired traits



The Reality:

- gene editing is not ready for embryo use (and in many places, not allowed)
- knowledge of the genetic factors associated with these complex traits is not well understood and for many, won’t be feasible for selection

testing for multiple traits (disease risk, physical features, athletic, musical, intellectual abilities)

fertileweb.com

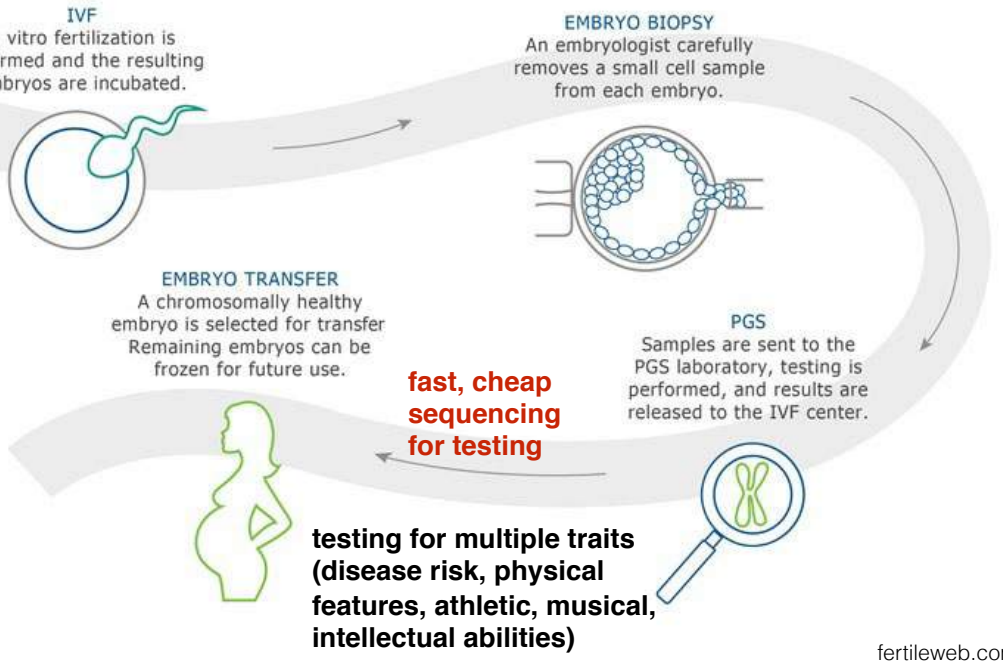
“Easy Preimplantation Genetic Diagnosis”

as explained by Henry Greeley

increase production of embryos

Need more eggs

- ovary biopsy
- grow eggs from stem cells
- convert body cells into eggs



fast, cheap sequencing for testing

testing for multiple traits (disease risk, physical features, athletic, musical, intellectual abilities)

fertileweb.com

making discretionary changes in DNA

Where will the line for approval get drawn?

Therapy — **Genetic Enhancement**

Deaf parents may prefer their offspring to be deaf too

pushy parents might want to boost their children's intelligence at all costs, even if doing so affects their personalities in other ways.

And if it becomes possible to tweak genes to make children smarter, should that option really be limited to the rich?

The Economist - "Editing Humanity" 8/22/2015

Next Week

Feb 13 solve a crime?
store information in DNA?

Feb 20 change my DNA?
create "designer babies"?

Feb 27 help me lose weight?
predict my death?

March 6 help us reach and colonize Mars?