CRISPR and Gene Editing: One tool to rule them all…

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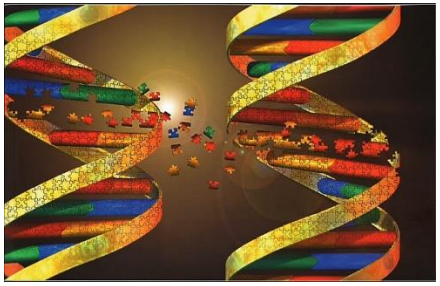
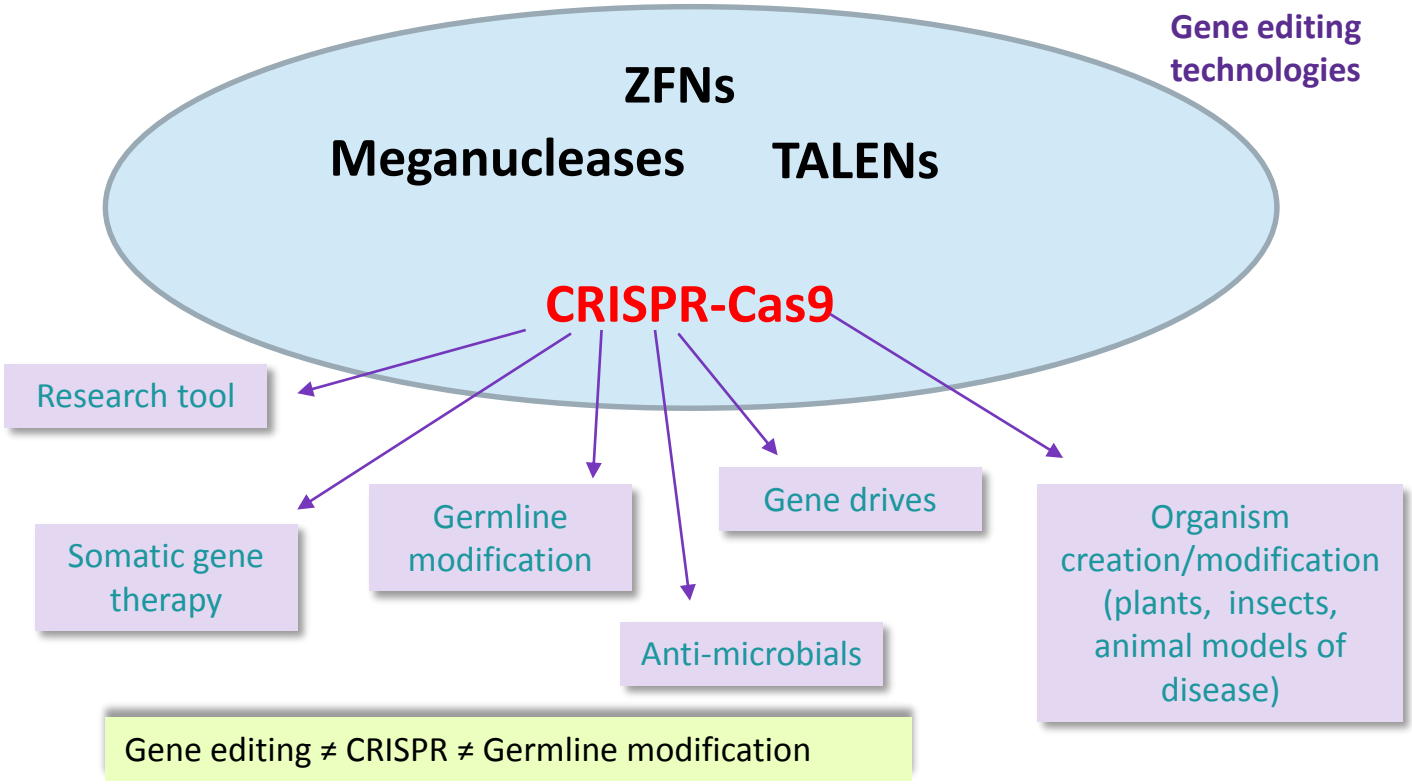
Associate Director for Science Policy
National Institutes of Health

Gene and genome editing is not new…

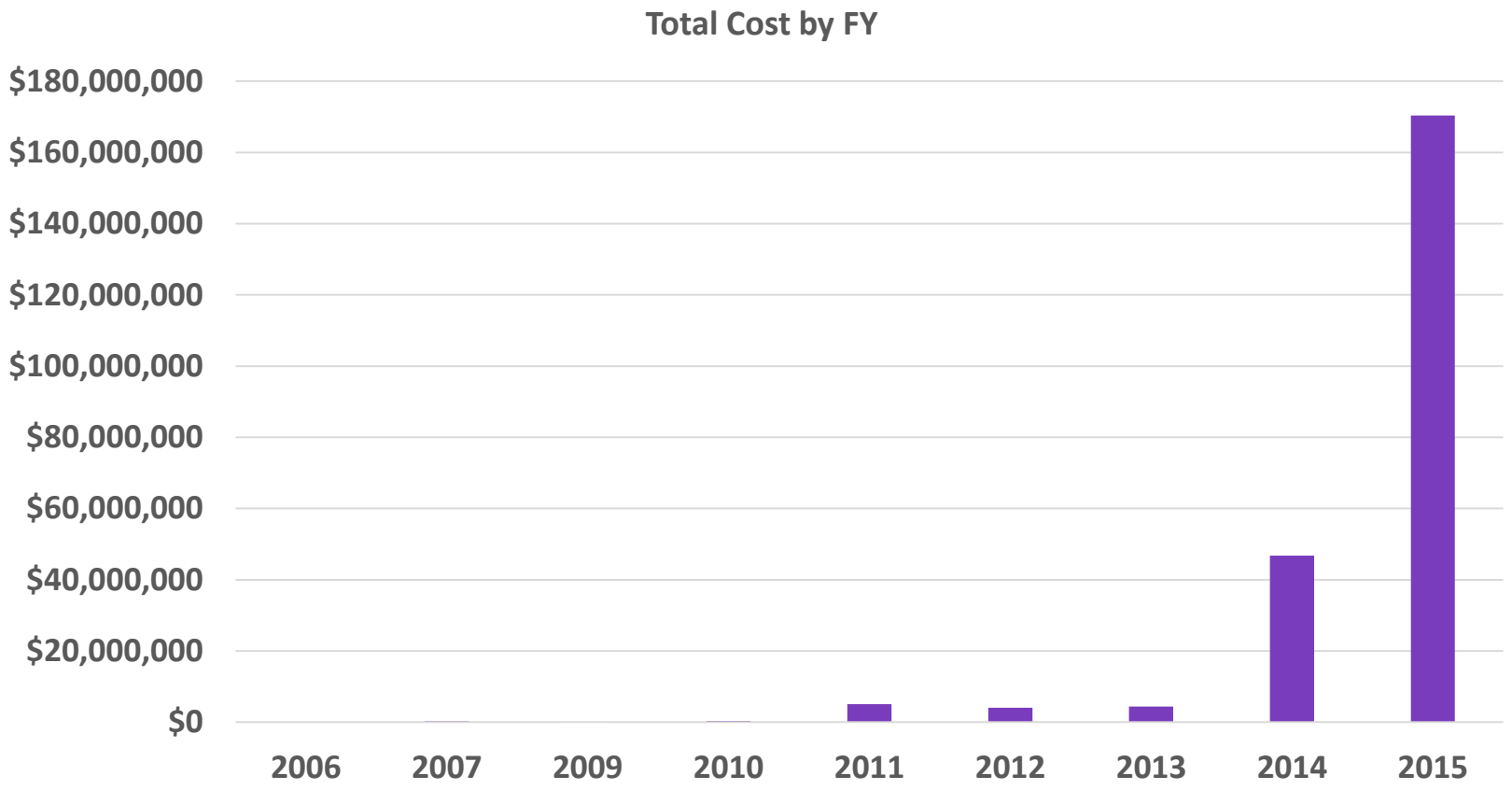
- Adding, subtracting, or replacing DNA
- Examples of older technologies:
  - Zinc finger nucleases (1991)
  - TALEN (2009)
- Latest kid on the block:
  - Clustered regularly interspersed palindromic repeats (CRISPR)
  - Naturally occurring bacterial immune defense
  - CRISPR-Cas9: One form of this system which can be used to more precisely target and edit DNA



Important semantics



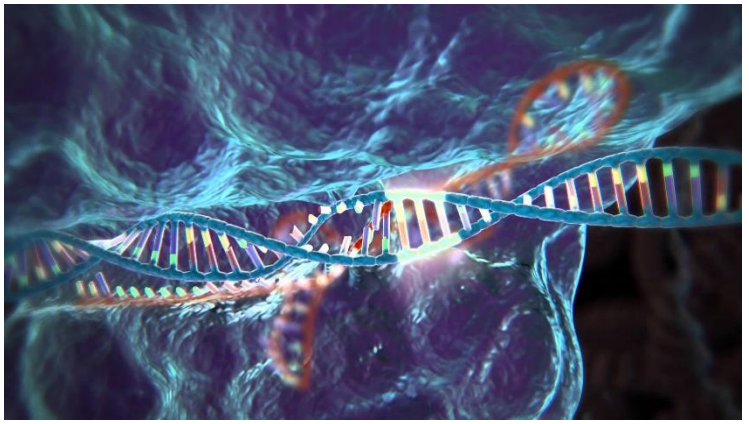
NIH Funding for Research Involving CRISPR/Cas9



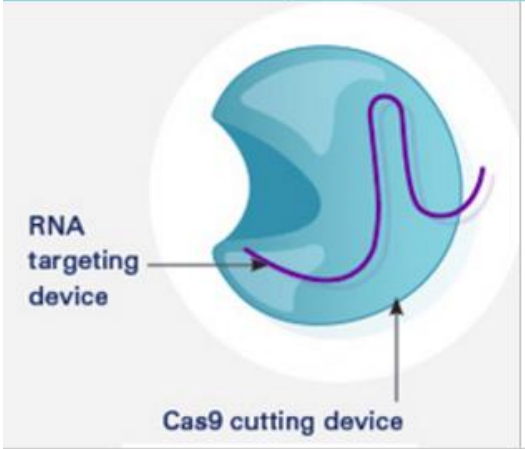
Total funding for projects identified as involving CRISPR by NIH RePorter

One tool, many uses…

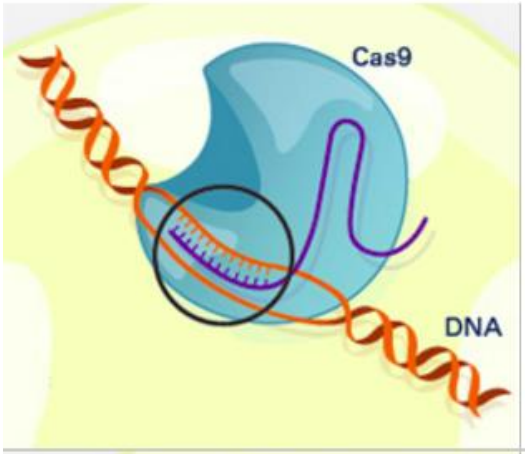
- Why the fuss?
  - Ease and precision of technology makes feasible experiments too difficult to conduct using older techniques
  - Multiple simultaneous changes
- Applications of CRISPR-Cas:
  - Research
  - Clinical applications
  - Human gene therapy
  - **Germline modification**
  - **Gene drives**



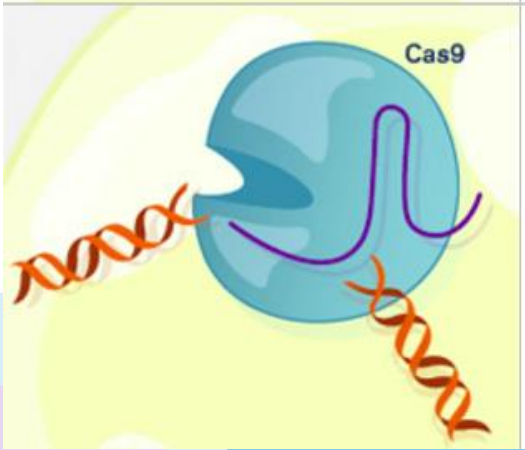
How the CRISPR System Works



The CRISPR system has two components joined together: a finely tuned targeting device (a small strand of RNA programmed to look for a specific DNA sequence) and a strong cutting device (an enzyme called Cas9 that can cut through a double strand of DNA).

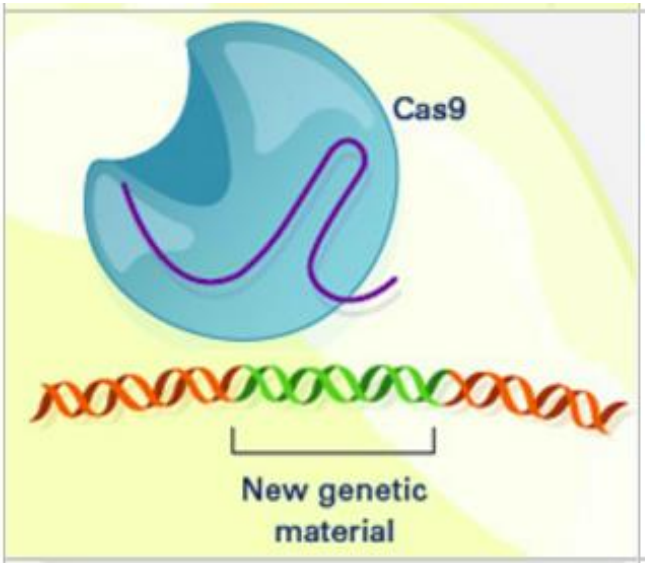


Once inserted into a cell, the CRISPR machine locates the target DNA sequence. CRISPR's RNA recognizes and binds to the target DNA (circled in black).

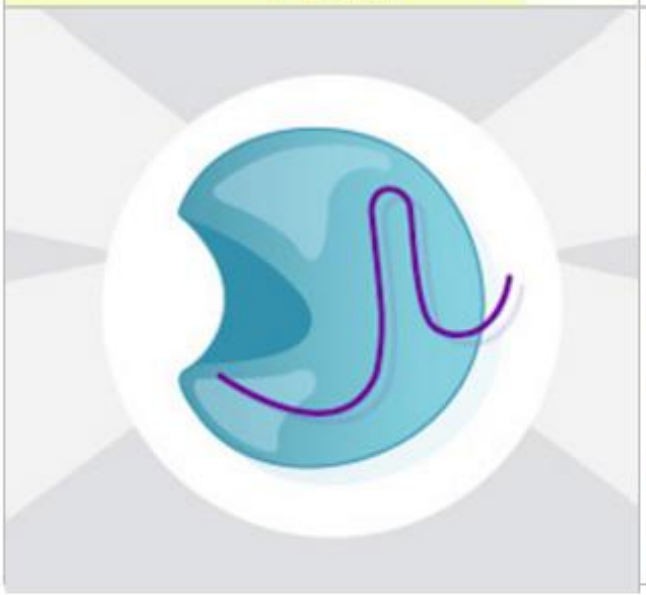


The Cas9 enzyme cuts both strands of the DNA.

Source: NIGMS, https://biobeat.nigms.nih.gov/2015/12/recognition-for-crispr-gene-editing-tool/



Researchers can introduce new genetic material, which the cell automatically incorporates into the gap when it repairs the broken DNA.



Among its many possible applications, the CRISPR system could be used to:

- Add a new gene that enables the organism to produce a pharmaceutical product (a biotechnology technique).
- Help treat genetic diseases.
- Create tailor-made model organisms to study human diseases.
- Help produce replacements for damaged or diseased tissues and organs.

Research transformation

- Ability to create model organisms
  - Increased species
  - Transgenic NHP
- Understanding of the genome
  - Epigenetics

Niu, Y., et al., (2014) Cell 156:836-843

Clinical applications

- Next generation of antimicrobials
  - Overcoming antibiotic resistance
- Human somatic gene therapy
- Human germline modification

nature International weekly journal of science

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News & Comment > News > 2016 > June > Article

NATURE | NEWS

First CRISPR clinical trial gets green light from US panel

The technique's first test in people could begin as early as the end of the year.

Sara Reardon

22 June 2016

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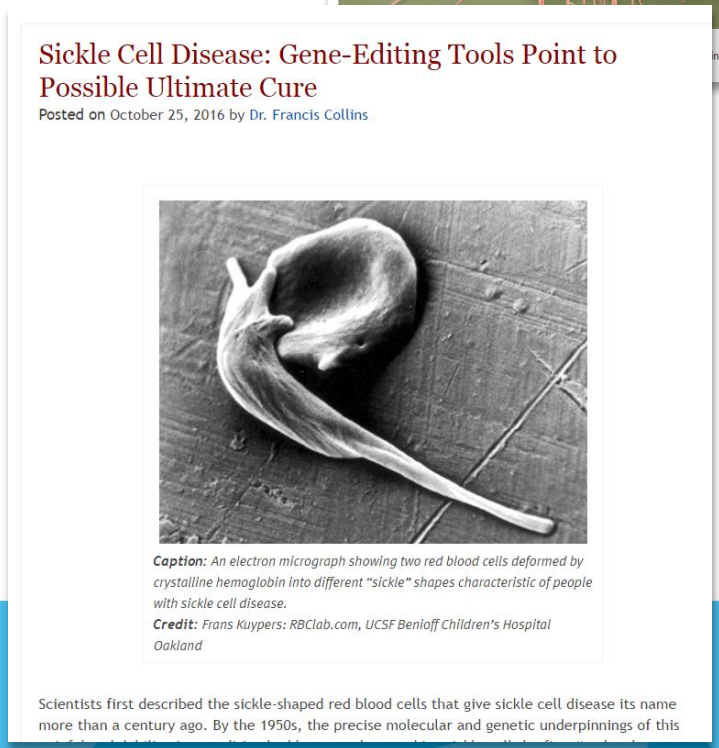
STEVE GSCHMEISSNER/SPL

nical trial to attack cancer



Sickle Cell Disease: Gene-Editing Tools Point to Possible Ultimate Cure

Posted on October 25, 2016 by Dr. Francis Collins

Caption: *An electron micrograph showing two red blood cells deformed by crystalline hemoglobin into different "sickle" shapes characteristic of people with sickle cell disease.*

Credit: *Frans Kuypers: RBClab.com, UCSF Benioff Children's Hospital Oakland*

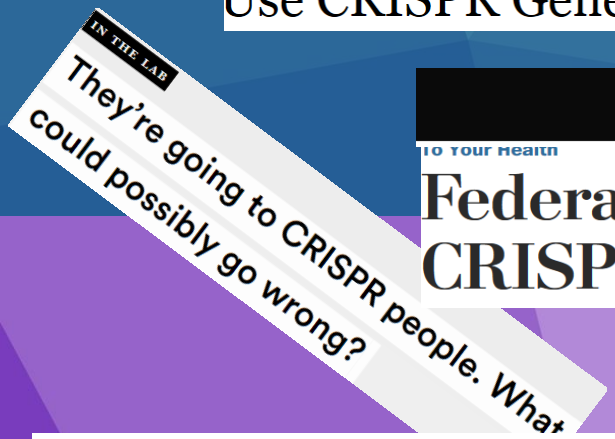
Scientists first described the sickle-shaped red blood cells that give sickle cell disease its name more than a century ago. By the 1950s, the precise molecular and genetic underpinnings of this

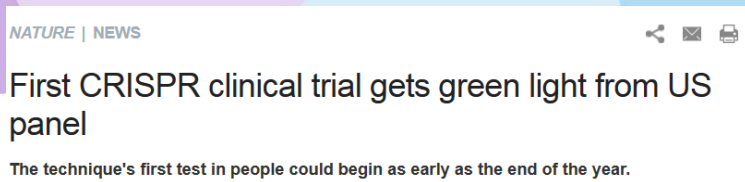
Human Somatic Gene Therapy

- ZFNs in multiple clinical trials
  - Disruption of CCR5 gene to confer HIV resistance
  - Introduction of genes to correct hemophilia B and mucopolysaccharidosis I
- TALENs
  - “off-the-shelf” approach to chimeric antigen receptor T cell immunotherapy trials in United Kingdom and reviewed by RAC
- CRISPR/Cas9
  - T cell immunotherapy protocol reviewed by RAC
  - First administration in China in 2016

A Cell Therapy Untested in Humans Saves a Baby With Cancer NYT 11/5/15

CRISPR RAC Review
Significant International Media Attention





Burning question:

- How to ensure science advances safely and ethically?
  - Need for policies and oversight framework that balances progress and safety

Human Germline Modification

Gene drives

Challenges

- **Safety**
  - Development of more precise and efficient systems to address off-target effects
  - Risk:benefit assessments will be needed for new applications
- **Governance**
  - New applications may raise need to revisit the adequacy of existing regulatory frameworks
- **Ethical, legal, and social issues**
  - Many concerns are not new but now more urgent as potentially greater impacts on humans and environment become more feasible

Human Germline Modification

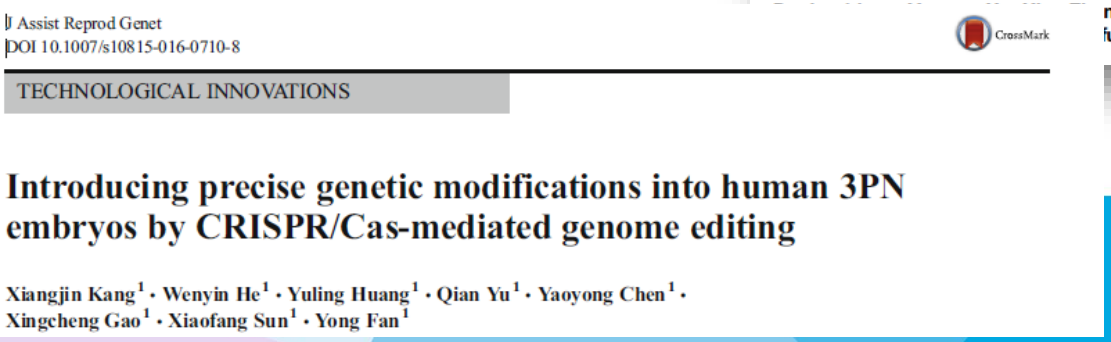
- Alteration of embryos, oocytes, or sperm
- Gene editing in non-viable (triploid) human embryos
  - April 2015- human beta globin gene repair
  - April 2016- CCR5 gene deletion

Protein & Cell

RESEARCH ARTICLE 2015, 6(5)

CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes

ng, Chenhui Ding, Rui Huang, Zhen Zhang, Jie Lv, Xiaowei Xie, u Bai, Zhou Songyang, Wenbin Ma, Canquan Zhou✉, Junjiu Huang✉



J Assist Reprod Genet
DOI 10.1007/s10815-016-0710-8

CrossMark

TECHNOLOGICAL INNOVATIONS

Introducing precise genetic modifications into human 3PN embryos by CRISPR/Cas-mediated genome editing

Xiangjin Kang[1] · Wenyin He[1] · Yuling Huang[1] · Qian Yu[1] · Yaoyong Chen[1] · Xingcheng Gao[1] · Xiaofang Sun[1] · Yong Fan[1]

Human Germline Modification Governance and Dialogue

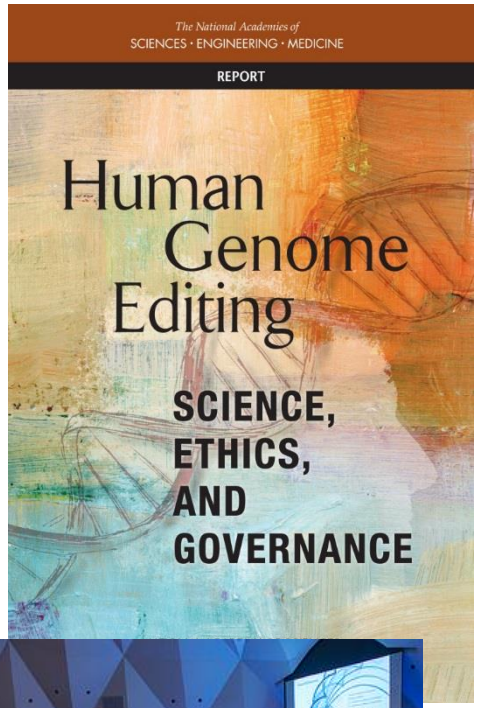
- Multiple countries have regulations banning human germline modification
- US regulations and policies
  - NIH statement April 2015- “NIH will not fund any use of gene-editing technologies in human embryos.”
  - Legislative and regulatory prohibitions
- Non-clinical research being conducted in some countries
  - China (CCR5, Beta globin in non-viable embryos)
  - UK (license for CRISPR/Cas9 in embryos up to days)
  - Sweden (embryos studied *in vitro* for 2 weeks)

Germline modification

- April 29, 2015: “NIH will not fund any use of gene-editing technologies in human embryos.” *–Francis Collins*
- “The NIH will not at present entertain proposals for germline alterations…” – Guidelines, Appendix M

National Academies Initiative

- Asilomar 2.0??
  - Two year effort, focused on humans
- Report released Feb. 2017
- Cautionary endorsement of germline editing
- Issues of enhancement…

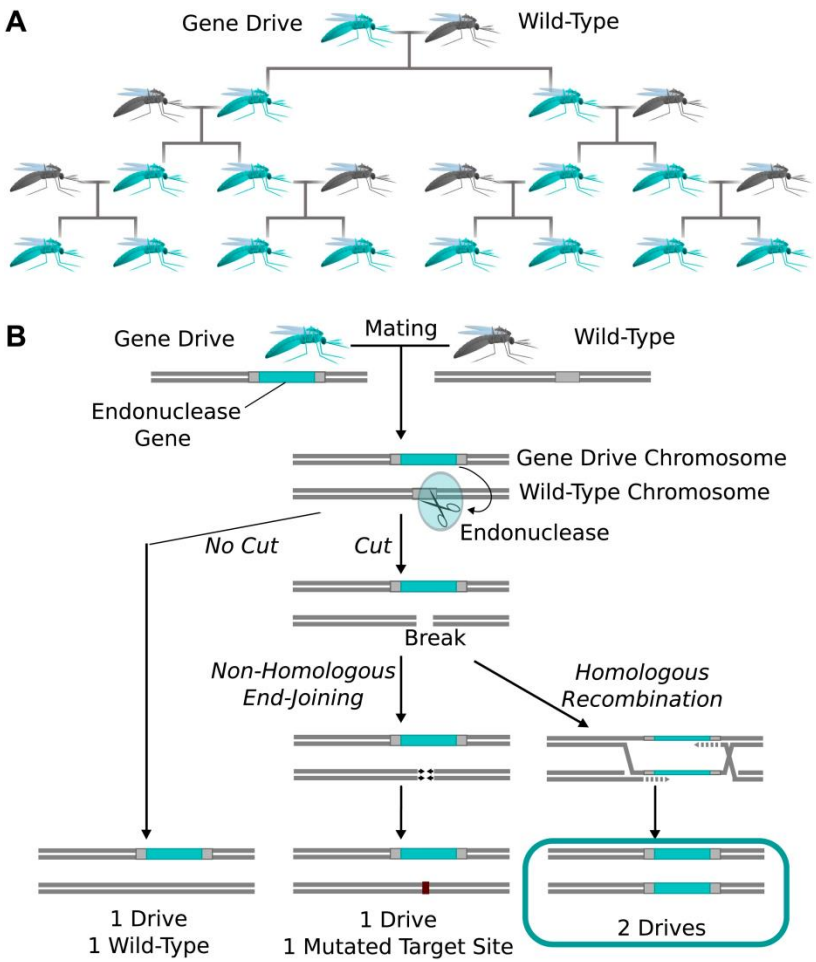


What are the concerns?

- Unknown long term health consequences
- Lack of consent
- Lack of clear need
- Public perception
  - Heritable changes

Gene Drives

- Technology for spreading engineered traits through populations of sexually reproducing organisms
- Potential public health, agriculture, and ecology applications



Esvelt, K., *et al*., eLife 2014;3:e03401

The latest BUZZ on gene drives

- Gene drives demonstrated in
  - Drosophila
  - Yeast
  - Mosquitoes
- Approaches to reduce the spread of disease
  - Population suppression by disruption of female fertility gene
  - Population modification by conferring parasite resistance

Highly efficient Cas9-mediated gene drive for population modification of the malaria vector mosquito *Anopheles stephensi*

Valentino M. Gantz[a,1], Nijole Jasinskiene[b,1], Olga Tatarenkova[b], Aniko Fazekas[b], Vanessa M. Macias[b], Ethan Bier[a,2], and Anthony A. James[b,c,2]

A CRISPR-Cas9 gene drive system targeting female reproduction in the malaria mosquito vector *Anopheles gambiae*

Andrew Hammond[1], Roberto Galizi[1], Kyros Kyrou[1], Alekos Simoni[1], Carla Siniscalchi[2], Dimitris Katsanos[1], Matthew Gribble[1], Dean Baker[3], Eric Marois[4], Steven Russell[3], Austin Burt[1], Nikolai Windbichler[1], Andrea Crisanti[1] & Tony Nolan[1]

Gene Drives
Potential Applications

- Public Health

Control spread of vector-borne infectious diseases (e.g., suppress population or interfere with infectious agent transmission in mosquitoes that cause malaria, Zika, etc.)

- Agriculture
  - Engineer weeds without herbicide resistance
  - Improvements in crops

Missouri botanical garden

US Geological Survey

- Ecology
  - Control invasive species (e.g., cane toads)
  - Protect vulnerable species (e.g., amphibians from fungi)

US Geological Survey

Gene Drives Concerns

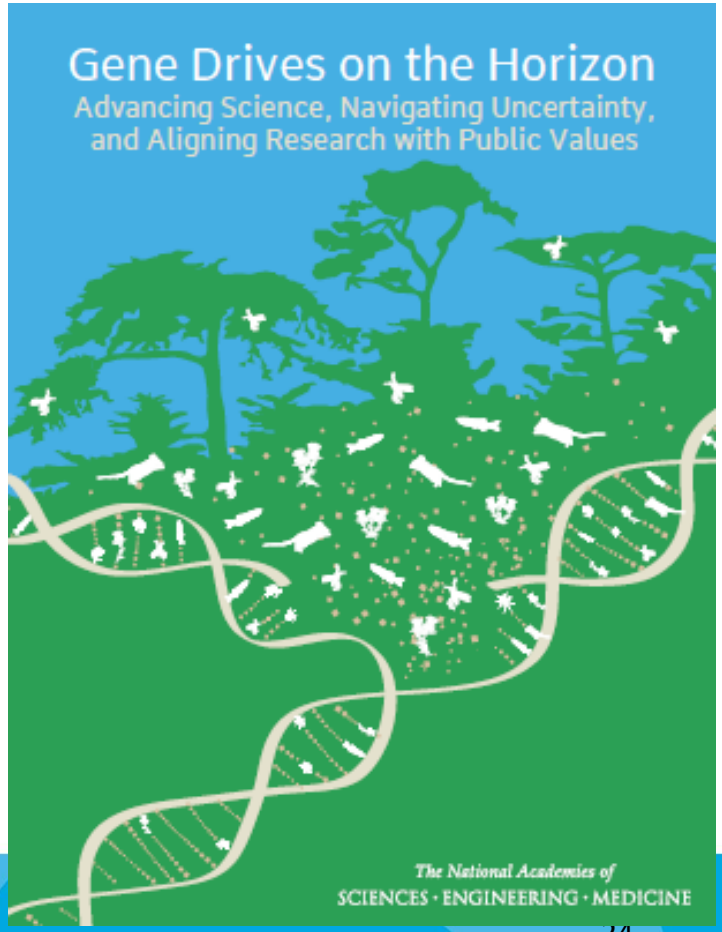
- Biosafety
  - Unknown risks to entire ecosystems
    - Spread into related species
    - Effect of alteration of targeted species on other species and environment
- Biosecurity
  - Potential for dual use
- Ethics
  - Selection of release sites
  - Need for engagement at community and international levels
- Governance
  - Adequacy of existing oversight mechanisms?
  - Lack of containment leading to international impacts

US National Academy of Sciences Study Gene Drive Research in Non-Human Organisms: Recommendations for Responsible Conduct

- NIH, FNIH, DARPA and Gates Foundation commissioned NAS study to examine scientific, regulatory, environmental, and ethical implications of research with, and release of, organisms containing gene drives
  - Report released June 8, 2016

NAS Report
Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values

- "There is insufficient evidence available at this time to support the release of gene-drive modified organisms into the environment. However, the potential benefits of gene drives for basic and applied research are significant and justify proceeding with laboratory research and highly-controlled field trials."



Gene editing… a WMD?!?

Statement for the Record

Worldwide Threat Assessment
of the
US Intelligence Community

Senate Armed Services Committee

James R. Clapper

Director of National Intelligence

February 26, 2015

MIT Technology Review

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Rewriting Life

Top U.S. Intelligence Official Calls Gene Editing a WMD Threat

Easy to use. Hard to control. The intelligence community now sees CRISPR as a threat to national safety.

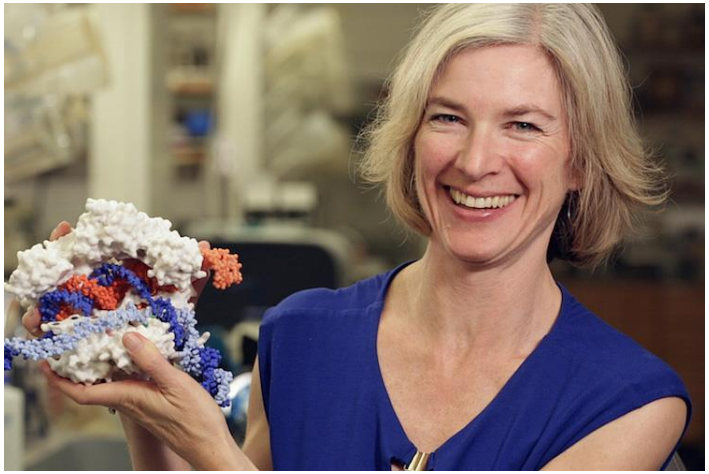
by Antonio Regalado February 9, 2016

Genome editing is a weapon of mass destruction.

That's according to James Clapper, U.S. director of national intelligence,

Good news, Jennifer Doudna's not worried…

"In terms of biosecurity risks, I don't think it's any riskier than lots of other things that are out there," she said. "It just sort of underscores that it's really powerful technology and we need to be thinking responsibly about how to use it." (*NASW, 2/18/16)*



Deep thoughts…

- Better policy approaches to emerging biotechnologies…
  - Proactive
  - Identification
  - Risk assessment
  - Past lessons

Resources

- **NIH Office of Science Policy**
  - Website: http://osp.od.nih.gov/
  - Blog: http://osp.od.nih.gov/under-the-poliscope
  - Twitter: https://twitter.com/cwolinetznih
  - **Subscribe to the OSP listserv** by sending an email to **LISTSERV@list.nih.gov** with “Subscribe OSP_News” in the message body

Bringing Science Policy Into Focus