HSTalks

Prof. Henry Greely – Stanford University, USA

The Risks and Benefits of Gene Drive Technology

Henry T. Greely

Law Professor and Director,
The Center for Law and the Biosciences
Stanford University
California, USA

1

A modern day Frankenstein's monster?

1818
- Mary Shelley publishes 'Frankenstein; or, The Modern Prometheus'
  - A story examining parental responsibilities
  - The rejection of his creation

1823
- The play 'Presumption; or, the 'Fate of Frankenstein' by Richard Brinsley Peake was performed
  - Implied that Dr. Frankenstein was taking over God's role
  - A result of humans overstepping

Should gene drive technology be viewed as another Frankenstein's monster? – which version?

2

Lecture outline

Gene drive

1. What is it?
2. What are its potential uses?
3. What are the risks?
4. How should we use it?

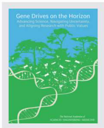
3

Prof. Henry Greely – Stanford University, USA

Lecture outline

The National Academies of SCIENCES ENGINEERING MEDICINE THE NATIONAL ACADEMIES PRESS

This PDF is available at http://nap.edu/23405 SHARE



Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values (2016)

DETAILS

230 pages | 7 x 10 | PAPERBACK
ISBN 978-0-309-43787-5 | DOI 10.17226/23405

What is a gene drive?

- **Genetic change that is preferentially maintained within the offspring**
- There are examples within nature:
  - Retroviruses
  - Retrotransposons
  - Alu elements
- **CRISPR**
  Clustered Regularly Interspaced Short Palindromic Repeats has enabled the targeted use of gene drive technology by humans

4

Gene editing techniques

- 1972 – Jackson, Symons and Berg developed **recombinant DNA**
- **TALENS** (transcription activator-like effector nucleases)
- **Zinc-finger nucleases**
- **CRISPR** – has big benefits compared to other techniques
  - Cheap
  - Easy
  - Effective
  - Reliable

Paul Berg

1910 Model T Ford

Jinek M. *et al. Science.* 2012 Aug 17;**337**(6096):816-21

5

The screen versions of these slides have full details of copyright and acknowledgements

Prof. Henry Greely – Stanford University, USA

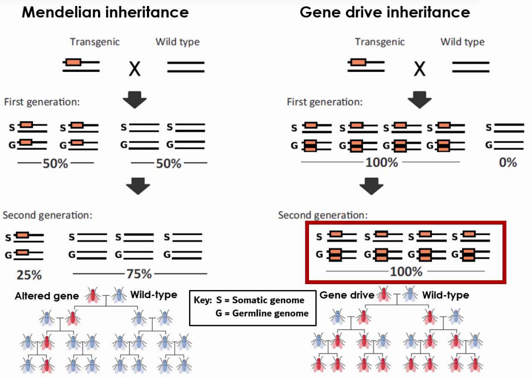
CRISPR gene drive

- Suggested by K. Esvelt *et al.* in 2014
- CRISPR construct is designed to stay within the offspring
- Can be used to introduce desired traits into a population

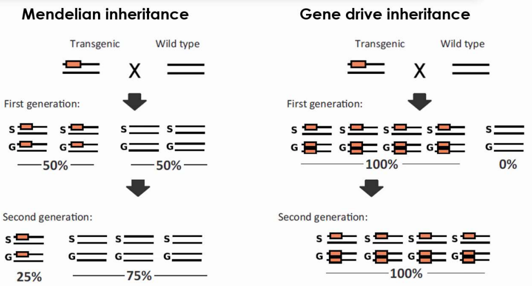
Kevin M Esvelt et al. *eLife.* 2014;**3**: e03401

6

CRISPR gene drive



CRISPR gene drive



- The mutation will still spread with up to 30% survival detriment
- Gene drive enables genetic changes to be spread within a population very rapidly

Prof. Henry Greely – Stanford University, USA

The limitations of gene drive

1. **Only suitable for sexually reproducing organisms – not clones**

Clones are widespread throughout the world

Bacteria · Microbes · Plants · Insects

2. **Species generation time**

12 Generations

≈ 2 months --------→ 2 years

≈ 30 years --------→ 360 years

7

The limitations of gene drive

3. **Population size**

$\frac{10000}{1000} = 10$ $\frac{7500000000}{1000} = 7500000$

The larger the population the longer it will take or the higher the number of mutants that need to be introduced

4. **Population connectedness**

If populations do not interact sexually then the mutations cannot be spread between them

The uses of gene drive

Controlled populations

Humans can control the breeding of animals/plants within most of agriculture

Breeding can be largely controlled within research

Gene drive is rarely used within these areas as there are other better/easier options

8

The uses of gene drive

Uncontrolled populations

- Includes most wild sexually reproducing populations within the environment
- Can include non-wild animals with hard to control breeding *e.g.* domestic cats

CRISPR can enable changes to population genetics without controlling breeding

The effects of gene drive

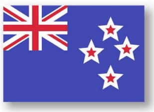
1. **Death**
2. **Population growth restriction**
3. **Beneficial traits**

9

The effects of gene drive

1. **Death**

- Shouldn't kill the organism before they reproduce
- Ideally cause death soon after reproduction
- Direct vs. indirect death (nutrient deficiency/drug reaction)
- May be used to selectively remove invasive species, which impact on native species
  - *E.g.* New Zealand plans to remove all invasive species by 2050

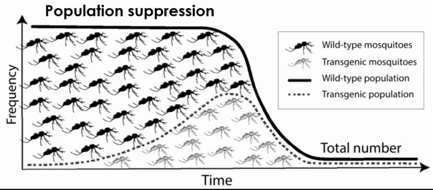


Prof. Henry Greely – Stanford University, USA

The effects of gene drive

2. Population growth restriction

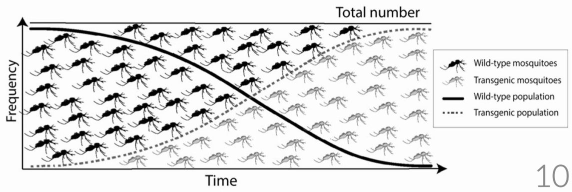
- Limit reproduction leading to a population decrease e.g. via **sterility**
  - Has been tried by Oxitec with some promising results
- Make all offspring a **single sex**
  - Affects the gender balance of the population and reduces its overall size



The effects of gene drive

3. Beneficial traits

- Can give populations **immunity** to certain diseases e.g. Malaria



10

The effects of gene drive

3. Beneficial traits

- Can give populations **immunity** to certain diseases e.g. Malaria

- Can help protect populations, which have no immunity to imported pathogens
  - Dutch elm disease (fungus)
  - Chestnut trees (*Cryphonectria parasitica* fungus)
  - Blackfooted ferret (sylvatic plague)
- **Non-immunity traits** include animal size and protection against temperature changes/droughts

Risks of successful gene drive

Successful and unsuccessful gene drive have different risks

Animal welfare

- Should not cause undue suffering to the affected animals
- Death should be humane

Environmental concerns

- Unexpected downstream consequences in the ecosystem, small changes can have a big effect

Removal of a different animals food source	Removal of a natural population limiter

Humans have previously disrupted a number of ecosystems through the introduction of foreign species
e.g. Kudzu (USA), rabbits (Australia), cane toad (Australia)

11

Risks of successful gene drive

Bioterrorism

- The intentional use of gene drive to harm species populations
- Relatively simple and cheap to perform
- Although probably not the most likely candidate system for bioterrorism
- Could be hard to identify

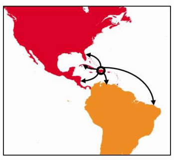
1. Animal welfare
2. Environmental effects
3. Bioterrorism

12

Risks when gene drive goes wrong

Loss of geographical specificity

- Gene drive may have negative effects if introduced outside of its specified area
- K. Esvelt has recanted some of his original ideas due to the risks
- This can be very hard to control



Loss of species specificity

- Could unintentionally affect other species
- Through species hybridization *e.g.* wolves and coyotes/dogs
- Virus mediated horizontal gene transfer

13

Prof. Henry Greely – Stanford University, USA

Risks when gene drive goes wrong

Loss of target specificity
- Naturally occurring DNA mutations can affect CRISPR
  - Can affect a different allele causing different effects
  - Can impact efficacy

Resistance
- Species can evolve resistance to the change
- Maintain mutations that disrupt CRISPR
- Or, evolve alternative pathways

The control of gene drive technology

Steps need to be taken to monitor and regulate this technology to ensure its safe and appropriate usage

http://nap.edu/23405

1. Registration
- Enables monitoring off all individuals performing experiments

2. Containment protocols
- To help prevent the accidental release of mutated animals into the environment

3. Approval
- To ensure the release of mutated animals is safe
- Could be hard to find an appropriate testing space

14

The control of gene drive technology

Steps need to be taken to monitor and regulate this technology to ensure its safe and appropriate usage

http://nap.edu/23405

4. Contingency plans
- Kill switches (unique to modified organisms)
- Daisy chain gene drives
- Diminishing gene drives
- Insurance (to provide compensation to those adversely affected)

5. Population surveillance
- Continued monitoring of the affected population and its associated ecosystem
- Could be hard to identify the exact cause of a change e.g. by the gene drive, environment or other mutations

Prof. Henry Greely – Stanford University, USA

The public and gene drive

Love your monster - *i.e.* take responsibility for the creation

vs.

Presumption - *i.e.* awareness of public feeling and understanding

How can public concerns be addressed?

- Provide regular information
- Transparency
- Highlight potential benefits
- Explain risks and combative tactics to avoid them
- Accept the public's decisions

GMO food often has a negative public response

- How do you deal with national boundaries?
- Different countries can have different concerns

15

Conclusions

- The possibilities of gene drive are huge
  - Enables the alteration of life around the world
- Humans have previously changed the biosphere
  - Fire to clear brush for hunting
  - Agriculture
  - Livestock farming (20x weight of wild mammals worldwide)
  - CO_2 levels
- Gene drive with CRISPR could allow us to make more intelligent changes
  - Must be **used with caution** and regulated, so it doesn't become a monster

Thank you!

16

HSTalks

By leading world experts