

Thinking Ahead: Editing Genomes Wisely

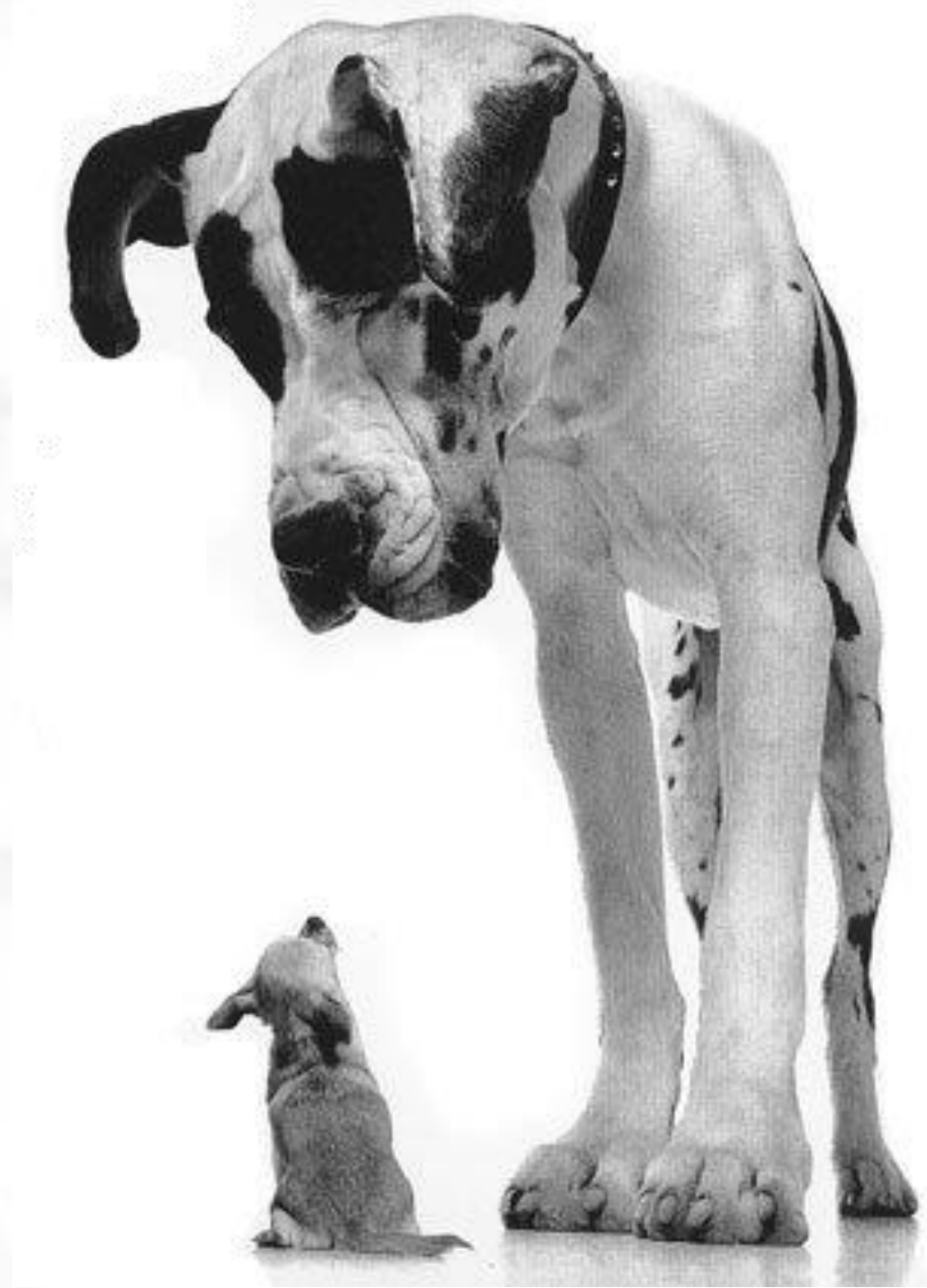
Kevin M. Esvelt, PhD
Assistant Professor, MIT Media Lab

Editing Genomes Wisely

K. Esvelt





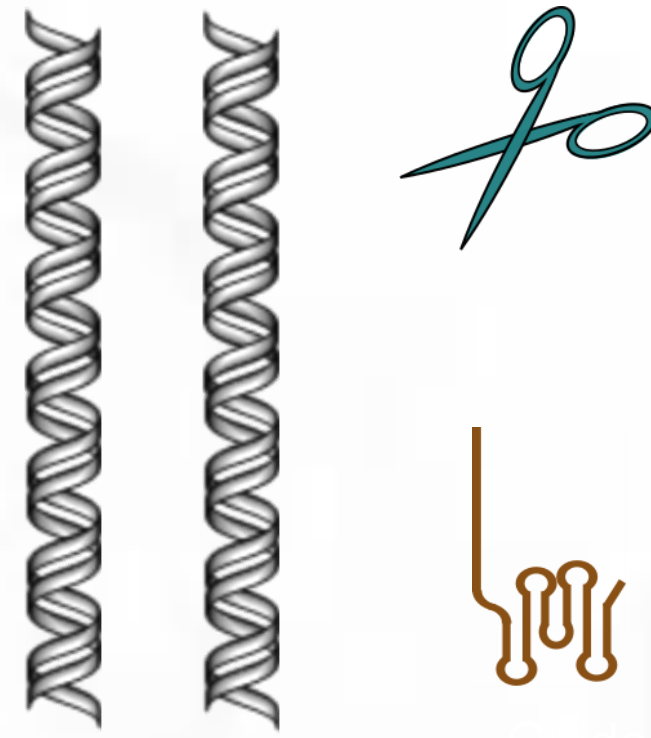


CRISPR



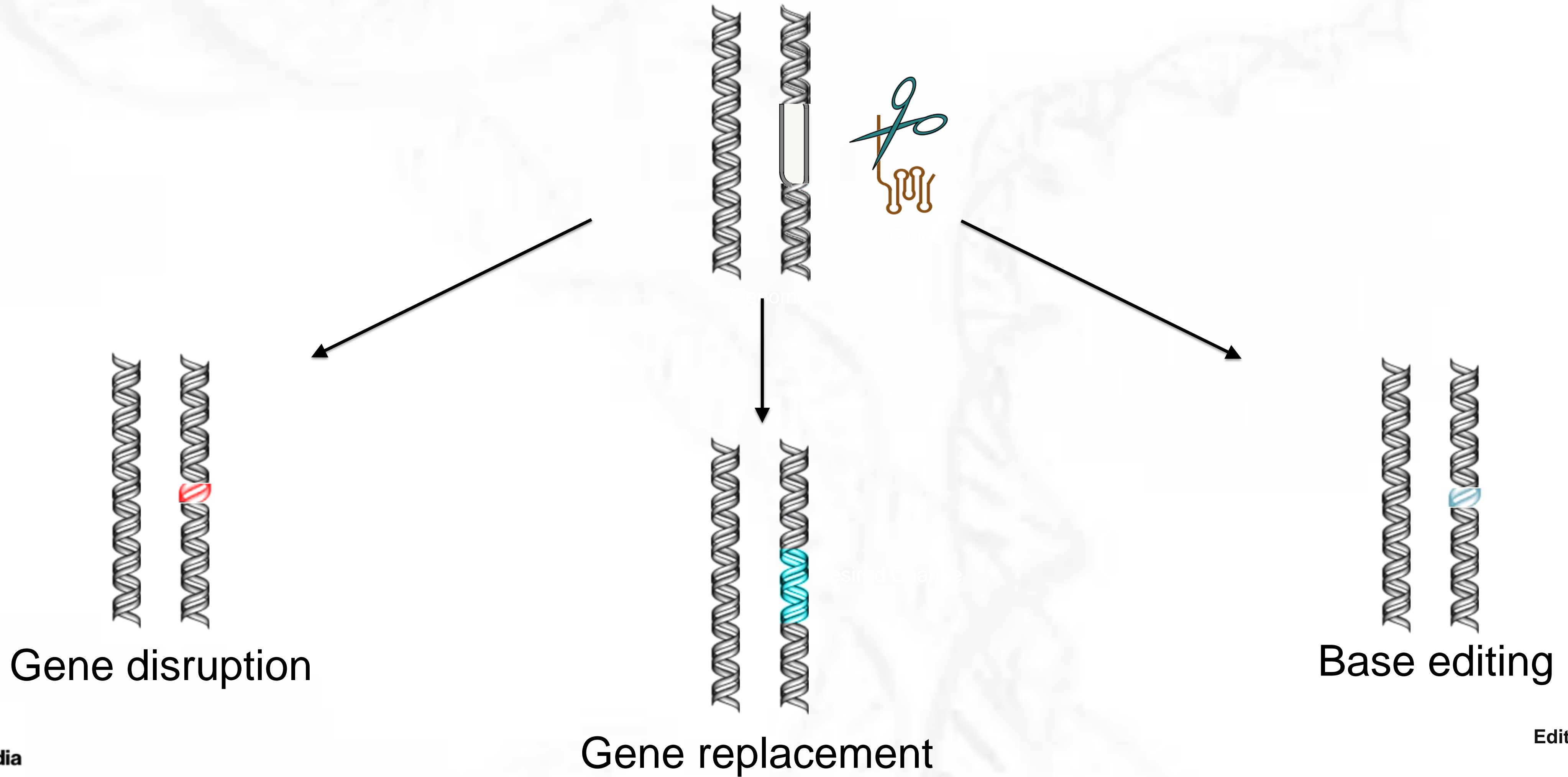
Genomes

CRISPR

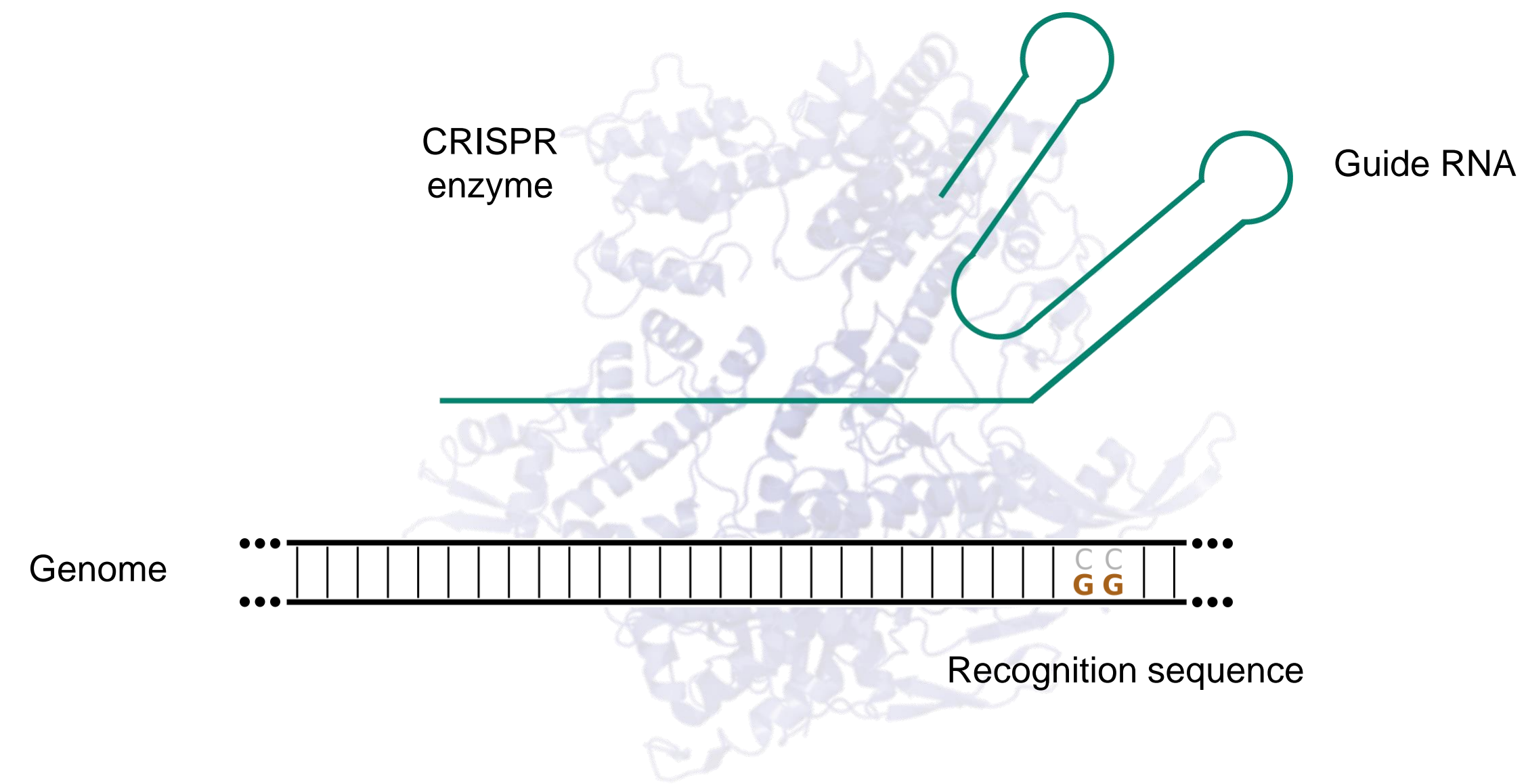


genom

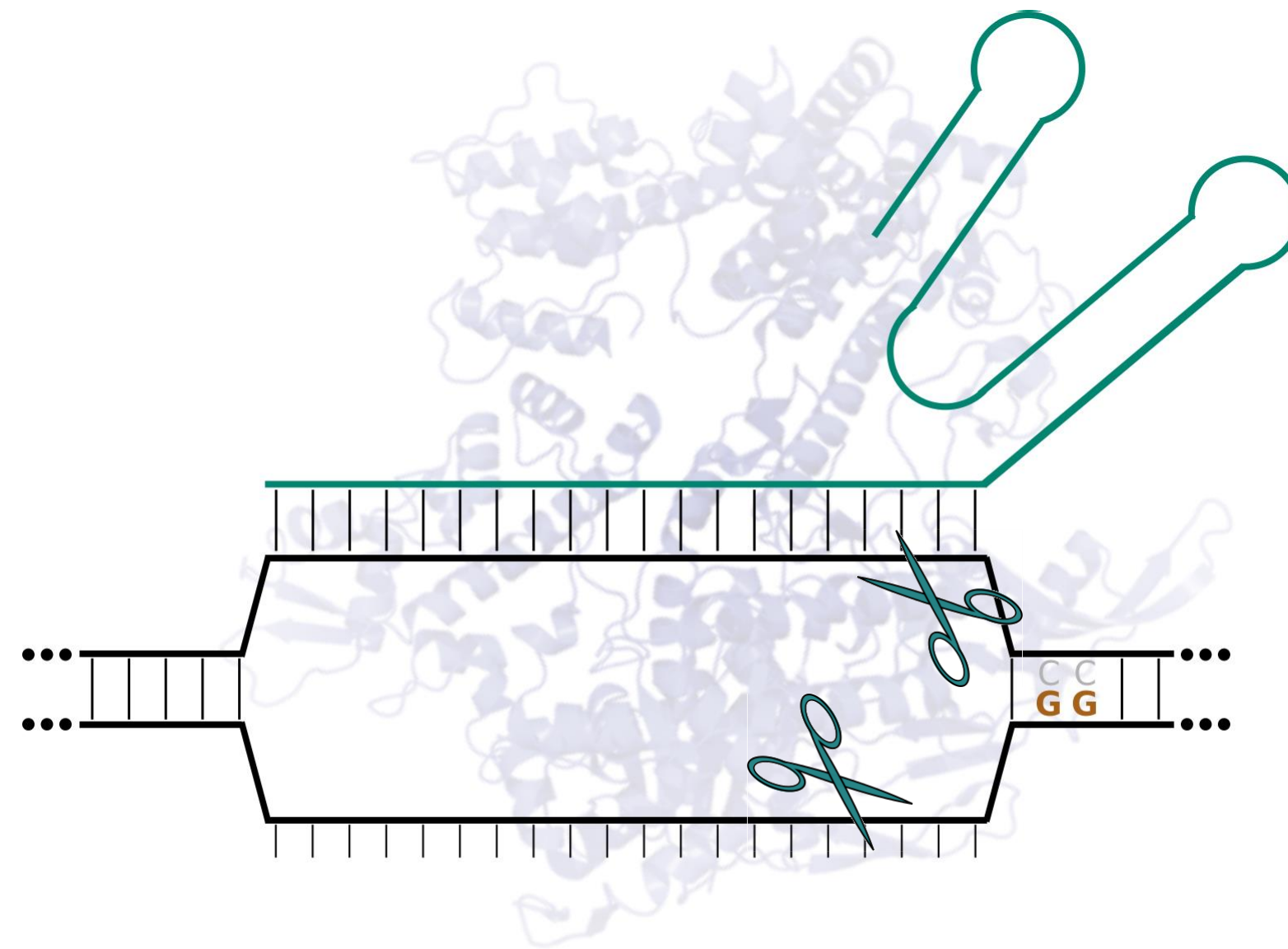
CRISPR



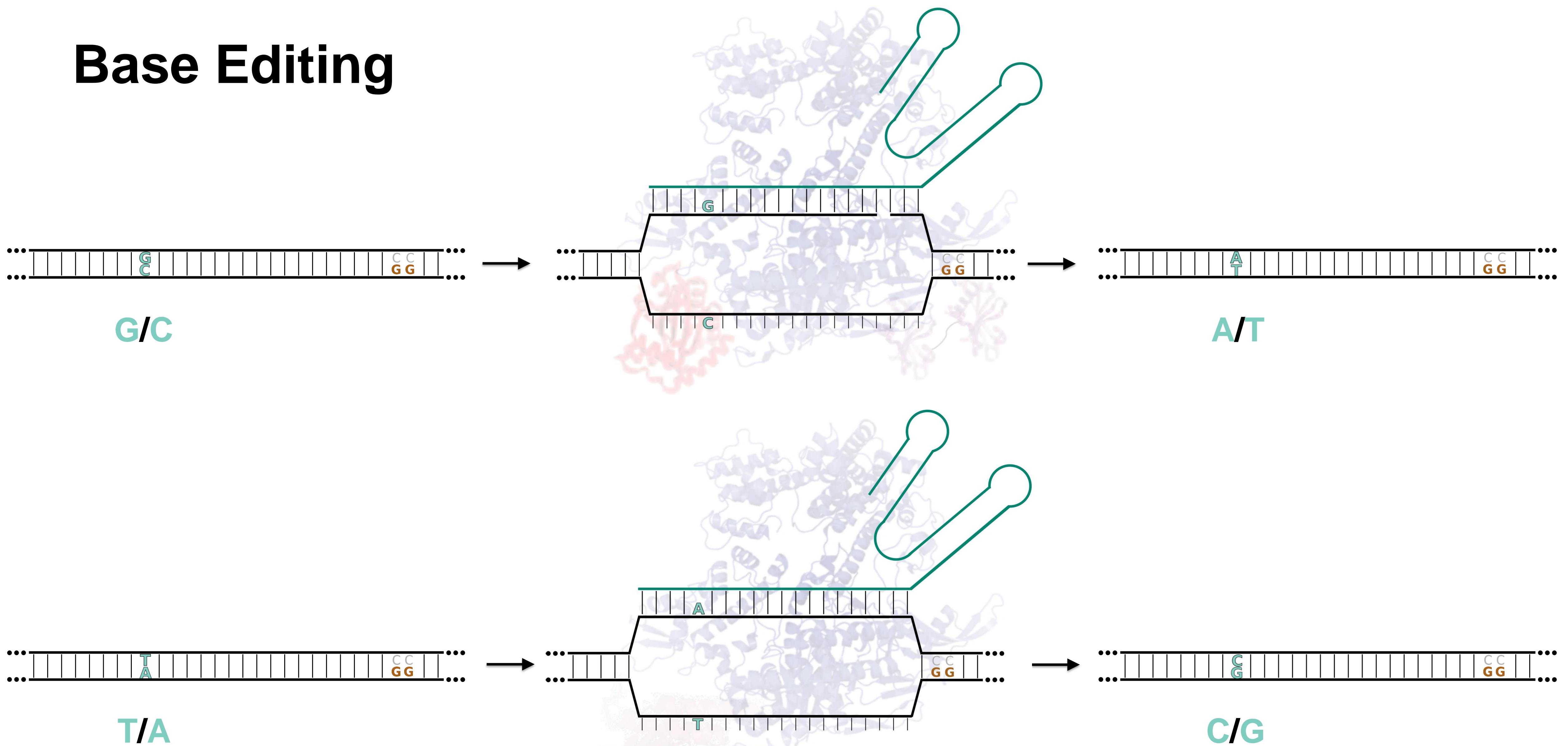
Gene Disruption & Replacement



Gene Disruption & Replacement



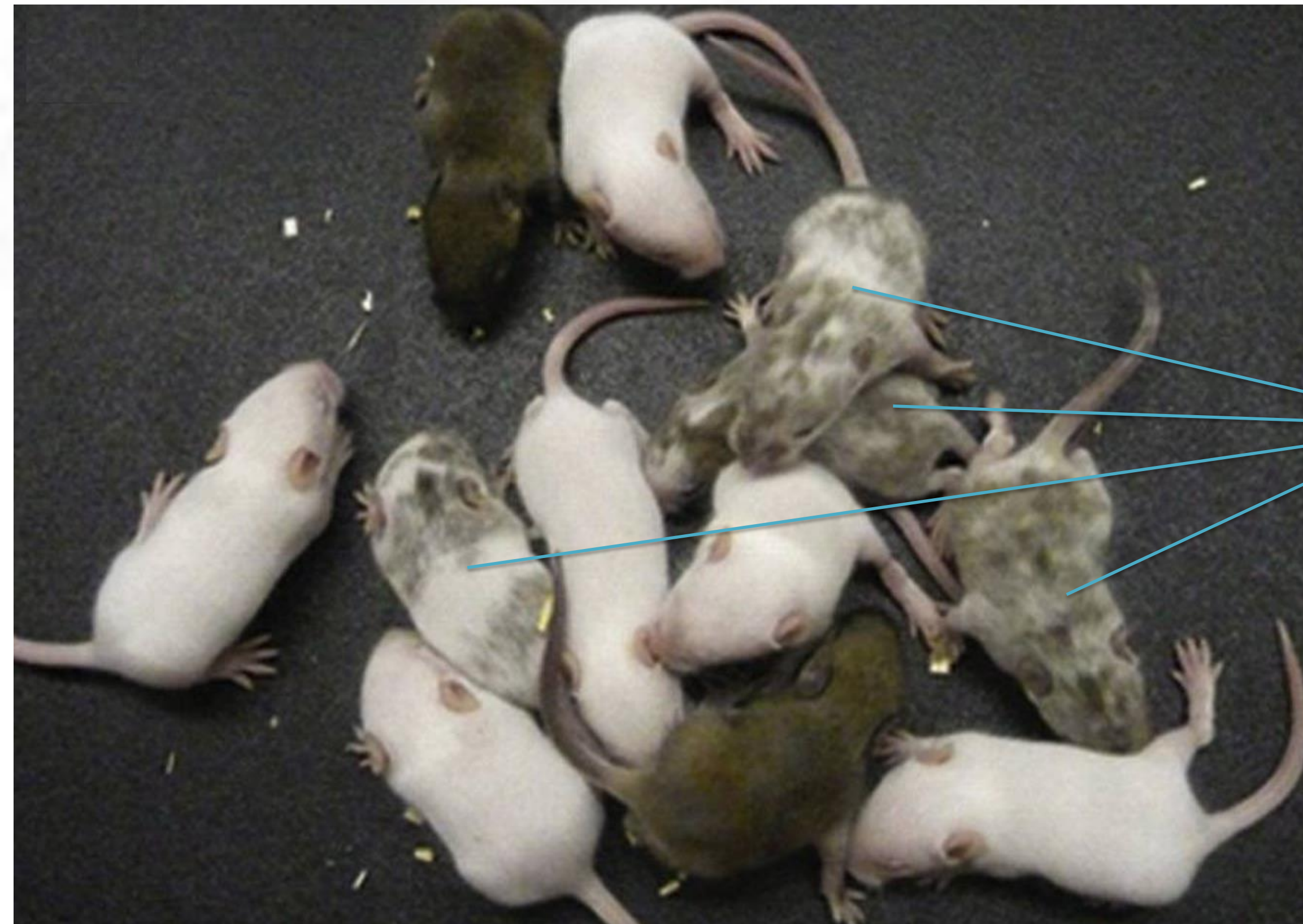
Base Editing



What About Future Generations?



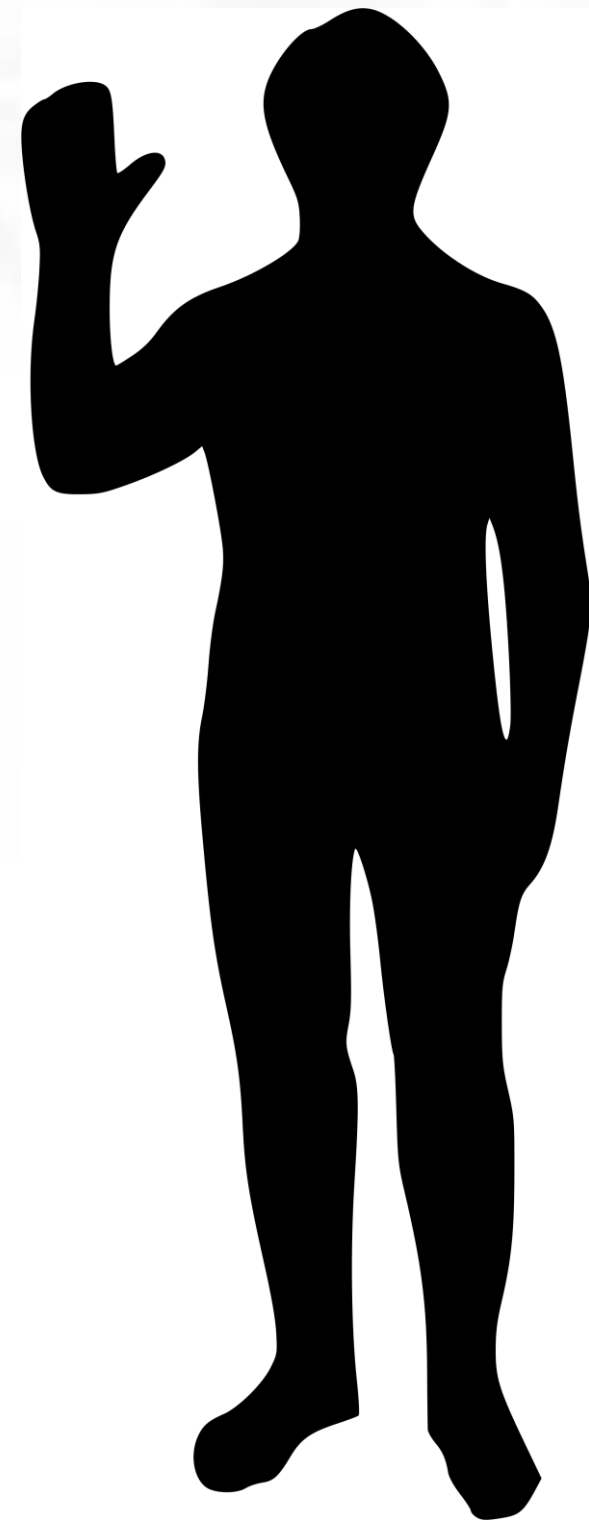
Editing Embryos: Unacceptable in Humans



Mosaic mice

Different edits in different cells = cannot sequence-confirm genome before implantation

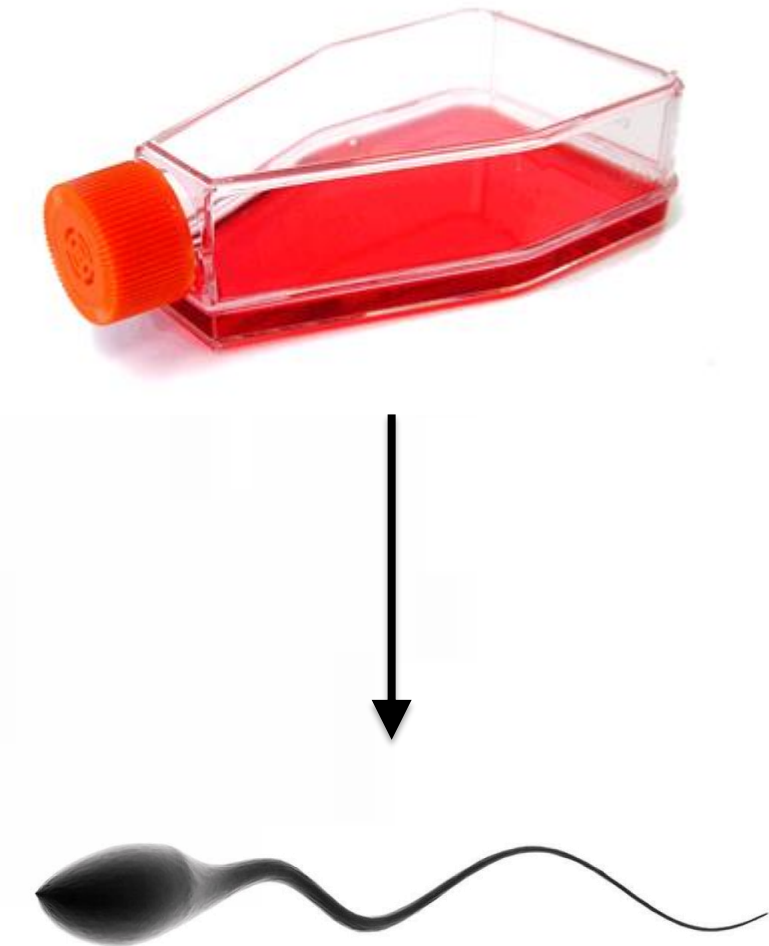
Technologies to Watch: Delivery & Differentiation



Edit male germ cells



Edit sperm or eggs



Turn cells into sperm or eggs

Editing Ecosystems



Ecological: Gene Drive

A gene drive is:

a **vertically transmitted** genetic element

that **reliably increases** in frequency

even if it **does not help the organism reproduce**

Gene drives are **ubiquitous in nature**, but could not be reliably harnessed pre-CRISPR

Self-Propagating Gene Drive

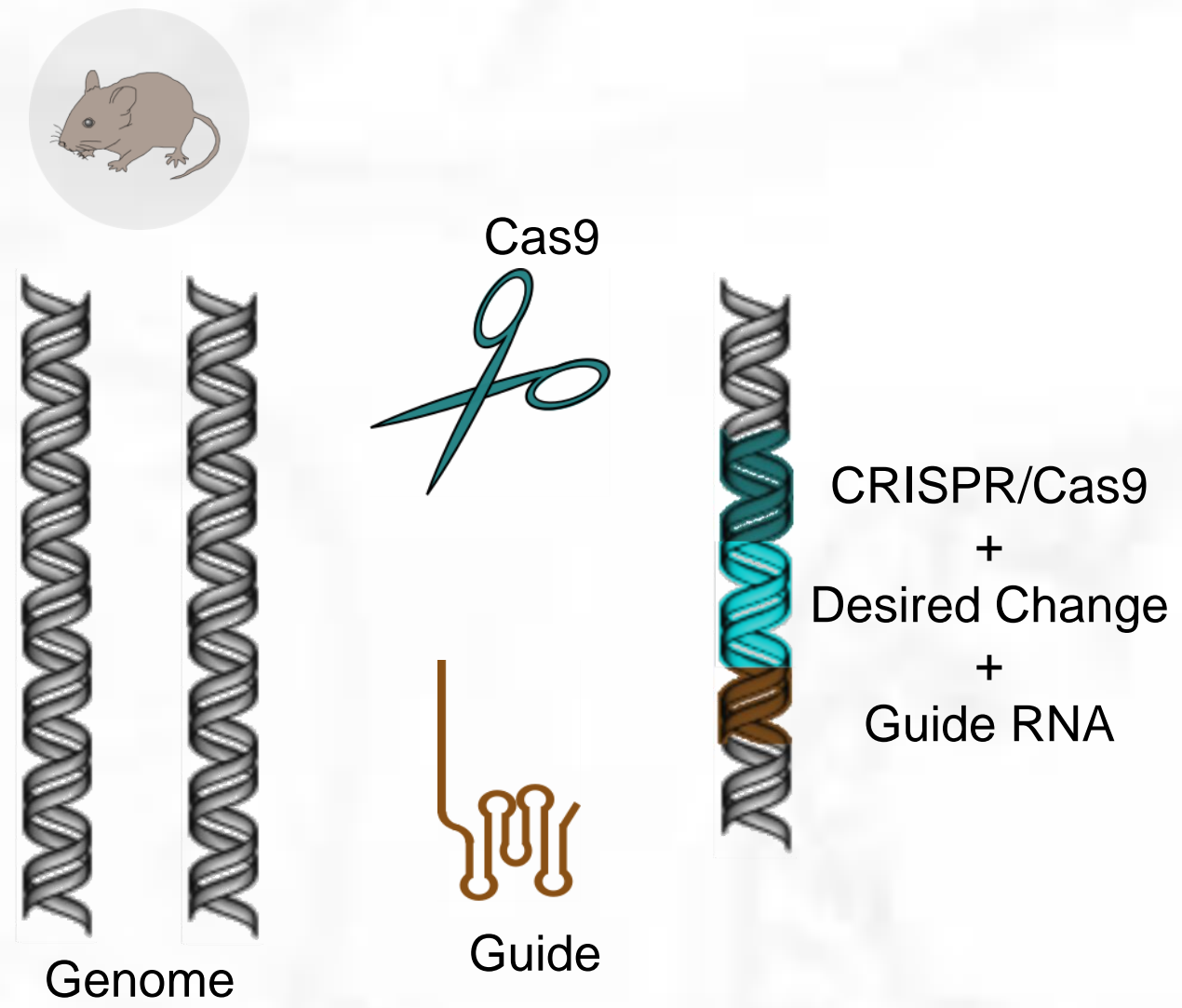


Genome

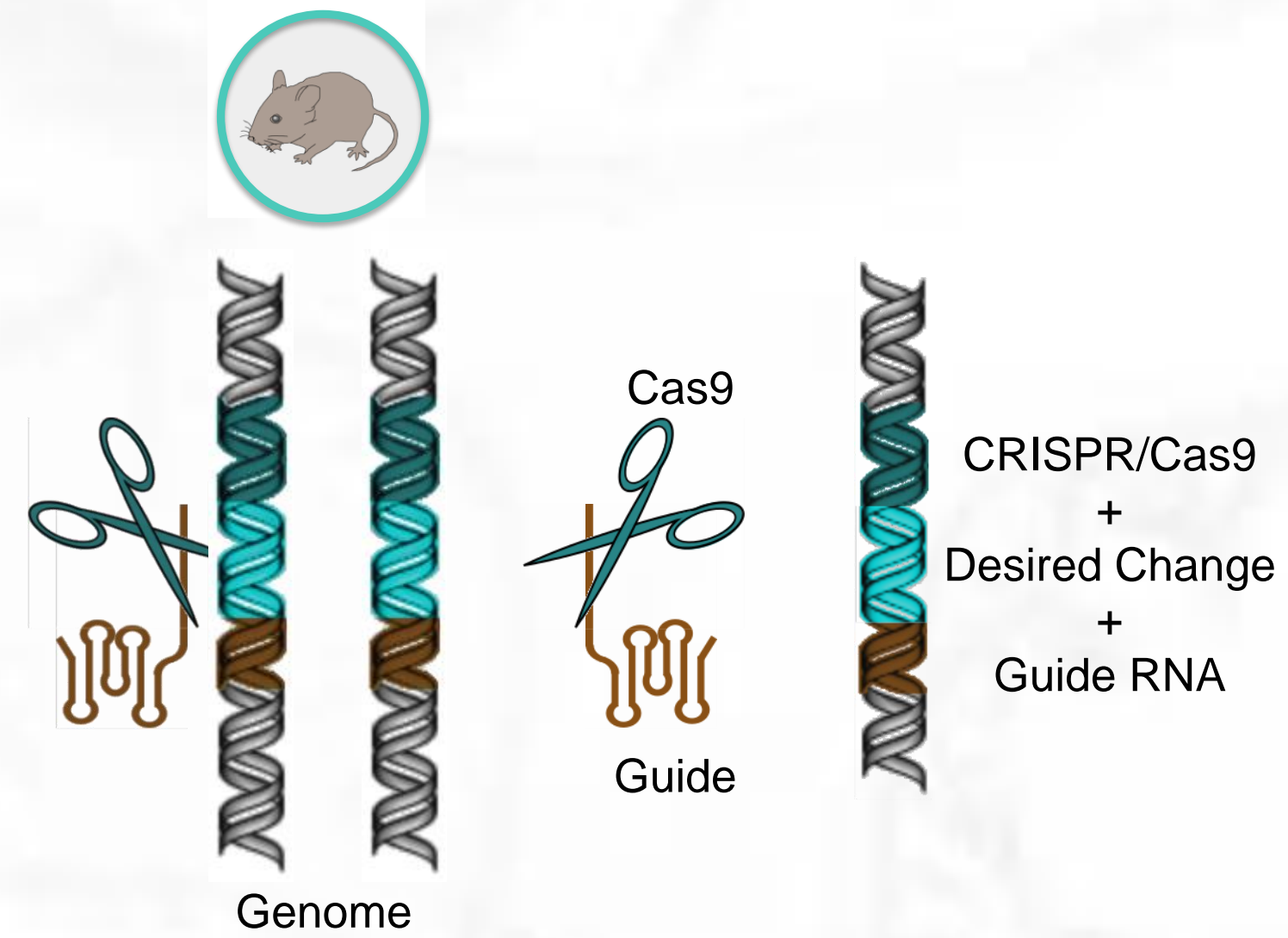


CRISPR/Cas9
+
Desired Change
+
Guide RNA

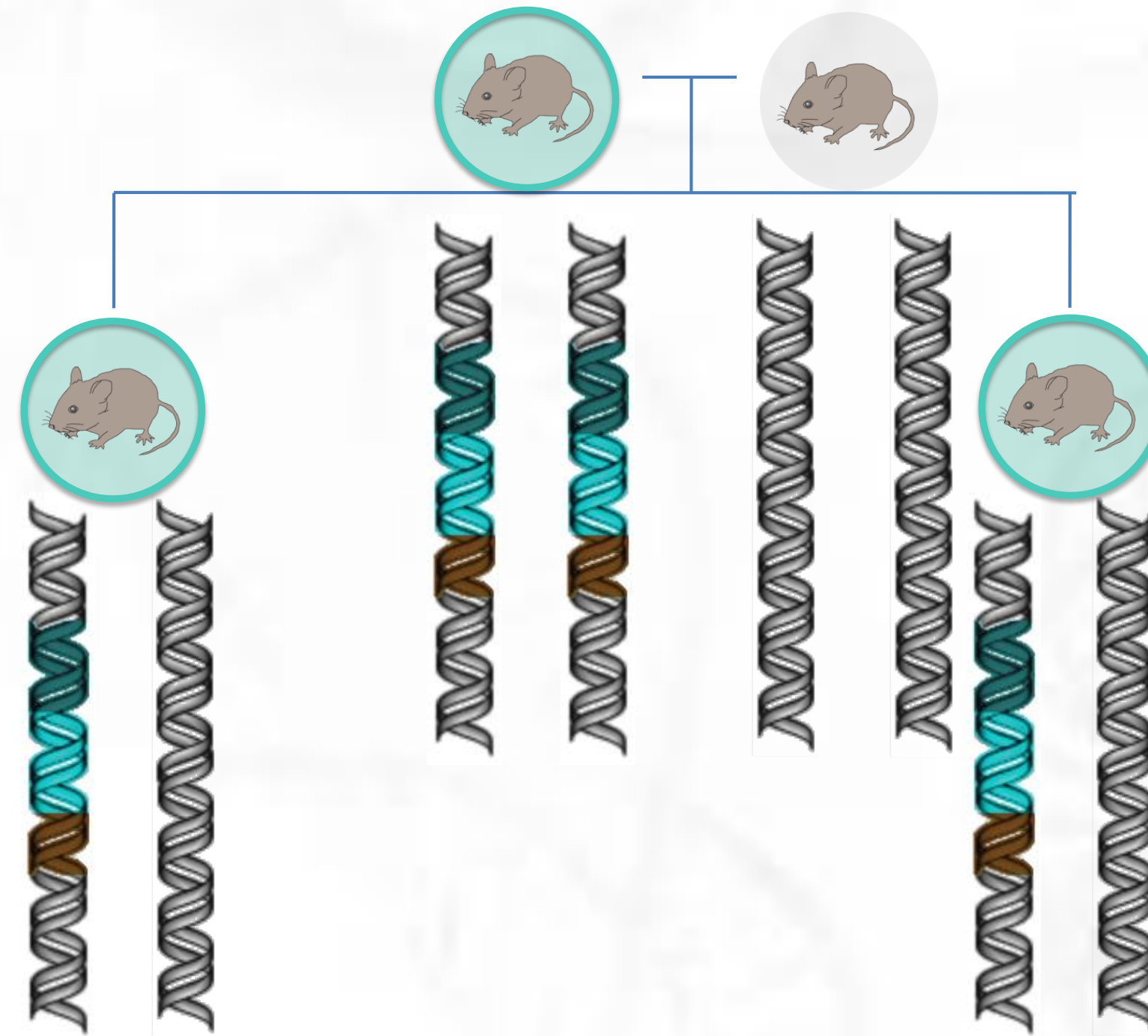
Self-Propagating Gene Drive



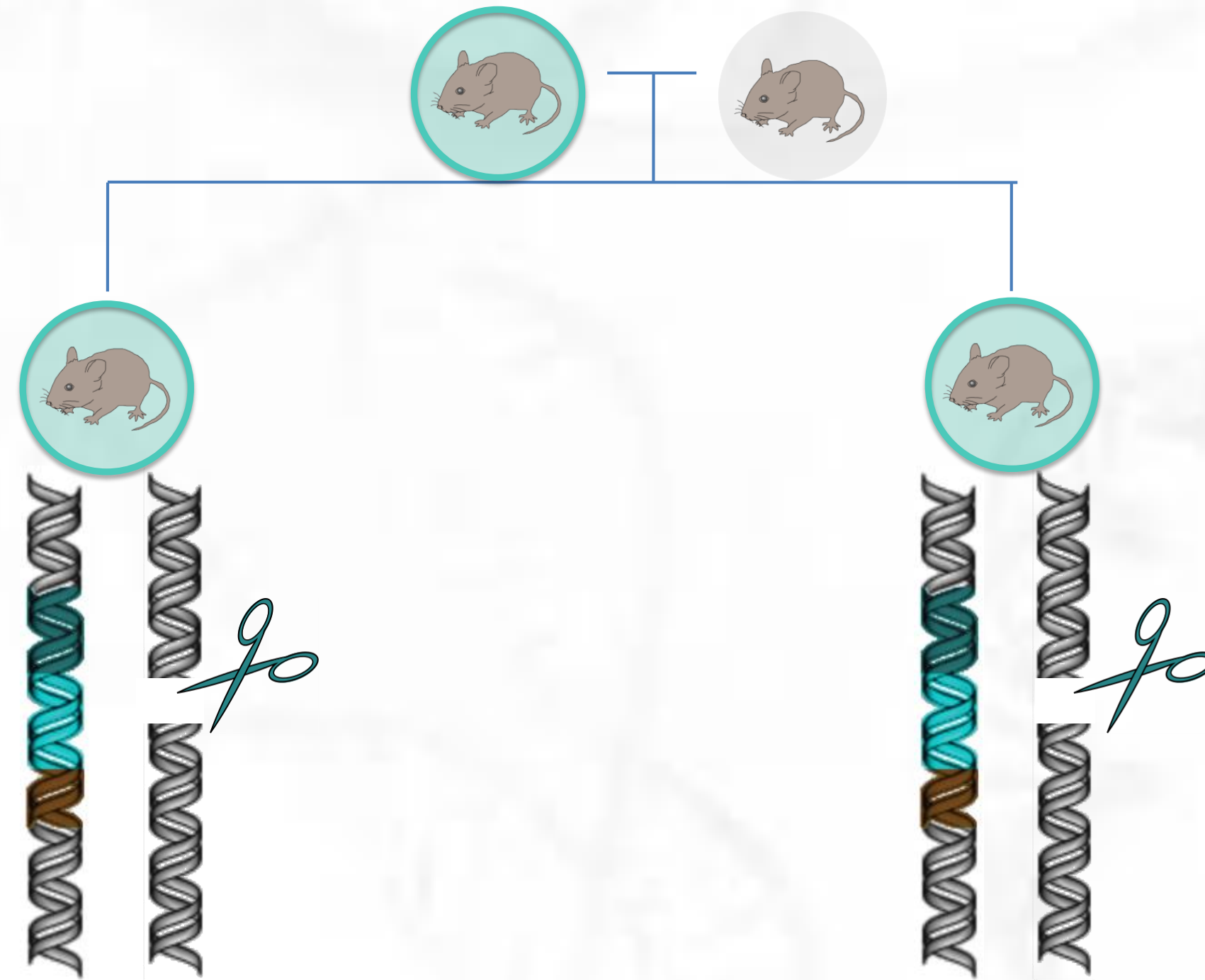
Self-Propagating Gene Drive



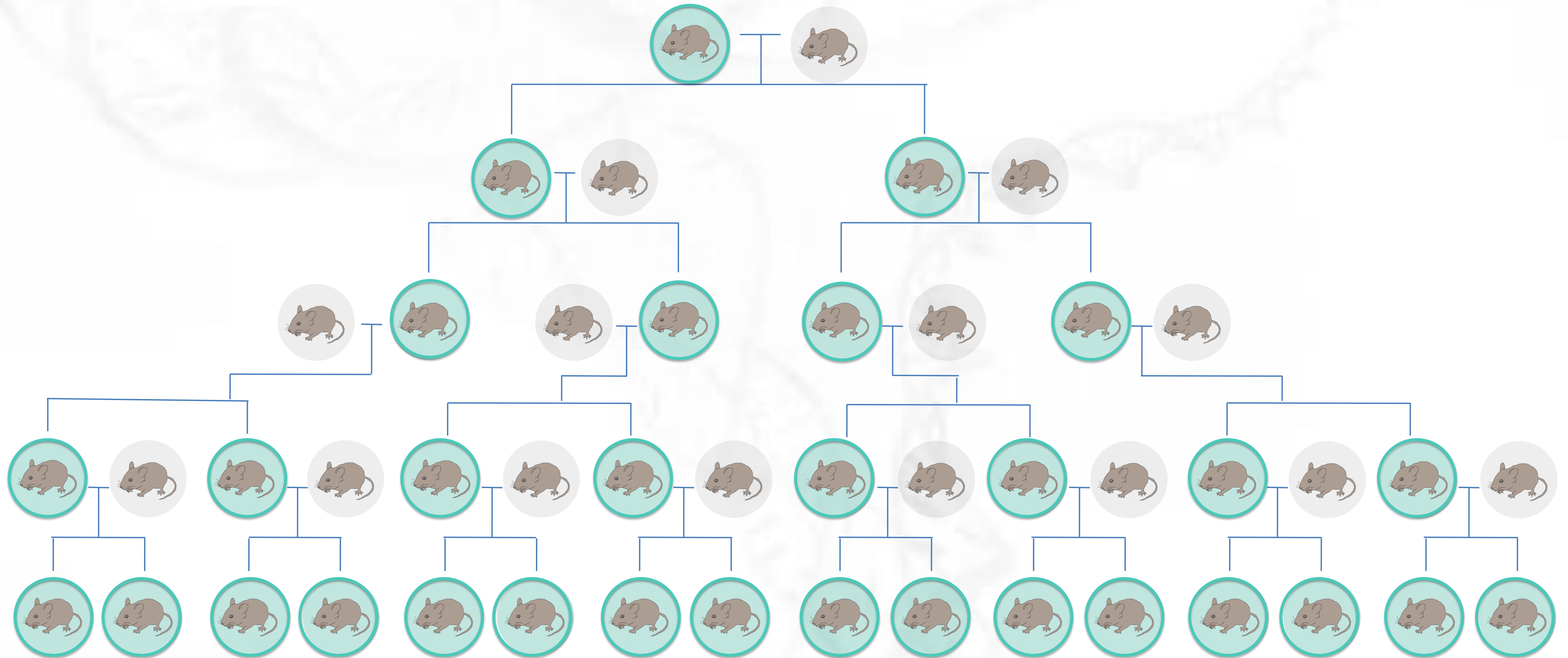
Self-Propagating Gene Drive



Self-Propagating Gene Drive



Self-Propagating Gene Drive



Requires exclusive **sexual reproduction**

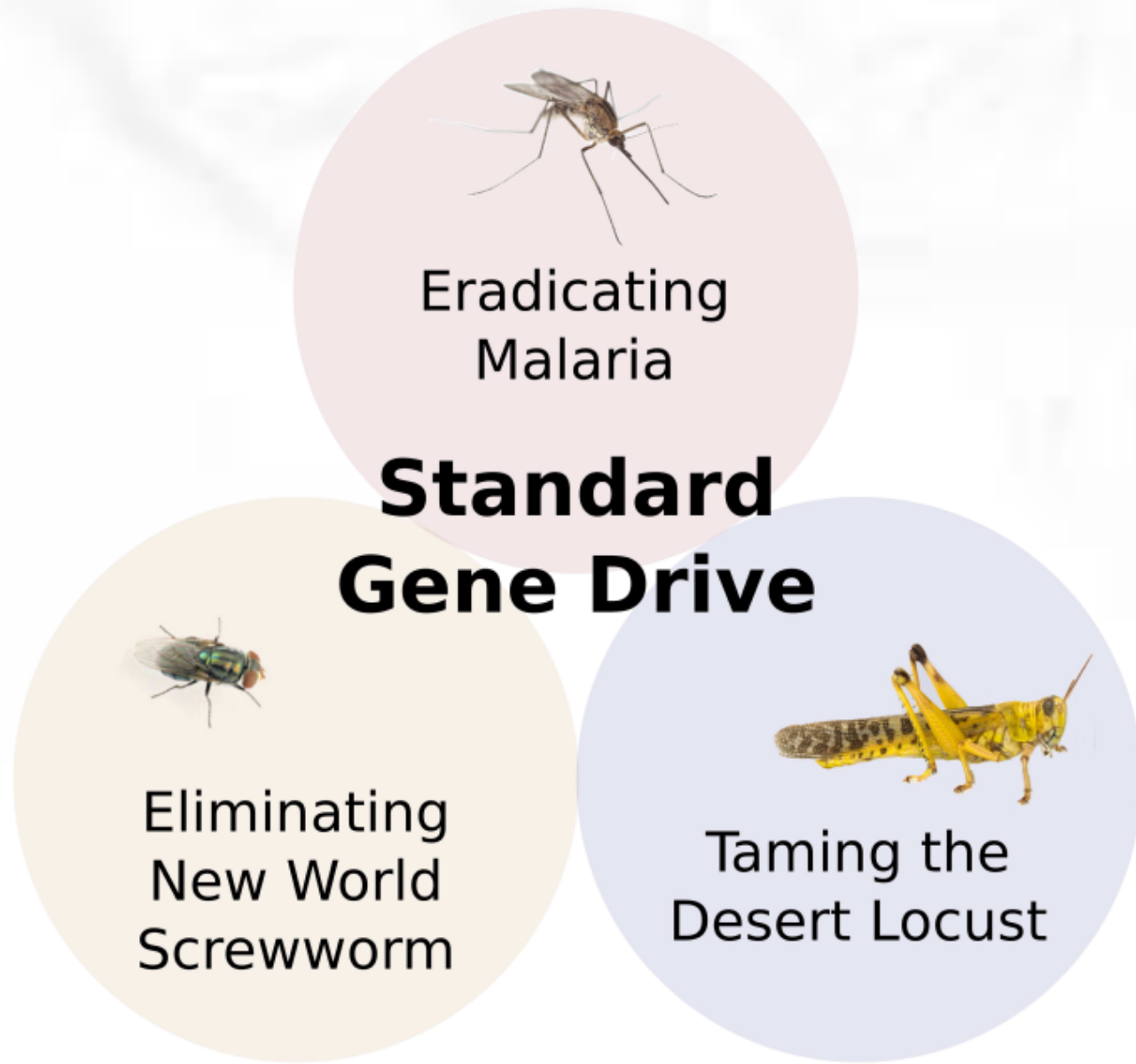
Speed depends on **gene flow** and **generation time**

Can **alter** or **suppress** populations

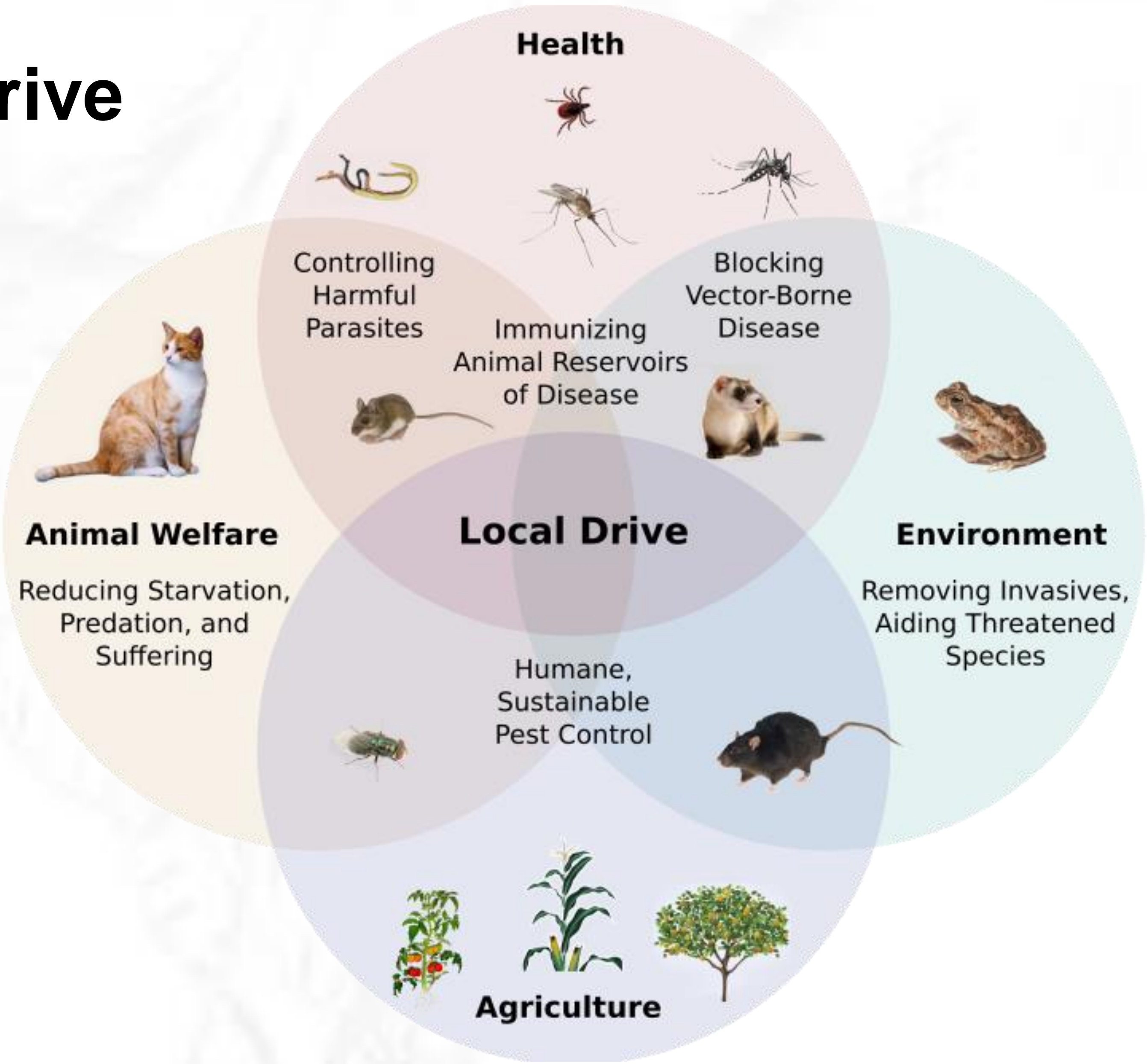
Changes can be **overwritten**

Accessibility limited by the difficulty of **delivering DNA**

Two Kinds of Gene Drive



May affect every population of the target species



Every community can decide without affecting others



Ecotechnology Development = Civic Governance

People who aren't informed of experiments **are denied a voice** in decisions intended to affect them - and cannot opt out



Ecotechnology Development = Civic Governance

Article 21

Everyone has the right to take part in the government of their country

The will of the people shall be the basis of the authority of government



Concerning RNA-guided gene drives for the alteration of wild populations

KEVIN M ESVELT*, ANDREA L SMIDLER, FLAMINIA CATTERUCCIA* AND GEORGE M CHURCH*

Scienceexpress

BIOTECHNOLOGY

Regulating gene drives

Regulatory gaps must be filled before gene drives could be used in the wild

By **Kenneth A. Oye**,^{1,2*}† **Kevin Esvelt**,^{3*} **Evan Appleton**,⁴ **Flaminia Catteruccia**,^{5,6} **George Church**,³ **Todd Kuiken**,⁷ **Shlomiya Bar-Yam Lightfoot**,² **Julie McNamara**,² **Andrea Smidler**,^{5,8} and **James P. Collins**⁹

cannot be used to engineer populations of viruses or bacteria. Second, a newly released drive will typically take dozens of generations to affect a substantial proportion of a target population, unless drive-containing organisms are released in numbers consti-

We pre-register all of our gene drive experiments



New Results

Daisy-chain gene drives for the alteration of local populations

Charleston Noble, John Min, Jason Olejarz, Joanna Buchthal, Alejandro Chavez, Andrea L Smidler, Erika A DeBenedictis, George M Church, Martin A Nowak, Kevin M Esvelt

doi: <https://doi.org/10.1101/057307>

This article is a preprint and has not been peer-reviewed [what does this mean?].



New Results

Daisy quorum drives for the genetic restoration of wild populations

John Min, Charleston Noble, Devora Najjar, Kevin Esvelt

doi: <https://doi.org/10.1101/115618>

This article is a preprint and has not been peer-reviewed [what does this mean?].



New Results

Daisyfield gene drive systems harness repeated genomic elements as a generational clock to limit spread

John Min, Charleston Noble, Devora Najjar, Kevin M Esvelt

doi: <https://doi.org/10.1101/104877>

This article is a preprint and has not been peer-reviewed [what does this mean?].

Sculpting Evolution - Ecological Engineering Grant Proposals

Burroughs Wellcome IRSA grant (funded June 2016): [full proposal](#)

USDA BRAG grant (denied July 2016): [summary full proposal](#)

NSF CAREER 2016 (highest rating but denied Nov 2016): [full proposal](#)

Greenwall Foundation Making a Difference grant (funded Nov 2016): [full proposal](#)

NIH DP2 New Innovator (funded Sep 2017): [summary full proposal](#)

DoD Tick-Borne Disease Research Program (funded Sep 2017): [lay abstract](#) [tech abstract](#) [full proposal](#) (does NOT involve gene drive)

DARPA Safe Genes (funded Sep 2017): [summary of research](#) [statement of work](#)

NSF CAREER 2017 (pending): [full proposal](#)

Precaution: Open gene drive research

Openness and collective oversight would reduce the risk of an accident involving gene drive, and may mitigate the backlash from such a disaster, while accelerating—not impeding—discovery. Journals, funders, policy-makers, and holders of intellectual property should work to ensure that all gene drive research is open from the proposal stage onward.

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NATURE | COLUMN: WORLD VIEW

Gene editing can drive science to openness

The fast-moving field of gene-drive research provides an opportunity to rewrite the rules of the science, says [Kevin Esvelt](#).

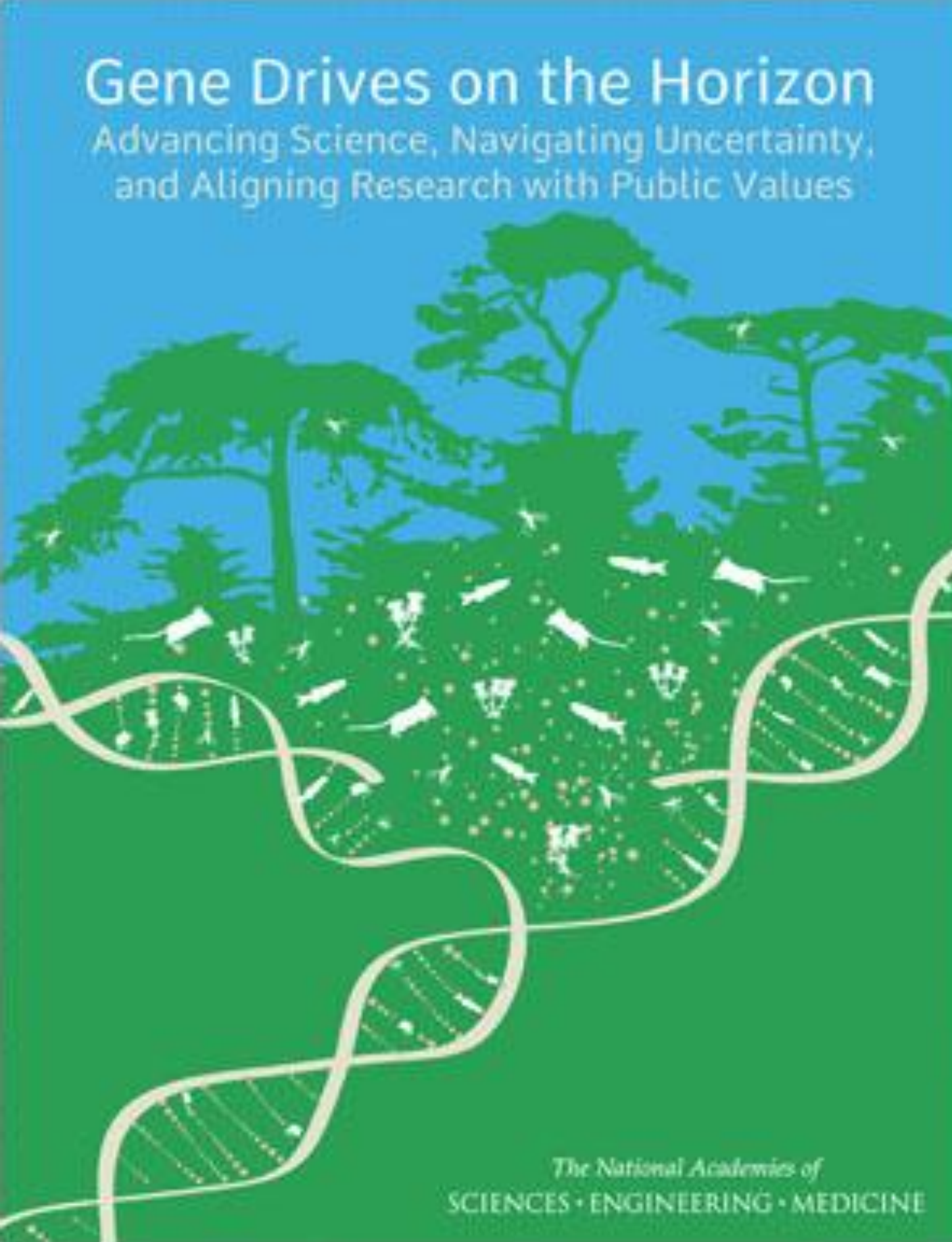
08 June 2016



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K. Esvelt

Esvelt KM (2016) *Nature*
Esvelt KM (2017) *Science*



“The best course of action is to ensure that those who would be affected by a proposed project or policy have an opportunity to have a voice in decisions about it.”

- U.S. National Academies report on gene drive

But it will not happen unless we change scientific incentives:

IP-holders, journals, funders, policymakers

Local, Open, Responsive Science

- **Address problems obvious to all**
- **Openly share proposals before experiments begin**
- **Actively invite concerns & community guidance**
- **Arrange for independent assessment**



Acknowledgements

Daisy-Chain Drive (Noble, Min et al 2016)

John Min **Joanna Buchthal** **Erika DeBenedictis**
 Charleston Noble George Church Andrea Smidler
 Alex Chavez Martin Nowak Jason Olejarz

Daisyfield Drive (Min et al 2017)

John Min
 Charleston Noble
Devora Najjar

Daisy Drive Aotearoa

John Min
Stephen Von Stetina
Ashton Strait
Devora Najjar
 Neil Gemmell
 Dan Tompkins
 The Kahui Maori

Daisy Quorum (Min et al 2017)

John Min
 Charleston Noble
Devora Najjar

Responsive Science

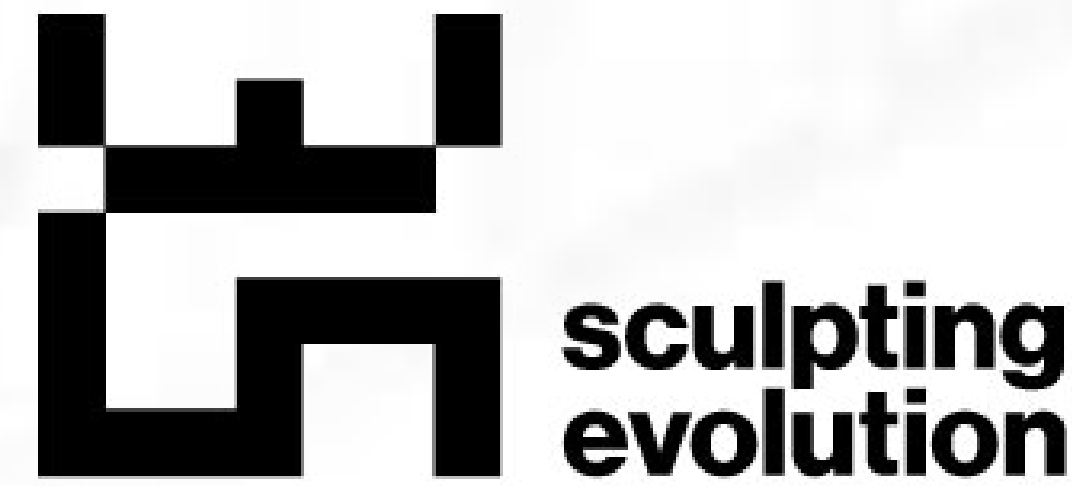
Avery Normandin
Devora Najjar
Dana Gretton
Joanna Buchthal
 Shlomiya Lightfoot
 Jeantine Lunshof
 Travis Rich
 Sam Weiss Evans

Mice Against Ticks

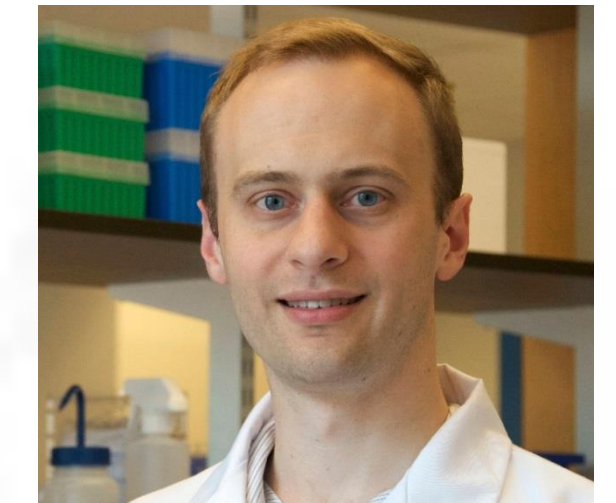
Joanna Buchthal Sam Telford
John Min Linden Hu
Devora Najjar Duane Wesemann
 The communities of Nantucket and
 Martha's Vineyard

Robotic PACE

Erika DeBenedictis



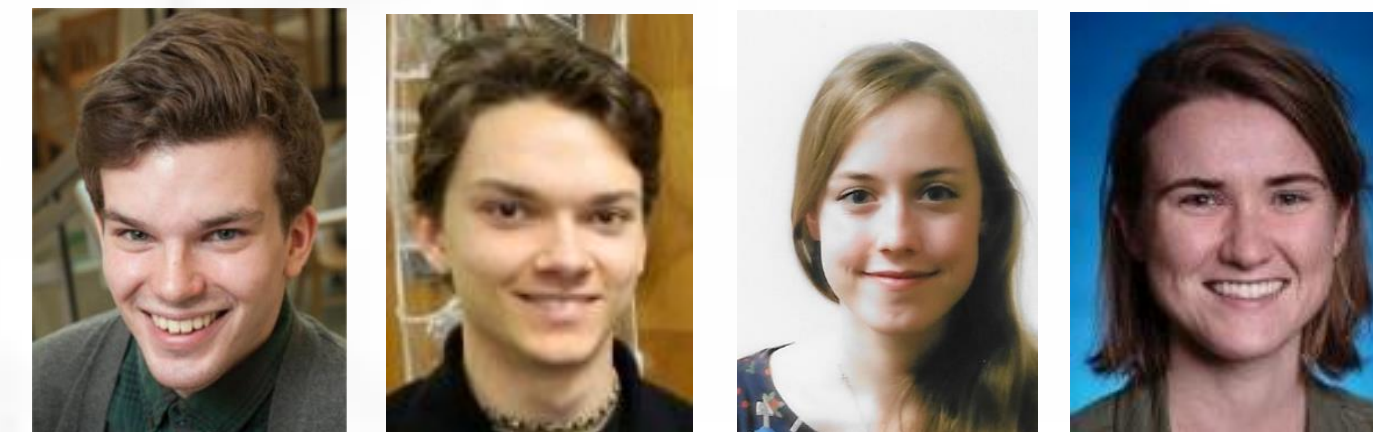
exploring evolutionary and ecological engineering



Kevin Esvelt



Stephen Von Stetina Kristina Bonikowski John Min Erika DeBenedictis Joanna Buchthal Cody Gilleland Devora Najjar



Avery Normandin Dana Gretton Ashton Strait Lily Fitzgerald



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www.responsivescience.org
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It is **HARD** to alter an entire population

It is **HARD** to suppress a population

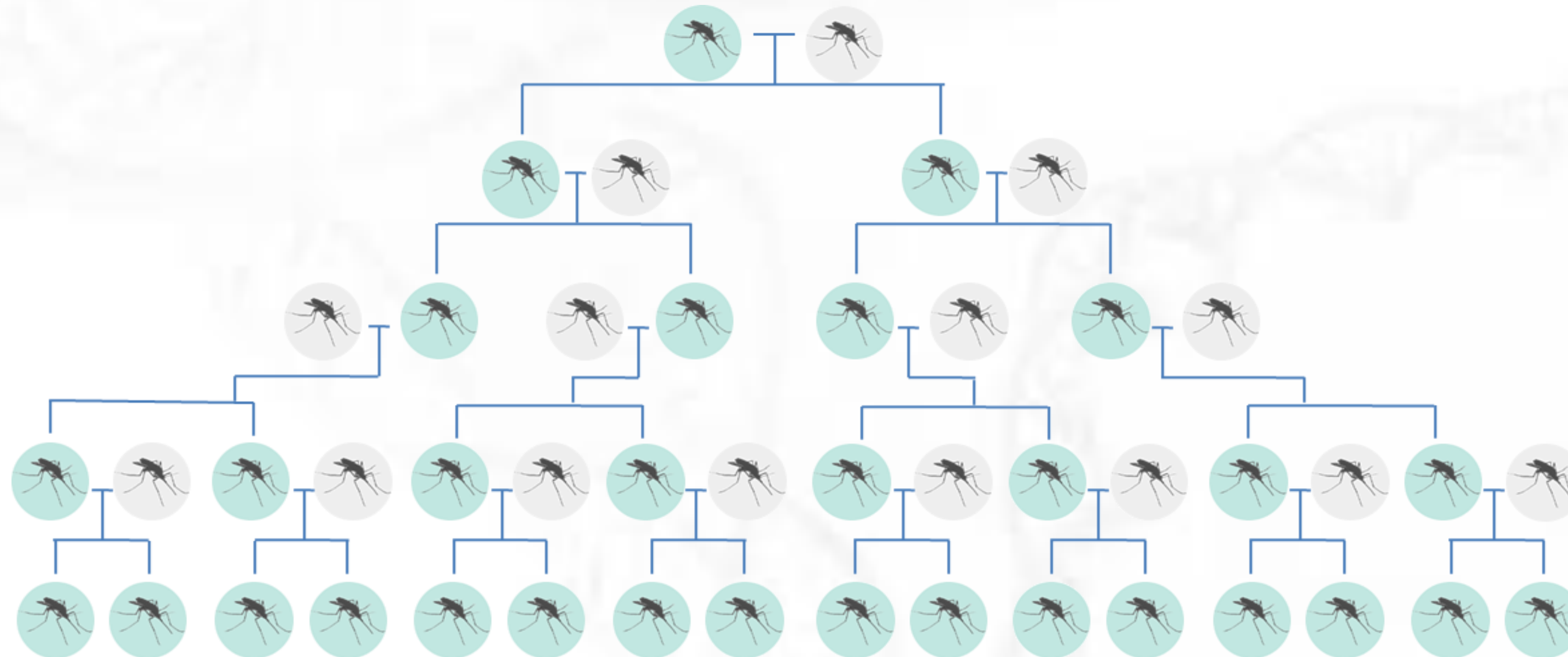
It is **EASY** to temporarily alter part of a population

CRISPR gene drive is a one-to-many technology

- **Accessible:** requires CRISPR transgenesis in sexual organism
- **Self-replicating:** capable of spread in the shared environment
- **Unilateral:** one individual can in principle release it on their own

However, it is unlikely to be physically dangerous

Slow: Takes Generations to Spread



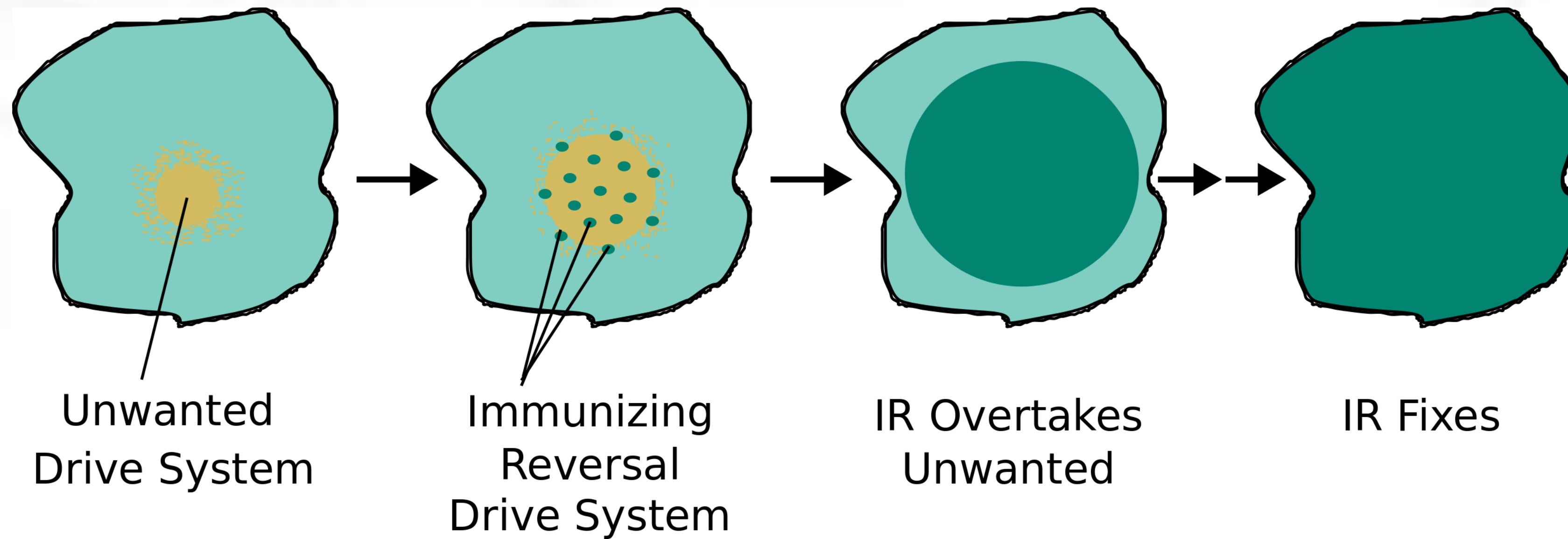
100-fold increase = 10+ generations under ideal conditions

1,000-fold increase = 15+ generations

Obvious (if you look): Sequencing

Eukaryotic expression signal + CRISPR element
should never occur in nature

Reliably Countered: Overwriting Drives



This should be able to restore the original phenotype, but not the genotype (yet)

Ecological changes *may not be reversible*

Anything slow, obvious, and easily blocked is not a major threat

The primary risk is to public perception of science & governance

Time required to spread is not relevant to social outcomes

Economic issues / trade barriers pose major security challenges