Genetic engineering of wild populations

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Are geneticists going into the wild ?

Human-driven genetic modifications

- Since 10,000 years: domestication of plants and animals
- Selective breeding

Genetically Modified Organisms

- GMO: an organism whose genetic material has been altered using genetic engineering techniques
- First GMOs: bacteria (1973), mouse (1973)
- Applications:
  - Biological and medical research
  - Production of pharmaceutical drugs, vaccines
  - Agriculture
  - …

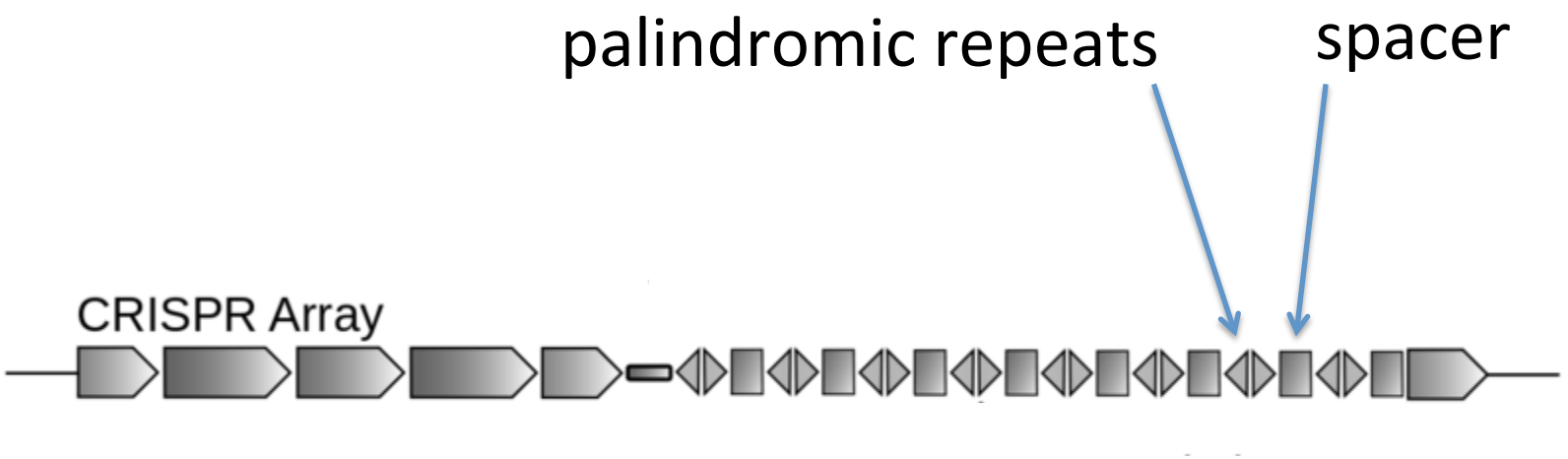
Human-driven genetic modifications

- Selective breeding:
  - Limited by the genetic diversity present in the population
  - Random mutations
- Genetic engineering:
  - Possibility to introduce any piece of DNA
  - Directed mutagenesis

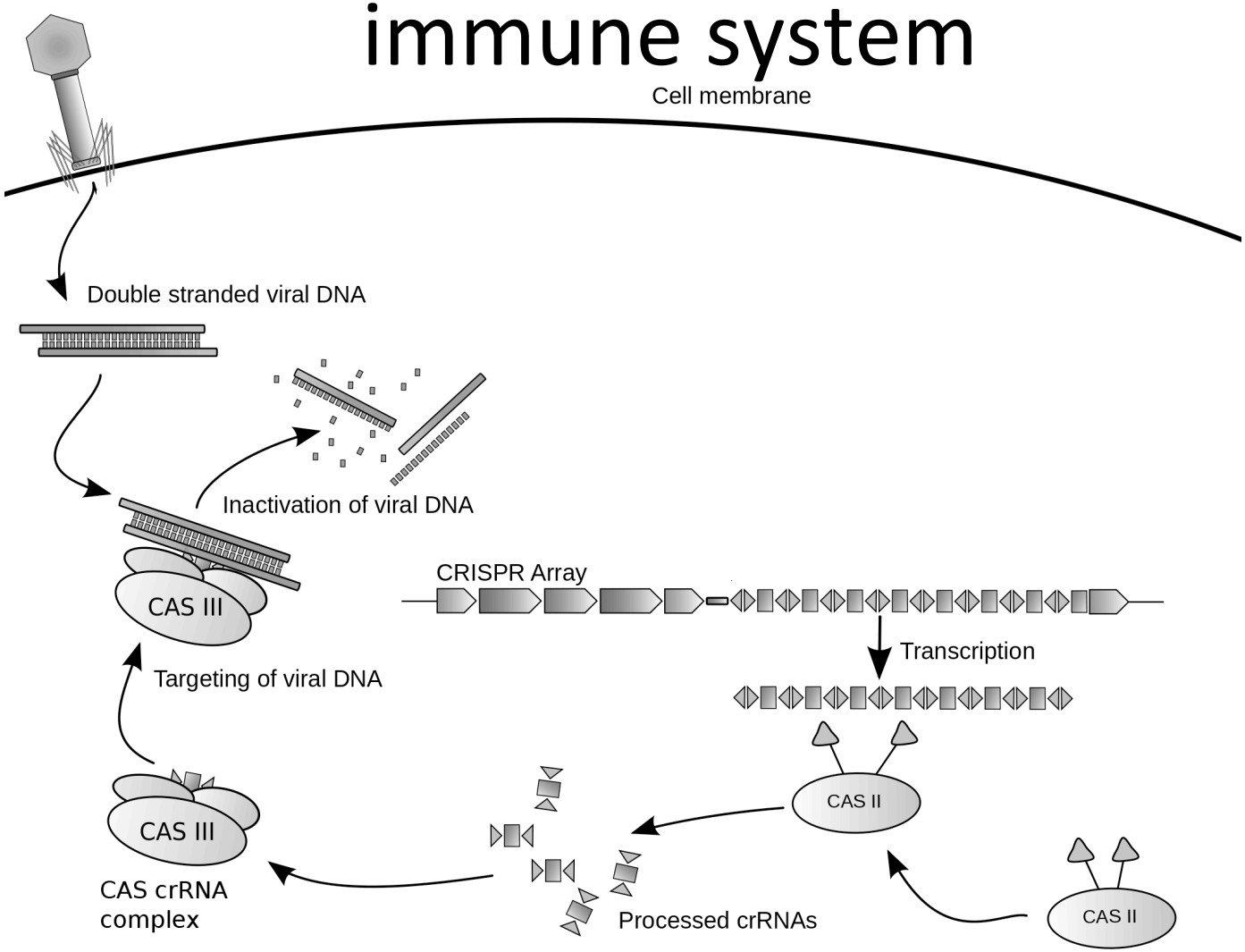
CRISPR/Cas system: a new versatile tool for genome editing

CRISPR/Cas system: a prokaryotic immune system

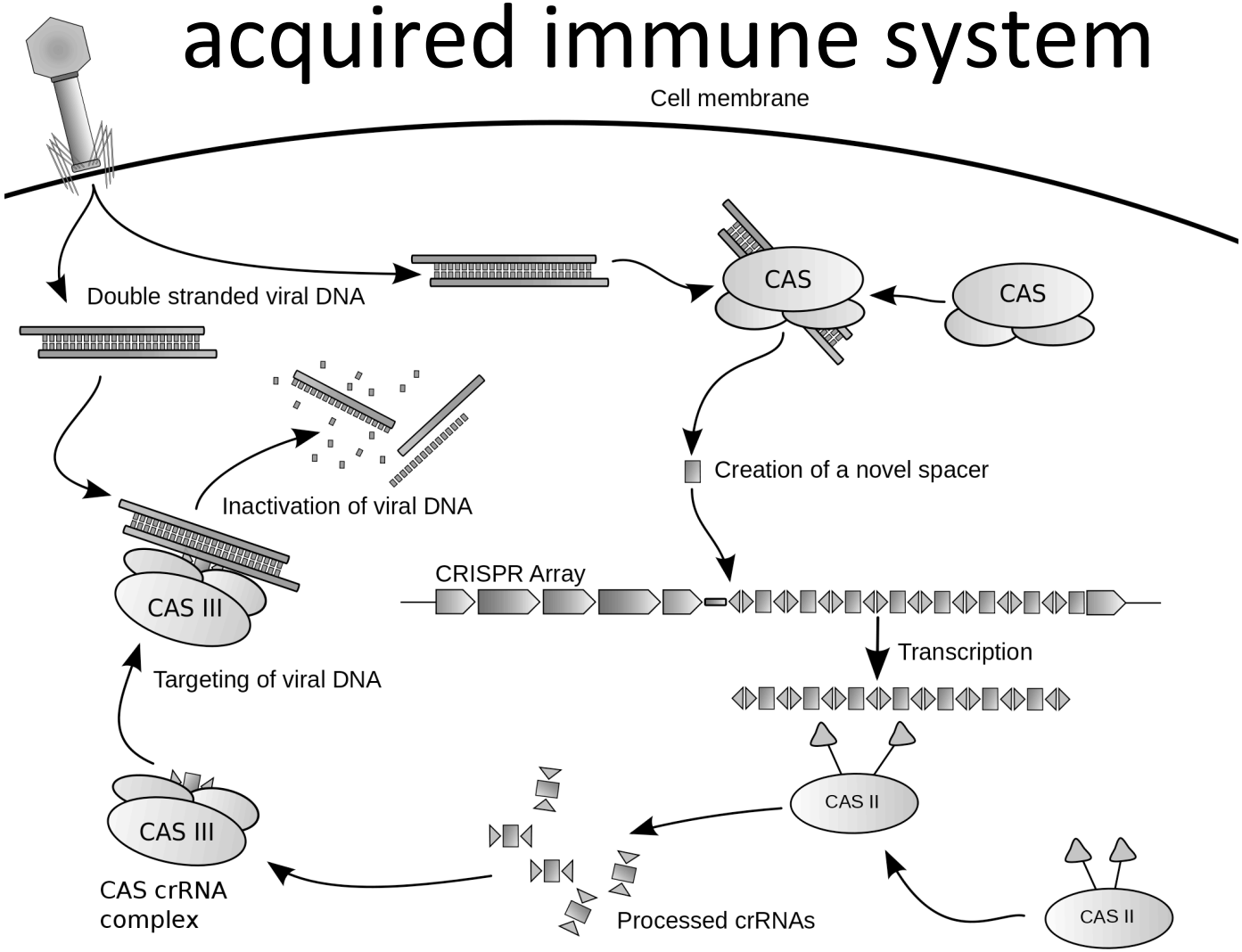
- CRISPRs (clustered regularly interspaced short palindromic repeats)
- Cas = CRISPR-associated genes



CRISPR/Cas system: a prokaryotic immune system



CRISPR/Cas system: a prokaryotic acquired immune system

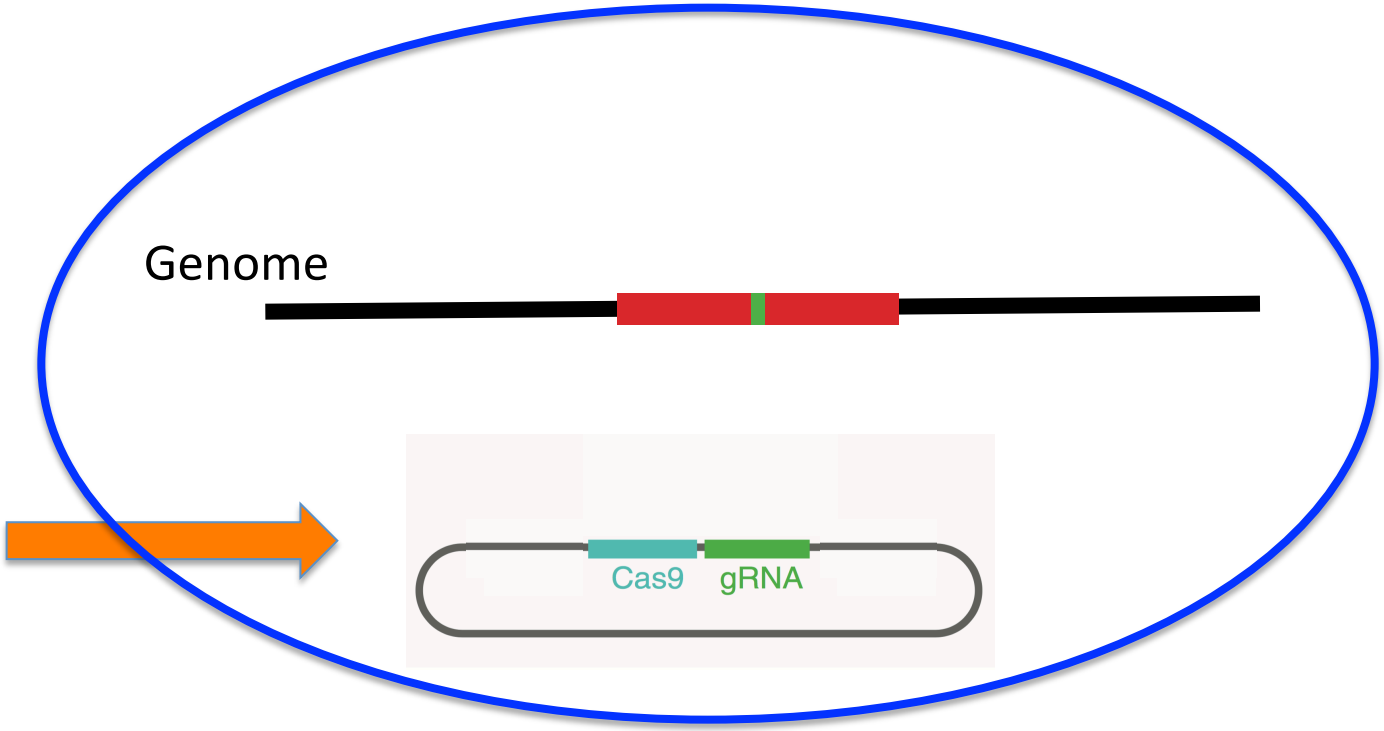


CRISPR/Cas system: a prokaryotic immune system

- Confers resistance to foreign genetic elements such as plasmids and phages
- Found in approximately 40% of sequenced bacteria genomes and 90% of sequenced archaea

CRISPR/Cas system: a versatile tool for genome editing

- CRISPR/Cas9 => double strand breaks (DSBs) at loci that are identical to the guide RNA (gRNA)



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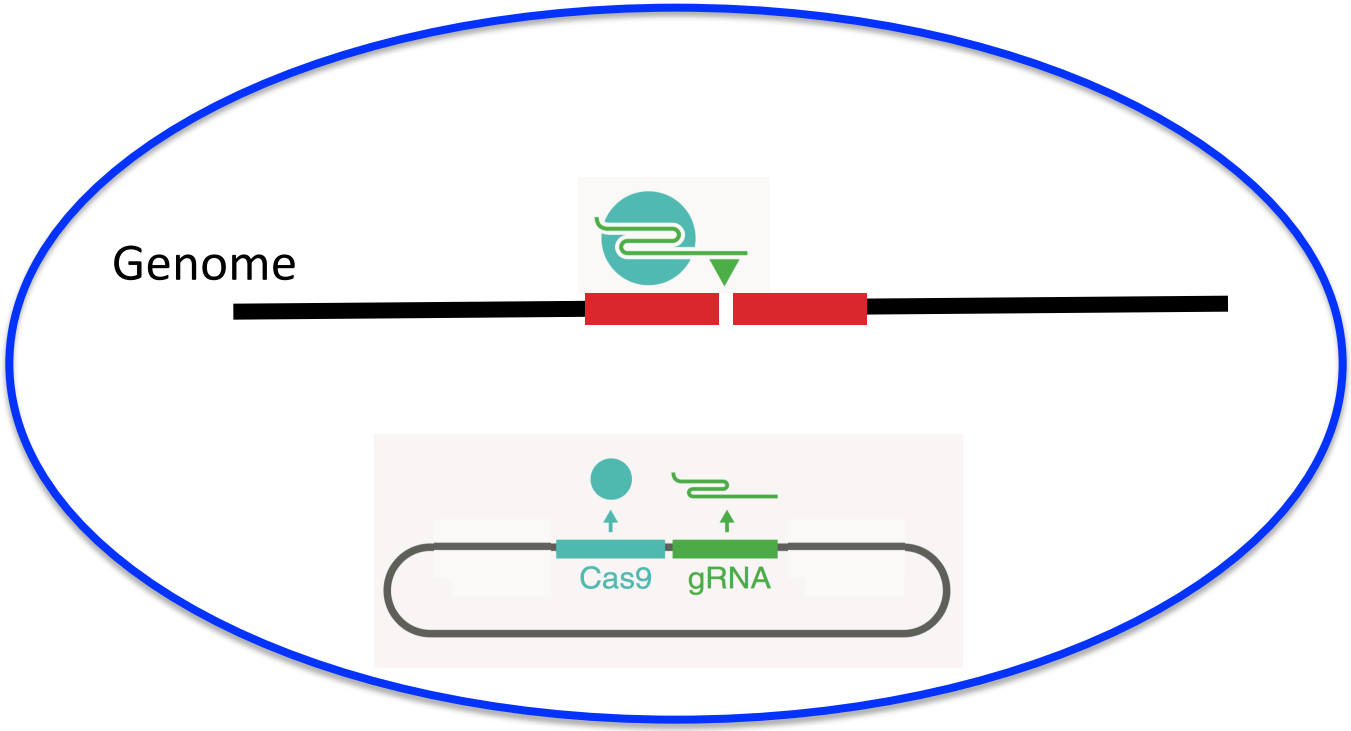
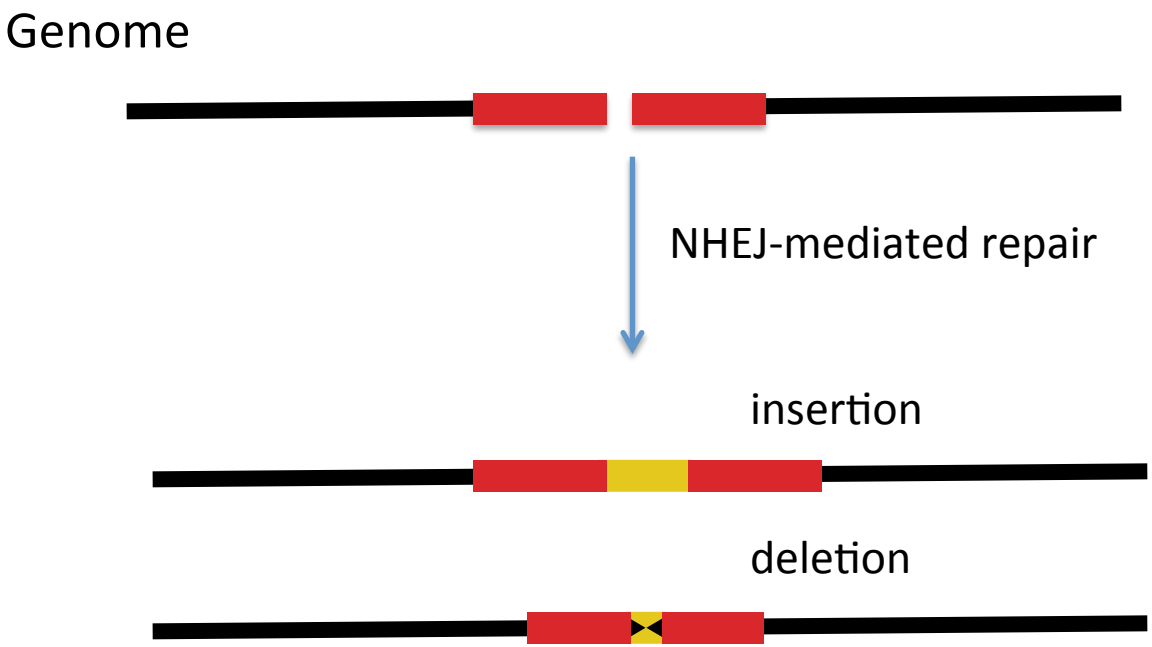
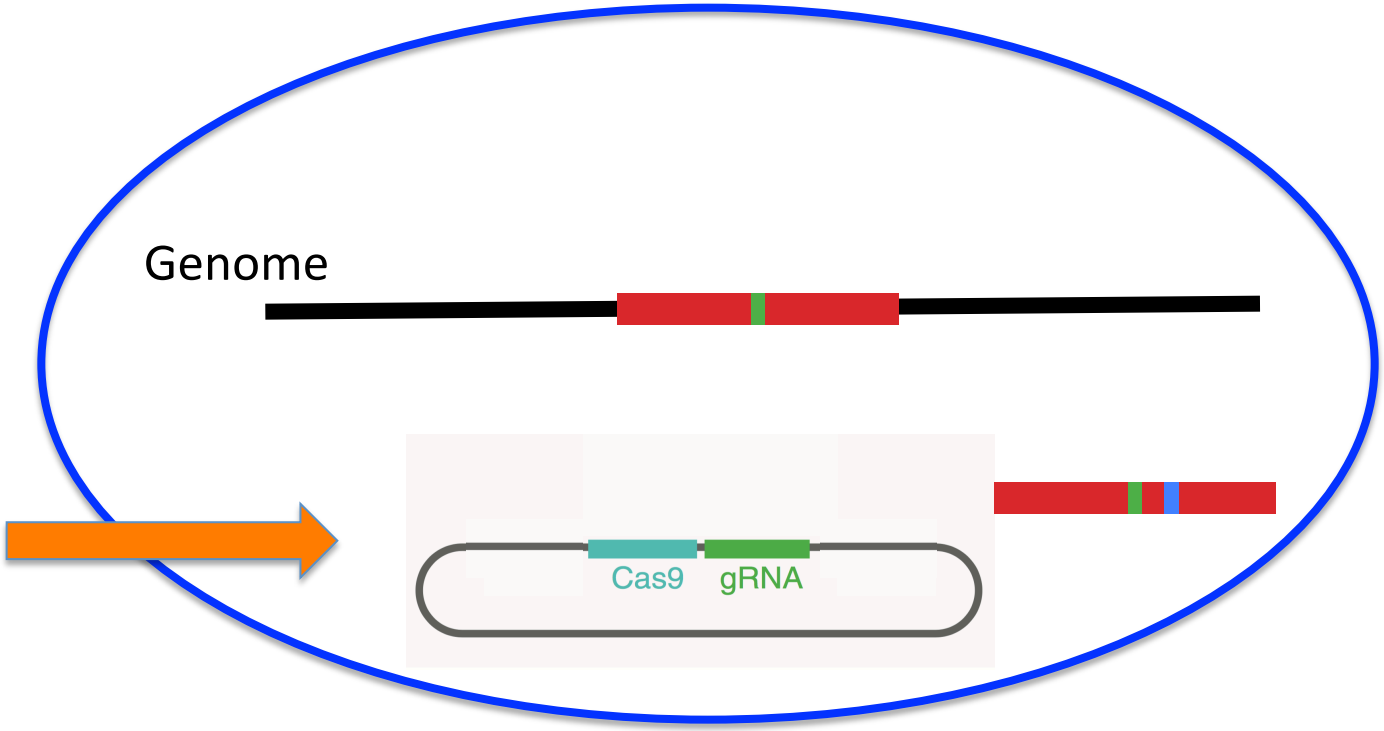


DSB repair (1): non-homologous end joining (NHEJ)



CRISPR/Cas system: a versatile tool for genome editing



CRISPR/Cas system: a versatile tool for genome editing

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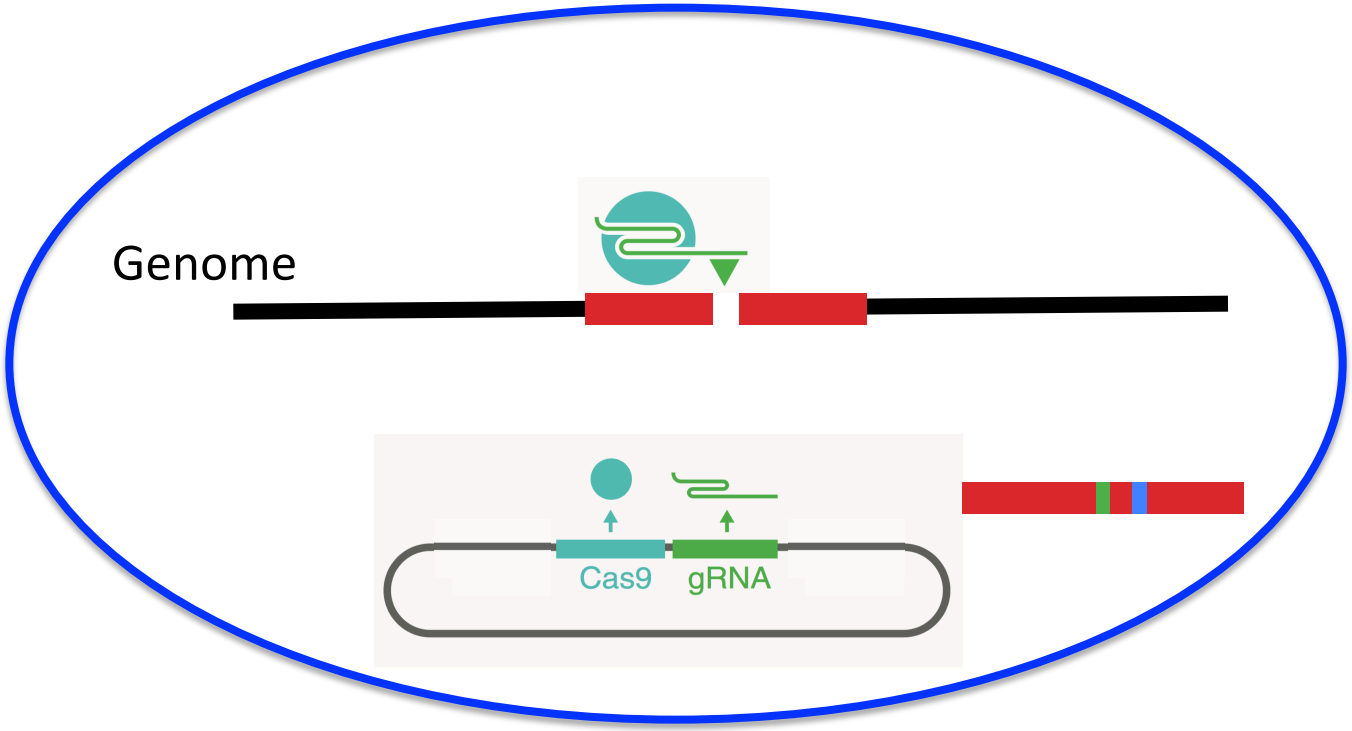
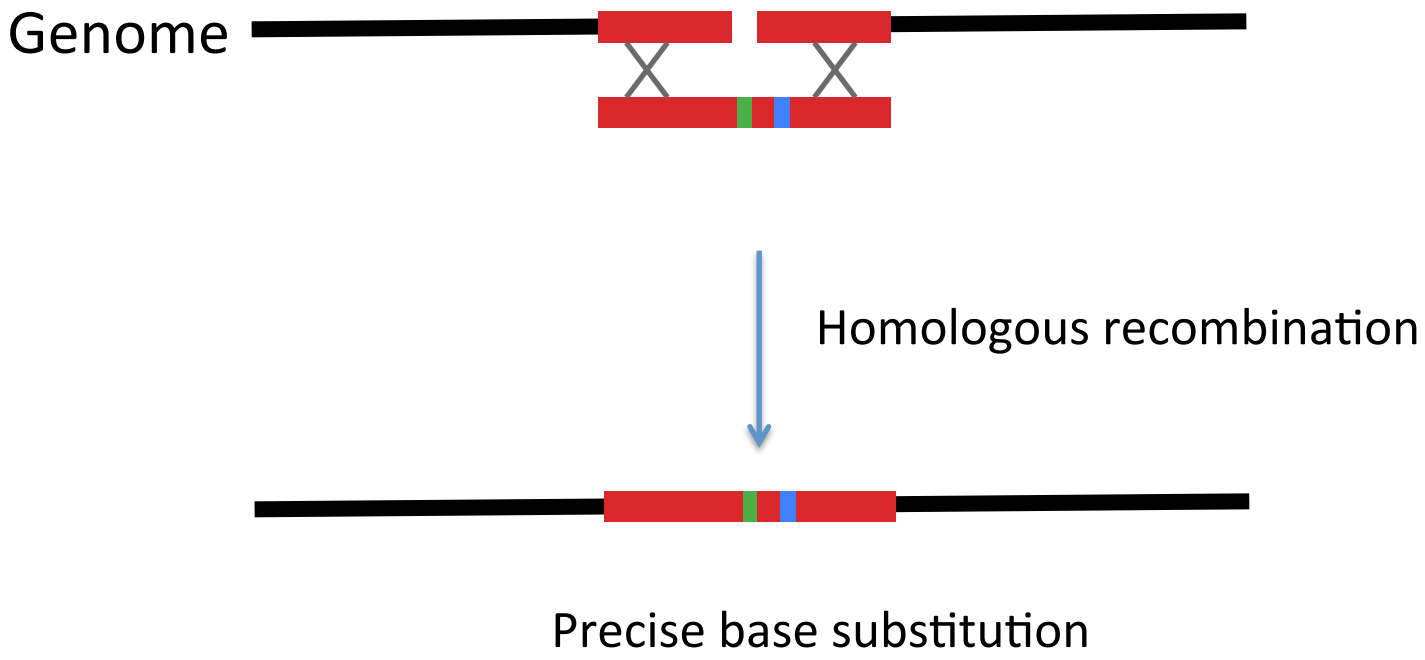
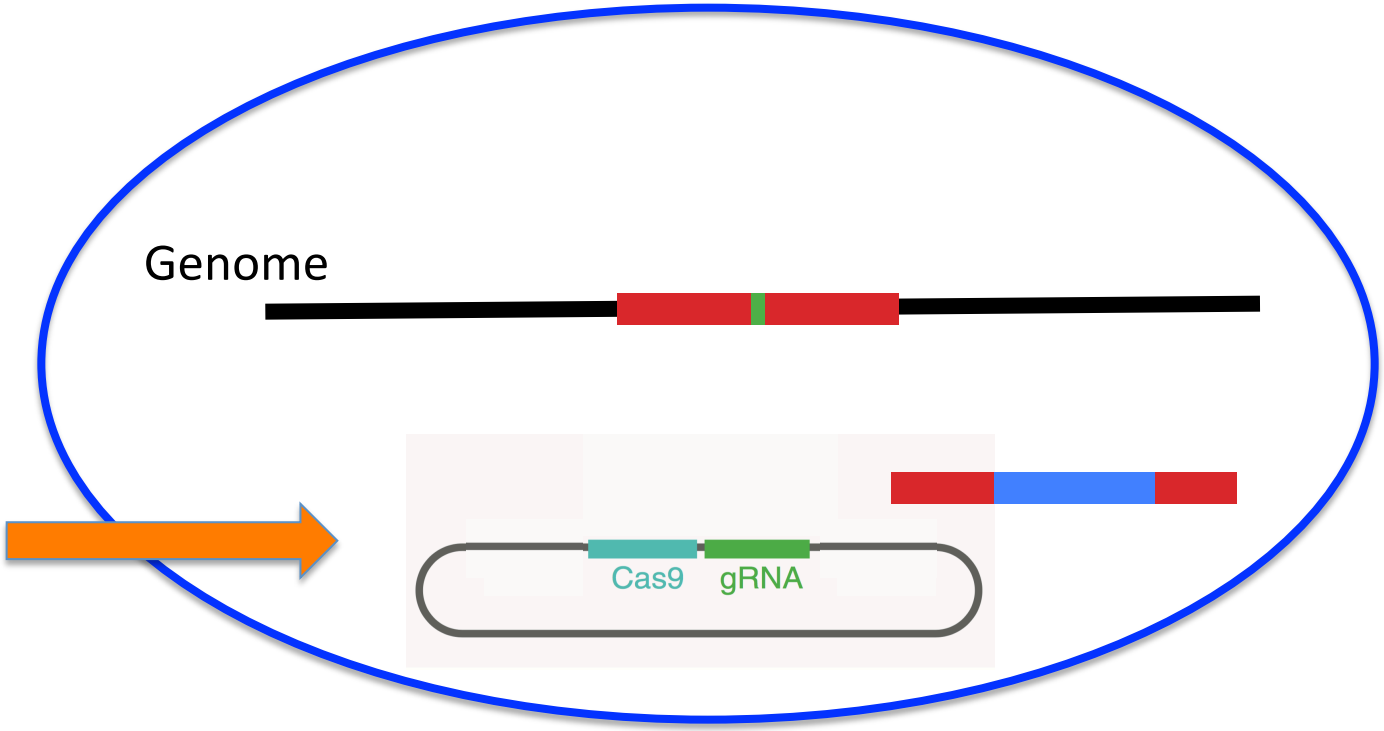


DSB repair (2): homologous recombination (HR)



CRISPR/Cas system: a versatile tool for genome editing



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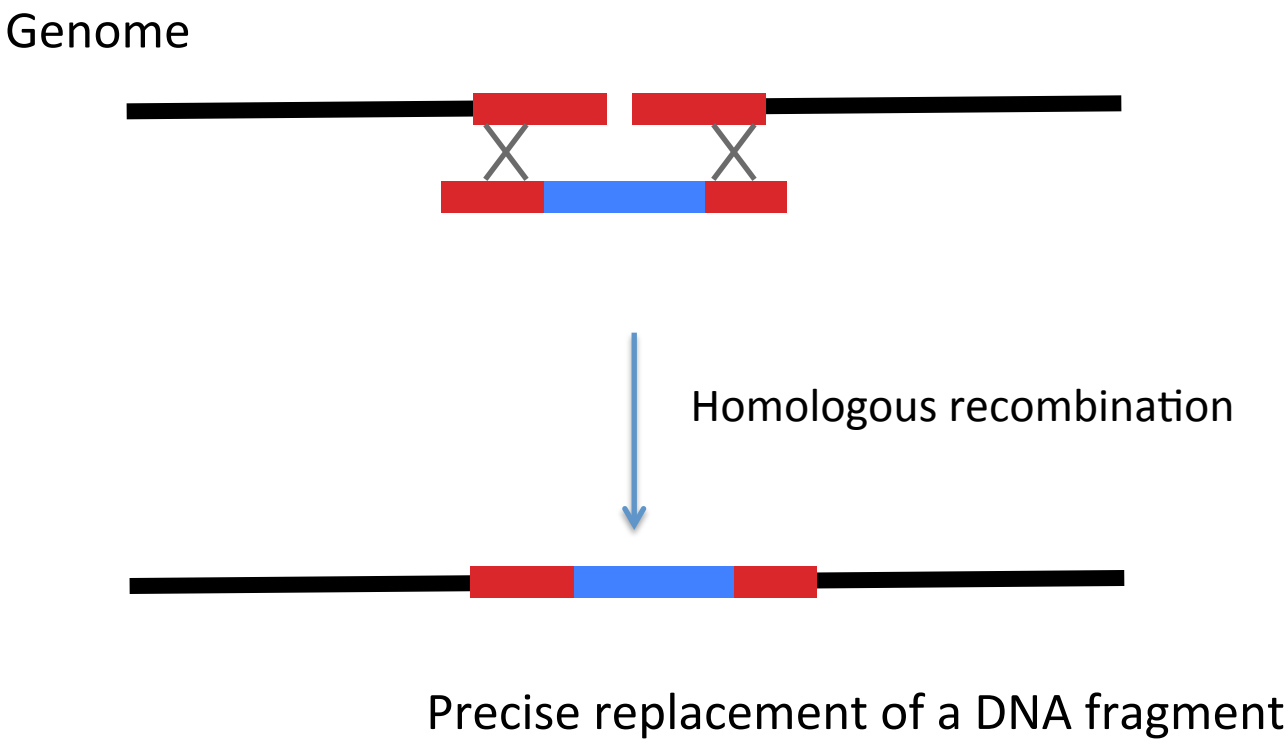
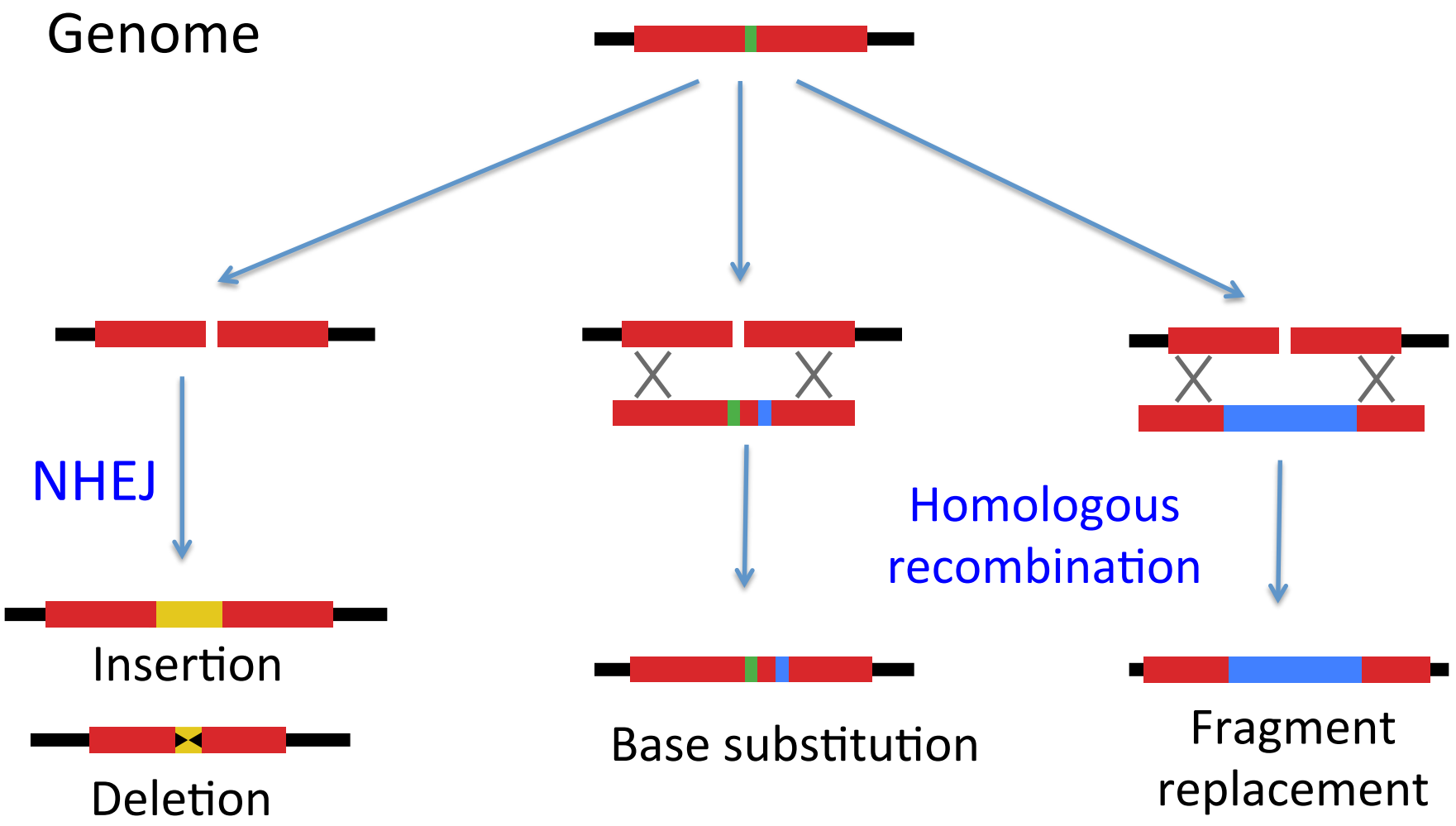


CRISPR/Cas system: a versatile tool for genome editing



CRISPR/Cas system: a versatile tool for genome editing (and other applications)

- CRISPR/Cas9 (2012): very efficient, cheap and simple (>> TALENs or Zn-Fn nucleases)
- Can work with any kind of organism (including non-model organisms)
- => a revolution for genetic engineering

Jinek M, Chylinski K, Fonfara I, Hauer M, Doudna JA, Charpentier E (August 2012). "A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity". Science. 337 (6096): 816–21

GENOME EDITING

The mutagenic chain reaction: A method for converting heterozygous to homozygous mutations

Valentino M. Gantz* and Ethan Bier*

SCIENCE

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PCR (1986) = polymerase chain reaction
MCR (2015) = mutagenic chain reaction

An efficient and simple method to spread a transgene into wild populations

Gene Drive

GENOME EDITING

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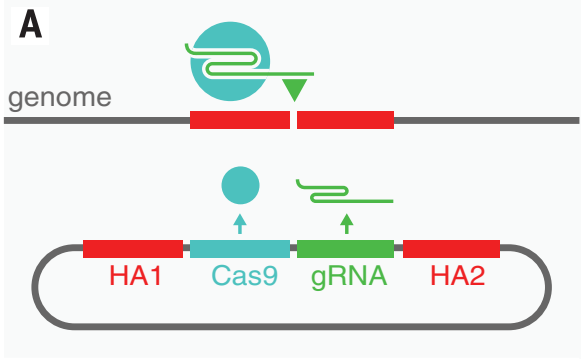
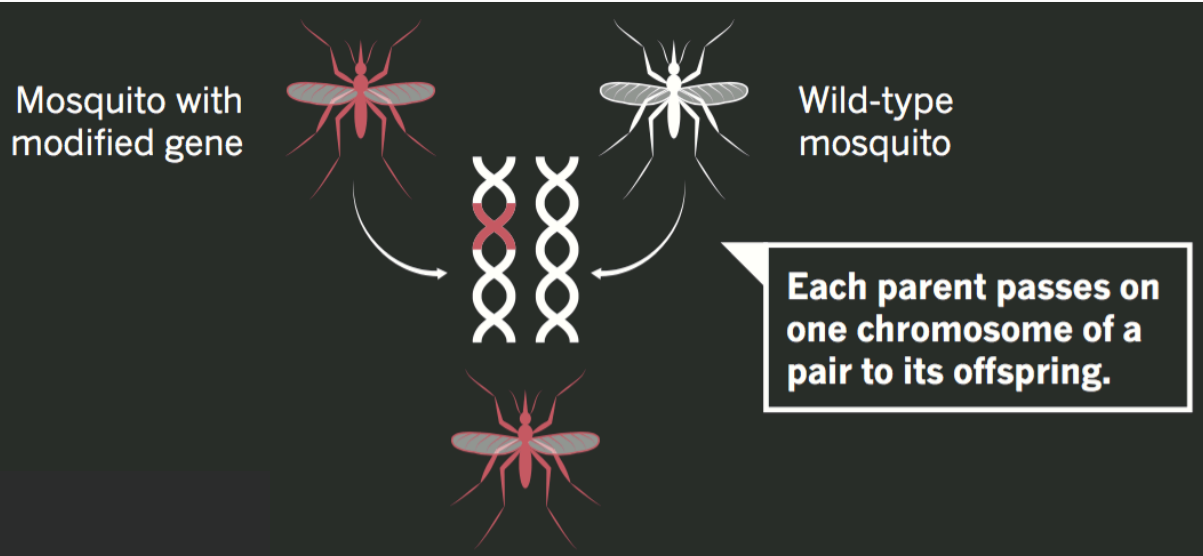
Valentino M. Gantz* **and Ethan Bier***

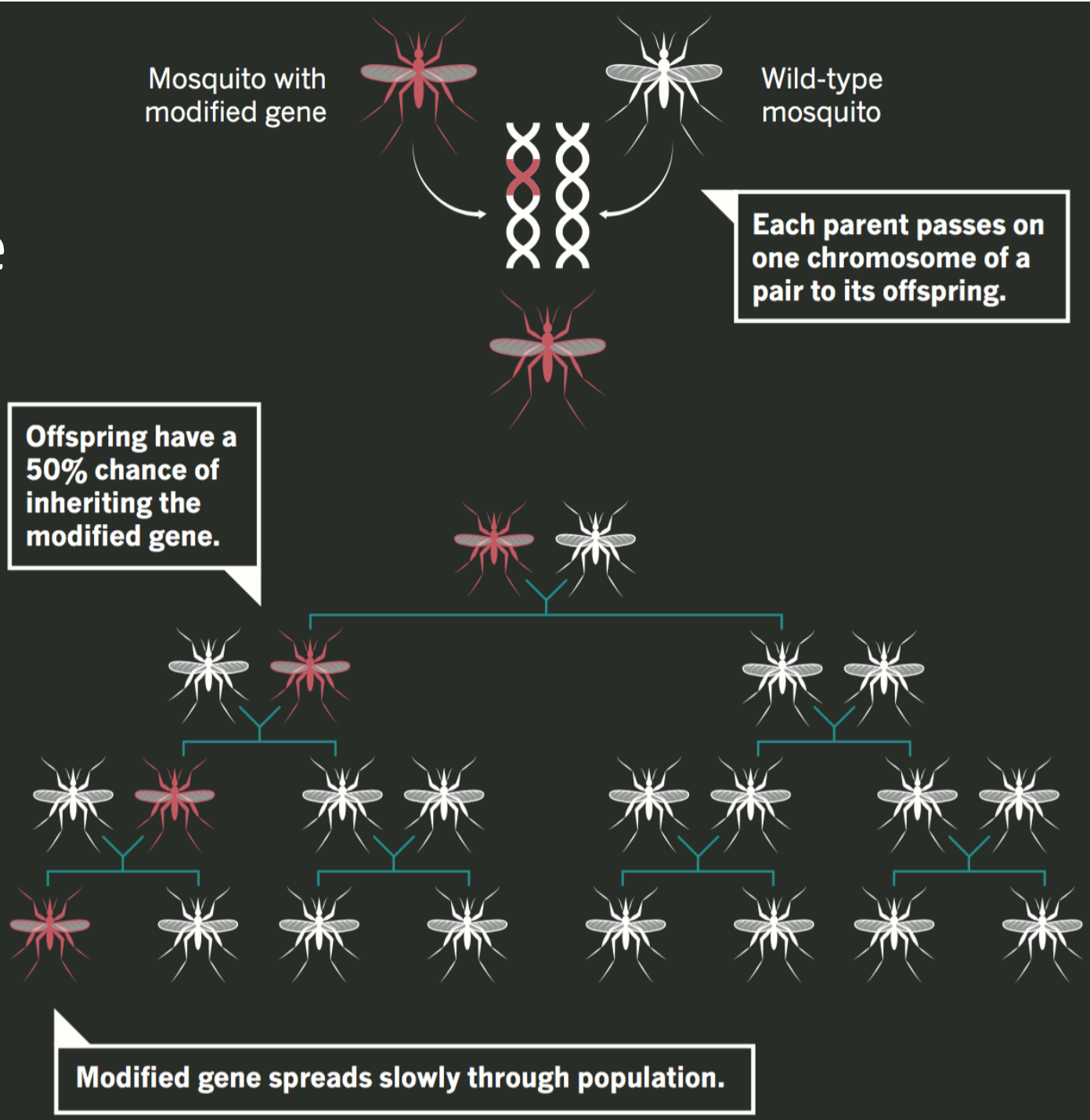


Standard inheritance



Ledford (2015)
Nature. 522:20

Standard inheritance



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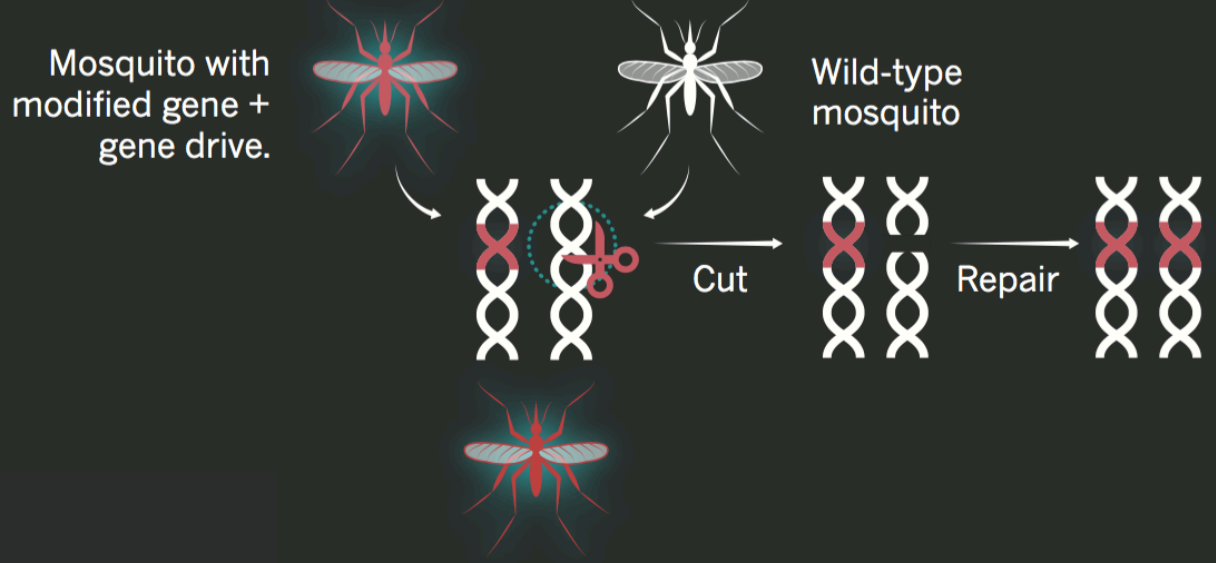
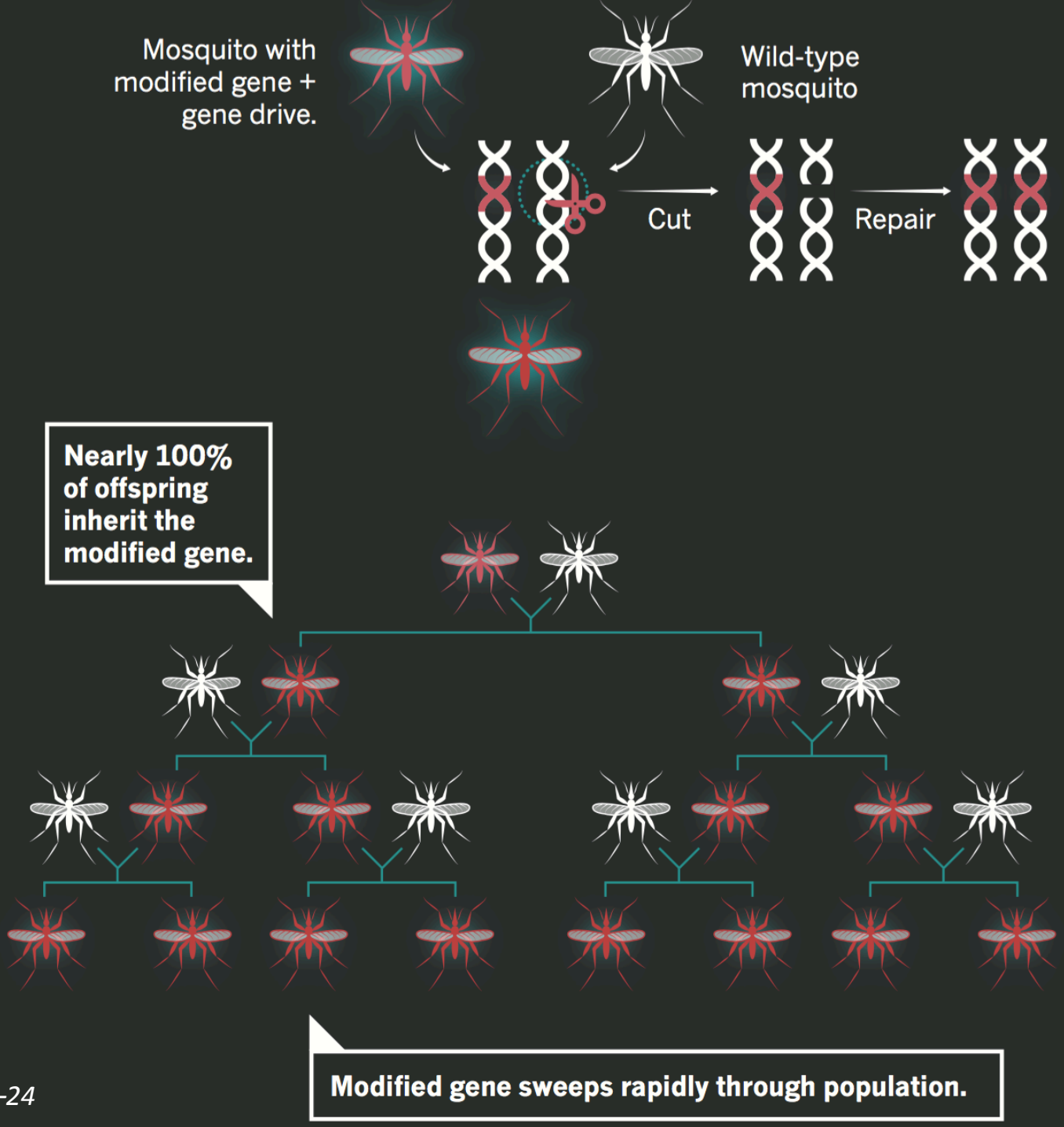
Gene-drive inheritance



Ledford (2015) Nature. 522:20–24

Gene-drive inheritance



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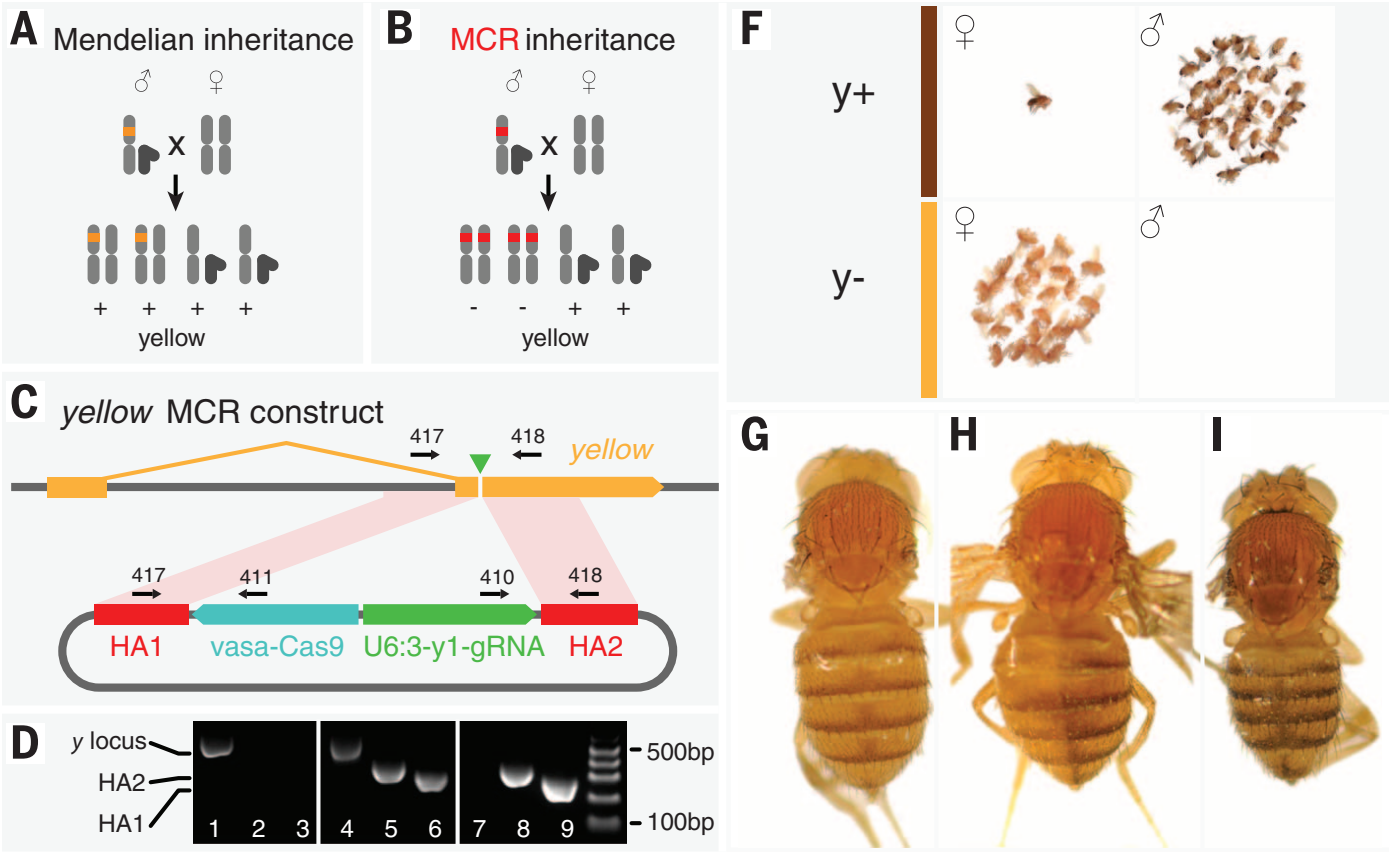

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The mutagenic chain reaction: A method for converting heterozygous to homozygous mutations

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$X^{-}Y \times X^{+}X^{+} \Rightarrow 50\% X^{-}X^{+} + 50\% YX^{+}$

$X^{-}X^{-} \times X^{+}Y \Rightarrow 50\% YX^{-} + 50\% X^{-}X^{+}$

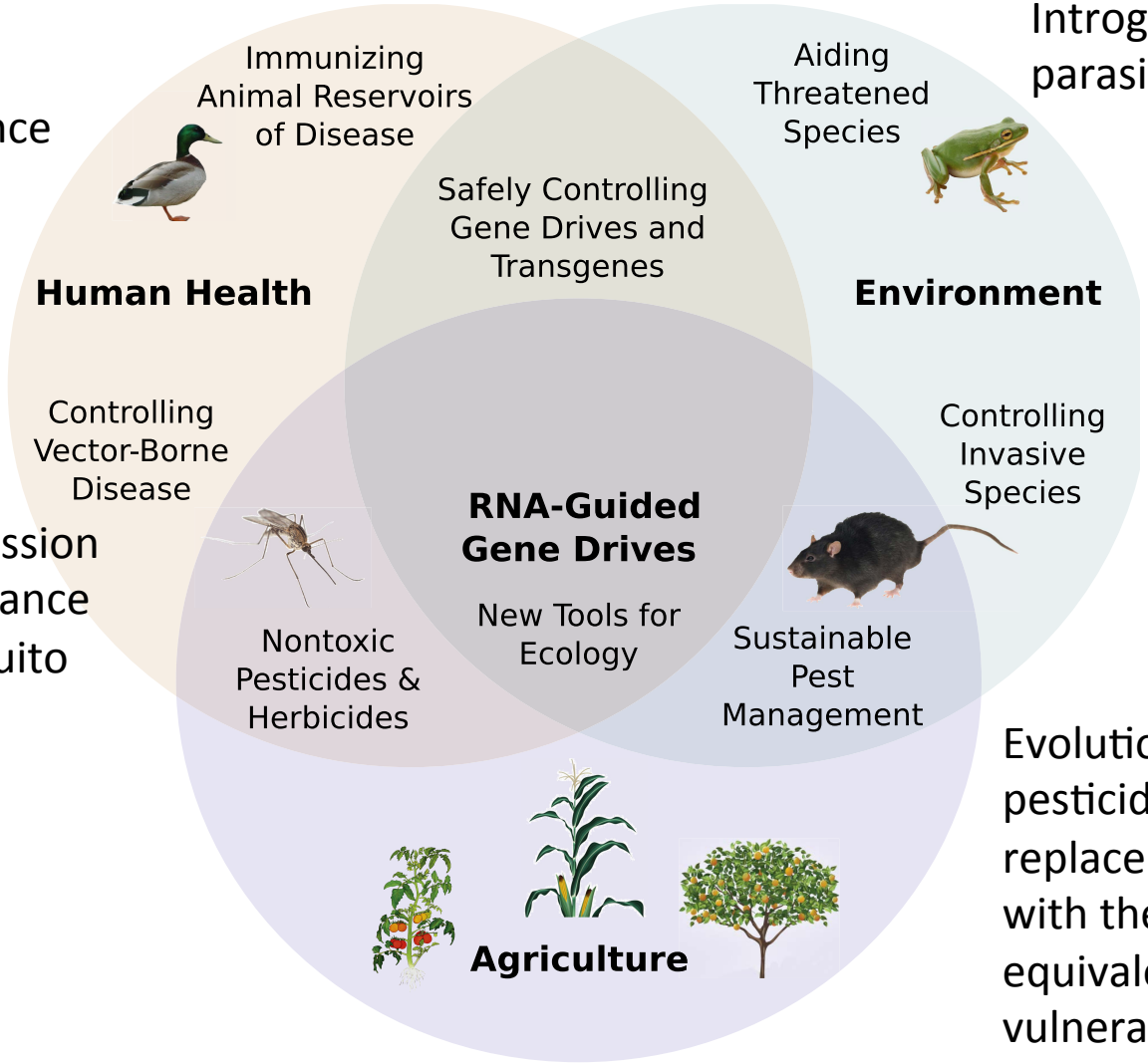
Crispr-Cas9 gene drive

- Very efficient
- Cheap & easy
- Limitiations
  - Sexual species
  - Short generation time

Potential applications

Introgression of parasite resistance

Malaria: Introgression of parasite-resistance genes into mosquito populations



Introgression of parasite resistance

Introgression of genes that affect fertility, sex ratio

Evolution of resistance to pesticides/herbicides: replace resistant alleles with their ancestral equivalents to restore vulnerability

Esvelt et al. (2014)
Elife. 3: 1–21

Ecological engineering

Risks

- Target specificity? (off-target DSBs)
- Population connectivity (control invasive species without affecting their native pops)
- Spreading of transgenes in closely related species
- Unintended ecological consequences (community dynamics)

Transparency, public discussion, and evaluation

- Potential benefits :
  - Eliminating insect-borne human diseases
  - Developing and supporting more sustainable agricultural models
  - Controlling environmentally damaging invasive species
- Concerns :
  - Ecological and human consequences ?
  - Gene drives are not stopped by countries borders

References

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