The Netherlands Commission on Genetic Modification (COGEM)

COGEM is an independent scientific advisory body that:

1. provides the government on request or on its own initiative with advice on the risks to human health and the environment of the production and use of GMOs.
2. informs the government of ethical and societal issues linked to genetic modification.

COGEM's appointed task covers all fields from agriculture to medicine and from contained use to deliberate release of GMOs.

COGEM consists of:

- 40 members, which are selected for their scientific expertise
- supported by a secretariat (8)

COGEM's opinions and reports are published on www.cogem.net

Trigger for research on gene drives

Alarming reports on the speed of transmission and risks of gene drives:

- CRISPR gene drives are passed on to all progeny
- A small number of organisms with CRISPR gene drives would be sufficient to modify or eliminate a whole population

Escape of an organism carrying a CRISPR gene drive could have serious consequences

- Experiments at highest containment level (IV)

Others questioned whether CRISPR gene drives would spread efficiently in wild populations

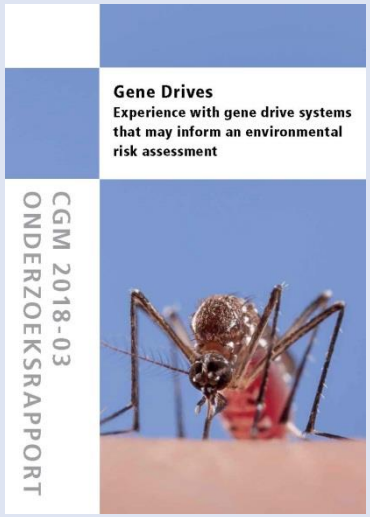
Trigger for research on gene drives

Natural gene drive systems

- Described in several organisms (mice, mosquitoes, fruit flies, etc.)
- Studied for decades
- What can be learned?

A research project on experiences with gene drive systems was commissioned

Perseus's report is available at www.cogem.net



Major conclusions

Experiences from field experiments (releases)

- Did the gene drive spread to other populations?
  - NO
- Complete suppression or replacement of the target population?
  - NO

The speed and dispersal area of a gene drive are determined by:

- Biology and population dynamics of the organism
- Efficacy of the drive
- Fitness costs of the gene drive and ‘cargo’ gene
- Environmental circumstances
- Presence or development of resistance

Each of these factors may serve as a brake, restricting spread of the gene drive

Major conclusions

Insights on CRISPR gene drives:

- Efficient in laboratory experiments
- No field experiments (releases)
- Prone to develop gene drive resistant alleles

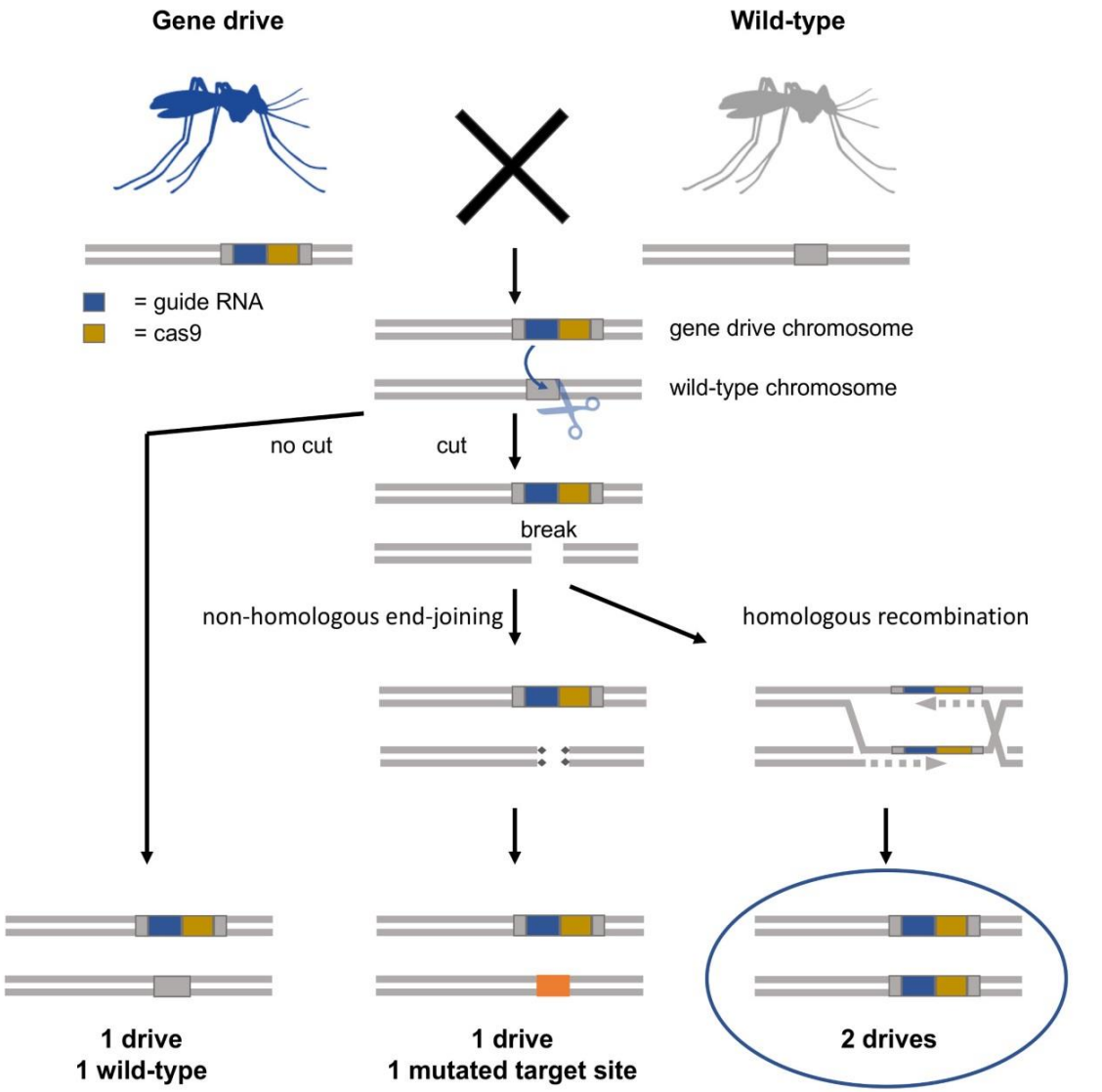


Figure adapted from Esvelt *et al.*, 2014

Major conclusions

Insights on CRISPR gene drives:

- Efficient in laboratory experiments
- No field experiments (releases)

- Prone to develop gene drive resistant alleles
- Several examples of resistance in laboratory experiments
- Resistance restricts spread of the gene drive

The concern that CRISPR gene drives would spread globally and suppress or replace all wild-type individuals must be nuanced

Conclusions of COGEM

- No indications that gene drives are able to spread uncontrollably after their release
- Partly due to the development of resistance, the chance that the escape of an organism carrying a CRISPR gene drive would cause the replacement or suppression of a complete population is negligible
  - Not necessary to assign activities with CRISPR gene drives to the highest containment level
  - Containment measures can be determined using standard procedures

Conclusions of COGEM

Development of CRISPR gene drives with reduced development of resistance (Champer *et al.,* 2018; Oberhorfer *et al.*, 2018)

These should ideally:

- Limit cleavage of target site to HDR window (early meiosis) (restrict production and persistence of endonuclease)
  - ➢ Not sufficient to prevent the formation of resistant alleles
- Use multiple guide RNAs (multiple target sites)
  - ➢ Reduced formation of resistant alleles, but..

    modest homing rates, frequent partial copying of the gene drive, problems with loading of the gRNAs?

Currently, no examples of efficient ‘resistant proof’ CRISPR gene drives

Conclusions of COGEM

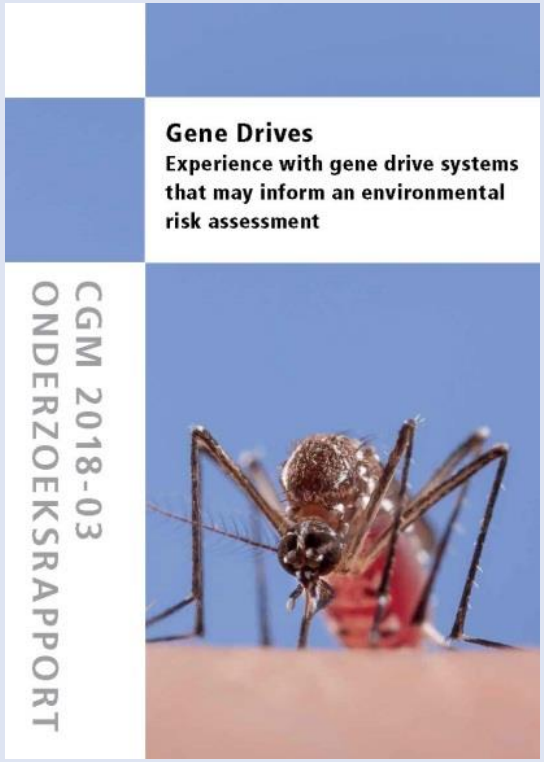
Development of CRISPR gene drives that overcome resistance: resistance results in sterility or mortality

- Cage experiments, two groups of mosquitoes eliminated (Kyrou et al., 2018)
- Not studied in the field
- Genetic diversity in natural populations is high
- GM mosquitoes are often less fit
- According to the scientists, it cannot be excluded that fertile gene drive resistant mosquitoes arise over time

➢ Doubts whether these specially designed CRISPR gene drives could replace or suppress complete wild populations, but this cannot be ruled out based on the available information

  ➢ Additional containment measures for these specially designed CRISPR gene drives

Questions?



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