# Built to spread, designed to stop: Exploring intrinsic biocontainment for self-sustaining gene drives

## Monitoring Gene Drives

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*A look at emerging strategies to limit the spread of self-sustaining gene drives through built-in, genetically encoded containment tools*

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Self-sustaining (low-threshold, homing-based) gene drives, powered by precise genetic engineering technologies such as CRISPR-Cas9, represent a promising tool for controlling diseases transmitted by insect vectors and managing invasive species. These gene drives function by inserting genetic modifications directly into targeted genomic locations and spreading them preferentially through populations by converting heterozygotes into homozygotes over subsequent generations (Bier, 2022; Raban et al., 2023). Preliminary results suggest that this “homing” mechanism ensures rapid propagation of desired traits into a population, requiring only small initial releases to achieve significant population-level effects, making them particularly and potentially effective for large-scale ecological interventions.

A critical feature of these homing-based gene drives is their self-sustaining nature, meaning they could autonomously maintain and amplify their presence in wild populations without ongoing human intervention. Unlike localised or self-limiting systems, the intrinsic biology of homing drives allows them to spread in the population beyond their original release area, potentially impacting extensive geographic ranges. This non-localising characteristic significantly enhances their utility for broad ecological challenges, yet simultaneously raises important ecological and regulatory concerns related to their containment and potential unintended impacts (Hay et al., 2021; Naegeli et al., 2020).

To ensure safer testing and deployment, there is growing interest in incorporating intrinsic genetic biocontainment measures directly into homing-based gene drive designs. These built-in controls could limit drive spread by requiring specific environmental conditions or by reducing their persistence over time (Chennuri et al., 2022; George et al., 2024). This approach would not only add a safeguard but also support regulatory efforts and public trust by demonstrating active risk management.

Several innovative intrinsic biocontainment mechanisms have emerged (Chennuri et al., 2022). This article examines six intrinsic biocontainment strategies that show promise for containing low-threshold, homing-based gene drives: chemically inducible systems, environmentally responsive designs, switchable drives using genetic code expansion, two-target homing drives, synthetic target-site drives, and self-eliminating or biodegradable gene drives. Each offers distinct mechanisms and considerations for achieving safer and more controlled applications in the field.

# Controlling gene drives with chemicals and temperature

Chemical-based gene drive control typically involves integrating gene drive components that can be activated or deactivated by specific small molecules. Such chemically controllable gene drives are among the earliest containment strategies proposed.  For instance, Chae et al. (2020) describe systems that employ recombinases activated by the drug RU486 to excise drive components, offering temporal control during lab or cage trials in *Drosophila melanogaster*.

Another chemical-based control strategy includes Inducible Gene Drives (IGDs), where the activity of gene-editing enzymes such as Cas9 can be stabilised or destabilised depending on the presence of specific chemical agents. Lopez Del Amo et al. (2020) highlighted experiments using trimethoprim to control Cas9 activity in a dose-dependent manner, providing a fine-tuned method of regulating gene drive propagation. Despite its potential, IGDs face certain challenges, such as unintended "leakiness", where low levels of gene drive activity occur even without chemical induction, potentially complicating risk management.

In addition to chemical inducibility, environmental responsiveness represents another promising layer of intrinsic control. Sanz et al. (2023) developed a temperature-sensitive gene drive system utilising the Cas12a nuclease in *D. melanogaster*. In their experiments, gene drive activity was effectively suppressed at lower temperatures (18°C), whereas higher temperatures (25°C–29°C) activated the drive's function. This temperature sensitivity provides a reversible and straightforward means of biocontainment, particularly advantageous for potential applications in regions with distinct seasonal temperature variations or controlled indoor environments.

These controllable systems, both chemical and environmental, could introduce valuable control options, but their field application requires a deeper understanding. The influence of natural environmental variability on drive activation, the stability of chemical inducers in complex habitats, and the resilience of target populations all merit further investigation.

# Switching genes on and off with synthetic tools

Switchable gene drives represent an advanced intrinsic biocontainment approach, relying on genetic code expansion to tightly and reversibly control gene drive functionality. Genetic code expansion involves incorporating non-natural amino acids (ncAAs) into gene-editing enzymes, such as Cas9, through engineered transfer RNA (tRNA) systems. This method allows gene drive components to become functional exclusively in the presence of the corresponding ncAA, providing highly precise temporal and spatial control over gene drive activity.

In a study by De La Torre and Chin (2022), this concept was successfully tested in mouse embryos. Cas9 was rendered dependent on ncAAs for expression, ensuring tight control and virtually eliminating leakiness. The system's precise control could reduce ecological risks significantly, particularly in sensitive environments requiring stringent containment. Furthermore, this approach enables researchers to switch gene drive activity on or off as required, offering flexibility for different

phases of research or implementation. This high degree of precision may offer strong biocontainment, particularly in early-stage research or high-sensitivity settings.

However, the practical use of this system faces significant barriers. Organisms must be engineered with synthetic genetic machinery, which is technically complex and could raise concerns around ecological fitness, regulatory compliance and public perception. Questions also remain around scalability and long-term genetic stability.

# Splitting the job: Two-target designs for better control

In conventional homing-based gene drives, the gene drive cassette is typically inserted at a single genetic locus, combining both the drive conversion function and the suppression effect. This design can face significant challenges, notably the formation of resistant alleles that can rapidly decrease gene drive effectiveness and complicate long-term population control efforts.

To address these issues, another strategy involves splitting the gene drive function across two independent genetic locations. Faber et al. (2024) proposed a two-target homing drive design in *D. melanogaster*, in which the drive conversion and population suppression effects are decoupled and placed at separate genomic loci. In this system, one locus is solely dedicated to gene drive propagation, ensuring efficient copying into subsequent generations. The second locus, independent of the drive conversion locus, imposes a fitness cost by disrupting critical genes, such as those required for female fertility or viability.

Willis and Burt (2021) supported this strategy through computational modelling, showing that such two-target designs effectively suppress populations even when substantial pre-existing resistance is present. Their models demonstrate that this biocontainment approach can tolerate genetic variations, providing flexibility for real-world implementation where perfect genetic differentiation is rare.

Despite their significant promise, two-target homing drives require careful design and empirical validation. Challenges remain regarding identifying suitable target loci, ensuring stable genetic constructs, and managing potential ecological interactions in diverse environmental contexts.

# Staying in the lab: Drives that target synthetic DNA only

Synthetic target-site drives offer an elegant solution to biocontainment by limiting drive activity to organisms with engineered sequences. These drives recognise and act only on synthetic DNA targets which are introduced in the lab and absent from wild populations.

Champer et al. (2019) demonstrated this system in controlled laboratory settings using *D. melanogaster*. Their experiments showed that synthetic target-site drives achieve comparable efficiency and resistance profiles to standard homing-based gene drive designs. By limiting propagation exclusively to organisms engineered with the synthetic sites, this method would provide a robust safeguard against unintended ecological spread.

The simplicity of these systems is a strength: no additional molecular switches or environmental triggers are needed. Unlike more complex biocontainment systems, synthetic site designs rely solely on the presence or absence of engineered DNA sequences. However, their main limitation lies in their applicability. Deploying this method in the wild would require pre-conditioning target populations with synthetic sites, which presents major technical and ecological challenges. Additionally, the long-term evolutionary stability of synthetic target sequences in dynamic natural environments remains uncertain, necessitating extensive research and monitoring.

# Built to disappear: Self-eliminating and biodegradable drives

Rather than controlling activation, some gene drives incorporate mechanisms to remove themselves from a population over time. Self-elimination mechanisms (SEMs) and Biodegradable Gene Drives (BDGs) rely on genetic constructs that are designed to naturally remove themselves from the genome after achieving their intended ecological effect, potentially restoring wild-type genetics in the process.

Zapletal et al. (2021) used modelling to investigate several genetic strategies that could enable a gene drive to remove itself from a population after a period of activity. This SEM approach involves recombinase enzymes, which are designed to recognise specific DNA sequences flanking the gene drive cassette. When activated, the recombinase cuts at these sites and deletes the entire drive sequence, halting its further spread. Another method uses a modified transposase system, enzymes that normally move DNA segments, to target short repeated sequences and excise the gene drive without reinserting it elsewhere. A third strategy, based on single-strand annealing, leverages the cell’s natural repair processes: when a targeted DNA break occurs between two identical flanking sequences, the repair machinery aligns the repeats and deletes the intervening gene drive. BGDs integrate these SEMs into a complete drive architecture. Modelling showed that even with modest removal efficiency (below 10%), these systems could substantially reduce gene drive persistence, making them promising candidates for applications requiring time-limited activity or reversible effects.

Despite their promise, SEMs and BGDs face important technical and ecological challenges. Their effectiveness relies on the stability and reliability of the engineered genetic constructs and their precise molecular function in diverse genetic backgrounds and ecological settings. Future work must focus on stabilising these systems and evaluating their performance in real-world settings.

# What happens beyond the lab? Real-world challenges and oversight

The transition of homing-based gene drive technologies from laboratory to field applications presents numerous real-world challenges. Although intrinsic biocontainment measures, such as the ones mentioned in this article, have demonstrated substantial promise under controlled conditions, their effectiveness and stability in complex ecological contexts remain uncertain.

George et al. (2024) highlight several critical barriers to deploying homing-based gene drives in natural ecosystems. Firstly, intrinsic biocontainment strategies require robust and standardised testing frameworks, which are currently limited. Evaluating these strategies under realistic environmental conditions is essential to accurately predict their performance and ecological interactions, yet this process can be technically challenging and costly.

Regulatory uncertainty further complicates the deployment of gene drives. Many existing regulatory frameworks were not originally designed for technologies as novel and powerful as gene drives, leading to ambiguity in approval processes and standards for ecological safety assessments. This uncertainty can deter investment and slow down technological innovation and practical implementation.

Additionally, intrinsic biocontainment strategies must navigate social acceptance and public trust. The historical controversy surrounding genetically modified organisms underscores the importance of transparency, stakeholder engagement and comprehensive risk communication. Public perception and acceptance play a pivotal role in the successful deployment of gene drives, necessitating careful alignment of scientific advancements with societal values and concerns.

To address these challenges, multi-stakeholder collaboration involving researchers, policymakers, regulatory agencies, industry representatives and local communities is essential. Developing clear regulatory guidelines, enhancing biosafety committee training, and establishing rigorous yet flexible testing protocols will facilitate the safe and effective translation of laboratory-tested biocontainment strategies into practical, real-world applications. These combined efforts will be critical for responsibly harnessing the potential benefits of gene drives while effectively mitigating ecological and societal risks.

# Conclusion: Containment by design, responsibility by default

Intrinsic biocontainment strategies are essential tools for the safe, scalable use of homing-based gene drives. Whether through controllable systems, population-specific targeting, synthetic restriction or programmed removal, these tools give developers the ability to match innovation with

responsibility.

Each approach brings its own strengths and challenges. What they share is the potential to make gene drive technologies more predictable, confined and acceptable to the public and regulators alike. For these systems to reach their full potential, they must be integrated into broader efforts involving testing, policy development and cross-sector collaboration.

With continued refinement and responsible stewardship, intrinsic containment strategies can help ensure that gene drives are not only effective, but also safe, ethical, and fit for purpose.

## *Note on terminology*

In this article, I'm using the terms self-sustaining, low-threshold, homing-based and non-localising gene drives interchangeably. These refer to gene drive systems with the following characteristics:

- *Homing-based*: Use CRISPR or similar tools to copy themselves into a specific DNA site during reproduction.
- *Low-threshold*: Capable of spreading from a small number of released individuals.
- *Self-sustaining*: Continue propagating through populations without further human intervention.
- *Non-localising*: Not inherently restricted to a geographic area; spread depends on the organism's natural movement.

## *Visual summary*

This infographic highlights the proposed intrinsic biocontainment strategies to help control self-sustaining, homing-based gene drives:

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