



Supplementary Materials for

Core commitments for field trials of gene drive organisms

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Published 18 December 2020, *Science* **370**, 1417 (2020)
DOI: 10.1126/science.abd1908

This PDF file includes:

Disclosure statements

Table 1 with full references

Disclosure statements

A Defense Advanced Research Projects Agency (DARPA) Safe Genes Program Grant (HR0011-17-2-0047) was awarded to O.S.A. and supports the work of K.C.L. O.S.A. is a founder of Agragene, Inc., has an equity interest, and serves on the company's Scientific Advisory Board. L.A. is supported by the Bill & Melinda Gates Foundation (INV-008549) and the UK Biotechnology and Biological Sciences Research Council (BBS/E/I/00007033 and BBS/E/I/00007034). C.B. is a member of NIH Novel and Exceptional Technology and Research Advisory Committee (NExTRAC) and Co-Chair of the NExTRAC Gene Drives in Biomedical Research Working Group. K.L.C. is a member of the Scientific Advisory Board for Synbal, Inc. C.I.E. is supported by a grant from the Bill & Melinda Gates Foundation, and the funders had no role or decision in C.I.E.'s authorship. K.E. is the author of patents on diverse gene drive technologies with Harvard University and MIT. S.W.E. received funding from the Schmidt Futures Foundation and sits on an advisory panel for the DARPA program that funded K.C.L. and O.S.A., but did not directly receive funding from DARPA. V.M.G. is a founder of and has equity interests in Synbal, Inc. and Agragene, Inc., companies that may potentially benefit from the research results. V.M.G. also serves on both the company's Scientific Advisory Board and the Board of Directors of Synbal, Inc. The terms of this arrangement have been reviewed and approved by the University of California, San Diego, in accordance with its conflict-of-interest policies. S.H. is funded by British Academy grants KF400306 and KF2\100179. E.H. is funded by USDA grant "Gene Drive Applications to Agriculture in Texas: Knowledge, Perceptions, and Values" (USDA Project # 2018-67023-27676), but this publication is not directly related to the work supported by that funding; and is an *ad hoc* member of the NExTRAC Gene Drives in Biomedical Research Working Group. M.J.P. received research funding support from the Open Philanthropy Project and the Smith Richardson Foundation on related topics, but this funding did not directly support her participation in this paper; received honoraria from the Nuclear Threat Initiative Biosecurity Innovation and Risk Reduction Initiative and Ginkgo Bioworks; and serves in various unpaid/volunteer roles at Revive & Restore, Engineering Biology Research Consortium, International Genetically Engineered Machine (iGEM) Competition, run by the iGEM Foundation, World Economic Forum Global Future Council on Synthetic Biology, NSF Center for Cellular Construction, Synthetic Biology Program at the Joint Genomics Institute, Biosecurity Task Force of the American Biosafety Association, and Research and Health Department of the World Health Organization Science Division. L.R. is co-founder of BioPolicy Solutions; there are no financial conflicts of interest associated with this work. R.S. coordinates the Genetic Biocontrol of Invasive Rodents Program, contributes to the Outreach Network for Gene Drive Research and World Health Organization Global Outbreak and Alert Response Network, participated in the 2019 NIH Gene Drive Research Forum, has contributed to work by Revive & Restore, and owns a consulting company Health Preparedness and Crisis Management and mutual funds with S&P500 holdings; there are no known conflicts of interest associated with these activities.

Table 1 with full references

Approach	Examples	Temporal Dynamics	Geographic Reach
Gene Drives (16, 17)	Linked-homing [#] (2, 4, 18–21), Medea (22–24), CleaveR(25, 26), TARE/TADE [#] (27, 28)	Self-propagating (low threshold)	Non-localized
	Translocations(29, 30), Underdominance [#] (31), UD ^{MEL} * (32), Tethered Homing (33)	Majority wins* (high threshold)	Localized
	Daisy [#] (34), split-homing [#] (1, 3, 35–37), Homer (38, 39), killer rescue (40, 41)	Self-limiting (temporally limited)	
Non-Drives	SIT [#] (42), RIDL [#] (43), fsRIDL [#] (44), pgSIT [#] (45)		

Table 1. Characteristics and examples of engineered population control technologies. Two broad types of engineered approaches exist to modify populations—one requires gene drive and the other relies on non-drive technologies. Multiple examples of these types of systems exist, which can have varied temporal dynamics including: Self-propagating with a low threshold (predicted to spread from a small release), to majority wins with a high threshold (predicted to spread into a population only when the transgene is present at >50%), to self-limiting which are temporally limited (can only spread or persist in population for a short period). These systems can fall under two broad categories from non-localized (predicted to spread beyond boundaries) to localized (predicted to spread within a localized population). For more details on the various examples and terminology see associated references. [#]Can be used for population suppression in some forms. *While UD^{MEL} does have a high threshold it does not always fall under “majority wins” temporal dynamics. Abbreviations: Medea, maternal effect dominant embryonic arrest; TARE/TADE, toxin-antidote recessive embryo/toxin-antidote dominant embryo; CleaveR, Cleve and Rescue; UD^{MEL}, maternal effect lethal underdominance; SIT, sterile insect technique; RIDL, release of insects carrying a dominant lethal; fsRIDL, female-specific release of insects carrying a dominant lethal; pgSIT, precision-guided sterile insect technique.

Main references

1. H. A. Grunwald, V. M. Gantz, G. Poplawski, X.-R. S. Xu, E. Bier, K. L. Cooper, Super-Mendelian inheritance mediated by CRISPR-Cas9 in the female mouse germline. *Nature*. **566**, 105–109 (2019).
2. V. M. Gantz, N. Jasinskiene, O. Tatarenkova, A. Fazekas, V. M. Macias, E. Bier, A. A. James, Highly efficient Cas9-mediated gene drive for population modification of the malaria vector mosquito *Anopheles stephensi*. *Proc. Natl. Acad. Sci. U. S. A.* **112**, E6736–43 (2015).
3. M. Li, T. Yang, N. P. Kandul, M. Bui, S. Gamez, R. Raban, J. Bennett, H. M. Sánchez C, G. C. Lanzaro, H. Schmidt, Y. Lee, J. M. Marshall, O. S. Akbari, Development of a confinable gene drive system in the human disease vector. *Elife*. **9** (2020), doi:10.7554/eLife.51701.

4. A. Simoni, A. M. Hammond, A. K. Beaghton, R. Galizi, C. Taxiarchi, K. Kyrou, D. Meacci, M. Gribble, G. Morselli, A. Burt, T. Nolan, A. Crisanti, A male-biased sex-distorter gene drive for the human malaria vector *Anopheles gambiae*. *Nat. Biotechnol.* (2020), doi:10.1038/s41587-020-0508-1.
5. National Academies of Sciences, Engineering, and Medicine, Division on Earth and Life Studies, Board on Life Sciences, Committee on Gene Drive Research in Non-Human Organisms: Recommendations for Responsible Conduct, *Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values* (National Academies Press, 2016).
6. O. S. Akbari, H. J. Bellen, E. Bier, S. L. Bullock, A. Burt, G. M. Church, K. R. Cook, P. Duchek, O. R. Edwards, K. M. Esvelt, V. M. Gantz, K. G. Golic, S. J. Gratz, M. M. Harrison, K. R. Hayes, A. A. James, T. C. Kaufman, J. Knoblich, H. S. Malik, K. A. Matthews, K. M. O'Connor-Giles, A. L. Parks, N. Perrimon, F. Port, S. Russell, R. Ueda, J. Wildonger, BIOSAFETY. Safeguarding gene drive experiments in the laboratory. *Science*. **349**, 927–929 (2015).
7. C. Emerson, S. James, K. Littler, F. (fil) Randazzo, Principles for gene drive research. *Science*. **358** (2017), pp. 1135–1136.
8. S. James, F. H. Collins, P. A. Welkhoff, C. Emerson, H. C. J. Godfray, M. Gottlieb, B. Greenwood, S. W. Lindsay, C. M. Mbogo, F. O. Okumu, H. Quemada, M. Savadogo, J. A. Singh, K. H. Tountas, Y. T. Touré, Pathway to Deployment of Gene Drive Mosquitoes as a Potential Biocontrol Tool for Elimination of Malaria in Sub-Saharan Africa: Recommendations of a Scientific Working Group. *Am. J. Trop. Med. Hyg.* **98**, 1–49 (2018).
9. D. Thizy, C. Emerson, J. Gibbs, S. Hartley, L. Kapiriri, J. Lavery, J. Lunshof, J. Ramsey, J. Shapiro, J. A. Singh, L. P. Toe, I. Coche, B. Robinson, Guidance on stakeholder engagement practices to inform the development of area-wide vector control methods. *PLoS Negl. Trop. Dis.* **13**, e0007286 (2019).
10. D. R. George, T. Kuiken, J. A. Delborne, Articulating “free, prior and informed consent” (FPIC) for engineered gene drives. *Proceedings of the Royal Society B: Biological Sciences*. **286** (2019), p. 20191484.
11. Z. Adelman, O. Akbari, J. Bauer, E. Bier, C. Bloss, S. R. Carter, C. Callender, A. C.-S. Denis, P. Cowhey, B. Dass, J. Delborne, M. Devereaux, P. Ellsworth, R. M. Friedman, V. Gantz, C. Gibson, B. A. Hay, M. Hoddle, A. A. James, S. James, L. Jorgenson, M. Kalichman, J. Marshall, W. McGinnis, J. Newman, A. Pearson, H. Quemada, L. Rudenko, A. Shelton, J. M. Vinetz, J. Weisman, B. Wong, C. Wozniak, Rules of the road for insect gene drive research and testing. *Nat. Biotechnol.* **35**, 716–718 (2017).
12. K. A. Oye, K. Esvelt, E. Appleton, F. Catteruccia, G. Church, T. Kuiken, S. B.-Y. Lightfoot, J. McNamara, A. Smidler, J. P. Collins, Biotechnology. Regulating gene drives. *Science*. **345**, 626–628 (2014).
13. R. Carballar-Lejarazú, A. A. James, Population modification of Anopheline species to control malaria transmission. *Pathog. Glob. Health*. **111**, 424–435 (2017).
14. J. Kuzma, Procedurally Robust Risk Assessment Framework for Novel Genetically Engineered Organisms and Gene Drives. *Regulation & Governance* (2019), , doi:10.1111/rego.12245.
15. Taitingfong, Taitingfong, Islands as Laboratories: Indigenous Knowledge and Gene Drives in the Pacific. *Human Biology*. **91** (2019), p. 1.

Supplemental references

16. J. Champer, A. Buchman, O. S. Akbari, Cheating evolution: engineering gene drives to manipulate the fate of wild populations. *Nat. Rev. Genet.* **17**, 146–159 (2016).

17. K. M. Esvelt, A. L. Smidler, F. Catteruccia, G. M. Church, Concerning RNA-guided gene drives for the alteration of wild populations. *Elife*. **3** (2014), doi:10.7554/eLife.03401.
18. K. Kyrou, A. M. Hammond, R. Galizi, N. Kranjc, A. Burt, A. K. Beaghton, T. Nolan, A. Crisanti, A CRISPR-Cas9 gene drive targeting doublesex causes complete population suppression in caged *Anopheles gambiae* mosquitoes. *Nat. Biotechnol.* **36**, 1062–1066 (2018).
19. A. Adolphi, V. M. Gantz, N. Jasinskiene, H.-F. Lee, K. Hwang, G. Terradas, E. A. Bulger, A. Ramaiah, J. B. Bennett, J. J. Emerson, J. M. Marshall, E. Bier, A. A. James, Efficient population modification gene-drive rescue system in the malaria mosquito *Anopheles stephensi*. *Nat. Commun.* **11**, 5553 (2020).
20. R. Carballar-Lejarazú, C. Ogaugwu, T. Tushar, A. Kelsey, T. B. Pham, J. Murphy, H. Schmidt, Y. Lee, G. C. Lanzaro, A. A. James, Next-generation gene drive for population modification of the malaria vector mosquito, *Anopheles gambiae*. *Proceedings of the National Academy of Sciences*. **117** (2020), pp. 22805–22814.
21. V. M. Gantz, E. Bier, Genome editing. The mutagenic chain reaction: a method for converting heterozygous to homozygous mutations. *Science*. **348**, 442–444 (2015).
22. O. S. Akbari, C.-H. Chen, J. M. Marshall, H. Huang, I. Antoshechkin, B. A. Hay, Novel synthetic Medea selfish genetic elements drive population replacement in *Drosophila*; a theoretical exploration of Medea-dependent population suppression. *ACS Synth. Biol.* **3**, 915–928 (2014).
23. A. Buchman, J. M. Marshall, D. Ostrovski, T. Yang, O. S. Akbari, Synthetically Engineered Medea Gene Drive System in the Worldwide Crop Pest, *D. suzukii*, , doi:10.1101/162255.
24. C.-H. Chen, H. Huang, C. M. Ward, J. T. Su, L. V. Schaeffer, M. Guo, B. A. Hay, A synthetic maternal-effect selfish genetic element drives population replacement in *Drosophila*. *Science*. **316**, 597–600 (2007).
25. G. Oberhofer, T. Ivy, B. A. Hay, Cleave and Rescue, a novel selfish genetic element and general strategy for gene drive. *Proc. Natl. Acad. Sci. U. S. A.* **116**, 6250–6259 (2019).
26. G. Oberhofer, T. Ivy, B. A. Hay, Gene drive and resilience through renewal with next generation selfish genetic elements. *Proc. Natl. Acad. Sci. U. S. A.* **117**, 9013–9021 (2020).
27. J. Champer, E. Lee, E. Yang, C. Liu, A. G. Clark, P. W. Messer, A toxin-antidote CRISPR gene drive system for regional population modification. *Nat. Commun.* **11**, 1082 (2020).
28. J. Champer, I. K. Kim, S. E. Champer, A. G. Clark, P. W. Messer, Performance analysis of novel toxin-antidote CRISPR gene drive systems. *BMC Biol.* **18**, 27 (2020).
29. A. B. Buchman, T. Ivy, J. M. Marshall, O. S. Akbari, B. A. Hay, Engineered Reciprocal Chromosome Translocations Drive High Threshold, Reversible Population Replacement in *Drosophila*. *ACS Synth. Biol.* **7**, 1359–1370 (2018).
30. C. F. Curtis, Possible use of translocations to fix desirable genes in insect pest populations. *Nature*. **218**, 368–369 (1968).
31. M. P. Edgington, L. S. Alpey, Conditions for success of engineered underdominance gene drive systems. *J. Theor. Biol.* **430**, 128–140 (2017).
32. O. S. Akbari, K. D. Matzen, J. M. Marshall, H. Huang, C. M. Ward, B. A. Hay, A synthetic gene drive system for local, reversible modification and suppression of insect populations. *Curr. Biol.* **23**, 671–677 (2013).

33. S. Dhole, A. L. Lloyd, F. Gould, Tethered homing gene drives: A new design for spatially restricted population replacement and suppression. *Evol. Appl.* **12**, 1688–1702 (2019).
34. C. Noble, J. Min, J. Olejarz, J. Buchthal, A. Chavez, A. L. Smidler, E. A. DeBenedictis, G. M. Church, M. A. Nowak, K. M. Esvelt, Daisy-chain gene drives for the alteration of local populations. *Proc. Natl. Acad. Sci. U. S. A.* **116**, 8275–8282 (2019).
35. N. P. Kandul, J. Liu, A. Buchman, V. M. Gantz, E. Bier, O. S. Akbari, Assessment of a Split Homing Based Gene Drive for Efficient Knockout of Multiple Genes. *G3* . **10**, 827–837 (2020).
36. A. Guichard, T. Haque, M. Bobik, X.-R. S. Xu, C. Klanseck, R. B. S. Kushwah, M. Berni, B. Kaduskar, V. M. Gantz, E. Bier, Efficient allelic-drive in *Drosophila*. *Nat. Commun.* **10**, 1640 (2019).
37. V. López Del Amo, A. L. Bishop, H. M. Sánchez C, J. B. Bennett, X. Feng, J. M. Marshall, E. Bier, V. M. Gantz, A transcomplementing gene drive provides a flexible platform for laboratory investigation and potential field deployment. *Nat. Commun.* **11**, 352 (2020).
38. N. P. Kandul, J. Liu, J. B. Bennett, J. M. Marshall, O. S. Akbari, A home and rescue gene drive efficiently spreads and persists in populations (2020), , doi:10.1101/2020.08.21.261610.
39. G. Terradas, A. B. Buchman, J. B. Bennett, I. Shriner, J. M. Marshall, O. S. Akbari, E. Bier, Inherently confinable split-drive systems in *Drosophila* (2020), , doi:10.1101/2020.09.03.282079.
40. F. Gould, Y. Huang, M. Legros, A. L. Lloyd, A Killer–Rescue system for self-limiting gene drive of anti-pathogen constructs. *Proceedings of the Royal Society B: Biological Sciences.* **275** (2008), pp. 2823–2829.
41. S. H. Webster, M. R. Vella, M. J. Scott, Development and testing of a novel killer–rescue self-limiting gene drive system in *Drosophila melanogaster*. *Proceedings of the Royal Society B: Biological Sciences.* **287** (2020), p. 20192994.
42. E. F. Knipling, Possibilities of Insect Control or Eradication Through the Use of Sexually Sterile Males¹. *Journal of Economic Entomology.* **48** (1955), pp. 459–462.
43. D. D. Thomas, C. A. Donnelly, R. J. Wood, L. S. Alphey, Insect population control using a dominant, repressible, lethal genetic system. *Science.* **287**, 2474–2476 (2000).
44. G. M. C. Labbé, S. Scaife, S. A. Morgan, Z. H. Curtis, L. Alphey, Female-specific flightless (fsRIDL) phenotype for control of *Aedes albopictus*. *PLoS Negl. Trop. Dis.* **6**, e1724 (2012).
45. N. P. Kandul, J. Liu, H. M. Sanchez C, S. L. Wu, J. M. Marshall, O. S. Akbari, Transforming insect population control with precision guided sterile males with demonstration in flies. *Nat. Commun.* **10**, 84 (2019).