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CRISPR-based gene drive in agriculture will face technical and governance challenges

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Comment on: **V Courtier-Orgogozo *et al*** (June 2017)
See reply: **V Courtier-Orgogozo *et al***

Courtier-Orgogozo *et al* [1] recently called for public debate about the use of CRISPR-based gene drive (GD) in agricultural pest management. We agree that this use of GD deserves specific attention, given that it would pose unique challenges to economic, social, ecological, and regulatory systems. However, many details in the report are oversimplified or imprecise; GD will likely face greater technical and governance challenges than suggested by the authors.

The authors conflate CRISPR-based gene editing with CRISPR-based gene drive, which is more intricate and tightly constrained by organismal and molecular factors including sequence length, the number of necessary components, and insect ecology. The authors suggest that GD will circumvent the need for domestication and organismal knowledge that apply to other forms of genetic engineering, but the organisms in which GD has been successfully demonstrated—yeast, mosquitoes, and fruit flies—are highly domesticated model species for which we have detailed genomic understanding. This knowledge is required to identify promoters for expression of CRISPR components and determine appropriate genes to disrupt, modify, or insert.

Although GD "theoretically works in any species that reproduces sexually", in practice, targeted pests must be amenable to laboratory-rearing and transformation. Efforts to engineer a GD Asian citrus psyllid incapable of transmitting the bacterium responsible for citrus greening disease have been undermined by the difficulty of transforming the insects using microinjection [2]. This multi-year and multi-million dollar project challenges the authors' claim that "it just takes a few months and about US$1,000 worth of consumables to construct a gene drive organism".

While the authors focus on species eradication, most GD experiments have been for the purpose of population replacement; there has been only one publication on population suppression. This study targeted female reproductive genes in mosquitoes, and while initially promising, resistance to the GD emerged [3]. Modeling has also shown that genetic variation may pose a significant barrier to field applications [4]. Thus, even GD organisms cannot "bypass the vagaries of evolution", as suggested.

The authors correctly assert that there is no regulation specific to CRISPR GD; however, GD organisms are expected to trigger regulation based on their characteristics [5]. The adequacy of current regulations [6] is being considered by the US National Academies of Science, Engineering, and Medicine (NASEM) [5] and the UN Convention on Biodiversity (CBD) [7]. NASEM did not "approve research on gene drive" as reported by the authors, but, like the CBD, suggested that an international moratorium is inappropriate. Both groups concluded that existing research is not sufficient to support environmental releases of GDs.

The authors aim to "initiate debate about the implications of [GD] releases", but dialogue has already begun. These conversations are drawing attention to potential long-term impacts of GD and the need for interdisciplinary and public input [6]. A number of institutions have hosted international workshops on GD science, ethics, and governance [8], and GD projects have incorporated molecular, ecological, regulatory, and social science expertise [2]. In a poignant example, Kevin Esvelt held town hall meetings last year before pursuing GD mice to reduce the spread of Lyme disease [9]. Agricultural GD may benefit from such assessments and public engagement processes being worked out in other realms.

Courtier-Orgogozo *et al* report that large corporations are pursuing licenses to use CRISPR but omit that these only allow gene editing; Monsanto's license explicitly prohibits gene drive research [10]. While concerns about commercial use are warranted, GD-based pest control is not likely to be profitable for large biotech companies. Instead, agricultural GDs are likely to be funded by the public and grower associations, as has been the case with sterile insect releases and most biocontrol programs [8].

In conclusion, Courtier-Orgogozo *et al* underestimate scientific, regulatory, and economic challenges to the agricultural use of GD. CRISPR GD is in its infancy, and it is not yet clear how the technology will evolve. Scientists, social scientists, regulators, advocacy groups, and public audiences have been and must continue to engage clearly and candidly with one another to shape the future of this technology.

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