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Using CRISPR-based gene drive for agriculture pest control

Virginie Courtier-Orgogozo[1], Baptiste Morizot[2] & Christophe Boëte[3]

Reply to: **SL Young** *and* ***N Gutzmann et al***

Stephen Young describes an alternative or complementary emerging strategy for controlling pests in agriculture: the use of artificial intelligence and robotic machines to physically destroy individual pests [1]. He emphasizes that, while genetics focuses on internal modifications of pests, such technological approaches rely on external manipulation. Robotic technology seems an attractive approach to eliminate pests given that it should have fewer long-term effects on the environment compared to pesticides or CRISPR-based gene drive (GD). We note, however, that robots might have a hard time dealing with rugged landscapes, small insects, burrowed eggs, or flying pests. The range of pest species that could potentially be targeted with GD is larger than with robots.

Gutzmann *et al* [2] argue that GD will face greater technical and governance challenges than suggested by our article. We agree with their points, although we did not develop these limitations in our paper. Indeed, GD is still technologically challenging and requires biological knowledge about the targeted species. Whether GD will be as effective in plants and vertebrates as it is observed in insects remains unknown. The problem of GD resistance is also real and acute at both the theoretical [3] and experimental [4] levels. Recent work suggests, however, that resistance might be overcome using multiplexed guide RNAs [5 and references therein]. Our paper is alerting on a technology that is clearly not yet applicable, but close.

The authors list various examples of public forums and workshops on GD ethics and governance. They appreciate that the glass of discussions is half full while we worry that it is half empty. Most discussions so far have been initiated by biologists, who are not unbiased in this dialogue, and no scientific or ethical consensus has emerged yet. The recent controversy and secrecy surrounding field trials with transgenic mosquitoes—carrying no gene drive—by Oxitec, despite calls for regulation oversight, demonstrate the lack of agreement and regulation [6,7]. The US National Academies of Science, Engineering, and Medicine might not have "approved" research on GD but they explicitly wrote that "the potential benefits of GD [...] justify proceeding with [...] highly-controlled field trials", which, to us, is already a big step forward [8].

Gutzmann *et al* also question the interests of large agro-biotech companies in using GD to control pests because this would yield little economical benefit. Unlike the coupling of resistant GMOs and specific pesticides commercialized by the same company, GD would indeed reduce the profits generated by the sale of pesticides. This argument is valid, but the question remains a matter of scale and actors. Any business or economic player who is experiencing a decline in agricultural yield owing to local pests that do not affect their competitors' production—and who operates on an economic model in which short-term yield is more important than long-term sustainability—is likely to seize GD as a technique that matches its objectives. This is what we call the structural compatibility between GD and extractivism.

It therefore is important to raise issues associated with the use of GD for agricultural pest control as we did in our paper. We join Gutzmann *et al* in wishing that all actors engage fully and honestly with each other to shape the future of GD and its potential applications for agricultural pest control.

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1 CNRS, Institut Jacques Monod, Université Paris Diderot, Paris, France. E-mail: virginie.courtier@ijm.fr
2 Ceperc, UMR 7304, Aix-en-Provence Cedex 1, France
3 ISEM, UMR544, CNRS-UM-IRD-EPHE, Université de Montpellier, Montpellier cedex 5, France
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Unintended consequences of 21st century technology for agricultural pest management

Stephen L Young

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

Courtier-Orgogozo *et al* [1] argue that public debate and better governance are needed to properly control the use of gene editing for controlling pests in agriculture. They are correct in their assessment that this "could lead to multiple and uncoordinated releases of gene drives into the wild, which is likely to cause unpredictable ecological disturbances with far-reaching consequences". However, the context of technology's dark side with regard to agricultural pests includes not just altering genes, but also manipulating the external environment.

For centuries, pests, which include weeds, have been able to elude or resist even the most sophisticated control methods. Before the development of genetically modified crops, weed management involved a combination of tactics that included biological, mechanical and chemical controls [2]. Roundup Ready™ (herbicide-resistant) crops seem to replace this diversified strategy with just one approach to improve efficiency and lower herbicide use and thereby costs. This single weed control tool could be considered precise, but only because crop plants are genetically manipulated and not by specifically targeting weeds to improve yields. Further, increased selection pressure(s) often result in weed species developing resistance to herbicides—or to any other individual tactic that is used repeatedly across narrow spatiotemporal scales. Similarly, gene drive, a technology that works internally within the target organism by manipulating or knocking out specific genes, promises to drastically increase yield again, yet has several unknowns.

In contrast, external technologies aim to roam crop fields using artificial intelligence and robots to seek and destroy individual pests or weeds [3]. Various agricultural companies [4] and research groups [5] already have an interest in weed management based on advanced robotics and deep learning technologies to identify and eliminate individual weeds from crop fields using a diversified strategy [6,7]. This could eliminate the problems associated with herbicides and lower selective pressure on target weed species to evolve resistance. However, there are valid questions whether using robots in agricultural fields is a safe and reliable strategy similar to the debate on the safety of driverless automobiles, airplanes or cargo ships.

Neither gene drive, an internal technology, nor smart machines, an external technology, have been fully debated in terms of unintended consequences or unknown long-term effects [8]. The path forward has never been clear, but bumbling along using a haphazard trial-and-error method is clearly not the most prudent strategy to employ with ever more sophisticated technology. As Courtier-Orgogozo *et al* point out, "a wider, public debate and dynamic governance" is needed, yet not just on the "right of humans to domesticate almost any species using gene drive", but the coordinated use of internal and external technologies for agricultural pest control.

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Crop and Soil Sciences Section, School of Integrative Plant Science, Cornell University, Ithaca, NY, USA. E-mail: sly27@cornell.edu
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CRISPR-based gene drive in agriculture will face technical and governance challenges

Nicole Gutzmann, Johanna E Elsensohn, Jessica Cavin Barnes, Jennifer Baltzegar, Michael S Jones & Jayce Sudweeks

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

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.

North Carolina State University, Raleigh, NC, USA. E-mail: negutzma@ncsu.edu
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