When biotech crosses borders

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Rapid action is needed to address loopholes in the international governance of self-dispersing genetically modified organisms (GMOs) purposefully released for the management of wild species and diseases.

The application of GMOs purposefully released into nature to address problems in public health, invasive species control, pest control and wildlife disease treatment is gathering pace. Such GMOs, particularly those that are self-dispersing, present new challenges for the international governance of biotech, challenges that current arrangements are ill-equipped to handle. Here, we highlight deficiencies in current regulatory frameworks as they relate to GMOs and argue for the need to establish a robust governance infrastructure for these types of products.

Biological control

Biological control has been used for over a century in wildlife management, for conserving wildlife species, protecting livestock, medicating a target population to ensure its survival, suppressing populations of pests or controlling parasites, diseases or disease vectors for public health. Biocontrol involves the introduction of a natural enemy into a target population with the aim of reducing the size of the target population by inducing mortality by predation or pathology. Proponents suggest biocontrol is an exercise in community reassembly, reestablishing an ecological balance to a target organism in a new environment[1]. Indeed, it has occasionally been used to control vertebrate pests[2,3] and to a much greater extent to control weeds and invertebrates[1,4].

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Despite successes, the history of biocontrol is also sprinkled with failures and disasters, typically where the natural enemy exhibits broader-than-expected host ranges, disperses from the intended target area or causes deleterious changes in ecosystem dynamics[5]. Finding efficacious and safe natural enemies is difficult, and although international best practice guidelines exist for biocontrol[4], testing is arduous and expensive, and it may not always be implemented effectively.

Another form of biocontrol is the sterile insect technique (SIT), which works by releasing a preponderance of infertile males into a target population that subsequently 'overflood' fertile wild males, dramatically reducing the proportion of productive matings, and thus leading to a population crash in the next generation[6]. SIT has been successfully used in the eradication of New World screwworm (*Cochliomyia hominivorax*) from parts of North and South America, medfly (*Ceratis capitata*) infestations of fruit crops from the United States, and tsetse fly and trypanosomosis from Zanzibar[7]. Although the sterile insects may spread beyond the initial target area, the sterile trait will not persist beyond the insects' life spans and SIT is highly specific to the target organism. Isolating lines of pest insects that yield healthy, sterile, all-male populations of sufficient number is difficult, and combined with substantial operating costs, can limit the utility and feasibility of SIT. Irrespective of cost, it provides an environmentally acceptable alternative to spraying with pesticides. As restrictions on pesticides tighten, (for example, in the European Union), SIT may well become more popular[8].

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When the remaining handful of New Zealand's kakapos were threatened with erisypelas infection, it was possible to vaccinate them by hand. For other threatened species, self-dispersing vaccines—made with recombiant technology—offer a new strategy for conservation, but will need tighter regulation.

In addition to the control of diseases detrimental to human health and agriculture by programs like SIT, biocontrol may be used to ensure survival of an endangered wildlife species through vaccination. In July 2004, several kakapo (*Strigops habroptilus*) were found dead in the course of a translocation program to move them between New Zealand offshore islands. The remaining birds were captured and vaccinated against an erysipelas outbreak[9]. In many cases vaccination needs individual administration, and although feasible for small confined populations, such as kakapo, this does limit the implementation of this method. Although conventional live vaccines may exist, a common barrier is the difficulty in finding a naturally occurring species that displays the full set of desired properties to make a vaccine useful (that is, good immunogenic response but no disease). The expanding capabilities of modern biotech may offer a way around these hurdles.

Biotech supports the ongoing development of a diversity of GMOs that would be purposefully released into nature for wildlife management goals (**Table 1**). Most of these products would be self-dispersing, for example, genetically modified (GM) insects used as disease-free insects to control human diseases carried by insects, such as *Plasmodium falciparum* in malaria, and GM viruses used as live vaccines to control diseases of wildlife or as immunocontraceptives to control invasive species. Targeting wild populations can be difficult. They can be distributed over a large or inaccessible area, are difficult to approach and treat, hard to separate from nontarget biota and, after a treatment, they can revert to their original state.

Compared with using traditional biological control agents, using self-dispersing GMOs to manage target populations may offer advantages in terms of specificity, reducing human-operator costs, increasing dispersal and persistence. However, self-dispersion raises complex governance questions. First, most regulatory systems try to reduce any risks from GMOs by favoring or mandating their containment where possible. And second, nations may differ in their opinion on the use of a specific self-dispersing GMO. In the following sections, we describe the main areas for which self-dispersing GMOs could offer a better solution than other approaches used to date.

Emergence of self-dispersing GMOs

Recombinant technologies (for example, transgenesis or site-directed mutagenesis) offer a means of modifying existing traits of candidate organisms, or conferring wholly new properties, which could be used in wildlife management applications. One important consideration is whether the GMOs are capable of self-dispersal or reproduction.

Nondispersive GMOs. Recombinant vaccines for wildlife are a leading example of nondispersive GMOs. Vaccination of wild carnivores with a recombinant vaccinia vaccine expressing rabies glycoprotein (VRG)[10] has been used to control rabies in Europe and North America. From 1989 to 1995, around 8.5 million doses of VRG vaccine were dispersed in Western Europe to vaccinate red foxes and in North America to vaccinate raccoons and coyotes. VRG was delivered through baits; it replicated within individual hosts, but did not transfer between individuals. Vaccination favored the survival of these species and reduced the frequency of human rabies cases[11]. In another example, to prevent canine distemper virus (CDV) in a relict wild population of the island fox (*Urocyon littoralis*), a subset of individuals were individually vaccinated with a canary-pox vectored CDV vaccine[12]. In this case, the recombinant virus was not able to replicate within the target species but expressed the foreign gene inducing protective immunity.

The above recombinant vaccines consist of nonreplicating or nondispersing virus. This can be viewed as a form of containment. Whereas containment is consistent with many regulatory approaches to reducing risks from GMOs, it limits their use in wild populations.

Self-dispersive GMOs. Recently, biotech is exploring the options for using self-dispersive GMOs to address free-ranging populations. Releasing GMOs into nature that are going to disperse into the wild populations introduces a new dimension in wildlife management. Concerns exist surrounding the considerable challenges that arise from the disseminating characteristic of self-dispersing GMO applications.

There is a growing list of self-dispersive GMO examples (**Table 1**). As the profile of wildlife disease continues to rise—as a threat to endangered species and/or to human health (for example, avian influenza or malaria)—novel strategies of disseminating vaccines[13] may become more attractive. Immunocontraception (the idea of vaccinating against pregnancy) using a disseminating vector has been, and continues to be, pursued in more than one nation for more than one pest[14–18]. Progress continues on systems for driving disease-preventing genes or genotypes through wild populations of insects[19–21], leaving the insect in the environment but suppressing the disease. In Australia, one research group is making progress in creating a male-only line of carp (*Cyprinus carpio*), the release of which would drive down invasive populations of the species in that country[22]. Altogether, self-dispersing GMOs are opening up a broad new front in the way we may manage wildlife issues in the near future.

The potential for international dispute

The goals of many of these self-dispersing GMO programs may be shared widely, within and between nations. The control of devastating human diseases is a laudable goal that meets the interests of many nations. So, too, is the protection of threatened biodiversity. That said, genetic modification is not in general a well-understood technology outside of science and does not have universal public and political support. Regardless of the consensus about the ends, the use of GM technology as a means for wildlife management may well be a source of conflict[23]. Conflicts become more complex as one adds more nations to the scenario, as might be the case in regional- or continental-scale programs of disease control (for which cross-border collaboration is a crucial element[11]).

A common goal may form a powerful unifying point about which to resolve any dispute over the use of self-dispersing GMOs. But in areas where common goals do not exist, the use of self-dispersing GMOs may lead to conflict. The following two cases illustrate this very well. In the first case, Spanish researchers have already developed[13] and carried out a field-trial[24] of a transmissible vaccinating GM myxoma virus to protect threatened Spanish rabbits (*Oryctolagus cuniculus*) from disease. Whereas Spanish interests lie in conserving the rabbit (a native prey species for endangered predators and a resource for hunting), the same species has had a devastating impact on biodiversity and agriculture in Australia (where it is an invasive species). The Spanish self-dispersing GMO protects rabbits against the very same viruses Australia has used for traditional rabbit biocontrol and its own immunocontraceptive self-dispersing GMO research[18] (**Table 1**). The goals pursued with self-dispersing GMO technology by these two nations are in direct opposition to each other: Spain exploited a vaccinating GM myxoma virus to protect an indigenous species, whereas Australia is investigating an immunocontraceptive GM myxoma virus to eradicate an invading species that has had devastating consequences for the local environment. Not surprisingly, Australian scientists are concerned, informed by the history of the spread of rabbit viruses since the 1900s[25–27].

The second case is the development in New Zealand of a immunocontraceptive

Table 1 Selected GMO research for wildlife management

GMO	Target	Objective	Nation	Mechanism	Mode of action	Stage of development	Self-dispersing	Refs.
Myxoma virus (MV)	Rabbit (*Oryctolagus cuniculus*)	Transmissible vaccine for European rabbits against myxomatosis and rabbit hemorrhagic disease	Spain	MV expressing the major capsid protein (VP60) of the rabbit hemorrhagic disease virus	Horizontal spread of the recombinant MV within the rabbit population generating protection against both diseases	Field trials completed but not yet approved for deployment	Yes	13,24,35
Vaccinia virus	Wild carnivores (e.g., foxes *Vulpes vulpes*)	Vaccine for wild carnivores against rabies	Europe/US	Vaccinia virus expressing the immunizing glycoprotein of rabies virus	Vaccine is delivered through baits; recombinant virus replicates in the host, inducing immunity against the virus	No primary publication, reviewed in refs.	No	10,11
MV	Rabbit (*O. cuniculus*)	Biocontrol of invasive rabbits by virally vectored immunocontraception (VVIC)	Australia	MV expressing oocyte antigen (zona pellucida 3 glycoprotein)	Horizontal spread of the recombinant MV within the rabbit population, generating autoimmune infertility in females	Programs winding down or discontinued (see refs.)	Yes	15,37
Murine cytomegalovirus (MCMV)	Mice (*Mus musculus*)	Biocontrol of mice in agricultural landscapes to suppress episodic population explosions by VVIC	Australia	MCMV expressing oocyte antigen (zona pellucida 3 glycoprotein)	Horizontal spread of the recombinant MCMV within the mouse population generating autoimmune infertility in females	Programs winding down or discontinued	Yes	4
Nematode (*Parastrongyloides trichosuri*)	Brushtail possum (*Trichosurus vulpecula*)	Biocontrol of invasive brushtail possums by parasite-vectored immunocontraception	New Zealand	Expression of zona pellucida glycoproteins (antigen) in parasitic nematode (*P. trichosuri*)	Horizontal spread of the recombinant *P. trichosuri* within the possum population, generating autoimmune infertility in females	Program underway, but no primary publications (see ref. 28)	Yes	28
European carp (*Cyprinus carpio*)	European carp	Control of invasive carp populations by massively skewing sex ratios to male ('daughterless carp')	Australia	Genetic inhibition of aromatase in embryonic development. Genetically female individuals revert to a male phenotype	Iterative release of recombinant carp resulting in the introgression of the masculinizing phenotype into wild populations. Absence of 'phenotypic' females compromises replacement capacity of population	Program under way but no publications	Yes	NA
Insect commensal midgut bacteria	*Anopheles* mosquitoes, *Rhodnius prolixus* and tsetse flies (*Glossina morsitans*)	Prevention of infection by rendering insect vector resistant to pathogen (*Plasmodium* spp., malaria; *Trypanosoma cruzi,* chagas; or *Trypanosoma brucei/rhodesiense/gambiense,* sleeping sickness)	Various	Genetic modification of commensal midgut bacteria to express an antiparasitic module (e.g., cecropin A or *G. morsitans* attacin). Hosts are said to be 'paratransgenic'	Release of paratransgenic insects resulting in the introgression of the recombinant bacteria into the population. Host insect is left in the environment but unable to host the pathogen	Programs underway, but no primary publications	Yes	19,38
Anopheles mosquitoes	Malaria parasites (*Plasmodium* spp.)	Mosquitoes rendered incapable of carrying and/or transmitting malaria	US, UK and Germany	Expression of antiparasitic effector molecules in the mosquitoes' midgut epithelia	Release of recombinant mosquitoes resulting in the introgression of malaria-incompatible genotype, thereby reducing transmission to humans	Research and development	Yes	39,40

Table 1 (continued)

GMO	Target	Objective	Nation	Mechanism	Mode of action	Stage of development	Self-dispersing	Refs.
Anopheles stephensi mosquito	*A. stephensi*	Reduction of malarial mosquito populations by SIT	UK	Male-specific expression of enhanced green fluorescent protein under the control of the beta-2 tubulin promoter	Automated fluorescence-based sorting of mosquito larvae to facilitate mass rearing and release of sterile, all-male batches into population	Proof of concept	No	41
Drosophila melanogaster (model system for insect pests)	Various insect pests	Sensitization of insect populations to pro-insecticides	Greece and UK	Expression of bacterial cytosine deaminase gene under the control of a female-specific promoter. Catalyzes the deamination of low-toxicity nucleoside analog 5-fluorocytosine to toxic 5-flurouracil	Release of recombinant insects resulting in the introgression of female-specific vulnerability to a low-toxicity chemical. Vertical transmission through unaffected male line (assisting introgression)	Proof of concept	Yes	42
Medfly (*Ceratis capitata*)	Medfly (and others)	Suppression of medfly pest by release of transgenic medfly that carry dominant-lethal genetic inserts	UK	Transformation with a one-component tetracycline-suppressible transactivator (tTA) system. The tTA molecule is lethal to juveniles at basal level of expression	Medfly raised in captivity in the presence of tetracycline. Upon release and mating with wild populations, juveniles with recombinant genotype produce tTA in absence of tetracycline, leading to death	Research and development	No	43

self-dispersing GM hardy nematode parasite against introduced Australian possums (*Trichosurus vulpecula*) (**Table 1**); in this case, the transfer of this self-dispersing GMO to nearby Australia seems dangerously probable[28]. Although New Zealand might be able to effectively suppress a disastrous invasive species with this self-dispersing GM nematode, the benefits to New Zealand's agriculture and biodiversity would come at the cost of a grave risk to Australian biodiversity.

Although many other cases will be much more subtle, these cases clearly illustrate the potential for international conflict over the application of a self-dispersing GMO. It is the very properties of dissemination and persistence that make self-dispersing GMOs nationally useful, but potentially problematic on a wider scale.

Interests in producing self-dispersing GMOs

In areas of recurring human epidemics, long-standing international dialog may have established a consensus on where the interests of all parties lie. Indeed, significant research funding may come from international bodies[23,29], allowing a negotiated process of defining technological goals and establishing limits on its deployment. In this case, there is an institutional context that establishes a set of interests for all innovators of self-dispersing GMOs with regard to the need to be respectful of international needs and sensitivities.

Even so, where the goals of the self-dispersing GMO research are exclusively defined intranationally, the institutional context may be strong in safeguarding the interests of the innovating nation without adequate regard for the interests of others. Research on self-dispersing GMOs is typically carried out under competitive and publicly accountable government schemes that reward benefit to the nation, which creates a political incentive for deployment. Career prospects for the workers or private enterprises involved might also be bolstered by the implementation of the technology. Regulation of the research and its products may be similarly domestically focused. Even in cases where regulation accounts for impacts on environments beyond national borders, the relevant expertise and advocacy may not be available in the innovating nation to adequately defend the interests of the country at risk. These situations do not provide clear guarantees for the prudent development and dissemination of a technology. Domestic pressures, incompetence or a lack of expertise makes global biodiversity vulnerable to future self-dispersing GMO developments.

A need for specific international regulation?

International agreements are not well equipped to govern GMOs purposefully released into nature, especially self-dispersing GMOs. There is a sparse *ad hoc* network of guidelines, commitments and sanitary provisions, but no integrated platform. This may have been sufficient for traditional approaches, but self-dispersing GMOs offer traits and strategies that are often without substantial equivalence, and may attract different legal oversight because of the use of recombinant technology in their production. This is already prompting many in the scientific community to call for a universal regulatory framework for oversight of self-dispersing GMOs (see **Box 1**).

The Convention on Biodiversity (CBD) addresses invasive species (Article 8 (h)), which theoretically covers any self-dispersing GMO that threatens to become invasive. The CBD also states that nations have the responsibility to ensure that activities within their jurisdiction or control do not cause damage to the environment of other countries, or areas beyond the limits of national jurisdiction. Even so, the parties to the CBD view the Cartagena Protocol on Biosafety (the Protocol) as the prime instrument for GMO regulation. The Protocol deals mostly with intentional transboundary movements of GMOs (for example, trade in living modified organisms). Only 2 of its 40 articles are particularly relevant to self-dispersing GMOs. They place responsibility on signatory nations to risk-manage unintentional transboundary movements of GMOs (Article 16.3), to cooperate in dealing with GMOs that may adversely affect biodiversity (Article 16.5) and to declare releases of GMOs that may result in unintentional spread (Article 17).

Although the CBD enjoys wide support (190 countries have ratified it), a significant block of nations (including Australia and the United States) has not ratified the Protocol (only 141 ratifications). Measures to ensure compliance and negotiation of its twin issues of liability and redress of damage done by GMOs have only just begun to be taken[30,31], and it is unclear what surveillance, emergency or corrective procedures could be successful against a self-dispersing GMO on the ground. The Protocol mandates assessment and notification of risks associated with self-dispersing GMOs, but has not yet provided any advisory opinion or special guidelines on the release of self-dispersing GMOs[29,32]. This somewhat tenuous coverage needs reinforcement.

Although in our view the Protocol is the international agreement most suitably placed to deal with the development and release of self-dispersing GMOs, other international bodies are relevant. In fact, the Protocol is beginning to establish collaborations with other international bodies concerned by GMOs in more specific contexts, such as the World Organization for Animal Health (OIE; Paris) or the International Plant Protection Convention (IPPC). The OIE deals with sanitary and scientific information in the veterinary field and has a wide international coverage (167 member countries in 2004). Recently, the OIE has been concerned by the new applications of biotech for veterinary purposes[33] and has had some discussion of self-dispersing GMOs at its meetings. The IPPC deals with introduction of organisms injurious to plants and has recently adopted a standard for dealing with GMOs risks[34]. The expertise of such organizations (for example, OIE expertise on recombinant vaccines for wildlife) should provide valuable input to the Protocol to establish guidelines for specific self-dispersing GMOs.

Box 1 What are people starting to say?

There is mounting concern about the oversight of self-dispersing GMOs among sections of the scientific community. Although only a few scientific critiques focusing on these organisms appear in the peer-reviewed literature[25–28,36,44], debates about these products have sparked great audience interest at different forums (for example, "The Rabbits and RHD Symposium: Disseminating Genetically Modified Organisms and Conflicting International Objectives" held at the 3rd International Wildlife Management Congress in Christchurch, New Zealand, December 1–5, 2003; the online conference "Biosafety Considerations in the Use of Genetically Modified Organisms for Management of Animal Population" organized by the Cartagena Protocol throughout the Biosafety Clearing-House, October 18 to November 15, 2004; the "Ad-Hoc Technical Expert Group on Risk Assessment", a sidebar meeting of experts within the Protocol Meeting, Rome, Italy, November 15–18, 2005; or the "Norway-Canada Workshop for Risk Assessment for Emerging Applications of Modern Biotechnology" held in Montreal, Canada, June 4–6, 2007). Inputs from scientific, management and other experts—as well as the general public—highlight the scientific uncertainty, the potential for controversy and on-ground localized demand for self-dispersive GMO technology.

The need for a universally agreed upon regulatory and institutional framework is a recurring theme[23,27,45]. Given the basic properties of self-dispersing GMO technology, there is growing recognition that the best way forward would be a proactive regulatory intervention that sets a framework for disseminating GMO research at its inception rather than its deployment. Intervention in the domestic activities of a sovereign nation is difficult. Nonetheless, agreements on pollution, resources and similar issues do just that[46,47]. The deliberate design of a self-dispersing GMO has much in common with biological weapons, too, which is also regulated by international treaty, despite deficiencies[48,49]. Universal to all is the need for negotiation and dialog, supported at high levels in an international forum.

Productive ways forward

Any international framework for regulation of self-dispersive GMOs must achieve the following: first, it should maintain consistent and consensual modes of problem definition, analysis and decision making; second, it should provide clear guidelines regarding minimal conditions for 'wise use'; and third, it should include instruments to ensure compliance. Regulatory frameworks should also be adaptive, especially in the dynamic arenas of ecology and technology, which make efficient communication a central feature.

The CBD is broad ranging and ambitious, and although enjoying near-universal ratification, it only sets a framework for action[35]. The Protocol has a tighter scope, represents a significant point of consensus among several nations, and sets operational guidelines for intentional movements of GMOs relatively well. However, its coverage of self-dispersing GMOs does not provide the proactive and prescriptive approach that is needed. Fortunately, the Protocol does contain scope for adaptation when it encounters such deficiencies.

With this in mind, we make several recommendations: first, we call on the parties to the Protocol to ensure that specific guidance or binding requirements for the development and use of self-dispersing GMOs are developed as soon as possible. Ultimately, these requirements would be best implemented under the provisions of an amended Protocol. However, this option has some significant shortcomings. Nations not party to the Protocol, including Australia (a pioneer of self-dispersing GMO technology) and the United States (a powerhouse of bioinnovation in general), would not be bound by these requirements. The Protocol's implications for trade, particularly in GM crops, formed a critical point of disagreement with this block of nations during its negotiation, and their concerns may be enduring. Expanding the Protocol's scope may mean conflating self-dispersing GMOs with GMOs for trade. The regulation of self-dispersing GMOs may come off second best. In this situation, serious consideration needs to be given to the establishment of a new and separate protocol. A new protocol could take a much more inclusive view of the use of organisms in wildlife management to cover non-GMO applications as well.

Second, either an entirely new Protocol or amended Protocol will take a significant amount of time to develop and implement, yet the application of self-dispersing GMOs is imminent. The most effective solution in the short term may be to engage other widely supported international arrangements, such as the OIE, in a coordinated fashion to explicitly address the challenges of self-dispersing GMOs. Such organizations can be encouraged to consider the issues and attempt to introduce control mechanisms relatively quickly. Nonmember nations of the Protocol could also participate. The lack of case histories on the matter could preclude the identification of gaps in the regulation of self-dispersing GMOs and how to solve them. Early examples of self-dispersing GMOs, such as those listed in **Table 1**, offer valuable learning opportunities, and should form the basis of a range of scientifically informed policy studies on their regulation.

Third, we echo calls (**Box 1**) for the rapid establishment of multidisciplinary working-groups, focusing on cases likely to be problematic, such as rabbit viruses. These working groups would ideally be bilateral or moderately multilateral in composition, with involvement from institutions like the OIE. They would establish mutually satisfactory guidelines for the development and deployment of current near-term self-dispersing GMOs (including modifications to existing technology, or discontinuation) and the identification of promising alternatives. We encourage the active engagement of stakeholders other than just the scientific and political elite on both pragmatic and ethical grounds[23,29], consistent with the spirit of the CBD.

The Biosafety Clearing-House (BCH), established by the Protocol to facilitate exchange of information and experience related to GMOs, could be a good framework to help in this task. The BCH is capable of hosting online conferences or other information-exchange mechanisms, such as online working groups. The parent website of the BCH, the clearing-house of the CBD, already serves as a virtual meeting portal for several working groups under the CBD. The technical infrastructure and support already exists. Working groups related to self-dispersing or nondispersing GMOs would fall within the mandate of the BCH, and would be likely to be supported by the CBD secretariat, which hosts the BCH. These virtual options would reduce the cost and might improve the feasibility of participating in the working groups for thrifty contributing governments.

Lastly, bilateral (or small-multilateral) working groups would be particularly relevant in situations of conflicting objectives for self-dispersing GMOs for biodiversity conservation and pest control, such as the possum or the rabbit cases previously described[26]. Discussions on these cases should recognize a crucial tenet of common ground: that pooling of expertise and co-investment in research will deliver better technologies, better on-ground results, which would facilitate the unified goal of appropriate management and not be directed toward partial solutions that exacerbate problems elsewhere.

At least one self-dispersing GMO is already a reality[13,36] and others will soon follow. The need for action is clear and pressing. Today, when biodiversity is so deeply threatened, we cannot afford to repeat the pattern of technological mistakes of the past.

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