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Dismay with GM maize

A science-based solution to public resistance against genetically modified crops that could be compatible with organic farming

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In 1974, the physician and writer Lewis Thomas published a collection of essays titled *The Lives of a Cell: Notes of a Biology Watcher*. In one of those articles, 'The Technology of Medicine', Thomas divides technological progress into three categories that he describes as "nontechnology", "halfway technology" and "high technology". Nontechnological solutions include bedside care—delivered by physicians, nurses or relatives—to ease a patient's suffering. Halfway technological advances deal with symptoms: "the kinds of things that must be done after the fact, in efforts to compensate for the incapacitating effects of certain diseases whose course one is unable to do very much about" (Thomas, 1974). Thomas lists organ transplantation and artificial organs as examples of a technology that is "by its very nature, at the same time highly sophisticated and profoundly primitive." Finally, high technology (high-tech) "is so effective that it seems to attract the least public notice; it has come to be taken for granted." The best example of high technology in medicine is the use of vaccines: cheap, efficient and easy to use, they prevent problems rather than treat symptoms. Yet, even though high-tech solutions seem simple to individuals now, they are nevertheless the results of enormous amounts of research—virology, immunology and microbiology were all needed to develop vaccines.

The development of agriculture might well be another example of Thomas's description of technological progress. For millennia, humans refined non-technological agricultural solutions such as breeding, crop rotation, irrigation, natural fertilizers, manual pest control and so on. The green revolution of a few decades ago heralded the era of halfway technology: artificial fertilizers, pesticides, mechanized agriculture, hybrid crops and other inventions. During the past few years, we have seen the emergence of high-tech agriculture: genetically modified (GM) crops and livestock based on a much improved understanding of plants, animals and microbes down to the molecular level and how these organisms interact with each other in ecosystems.

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> **…the answer to public resistance is neither to give up on the technology nor to sweep aside public concerns, but to address these concerns […] by developing science-based solutions…**

These developments have enormous potential, much like the green revolution of a few decades ago, which enabled huge gains in agricultural productivity. However, new technologies are seldom perfect from the outset. The automobile is an illustrative example: it gives us personal mobility, but has major negative effects on humans and the environment. Car designers have therefore developed a range of improvements to increase safety and decrease noise, air pollution and energy consumption. Similarly, although the high-tech revolution in agriculture—especially the genetic manipulation of crop plants—has generated a lot of enthusiasm, given the challenge of feeding a growing human population in a sustainable way, GM technology has also raised valid concerns that we need to address. Doing so could help us to avoid potential negative outcomes and might help to reduce public opposition to GM crops.

In Europe, the public remains largely sceptical of GM crops. In turn, European opposition impedes the technology in other parts of the world, especially its application in developing countries that could benefit most. However, the answer to public resistance is neither to give up on the technology nor to sweep aside public concerns, but to address these concerns as far as possible by developing science-based solutions that enhance efficacy and safety. Using the example of pest-resistant GM maize encoding the Bt toxin, I will demonstrate how more sophisticated techniques for genetic modification could address environmental concerns and might even generate GM varieties that are compatible with the principles of organic farming. Bt maize is an illustrative example as intense research has gone into measuring its impact. The results demonstrate how valid concerns can be addressed by more innovative strategies to generate GM crops.

Maize has a long tradition of cultivation. Several thousand years of breeding have led to a plant that is distinctly different to teosinte, its progenitor from Mexico (Doebley *et al*, 2006). Yet, it is still possible to cross cultivated maize and teosinte (Parrott, 2010), which illustrates the wide genetic diversity and phenotypic variation within the species. As maize is one of the most important food crops, it was an obvious choice for genetic manipulation in order to increase yield. GM maize carrying transgenes that confer pest resistance or

herbicide tolerance are already grown in many countries. However, in Europe, only the Bt maize MON810, developed by Monsanto, and the herbicide-tolerant maize T25 have been approved for commercial use (Park *et al*, 2011). T25 is not grown in Europe, however, and will not be further discussed here. MON810 confers resistance to the European corn borer (*Ostrinia nubilialis*), a major insect pest of maize (Sanahuja *et al*, 2011). After the first approval of MON810 in 1998, intense discussions in Europe about the potential risks to human health and the environment halted the commercial growth of MON810 in some EU member countries (Park *et al*, 2011).

A major concern about GM crops has been the use of antibiotic resistance markers to select transgenic plants. However, more sophisticated techniques to transfer genetic material, such as sequence-specific zinc-finger nucleases (Puchta & Hohn, 2010) or TALE (transcription-activator-like effector) nucleases (Boch, 2011), now allow the generation of transgenic plants without the need for antibiotic resistance genes or other markers. Moreover, these novel techniques modify the plant genome at a precise location and thereby avoid random insertion of the transgene and genomic rearrangements. These techniques have even been further improved recently (DeFrancesco, 2011) and should become the gold standard for generating GM crops.

MON810 pest-resistant maize is a transgenic plant as it contains a gene from another, sexually incompatible organism: it expresses the gene encoding the Cry1Ab protein from the soil-born bacteria *Bacillus thuringiensis*. The so-called Bt protein confers high selective toxicity to some *Lepidora* species including the European corn borer. Its mode of action is quite complex and involves several steps, which possibly explains the restricted action of the toxin (Soberón *et al*, 2010).

Nevertheless, the Bt toxin might also harm other, beneficial insects. Whether this is a realistic concern has not been fully elucidated, although most research so far indicates no or few negative effects on other insect species (Ricroch *et al*, 2010). Of course, we must realize that any human interference to protect plants from pests inevitably alters the environment, simply because pest control reduces the population size of the species targeted. This is true both for GM crops and for biological pest control measures, such as spraying the Bt toxin itself. So far, no negative effects on non-target organisms have been observed in the field, even though Bt maize has been grown for more than 10 years; in fact, 63% of maize grown in USA produces Bt toxin (Naqvi *et al*, 2011). That the broad application of Bt maize might have ecological consequences seems unlikely, but only the future will tell. A related concern is the emergence of Bt-resistant insects; farmers are therefore required to plant patches of regular maize to provide a refuge for Bt-sensitive insects to reduce the selective pressure to develop resistance (Tabashnik, 2010).

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Beyond environmental impacts, a further concern is that Bt protein could be toxic to mammals including humans (de Vendômois *et al*, 2010). Bt maize is mainly used for feeding cows and a recent long-term study over 25 months demonstrated no effect on milk composition or body condition (Steinke *et al*, 2010). Furthermore, it has been shown that Bt protein is absent in bovine blood plasma (Paul *et al*, 2008) and milk (Guertler *et al*, 2009) in cows fed with Bt maize. However, corresponding studies have revealed the presence of Bt toxin in the faeces (Paul *et al*, 2010), in addition to Bt protein released from the decaying waste of Bt maize fields (Tank *et al*, 2010). In both cases, it is unknown whether the concentration of the toxin is high enough to affect the ecosystem.

More than 10 years of research and experience with GM Bt maize show no evidence for adverse effects on human health or on the environment. Even so, I think it is prudent to label GM products sold for human consumption in order to guarantee free choice for consumers and thereby help to generate trust. It is also essential to continue to monitor for any, as yet unknown, adverse effects on the environment from the commercial use of GM crops (Wilhelm *et al*, 2009). If future studies were to reveal an adverse effect on human health or the environment, we would still be in a position to stop the growth of Bt maize. There is no indication that an adverse effect will not be reversible.

The most serious problem is the outcrossing of the Bt transgene into other maize varieties: this is not a risk but a reality. Several reports have shown the presence of transgenes in maize landraces in Mexico, although the Mexican government has not approved the commercial use of GM maize (Dyer *et al*, 2009; Snow, 2009). The information available does not allow firm conclusions to be drawn about whether outcrossing was a result of pollen-mediated gene transfer from crops in the USA or illegal crops in Mexico, or careless seed management. In any case, it illustrates the ease with which transgenes can spread. This should come as no surprise, as mixing of various landraces has been well documented in Guatemala (Parrott, 2010) and gene transfer between modern hybrid varieties into traditional landrace populations of maize has been observed in Italy (Bitocchi *et al*, 2009).

Opponents of GM crops and environmentalists are not the only people concerned about the outcrossing of transgenes. Food producers who support GM crops in principle also have concerns. The North American Miller's Association has expressed concerns about Enogen™, a GM maize variety produced by Syngenta for cost-efficient ethanol production. The Association fears that the transgene—an optimized amylase—might contaminate other varieties, which could cause sticky tortillas, dense corn puffs and gummy bread (Waltz, 2011). Importantly, the outcrossing of a transgene into landraces and wild relatives might not, eventually, be reversible. This seems especially likely for herbicide-tolerant maize, because the extensive use of the corresponding herbicide creates strong selective pressure.

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Pollen-mediated transgene transfer is the most important form of outcrossing, as wind or insects can carry pollen over long distances. Seed dispersal is another risk that can occur during the harvest, transport and seeding of a crop, or by animals. Given that it is obviously not possible to prevent seed dispersal or the pollen-mediated spread of a transgene for a variety of reasons, we need a high-tech solution that addresses the cause of the problem. We need GM plants that produce no 'functional' pollen and that can grow seeds—the actual plant product—without fertilization.

Many plants can reproduce asexually by using either of two strategies: vegetative propagation by rhizomes, bulbs and other plant parts, which is quite common, and apomixis, a process found in more than 400 angiosperms, which produces seeds without previous meiosis and fertilization. Apomixis has been shown to be under complex genetic control with some species specificity (Spillane *et al*, 2004); in fact, most crop plants including maize are not apomictic. Maize does have an apomictic wild relative, *Tripsacum*, but introgression of apomixis into maize by conventional breeding has so far not been successful, possibly owing to epigenetic factors (Leblanc *et al*, 2009). In fact, two DNA methyltransferases (Garcia-Aguilar *et al*, 2010) and an argonaute protein (Singh *et al*, 2011) were found to play a role in the differentiation between apomictic and sexual reproduction, which suggests epigenetic regulation.

However, scientists have induced at least partial apomictic pathways in maize by mutagenesis of the genes *elongate1* (Rhoades & Dempsey, 1966) and *ameiotic1* (Pawlowski *et al*, 2009), both of which control meiosis. These results indicate that it might be possible to generate apomictic maize but it would be necessary to combine it with male sterility to avoid the potential spread of the apomixis trait to wild plants through pollen (Spillane *et al*, 2004).

To stop pollen-mediated gene flow, a wide variety of strategies has been proposed including chloroplast transformation, transgene excision, cleistogamy (non-opening flowers) or cytoplasmic male sterility (Moon *et al*, 2010; Hüsken *et al*, 2010). All these approaches have been studied in various plants with some success, but the efficiency and instability of each trait is still a major problem. Another option could involve pollen-specific deletion of the transgene (Moon *et al*, 2010). However, this approach is not appropriate either, as the pollen would still be able to transmit the apomictic trait to other plants. Therefore, lack of pollen formation would be essential for GM crops, and it should be achieved by permanent gene loss. Since maize has not been studied systematically, a major scientific investment is needed to work out how to efficiently prevent pollen-mediated gene flow.

The use of apomictic, sterile maize as a standard platform from which to develop GM varieties would address the major environmental concerns about GM crops and could thereby contribute to greater public confidence in green gene technology. By using these specific varieties under the stricter standards of organic farming, such as the ban on the use of artificial pesticides, herbicides or fertilizers, appropriate apomictic GM plants might become acceptable to organic farmers. Even if not,

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a sceptical organic farmer could no longer object to GM maize being grown next to his fields, if pollen-mediated gene transfer is no longer possible. The absence of GM pollen would also solve the problem of contaminating honey with transgenic DNA. Generally, the generation of GM crops should use our most advanced technologies, such as sequence-specific nucleases. Moreover, the GM plant itself should not be able to disseminate the transgene to other plants. Finally, any sterile apomictic GM plant should be carefully studied before it is used commercially in order to determine that it does not have other negative effects on the environment.

> **Generally, the generation of GM crops should use our most advanced technologies…**

Obviously, the development of apomictic sterile maize and other crops as a safeguard against gene flow constitutes a major challenge for plant biotechnology. However, this investment would signal to the public that science takes seriously their major concerns about GM crops. The application of this novel technique would also be useful for other GM crops that have a much higher potential for outcrossing, such as alfalfa and sugar beet. In the long run, it would also enable or ease the production of highly specific compounds, such as pharmaceutical proteins, in GM plants (Naqvi *et al*, 2011).

Given that we need to increase agricultural production in a sustainable way to feed the growing human population, it is not a question of whether but how we use science. Possibly, this will involve GM crops as they have the potential to become the true high technology in agriculture: plants that have greater resistance, higher yields and are easier to grow without the need for artificial pesticides, fertilizers and heavy mechanization. Nevertheless, the opposition to GM crops in Europe has shown that we have to be careful how that science is applied. We should therefore strive for real high-tech solutions that solve the problem—in this case, gene transfer from GM maize—instead of fiddling with the symptoms or abandoning the technology altogether.

CONFLICT OF INTEREST

The author declares that he has no conflict of interest.

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