"Genetically Modified Lite" placates public but not activists

New technologies to manipulate plant genomes could help to overcome public concerns about GM crops

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The public debate over the alleged health and environmental risks of genetically modified (GM) crop plants, which has been festering for more than two decades, may be about to take a new turn in light of novel technologies to manipulate plant genomes. These include the two related techniques of cisgenic and intragenic modification that involve the import of genes from closely related, sexually compatible plant species, or that modify the plant genome without involving any foreign DNA (Fig 1). Other techniques in the pipeline should be able to modify gene expression to create new phenotypes without the need to import DNA from elsewhere. By contrast, current transgenic manipulation techniques involve the transfer of DNA into plants from unrelated species, such as *Bacillus thuringiensis*, the toxin gene of which was used to generate pest resistant GM maize and cotton. Moreover, unlike the old "scatter gun" approaches that were used to transfer genes into plant cells, some of the new technologies are highly specific for manipulating the target genome, even down to exchanging single nucleotides.

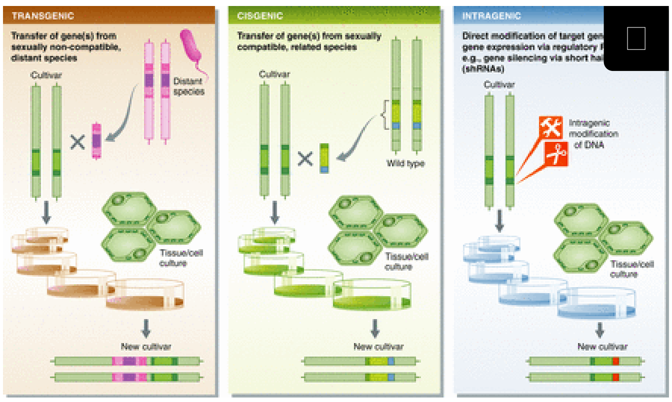

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Figure 1.

Transgenic, cisgenic and intragenic genetic modification of crop plants.

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These advances raise regulatory issues—notably whether plants modified using cisgenic or intragenic techniques should still be regulated as transgenic—but should also breathe new life into the debate about the regulation and public acceptance of GM crops. Some plant scientists believe that these new approaches provide an opportunity to outmanoeuvre the anti GM activists by changing the terms of the debate. Because the new techniques can be described—albeit spuriously—as being more “natural”, they may convince a wary public that the resulting crops are not “Frankenfood” and carry less risk to health and the environment. “Some of my colleagues and I plan to switch the term to ‘precision breeding’ as a more practical descriptor that avoids scientific jargon and terms which have been demonized to scare ignorant, but not stupid, people,” explained Dennis Gray, a developmental biologist and Editor in Chief of *Critical Reviews in Plant Sciences*. “We need now to start to talk about the new stuff and do a better job of it.”

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Researchers and biotech companies argue that plants modified using cisgenic and intragenic methods should be treated in the same way as plants modified through traditional breeding methods. However, there is an important distinction between the terms that may cause them to be perceived and regulated differently. Cisgenesis involves the artificial transfer of specific genes between sexually compatible organisms. Intragenesis is increasingly interpreted as the transfer of DNA fragments with the potential to create novel genes that could not arise in nature [1], or the use of antisense or RNA interference (RNAi) to silence target genes [2]. The critical distinction is that the phenotypes of cisgenic plants could always, in principle, be achieved through conventional breeding—albeit over a longer term and with less accuracy—whereas intragenesis can yield novel phenotypes beyond the reach of breeding.

Given this distinction, some regulators are veering towards treating the two differently such that cisgenesis is viewed as comparable to traditional breeding, while intragenesis is seen as more similar to current GM plants such as Bt cotton. This is the line taken by the European Food Safety Authority (EFSA) in response to a request from the European Commission (EC) for a scientific opinion on the threats that cisgenic and transgenic plants might pose, as well as the applicability of the existing GMO guidance documents for their risk assessment. EFSA found that “similar hazards can be associated with cisgenic and conventionally bred plants, while novel hazards can be associated with intragenic and transgenic plants.” The organization concluded that the existing European guidelines for the assessment of food and feed safety and environmental risk were applicable for the evaluation of cisgenic and intragenic plants and did not need to be developed further [3].

This appeared to be good news for advocates of cisgenic crops, but EFSA also indicated that both cisgenic and intragenic crops should be subjected to the genetically modified organism guidance for food safety and environmental risk, albeit that the data required could be reduced on a case by case basis. EFSA emphasized that “both cisgenesis and intragenesis can produce variable frequencies and severities of unintended effects.” There has been no further development since the EFSA opinion, according to Inger Holme, senior researcher at Aarhus University in Denmark. “It has been over a year since the relatively positive report from the EFSA came out and nothing to my knowledge has happened since then,” she said, suggesting that the EU has been bogged down by differing opinions among members states.

A slightly more relaxed regulatory approach has been taken in the USA, where the Environmental Protection Agency has proposed to exempt cisgenics from GMO regulation altogether, although only when applied in the context of protecting against pests [4]. Use of cisgenic technology to express other traits would still have to be approved by the US Department of Agriculture, as with transgenic GMOs.

While regulators have been pondering the implications of cisgenic and transgenic modification, advocates and opponents of GM crops have tried to engage the public in the debate. So far, public opinion seems to be more favourable towards cisgenic plants because they do not contain genes from unrelated species. For example, the 2010 EC Eurobarometer survey of public attitudes to various issues in the life sciences compared views on apples produced by either cisgenic or transgenic modification. It found that 55% of people across the 27 EU member states were in favour of cisgenic apples, compared with 33% support for transgenic ones (http://ec.europa.eu/public_opinion/archives/ebs/ebs_341_winds_en.pdf).

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Such findings represent a partial success for the cisgenic movement, which was started by Henk Schouten *et al* at Wageningen University in the Netherlands [5]. "I invented cisgenesis as a result of listening carefully to positions of the public, and to arguments of ethicists," Schouten said. "I invented it based on a series of discussions between sociologists, ethicists, philosophers, and biotechnological experts."

Not all plant scientists agree with the idea of relabeling transgenic plants. For some, doing so would legitimize the extreme views of radical environmentalists who are against any form of genetic manipulation, and might also make it harder to gain regulatory approval for potentially beneficial transgenic technologies. "Broadly, despite some initial enthusiasm, I don't like to endorse the term cisgenics, because it capitulates to the view that there is something wrong with transgenics," said Jonathan Jones, a senior plant scientist at The Sainsbury Laboratory in Norwich, UK. "There is nothing wrong with Bt proteins in plants and this system will never be cisgenic."

To highlight the limitations of cisgenic techniques and the need to build support for transgenics, Jones cited a Mexican study that is using a bacterial gene to allow plants to metabolize phosphites instead of phosphates [6]. The study aims to reduce the plant's need for both phosphorus—which is a non renewable resource—and the use of herbicides to which many weeds have developed resistance. The authors reported that under greenhouse conditions, the transgenic plants require 30–50% less phosphorus when fertilized with phosphite to achieve comparable productivity. Furthermore, when grown in competition with weeds, they accumulate two times greater biomass than when fertilized with orthophosphate because the weeds cannot metabolize the phosphite. "I'm a big fan of the potential of this system, which will also never be cisgenic," Jones said. "There is nothing *per se* wrong with cisgenic," he continued, "but it lends itself to religious discussions, such as how closely related does the source plant have to be to qualify as cisgenic and not transgenic. In that regard it resembles another weasel word, 'natural'."

Many advocates of cisgenesis, however, are equally vehemently opposed to conceding ground to activists and do not see the term as capitulation but rather as a natural progression from transgenic techniques. "It has only been very recently that science has advanced to the point where genes, promoters and other needed elements could be identified in a number of crops via computer analyses and then moved between sexually compatible relatives for the testing of desired traits," Gray explained. "With the development of this technology, we are finally able to take the next logical and biologically sound step beyond the inherent meiotic chaos of conventional breeding. Instead of mixing all of the genome together and screening thousands of progeny to see what comes out, we can now insert a single host plant derived trait without disturbing all of the others—then screen for desirable individuals nonetheless—just as is required in breeding. We now are able to add precision breeding to our tool kit for crop improvement.”

Gray agreed that transgenic approaches are still needed in cases where the desired gene cannot be found more readily among related species. But he argued that many plant scientists have yet to take full account of the profound changes in genomics technology that makes cisgenics and intragenics highly promising under the banner of precision breeding.

The debate over safety still hinges on the unintended consequences of genome manipulation, whether the techniques involved are cisgenic, intragenic or transgenic. Only the most diehard of opponents want a moratorium on the use of all technology to assist plant breeding, but even more moderate opponents are still against the artificial transfer of genetic material between organisms, for now at least. Among them is Vyvyan Howard, Professor of Bioimaging at the University of Ulster in the UK. “My main concern over the release of GM food crops in general is the lack of relevant risk assessment for many aspects,” he said. “There are strong arguments that the techniques used for introducing genes into cells will cause some unpredictable effects, one of which would be to produce novel protein fragments.”

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Howard contends that cisgenics is just transgenics under another name, because it uses similar technologies. “In cisgenesis, the insertion of the transgene can still create insertional mutagenic effects. In addition, the insertion of the cisgenic transgene will also create a novel combination of genes and a new network of gene interactions in the host organism. Furthermore, the generation of a cisgenic GMO still involves the use of plant tissue culture, a recognised highly mutagenic process, with many mutations carrying through to the final transgenic organism and marketed product. All of these effects either individually or in combination disrupt the functioning of the host genome, altering the biochemistry of the organism beyond the intended effect.” Howard acknowledged the potential power and scope of genetic modification in general, but called for better risk assessment technology. “Currently, I think that the levels of uncertainty surrounding the technology do not justify the rapid universal deployment of genetically engineered foods, which could cause potentially irreversible changes to the human food chain and ecosystems that could affect future generations.”

Other sceptics take a slightly softer stance in the belief that the regulatory regime is adequate but should not be relaxed for cisgenic plants. In this camp is Belinda Martineau—formerly at the University of California Davis Genome Centre—who helped commercialize a genetically engineered tomato, but who is now sceptical of the motives of some of those involved in cisgenics. “The fact that to date cisgenic transfer involves the same techniques as transgenic transfer means that these products still need to be regulated on a case by case basis,” she commented. “In the meantime, the response of the biotech industry is also a strategy to reduce not only public opposition but also regulation of these so called ‘cisgenic’ crops.”

Scientists in favour of cisgenic modification do not pretend that the consequences of genetic modification are fully predictable, but they argue that the unseen consequences are on the same scale as those found in nature and in conventional breeding. “Crossing with wild relatives, which is normal in conventional breeding, introduces many times more uncertainties in terms of rearrangements, activities of transposable elements, millions of

SNPs [Single Nucleotide Polymorphisms] and intron deletions,” Schouten said. “The introduction of a cisgene changes far less in the genome compared to conventional introgression breeding. The only uncertainty is the place of insertion.” Schouten added that cisgenesis has been observed to occur naturally [7].

Gray argues that the case against the “unintended consequences” argument fails to take account of what is known about the molecular basis of reproduction. “Many genetic changes occur commonly with meiosis,” he said. “Crossing over occurs; moving entire pieces of one chromosome to another, with or without duplication. Also, jumping genes (transposons) are common and unregulated. They move around and incorporate somewhat randomly during meiosis. The trans promoters are known to activate genes nearby, causing unanticipated events, just as mentioned by the naysayers. But the kicker, that exposes blinding ignorance and that the naysayers don't understand, is that in nature and breeding, most successful fertilizations are lethal due to the wide variations caused by meiosis. This is why a breeder must pollinate so much and then plant thousands of resulting seeds to find the ‘one’ that ‘randomly’ happened to have the desired trait without other problems.”

These arguments will never convince true opponents though, some of whom argue that even pre GM era technologies, such as irradiation to assist traditional breeding, are inappropriate. “These are procedures which a number of those opposed to GM believe should also have been against at the time,” said Peter Melchett, Policy Director of the Soil Association, a UK body set up in 1946 to campaign for low intensity farming. Melchett emphasized, though, that apart from opposing GM, which is non negotiable as far as he is concerned, the Soil Association is strongly in favour of developments that do not involve the transfer of genetic material. Moreover, he is not even opposed to genome manipulation *per se*: “We are very interested in epigenetics and agree that there may be significant potential, but as far as I am aware, at the moment it would not be possible to know what environmental conditions would be needed to produce particular effects in subsequent generations of plants,” he said.

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Both the opponents and proponents of GM biotechnology seem to agree that the discussion about cisgenic or intragenic versus transgenic is in many ways about semantics and public relations. Nevertheless, the issues and opportunities raised by the technological developments are real and do need to be discussed. If these new genetic techniques are more acceptable to the public, can they be used to improve productivity in agriculture while reducing its environmental impact? Can they realise the promise of GM crops while reassuring a wary public that has already made up its mind about the risks of GM?

Footnotes

The author declares that he has no conflict of interest.

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