



## Review

**Cite this article:** Pickett JA *et al.* 2014

Delivering sustainable crop protection systems via the seed: exploiting natural constitutive and inducible defence pathways. *Phil. Trans. R. Soc. B* **369**: 20120281.

*Phil. Trans. R. Soc. B* **369**: 20120281.

<http://dx.doi.org/10.1098/rstb.2012.0281>

One contribution of 16 to a Discussion Meeting Issue 'Achieving food and environmental security: new approaches to close the gap'.

### Subject Areas:

biotechnology, ecology, plant science

### Keywords:

sustainability, crop protection, pest management, breeding, genetic modification, push–pull technology

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# Delivering sustainable crop protection systems via the seed: exploiting natural constitutive and inducible defence pathways

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To reduce the need for seasonal inputs, crop protection will have to be delivered *via* the seed and other planting material. Plant secondary metabolism can be harnessed for this purpose by new breeding technologies, genetic modification and companion cropping, the latter already on-farm in sub-Saharan Africa. Secondary metabolites offer the prospect of pest management as robust as that provided by current pesticides, for which many lead compounds were, or are currently deployed as, natural products. Evidence of success and promise is given for pest management in industrial and developing agriculture. Additionally, opportunities for solving wider problems of sustainable crop protection, and also production, are discussed.

## 1. Introduction

As we develop more sustainable food production systems to accommodate dramatic human population rise and climate change, an integral component of these will be protection against pests, pathogens and antagonistic plants [1–3]. Current food, and specifically crop-based, production is heavily dependent on seasonal inputs, which can involve extremely high costs with regard to carbon footprint, particularly for nutrient production and delivery, which render dependent production systems unsustainable. It is often argued that organic agriculture solves this problem, but it mostly lacks technologies for intensive food production [4], thereby potentially wasting land [5,6]. Indeed, the use of some organic inputs in arable agriculture would require, because of intrinsic instability, a high carbon footprint, for example, the widespread deployment of industrially produced pathogens and botanical products against pests. Local production could alleviate this, but would be dangerous without strict quality control, and the use of natural inoculation or exotic release of beneficial insects is mostly ineffective. For the future, crop protection will need to be even more effective so that the carbon footprint associated with seasonal inputs, such as nitrogen fertilizers, and the energy expended on delivery and soil preparation is at least directed at food production and not consumed by pests, diseases or weeds. Thus, the 2009 Royal Society report chaired by Sir David Baulcombe, FRS, concluded that 'There is a pressing need for the "sustainable intensification" of global agriculture in which yields are increased without adverse environmental impact and without the cultivation of more land' [7, p. ix]. Certainly, for crop protection, this will require a much more knowledge-intensive form of technology already appearing as decision support systems [8], but with delivery of pest management interventions by the cropping system itself. The obvious route is delivery by the seed, and new breeding approaches, including introgression of ancestral or other alien species [9], along with genetic modification (GM), now being seen as extremely valuable in the landscape context [10], will be essential in bringing much

**Table 1.** Current highly effective pesticides are SLMs inspired by natural product leads and, for some, are natural products.

insecticide	target	natural product lead
pyrethroid	sodium channel/activators	pyrethrin I
indoxacarb/metaflumizone	sodium channel/blockers	X
organophosphate/carbamate	acetylcholinesterase	X
neonicotinoid	nAChR	nicotine/epibatidine
spinosad	nAChR	spinosyns
butenolide	nAChR	stemofoline
cyclodiene/fiproles	chloride channel/gaba	X
abamectin	chloride channel/glutamate	avermectins
diamide	calcium release channel (muscle)	(ryanodine)
tetramic acid	acetyl CoA carboxylase/inhibitor	X

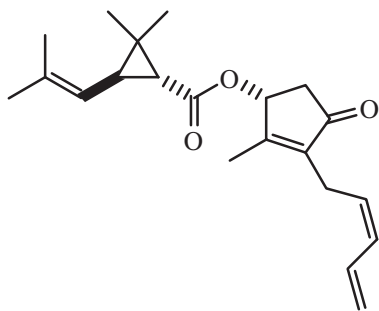
more robust and sustainable traits than those presently available from the narrow genetic variation present in elite crop cultivars and their breeding lines. Furthermore, harvests delivered by seasonally sown annuals will need, for the longer term, to be replaced by perennial arable crops taking genetics from a wider plant diversity, as well as opportunities being developed employing companion cropping, e.g. push–pull [11]. Increased numbers of people will need to be engaged with the new agriculture, including the existing high rural population levels in developing agriculture, and by stabilizing or even increasing rural populations for industrial agriculture. This will be paid for partly by drastically increased food prices, but predominantly by replacement of seasonal inputs. Educational resources will need to be raised significantly, as also concluded by Baulcombe *et al.* [7], to provide training for the new agricultural workforce capable of managing more information intensive practices. The advantages of reduced land preparation, i.e. no tillage, have already been noted [12] and tillage would be obviated seasonally by the perennialization of arable crops. The greater investment in root systems will offer other advantages for water and nutrient utilization. However, more attention must be given to root protection and wider conservation and exploitation of the rhizosphere [13]. The stabilization of rural populations in genuinely increased intensification of sustainable food production will remove the persistent and progressive depopulation of rural regions to towns. This is essential if we are to prevent the completely unmanageable predictions of 70% of the world's population living in towns by 2050 [14], at least for the developing world, which shows no ability whatsoever for satisfactorily accommodating such an inundation. Indeed, green revolution technologies involving fertilizers, seasonally purchased seed and pesticide use [1–3] lend themselves to having fewer farmworkers on the land. Together with land grabbing [15,16], this can be strongly antagonistic to the intensification of food production based on currently high rural populations and to the employment of a stabilized rural population in developed agricultural regions. Both issues are potentially solved by the use of more knowledge-intensive approaches that lower seasonal inputs. For development, there are many opportunities for upgrading value chains [17], but sustainable staple food production needs to be established first so as to provide the basis for on-farm diversification, particularly for the growing numbers of undernourished farming communities.

A suite of approaches are considered for delivering sustainable crop protection with evidence of efficacy from the

laboratory, via field trials to farmer practice, using resources from plant diversity, new breeding approaches and GM, using not only constitutive defence processes, but also inducible systems. In order to produce robust effects, these approaches exploit small lipophilic molecules (SLMs) for plant protection and as defence elicitors, which are physically similar to current pesticides and are now being targeted away from the focus on largely less robust protein-based pest and pathogen resistance traits. Following evidence of practical success and laboratory promise, new opportunities will be raised for alleviating problems of agricultural production, including the generation of the highly powerful greenhouse gases methane and nitrous oxide.

## 2. Basis for strategy

Synthetic eradicator pesticides remain the main intervention against insect pests, pathogens and weeds in spite of successful conventional breeding programmes and approaches involving GM. To provide such robust interventions via seed and other planting material, plant secondary metabolism becomes the target because such secondary metabolites, by displaying similar physical and biochemical properties, can act robustly in plant defence and have provided the lead compounds for pesticides or are themselves produced as natural products. For insect control where the targets are animals, and thereby physiologically closer to ourselves compared with plant pathogens and weeds, further considerations of selectivity are needed. In addition, the eventual deployment would need effective stewardship so the selection for resistance is minimized. In table 1 are listed some current insecticides and molecular targets that underpin their activity. The butenolides, e.g. flupyradifurone, are very recent introductions [18]. Natural product leads are quoted where some, for example, pyrethrin I, a major component of the natural extract of the pyrethrum daisy, *Tanacetum cinerariifolium*, are widely used and some, including the spinosyns (from *Saccharopolyspora spinosa*) and avermectins (from *Streptomyces avermitilis*) are produced by fermentor systems as natural products and are then incorporated as commercial insecticides. Thus, there are a range of potential targets where natural biosynthetic pathways exist and which could be transferred into crop plants. For pyrethrin I (figure 1), which provided the lead for Michael Elliott and colleagues at Rothamsted to invent the synthetic pyrethroids, including permethrin, cypermethrin and deltamethrin [19], and which are still the main interventions,



**Figure 1.** Pyrethrin I.

via bed-nets, against malaria vectors, e.g. *Anopheles gambiae* s.s., the biosynthetic pathway remains an area of study (Kazuhiko Matsuda, Kinki University, Japan 2013, personal communication). This pathway brings together chrysanthemic acid, generated via the isoprenoid pathway, with an alcohol generated via the unsaturated fatty acid oxidative cascade. The pathway has thus far eluded a GM route to exploitation. However, many other plants, including crop plants, have defence pathways, for example the cyanogenic glycosides, which are found across diverse taxa, and the glucosinolates from the order Brassicales, in particular vegetables and oilseeds in the Brassicaceae. Opportunities exist for exploiting these by GM [20–22]. In cereals, such as maize, wheat and rye, there is the hydroxamic (benzoxazinoid) pathway. All of these defence systems are held as the non-phytotoxic glycosides from which the biocidal aglycone (figure 2) is released on tissue damage, and this release would need to be taken into account if these pathways are to be exploited. The benzoxazinoid biosynthetic pathway, and the related genetics, have been fully elucidated for maize [23] and wheat [24,25]. After the first committed step of the pathway that creates indole, a series of cytochromes P450 in the Cyp71C series take this through to DIBOA and DIMBOA, latter via the glucoside (figure 2). Localized feeding by aphids, e.g. the barley yellow dwarf virus vector *Rhopalosiphum padi* (bird cherry-oat aphid), on wheat, causes the glucoside stored in vacuoles to be hydrolysed to DIMBOA via the upregulation of the glucosidase [26]. By knocking out the gene for the first committed step in maize, aphid susceptibility can be raised significantly [27]. Thus, the pathway is potentially useful in crop protection, particularly for cereals. However, an extensive investigation of elite wheat varieties and their breeding lines shows that levels are too low, and tissue expression patterns inappropriate, for exploitation by conventional breeding. The ancestral plant *Aegilops speltoides* (goatgrass), associated with the B genome of hexaploid wheat, can contain high levels of benzoxazinoids and associated aphid resistance. Thus, with the tools of alien introgression [9], and particularly as the genetics associated with benzoxazinoid biosynthesis are co-located even in the hexaploid wheat genomes [24], the increased expression of the pathway can be targeted for pest resistance in wheat as well as by the increased expression by GM technologies, now facilitated by the publication of the shotgun sequencing of the bread wheat genome [28]. Once sufficient levels are secured in the vacuoles of the vegetative tissues, then pests, including aphids, and also some diseases, could cause the release of the strongly pesticidal aglycones, e.g. DIMBOA.

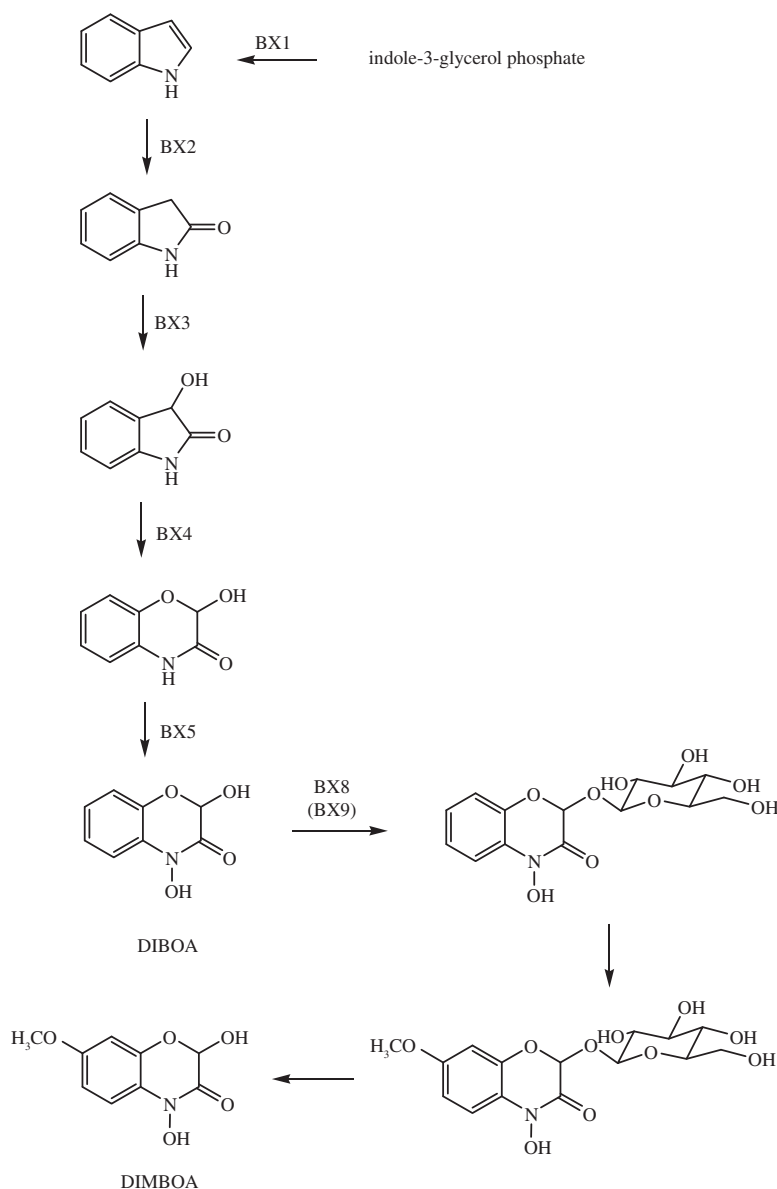
### 3. Semiochemical targets

In planning delivery of pest control for the long term, the target will be natural metabolites that, acting by non-toxic

modes of action, affect, in more sophisticated ways than current pesticides, behavioural and developmental processes in pest organisms. Such natural products are exemplified as insect pheromones and other semiochemicals, which comprise natural chemicals that affect development or behaviour of organisms [29]. Volatile pheromones and other semiochemicals represent tools that can be used before pest or pathogen development and for insect pests, often before contact with the host plant. Volatile semiochemical identification is facilitated by electrophysiological recordings from entire antennae or even individual olfactory neurons and has allowed identification of processes by which semiochemicals are employed in the choice and location of hosts [29]. This involves the recognition of either the complex mixture or semiochemicals that are specific to the host [29–31]. Interfering with this process by modifying the ratios in the mixture or by adding semiochemicals from non-host taxa is feasible to deliver in the field, simply by changing the amount of one compound, and could thereby prevent or reduce pest colonization. Stress of insect colonization can relate to this type of non-host signalling and can additionally be exploited, in conservation biological control, for attracting organisms antagonistic to the insect pests, for example, predators and parasitoids [29]. There are many examples of such approaches. Thus, for interference with mixture recognition, the orange wheat blossom midge, *Sitodiplosis mosellana*, employs a multi-compound mixture of wheat semiochemicals, including 6-methyl-5-hepten-2-one which, when increased several-fold from the natural ratio, interferes with attraction [30]. With host-specific semiochemistry, although insects specifically adapted to brassicaceous plants employ volatile catabolites of glucosinolates, particularly alkenyl isothiocyanates, to select hosts, these same semiochemicals are repellent, or at least mask the host recognition semiochemicals of non-brassicaceous hosts for pests feeding on other plants. The biosynthesis and genetics for the alkenylglucosinolates [20] can be manipulated to affect host location (Jing-Jiang Zhou 2013, Rothamsted Research, UK, personal communication).

### 4. Aphid alarm pheromone

During the development of the above strategies, a more direct GM approach was suggested [32] in which it was proposed that aphid pests could be repelled and their parasitoids attracted by heterologously expressing genes for the biosynthesis of the aphid alarm pheromone, which is produced by aphids and naturally causes these effects. After widespread advances in genetic engineering in plants so as to manage secondary metabolism, the model plant *Arabidopsis thaliana* was modified to express the gene for the synthesis of the aphid alarm pheromone, comprising the sesquiterpene (*E*)- $\beta$ -farnesene (EBF) [33]. EBF has to be produced in very high purity otherwise other sesquiterpenes, particularly (1*R*,4*E*,9*S*)-caryophyllene, normally produced together with EBF in plants, are detected by separate olfactory neurons highly sensitive to either EBF or the caryophyllene in the aphid [34] or their predators [35] and prevent the intended insect response. Production of pure EBF was achieved by engineering a gene from the mint plant, *Mentha piperita* [36], such that genetically modified *A. thaliana* both repelled the peach-potato aphid, *Myzus persicae*, and caused increased foraging by the parasitoid



**Figure 2.** Benzoxazinoid biosynthesis in cereals.

wasp *Diaeretiella rapae*, both insects being adapted to brassicaceous plants [33].

After codon optimization for monocotyledons, the synthetic *M. piperita* EBF synthase has been expressed in an elite wheat variety, Cadenza, normally sown as a winter or spring crop, via gene gun technology [37] but without yielding EBF. Thus, the synthetic gene for synthesizing the precursor, farnesyl diphosphate, was added, again without success. However, by targeting the two synthetic genes to the plastid [38–40], EBF could be produced (H. D. Jones 2013, unpublished data). Volatiles from these GM wheats gave a strong alarm response for cereal aphids in laboratory assays. Also, parasitoid wasps spent longer foraging on the GM wheat plants under field simulation.

An application for investigating effects in the field was made to the independent Government advisory group, the Advisory Committee on Releases to the Environment and was approved by the Secretary of State for Environment, Food and Rural Affairs, in September 2011, and this led to field trials of spring-sown GM wheat against the unmodified variety. Although there was opposition to the trial from elements of the public, a conscientious programme of engagement achieved support from many members of the

public and official agencies, and the trial went ahead in 2012. Further trials for 2013 are in progress and will determine the next steps in developing this approach to pest control. An important issue in maximizing the effects of aphid alarm pheromone production is the timing of its production. Further work is planned to move forward from the constitutive expression of inserted transgenes, as employed here, to a more refined pattern of transgene expression. Inducible expression of defence traits could also benefit other commercial GM-based pest control. If made to work and deployed widely, resistance may develop in the pest population involving a form of habituation. It is unlikely that aphids could evolve away from using an alarm pheromone because of ecological selection pressure, but they could certainly employ, in developing such resistance, a compound other than EBF. Indeed, there is wide evidence of such evolutionary changes in pheromone composition [41,42] and, for the aphid alarm pheromone, could involve replacement of EBF with a minor component, (*E,E*)- $\alpha$ -farnesene, observed previously [43]. However, rather than to have to develop an entirely new toxophore, as would be the case for insecticide resistance, the gene for the biosynthesis of (*E,E*)- $\alpha$ -farnesene could be readily substituted for the EBF synthase.

## 5. Companion cropping

Although the new breeding and GM technologies for delivering semiochemical-based pest control are still very much in the development stages, the use of companion crops has demonstrated the value of semiochemical-based crop protection via plants. The most dramatic demonstration of its value has been achieved in sub-Saharan Africa, without competition from the pest control technologies of high-input agriculture, which are not adopted by the majority of farmers in this region. The technology has been described in detail [11] and involves ‘push’ effects on insect pests, and at the same time exploiting conservation biological control by increasing foraging by parasitoid wasps. Both processes are based on the release of semiochemicals, from intercrops, that initiate stress signals associated with herbivory. These compounds include the homoterpenes or, more correctly, tetranorterpene that are formed when plants are damaged and reduce colonization by herbivores and recruit foraging parasitoids [29]. The trap ‘pull’ crop is a highly attractive plant that draws pests away from the main crop. Both inter- and trap crops have value as forage for farm animals. A leguminous intercrop developed for push–pull in the *Desmodium* genus fixes nitrogen and controls weeds, particularly the African witchweed *Striga hermonthica* [44,45]. The companion cropping system adopted should involve intensification with minimal increase in main crop spacing. The overall yield must be greater per unit area compared with normal farmer practice, even where a trap crop is deployed, and must be assessed in terms of farmer benefit [46].

## 6. Defence gene elicitors

When plants are damaged, defence genes are expressed and can produce semiochemicals, for example the homoterpenes. Plant hormones, including jasmonic acid, can be involved in this elicitation, but other deleterious effects on the plant may ensue. Although widely recognized as highly promising [47,48], it must be borne in mind that there could be negative effects of cross-talk between other signalling pathways and anti-nutritional or acceptability effects on the food products. However, *cis*-jasmonone has been identified [49,50], apparently without such disadvantages, and patented as a volatile plant defence elicitor. *cis*-Jasmonone signals differentially from jasmonic acid [51,52] and can be used to increase defence against pests, and for conservation biological control by exploiting natural populations of parasitoids in crops, for example wheat, in the field [53], and others, such as cotton [54], soya bean [55] and sweet pepper [56] in the laboratory. The promoter sequences for defence-related genes upregulated in *A. thaliana* by *cis*-jasmonone have been placed upstream of marker genes for luciferase and GUS [51,52] and, with appropriate engineering, will be used to ‘switch on’ the EBF biosynthesis in genetically modified wheat (see §4) in a refinement of the current constitutive expression. Other elicitors or gene suppressors are available from caterpillar regurgitant [57], aphid feeding [58] and via the rhizosphere [59] or arbuscular mycorrhizal hyphae transmitting stress elicitor signals from damaged to undamaged plants [60]. *cis*-Jasmonone passes into the plant without damage, but the other elicitors listed above require a plant lesion caused by insect feeding. However, the existence of a potentially valuable new type of elicitor has

emerged from the push–pull programme, in which eggs of the moth pest *Chilo partellus* are associated with an elicitor that enters the intact plant and causes a systemic elicitation of homoterpene production, attracting not only egg parasitoids, but also larval parasitoids, with the plant seemingly anticipating the ensuing development of larvae. This was first observed in maize land races but not in commercial hybrid varieties [61], and then in maize from farmer field gathered seed or open pollinating varieties (OPVs) [62]. This trait will be exploited for maize and sorghum as part of an initiative funded by the UK agencies Biotechnology and the Biological Sciences Research Council (BBSRC) and the Department for International Development, together with the Bill & Melinda Gates Foundation (‘Achieving sustainable *Striga* control for poor farmers in Africa’) and will provide African farmers with new OPVs with enhanced pest resistance as well as the possibility of licensing genes developed in Africa for industrial agricultural plant breeders in the north.

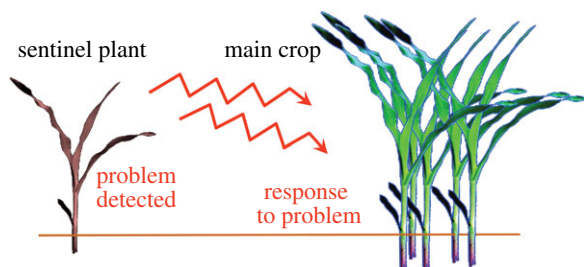
## 7. Sentinel crops

Having plants that respond to pest development-related elicitors opens up the opportunity to develop ‘smart’ agricultural practices in the extension of decision support systems already in use and under further development (see Introduction). This would allow rapidly developing pests or diseases, for example soya bean rust caused by the fungal pathogen *Phakopsora pachyrhizi*, first to impact sentinel plants responding by the upregulation of visual markers, which would allow early deployment of fungicides. This elicitation could then be linked to the induction of plant defence either directly or via a new type of sentinel plant, as depicted in figure 3. Already, these options are being investigated in an Anglo-Brazilian collaboration between BBSRC and Embrapa (UK–Brazil partnership: ‘The chemical ecology of crop–plant–rust–pathogen interactions for underpinning novel crop protection strategies’) involving Rothamsted Research and The Sainsbury Laboratory [63] and Embrapa Soja (C. B. Hoffmann-Campo, R. Abdelnoor and S. Lima).

## 8. Wider opportunities

The rhizosphere-generated secondary metabolites responsible for the inhibitory effects of *Desmodium* spp. on *S. hermonthica* (see §5) have been identified as di-C-glycosides of flavonoids, including apigenin. Transforming legumes, for example cowpea, with the C-glycosyl transferases that transfer the sugars glucose and arabinose to precursors of the flavonoids [64] is being investigated, so as to produce edible beans from plants that will possess the parasitic weed-controlling trait found only in *Desmodium* spp. This approach to exploiting allelopathic effects could have wider value in weed control in industrial agriculture.

Allelopathic effects could be harnessed by genetically engineering the associated secondary plant metabolism to reduce methane emission from ruminant husbandry, an essential practice in using land that can support only grass and other animal forages for human food. Whether using synthetic or natural nitrogenous nutrients, nitrous oxide (N<sub>2</sub>O) is a waste of fixed nitrogen and is an extremely powerful greenhouse gas. Certain savannah grasses, e.g. *Brachiaria* spp., inhibit this process by means of secondary metabolites released into the rhizosphere [65] that could also be exploited



**Figure 3.** Smart sensing to optimize farm inputs: sensitive sentinel plants detect problem, not just pests, diseases and weed competition but also depleted or excess nutrients and water and signal to main crop of smart plants, with natural response to a signal linked to gene expression (by GM) to deal with the problem.

by the approaches being developed here. Pathways to these metabolites and many others appear to be associated with gene clusters [66], as for the benzoxazinoid biosynthesis or the avenacins [67], and provide support via bioinformatics for identifying genes in newly targeted pathways.

## 9. Perennial crop plants

The benefits of perennial arable crop plants have been mentioned (see Introduction), but protection against competing organisms augmented by those exploiting these more apparent plants will be even more challenging. Such protection must be delivered through the planting material and opportunities for ‘switching on’ genes by pest, disease and weed-related elicitors must be explored now. Already, there are programmes on perennial wheat in the US (Washington State University, Pullman) and non-irrigated rice (Food Crops Research Institute, Kunming and Beijing Genetics Institute, Shengzhen) in China. In Africa, we see a rapid increase in smallholder cultivation of non-irrigated rice, i.e. NERICA (NEw Rice for AfrICA), but this can be heavily infested with *S. hermonthica*, which is readily controlled by intercropping with *Desmodium intortum* [44]. This demonstrates an opportunity to employ a secondary metabolite-based solution delivered by plants, and already perennial rice from the Food Crops Research Institute, Kunming and Beijing Genetics Institute, Shengzhen is being protected effectively by the intercrop against the parasitic weed. Other recent methods for crop protection are being developed widely, such as priming of seed and using seed film coating. For example, a study on tomato seeds treated with jasmonic acid showed an increased resistance to spider mites, caterpillars and aphids

and the necrotrophic fungal pathogen *Botrytis cinerea*, whereas seed treatment using  $\beta$ -aminobutyric acid gave defence against powdery mildew disease caused by *Oidium neolycopersici* [68]. Future work will need to explore the generality and robustness of these approaches.

## 10. Conclusion

Agricultural ecosystems are vulnerable to attack by adapted pests, weeds and diseases because they provide an environment with large areas of lush, fertilized crop in which such organisms can thrive [69]. Crops are often less resistant than their wild ancestors because they have been selected for yield and human nutrition and have lost defence traits during domestication, especially when bred in a pesticide-treated background. Thus, there is a need to enhance plant defence capabilities in crop plants. This can be done through the conventional breeding and development of plant defence activator agrochemicals, but there are much wider possibilities via GM techniques. Crop protection via the seed can also be delivered by companion cropping as in the push–pull system, which makes agriculture more resilient to pest attack. However, companion crops need to be chosen on the basis of a scientific understanding of host and non-host plant interactions to ensure that they release the correct semiochemicals to protect the main crop. Innovative approaches to crop protection are needed to make agriculture more efficient in terms of resources used (land, water, energy, nutrients) by reducing waste. They are the key to the sustainable intensification of arable agriculture.

**Funding statement.** Rothamsted Research receives grant-aided support from the Biotechnology and Biological Sciences Research Council (BBSRC) of the United Kingdom, specifically including BBSRC grants BB/G004781/1 (a new generation of insect resistant GM crops: transgenic wheat synthesising the aphid alarm signal), BBH0017/1 (elucidating the chemical ecology of belowground plant to plant communication), BB/I002278/1 (enhancing diversity in UK wheat through a public sector pre-breeding programme) and BB/J011371/1 (‘smart’ cereals for management of stemborer pests in staple cereals in Africa). The International Centre of Insect Physiology and Ecology (*icipe*) appreciates the core support from the Governments of Sweden, Germany, Switzerland, Denmark, Norway, Finland, France, Kenya and the UK. The work on push–pull technology was primarily funded by the Gatsby Charitable Foundation, Kilimo Trust and the European Union, with additional support from the Rockefeller Foundation, Biovision, McKnight Foundation, Bill and Melinda Gates Foundation and the UK Government Department for International Development (DFID).

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