Possibilities for rationally exploiting co-evolution in addressing resistance to insecticides, and beyond

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ABSTRACT

Certain biorational chemical agents used against insect pests impact essential stages or processes in insect life cycles when applied for pest management. Development of resistance to these agents, while involving main-tenance of the natural role of the chemical agent, frequently requires the evolution of a new chemical structure by the resistant organism. When considering the process of resistance development, one could theoretically consider biorational structural determination rather than the less predictable or feasible generation of a novel replacement insecticide. At first consideration, this process might exclude toxicants such as typical pest control agents and rather be a phenomenon reserved principally for signalling processes such as are fulfilled by pher-omones and other semiochemicals. However, because there is a unique co-evolutionary relationship between chemical defence and the physiology of the antagonistic organism, this process can be further explored for potential to overcome resistance to toxins. Given further consideration, newly evolved chemical defences may rationally provide options for new resistance-defeating chemistry. This review therefore discusses the potential for overcoming insecticide resistance through targeted application of this approach. Potential for use of a similar approach to counteract fungicide and herbicide resistance is also considered. Furthermore, the possible appli-cations of this approach to address drug or pharmaceutic resistance are also considered.

1. Introduction

There is growing evidence from animal signalling processes via pheromones that, under evolutionary pressure or merely species isola-tion, related biosynthesis and receptor molecular recognition systems evolve in synchronous steps during the selection process [1–3]. The mechanism(s) by which new pheromonal components can be generated during evolution has been determined [4,5]. This structurally intuitive approach can apply generally and the idea has recently been elaborated for plant volatile-mediated signalling [6] Fig. 1. Here, we propose testing the hypothesis that, for toxins, the ecological benefit to a plant, or other producing organism, could generate selection pressure for structural redesign to overcome resistance in the antagonistic organism. Thus, the natural arms race, for example between plant defence sys-tems, specifically based on plant secondary metabolites, and the adaptation to such defences by herbivorous insects or other pests, could be turned against the pest. This creates the possibility of intervening in a precisely targeted strategy via genome editing tools to give a strategic edge to the plant producing the toxin. To test this general approach, insecticides and other toxicants require further consideration for iden-tification of opportunities for field, simulated field or environmentally controlled studies to capture, maximally, the evolutionary diversity underpinning the process of co-evolution when considering the ability to harness resistance evolution to pesticides.

2. Background to insecticide resistance

Economically, insecticide resistance is most important for agri-cultural crop protection and attempts have been made to consider currently registered insecticides [7] according to their modes of action [8], via a predominantly industry-based consortium (the Insecticide Resistance Action Committee, IRAC) [9] in order to plan deployment of strategies to overcome resistance. Perhaps the most socially important issue impacting resistance development relates to the success of con-trolling malaria transmission by the utilisation of bed nets treated with insecticides, mainly the pyrethroid permethrin [10], invented originally by Michael Elliott and colleagues at Rothamsted Research UK [11]. In this case, resistance to permethrin and the entire pyrethroid class could

Abbreviations: IRAC, Insecticide Resistance Action Committee; IVCC, Innovative Vector Control Consortium; ESAC, External Scientific Advisory Committee; SLM, small lipophilic molecule; Bt, Bacillus thuringiensis

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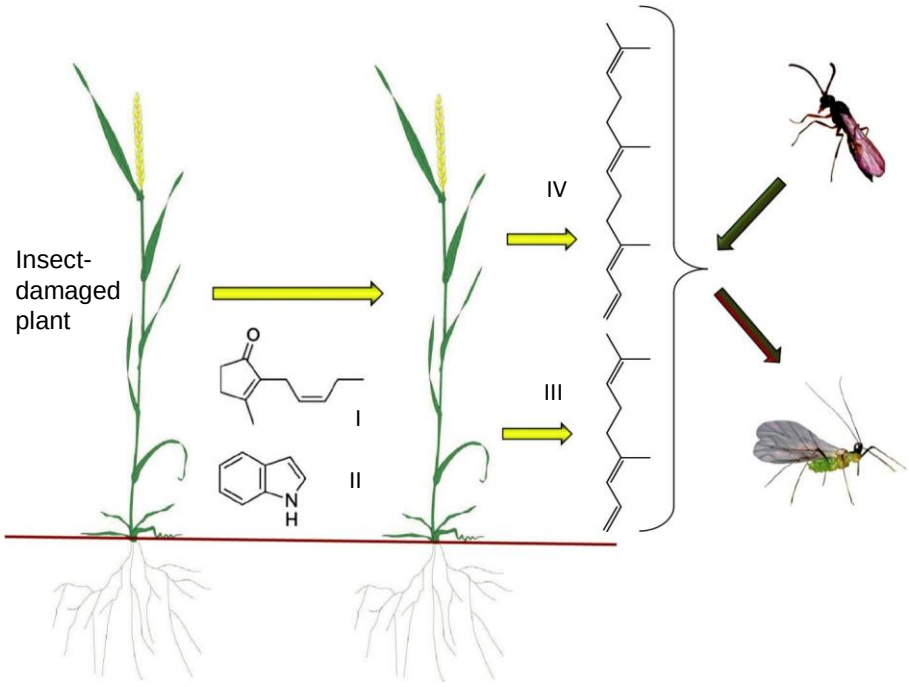

Fig. 1. Intensive use in agricultural crop protection of volatile signals from damaged plants inducing defence in intact plants, e.g. I and II, and secondary signals, e.g. III and IV, which repel pests (aphids) and attract natural enemies (parasitoid wasps), will cause selection for resistance. Without these signals, both plants and pests will be disadvantaged and so re-sistance will involve production of new chemical signals. These can be identified and used to overcome the initial resistance [6].

potentially derail malaria control [12].

In anticipation of these serious resistance problems and associated human consequences, J. Hemingway and colleagues, principally from the Liverpool School of Tropical Medicine, founded the Innovative Vector Control Consortium (IVCC), with funding initially from the Bill & Melinda Gates Foundation, to repurpose crop protection insecticides and, more particularly, to help fund the agricultural chemical industry in the design of novel mosquito adulticides that overcome current re-sistance mechanisms active against the vectors, e.g. the mosquito Anopheles gambiae s.s., and the causative pathogens, e.g. Plasmodium falciparum. IVCC is currently led by N. Hamon, who is also pursuing new approaches for registration and approval of public health-related chemistry, particularly against vector-borne pathogens, through an expedited review procedure [13]. The design and development process of IVCC is advised by an External Scientific Advisory Committee (ESAC1) chaired by the author, J. Pickett and upon which J. Bloomquist (to whom this paper is dedicated) has prominently served. The in-volvement of the agricultural chemical industry is essential to secure necessary expertise and resources, which are currently not readily available in the public sector. This relates to the important fact that, although insecticide design is a process conducted as rationally as possible, and becoming ever more so in the industry, an ever increas-ingly large throughput of compounds, specialist formulation technolo-gies and high level testing (including on non-target organisms) are re-quired for success. This process has been described in detail by members of ESAC1, J. Turner, C. Ruscoe and T. Perrior [14], and should be considered wherever rational design of insecticides is proposed, particularly when compound selection is based on in vitro bioassay.

The IVCC associated activities are likely to invent several new mosquito adulticides with novel chemistry and modes of action. Application of cutting-edge molecular techniques, including advanced studies, is set to effect further developments in rational design of in-secticides active against newly resistant pests [15]. New genome editing tools, such as CRISPR/Cas9 mediated gain-of-function mutations in single-copy target genes for insecticide target sites, provide further opportunities for defining insecticide resistance mutations relating to function [16]. These and other related tools are currently being applied in studies directed at controlling invasive pest species including ro-dents, carp and cane toads (Rhinella marina) besides enhancing health and welfare in the poultry industry [17].

3. Relationship between commercial insecticides and natural products

Current insecticides are generally efficaceous and, provided their deployment strictly follows label requirements, present extremely low risks to human and environmental health. Most recently registered in-secticides are small lipophilic molecules (SLMs) relating to, or mi-micking secondary metabolites of plants and other organisms. Long term research in the public sector, to avoid largely unevidenced media and public criticism, has typically targeted SLMs that act by modes of action that are non-toxic to mammalian systems. For example, certain SLMs affect behavioural and developmental processes in pest organisms similar to insect pheromones and other semiochemicals. Such oppor-tunities also include “switching on” genes for the biosynthesis of these semiochemicals by members of another set of SLMs that act as plant activators, thereby avoiding use of constitutive promoter sequences potentially aggravating resistance development.

This approach was advocated in the 1980s, including targeted re-search to elicit the expression of the aphid alarm pheromone [18]. The aphid alarm pheromone repels aphids and increases foraging by para-sitoids attacking aphids, but plant molecular genetics needed to be further refined until pheromone expression could be achieved in the model plant Arabidopsis thaliana to give repellency of aphids and in-creased parasitoid foraging in the laboratory [19]. Later, the same ef-fects in the laboratory were obtained with stably transformed lines of GM wheat in the commercially elite cultivar, Cadenza. However, in three separate UK field trials, the transformed wheat did not control wild aphid populations or significantly raise levels of attack of aphids by parasitoids [20]. This work, along with studies conducted more globally, continues, and is based on the concept that resistance can be rationally overcome [6], even where false cues are used against the herbivorous pest or the organisms potentially controlling the pest [21].

Testing the hypothesis for SLMs active by conventional toxic modes of action requires an essential defensive role for the SLMs, in an or-ganism capable of producing new SLMs by a process of co-evolution with the pest. Such possibilities occurring naturally have already been discussed at length, particularly since the publication, “Butterflies and

Plants: A Study in Co-evolution" by Ehrlich and Raven (1964) [22], in which they suggest that the great diversity of plant secondary meta-bolites plays a central role in defence against insects and that the in-teractions between plants and insect herbivores represent an evolu-tionary arms race, with plants developing new defences and insects continually developing new countermeasures. In order to provide re-sources for such a process, plants often produce a wide range of diverse secondary metabolites without apparent function. Plant production of such chemical diversity may be exploited by other pest species in re-sponse to changes in evolutionary pressure [23]. The availability of the host plant can further impact the process [24]. This process, tested as the screening hypothesis, was originally described by Jones and Firn [25,26]. Van Valen [27] earlier introduced the Red Queen-hypothesis which states that organisms in the co-evolutionary arms race would have constantly adapt or evolve, not only to gain reproductive ad-vantage, but also to simply survive or remain extant. Red Queen dy-namics has been discussed for over 40 years in the context of evolu-tionary adaptation, sexual reproduction and host parasite relationships [28] and the original work of Ehrlich and Raven is critically reviewed [29].

The scene is therefore set for testing the hypothesis, provided that the pesticides themselves, or at least their respective substrates/lead compounds are present naturally, thereby rendering the organisms possessing them with identifiable genes associated with their bio-synthesis. In an attempt to identify new GM targets for crop plant protection, novel defence pathways have been reviewed [30]. One in-teresting example focuses on a particular butenolide insecticide flu-pyradifurone, trade name Sivanto [31]. The lead compound, stemofo-line, is found in the plant Stemona japonica, and comprises a complicated isoprenoidal alkaloid structure, the biosynthesis of which has fortunately been elucidated [32]. Flupyradifurone has a cleverly simplified structure not present naturally. However, successful synth-esis followed by biological assay has shown that, by the rational route of providing the final synthase enzyme with novel substrates, iso-prenoidal analogues can be created with high activity [33] and so a biosynthetic pathway could theoretically be reconstituted in planta to yield a biologically active, non-natural SLMs in this insecticidal class.

Such biorational approaches will undoubtedly benefit specifically from the recent availability of novel genome editing tools and asso-ciated approaches. Another plant producing a highly active insecticidal lead compound, pyrethrin I, is Tanacetum cinariifolium from which the pyrethroid insecticides were developed, see above [10,11]. Although the pathway of biosynthesis for the natural pyrethrin is currently under elucidation [34], these compounds are only exceptionally active as defence metabolites [35] in T. cinariifolium and so a similar biochemical transformation/development would be needed as for the butenolides described above. Thus, natural product insecticides, or the lead com-pounds for these, and probably some synthetic analogues, are already potentially available from insecticide-producing organisms, including existing plants, or through generation by GM organisms possessing the appropriate ecological profiles for the next phase of hypothesis testing.

4. Opportunities for testing co-evolution in overcoming resistance to insecticides

Having established that plants, and other potentially evolving or-ganisms such as microbes, are available for incorporation or enhance-ment of various biosynthetic pathways to generate insecticides, fungi-cides or bioherbicides, organisms occurring in genetically diverse and highly numerous populations should also to be targeted for further study. Conducting such studies initially in isolation from commercial crops or by protection of food crops is an important consideration; however, this could potentially be achieved by performing initial stu-dies with an annual industrial crop plant of significance. One possible crop might be the malvaceous cotton plant, Gossypium hirsutum, cur-rently experiencing co-evolution with a common insect pest, the whitefly Bemisia tabaci. Such studies would preferentially be conducted in the field, as it is well known that laboratory selection for resistance traits generally offers an insufficient population size for traits selected naturally [36]. Field selection experiments would inevitably need to be conducted for many seasons for the plant to overcome expected re-sistance in the whitefly pest to the initially expressed insecticide, which would be essential for survival of the GM cotton. Seed, albeit non-hy-brid, would then need to be collected and screened each season under field conditions for valuable traits to overcome whitefly resistance. Under such circumstances, preferably, there should be a significantly higher rate of selection pressure and evolution of useful traits, and thereby co-evolution, between the insecticide-producing organism, in this case the plant, and the pest.

A high rate of evolution could also be achieved by employing mi-crobial organisms as either or both the producing and responding or-ganisms, or surrogates of these. GM crop plants already express genes for molecular fragments of the microbial toxins originating from the soil bacterium Bacillus thuringiensis (Bt). Although extremely large acreages of such modified crops are currently under production, the crops themselves are expressing Bt toxins, and are being grown annually and with limited phenotypic diversity, and therefore are inherently limited in deriving evolutionary advantage in the current system from new toxin designs to overcome resistance.

Production of the crop in the wild, together with its pest population, would represent a restrictively large resource, and to use the Bt toxins, which are mainly active against lepidopterous pests, would obviate use of the hemipterous B. tabaci as the responding organism. Nonetheless, the Bt toxins could be a profitable target, with current evolutionary biological considerations being brought to bear on the development of resistance to Bt toxins [37,38] and new mechanisms identified [39].

Spinosad™, a mixture of spinosyns A and D, produced by the mi-crobial actinomycete Saccharopolyspora spinosa, could potentially be a useful target as the biosynthetic pathway has currently been studied commercially and there are relatively amenable dipterous pests showing resistance [40,41]. However, as with Bt, direct use of S. spinosa would again obviate use of the most favourable dipterous insects as the pest. Abamectin, as a mixture of avermectins B_{1a} and B_{1b}, also produced by an actinomycete, Streptomyces avermitilis, has been in operational use widely for over 20 years, a relatively long evolutionary period, with well-studied resistance worldwide in the diamondback moth, Plutella xylostella [42]. However, this insecticide class also possesses nemato-cidal activity and associated resistance, e.g. to the barber's pole worm, Hemonchus contortus [43] among others, which would allow develop-ment of a higher throughput aqueous bioassay for the responding or-ganism. Resistance in these noteworthy parasites of grazing livestock is currently under investigation in Australia and such parasites are targets of novel approaches for management including relatively costly vac-cines and repeated use of therapeutics (R. Woodgate, Charles Sturt University, personal communication, 2018). Novel but cost effective measures for efficacious pest and resistance management would therefore be of considerable importance in the global grazing livestock industry.

Primary industrial screens for insecticidal activity already include bioassays using aqueous media, e.g. for mosquito and other fly larvae. Indeed, the Diptera have some of the shortest life-cycles for the insect class of arthropods, including other muscid pests such as the horn fly, Haematobia irritans. Combining these properties, along with an aquatic larval phase, the shortest life-cycle currently identified is for the dark rice field mosquito, Psorophora confinnis [44]. Thus, by expressing the natural biosynthetic pathway, or the pathway developed from use of synthetic biology, for the insecticide, in a rapidly cycling microbe ed-ible to the larvae, and allowing this population to co-evolve by inter-actions with the larval stage of the short sexually-cycling mosquito, new insecticides overcoming resistance could potentially be readily selected in the GM microbe population. The use of synthetic biology techniques to build pathways to non-natural toxins opens the approach to much

wider toxin classes. This approach can then be further exploited by deploying these pathways in microbes such as the actinomycetes, al-ready powerfully expressing toxins in which increased chemical di-versification, effected by interspecies interactions, is well known [45]. Therefore, rather than a major synthesis programme searching for new resistance-obviating insecticides, the rational identification of new in-secticide or parasite leads produced in this assay could rapidly provide new commercial compounds or promising leads.

5. Possibilities for fungicide, herbicide and even drug resistance

5.1. Fungicide resistance

For overcoming fungicide resistance, one interesting example fo-cuses on the strobilurins, including azoxystrobin, which inhibit the respiratory chain at complex III, and have structures based on natural strobilurins originating from a basidiomycete, the pinecone cap fungus Strobilurus tenacellus [46]. Strobilurin biosynthesis is relatively straightforward, involving the phenylalanine ammonia-lyase pathway, and a diversity of related fungicidal products can be obtained from other basidiomycete species such as the porcelain fungus, Oudemansiella mucida. Nonetheless, following arguments above, the pathway would need to be transferred, preferably to a microbe that would be attacked by an appropriate fungal pathogen, of which there are many. In this case, such a microbe could be a close surrogate for a higher plant such as an algal species, but with a short sexual cycle, Fig. 2.

Current research by the authors is now focused on the identification and culture of other rare and slow-growing soil microbiota, including actinomycetes, archaea, bacteria and fungi. In this case, these organ-isms are well-known for their unique antibiotics and may also provide new leads for production of unusual and bioactive metabolites active as fungicides or other pesticides, but may also provide resources for the introduction of novel biosynthetic pathways into more commonly en-countered organisms that are easier to culture and regenerate for bio-control purposes.

5.2. Herbicide resistance

Relatively few herbicides have natural product leads and in some cases more elaborate synthetic biological routes would need to be constructed in the producing organism. However, several examples of commercial herbicides generated from natural product leads or natural products under patent are available for further consideration and de-velopment. One example of a lead plant-produced metabolite with ex-ceptional activity as a bioherbicide is that of m-tyrosine, a simple non-protein amino acid produced naturally by Festuca rubra and other re-lated species [47], Fig. 3. This highly active molecule is biosynthesized from phenylalanine in only certain weed-suppressive fine fescue turf-grasses; in contrast, related analogues o- and the more commonly en-countered p-tyrosine, are inactive. Activity as a bioherbicide is pre-sumed to be associated with protein mis-incorporation and subsequent impacts on cell wall biosynthesis and respiration [48], both primary metabolic processes in developing seedlings. Both phenylalanine and p-tyrosine, along with other bioactive non-protein amino acids and pre-cursors such as (S)-canavanine, are typically inexpensive and readily available, as are many [49]. At this time, seed mixtures of fine fescue turfgrasses with potential for enhanced exudation of these metabolites are planted in North America along thousands of miles of highways for weed suppression and drought tolerance, i.e. DOT (Department of Transportation) fine fescue mix [50]. Given the simplicity of this bio-synthetic pathway, it is likely that GM plants could be readily designed for enhanced exudation of m-tyrosine or other tyrosine analogues by their living roots. Interestingly, m-tyrosine is also known to be produced by a naturally occurring bacterial species associated with oxidative stress, suggesting the pathway could be easily transferred to numerous microorganisms [47,51].

In another example, the herbicide mesotrione, a 4-hydro-xyphenylpyruvate dioxygenase inhibitor, relates to the lead compound leptospermone produced by a commonly occurring myrtaceous plant, the lemon bottlebrush, Callistemon citrinus [52]. It is tempting to suggest that in this case the plant could be used as the co-evolving producer organism, as leptospermone was identified following bioassay-guided fractionation of extracts from soil surrounding the plant and the plant itself. The plant also exhibited strong allelopathic effects by eliminating

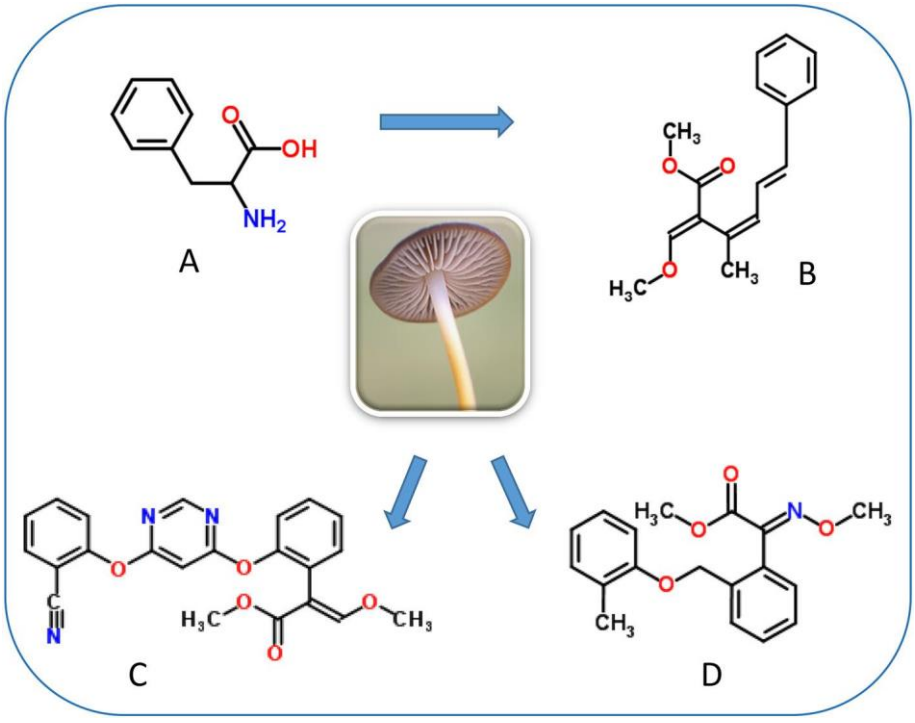

Fig. 2. Strobilurus tenacellus converts phenylalanine (A) to strobilurin A (B). The strobilurins have proven to be effective fungicidal lead molecules for the lar-gest class of fungicides sold globally, the strobilurins, including azoxystrobin (C) marketed by Syngenta and kresoxim-methyl (D) marketed by BASF. Subjecting fungi in this genus to stress induced by competition may result in the rapid evolution and discovery of additional novel molecules for biocon-trol of pathogens or serving as leads for new fungi-cides.

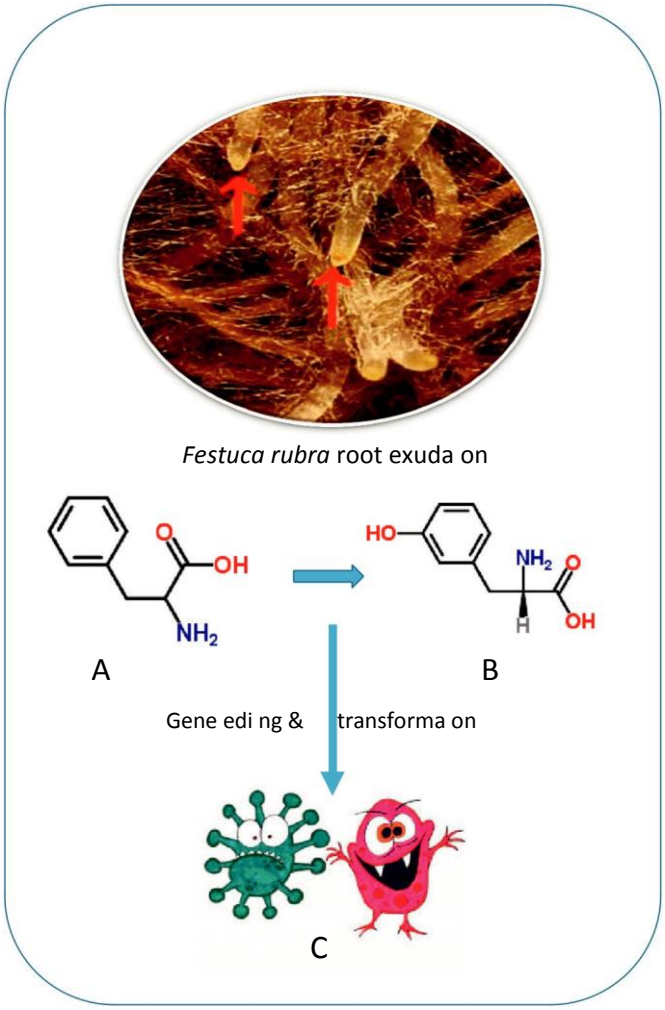

Fig. 3. Certain Festuca spp. produce a unique non-protein amino acid that is released into the rhizosphere from its living roots. Phenylalanine (A) has been identified as the precursor of the potent bioherbicide m-tyrosine (B) in fine leaf fescue. Introduction of this pathway into selected microbes of interest (C) through genomic editing could result in the ability to dispense the bioherbicide on demand more cost-effectively in the rhizosphere or create an opportunity to produce additional molecules that may serve as synthetic leads to generate products that have a longer half-life in soil than m-tyrosine.

plant growth in its vicinity. One rational approach, particularly since the plant is perennial and slow-growing, would be to transfer the bio-synthetic pathway from the plant to a microbe, as previously suggested. Interestingly, the discovery of leptospermone was made in California, where bottlebrush is non-native but is frequently grown. However, the botanical diversity in the country of origin (Australia) for C. citrinus may offer resistant plants that could themselves be used in an appro-priate ecologically managed strategy to expedite production of new resistance-overcoming herbicides. These new herbicides may represent novel natural product leads, but knowledge related to the transforma-tion of leptospermone to the more active and stable molecule meso-trione would suggest a rational approach to designing a new commer-cial herbicide from these new leads. Other higher plants with shorter lifecycles could also be employed as GM-producer organisms, such as members of the Brassicaceae. However, algae could again be considered as model organisms for further study, involving both producers and responders. The green alga, Chlamydomonas reinhardtii, is a well-studied industrial organism which is normally haploid and so genetic altera-tions or mutations are observed immediately, without gene introgres-sion in a potentially co-evolutionary process [53,54].

5.3. Drug resistance

For drug resistance, and particularly antibiotic resistance, the op-portunities are perhaps even more promising. There is already evidence that, for example, because methicillin-resistant Staphylococcus aureus is now known to have evolved long before the introduction of methicillin into clinical practice [55], the diversity of extant responding organisms is already available for selection of new antibiotics. The essential step for the process to produce new antibiotics not yet resisted is then to create a new micro-organism that is at the outset evolutionarily de-pendent upon the antibiotic for which a resistance-overcoming re-placement is needed. One example of a unique approach towards screening for novel antibiotics was first suggested by Ling et al. [56], who employed the use of the i-chip (isolation chip) for soil burial and microbial isolation. This simple and small series of nano-sized screening chambers present in the chip allowed for successful incubation and potential isolation of novel, slow-growing microbes in situ in the low-nutrient, partially aerobic soil solution over time. The successful gen-eration of a functional i-chip subsequently resulted in the discovery of the novel antibiotic teixobactin [56]. The screening system employed in soil, in the presence of thousands of other unique microbes, generated a novel organism producing an antibiotic with a novel mode of action not yet resisted, in a process which involved the screening of only ~ 10,000 individual chambers for their respective microbes exhibiting antibiotic-producing potential, a remarkable feat considering it had been over 15 years since the past novel family of antibiotics was discovered.

6. General considerations

According to Turner et al., [14], modifications to the physiochem-ical properties of the natural product lead may be essential for practical use, a frequent requirement also for all other toxins discussed above. Such modifications need also to be associated with the compound placed by GM into the rapidly evolving producer organism and with the caveat that this organism must essentially benefit by its presence. Nonetheless, this issue is accommodated by the herein often stated potential need to exploit synthetic biology in the GM design process for the producer organism. As numerous plants already produce copious quantities of small molecules ranging in their polarity by root and shoot exudation, this is not such a far-fetched proposition [48,57].

Above, specific approaches that might give best results in at-tempting to exploit co-evolution in overcoming resistance to in-secticides and other toxins are discussed, including both plants and microbes as generators of novel leads or as the successful adaptors to a changing environment through rapid evolutionary adaptation. Once a chemical target and the associated biological system have been se-lected, mathematical modelling [58] will then predict, on the basis of resistance frequency observed in natural circumstances, the population sizes needed for the producer and responding organisms. The approx-imate time-lines will be determined from the rates of passage of the organisms through sexual reproduction. The initial populations will need to exhibit sufficient genetic diversity for the selection processes to operate effectively and this requirement must be accommodated in the precise ways in which the biosynthetic pathways are transferred, via GM or synthetic biology, to the producer organisms, a process also re-quiring tailoring to the life cycles of the specific organisms chosen.

7. Conclusions

By creating suitable organisms, particularly fast developing plants or microbes, that are dependent on an insecticide or other toxin in the arms race against evolving responding organisms, it can be expected that co-evolution will cause the producer organism to generate re-sistance-overcoming toxins. The choice of organisms created by GM and via synthetic biology to act as producers or responders requires the timely evolution of both producers and responders. This process is

similar to that of wild-type species, hence the targeting, where possible, of appropriately sexually cycling organisms including microbes ex-hibiting frequent mutations, and where screening of very large popu-lations can be easily accommodated. Of course, a prerequisite is that the responding organism is antagonistic to the producing organism which is, in turn, dependent for survival on the toxin being produced.

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