

Scotland's Rural College

## The rise, fall and resurrection of chemical induced resistance agents

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## The rise, fall and resurrection of chemical induced resistance agents

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# 1 The rise, fall and resurrection of chemical induced resistance agents

2 *Running title: Chemical IR: rise, fall and resurrection*

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10

## 11 **Abstract**

12 Since the discovery that the plant immune system could be augmented for improved  
13 deployment against biotic stressors through the exogenous application of chemicals that  
14 lead to induced resistance (IR), many such IR-eliciting agents have been identified. Initially it  
15 was hoped that these chemical IR agents would be a benign alternative to traditional  
16 chemical biocides. However, owing to low efficacy and/or a realisation that their benefits  
17 sometimes come at the cost of growth and yield penalties, chemical IR agents fell out of  
18 favour and seldom used as crop protection products. Despite the lack of interest in  
19 agricultural use, researchers have continued to explore the efficacy and mechanisms of  
20 chemical IR. Moreover, as we move away from the approach of 'zero tolerance' toward  
21 plant pests and pathogens toward integrated pest management, chemical IR agents could  
22 have a place in the plant protection product list. In this review, we chart the rise and fall of  
23 chemical IR agents, and then explore a variety of strategies used to improve their efficacy  
24 and remediate their negative side effects.

## 25 **Keywords**

26 **Induced resistance, priming, IPM, trade-offs, synergistic, biological control**

## 27 1 INTRODUCTION

28 In recent decades, the philosophy behind the control of plant pests and pathogens has been  
29 driven by a 'zero tolerance' approach, where elimination of the causal agent is the unstated  
30 aim. As this has rarely, if ever, been achieved, the extreme selection pressure exerted on the  
31 surviving pest and pathogen populations presents obvious dangers, such as rendering  
32 genetic resistance ineffective or resulting in populations acquiring resistance to biocidal  
33 chemical agents. An alternative, however, is to take advantage of recent advances in our  
34 understanding of plant-microbe interactions and use alternative control strategies that  
35 leverage the plant immune system in a systems context, namely Integrated Pest (/crop)  
36 management.

37 Plants possess a sophisticated innate immune system that provides the first line of defence  
38 against attackers. This is controlled by a complex network of interconnected signalling  
39 pathways that are directly activated upon recognition of Microbe-Associated Molecular  
40 Patterns (PAMPs) and/or Damage-Associated Molecular Patterns (DAMPs). The model of  
41 plant-pathogen interactions by Jones and Dangl (2006)<sup>1</sup>, also referred to as the 'zig-zag'  
42 model, is perhaps the most popular model of the plant innate immune system which  
43 distinguishes three forms of disease resistance. Effector-triggered immunity (ETI) –  
44 commonly known as race-specific or vertical resistance – is a qualitative form of disease  
45 resistance that relies on the presence of single resistance genes (*R*). The associated *R*  
46 proteins enable direct or indirect recognition of susceptibility-inducing pathogen effectors  
47 and activate a rapid immune response, which is typically associated with hypersensitive cell  
48 death. Accordingly, ETI provides high levels of protection against biotrophic pathogens.<sup>2</sup>  
49 However, because of its monogenic nature, ETI has a narrow range of taxonomic  
50 effectiveness and limited durability due to the evolutionary pressures on pathogens to

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3 51 evolve alternative effectors, thereby avoiding recognition by R proteins.<sup>3,4</sup> Pattern Triggered  
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5 52 Immunity (PTI) is a quantitative form of disease resistance, which provides high level  
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7  
8 53 resistance against a broad range of attackers. PTI is triggered by a multitude of conserved  
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10  
11 54 molecular patterns that are produced during infestation or infection by pests and diseases,  
12  
13 55 respectively, which activate a range of different pathways and defence mechanisms that  
14  
15 56 become active at different stages of the interaction. However, PTI is not sufficiently  
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17  
18 57 effective against virulent pathogens<sup>1,5</sup>, which employ effector molecules that subvert PTI-  
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20  
21 58 controlling pathways, a process commonly referred to as Effector-Triggered Susceptibility  
22  
23 59 (ETS).<sup>1,6</sup> In addition to PTI-suppressing effectors, ETS by biotrophic pathogens also involves  
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25 60 2<sup>nd</sup> level effectors that suppress ETI-related signalling and hypersensitive cell death-  
26  
27  
28 61 related.<sup>1,7,8</sup> Within the framework of the zig-zag model by Jones and Dangl (2006)<sup>1</sup>, the  
29  
30 62 residual level of resistance after ETS-mediated repression of PTI and ETI is referred to as  
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32 63 basal resistance (BR)<sup>1</sup>. Since its inception, the zig-zag model has been interpreted as a co-  
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34  
35 64 evolutionary arm's race, during which pathogens evolved ETS to suppress PRR-dependent  
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38 65 PTI and plants counter-evolved R-proteins to recognise effector activity and activate ETI.  
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40  
41 66 Although proven exceedingly useful for the conceptual interpretation of plant innate  
42  
43 67 immunity and evolution, the zig-zag model is not without limitations.<sup>9</sup> Foremost among  
44  
45 68 them is that the model only represents plant innate immunity against biotrophic pathogens.  
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47  
48 69 Furthermore, while it is acceptable to portray ETI, PTI and BR as different types of resistance  
49  
50 70 within an evolutionary context, they are remarkably similar from a mechanistic point. All  
51  
52 71 three types of resistance share similar signalling pathways and defence mechanisms that  
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54  
55 72 become active during different stages of the interaction with avirulent, non-host and  
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57  
58 73 virulent pathogens, respectively.<sup>10,11</sup> These pathways and mechanisms include relatively  
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60 74 early-acting local defences, such as the accumulation of reactive oxygen species and cell

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3 75 wall reinforcements.<sup>12–15</sup> Also, there are later-acting defences that are controlled by *de novo*  
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6 76 produced defence hormones, such as salicylic acid (SA), jasmonic acid (JA), ethylene (ET) and  
7  
8 77 abscisic acid (ABA),<sup>16,17</sup> which all interact with each other to prioritise and fine tune an  
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10 78 appropriate immune response.<sup>18,19</sup> Hence, from a mechanistic point of view, there is no  
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12  
13 79 clear partition between ETI, PTI and BR.

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15  
16 80 Although the plant innate immune system protects against the majority of potentially  
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18 81 hostile microbes, it cannot prevent infection and damage by virulent pathogens. To  
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20  
21 82 minimise damage by these attackers, plants have evolved the ability to augment the level of  
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23 83 innate immunity by forming a memory of previous pathogen encounters, resulting in a  
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26 84 faster and/or stronger deployment of inducible plant defence mechanisms upon subsequent  
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28 85 encounters. This so called **defence priming** results in induced resistance (IR), which is a form  
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30  
31 86 of phenotypic plasticity and can thus be regarded as plant acquired immunity.<sup>20</sup> IR is often  
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33 87 systemically expressed and has the benefits of being durable with broad-spectrum  
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36 88 effectiveness, while also providing protection that is stronger than BR.<sup>21</sup> Given the ability to  
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38 89 augment plant resistance, many natural and synthetic IR-eliciting agents have been  
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41 90 identified and characterised in detail. However, to date, these products are not widely  
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43 91 employed in crop protection schemes. In this review, we assess the rise of IR agents, initially  
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45 92 seen by some as silver bullet solutions for benign crop protection, and their subsequent fall  
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48 93 out of favour, owing to low efficacy and/or a realisation that their benefits sometimes come  
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50 94 at the cost of growth and yield penalties. Finally, we explore how we can use our increased  
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52 95 understanding of host-microbe interactions to facilitate a resurrection of IR agents as  
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55 96 tailored components of plant protection methods that are implemented in a systems  
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57 97 context, namely within Integrated Pest Management (IPM).

## 98 2 THE RISE AND FALL OF CHEMICAL IR AGENTS

99 Six decades ago, Ross (1961)<sup>22</sup> observed that localised infection of tobacco plants with  
100 tobacco mosaic virus (TMV) leads to immunity in distal non-infected leaves. This so called  
101 systemic acquired resistance (SAR) is a form of IR and is dependent on the plant defence  
102 hormone salicylic acid (SA) and the defence regulatory protein NPR1.<sup>23</sup> Activation of this  
103 pathway results in direct activation and priming of a wide range of different basal defence  
104 mechanisms, including the production Pathogenesis Related (PR) proteins. The priming  
105 associated with SAR can provide long-lasting protection against a broad spectrum of (hemi-  
106 )biotrophic pathogens.<sup>20,22–24</sup> In subsequent studies, it became clear that there are  
107 additional IR responses, which are controlled by partially different signalling pathways.  
108 environmentally, which is triggered by root colonisation with beneficial soil microorganisms,  
109 such as plant growth-promoting rhizobacteria (PGPR), endophytic plant growth-promoting  
110 fungi (PGPF) and arbuscular mycorrhizal fungi (AMF), is under control by a signalling  
111 pathway partially different from SAR. In *Arabidopsis*, ISR is dependent on the defence  
112 regulatory protein NPR1 but operates independently of SA.<sup>25</sup> Instead, ISR is typically based  
113 on a priming of JA- and ET-dependent signalling pathways.<sup>26,27</sup> Based on prior discovery of  
114 JA as a wound-responsive defence hormone in plants,<sup>28</sup> JA and its methylated derivative  
115 methyl-jasmonic acid (MeJA) have often been used as chemical IR agents against herbivores  
116 and necrotrophic pathogens.<sup>29,30</sup> Moreover, while SAR is predominantly effective against  
117 biotrophic pathogens, ISR is more effective against necrotrophic pathogens.<sup>31,32</sup> Further  
118 evidence, for the existence of alternative forms of IR came from the characterisation of  $\beta$ -  
119 aminobutyric acid-induced resistance (BABA-IR). BABA is a non-protein amino acid that is  
120 produced in low concentrations by stressed plant tissues.<sup>33</sup> Perception of BABA is  
121 dependent on the IBI1 receptor gene, which encodes an aspartyl-tRNA synthetase and

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3 122 controls BABA-IR against downy mildew and necrotrophic fungi.<sup>34</sup> Furthermore, the  
4  
5 123 underlying signalling pathways of BABA-IR vary according to the challenging pathogen and  
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8 124 can either be SA-dependent or SA-independent<sup>35,36</sup>, providing broad-range protection  
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10 125 against biotrophic and necrotrophic pathogens.<sup>37</sup> The three classic examples of SAR, ISR and  
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13 126 BABA-IR illustrate IR is controlled by a variety of different defence signalling pathways,  
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15 127 depending on the eliciting agent, plant species and challenging pathogen. Despite this  
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18 128 diversity, all IR responses share the common characteristic that they augment the  
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20 129 effectiveness of BR through either a direct up-regulation or a priming of basal defence  
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23 130 mechanisms.<sup>20</sup>

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26 131 To maximise the benefits of SAR, White, (1979)<sup>38</sup> showed that injections of SA, aspirin and  
27  
28 132 benzoic acid, each elicited SAR against *tobacco mosaic virus* (TMV) in tobacco. This  
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30 133 pioneering experiment showed that SAR can be triggered without having to infect plants  
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33 134 with pathogens and heralded an era of research into chemical IR agents. Research  
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36 135 throughout the 1980s and 1990s led to the development of several functional SA analogues  
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38 136 that act as potent SAR inducers, of which the best known are 2,6-dichloroisonicotinic acid  
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40 137 (INA) and its derivative Acibenzolar-S-methyl (ASM). INA was shown to provide high level of  
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43 138 protection in different crops including barley, cucumber and rice.<sup>39–41</sup> Similarly, ASM showed  
44  
45 139 high resistance-inducing efficacy in a range of different crop pathosystems.<sup>42–45</sup> Based on  
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48 140 these results, Syngenta launched Actigard®/Bion® as the first commercial IR agent, which  
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50 141 includes ASM as the active ingredient. Other IR agents, such as BABA<sup>33,37</sup> and Chitosan, a  
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52 142 polymeric derivative of chitin<sup>46</sup>, yielded similarly high levels of crop protection against  
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55 143 economically devastating plant diseases. Accordingly, IR agents emerged as an appealing  
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58 144 alternative to fungicides, since they show little or no direct toxicity towards the pathogen or  
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3 145 environment, while providing broad-spectrum protection through augmentation of durable  
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6 146 BR.<sup>47</sup>  
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9 147 However, the initial ambition to employ chemical IR agents as main-stream crop protection  
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11 148 products never materialised, which was largely due to undesirable non-target effects on  
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13 149 plant growth and seed. This was first highlighted by Heil *et al.* (2000)<sup>48</sup>, who showed that  
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16 150 wheat plants treated with ASM had lower biomass, developed fewer shoots and produced  
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18 151 fewer seeds compared with untreated plants and this was particularly pronounced in plants  
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21 152 grown with a limited nitrogen supply. Although a direct up-regulation of basal defence  
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23 153 mechanisms could achieve high levels of protection, the associated costs made these agents  
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26 154 less attractive for commercial exploitation as crop protection products. It was argued that  
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28 155 the deployment of IR agents is only beneficial under conditions of high disease pressure,  
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31 156 where the associated costs are outweighed by the benefits of disease protection.<sup>48-51</sup>  
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33 157 Besides being metabolically costly, IR activators could also be phytotoxic. INA and its  
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35 158 derivatives were deemed too toxic for agricultural use.<sup>52</sup> Similarly, BABA was found to cause  
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38 159 toxicity via inhibition of AspRS enzyme activity.<sup>34</sup> A third obstacle associated with chemical  
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41 160 IR agents is that their efficacy can be highly variable between plant genotypes. In both  
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43 161 cucumber<sup>40</sup> and soybean<sup>53</sup> INA efficacy varied by genotype. Efficacy may also be affected by  
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45 162 the pathogen strain. In tomato, disease protection by BABA not only varied by host  
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47  
48 163 genotype but also by *Phytophthora infestans* isolate.<sup>54</sup> Additionally, there is compelling  
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50 164 evidence that environmental conditions affect the outcome of chemically induced IR.<sup>55,56</sup>  
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53 165 Furthermore, chemically induced IR is generally transient lasting at most weeks<sup>57-60</sup> which  
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55 166 necessitates multiple applications. This complex interplay of variables affecting IR efficacy  
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58 167 has impeded wide-spread adoption of chemical IR agents in agriculture and horticulture.  
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### 168 3 THE RESURRECTION OF CHEMICAL IR AGENTS

#### 169 3.1 Plant defence priming

170 The costs associated with prolonged expression of defences, has resulted in the evolution of  
171 **priming** as a more cost-efficient strategy for IR, which allows plants to mount a faster  
172 and/or stronger BR response against attackers.<sup>61,62</sup> Although priming typically manifests  
173 itself as a long-term consequence of transient defence induction to biotic stress, chemical IR  
174 agents can serve as suitable priming stimuli when applied in relatively low doses.<sup>50</sup> In some  
175 instances, plants receiving such treatments have been shown to display minimal defence  
176 induction before pathogen encounter, although their effectiveness tends to be lower than  
177 chemically induced IR mediated by direct up-regulation of defences.<sup>63,64</sup> Furthermore, IR via  
178 priming is still associated with a reduction in plant growth and seed set, albeit minor, which  
179 can make it unfavourable in stress-free conditions.<sup>20,62,65</sup> However, these costs are  
180 outweighed by the benefits of protection under stressful conditions.<sup>62,63,66</sup> Given the  
181 significance of priming for plants in their natural environment, it has strong potential to be  
182 developed into an energetically (and environmentally) benign plant protection strategy. To  
183 this end, it is necessary to ascertain how a given IR chemical behaves - for instance, at what  
184 concentrations do IR agents switch from priming activity to a more costly direct induction of  
185 basal defences? Regardless of the nature of the priming stimuli, Martinez-Medina *et al.*  
186 (2016)<sup>62</sup> proposed a set of sequential criteria that must be satisfied, namely 1) a memory of  
187 the priming stimulus with a low fitness cost, and 2) a stress trigger that induces a faster  
188 and/or stronger defence response resulting in improved disease protection. Indeed, since  
189 the potential of priming was highlighted by Conrath *et al.* (2006)<sup>61</sup>, the capacities of priming  
190 chemicals, both natural and synthetic, have been documented in a variety of plant  
191 pathosystems.<sup>67</sup> Although it is now commonly acknowledged that the use of priming

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3 192 chemicals in agriculture is reduced by their limited efficacy and variable performance,  
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6 193 optimising their potential as components of IPM is becoming appealing.<sup>68–70</sup>  
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### 9 194 **3.2 Integrating chemical IR agents in to IPM**

10 195 IPM is a strategy for combating plant pests and diseases, using all available environmentally  
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13 196 benign methods whilst minimising the applications of chemical pesticides, to keep them  
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15 197 below the economic injury level (EIL) threshold. Chemical IR agents fit well into IPM as they  
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18 198 can be a replacement for a conventional pesticide or they could be a means of reducing  
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20 199 their dosage. Moreover, other components commonly used in IPM could be used as means  
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23 200 to improve some of the problems associated with chemical IR agents and thus make them  
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25 201 more efficacious. However, IPM is applied to multiple crops with multiple pathogens, some  
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28 202 of which are coincidental in time and/or space. Therefore, it is important to understand the  
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30 203 principles whereby IPM components are combined and how these will impact different  
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33 204 host-pathosystems. In the remainder of this review, we explore various approaches to  
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35 205 improve the efficacy of chemical IR agents (Table 1), and discuss how these can be included  
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37 206 within IPM strategies.  
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214 Table 1: Strategies used to improve the efficacy of chemical IR agents.

Strategy	Agent(s)	Pathosystem		Effect	Ref
Combining biocontrol and chemical IR	MeJA – <i>T. harzianum</i>	wheat	<i>Bipolaris sorokiniana</i>	Reduced symptoms. Combination more effective than either treatment alone. Increased biomass	71
	MeJA – SA – <i>T. harzianum</i>	tomato	<i>Fusarium oxysporum</i>	Synergistic induction of defences. Increased biomass	72
	ASM – <i>T. harzianum</i>	faba bean	<i>Botrytis fabae</i>	Combination improved efficacy	73
			<i>Botrytis cinerea</i>	Combination gave complete protection	
	ASM – <i>A. pullulans</i>	kiwifruit	<i>Pseudomonas syringae</i>	Combination improved efficacy	74
Combining chemical IR agents	ASM – BABA – <i>cis</i> -jasmone	barley	<i>Ramularia collo-cygni</i>	Improved efficacy. Reduced toxicity	75
	ASM – BABA	grapevine	<i>Plasmopara viticola</i>	Additive protective effective	76
Combining chemical IR agents and fungicides	BABA – Mancozeb	potato	<i>Phytophthora infestans</i>	Synergistically increased its fungicide efficacy.	77
		tomato			
		cucumber	<i>Pseudoperonospora cubensis</i>		
	BABA – Fluazinam	potato	<i>Phytophthora infestans</i>	Full fungicide activity achieved with a 20–25% lower dose	78
	ASM – Mancozeb	chickpea	<i>Didymella rabiei</i>	ASM application frequency reduced. Improved grain yields.	79
	BABA – Fosetyl-Al	grapevine	<i>Plasmopara viticola</i>	Additive protective effective with half recommended fungicide dose	76
BABA – N-(Trichloromethylthio) Phthalimide					
Rationally designed IR agents Ionic Pairing	[BABA <sup>-</sup> ] [Cholinium <sup>+</sup> ]	tobacco	tobacco mosaic virus	Reduced phytotoxicity	80
	[ASMCOO <sup>-</sup> ] [Cholinium <sup>+</sup> ]			Reduced phytotoxicity. Improved disease resistance	
	[INA <sup>-</sup> ] [Cholinium <sup>+</sup> ]			Improved disease resistance	
Rationally designed IR agents Structural analogues	L1-3a and L1-4a novel benzotriazole	cucumber	<i>Botrytis cinerea</i>	Efficacy comparable to ASM	81
		tomato	<i>Phytophthora infestans</i>		
	RBH new IBI1 ligand	<i>Arabidopsis</i>	<i>Hyaloperonospora arabidopsidis</i> <i>Plectosphaerella cucumerina</i>	Resistance to both biotrophic and necrotrophic pathogens without growth retardation	82
Multi-action IR agents	Strobilurins (Broad-spectrum fungicides)	wheat		Improved plant growth	83
		tobacco	<i>Pseudomonas syringae</i> tobacco mosaic virus	The strobilurin pyraclostrobin conferred IR in SAR	84

				deficient <i>NahG</i> transgenic tobacco	
	1-isothiocyanato-4-methylsulfinylbutane	<i>Arabidopsis</i>	<i>Hyaloperonospora arabidopsidis</i>	Induced resistance Direct antimicrobial action	85
			<i>Plectosphaerella cucumerina</i>		
			<i>Pseudomonas syringae</i>		
Transgenerational IR	Aescin	<i>Arabidopsis</i>	<i>Pseudomonas syringae</i>	A member of the antimicrobial saponins. Induced resistance	86
	BABA	<i>Arabidopsis</i>	<i>Hyaloperonospora arabidopsidis</i>	Progeny became more responsive to BABA priming	87
			<i>Pseudomonas syringae</i>		
	BABA	common bean	<i>Pseudomonas syringae</i>	Enhanced transgenerational resistance	88
	INA				
MeJA	<i>Arabidopsis</i>	Caterpillar	Increased resistance in progeny to caterpillar herbivory	89	

215

### 216 3.3 Combining biocontrol and chemical IR

217 One approach to increase the protection levels of chemical IR agents is to combine them  
 218 with other agents. Several studies have shown that chemical IR agents and biological control  
 219 agent (BCAs) in combination results in improved disease control. BCAs are naturally  
 220 occurring communities antagonistic to specific plant pests and pathogens that have  
 221 minimal non-target effects<sup>90</sup> and a common component of IPM. The most investigated BCAs  
 222 in this regard are the *Trichoderma spp*, which grow chemotropically toward the roots of  
 223 many crop species. In the roots, they produce various metabolites that promote plant  
 224 growth through enhanced nutrient availability. Furthermore, the *Trichoderma* also induce  
 225 plant defence pathways and ultimately inhibit plant pathogens<sup>91</sup>. In bread wheat plants  
 226 (*Triticum aestivum* L.) receiving combined MeJA and *Trichoderma harzianum* UBSTH-501,  
 227 spot blotch (*Bipolaris sorokiniana*) symptoms were reduced significantly in comparison to  
 228 plants receiving either treatment alone. The efficacy of this combined treatment  
 229 corresponded with enhanced production of the plant development and growth promoter,

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3 230 indole acetic acid in the plant rhizosphere.<sup>71</sup> In another study, MeJA, SA and *T. harzianum*  
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6 231 treatments individually gave a similar level of protection against *Fusarium oxysporum* wilt  
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8 232 disease in tomato. However, their combination resulted in a synergistic induction of tomato  
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10 233 antioxidant defences against *F. oxysporum*.<sup>72</sup> Similarly, combining *T. harzianum* and ASM  
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13 234 was significantly better at controlling *Botrytis fabae* disease severity in faba bean plants  
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15 235 than either treatment alone.<sup>73</sup> Whilst in most cases the complementary protection  
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18 236 conferred by BCAs and chemical elicitor combinations is not complete, in some cases it has  
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20 237 been possible to give a high level of protection. A combination of *T. harzianum* and ASM was  
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23 238 shown to give complete protection in faba bean plants against *Botrytis cinerea* infection.<sup>73</sup>  
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25 239 Other BCAs have also shown to complement chemical IR agents. For instance, the  
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28 240 saprophytic yeast-like fungus *Aureobasidium pullulans* CG163 in combination with ASM  
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30 241 showed significantly reduced leaf spot incidence compared to untreated plants. The  
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33 242 CG163+ASM combination treatment was more effective than either treatment alone.  
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35 243 Furthermore, in plants receiving both treatments there was significant upregulation in  
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38 244 expression of the defence related genes *PR1*, Class IV chitinase and  $\beta$ -1,3-glucosidase. This  
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40 245 change in gene expression correlated positively with treatment efficacy and expression was  
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43 246 highest in plants receiving the combined CG163+ASM.<sup>74</sup>  
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45  
46 247 BCA-chemical IR agent combinations, in addition to improving the protective efficacy, have  
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48 248 also been shown to improve growth. In bread wheat plants, combined MeJA and *T.*  
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50 249 *harzianum* treatment resulted in significantly higher biomass, both in the presence and  
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52  
53 250 absence of *B. sorokiniana* infection.<sup>71</sup> In tomato, combining MeJA or SA with *T.*  
54  
55 251 *harzianum* improved the protection against *F. oxysporum* disease incidence more than  
56  
57  
58 252 treatment with SA or MeJA alone. Furthermore, due the improved protection, biomass was  
59  
60 253 also significantly higher in plants receiving the combined treatment. <sup>72</sup>

### 254 **3.4 The compatibility of chemical IR agents with biocontrol organisms**

255 Given the broad-spectrum effectiveness of non-host immunity, chemical treatments  
256 intended to trigger IR responses against plant antagonists could also cause deleterious  
257 effects on plant mutualists, and so the combinations of chemical IR agents and BCAs in IPM  
258 needs careful selection. Examining the effects of IR establishment by ASM application on  
259 soybean-rhizobia and soybean-AMF mutualisms, *in vitro* the chemical had no direct effect  
260 on the growth of the rhizobia *Bradyrhizobium japonicum* and only a slight inhibition at very  
261 high doses on the AMF *Glomus mosseae*. However, both seed and foliar spray  
262 application caused increased IR biochemical markers, reduced *B. japonicum* soybean  
263 symbiosis efficiency and reduced *G. mosseae* mycorrhization in soybean.<sup>92</sup> A similar finding  
264 was also reported by de Román *et al.* (2011)<sup>93</sup> who found foliar treatment of soybean with  
265 ASM led to a significant, but moderate, defence response in the plant roots which  
266 transiently decreased AMF colonisation. This defence induction was not associated with an  
267 allocation cost, and so the negative effects on AMF colonisation were likely due to defence  
268 induction rather than changes in resource allocation. Nevertheless, chemical IR treatments  
269 do not always impact plant mutualists negatively and it seems that with some chemicals,  
270 certain doses and appropriate application methods, they can be used together without  
271 disadvantage to plant mutualists. In sunflower, the effects of ASM and BABA on the downy  
272 mildew *Plasmopara helianthi* and the AMF *G. mosseae* differed by application method.  
273 When applied as a soil drench, the chemicals gave a 50-55% protection against the downy  
274 mildew - while ASM application decreased *G. mosseae* colonisation, BABA application did  
275 not. When applied as a foliar spray, protection increased to 80% and neither chemical  
276 impacted *G. mosseae* colonisation. *In vitro*, ASM had an inhibitory effect on *G. mosseae*  
277 germination, however BABA promoted germination.<sup>94</sup> In other studies, the negative effects

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3 278 of chemical IR agents on plant mutualists was shown to be dose-dependent. In soybean, SA  
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6 279 root application had no impact at lower doses typically used to induce resistance and only  
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8 280 had a negative impact at very high doses.<sup>95</sup> Similarly, MeJA root application to cucumber  
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11 281 could negatively or positively effect mycorrhizal colonisation, with higher doses reducing  
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13 282 growth and lower doses promoting it.<sup>96</sup>

### 16 283 **3.5 Combining chemical IR agents**

17  
18 284 Combining different chemical IR agents has also shown promise under field conditions. In  
19  
20  
21 285 barley, Walters *et al.* (2011)<sup>75</sup> found improved control of powdery mildew using ASM, BABA  
22  
23 286 and JA combined treatments. Given the growth costs associated with higher and more  
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25  
26 287 protective doses in many chemical IR agents, using low doses of multiple agents for additive  
27  
28 288 or synergistic IR effects with minimal growth costs is a potential means of improving their  
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30  
31 289 efficacy. In one study, Reuveni *et al.* (2001)<sup>76</sup> established that BABA – ASM mix applied at  
32  
33 290 half the recommended dose had an additive effect, effectively controlling *Plasmopara*  
34  
35  
36 291 *viticola* in grapevines. Despite this early promise, the strategy of combined chemical IR  
37  
38 292 agents has received little further attention.

### 41 293 **3.6 Combining chemical IR agents and fungicides**

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43 294 Similarly, results from chemical IR agent – biocide combinations show a complementary  
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45  
46 295 potential in which any deleterious effects of both protection products can be reduced. An  
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49 296 application of a mixture of BABA and the fungicide mancozeb was significantly more  
50  
51 297 effective at controlling potato late blight (*P. infestans*) as well as tomato and cucumber  
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53 298 mildew (*Pseudoperonospora cubensis*) than either BABA or mancozeb alone. The inclusion  
54  
55  
56 299 of BABA in the mancozeb fungicide synergistically increased its efficacy in plants with 5:1  
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58 300 BABA: mancozeb showing the highest synergy factor. Application of the BABA and  
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3 301 mancozeb mixture did not have a synergistic interaction in controlling the pathogens *in*  
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5 302 *vitro*, thus demonstrating BABA-induced resistance enhanced mancozeb fungicide efficacy  
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7  
8 303 with lower doses required to control disease.<sup>77</sup> In potato, a combination of BABA and the  
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10 304 fungicide Fluazinam resulted in a synergistic action against late blight. Furthermore, full  
11  
12  
13 305 Fluazinam activity was achieved with a 20–25% lower dose under field conditions.<sup>78</sup>  
14  
15 306 Likewise, ASM efficacy improved in combination with mancozeb. In chickpea plants,  
16  
17 307 repeated ASM application protected against chickpea blight (*Didymella rabiei*) but also  
18  
19 308 resulted in yield penalties. Instead, using a ASM – mancozeb mix, with reduced application  
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21 309 frequency, grain yields were better than those achieved with ASM or mancozeb applications  
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23 310 alone.<sup>79</sup>

### 28 311 **3.7 Dual action IR agents**

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30 312 Besides the combination of chemical IR agents with fungicides, another strategy employed  
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32 313 to improve their performance has been identifying compounds combining biocidal and IR  
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34 314 activity. One group of chemicals with such dual modes of action are the strobilurins,  
35  
36 315 introduced in the 1990s as broad-spectrum fungicides. It became apparent they also  
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38 316 improved plant health and yield in the absence of disease pressure and prime plant  
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40 317 defences. In *NahG* transgenic tobacco deficient in SAR, the strobilurin Pyraclostrobin  
41  
42 318 enhanced resistance to *Pseudomonas syringae* and TMV by priming *PR-1* gene  
43  
44 319 activation.<sup>83,84</sup> In an effort to find dual action compounds Schillheim *et al.* (2018)<sup>85</sup>  
45  
46 320 developed a high-throughput assay to screen cultured parsley for compounds that prime  
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48 321 the secretion of antimicrobial phytoalexins and found 1-isothiocyanato-4-  
49  
50 322 methylsulfinylbutane (SFN). In *Arabidopsis*, this compound primed *WRKY6* gene expression  
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52 323 and reduced susceptibility to *Hyaloperonospora arabidopsidis*. Additionally, SFN showed  
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54 324 broad antimicrobial action, directly inhibiting the growth of the oomycete *H. arabidopsidis*,

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3 325 the fungus *Plectosphaerella cucumerina* and the bacterium *P. syringae*. Also turning to  
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6 326 natural plant antimicrobials to find dual action molecules, Trdá *et al.* (2019)<sup>86</sup> compared the  
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8 327 antifungal activities of several members of the Saponins, a group of compounds found in  
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10 328 several plant species and considered antimicrobial. Among the saponins tested, aescin  
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12  
13 329 showed the strongest antifungal activity. In terms of plant defence induction, aescin showed  
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15 330 strong defence induction in Rapeseed against *Leptosphaeria maculans* and in *Arabidopsis*  
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17 331 against *P. syringae*.

### 21 332 **3.8 Rationally designed chemical IR agents**

22  
23 333 In other approaches, researchers used rational design to develop a range of new or  
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25 334 modified IR molecules. To improve efficacy and reduce phytotoxicity, Kukawka *et al.*  
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28 335 (2018)<sup>80</sup> took the approach of ionic pairing by combining various IR agents with the  
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30 336 cholinium cation to form ionic liquids (ILs). BABA, ASM and INA ionically bonded to  
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33 337 cholinium – an essential nutrient in the cells of many organisms and which is non-toxic and  
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35 338 biodegradable<sup>97</sup> – were tested on the tobacco-TMV pathosystem. ASM and INA, paired with  
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38 339 cholinium, had improved disease resistance efficacy. BABA disease efficacy decreased  
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40 340 slightly; however, its phytotoxicity, along with that of ASM, drastically reduced.

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43 341 Since the development of INA and ASM, improvements in large-scale chemical screens and  
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45 342 computer aided drug design have enabled the screening of vast numbers of chemicals for IR  
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48 343 properties at a relatively low cost. Chang *et al.* (2017)<sup>81</sup> virtually screened the Maybridge  
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50 344 database, a collection of over 53,000 organic compounds, using the chemical structures of  
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53 345 ASM, MeSA and SA to identify three benzotriazole lead compounds. From one of these (L1),  
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55 346 which had a 3D structure similar to ASM, two derivatives (3a and 4a) were potent SAR

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3 347 activators. Both L1-3a and 4a gave high protection in a several pathosystems including  
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5 348 cucumber- *B. cinerea* and tomato- *P. infestans*.

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9 349 In addition to screening for structural analogues of known IR molecules, using knowledge of  
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11 350 IR receptor structure has been another approach taken to find novel IR ligands. Buswell *et*  
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13 351 *al.* (2018)<sup>82</sup>, in an attempt to find BABA analogues that induce resistance without stunting  
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16 352 plant growth, started with the structure of the BABA receptor IBI1 and through site-directed  
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18 353 mutagenesis, found that an (I)-aspartic acid-binding domain was critical for BABA  
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21 354 perception. Using ligand-interaction modelling of the binding domain they screened a library  
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23 355 of  $\beta$ -amino acids and identified seven resistance-inducing compounds, of which  
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26 356 (*R*)- $\beta$ -homoserine (RBH) had the strongest activity. RBH, like BABA conferred resistance to  
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28 357 both biotrophic and necrotrophic pathogens in taxonomically unrelated plant species but  
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30  
31 358 without the growth retardation associated with BABA.

### 32 33 34 359 **3.9 Selecting optimal pathosystems for priming**

35  
36 360 Understanding species, cultivar and pathogen-dependent responses to chemical IR  
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38 361 treatments is crucial to selecting pathosystem appropriate treatments. Chemical IR agent  
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41 362 efficacy in some instances is known to be cultivar dependent. In several cultivars of spring  
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43 363 barley induced resistance to *Rhynchosporium commune* (formerly *Rhynchosporium. secalis*)  
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46 364 by combined BABA, ASM and MeJA treatment resulted in infection levels that ranged from  
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48 365 high to non-existent.<sup>98</sup> In other studies, chemical IR treatment efficacy was shown to be  
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51 366 influenced by cultivar resistance levels. In tobacco infected with *Peronospora*  
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53 367 *hyoscyami f.sp. tabacina*, ASM provided effective control in partially resistant cultivars, but  
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55  
56 368 not susceptible cultivars.<sup>99</sup> Likewise, in cucumber INA efficacy against *Sphaerotheca*  
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58 369 *fuliginea* infection was best in partially resistant cultivars.<sup>40</sup> In contrast, both ASM and INA  
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3 370 efficacy against *Sclerotinia sclerotiorum* in soybean was superior in susceptible cultivars.<sup>53</sup>  
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6 371 Similarly, the efficacy of chemical IR agents can also depend on the identity of the attacking  
7  
8 372 pathogen. In tomato, ABA application lead to antagonistic cross-talk between the ABA- and  
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10 373 SA-responsive defense pathways, resulting in increased susceptibility to *B. cinerea*<sup>100</sup>, while  
11  
12 374 in *Arabidopsis* pre-treatment with SA caused cross-talk between the SA and JA-dependent  
13  
14 375 defense, causing increased susceptibility to *Alternaria brassicicola*.<sup>101</sup> In barley, saccharin, a  
15  
16 376 derivative of probenazole, gave high levels of protection against the biotrophic fungi  
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18 377 *Blumeria graminis*<sup>102</sup> and the hemibiotrophic fungus *R. commune*<sup>103</sup>, while in *Arabidopsis* it  
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20 378 protected against infection by hemibiotrophic *P. syringae* DC3000.<sup>104</sup> However, saccharin of  
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22 379 *Arabidopsis* also caused increased susceptibility to the necrotrophic pathogens *B. cinerea*  
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24 380 and *Pectobacterium carotovorum*, presumably due to antagonistic signalling cross-talk.  
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26 381 Indeed, saccharin treatment of *Arabidopsis* resulted in the upregulation of SA-responsive  
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28 382 genes and the simultaneous downregulation of JA-responsive genes.<sup>104</sup> In addition to some  
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30 383 chemical IR agents resulting in increased susceptibility to some pathogens, mixtures of  
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32 384 chemical IR agents may lead to undesirable outcomes due to the complex cross-talk  
33  
34 385 between plant defence pathways. However, apart from considerable evidence that SA and  
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36 386 JA dependent defence pathways are antagonistic <sup>105</sup>, there is evidence of the simultaneous  
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38 387 expression of SA- and JA-mediated defences.<sup>106–109</sup> Mur *et al.*, (2006)<sup>110</sup> found that co-  
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40 388 treatment of tobacco and *Arabidopsis* with relatively low concentrations of SA and JA  
41  
42 389 resulted in transient synergistic effects on the expression of SA- and JA-dependent defence  
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44 390 genes, while higher concentrations of these hormones resulted in antagonism.<sup>110</sup> In wheat,  
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46 391 simultaneous application of MeJA and *T. harzianum* followed by challenge with *B.*  
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48 392 *sorokiniana* resulted in the induction of both JA- and SA-dependent defence signalling. *T.*  
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50 393 *harzianum*-treated plants showed increased SA levels, enhanced accumulation of total free  
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3 394 phenolics and increased activities of defence-related enzymes, but addition of MeJA to *T.*  
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5 395 *harzianum* treatment did not affect SA induction.<sup>71</sup> By contrast, in freesia inflorescences,  
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7 396 MeJA significantly reduced *B. cinerea* disease severity but the addition of ASM to MeJA  
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9 397 significantly reduced its efficacy.<sup>111</sup> Similarly, in barley, combined treatment of ASM, BABA,  
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11 398 and cis-jasmone activated SAR, while suppressing the JA signalling pathway.<sup>75</sup> Treatment  
12  
13 399 resulted in an up-regulation of the SAR marker *PR1-b* and a substantial down regulation of  
14  
15 400 the *LOX2* gene involved in JA biosynthesis. Furthermore, plants receiving this combination  
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17 401 treatment became resistant to powdery mildew, which is effectively controlled by SA-  
18  
19 402 dependent defences. At the same time, plants became more susceptible to the hemi-  
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21 403 necrotrophic leaf spot pathogen *Ramularia collo-cygni*, which is controlled by JA-dependent  
22  
23 404 defences.<sup>75</sup>

### 3.10 Transgenerational IR

24  
25 405 Since the first systematic studies by Ross in the 1960s, IR has been portrayed as a long-  
26  
27 406 lasting resistance response. Only recently, this aspect of IR has gained renewed attention in  
28  
29 407 the context of epigenetic regulation. Seeds or seedlings treated with chemical IR agents  
30  
31 408 develop a long-lasting priming that can be maintained for several weeks<sup>58,112</sup>. Furthermore,  
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33 409 following sporadic early reports that progeny from biotic stress-exposed plants, such as  
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35 410 tobacco by TMV<sup>113</sup> and wild radish by caterpillars<sup>114</sup>, there is now solid evidence from  
36  
37 411 independent studies that priming can be transmitted epigenetically to following  
38  
39 412 generations. Slaughter *et al.* (2012)<sup>87</sup> reported that progeny of BABA-treated *Arabidopsis*  
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41 413 displayed enhanced resistance to *H. arabidopsidis* and *P. syringae*, which was associated  
42  
43 414 with increased responsiveness to priming treatment by BABA ('primed to be primed').<sup>87</sup>  
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45 415 Walters and Peterson (2012)<sup>115</sup> showed that barley from acibenzolar-S-methyl- and  
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47 416 saccharin-treated parents exhibited enhanced resistance to infection by *R. commune*.  
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3 418 Furthermore, treatment of common bean with both BABA and INA resulted in  
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5 419 transgenerational IR against *P. syringae*<sup>88</sup>, while MeJA-treated *Arabidopsis* was found to  
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7 420 produce progeny that is primed for JA-dependent defences against herbivory.<sup>89</sup> A suite of  
8  
9 421 recent *Arabidopsis*-based studies have shown that transgenerational IR relies on a complex  
10  
11 422 interplay of DNA (de)methylation pathways in the plant.<sup>20,116–119</sup> Despite these promising  
12  
13 423 new insights, the potential of IR agents to exploit transgenerational IR in the field has  
14  
15 424 received limited attention. The main obstacles come from the relative weakness of  
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17 425 transgenerational IR, as well as costs arising from increased susceptibility to other (a)biotic  
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19 426 stresses.<sup>116,120</sup> A potentially more promising strategy for the exploitation of  
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21 427 transgenerational IR comes from direct manipulation of the epigenetic makeup of the plant.  
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23 428 Furci *et al.* (2019)<sup>119</sup> identified selected hypo-methylated regions of DNA in the *Arabidopsis*  
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25 429 genome, which provided near complete levels of primed resistance against downy mildew  
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27 430 and that remained stable over at least 8 generations of inbreeding.

### 3.11 Chemical IR in practical crop protection

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38 432 With the continuing expansion of our understanding of the mechanistic basis of IR, the  
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40 433 characterisation of the action of many chemical IR agents in many pathosystems and the  
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42 434 availability of more effective agents, it is reasonable to hope that these agents have the  
43  
44 435 potential to become widely used crop protection products. In the field, prediction of the  
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46 436 actions of applied chemical IR agents is difficult as this is a relatively uncontrolled  
47  
48 437 environment where many abiotic and biotic stresses will trigger plant responses that can  
49  
50 438 lead to complex interactions with the agents<sup>51,121,122</sup> and so their use must be carefully  
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52 439 targeted. However, in more controlled environments such as glasshouses or highly  
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54 440 controlled vertical farming chambers, their potential is high. Under such controlled  
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56 441 conditions, it should be possible to combine IPM measures that include chemical IR agents

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3 442 in a way that has more predictable outcomes. Also, under these controlled environments,  
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5 443 there is a scope for formulating bespoke treatments that are highly targeted to the biotic  
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7 444 stress vulnerabilities of the system. Furthermore, for organic growers that desire natural  
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9 445 means of protecting produce, the exploitation of IR agents can fulfil such requirements.  
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11 446 Indeed, interest in 'natural' protection products is growing. The global plant Biostimulants (a  
12  
13 447 term used for commercial products that are marketed as stimulants of natural plant growth  
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15 448 and/or protection) market is forecast to reach USD4.5 billion by 2027 and have an annual  
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17 449 growth rate of 11.2% during the period 2020-2027.<sup>123</sup> In order to provide improved products  
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19 450 to this growing market, it is necessary to increase the translation of the growing mechanistic  
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21 451 knowledge of IR, in to applied research that incorporates chemical IR in to IPM.  
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#### 29 452 **4 CONCLUSION**

30 453 Chemical IR agents that lack biocidal action but instead augment plant resistance to  
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32 454 invaders may be a viable option in the tool kit for plant pest and pathogen control. These  
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34 455 chemical IR agents, initially billed as cost free potential alternatives to conventional  
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36 456 pesticides, have not been widely used in agriculture, limited by their insufficient efficacy  
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38 457 compared with conventional biocides, variable efficacy and yield penalties. Although,  
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40 458 achieving levels of disease control with chemical IR agents that are on par with conventional  
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42 459 pesticides may be ambitious, as we slowly move away from the philosophy of 'zero  
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44 460 tolerance' in the control of plant pests and pathogens, the integration of chemical IR agents  
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46 461 into IPM strategies, in which the aim is to keep pests and pathogens below the economic  
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48 462 injury level, has merit.  
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55 463 We have outlined potential strategies by which the efficacy of chemical IR agents as  
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57 464 components of IPM might be optimised (Figure 1). The efficacy of these chemicals depends  
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3 465 on the pathosystem in question and through experimentation, it is possible to optimise their  
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5 466 performance. In the process of optimisation, several successful approaches have been  
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7 467 demonstrated. The combination of chemical IR agents with plant mutualists and with other  
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9 468 chemical IR agents have resulted in both increased protection and reduced toxicity.  
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11 469 Similarly, chemical IR agents in combination with fungicides can reduce the required dosage  
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13 470 of the latter. Furthermore, rational molecule design approaches hold the promise of a new  
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15 471 and more effective generation of chemical IR agents. While in terms of breeding crops more  
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17 472 responsive to these treatments, the phenomenon of transgenerational IR holds promise.  
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19 473 These approaches must be based on an understanding of not only their known mechanisms  
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21 474 of crop protection, but also the range of outcomes from experimentation with dose,  
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23 475 environment and pathosystem combination. These are strategies that could result in  
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25 476 considerable progress towards more robust IPM exploiting a novel range of tools to best  
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27 477 effect and drive the development of new crop protectants designed for high efficacy in IPM  
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29 478 application.  
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40 **Figure 1:** *Improving chemical IR efficacy* – Existing agents or new agents developed in rational design  
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42 481 (Chem-IR) are tested in target pathosystems until effective agent(s) are found. The efficacy can be  
43  
44 482 further improved in combination with other treatments and effective strategies can be further  
45  
46 483 combined. Efficacious treatments can be tested in trans-generationally-primed plants and the cycle  
47  
48 484 repeated until an optimal treatment that can be integrated in to an effective IPM strategy.  
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For Peer Review

496 **References**

- 497 1 Jones JDG, Dangl JL. The plant immune system. *Nature* 2006; **444**: 323–329.
- 498 2 Cui H, Tsuda K, Parker JE. Effector-triggered immunity: From pathogen perception to robust defense.  
499 *Annu Rev Plant Biol* 2015; **66**: 487–511.
- 500 3 García-Arenal F, McDonald BA. An Analysis of the Durability of Resistance to Plant Viruses.  
501 *Phytopathology* 2003; **93**: 941–952.
- 502 4 Mundt CC. Durable resistance: A key to sustainable management of pathogens and pests. *Infect Genet  
503 Evol* 2014; **27**: 446–455.
- 504 5 Couto D, Zipfel C. Regulation of pattern recognition receptor signalling in plants. *Nat Rev Immunol*  
505 2016; **16**: 537–552.
- 506 6 Pel MJC, Pieterse CMJ. Microbial recognition and evasion of host immunity. *J Exp Bot* 2013; **64**: 1237–  
507 1248.
- 508 7 Rajamuthiah R, Mylonakis E. Effector triggered immunity activation of innate immunity in metazoans  
509 by bacterial effectors. *Virulence*. 2014; **5**: 697–702.
- 510 8 Thordal-Christensen H. A holistic view on plant effector-triggered immunity presented as an iceberg  
511 model. *Cell. Mol. Life Sci.* 2020; **77**: 3963–3976.
- 512 9 Pritchard L, Birch PRJ. The zigzag model of plant-microbe interactions: Is it time to move on? *Mol Plant  
513 Pathol* 2014; **15**: 865–870.
- 514 10 Tsuda K, Katagiri F. Comparing signaling mechanisms engaged in pattern-triggered and effector-  
515 triggered immunity. *Curr. Opin. Plant Biol.* 2010; **13**: 459–465.
- 516 11 Naveed ZA, Wei X, Chen J, Mubeen H, Ali GS. The PTI to ETI Continuum in Phytophthora-Plant  
517 Interactions. *Front. Plant Sci.* 2020; **11**: 593905.
- 518 12 Luna E, Pastor V, Robert J, Flors V, Mauch-Mani B, Ton J. Callose deposition: A multifaceted plant  
519 defense response. *Mol. Plant-Microbe Interact.* 2011; **24**: 183–193.
- 520 13 Qi J, Wang J, Gong Z, Zhou JM. Apoplastic ROS signaling in plant immunity. *Curr. Opin. Plant Biol.* 2017;  
521 **38**: 92–100.
- 522 14 Bacete L, Mélida H, Miedes E, Molina A. Plant cell wall-mediated immunity: cell wall changes trigger  
523 disease resistance responses. *Plant J* 2018; **93**: 614–636.
- 524 15 Kuźniak E, Kopczewski T. The Chloroplast Reactive Oxygen Species-Redox System in Plant Immunity  
525 and Disease. *Front. Plant Sci.* 2020; **11**: 12.
- 526 16 Ton J, Flors V, Mauch-Mani B. The multifaceted role of ABA in disease resistance. *Trends Plant Sci* 2009;  
527 **14**: 310–317.
- 528 17 Pieterse CMJ, Van Der Does D, Zamioudis C, Leon-Reyes A, Van Wees SCM. Hormonal modulation of  
529 plant immunity. *Annu Rev Cell Dev Biol* 2012; **28**: 489–521.
- 530 18 Koornneef A, Pieterse CMJ. Cross Talk in Defense Signaling: Figure 1. *Plant Physiol* 2008; **146**: 839–844.
- 531 19 Vos IA, Moritz L, Pieterse CMJ, Van Wees SCM. Impact of hormonal crosstalk on plant resistance and  
532 fitness under multi-attacker conditions. *Front Plant Sci* 2015; **6**: 639.

- 1  
2  
3 533 20 Wilkinson SW, Magerøy MH, López Sánchez A, Smith LM, Furci L, Cotton TEA *et al.* Surviving in a  
4 534 Hostile World: Plant Strategies to Resist Pests and Diseases. *Annu Rev Phytopathol* 2019; **57**: 505–529.  
5  
6 535 21 Walters D, Walsh D, Newton A, Lyon G. Induced Resistance for Plant Disease Control: Maximizing the  
7 536 Efficacy of Resistance Elicitors. *Phytopathology* 2005; **95**: 1368–1373.  
8  
9 537 22 Ross AF. Systemic acquired resistance induced by localized virus infections in plants. *Virology* 1961; **14**.  
10 538 doi:10.1016/0042-6822(61)90319-1.  
11  
12 539 23 Sticher L, Mauch-Mani B, Métraux and J. Systemic acquired resistance. *Annu Rev Phytopathol* 1997;  
13 540 **35**: 235–270.  
14  
15 541 24 Spoel SH, Dong X. How do plants achieve immunity? Defence without specialized immune cells. *Nat*  
16 542 *Rev Immunol* 2012; **12**: 89–100.  
17  
18 543 25 Pieterse CM, van Wees SC, Hoffland E, van Pelt JA, van Loon LC. Systemic resistance in Arabidopsis  
19 544 induced by biocontrol bacteria is independent of salicylic acid accumulation and pathogenesis-related  
20 545 gene expression. *Plant Cell* 1996; **8**: 1225–37.  
21  
22 546 26 Pieterse CMJ, Van Wees SCM, Van Pelt JA, Knoester M, Laan R, Gerrits H *et al.* A novel signaling  
23 547 pathway controlling induced systemic resistance in arabidopsis. *Plant Cell* 1998; **10**.  
24 548 doi:10.1105/tpc.10.9.1571.  
25  
26 549 27 Pieterse CMJ, Zamioudis C, Berendsen RL, Weller DM, Van Wees SCM, Bakker PAHM. Induced systemic  
27 550 resistance by beneficial microbes. *Annu Rev Phytopathol* 2014; **52**: 347–375.  
28  
29 551 28 Farmer EE, Ryan CA. Octadecanoid Precursors of Jasmonic Acid Activate the Synthesis of Wound-  
30 552 Inducible Proteinase Inhibitors. *Plant Cell* 1992; **4**: 129–134.  
31  
32 553 29 Délano-Frier JP, Martínez-Gallardo NA, Martínez-De La Vega O, Salas-Araiza MD, Barbosa-Jaramillo ER,  
33 554 Torres A *et al.* The effect of exogenous jasmonic acid on induced resistance and productivity in  
34 555 amaranth (*Amaranthus hypochondriacus*) is influenced by environmental conditions. *J Chem Ecol* 2004;  
35 556 **30**: 1001–1034.  
36  
37 557 30 Mageroy MH, Wilkinson SW, Tengs T, Cross H, Almvik M, Pétriacq P *et al.* Molecular underpinnings of  
38 558 methyl jasmonate-induced resistance in Norway spruce. *Plant Cell Environ* 2020; **43**: 1827–1843.  
39  
40 559 31 Ton J, Van Pelt JA, Van Loon LC, Pieterse CMJ. Differential Effectiveness of Salicylate-Dependent and  
41 560 Jasmonate/Ethylene-Dependent Induced Resistance in *Arabidopsis*. *Mol Plant-Microbe Interact* 2002;  
42 561 **15**: 27–34.  
43  
44 562 32 Van Wees SC, Van der Ent S, Pieterse CM. Plant immune responses triggered by beneficial microbes.  
45 563 *Curr. Opin. Plant Biol.* 2008. doi:10.1016/j.pbi.2008.05.005.  
46  
47 564 33 Thevenet D, Pastor V, Baccelli I, Balmer A, Vallat A, Neier R *et al.* The priming molecule  $\beta$ -aminobutyric  
48 565 acid is naturally present in plants and is induced by stress. *New Phytol* 2017; **213**: 552–559.  
49  
50 566 34 Luna E, van Hulten M, Zhang Y, Berkowitz O, López A, Pétriacq P *et al.* Plant perception of  $\beta$ -  
51 567 aminobutyric acid is mediated by an aspartyl-tRNA synthetase. *Nat Chem Biol* 2014; **10**: 450–456.  
52  
53 568 35 Zimmerli L, Jakab G, Métraux JP, Mauch-Mani B. Potentiation of pathogen-specific defense  
54 569 mechanisms in Arabidopsis by  $\beta$ -aminobutyric acid. *Proc Natl Acad Sci U S A* 2000; **97**: 12920–12925.  
55  
56 570 36 Ton J, Jakab G, Toquin V, Flors V, Iavicoli A, Maeder MN *et al.* Dissecting the beta-aminobutyric acid-  
57 571 induced priming phenomenon in Arabidopsis. *Plant Cell* 2005; **17**: 987–99.  
58  
59 572 37 Cohen Y, Vakinin M, Mauch-Mani B. BABA-induced resistance: milestones along a 55-year journey.  
60

- 1  
2  
3 573 *Phytoparasitica* 2016; **44**: 513–538.  
4  
5 574 38 White RF. Acetylsalicylic acid (aspirin) induces resistance to tobacco mosaic virus in tobacco. *Virology*  
6 575 1979; **99**: 410–412.  
7  
8 576 39 Kogel KH, Beckhove U, Dreschers J, Munch S, Romme Y. Acquired resistance in barley. The resistance  
9 577 mechanism induced by 2, 6-dichloroisonicotinic acid is a phenocopy of a genetically based mechanism  
10 578 governing race-specific powdery mildew resistance. *Plant Physiol* 1994; **106**: 1269–1277.  
11  
12 579 40 Hijwegen T, Verhaar MA. Effects of cucumber genotype on the induction of resistance to powdery  
13 580 mildew, *Sphaerotheca fuliginea*, by 2, 6-dichloroisonicotinic acid. *Plant Pathol* 1995; **44**: 756–762.  
14  
15 581 41 Schweizer P, Buchala A, Métraux JP. Gene-expression patterns and levels of jasmonic acid in rice  
16 582 treated with the resistance inducer 2,6-dichloroisonicotinic acid. *Plant Physiol* 1997; **115**: 61–70.  
17  
18 583 42 Görlach J, Volrath S, Knauf-Beiter G, Hengy G, Beckhove U, Kogel KH *et al.* Benzothiadiazole, a novel  
19 584 class of inducers of systemic acquired resistance, activates gene expression and disease resistance in  
20 585 wheat. *Plant Cell* 1996; **8**: 629–643.  
21  
22 586 43 Benhamou N, Bélanger RR. Benzothiadiazole-mediated induced resistance to *Fusarium oxysporum* f.  
23 587 sp. *radicis-lycopersici* in tomato. *Plant Physiol* 1998; **118**: 1203–1212.  
24  
25 588 44 Benhamou N, Bélanger RR. Induction of systemic resistance to *Pythium damping-off* in cucumber  
26 589 plants by benzothiadiazole: Ultrastructure and cytochemistry of the host response. *Plant J* 1998; **14**:  
27 590 13–21.  
28  
29 591 45 Godard JF, Ziadi S, Monot C, Le Corre D, Silué D. Benzothiadiazole (BTH) induces resistance in  
30 592 cauliflower (*Brassica oleracea* var *botrytis*) to downy mildew of crucifers caused by *Peronospora*  
31 593 *parasitica*. *Crop Prot* 1999; **18**: 397–405.  
32  
33 594 46 Trotel-Aziz P, Couderchet M, Vernet G, Aziz A. Chitosan stimulates defense reactions in grapevine  
34 595 leaves and inhibits development of *Botrytis cinerea*. *Eur J Plant Pathol* 2006. doi:10.1007/s10658-006-  
35 596 0005-5.  
36  
37 597 47 Alexandersson E, Mulugeta T, Lankinen Å, Liljeroth E, Andreasson E. Plant Resistance Inducers against  
38 598 Pathogens in Solanaceae Species-From Molecular Mechanisms to Field Application. *Int J Mol Sci* 2016;  
39 599 **17**. doi:10.3390/ijms17101673.  
40  
41 600 48 Heil M, Hilpert A, Kaiser W, Linsenmair KE. Reduced growth and seed set following chemical induction  
42 601 of pathogen defence: Does systemic acquired resistance (SAR) incur allocation costs? *J Ecol* 2000; **88**:  
43 602 645–654.  
44  
45 603 49 Heil M, Baldwin IT. Fitness costs of induced resistance: Emerging experimental support for a slippery  
46 604 concept. *Trends Plant Sci.* 2002; **7**: 61–67.  
47  
48 605 50 Walters D, Heil M. Costs and trade-offs associated with induced resistance. *Physiol. Mol. Plant Pathol.*  
49 606 2007; **71**: 3–17.  
50  
51 607 51 Walters DR, Fountaine JM. Practical application of induced resistance to plant diseases: An appraisal of  
52 608 effectiveness under field conditions. *J. Agric. Sci.* 2009; **147**: 523–535.  
53  
54 609 52 Bektas Y, Eulgem T. Synthetic plant defense elicitors. *Front Plant Sci* 2014; **5**: 804.  
55  
56 610 53 Dann E, Diers B, Byrum J, Hammerschmidt R. Effect of treating soybean with 2,6-dichloroisonicotinic  
57 611 acid (INA) and benzothiadiazole (BTH) on seed yields and the level of disease caused by *Sclerotinia*  
58 612 *sclerotiorum* in field and greenhouse studies. *Eur J Plant Pathol* 1998; **104**: 271–278.

- 1  
2  
3 613 54 Sharma K, Butz AF, Finckh MR. Effects of host and pathogen genotypes on inducibility of resistance in  
4 614 tomato (*Solanum lycopersicum*) to *Phytophthora infestans*. *Plant Pathol* 2010; **59**: 1062–1071.  
5  
6 615 55 Dietrich R, Ploss K, Heil M. Growth responses and fitness costs after induction of pathogen resistance  
7 616 depend on environmental conditions. *Plant, Cell Environ* 2005; **28**: 211–222.  
8  
9 617 56 Walters DR. Induced resistance: Destined to remain on the sidelines of crop protection?  
10 618 *Phytoparasitica*. 2010; **38**: 1–4.  
11  
12 619 57 Knoth C, Salus MS, Girke T, Eulgem T. The synthetic elicitor 3,5-dichloroanthranilic acid induces NPR1-  
13 620 dependent and npr1-independent mechanisms of disease resistance in arabidopsis. *Plant Physiol* 2009;  
14 621 **150**: 333–347.  
15  
16 622 58 Luna E, López A, Kooiman J, Ton J. Role of NPR1 and KYP in long-lasting induced resistance by  $\beta$ -  
17 623 aminobutyric acid. *Front Plant Sci* 2014; **5**. doi:10.3389/fpls.2014.00184.  
18  
19 624 59 Sós-Hegedús A, Juhász Z, Poór P, Kondrák M, Antal F, Tari I *et al.* Soil Drench Treatment with  $\beta$ -  
20 625 Aminobutyric Acid Increases Drought Tolerance of Potato. *PLoS One* 2014; **9**: e114297.  
21  
22 626 60 Rodriguez-Salus M, Bektas Y, Schroeder M, Knoth C, Vu T, Roberts P *et al.* The synthetic elicitor 2-(5-  
23 627 Bromo-2-Hydroxy-Phenyl)-thiazolidine-4-carboxylic acid links plant immunity to hormesis1. *Plant*  
24 628 *Physiol* 2016; **170**: 444–458.  
25  
26 629 61 Conrath U, Beckers GJM, Flors V, García-Agustín P, Jakab G, Mauch F *et al.* Priming: Getting Ready for  
27 630 Battle. *Mol Plant-Microbe Interact* 2006; **19**: 1062–1071.  
28  
29 631 62 Martinez-Medina A, Flors V, Heil M, Mauch-Mani B, Pieterse CMJ, Pozo MJ *et al.* Recognizing Plant  
30 632 Defense Priming. *Trends Plant Sci.* 2016; **21**: 818–822.  
31  
32 633 63 van Hulst M, Pelsler M, van Loon LC, Pieterse CMJ, Ton J. Costs and benefits of priming for defense in  
33 634 Arabidopsis. *Proc Natl Acad Sci* 2006; **103**: 5602–5607.  
34  
35 635 64 Wang K, Liao Y, Kan J, Han L, Zheng Y. Response of direct or priming defense against *Botrytis cinerea* to  
36 636 methyl jasmonate treatment at different concentrations in grape berries. *Int J Food Microbiol* 2015.  
37 637 doi:10.1016/j.ijfoodmicro.2014.11.006.  
38  
39 638 65 Douma JC, Vermeulen PJ, Poelman EH, Dicke M, Anten NPR. When does it pay off to prime for  
40 639 defense? A modeling analysis. *New Phytol* 2017; **216**: 782–797.  
41  
42 640 66 Walters DR, Fountaine JM. Practical application of induced resistance to plant diseases: an appraisal of  
43 641 effectiveness under field conditions. *J Agric Sci* 2009; **147**: 523.  
44  
45 642 67 Walters DR, Newton AC, Lyon GD. *Induced Resistance for Plant Defense: A Sustainable Approach to*  
46 643 *Crop Protection*. 2014 doi:10.1002/9781118371848.  
47  
48 644 68 Stout MJ, Zehnder GW, Baur ME. Potential for the use of elicitors of plant resistance in arthropod  
49 645 management programs. *Arch Insect Biochem Physiol* 2002; **51**: 222–235.  
50  
51 646 69 Vallad GE, Goodman RM. Systemic Acquired Resistance and Induced Systemic Resistance in  
52 647 Conventional Agriculture. *Crop Sci* 2004; **44**: 1920–1934.  
53  
54 648 70 Bruce TJA, Smart LE, Birch ANE, Blok VC, MacKenzie K, Guerrieri E *et al.* Prospects for plant defence  
55 649 activators and biocontrol in IPM – Concepts and lessons learnt so far. *Crop Prot* 2017; **97**: 128–134.  
56  
57 650 71 Singh UB, Malviya D, Singh S, Kumar M, Sahu PK, Singh H V. *et al.* *Trichoderma harzianum*-and methyl  
58 651 jasmonate-induced resistance to *bipolaris sorokiniana* through enhanced phenylpropanoid activities in  
59 652 bread wheat (*Triticum aestivum* L.). *Front Microbiol* 2019; **10**. doi:10.3389/fmicb.2019.01697.  
60

- 1  
2  
3 653 72 Zehra A, Meena M, Dubey MK, Aamir M, Upadhyay RS. Activation of defense response in tomato  
4 654 against *Fusarium* wilt disease triggered by *Trichoderma harzianum* supplemented with exogenous  
5 655 chemical inducers (SA and MeJA). *Rev Bras Bot* 2017; **40**: 651–664.
- 7 656 73 Abd El-Rahman SS, Mohamed HI. Application of benzothiadiazole and *Trichoderma harzianum* to  
8 657 control faba bean chocolate spot disease and their effect on some physiological and biochemical traits.  
9 658 *Acta Physiol Plant* 2014; **36**: 343–354.
- 11 659 74 de Jong H, Reglinski T, Elmer PAG, Wurms K, Vanneste JL, Guo LF *et al.* Integrated use of  
12 660 *aureobasidium pullulans* strain CG163 and acibenzolar-S-methyl for management of bacterial canker in  
13 661 kiwifruit. *Plants* 2019; **8**. doi:10.3390/plants8080287.
- 15 662 75 Walters DR, Havis ND, Sablou C, Walsh DJ. Possible trade-off associated with the use of a combination  
16 663 of resistance elicitors. *Physiol Mol Plant Pathol* 2011; **75**: 188–192.
- 18 664 76 Reuveni M, Zahavi T, Cohen Y. Controlling downy mildew (*Plasmopara viticola*) in field-grown  
19 665 grapevine with  $\beta$ -aminobutyric acid (BABA). *Phytoparasitica* 2001; **29**: 125–133.
- 21 666 77 Baider A, Cohen Y. Synergistic interaction between BABA and mancozeb in controlling *Phytophthora*  
22 667 *infestans* in potato and tomato and *Pseudoperonospora cubensis* in cucumber. *Phytoparasitica* 2003;  
23 668 **31**: 399–409.
- 25 669 78 Liljeroth E, Bengtsson T, Wiik L, Andreasson E. Induced resistance in potato to *Phytophthora infestans*–  
26 670 effects of BABA in greenhouse and field tests with different potato varieties. *Eur J Plant Pathol* 2010;  
27 671 **127**: 171–183.
- 29 672 79 Sharma KD, Sharma V, Singh R, Nayyar H. Control of chickpea blight disease caused by *Didymella rabiei*  
30 673 by mixing resistance inducer and contact fungicide. *Crop Prot* 2011; **30**: 1519–1522.
- 32 674 80 Kukawka R, Czerwoniec P, Lewandowski P, Pospieszny H, Smiglak M. New ionic liquids based on  
33 675 systemic acquired resistance inducers combined with the phytotoxicity reducing cholinium cation. *New*  
34 676 *J Chem* 2018; **42**: 11984–11990.
- 36 677 81 Chang K, Chen JQ, Shi YX, Sun MJ, Li PF, Zhao ZJ *et al.* The discovery of new scaffold of plant activators:  
37 678 From salicylic acid to benzotriazole. *Chinese Chem Lett* 2017; **28**: 919–926.
- 39 679 82 Buswell W, Schwarzenbacher RE, Luna E, Sellwood M, Chen B, Flors V *et al.* Chemical priming of  
40 680 immunity without costs to plant growth. *New Phytol* 2018; **218**: 1205–1216.
- 42 681 83 Beck C, Oerke EC, Dehne HW. Impact of strobilurins on physiology and yield formation of wheat.  
43 682 *Meded Rijksuniv Gent Fak Landbouwkd Toegep Biol Wet* 2002; **67**.
- 45 683 84 Herms S, Seehaus K, Koehle H, Conrath U. A strobilurin fungicide enhances the resistance of tobacco  
46 684 against tobacco mosaic virus and *Pseudomonas syringae* pv *tabaci*. *Plant Physiol* 2002; **130**: 120–127.
- 48 685 85 Schillheim B, Jansen I, Baum S, Beesley A, Bolm C, Conrath U. Sulforaphane modifies histone H3,  
49 686 unpacks chromatin, and primes defense. *Plant Physiol* 2018; **176**: 2395–2405.
- 51 687 86 Trdá L, Janda M, Macková D, Pospíchalová R, Dobrev PI, Burketová L *et al.* Dual Mode of the Saponin  
52 688 Aescin in Plant Protection: Antifungal Agent and Plant Defense Elicitor. *Front Plant Sci* 2019; **10**: 1448.
- 54 689 87 Slaughter A, Daniel X, Flors V, Luna E, Hohn B, Mauch-Mani B. Descendants of Primed Arabidopsis  
55 690 Plants Exhibit Resistance to Biotic Stress. *PLANT Physiol* 2012; **158**: 835–843.
- 57 691 88 Martínez-Aguilar K, Ramírez-Carrasco G, Hernández-Chávez JL, Barraza A, Alvarez-Venegas R. Use of  
58 692 BABA and INA As activators of a primed state in the common bean (*Phaseolus vulgaris* L.). *Front Plant*

- 1  
2  
3 693 *Sci* 2016; **7**. doi:10.3389/fpls.2016.00653.
- 4  
5 694 89 Rasmann S, De Vos M, Casteel CL, Tian D, Halitschke R, Sun JY *et al.* Herbivory in the previous  
6 695 generation primes plants for enhanced insect resistance. *Plant Physiol* 2012; **158**: 854–863.
- 7  
8 696 90 Cook RJ. Advances in Plant Health Management in the Twentieth Century. *Annu Rev Phytopathol* 2000;  
9 697 **38**: 95–116.
- 10  
11 698 91 Mukherjee PK, Horwitz BA, Herrera-Estrella A, Schmoll M, Kenerley CM. Trichoderma Research in the  
12 699 Genome Era . *Annu Rev Phytopathol* 2013; **51**: 105–129.
- 13  
14 700 92 Faessel L, Nassr N, Lebeau T, Walter B. Chemically-induced resistance on soybean inhibits nodulation  
15 701 and mycorrhization. *Plant Soil* 2010; **329**: 259–268.
- 16  
17 702 93 de Román M, Fernández I, Wyatt T, Sahrawy M, Heil M, Pozo MJ. Elicitation of foliar resistance  
18 703 mechanisms transiently impairs root association with arbuscular mycorrhizal fungi. *J Ecol* 2011; **99**: 36–  
19 704 45.
- 20  
21 705 94 Tosi L, Zizzerini A. Interactions between *Plasmopara helianthi*, *Glomus mosseae* and two plant  
22 706 activators in sunflower plants. *Eur J Plant Pathol* 2000; **106**: 735–744.
- 23  
24 707 95 Lian B, Zhou X, Miransari M, Smith DL. Effects of salicylic acid on the development and root nodulation  
25 708 of soybean seedlings. *J Agron Crop Sci* 2000; **185**: 187–192.
- 26  
27 709 96 Toby Kiers E, Adler LS, Grman EL, Van Der Heijden MGA. Manipulating the jasmonate response: How  
28 710 do methyl jasmonate additions mediate characteristics of aboveground and belowground mutualisms?  
29 711 *Funct Ecol* 2010; **24**: 434–443.
- 30  
31 712 97 Hou X-D, Liu Q-P, Smith TJ, Li N, Zong M-H. Evaluation of Toxicity and Biodegradability of Cholinium  
32 713 Amino Acids Ionic Liquids. *PLoS One* 2013; **8**: e59145.
- 33  
34 714 98 Walters DR, Havis ND, Paterson L, Taylor J, Walsh DJ. Cultivar effects on the expression of induced  
35 715 resistance in spring barley. *Plant Dis* 2011; **95**: 595–600.
- 36  
37 716 99 Perez L, Rodriguez ME, Rodriguez F, Roson C. Efficacy of acibenzolar-S-methyl, an inducer of systemic  
38 717 acquired resistance against tobacco blue mould caused by *Peronospora hyoscyami* f. sp. *tabacina*. *Crop*  
39 718 *Prot* 2003; **22**: 405–413.
- 40  
41 719 100 Audenaert K, De Meyer GB, Höfte MM. Abscisic acid determines basal susceptibility of tomato to  
42 720 *Botrytis cinerea* and suppresses salicylic acid-dependent signaling mechanisms. *Plant Physiol* 2002;  
43 721 **128**: 491–501.
- 44  
45 722 101 Spoel SH, Johnson JS, Dong X. Regulation of tradeoffs between plant defenses against pathogens with  
46 723 different lifestyles. *Proc Natl Acad Sci U S A* 2007; **104**: 18842–18847.
- 47  
48 724 102 Boyle C, Walters DR. Saccharin-induced protection against powdery mildew in barley: effects on  
49 725 growth and phenylpropanoid metabolism. *Plant Pathol* 2006; **55**: 82–91.
- 50  
51 726 103 Walters DR, Paterson L, Walsh DJ, Havis ND. Priming for plant defense in barley provides benefits only  
52 727 under high disease pressure. *Physiol Mol Plant Pathol* 2008; **73**: 95–100.
- 53  
54 728 104 Phuong LT, Fitrianti AN, Luan MT, Matsui H, Noutoshi Y, Yamamoto M *et al.* Antagonism between SA-  
55 729 and JA-signaling conditioned by saccharin in *Arabidopsis thaliana* renders resistance to a specific  
56 730 pathogen. *J Gen Plant Pathol* 2020; **86**: 86–99.
- 57  
58 731 105 Thaler JS, Humphrey PT, Whiteman NK. Evolution of jasmonate and salicylate signal crosstalk. *Trends*  
59 732 *Plant Sci.* 2012; **17**: 260–270.

- 1  
2  
3 733 106 Clarke JD, Volko SM, Ledford H, Ausubel FM, Dong X. Roles of salicylic acid, jasmonic acid, and ethylene  
4 734 in cpr-Induced resistance in arabidopsis. *Plant Cell* 2000; **12**: 2175–2190.
- 5  
6 735 107 Imanishi S, Nakakita M, Yamashita K, Furuta A, Utsuno K, Muramoto N *et al.* Aspirin and salicylic acid  
7 736 do not inhibit methyl jasmonate-inducible expression of a gene for ornithine decarboxylase in tobacco  
8 737 BY-2 cells. *Biosci Biotechnol Biochem* 2000; **64**: 125–133.
- 9  
10 738 108 van Wees SC, de Swart EA, van Pelt JA, van Loon LC, Pieterse CM. Enhancement of induced disease  
11 739 resistance by simultaneous activation of salicylate- and jasmonate-dependent defense pathways in  
12 740 *Arabidopsis thaliana*. *Proc Natl Acad Sci U S A* 2000; **97**: 8711–6.
- 13  
14 741 109 Betsuyaku S, Katou S, Takebayashi Y, Sakakibara H, Nomura N, Fukuda H. Salicylic Acid and Jasmonic  
15 742 Acid Pathways are Activated in Spatially Different Domains Around the Infection Site During Effector-  
16 743 Triggered Immunity in *Arabidopsis thaliana*. *Plant Cell Physiol* 2018; **59**: 8–16.
- 17  
18 744 110 Mur LAJ, Kenton P, Atzorn R, Miersch O, Wasternack C. The outcomes of concentration-specific  
19 745 interactions between salicylate and jasmonate signaling include synergy, antagonism, and oxidative  
20 746 stress leading to cell death. *Plant Physiol* 2006; **140**: 249–262.
- 21  
22 747 111 Darras AI, Joyce DC, Terry LA. Methyl jasmonate and acibenzolar-S-methyl protect cut *Freesia hybrida*  
23 748 inflorescences against *Botrytis cinerea*, but do not act synergistically. *J Horti Sci Biotechnol* 2011; **86**:  
24 749 74–78.
- 25  
26 750 112 Worrall D, Holroyd GH, Moore JP, Glowacz M, Croft P, Taylor JE *et al.* Treating seeds with activators of  
27 751 plant defence generates long-lasting priming of resistance to pests and pathogens. *New Phytol* 2012;  
28 752 **193**: 770–778.
- 29  
30 753 113 Roberts DA. Acquired resistance to Tobacco mosaic virus transmitted to the progeny of hypersensitive  
31 754 Tobacco. *Virology* 1983; **124**: 161–163.
- 32  
33 755 114 Agrawal AA, Laforsch C, Tollrian R. Transgenerational induction of defences in animals and plants.  
34 756 *Nature* 1999; **401**. doi:10.1038/43425.
- 35  
36 757 115 Walters DR, Paterson L. Parents lend a helping hand to their offspring in plant defence. *Biol Lett* 2012;  
37 758 **8**: 871–873.
- 38  
39 759 116 Luna E, Ton J. The epigenetic machinery controlling transgenerational systemic acquired resistance.  
40 760 *Plant Signal Behav* 2012; **7**: 615–618.
- 41  
42 761 117 López Sánchez A, Stassen JHM, Furci L, Smith LM, Ton J. The role of DNA (de)methylation in immune  
43 762 responsiveness of *Arabidopsis*. *Plant J* 2016; **88**: 361–374.
- 44  
45 763 118 Stassen JHM, López A, Jain R, Pascual-Pardo D, Luna E, Smith LM *et al.* The relationship between  
46 764 transgenerational acquired resistance and global DNA methylation in *Arabidopsis*. *Sci Rep* 2018; **8**:  
47 765 14761.
- 48  
49 766 119 Furci L, Jain R, Stassen J, Berkowitz O, Whelan J, Roquis D *et al.* Identification and characterisation of  
50 767 hypomethylated DNA loci controlling quantitative resistance in *Arabidopsis*. *Elife* 2019; **8**.  
51 768 doi:10.7554/eLife.40655.
- 52  
53 769 120 López Sánchez A, Pardo DP, Furci L, Roberts M, Ton J. Costs and benefits of transgenerational acquired  
54 770 resistance in *Arabidopsis*. *Authorea Prepr* 2020.
- 55  
56 771 121 Bruce TJA. Variation in plant responsiveness to defense elicitors caused by genotype and environment.  
57 772 *Front Plant Sci* 2014; **5**. doi:10.3389/fpls.2014.00349.
- 58  
59  
60



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773 122 Walters DR, Havis ND, Paterson L, Taylor J, Walsh DJ, Sablou C. Control of foliar pathogens of spring  
774 barley using a combination of resistance elicitors. *Front Plant Sci* 2014; **5**. doi:10.3389/fpls.2014.00241.  
775 123 Global Industry Analysts Inc. Plant Biostimulants - Global Market Trajectory & Analytics.  
776 2020[https://www.strategyr.com/market-report-plant-biostimulant-forecasts-global-industry-analysts-](https://www.strategyr.com/market-report-plant-biostimulant-forecasts-global-industry-analysts-inc.asp)  
777 [inc.asp](https://www.strategyr.com/market-report-plant-biostimulant-forecasts-global-industry-analysts-inc.asp).  
778

For Peer Review

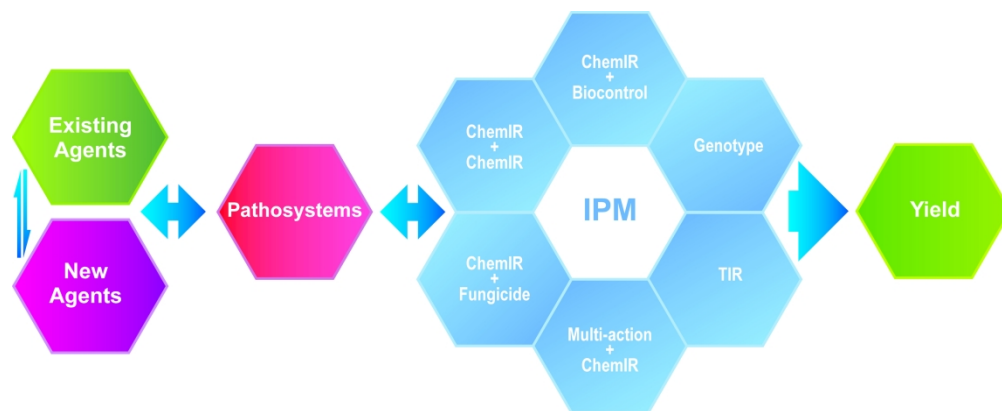


Figure 1: Improving chemical IR efficacy – Existing agents or new agents developed in rational design (Chem-IR) are tested in target pathosystems until effective agent(s) are found. The efficacy can be further improved in combination with other treatments and effective strategies can be further combined. Efficacious treatments can be tested in trans-generationally-primed plants and the cycle repeated until an optimal treatment that can be integrated in to an effective IPM strategy.

136x55mm (600 x 600 DPI)