Fungal Biology 123 (2019) 558–564

Contents lists available at ScienceDirect

Fungal Biology

journal homepage: www.elsevier.com/locate/funbio

Food security in 2044: How do we control the fungal threat?

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ARTICLE INFO

Article history:
Received 18 February 2019
Received in revised form
18 April 2019
Accepted 29 April 2019
Available online 7 May 2019

Corresponding Editor: Ian Singleton

Keywords:
Climate change
Crops
Diseases
Globalization
Integrated disease management (IDM)
Pathogens

ABSTRACT

Plant fungal pathogens place considerable strain on agricultural productivity and threaten global food security. In recent decades, advances in crop breeding, farming practice and the agrochemical industry have allowed crop yields to keep pace with food demand. In this opinion article, we speculate on which recent technological advances will allow us to maintain this situation into the future. We take inspiration that it is 25 y since the first plant disease resistance genes were cloned, and imagine if and how agricultural control of pathogens will be achieved by the year 2044. We examine which technologies are best poised to make the jump from lab bench to field application, and propose that future control measures will likely depend on effective integrated disease management.

1. 25 y of disease resistance genes

In nature, plants face a continuous challenge from a myriad of attackers. In agricultural systems, a combination of mass monocultures that are often susceptible to particular diseases and ideal pathogen growth conditions can lead to disease epidemics that significantly impact crop productivity. Enhancing crop yields in the 20th and early 21st centuries, when a rapidly expanding population demanded significant increases in food production, was achieved through contributions from improved farming practice, the plant breeding and agrochemical industries and advances in plant genetics. How society addresses the issue of food security in a changing environment over the coming years represents one of the major challenges of our time.

The application of molecular methods and recombinant DNA technologies to basic plant research began in the early 1980s. A particularly fertile period for research into plant diseases occurred around 25 y ago in the early 1990s. During this phase, the first plant disease resistance (*R*) genes were cloned and characterised. Beginning in 1992 with the description of the *Hm1 R* gene in maize (Johal and Briggs, 1992) followed closely by *Pto* and *Cf-9*, both from tomato (Jones et al., 1994; Martin et al., 1993), and leading to the description of many others across numerous pathosystems in subsequent years (reviewed Kourelis and van der Hoorn (2018)). The identification and in-depth exploration of *R* gene function both shed light on fundamental mechanisms of plant immunity, and offered huge promise in the reduction or elimination of disease from agriculture. Yet true to form, pathogens have resisted these efforts. Incorporation of disease resistances into breeding programs has met with mixed success. This has been partially due to the narrow spectrum of activity of many of the first R genes to be identified, but also due to political pressure and negative public sentiment towards early generations of genetically-modified (GM) plants.

The promise offered by the original clutch of *R* gene discoveries prompted us to ask; to what extent could those at the coalface of basic research have anticipated the impact these discoveries would have on agriculture 25 y later? To extend this question, can those of us working in the same field in 2019 predict those technologies and discoveries that will impact on agriculture in 2044, another quarter century from now? To address this issue, we briefly summarise

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https://doi.org/10.1016/j.funbio.2019.04.006
1878-6146/

some of the most notable advances in plant disease research of the past 25 y. This summary is not intended to be exhaustive, merely to highlight how far research has progressed since the first *R* genes were characterised. We continue by outlining the most significant challenges facing agriculture today, before speculating to what extent recent advances will allow us to tackle these problems in the coming quarter century.

1.1. What have we learnt since 1994?

The biggest change since the early phase of *R* gene discovery has arguably been the technological advances associated with next-generation sequencing (NGS) and other "'omics technologies". The adoption of these methods has enabled researchers to analyse both plants and pathogens at the genome-wide scale, with the generation of millions of bases of data from single sequencing runs. This era began with significant contribution from the fungal kingdom, with the first eukaryotic genome sequence that of the yeast *Saccharomyces cerevisiae* (~12 Mb) in 1996 (Goffeau et al., 1996). This highly collaborative effort involved researchers from nearly 100 laboratories working over several years using varying sequencing methods available at the time. Nearly a decade later, a smaller consortium released the genome of the first plant pathogenic fungus, the rice blast pathogen *Magnaporthe grisea* (~40 Mb) (Dean et al., 2005). The first plant genome was that of *Arabidopsis thaliana*, completed and published in 2000 (The Arabidopsis Genome, 2000). This would be followed by genome sequencing projects for hundreds of other plant species. Indeed for Arabidopsis, there now exists publically available sequences for thousands of accessions (Alonso-Blanco et al., 2016). As sequencing and computational power has grown, genomic resources have expanded to include numerous crop species with genomes of greater scale and complexity than the ~125 Mb Arabidopsis genome. Recent publication of the reference sequence for hexaploid wheat (15.4–15.8 Gb) being a notable and particularly celebrated achievement (Appels et al., 2018). The driver of this rapid escalation in the amount of genomic data available has been the reduction in cost of sequencing technologies. Whilst sequencing of the Arabidopsis genome took 10 y at a cost of ~$100 m, it is now commonplace for sequencing projects to output hundreds or thousands of equivalent genomes for a fraction of the cost and be the efforts of a single laboratory. Utilising the same technology platforms, whole transcriptome sequencing (RNAseq) has facilitated in-depth analysis of both coding and non-coding portions of plant and fungal genomes. Targeted approaches specifically designed to target gene families known to be involved in disease resistance have taken advantage of these methods to rapidly identify novel sources of genetic resistance in plants. Sequencing-based methods are no longer luxury hypothesis generators. Approaches such as MutRenSeq and AgRenSeq (Arora et al., 2019; Steuernagel et al., 2016) for example, use sequencing technologies as workhorse tools for the rapid identification of novel *R* genes for potential incorporation into plant breeding programs.

The use of model pathosystems has allowed us to better understand the roles of both plant immune receptors and pathogen virulence genes. Shortly after the cloning of *Pto* from tomato, the Guard Model was first described (Van der Biezen and Jones, 1998). This theory, later generalised for all effector proteins (Dangl and Jones, 2001), predicts that *R* gene-mediated resistance is triggered by the activation of R proteins when there is a modification of the "guarded" targets of pathogen effectors. This therefore explains why different effectors can be recognised by the same R protein. In following years, the plant receptor of the bacterial microbial/pathogen-associated molecular pattern (MAMP/PAMP) Flg22 was identified (Gomez–Gomez and Boller, 2000). This led to description of what is known as the "zig zag model" (Jones and Dangl, 2006). This model explains the two different branches of activity of the innate immune system, and differs between pattern recognition receptors (PRRs) that are responsive to MAMPs/PAMPs and R proteins. Moreover, receptor targets and other environmental stimuli were soon linked to induction of resistance. A major milestone in understanding of the plant immune system was the demonstration that salicylic acid (SA) is a plant hormone with a role in plant defence. From its discovery, many other plant hormones, such as jasmonic acid (JA), abscisic acid (ABA) and ethylene (ET) have been described to modulate plant signalling events that fine-tune defence responses against specific pathogens (Bari and Jones, 2009). In addition to innate immunity, the scientific community also speculated on the existence of another layer of defence that could be seen as an adaptive immune system. This phenomenon, known as priming, was first described in 1998 (Thulke and Conrath, 1998). Priming is expressed when after an initial stimulus, that can warn of an upcoming attack, plants are able to activate defence mechanisms faster and/or stronger upon subsequent attack, compared to naive plants (Conrath et al., 2006). The first studies demonstrated that whilst pre-treatment of parsley cell suspensions with SA did not trigger defence gene expression, enhanced expression was observed when cells were subsequently treated with the pathogen *Phytophthora sojae*, in comparison with cells pre-treated with water (Kauss et al., 1992; Thulke and Conrath, 1998). Some of the chemical elicitors that are today associated with the expression of priming were described a long time ago. For instance, the non-protein amino acid b-amino butyric acid (BABA) was first discovered in 1964 during screening for compounds that activate resistance responses in cell cultures (Papavizas, 1964). However, it was not until the early 2000s that researchers demonstrated that BABA-induced resistance was based on priming of different defence signalling pathways (Ton and Mauch-Mani, 2004; Zimmerli et al., 2000). Within a few years of the first *R* gene characterisation, our understanding of plant immune signalling increased immensely. This has presented the opportunity for exploitation of the plant immune system as a tool to fight disease.

Descriptions of the first plant *R* genes (and corresponding pathogen *Avr* genes) made clear the role of protein-coding components of plant and microbial genomes at determining the outcomes of disease interactions. In addition, a series of discoveries in the 1990s and 2000s made clear the importance of RNA-based immunity to plant health. It had long been known that plants subject to viral infection could produce fresh growth that had developed immunity (Wingard, 1928). Plant virologists subsequently identified that transgenic plants expressing untranslatable sections of viral proteins were more resistant to infection than non-transgenic controls (Lindbo and Dougherty, 1992). This indicated that RNA rather than protein could confer antiviral immunity. The seminal discovery of small interfering RNA (siRNA) in plants (Hamilton and Baulcombe, 1999) and latterly microRNA (miRNA) (Reinhart et al., 2002) indicated that RNA could function both as an antiviral immune system and as regulator of endogenous gene expression. Together they became known as small RNA (sRNA) and the phenomenon as RNA silencing or RNA interference (RNAi). Further characterisation of sRNAs revealed huge diversity of non-coding RNA pathways present in plants. This included identification of families of RNA-processing enzymes such as the Dicer-like (DCL) and Argonaute (AGO) ribonucleases that regulate their biogenesis and function as they do in metazoans. The implications of sRNA regulation extended into gene expression, DNA methylation and epigenetics. Indeed, expression of *R* gene families can be subject to sRNA mediated control (Zhai et al., 2011). Knowledge of how RNA silencing mechanisms function in plants has led to technologies such as Virus-Induced Gene Silencing (VIGS) (Ratcliff

et al., 2001) and Host-Induced Gene Silencing (HIGS) (Nowara et al., 2010). VIGS tools have found particular utility amongst basic researchers wishing to explore fundamental gene function in plants via rapid, medium-throughput screens. HIGS has been explored both in terms of a lab tool to interrogate pathogen gene function (particularly for unculturable biotrophic fungi) but also as an applied crop protection strategy. Proof of concept studies demonstrate that transgenic HIGS plants can have increased resistance to fungal pathogens (Nowara et al., 2010). More recently, reports of cross-kingdom RNAi between plants and pathogenic fungi (Weiberg et al., 2013) and spray-induced gene silencing (SIGS) (Koch et al., 2016) have raised the intriguing possibility of RNA-based fungicides for disease control.

Since the first generation GM crops were developed in the 1980s, there has been the pressing need for increased precision for the introduction of mutation or transgenes into elite germplasm. The 2000s saw the development and commercialisation of numerous technologies such as the zinc-finger nucleases (ZFNs) (Urnov et al., 2010), transcription activator-like (TAL) effector nucleases (TALENs) (Miller et al., 2010) and clustered regularly interspaced short palindromic repeats (CRISPR) (Doudna and Charpentier, 2014) as a means of introducing highly-specific genomic changes. Collectively referred to as genome editing, these technologies permit a level of control unimaginable to the developers of early GM crops. They differ from early GM methods as modified plants have the potential to be indistinguishable from those where mutation has occurred randomly by natural processes. TALEN and CRISPR technologies in particular have already been utilised for modification of disease susceptibility alleles against both bacterial and fungal plant pathogens (Li et al., 2012; Wang et al., 2014).

Whilst many of the discoveries and technologies described above have had significant impact in the study of plant pathogens in the lab, many have yet to realise their full potential in commercial agriculture. For control of pathogens in the field we have remained largely dependent on deployment of synthetic fungicides. Chemical control of pathogens has been partly responsible for the significant increase in crop yields in recent decades. The 1990s and 2000s saw the introduction of the broad-spectrum QoI and SDHI classes of fungicides which provided high levels of control against several classes of pathogens, coupled with excellent human and environmental safety profiles (Lucas et al., 2015). Nonetheless, resistance or tolerance to chemical control has unfortunately continued to develop amongst pathogen field populations. This, coupled with a more hostile regulatory environment and a reduced pipeline of new active ingredients suggest the level of control provided today should not be taken for granted in the future.

2. Present and future challenges

One of the biggest challenges facing humanity is the 70 % increase in global agricultural productivity required to feed more than 9 billion inhabitants (Godfray et al., 2010). Crucially, much crop yield is lost to pests and diseases (Savary et al., 2019). Global agricultural losses attributed to fungal and oomycete pathogens is approximately $60bn annually, representing 10–23 % of total yield loss (Fisher et al., 2012). This high percentage takes account of fungicide application (Bebber and Gurr, 2015), currently one of the most effective methods of disease control. An extensive study of the global distribution of crop pests and pathogens demonstrated that the total crop production of an individual country plays the principal role in the likelihood of pathogen emergence. Therefore, increasing crop production is likely to lead to a greater number of pathogens (Bebber et al., 2014), thus acting as a limit to the upscaling of food production. In assessing the challenges agricultural systems will face in the future, we have broadly classified the threats into the following categories:

2.1. Climate change

The success of fungal (and oomycete) pathogens relies on the fact that they are highly adaptable to the environment, can rapidly overcome plant resistance and can become multi-host pathogens thanks to their mixed models of reproduction and large population sizes. Crucially, in 25 y, we are predicted to live on a different planet. Greenhouse gas emissions, particularly CO_2, will continue to rise and will have numerous consequences. For instance, all projections predict that the temperature will continue to rise due to these emissions (IPCC, 2014). This trend, observed since the industrial revolution, seems unstoppable and even under achievable scenarios where emissions are drastically reduced, the temperature is predicted to increase (IPCC, 2014). In 2014, the Intergovernmental Panel on Climate Change (IPCC) published in their Fifth Assessment Report (AR5) that the mean global temperature of the Earth's surface will increase between 0.3 and 0.7 °C in the period 2016–2035, compared to the period 1986–2005 (well-after industrial development). This is perilously close to the values that scientists have calculated as a threshold for stability. The consequences of this raised CO_2 concentration and temperature are endless, including (i) the melting of ice at the poles rising sea levels, (ii) the increase evaporation from land resulting in drought, (iii) meteorological imbalance resulting in extreme weather events and (iv) changes in global sea and land ecosystem harmony. For fungal pathogens, these changes may bring advantages. For example, it has been shown that higher temperatures are linked to enhanced virulence of the rice fungal pathogen *Magnaporthe oryzae* (Onaga et al., 2017). In addition, virulence of the devastating wheat fungal pathogens *Fusarium graminearum* and *Zymoseptoria tritici* were increased at elevated CO_2 concentrations (Váry et al., 2015). In this study, the authors tested the effect of enhanced CO_2 on expression of plant defence mechanisms and found differences in the capacity of plants have to mount effective responses against both pathogens. Worryingly, many studies have now proven the additive effect of different abiotic stresses on plant immunity. For instance, responses to simultaneous temperature and drought has been shown to be important in many plant species (Fahad et al., 2017; Rizhsky et al., 2004) and altered rainfall regimes, where flooding or drought periods occur unexpectedly, has been demonstrated to trigger changes in pathogen infection and plant defence strategies (Swinfield et al., 2012). Therefore, impacts of climate change on both pathogen virulence and plant resistance must be further examined. In addition, global climate change will expand the habitat ranges of many pathogens, making previously uninhabitable regions vulnerable to invasion.

2.2. Globalization

We now live in a highly interconnected world. Mass movements of people between countries are frequent, international air travel is affordable to many and millions of tonnes of livestock, plant material and other goods are shipped across the globe each year. These human-driven factors facilitate the emergence of new agricultural threats (Fisher et al., 2012). Mathematical models have estimated the risks climate change and globalization in the potential emergence of a new disease. Whereas climate change was assigned as medium-low risk, globalization was identified to have a large-medium risk (Dehnen-Schmutz et al., 2010). The reasons for this high risk potential is the dynamism of the agricultural production system, and consequently disease, portability that ultimately makes plants the best vehicles for diseases. Therefore, in the next

25 y, the combined impact of climate change and globalization will expand the areas of the world classified as at high-risk of disease outbreak (Bebber et al., 2013).

2.3. Pathogen evolution and crop monocultures

Agricultural systems are highly vulnerable to the emergence of new strains of pathogens. The deployment of single *R* genes in monoculture crops, or over-reliance on chemical control applies selection pressure that quickly leads to the evolution of highly adapted strains. Moreover, pathogen evolution and its capacity to adapt to different climate conditions drive infections in new host plants (Warman and Aitken, 2018). In the past few decades, we have already seen different disease emergence scenarios that have been proven catastrophic. For instance, the emergence of new highly virulent strains of the oomycete pathogen *Phytophthora infestans* invokes memory of the devastated potato harvests witnessed during the Irish Famine of the 1840s. The strain Blue13, first identified in the Netherlands in 2004, has now been identified in many countries in Europe, including the UK. This represents a high-level threat for Solanaceous crops due to the limited effect of fungicides (Schepers et al., 2018). In addition, panama disease of banana, caused by the fungal pathogen *Fusarium oxysporum*, has evolved and spread across many regions of Africa resulting in the devastation of plantations (Warman and Aitken, 2018). The incidence and destruction capacity of *F. oxysporum* in bananas is linked to crop monocultures, as technically 100 % of the exported bananas belong to the same cultivated variety, known as Cavendish. Surprisingly, this is not the first time that we see this event. In the 1950s, worldwide banana production was compromised due to another strain of the same pathogen, the Tropical Race 1 (TR1) strain, which forced the replacement of banana cultivar Gros Michel with the (at the time) resistant Cavendish cultivar. How is it possible that after such major disruption in banana production, and with more than 1000 wild banana varieties available, clones are still the only method of reproduction for this crop? The answer most likely lies in the fact that agricultural intensification seeks the most uniform and consistent production phenotypes (e.g. similar size fruit, similar height trees) which then benefits from clonal plantations. Uniformity and standardization result in reduced genetic variability through the intensive exploitation of monocultures, thus greatly expediting spread of disease.

2.4. Legislation

As described above, fungal pathogens are largely controlled by the use of fungicides. However, their use is increasingly regarded as unsustainable. Recently, the Europe Union (EU) has legislated against the use of many pesticides due to toxicity to human health and the environment (Directive 2009/128/EC, 2009). This direct control over how agrochemical companies market their products within the EU, and making it more difficult to import products originating from outside EU borders, means European farmers cannot rely on the use of pesticides to stop the spread of emerging pathogens. Crucially, current legislation has led to the withdrawal of copper-based fungicides in standard farming, currently used to effectively control various fungal diseases in mainland Europe. All these limitations in the use of pesticides, even when required to achieve sustainable food production, represent a major perturbation to the agricultural system that leaves the market in a position of deep bio-insecurity. It is estimated that the ban on certain pesticide products will represent a 36 % drop in UK farming profits (NFU, 2019). Apart from fungicide application, the use of disease resistant crop varieties has proven highly effective in the past few decades. Classical breeding techniques are still carried out with major success although improvements tend to be incremental. Scientific development has brought new techniques, such as GM Organisms (GMOs) and gene editing strategies such as CRISPR-Cas9 that could speed up the development of new varieties or lead to a step-change in efficacy. Whilst these techniques have huge potential for agritech development, opposition lobby groups and ultimately legislation have prevented their full exploitation. GM crops have always been placed under very strict legislation in the EU. Very recently, the EU controversially incorporated CRISPR-Cas9 technology into the genetically modified category, therefore considering modern gene editing techniques the equivalent of thirty year-old GM technology, despite the vast differences in methodology, precision and end-product. This ruling significantly undermines its use in a commercial setting (Court of Justice of the European Union, 2018).

3. A variable future ahead

By 2044, the world will have changed significantly. It is likely that recent research will impact dramatically on how we grow plants, what we eat and how we interact with the environment. Some things are clear: the planet will be warmer, atmospheric CO_2 will be higher and globalization will have embraced even more of the world's growing population. Will current developments be enough to feed a high-quality, nutritious diet to a global population approaching 9.5bn individuals? Do we need another green revolution that brings a breakthrough in crop protection? Are we pointing research to the right direction that will allow us to achieve those goals?.

In our opinion, it is unlikely that a silver bullet exists to solve the diverse range of issues presented here. Our success therefore is dependent on our capacity to control pathogen mobility, adaptation and evolution. Considerable resources are expended to prevent the spread of pathogens across international borders with a good degree of success. However, measures that restrict pathogen movement cannot solve problems related to rapid pathogen adaptation and evolution. Therefore, which recently developed technologies will allow us to overcome the pathogen threat? Here we speculate on a handful of leading candidate technologies, and make a light-hearted prediction at their adoption into agricultural practice by the year 2044.

3.1. Omics technologies

Genome sequencing (and other omics platforms) have transformed the speed and scale of work performed in basic research. In addition, genome editing has provided a step-change in the ability of researchers to introduce highly specific genetic alterations in lab-scale experiments. The coming years will test the extent to which these technologies can guide and inform agricultural decisions. For farmers in 2044, sequencing-based diagnostics of field samples will be possible in close to real-time. This will provide information related to the diversity of pathogen populations such as effector gene repertoire and fungicide sensitivity profiles. This will inform on how local fungal populations are evolving, guiding both planting decisions of crop varieties that harbour robust resistance or informing farmers of the most effective chemical treatments available for targeting particular pathogen races in their crop. For plants, sequencing technologies will have facilitated creation of libraries containing diverse *R* genes from wild relatives of the world's most important crops. How effectively this resource will have been integrated into practice remains linked to both technical and legislative issues surrounding gene editing. These technologies will offer novel ways to incorporate multiple resistances in a gene stacking approach without the yield penalties associated with

conventional breeding. Given the progress made in such short time, it is inevitable that technical challenges associated with incorporation of complex *R* (or other) gene stacks will be overcome. However, the biggest question remains how this technology will be regulated. It is likely that the ultimate societal impact will be determined by political decisions in different regions of the world *(Impact score in 2044: 8/10)*.

3.2. Plant immune priming

It could be argued that in global terms, any strategy that allows a pathogen to reproduce will eventually fail to prevent adaptation or evolution. Exploitation of the plant immune system, even if it represents a very sophisticated way to provide protection, is not likely to restrain pathogens for generations to come. The reasons for this are that (i) priming can bring side effects due to crosstalk effects between hormonal signalling pathways (e.g. relocation of energy resources allocation in the plant or enhanced susceptibility to other pathogens) and (ii) the expression of priming rarely provides 100 % protection, which could allow pathogens to complete their life cycles and therefore adapt or evolve (Impact score in 2044: 6/10).

3.3. Mixed planting & other agricultural practices

Similarly, the use of monocultures should be avoided, as if new strains evolve to overcome plant resistance, a barrier of plant genetic diversity could potentially slow down or even hinder the spread of a pathogen. Exploiting this concept, the scientific community is increasingly referring to the need of mixed cultivations. It has been demonstrated that even if the number of diseases in mixed plots is higher than in monocultures, the incidence of those diseases is reduced as it cannot properly spread (Mulumba et al., 2012). This concept, comparable with what we know in humans as herd immunity, ultimately provides physical and molecular barriers against pathogenic infections. However, the use of mixed planting will present significant challenges to the food production chain. For example, mixed planting of wheat cultivars by farmers may be incompatible with the needs of millers, who require homogeneity in their raw materials in order to guarantee their end-product. In addition, other agricultural practices may be specifically deployed depending on pathosystem. For example, the wheat stem rust pathogen (*Puccinia graminis* f. sp. *tritici*) reproduces asexually on wheat and must infect a secondary host (barberry) to complete the sexual part of its life cycle. Limiting barberry planting in proximity to wheat crops limits the rate of sexual reproduction (and evolution) and slows the rate at which the pathogen can overcome presently resistant varieties. Such a strategy has proved tremendously successful in the US and Europe, and great care must be taken not to relax these practices and allow the pathogen to regain a foothold (Impact score in 2044: 9/10).

3.4. Microbiomes & biocontrol

Despite our focus on plant diseases, not everything microbial is pathogenic, and plants rely on interactions with other microorganisms to remain healthy. In recent years, there has been a bloom in the research that links the plant microbiome (defined as the entire microbial community associated with an organism) to different phenotypes, including disease resistance. For instance, it has been shown that beneficial microorganisms present in natural microbiomes have been linked with an enhanced growth, yield and disease resistance (Mueller and Sachs, 2015). Recently, the role of plants in the establishment of a root microbiome has been identified: Stringlis and colleagues have demonstrated that the exudation of coumarin promotes the formation of an specific microbiome with the capacity to increase plant health (Stringlis et al., 2018). How do mixed plantations affect microbial community? Can different strategies designed to prevent pathogenic infections hinder the establishment of beneficial microbial communities associated with plants? Or by contrary, can different plant species attract a much higher number of microorganisms that would provide a “richer microbiome” with better protective characteristics? Further researcher is certainly needed in this topic to increase our understanding of how specific plant species modulate their root microbiome for their benefit. This will be crucial for our advancement in crop protection against fungal pathogens. (Impact score in 2044: 7/10).

3.5. Conventional agrochemicals

In 25 y the legislation surrounding use of conventional fungicides in will be considerably stricter than today. The use of Maximum Residue Limits (MRLs, i.e. threshold values of residues that can be found in a food product) make the use of these type of chemicals unappealing. For instance, many fungicides will no longer be used in a post-harvest setting due to very low MRLs. Regulation through MRLs occurs in a highly dynamic way, which means that the agritech industry needs to rapidly adjust to new standards and protocols, as well as develop new effective products to protect their crops. If no sufficient level of innovation is achieved, there may have to be transition to use of less effective chemical products to comply with regulations. The development of next-generation SDHI fungicides will provide protection in the short run, however reports of field resistance to these products have already emerged (Yamashita and Fraaije, 2018). Unless other “blockbuster” active ingredients with exemplary safety profiles were to be developed, then farmers in 2044 will have to be considerably less reliant on chemical control than in 2019. (Impact score in 2044: 4/10).

3.6. Novel agrochemicals

RNA-based fungicides are an appealing alternative to the gradual loss of control currently being witnessed with conventional fungicides in agriculture. RNA fungicides have been demonstrated in proof-of-concept studies against major pathogens such as *B. cinerea* and *F. graminearum* amongst others. In addition, one might assume that environmental toxicity issues might be less concerning for RNA-based control than for conventional fungicides. Finally, the issue of fungicide resistance could be countered by the rapid custom redesign of RNA molecules to target a panel of other essential fungal genes. Nonetheless, there are a number of obstacles in the way of the widespread adoption of this technology. It has yet to be demonstrated that the quantities of bioactive RNA molecules required can be manufactured at a cost that would make this technology economically viable. In addition, it would be unwise to assume that this technology would have similar efficacy across all pathosystems. Recent reports indicate that some pathogens such as *Z. tritici* appear unaffected by application of potentially toxic sRNA molecules. Others such as *U. maydis* lack the functional RNAi machinery to effectively silence essential fungal genes. In our opinion, fundamental differences in evolutionary history and how different species of fungi interact with nucleic acids in their environment will limit the utility of this technology to niche applications. *(Impact score in 2044: 5/10)*.

4. Conclusion: towards tailored-made integrated disease management

Similar to Integrated Pest Management (IPM), Integrated Disease Management (IDM) is defined as a combination of strategies that

aim to reduce levels of disease below a point of injury. This combined approach determines that where possible, the least disruptive control methods should be utilised as a priority. However, considering the need to prevent pathogen reproduction and limit rate of evolution as discussed above, there is not a “one size fits all” approach to achieve this aim. Strategies need to be developed that keep the level of damage under a threshold that prevents pathogen reproduction. Tailor-made and comprehensive IDM programs will increase our chances of success but many factors must be taken into consideration during planning. This need has already been acknowledged by scientists and work to develop multi-approach strategies has already began (Luna, 2016). How will specific environments alter pathogen performance or behaviour? What changes can be expected in the spatial and temporal distribution of individual pathogen species? How will the plant immune system adapt to new climate events? What are our most effective weapons and what are the potential tradeoffs? Some of these questions still remain unanswered. However, research is advancing towards providing information that will lead to the development of informed solutions. It is our opinion that the most effective control of fungal pathogens in crops will be achieved through a combination of many of the techniques and tools discussed in this article. Farmers may need to make changes to the way they plant, rotate and manage their crops. Plant breeders and scientists will need to cooperate to produce innovative ways of incorporating novel and more robust forms of disease resistance. The agrochemical industry will have to adapt to a harsher regulatory environment, and with a pipeline that promises fewer novel active ingredients. Finally, legislators must listen to concerns of scientists, farmers and stakeholders when making important decisions on rulings related to agritech.

Viewed holistically, this challenge can seem rather daunting. However, globalization not only works towards increased mobility of goods and people (or the spread of pathogens!), but also towards facilitating knowledge exchange. Exploiting this precious movement of information will speed up the development of these urgently needed strategies through an integrated exchange of knowledge and best practice.

Acknowledgements

This work was funded by the BBSRC Future Leader Fellowship BB/P00556X/1 and BB/P00556X/2 and a Rank Prize Funds New Investigator Award to E.L. The JABBS Foundation supports the Birmingham Institute of Forest Research and both GJK and EL.

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