9 The Future Prospects for Fungicides and Fungal Disease Control

Key Points

- The incessant rise in food demand means that all reliable methods of crop protection must be deployed at full efficiency.
- Global warming and biosecurity failures are likely to further impact crop protection.
- Many existing fungicides are likely to be phased out due to regulatory challenges.
- Fungicide resistance demands that resistance management strategies are used – this increases the need for new actives with new MOAs.
- The pipeline for new actives is working but at ever-increasing cost. Genomics and molecular modelling are likely to have an increasing impact.
- IDM will become standard practice. Better methods to select genetically resistant crops will bear fruit.
- Transgenic (GM) methods to deliver disease resistance have not developed due to public reluctance to accept transgenic crops.
- Developing genetically modified (GM) traits to replace or more likely supplement fungicides will require a major research effort.

Food Demand and Disease Threats

The world's population is growing at a faster pace than ever before and looks set to increase until at least 2050. The population needs to be fed and needs somewhere to live. Hence more food needs to be grown on less land with less water. To reduce the levels of food insecurity that already exist in parts of the world and to prevent food deficits occurring in more productive regions, efficient and effective methods of crop production must be introduced and maintained.

There are many reasons to believe that the disease pressure on the crops will increase. Global warming will have varied and rather unpredictable effects on crop diseases (Carlton *et al.*, 2012; West *et al.*, 2012) but generally will decrease food security. Global warming and ever-increasing international travel and trade will reduce or even eliminate the power of national quarantine agencies to keep exotic pathogens out of their countries. History teaches that plant pathogenic fungi will always challenge our ability to produce food in quantity and of an acceptable quality. In adopting the highly efficient practice of crop monoculture, the risk of crop failure from plant diseases has increased from something of occasional and marginal importance that could be sustained in an unsophisticated society, to a serious and continual problem often resulting in devastating yield losses and widespread social disruption.

Although the introduction of monocultures provided crop pathogens with an ideal environment in which to multiply, the situation in some crops was exacerbated by techniques that were subsequently adopted to manage other problems. In cereals, the drive to increase yield through the use of improved varieties and higher fertilizer inputs highlighted the value of good weed control. The ensuing spiral towards higher yields through the increasing use of fertilizers and herbicides eventually hit the yield-limiting factor of plant disease. Fungicides allowed yet more fertilizer to be used, to achieve even greater yields.

The effects of crop disease cannot be trivialized because they are never far away. Current estimates suggest that without fungicides we would lose up to one-third of yield, depending on the crop. In some circumstances, total loss is possible. Even in Europe, famine and food shortage were only a few harvests ago and the threat of their return has not disappeared. This reality necessitates the use of crop protection management systems that contain fungicides as an integral component.

The development and use of fungicides in crop protection is a success story. It is a story that has developed from their earliest and crude application in agriculture and horticulture, through a series of technological evolutionary steps, to a point where products are able to exert safe, broad-spectrum control for extended periods, or to work precisely to protect against attack by specific pathogens, or even to influence the host itself to combat infection. However, the process of improvement in crop disease management continues and the next 20 years are likely to witness even greater changes in fungicide technology and use.

Loss of Existing Fungicides

We have already seen (Chapter 8) that regulations initiated in Europe have led to the withdrawal of many active compounds. The ever-tightening regulatory demands, at least in Europe, will increase the pressure on the remaining compounds. The DMI group is already under serious threat and its loss could have a massive impact on the quantity and quality of food production worldwide.

Fungicide resistance preceded the withdrawal of the MBC class of fungicides by some years. Other fungicides afflicted significantly by resistance (see Chapter 6), including the DMI, QoI, PA, CAA and SDHI groups, remain in use. Indeed, predictions that QoIs would become useless through resistance have proved very wide of the mark. Instead fungicide resistance management strategies have ensured their continued use. The strategies involved mixtures and alternations of fungicides. Hence there is a strong demand for new fungicides to fulfil roles in resistance management.

The Discovery Process

The pace of fungicide discovery shows no sign of slowing up (Chapter 4). Instead, new actives and new MOAs are being as released as fast as ever. This may be because the consolidation of fungicide discoveries into ever fewer but larger companies (Syngenta, BASF and Bayer) has increased the efficiency of the discovery processes.

Nonetheless, the low-hanging fruit have been picked. The unique biomolecules in fungi, particularly the ergosterol biosynthesis pathway, have been thoroughly examined for fungicide targets. It seems inevitable that newer fungicides will require a more expensive discovery pathway than existing ones.

Genomics has not yet had a profound impact on the processes of fungicide discovery. However we now have the situation in which the genome sequences of all relevant organisms, both the target fungi and the non-targets, are obtained or could be with only trivial effort. It is therefore possible to imagine a genomics-led discovery process in which molecules will be designed only to bind and inhibit key enzymes in the fungi and have no effect on non-target organisms. This is theoretically more straightforward than designing a pharmaceutical for a non-infectious human disease. Such a development would require a major effort in genomics and automated protein structure prediction.

Genetic Disease Control

Crop diseases are exceptional events, as all plants have natural defence systems to repel most fungal challenges. Molecular plant breeding allows breeders to combine in one cultivar all the best alleles of disease resistance genes as well as other desirable traits, as long as markers for the genes of interest have been discovered. Despite the fact that genome sequences for many major crops are now available, this process has not progressed as fast as was predicted and, to date, only major resistance gene markers are in general use. The quantitative and minor genes typical of so many resistance phenotypes have been harder to pin down. Developing the understanding of pathogenicity mechanisms in more fungi and better genomic resources for more crops will accelerate this process.

Transgenic (GM) Disease Control

Mechanisms that permit the transfer of alien genes into plants have been available for over 25 years (Binns, 2002). Several characteristics have been researched in breeding programmes, such as nitrogen fixation, drought tolerance and the modification of protein components and their storage. The GM technologies were new and deemed to be commercially risky, so the chemical companies pursued only the biggest markets with the greatest profit potential. Hence the great majority of GM crops released to date involve genes for herbicide resistance and for insect tolerance. Resistance to viruses has also been successfully deployed.

As long ago as 1991, it was shown that the expression of alien genes controlling hydrolytic enzyme activity in transgenic tobacco and oilseed rape resulted in increased resistance to infection by *R. solani* (Broglie *et al.*, 1991). Many other traits have been examined and tested in laboratory-scale experiments but, to date, no commercial crops with transgenic disease resistance have been released (Logemann *et al.*, 1992; Toubart *et al.*, 1992; Gurr and Rushton, 2005).

The reasons for this glaring failure are partly scientific but also partly political. Developing a GM disease resistance trait is beset with many of the same difficulties as developing a new fungicide; the GM trait should generate good levels of disease resistance against a wide spectrum of pathogens and should be safe. Research was carried out on a wide scale in both university and chemical company laboratories.

Indeed, many chemical companies bought seed companies so as to have a route to market the new disease resistance traits.

The first major disease resistance genes (R-genes) were cloned and analysed around 1994 (Jones *et al.*, 1994; Hammond-Kosack and Jones, 1997). The first thought was to express these genes in other plants to see whether they conferred resistance. However, it soon became apparent that R-genes were very specific and only worked in the species or at best the family from which they were derived (Gurr and Rushton, 2005). Hence this route has limited spectrum and has not attracted sufficient commercial interest.

Activation of resistance genes during infections leads to the production of a defence response which somehow kills the fungus (Anderson *et al.*, 2005). So-called PR (pathogenesis related) genes producing chitinases and glucanases were among the induced genes. The release of active oxygen was also involved. Hence many people pursued the idea that enhanced expression of these genes would lead to resistance. This strategy has been undermined to some extent by the growth reductions seen in plants expressing PR proteins that outweigh the potential benefit of disease resistance.

Another line of thought was to deploy antifungal proteins in transgenic plants (Jach *et al.*, 1995). These are diverse proteins with potent activity against several fungi. However such traits have failed the very stringent animal toxicology tests.

The latest research involves the use of RNA interference to inhibit the expression of fungal genes essential for infection (Nowara *et al.*, 2010; Duan *et al.*, 2012; Panwar et al., 2013). The mRNA is targeted by a short RNA molecule that is complementary in sequence. This creates a short stretch of double-stranded RNA (dsRNA). dsRNA is efficiently detected in plants by a set of enzymes that cleave the RNA and inactivate it before it is translated into proteins. This is a very promising technology that can be delivered either by direct delivery of RNA molecules instead of a chemical fungicide or via expression of the RNA in the infected plant tissue. The proponents of this technology predict its widespread use in the next 5–15 years. It seems likely that a combination of chemical, conventional genetic and GM traits using antifungal genes, signalling molecules and RNA interference will become the norm in the next decades.

Developments in GM disease resistance have so far failed to progress to market. The scientific questions are tough but surely would have been solved had the level of investment present through the 1980s and 1990s been maintained. However the backlash against GM products that emerged in Europe in 1996 following the 'mad-cow disease' outbreaks caused both public- and private-sector organizations to cut back investments in this area. GM herbicide- and insect-resistant crops have been grown on a huge area and no deleterious effects have been reported. Nonetheless, no relaxation of the regulations has been forthcoming albeit there are signs of reduced anxiety at the moment. We will see whether investment now increases to exploit the potential of the GM disease resistance market.

Market Development

The last decades have seen a major consolidation in the fungicide market. Currently only three major companies are engaged in the full range from discovery to marketing.

A further merger within these companies seems unlikely. It is also hard to imagine how a new company could enter the market for conventional fungicides. Generic manufacturers are increasing in number and global importance, especially as China, India and many other tropical and semi-tropical countries become both fungicide users and manufacturers. There is the potential for new companies to enter the arena through the provision of GM traits, but the extremely demanding regulatory burden makes this unlikely. Clearly, the future for fungicide discovery is firmly fixed within a few very large companies.

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