

Mini Review

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Toward an Individualized Medicine Model for Plant Health

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Introduction

Plant pests and pathogens, and the damage they cause, have a great impact on both human and plant health. Pest and pathogen effects include yield reductions of ~40% worldwide due to direct damage, a reduction in food quality, and decreased food safety due to pesticides that can impact the health of workers who apply them and people who consume residue contaminated food. The approaches we use for managing diseases in humans and crops varies greatly.

It is interesting to contrast the differing approaches to health management for plants versus people and animals. Disease management in humans focuses on treating individuals while treatment of disease in crops focuses mainly on treating populations of plants, usually with fields as the functional unit treated. The main driver of these differences is cost, where relatively high costs to test, diagnose, and treat individuals is the norm with humans and animal disease. In contrast, the low return on investment for agricultural producers demands that entire fields be protected from disease at relatively low cost to so that food production can remain profitable. Indeed, pest and disease management in agriculture can result in abandonment of fields that cannot be treated cost effectively.

Technological advances, especially in next generation sequencing (NGS) and RNA interference (RNAi), are increasing the

efficiency of managing crop pests and pathogens and are likely to move us toward an individualized medicine model for management of plant health in agricultural systems. While these approaches are currently cost prohibitive for commodity scale crops, some of these technologies are becoming cost effective for high value crops, especially vegetatively propagated crops where the value of mother plants that clones are derived already justify the expense high intensity disease management approaches. As costs come down over time, these technologies are also likely to find their way into lower value vegetable and commodity crop production systems.

Disease surveillance to prevent disease establishment is one of the main methods for protecting crops where NGS will have a growing impact over the near-term impact. And as an increasing focus on sustainability continues to decrease pesticide use, novel approaches for pest and disease control like RNAi will find broader application. And while sustainability is a laudable goal, consumer demand for softer food and more sustainable food production systems will accelerate this trend.

Next Generation Disease Surveillance

Current disease screening systems are cumbersome as they require a separate specific test for each pathogen screened for which can result in 5-10 or more ELISA and PCR assays being



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utilized for pathogen testing. Further, all of these tests have the limitation of being specific to the pathogen tested for and therefore blind to other pathogens not tested for. Next generation sequence offers the potential to identify all pathogens in a sample by using bioinformatics approaches to sift through genome scale sequence data to find pathogen specific sequence signatures. Proof of principal level work has shown promise for using NGS based surveillance systems for agricultural pests and diseases [1,2]. This early success suggests these systems will be more widely adopted as the technology improves and the cost comes down.

The largest current challenges to using NGS for pathogen screening are the difficulty in sifting through large data sets that are populated with mostly host sequence to find the “needle in a haystack” pathogen signatures, and the cost of NGS sequencing. Improvements in bioinformatics routines, as well as the increasing number and quality of host genome sequences that can be used to subtract host sequences out of datasets, will continue to improve the efficiency of this approach. While NGS sequencing is still more expensive than a single ELISA or PCR assay, the ability to multiplex for many pathogens in a single NGS run, combined with the possibility of barcoding individual plant samples so that several can be included in a single NGS run, are already making NGS based pathogen detection systems cost competitive in situations where multiple pathogens need to be screened for. NGS based systems also have the advantage of potentially finding all of the pathogens present, including new and unexpected pathogens as well as never seen before variant strains, whereas ELISA and PCR based assays are limited to the specific pathogens identified by the particular anti-sera or primer sets used.

Since viruses have a small number of genes that should be relatively easy to screen for, and because they replicate to relatively high levels, NGS systems for virus screening are likely to be adopted first. The fact that pathogen signatures are spread over a much larger number of genes in bacteria and fungi make these pathogens more difficult to screen for. However, NGS screening for bacterial and fungal pathogens will improve as the ability to subtract host sequences out of NGS datasets improves and the representation of bacterial and fungal pathogen sequences in databases increases.

Even at current price points NGS based pathogen detection schemes are likely to provide an economic benefit to high value crops and in some select settings for vegetable crops. High value crops that are propagated vegetatively via cuttings from a small number of high value mother plants such as wine grapes, citrus stock, cannabis, and similar are likely to have a positive ROI for NGS based screening systems today. As costs come down and efficiency goes up, NGS based pathogen screening systems are also likely to find broader utility in lower value crops, especially in production systems that rely on vegetative propagation or mass-produced seedlings like those commonly used in potato and tomato cultivation.

RNAi moves toward mainstream

While improved surveillance systems are likely to decrease disease introductions in the future, agricultural producers will still have to treat disease outbreaks that will inevitably end occur

in production fields. All while sustainability concerns are leading continuing to reductions in synthetic pesticides available for use as with current attempts to limit or ban the use of neonicotinoid insecticides [3].

Thus, growers are likely to have fewer chemical tools for treating disease in crops in the future, as well as increased incentives for adopting consumer friendly alternatives to synthetic pesticides.

RNAi is a promising alternative to synthetic pesticides for managing pests and diseases in a sustainable manner. RNAi works by down regulating expression of target genes and can be create pathogen resistance by “turning off” (greatly reducing) expression of essential pathogen genes [4]. This is accomplished by using double stranded RNA to induce the RNAi pathway.

The benefits of RNAi based approaches include high target specificity, low off target effects, and low human / environmental risk. RNAi has been used to effectively control a variety of plant pathogens for a little over two decades. It has been especially effective against viral pathogens. For most of this time, genetic engineering has been used introduce genes that express dsRNA molecules in plants. Consumer resistance to GMO crops has severely limited the adoption of this approach. While not broadly utilized, GMO plants with RNAi based virus resistance have found their way to market in a few isolated cases like common beans engineered for RNAi based resistance against Bean Golden Mosaic Virus which have been approved for use in Brazil [5,6].

While much of the early RNAi based resistance, work focused on plant viruses, more recent work has shown that RNAi can also be used to confer resistance to fungal pathogens and insect pests. This is achieved by expressing a dsRNA that targets an essential gene in the fungus or insect. In many cases, this dsRNA is taken up and silences the gene in the fungus or insect. This approach has been shown to be effective for several widely varied insect pests and fungal pathogens [7,8]. This technology has matured to the point of commercialization with the release of a corn line that expresses an RNAi molecule which targets an essential gene in corn root worm in 2022 (Smartstax-pro, Bayer Crop Sciences, <https://traits.bayer.com/corn/Pages/SmartStax-PRO.aspx>).

Moving forward, the promise of RNAi to confer synthetic pesticide free resistance to a variety of pests and pathogens will largely be limited by consumer acceptance, at least over the near term. As with other genetically engineered traits, RNAi based pest and pathogen control strategies are likely to be readily adopted in crops used for animal feed and fiber (corn, cotton, and soy). However, until consumer resistance to GMO crops is overcome RNAi based solutions will be slow to be adopted for crops that are consumed by humans. The fact that RNAi technology will reduce synthetic pesticide use is likely to be a main point in overcoming consumer acceptance of GMO food crops.

Consumer resistance to GMO crops has spurred development of methods to apply RNAi technology without the use of genetically engineered plants. Bacterial mediated and spray delivery are two promising methods delivering RNAi inducing dsRNA's into plants without the use of genetic engineering [9,10]. Spray induced gene

silencing (SIGS) is particularly promising since it would not involve the use of engineered bacteria for delivery of dsRNA's to plants [11]. These GMO-free delivery methods also have the advantage of increased flexibility since the dsRNA sequence can be altered much more quickly without the lag time associated with GMO plant development. This flexibility is likely to allow SIGS to be adapted to specific strains of the pest or pathogen targeted in near real time, potentially on a field by field or potentially even plant by plant basis in the case of high value mother plant that crops are clonally propagated from.

Conclusion

Advances in technology will contribute to paradigm shifts in disease screening and treatment in the near future. These advances will include expanded use of NGS for pest and pathogen surveillance as well as RNAi based approaches for pest and pathogen management. These advances will increase the efficiency of pest and pathogen control while also increasing the sustainability of agricultural production. Further, the adoption of these technologies will also be driven by consumer demand for higher quality and softer food produced with fewer synthetic pesticides.

When combined, NGS based surveillance and RNAi based treatment will allow rapid high-resolution detection and treatment of pests and pathogens on ever decreasing scales. This is especially true for high value crops like wine grapes, citrus stock, specialty cannabis, and other high value crops that are vegetatively propagated from a small number of starter stock plants. Indeed, these cropping systems may adopt an individualized medicine model for plant health in the near future. While treatment of individual plants is farther off for lower value vegetables and commodity crops, the increased flexibility and precision of these new applications will result in more efficient control of pest and pathogen problems on ever decreasing scales.

Acknowledgement

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Conflict of Interest

No conflict of interest.

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