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Biological products for sustainable crop protection

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Rising demand for alternatives to broad-spectrum conventional pesticides is driving investment in the development of environmentally friendly biological crop protection products that support sustainable agriculture. This report reviews the background to this growth and discusses some of the novel techniques being deployed, including RNA interference (RNAi) and individual companies engaged in development and commercialisation.

Crop protection products boost farming yields

The United Nations' (UN's) second sustainable development goal is to eliminate hunger globally. Plant pests can cause significant losses to crop yields, posing a major threat to food security, so improving crop yields through the continued application of crop protection products will be key to achieving this goal. Better yields will also help reduce the volume of greenhouse gases emitted per tonne of food produced, supporting initiatives to combat climate change. Significantly, the UN is promoting the adoption of sustainable agricultural techniques as a central part of achieving its goal of eradicating hunger. This means that farmers will need to switch from using broad-spectrum conventional pesticides to more environmentally friendly alternatives.

Switch to biological crop protection products

This shift away from conventional crop protection products has already started. It is being driven by consumer and government concerns about food safety and the environment, which are translating into greater consumption of organic food and legislation banning some conventional pesticides. In addition, the efficacy of conventional products is declining as pests develop resistance to them. Consequently, while the global crop protection market is predicted to grow at a CAGR of 3.7% between 2021 and 2026, the shift away from conventional pesticides means that the global agricultural biological control agents market is expected to grow at a CAGR of 14.5% between 2019 and 2025.

RNA: A biological approach attracting attention

RNA techniques, which mimic natural processes for regulating the production of proteins, are attracting a lot of attention at present. This is partly because of the use of mRNA in COVID-19 vaccines, and partly because of the market capitalisation of over US$1bn achieved by GreenLight Biosciences Holdings (GRNA:US) at its initial public offering (IPO) in February 2022. This report therefore reviews alternative techniques for manufacturing and delivering RNA-based products, concluding that bioengineered yeast, as developed by Renaissance BioScience for example, potentially has significant advantages with regards to both cost of production and ease of administration. The report also discusses some of the alternative biological approaches that involve triggering the natural defences of plants, mimicking substances produced by plants themselves to deter predators and synthesising beneficial agents in the plant biome.

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Eliminating hunger with sustainable crop protection products

UN embeds sustainable agriculture in its goals

The UN's '2030 Agenda for Sustainable Development', which was adopted by all UN member states in 2015, provides a 'shared blueprint for peace and prosperity for people and the planet, now and into the future'. The second of the UN's 17 sustainable development goals is 'zero hunger'. This goal seeks to end hunger, improve nutrition and ensure food security but not at the expense of the environment as it also seeks to promote sustainable agriculture.

Crop protection products required to improve or maintain yields

This caveat in favour of sustainable agriculture is significant. This is because since the second world war arable farmers have increased yields by using a range of toxic substances to kill insects, worms, moulds and other living organisms that attack plants and to kill weeds that would otherwise choke the crop. According to the UN's Food and Agriculture Organisation (FAO), crop pests, bacterial blight and other diseases result in crop loss of around 20–40% of agricultural output globally each year. Plant diseases cost the global economy around $220bn annually and invasive insects around US$70bn. Studies published by the Weed Science Society of America in 2016 found an average yield loss over a seven-year period of 52% in corn and 49.5% in soybean crops when all weed control practices were eliminated, which it calculated would have cost growers in the United States and Canada about $43bn annually. Moreover, crop losses are expected to get worse. A paper by Deutsch et al. in 2018 predicts a 10–25% increase in insect damage per global temperature degree increment in the next few years, with the main problems being in the temperate regions.

The need to improve yield and thus to continue to use crop protection products remains. Based on projections of population and economic growth, the FAO predicts that global demand for agricultural commodities, including for non-food uses such as biofuels, will grow by 1.2% per year over the coming decade. Around 87% of the increase in global crop production needed to meet this demand will be related to productivity improvements and only 6% from expanded land use and 7% from an increase in cropping intensity. Better yields will also help reduce the volume of greenhouse gases emitted per tonne of food produced, supporting initiatives to combat climate change.

Adoption of biological pesticides

However, over the last three decades, interest in organic food and farming across the globe has driven a shift from conventional pesticides to chemical-free, biological products. This transition is being accelerated by greater consumer interest in the provenance of food and in food safety and quality, as well as concerns about soil quality and the environment. These are resulting in the enactment of legislation to reduce the use of certain pesticides which have been shown to have a detrimental impact on the environment. These legislative changes mean farmers need to find alternative techniques to improve yield. Moreover, most of the primary pest species affecting the major crops and human health have developed resistance to many of the available insecticides since the introduction of synthetic organic insecticides, with the top pests exhibiting resistance to nearly 100 different insecticides. Farmers therefore need to apply increasing amounts to achieve the same effects. Biological crop protection products represent an innovative way for farmers to overcome this resistance, adopting methodologies that apply different products to successive generations of pests to prevent them from evolving resistance to any one pesticide.

Exhibit 1: Interview with Dr John Husnik, CEO of Renaissance BioScience, on the global crop protection market

Source: Edison Investment Research

Restrictions on glyphosate plant protection products

The herbicide most frequently used both worldwide and in the EU is glyphosate, which is the active ingredient in Monsanto's Roundup. Glyphosate has been used for several decades and is typically applied before crops are sown to eliminate competing plants and thus encourage crop growth. Applying herbicide at that point eliminates or minimises the need to use ploughing machines, thus reducing soil erosion and carbon emissions. Glyphosate is also used to a lesser extent as a pre-harvest treatment to facilitate better harvesting by regulating plant growth and ripening. Although there was a landmark case in 2018 requiring Monsanto (which was acquired by Bayer in 2018) to pay US$39.2m in compensatory damages and US$250m in punitive damages for failing to warn consumers that exposure to Roundup weedkiller causes cancer, glyphosate is still widely used. Bans on its use by individual countries such as Germany (from 2024) and Kuwait, and individual states such as Kerala and Punjab in India, remain the exception rather than the rule. While glyphosate is currently only approved for use in the EU until 15 December 2022, the group of member states reviewing whether to renew approval concluded in June 2021 that the substance did not pose any hazard to human health or the environment as long as it is used according to directions, though it reduced the levels of glyphosate to which people can safely be exposed over a specified period. Environmental activists are currently challenging the independence of the studies used to reach this conclusion. Regardless of the outcome of this particular review, it is clear that traditional pesticides are facing an increasingly more stringent regulatory environment.

Ban on neonicotinoid pesticides

Neonicotinoids are a group of insecticides used on a wide variety of crops. They work by affecting the central nervous systems of pests so that when insects such as aphids latch onto crops, they are paralysed, drop off the plant and die. Research has shown that pollinators visiting treated crops can suffer the same fate. In January 2020, the US Environment Protection Agency (EPA) introduced restrictions on when the pesticides can be applied to flowering crops but stopped short of a blanket ban. In 2018 the EU extended the ban on using three neonicotinoids (clothianidin, imidacloprid and thiamethoxam) on all field crops because of the serious danger they pose to bees and other pollinators. The legislation means these active agents can only be used in closed greenhouses. Alternatives will need to be found for open field use, particularly because otherwise the ban is likely to encourage use of pesticide sprays, which also kill pollinators.

Demand for biological crop protection products is growing rapidly

According to a report from Mordor Intelligence published in January 2022, the global crop protection chemicals market was valued at US$61.3bn in 2020 and it is projected to reach US$73.5bn in 2026 (ie a CAGR of 3.7% between 2021 and 2026). Within this market, the biological segment is growing very rapidly. A report published by BIS Research in December 2020 predicted that the global agricultural biological control agents market would grow from US$3.3bn in 2019 to $7.4bn by 2025, a CAGR of 14.5%.

Emergence of alternative crop protection techniques

The sustained and rising interest in organic food and farming across the globe has led to the development of many types of chemical-free, biological-based products. We discuss several alternative approaches towards developing biological-based products in this section, leading with RNAi because of the heightened interest in the technique following the successful development of highly effective mRNA-based COVID-19 vaccines.

Switching off genes that produce proteins

RNAi is a natural cellular process in which the production of a specific protein required for normal function or growth is prevented. There are two ways of deploying RNAi treatments for crop protection. The first is to genetically modify crops so they synthesise specific RNAi molecules. For example, in 2017 Monsanto received EPA approval for an RNAi-based crop protection product, SmartStax Pro, which targets corn rootworm, a pest that costs US farmers an estimated $1bn annually in damage and control measures. In this approach, corn plants are genetically modified to produce a specific RNAi molecule that turns off the production of a key protein required for the proper function of cell membranes, so when a corn rootworm feeds on the corn plant it ingests the RNAi insecticide and dies. In January 2021, Bayer announced that it had received the final safety certificate for import and food/feed use from China's Ministry of Agriculture and Rural Affairs for corn rootworm that had been genetically modified in this way. Approval in this major potential market triggered the go-ahead for a commercial introduction of SmartStax PRO technology in the United States during 2022.

The second way of deploying RNAi-based pesticides is to manufacture them in a factory and then spray them on foliage where they either affect the insect or other pathogen directly or are taken up by the plant's vascular system and are transmitted to the pest when it eats the plant. Monsanto is also working on this type of SIGS (spray-induced gene silencing) pesticide. Following successful trials using RNAi technology for controlling varroa mites attacking bees, Bayer submitted a registration application for BioDirect to the EPA in 2019. This was the first EPA submission for an exogenously applied, RNA biopesticidal active ingredient in the industry. In May 2021, GreenLight Biosciences announced that it had acquired rights to portions of Bayer's topical RNA IP portfolio including the technology for protecting honeybees against Varroa mites.

Other companies are following with pesticides targeting different plant predators. For example, GreenLight Biosciences, Renaissance BioScience and Syngenta (SYT:US) are conducting trials using RNAi-based insecticide to treat Colorado potato beetle infestations. New techniques are required to attack the Colorado beetle because the potato and other plants in the nightshade family have poisonous alkaloids in their leaves, so the beetle has evolved mechanisms to metabolise toxins, including chemical pesticides such as the imidacloprid neonicotinoid. However, the beetle does not have nucleases in its gut capable of degrading the RNAi pesticide. Startup AgroSpheres is developing an encapsulated RNAi product for attacking fall armyworm larvae and a biofungicide.

Exhibit 2: Potato plant protected from Colorado potato beetle by RNAi biopesticide during laboratory trial

Source: Renaissance BioScience

Exhibit 3: Control experiment showing damage from Colorado potato beetle on unprotected potato plant

Source: Renaissance BioScience

The second approach goes a long way to address consumer concerns about genetically modified crops. In addition, it potentially takes less time to build up approvals across a range of crops affected by the same pest, as it is not necessary to create genetically modified versions of each crop type. Also, many agricultural species such as perennials are not amenable to genetic manipulation. However, unlike a conventional pesticide, topically applied RNAi breaks down after a few days' exposure to the environment if not protected, can be prohibitively expensive (see below) and does not work for all types of pests. For example beetles and weevils are considered highly susceptible to RNAi while insects in the order butterflies and moths are considered recalcitrant.

Triggering the natural defensive mechanism of plants

Many plant pathogens produce harpin proteins. As a result, the plants attacked by those pathogens have developed receptors on their seeds, roots or leaves that detect harpin proteins and respond to their presence with a fast release of cellular calcium and an increase in plant metabolic activity, photosynthesis and nutrient uptake stimulating a vigorous growth response. This effect occurs in all agronomically important crops including field crops, vegetables, tree fruit, vines and speciality crops. It has been harnessed by AIM-listed Plant Health Care (PHC:LN**)**, which has developed a patented-product, Harpin αß, which is currently being sold primarily for application to corn, apples, cherries and blueberries in the United States and sugar cane in Brazil. The company has also recently launched its first peptide-based product, which is being used to improve the yield of soy beans in Brazil. Peptides are short chains of amino acids that can mimic the active sites of larger, naturally occurring proteins to which plants have evolved a defensive response. Applying a peptide thus triggers a plant's natural defence system. Plant Health Care modifies the amino-acid sequence of its peptides to make them better at inducing resistance to pests and diseases in plants, to improve the tolerance of plants to drought or to accelerate root growth.

Mimicking pest deterrents produced by plants

Terpenes are aromatic compounds found in many plants that create the characteristic smell of lavender, pine and orange peel. Plants manufacture terpenes to protect themselves against herbivores, insects, pathogenic fungi and bacteria as well as to attract pollinators. The deterrent effect of terpenes is being deployed by Eden Research (EDEN:LN), which has developed a micro-encapsulation technology branded as Sustaine, which protects the terpenes in slow release microspheres. The protective microspheres are produced from yeast extract so they are free from polymers or microplastic and are biodegradable. Importantly, since micro-encapsulated terpenes are exempt from pesticide residue limits, they can be used up to the point of harvest. This helps prevent damage to fruit in the critical last weeks of the season, which can result in rot during storage and food loss. Eden has launched two products so far that have both received approvals

for use on a range of crops in several countries. One is a fungicide, the other product kills root knot nematodes. Bio-Gene Technology (BGT:ASX) is also developing crop protection and other products based on naturally occurring compounds produced by plants. The active ingredient in Flavocide is a synthetic beta-triketone which is identical in structure to a compound found in Australian flora, but not in commercial quantities. Qcide is based on tasmanone, which is found in oil extracted from a specific cultivar of eucalyptus tree, the Gypmie Messmate.

Mimicking plants' own fungicides

In the same way that human beings have many different types of bacteria in their guts, which are key to us staying healthy, plants are host to many types of microbes on their outside surfaces and their internal tissues, as well as in the surrounding soil. This collection of microbes, the plant microbiome, has evolved in such a way to benefit both the host and the associated microbes, with some microbes having a role in controlling agricultural pests. Lavie Bio is using the MicroBoost AI computational predictive biology platform from its parent company Evogene (EVGN:US) to create biopesticides. MicroBoost AI uses its proprietary database to screen the microbes found naturally in the plant biome for pesticidal properties. The software then identifies relevant candidate properties and then uses the database and proprietary apps to suggest optimal candidates and candidate combinations so that the desirable properties are enhanced and undesirable properties are eliminated.

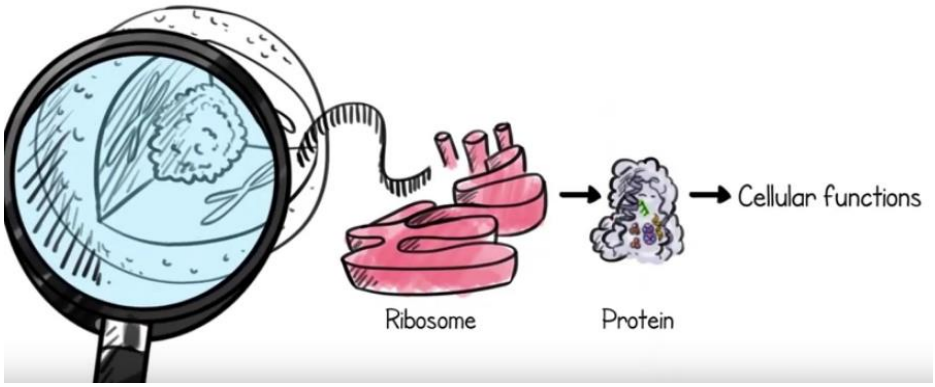
Spotlight on RNAi technology

RNA-based techniques have received a great deal of attention recently because of their deployment in new types of COVID-19 vaccines. As mentioned earlier, RNA-based techniques are also being used to develop biological crop protection products. We take a closer look at those in this section.

How RNAi works

In normal circumstances a molecule of messenger RNA (mRNA) carries information encoded in a cell's DNA to the cell's ribosomes where the proteins driving cellular function are made. RNAi molecules, which also occur naturally, target and facilitate the degradation of specific mRNA molecules. This reduces the production of specific proteins and thus modifies cell function.

Exhibit 4: Video showing RNAi technology in practice



Source: Renaissance BioScience

In the RNAi technique, double-stranded RNA (dsRNA) molecules similar in structure to the target mRNA molecules are synthesised at scale, enter the cell and destroy the target mRNA molecules, thus reducing production of a specific protein. This is used to develop pest control products because by targeting mRNA that is required for life in a particular pest, that specific mRNA can be

selectively silenced, resulting in death of the pest. Importantly, a product designed to kill Colorado potato beetle, for example, should not be harmful to pollinators or farm workers. Humans have a long history of dietary consumption of considerable amounts of dsRNA from virus-infected plant material without any indication of detectable effects, probably because the dsRNA is broken down by stomach acids. We have noted above that the EPA has already approved the first RNAi pesticide.

While this is not the topic of this report, the technology also has substantial potential in healthcare, for example by reducing the production of proteins required for virus replication, thus controlling human viral infections, or by reducing the secretion of inflammatory proteins related to inflammatory bowel disease. Compared with conventional agents, RNAi treatment selectively exerts its therapeutic effects in intestinal tissues rather than causing immunosuppression in the entire body. RNAi technology is already being used to develop treatments for human diseases, for example Arbutus Biopharma (ABUS:US) is developing treatments for the Hepatitis B virus.

Manufacturing RNAi cost-effectively

RNAi molecules can be highly effective pesticides but manufacturing them needs to be scalable as well as cost-effective so that farmers using the new pest control methods generate acceptable returns. Traditionally, the production of these molecules relied on chemical synthesis, which was prohibitively expensive and could only reliably produce short RNA molecules. Advances in bioengineering have found that certain microorganisms, particularly baker's yeast (*S. cerevisiae*) and *E. coli*, can be converted to be cost-effective and scalable 'microbial cell factories' for manufacturing bioactive RNAi molecules. The genome of baker's yeast is well understood and there are many modern genomics methods, including CRISPR–Cas9 technology, available to modify the yeast genome. The methods insert the genetic instructions into a yeast's genome, modifying it to produce a specific molecule. Baker's yeast is generally regarded as safe for the production of biopharmaceuticals, for example bioengineered baker's yeast is used to produce therapeutic insulin. Consequently the processes used for fermenting are well established, and available at scale, as are the techniques for extracting the desired molecules and purifying them. In addition, the raw materials involved are relatively low cost. These factors reduce the cost of production compared to chemical synthesis. Privately held bioengineering company Renaissance BioScience, which has developed a platform technology that bioengineers yeast to create an all-in-one production and delivery vector, states that its proprietary strains of yeast containing high concentrations of RNA molecules can be produced at scale for US$2 per kilogram. The company expects this to compare favourably on a cost-in-use basis with GreenLight Biosciences, which states that its process (see below) allows it to produce agricultural grade dsRNA at high volumes but at a cost of US$1/gram, and with biotechnology start-up RNAissance AG, which has a proprietary microbial platform which it claims can manufacture dsRNA at under $1–2/gram at commercial scale.

Manufacturing stable, easily administered RNAi products

Using yeast to manufacture RNAi-based crop protection products has other advantages too. Firstly, yeast is highly robust and stable, so it protects the RNA from degradation during fermentation and storage and in the field, giving it a longer active life than other RNA delivery mechanisms. For Renaissance BioScience, this means that the company expects its crop protection products to be stable far longer than any other RNA-based pesticide after being sprayed onto a farmer's field, potentially reducing the number of applications required and further enhancing the economic advantage compared with other RNA-based products. Secondly, many pests readily ingest yeast, so this is an efficient way of administering the active ingredient to the target pest. Finally, unlike chemical-based pesticides, both inactivated yeast and RNAi pesticides are considered environmentally friendly. Yeast is naturally biodegradable over time and since it is deactivated prior

to delivery to the field there is no risk of microbial contamination of the environment. There is a relatively low chance of toxicity as the RNA technology is highly target specific. The plant on which the dsRNA is sprayed and non-target insects are not affected. Researchers are also evaluating the use of clay nanoparticles and liposome complexes as protective mechanisms.

Companies developing RNAi-based crop protection products

GreenLight Biosciences has developed a proprietary cell-free manufacturing platform that produces dsRNA products. The company expects to launch its RNA-based pesticide targeting the Colorado potato beetle (*Leptinotarsa decemlineata*) in 2022, while its pesticide targeting the Varroa mite (Varroa destructor) is currently undergoing field trials. It is also developing a product to combat powdery mildew, which blights soft fruits like grapes and strawberries.

Renaissance BioScience's second-generation proprietary yeast strains are bioengineered to produce and deliver dsRNA that is capable of triggering specific RNAi in target organisms. The company is currently developing yeasts for use in crop protection. In late 2021, it announced that an independent proof-of-concept test conducted on Colorado potato beetle larvae showed a 98.3% mortality rate and greatly reduced the amount of plant damage caused by the beetle. Importantly, the company's approach means that it is possible to include multiple different gene targets in each cell of the delivery system, thereby greatly reducing or eliminating the potential for Colorado potato beetle to develop resistance to the biopesticide. Further field trials are upcoming. The company's patented first-generation technologies are already commercially licensed. One of the technologies is bioengineered yeast for use in wine, beer and cider production that does not produce hydrogen sulphide, with its associated smell of rotten eggs, during fermentation, significantly improving the quality of end-products. The second bioengineered yeast technology is an enzyme-producing baker's yeast that reduces the formation of the carcinogen acrylamide when carbohydrate-based foods are heated to 120°C or more. This is significant because the US Food & Drug Administration (FDA) and other food regulators have recommended that acrylamide formation in foods needs to be reduced because of acrylamide's potential to negatively affect human health.

In the longer term, Renaissance BioScience plans to deploy its RNA production and oral delivery platform technology in animal and human health products. This ability to apply a platform technology to multiple markets is similar to the way that the Bill Gates-backed company Ginkgo Bioworks (NYSE: DNA), which completed its IPO in September 2021, intends to use its bioengineering technology platform in applications as varied as flavourings and fragrances for foods, next-generation antibiotics and plants that manufacture their own fertiliser.

RNAissance is a spin-out from the Donald Danforth Plant Science Center backed byTechAccel, a private technology and equity development company focusing on agriculture and animal health. Its lead product is a sprayable RNA pesticide that targets the diamondback moth, a pest which the company estimates causes more than US$4bn in crop losses annually. Other targets include fall armyworm, cutworms, earworms, cabbage looper and European corn borer. The product is currently in early field trials.

Investment in companies offering novel crop protection technologies

Investment in crop protection is growing

According to Finistere Ventures, crop protection is one of the most highly invested segments in agtech, attracting some US$4.5bn in disclosed venture capital funding between 2010 and 2020. Around US$3.8bn of this has been invested into crop protection start-ups, primarily those involved in developing biological products, since the start of 2015.

Considering the companies profiled in this note, agricultural chemical and seed company Corteva (CTVA:US) invested $10m in Lavie Bio in August 2019, following which it held a 30% stake, leaving Evogene with the remaining 70%. In September 2021 AgBiome raised US$116m in a Series D round, which was led by Blue Horizon and Novalis, taking the total raised by the company up to that point to over US$200m. Bayer and Syngenta also have strategic investments in the company. AgBiome anticipates acquiring some smaller companies that have a product in commercial use to expand its pipeline in addition to its organic growth.

These investments are dwarfed by GreenLight Biosciences' IPO in February 2022 through a reverse merger with a special purpose acquisition company. The stock currently has a market capitalisation of US$1.25bn, highlighting investor interest in the broad potential applications of RNAi technology.

In our opinion, the societal shifts that are driving both the adoption of more environmentally friendly farming practices and environmentally responsible investing could create a significant number of investment opportunities in biological crop protection.

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