Science & technology

Controlling agricultural pests

RNA, good for vaccines, can also be used as a pesticide

A new approach to debugging

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RIBONUCLEIC ACID (RNA), once little-known outside biological circles, has recently become the molecule de nos jours. The reason is its role in covid-19 vaccines. The RNA molecules in these encode spike, a coronavirus protein. So, when the protein-making machinery of a body cell encounters such RNA, spike is what it makes. That lets the vaccinee's immune system learn to recognise a crucial part of the enemy before the real thing turns up.

Helping to make proteins is not, however, RNA's only job. Among many other things it is central to a process called RNA interference, which prevents, rather than facilitates, the manufacture of specific proteins. RNAi, as this activity is called for short, has also been investigated medically. It has been approved for use against four genetic diseases and is under investigation for the treatment of more than a dozen others. That is good. Some biologists, though, think RNAi may have an important non-medical use as well, as a precisely targeted, environmentally friendly pesticide.

The theory is simple. Identify a protein crucial to the survival of the pest in question. Tailor a specific interfering RNA molecule to sabotage production of that protein. Deliver it into the bodies of the pests. Then wait for them all to die. In practice, of course, things are more complicated. Delivery mechanisms have to be designed and regulatory hoops jumped through. But until recently, the biggest obstacle was cost. Life-saving medicines can be expensive. Pesticides must be cheap. One side-effect of all the medical RNA work, however, has been to bring the cost of making the stuff down. As Michael Helmstetter, the boss of RNAissance Ag, a firm in Kansas which is developing RNA-based pesticides, observes, "a gram of RNA cost $100,000 when we started. By 2014 it was $100 a gram. Now it's a dollar a gram."

Running interference

Top of the list of potential beneficiaries are honeybees. These semi-domesticated insects, important not only for their eponymous product, but also as pollinators, are plagued by *Varroa destructor*, a mite a couple of millimetres across (pictured above, on the head of a pupating bee). *Varroa* mites live by attaching themselves to, and feeding on, bees. This weakens or kills the hosts and also spreads viruses around a hive. Some suspect *Varroa* plays a role in colony-collapse disorder, a mysterious phenomenon in which most of a hive's workers desert for no apparent reason.

Beekeepers have tried all sorts of ways of attacking *Varroa* mites. Some place plastic strips laced with amitraz, a pesticide reckoned particularly effective against mites, at the entrances to hives. Others vaporise oxalic acid, which has a similar reputation, and pump it into the hive. Others still run breeding programmes, selecting for bees that resist infestation. None has succeeded in solving the *Varroa* problem. At best, these approaches keep the mites' numbers just below the threshold of crisis.

GreenLight Biosciences, a company in Boston, wants to help. It has bought from Bayer, a German pharmaceutical and life-science firm, the rights to an experimental *Varroa* pesticide based on RNAi. Andrey Zarur, GreenLight's boss, hopes this will succeed where other methods fail because it attacks the mite's lifecycle in a way mere chemical interventions cannot.

That the mites spend so much time hidden in the honeycomb makes them hard to attack. And this is where GreenLight hopes its RNA will win through. In field trials in the state of Georgia the firm's operatives are feeding that RNA to the bees themselves—mixing it in sugar water which the workers drink and make honey from to lay a biotechnological trap for the mites by lacing their birthplace with the stuff. By lowering the cost of RNA production and so allowing much more of it to be used, Mr Zarur thinks he can deliver more RNA to the mites, succeeding where Bayer and others did not.

Varroa mites are not, though, the only pests in GreenLight's crosshairs. It also has its sights trained on Colorado potato beetles, which can devastate crops if not controlled. In their case the RNA is simply sprayed onto an infested field and the beetles munch it up. And, though it is cagey about the details, the firm says it has 13 other hostile organisms under investigation, too. These include the fall armyworm, a moth caterpillar that chomps through everything from tobacco to oranges, and the caterpillars of the diamondback moth, the world's worst pest of brassicas, a group which includes cabbages, cauliflowers, broccoli, Brussels sprouts and oilseed rape. Nor is the RNAi approach limited to attacking animals. In principle, any organism is susceptible to it. GreenLight's target list therefore also

Cell game

Not surprisingly, GreenLight has rivals in its quest to develop RNA pesticides. At least two other American companies are working on them as well. RNAissance Ag, Dr Helmstetter's firm, is gunning for the potato beetle and the fall armyworm. AgroSpheres, in Charlottesville, Virginia, is going after Diamondback moths. All three enterprises think they can make RNA cheaply enough for it to be sprayed onto fields. But they do so in different ways.

GreenLight employs a process called cell-free biology, which is more akin to chemistry than conventional biotechnology. Eliminating the need to coddle fussy micro-organisms, says Mr Zarur, simplifies and cheapens things dramatically. But the more traditional approach taken by RNAissance and AgroSpheres, of growing their RNA molecules inside modified bacteria, offers advantages, too. Packaging the RNA in bacterial cells in this way protects the molecules. It also allows the companies' biotechnologists to add features to the cell walls, such as stickiness that stops them slipping off the leaves of plants.

Spraying RNA onto crops is not, however, the only way to get it into pests. Though it has abandoned its honeybee technology, Bayer is developing a genetically modified maize which produces RNA that kills beetle larvae called corn rootworms. A group at the University of Florida is taking a similar approach to *Diaphorina citri*, an insect (see box) that spreads a bacterium which causes citrus-greening disease, a serious threat to orange groves.

RNA spraying has advantages, though. A farmer can use it on existing crops, rather than having to replant with transgenic versions. The regulations are less onerous than for the creation of transgenic organisms. And in Europe, where transgenic crops are banned in many places, governments seem open to RNA-based pesticides.

Andreas Vilcinskas, an entomologist at the Fraunhofer Institute's campus in Giessen, Germany, who is working with GreenLight, says the German government now supports their development. It has good reason to. In 2018 the European Union banned the outdoor use of three types of neonicotinoids, a popular class of pesticides. Since then, Germany, France and Poland have all had to reverse this ban on an emergency basis after aphids spread like wildfire. Ironically, neonicotinoids were banned to help bees. Promoting RNA as a pesticide might thus, as it were, kill many bugs with one stone. ■

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