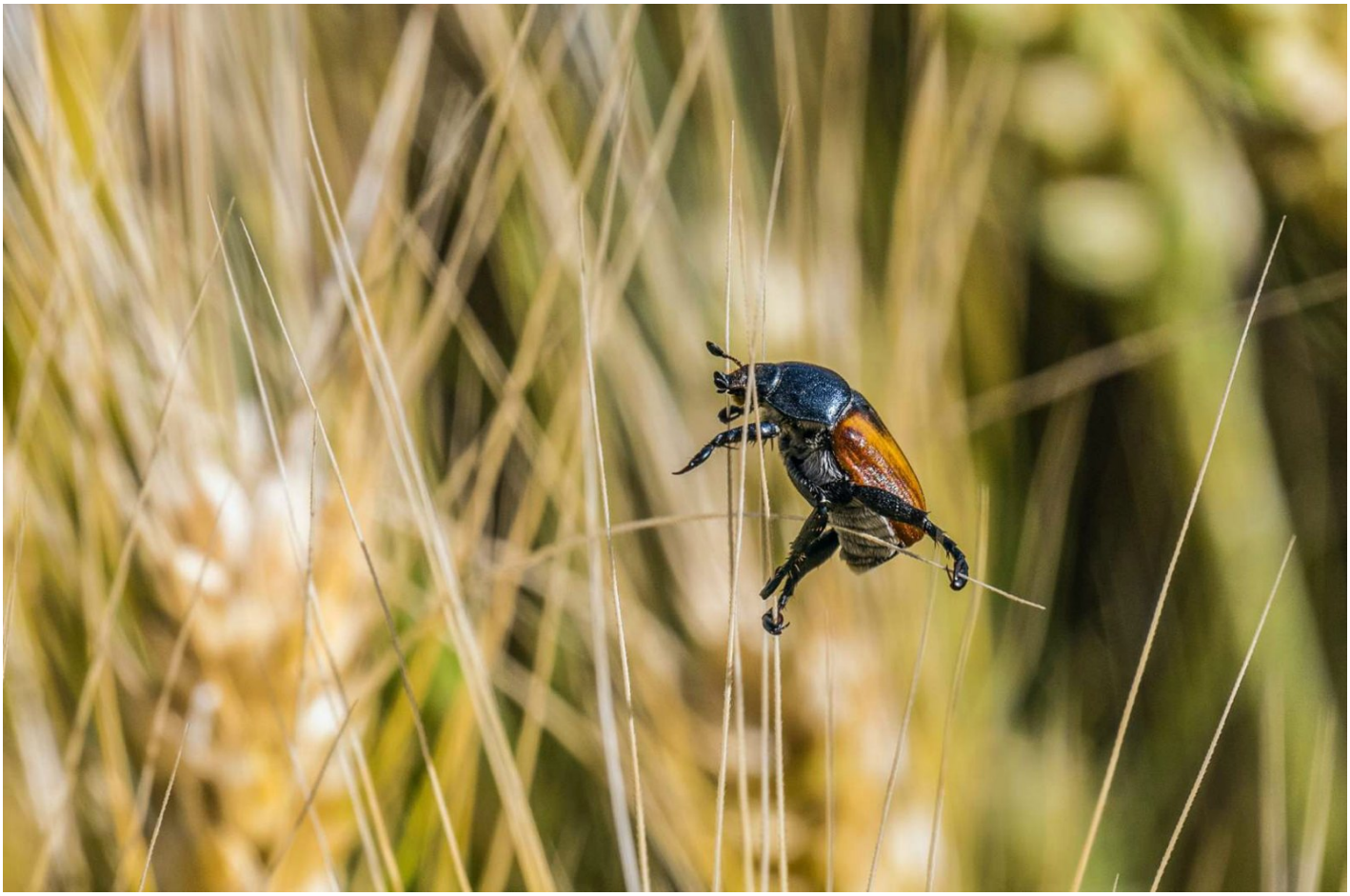
Crop Protection Gets A Boost With Biotechnology

InsectiGen
University of Georgia
University of Georgia Research Foundation



Big problems can come in small packages. Case in point: The insect pests that feed on crops. Each year, these tiny creatures cause large-scale agricultural devastation around the world. For farmers, that erodes revenue worth billions of dollars and also contributes to steeper food prices. This poses a particularly worrisome trend in developing nations, where growing populations already struggle to afford the sustenance they need.

InsectiGen Inc. plans to help squash that bug problem.

> *The scientific discovery has led to increased effectiveness of widely used biopesticides and genetically modified crops — without damaging the environment.*

On the Farm, Bacteria Lend a Hand

To understand how InsectiGen's product, BtBooster, can improve insect control, it helps to know a little about the type of pesticide it enhances: Bacillus thuringiensis, or Bt.

Bt is a form of bacteria commonly found in soil. Thousands of Bt strains exist today, and these bacteria have a valuable property. When eaten by certain insect larvae, Bt proteins turn toxic, killing the larvae within a couple days. That function was discovered a century ago, and farmers have used Bt toxins to help protect their crops for decades. Worldwide, it represents the most commonly used biopesticide. Considering the benefits Bt offers, it's easy to understand why.

Unlike some pesticides, Bt doesn't kill haphazardly. That's because each Bt strain works like a lock and key, matching up with gut receptors in different insect larvae. As a result, it can target specific pests and let helpful insects thrive. Bt is also biodegradable, so it avoids problems linked to conventional chemical pesticides, such as potential harm to nearby livestock or wildlife or contamination of soil and water.

In the mid-1990s, farmers began planting cotton and corn crops that contained the Bt gene. These genetically modified plants produce the Bt protein that kills insect larvae. Since the introduction of Bt plants, their use has grown dramatically. In 1997, Bt crops represented 8 percent of U.S. corn acreage and 15 percent of U.S. cotton acreage, according to the U.S. Department of Agriculture. By 2010, those figures had surged to 63 percent for corn and 73 percent for cotton.

Giving Bt a Much-Needed Boost

While Bt has significant benefits — like the ability to selectively kill insects — it hasn't eradicated agriculture pests. To glimpse the problem's enormity, consider that for U.S. farmers, the cost of insect treatments and crop loss due to the corn rootworm can reach $1 billion annually, according to a Journal of Economic Entomology article. And that's just the toll taken by one insect species, in one country.

Several shortcomings have kept Bt from making a bigger dent in the pest problem. It works well on some insects but has little effect on others. Concerns about Bt's effectiveness have grown, as insects show signs of building resistance (one recent documented case is the fall armyworm, a well-known corn and cotton pest). Plus, Bt is a relatively expensive biopesticide, so it's costly for farmers.

InsectiGen addresses those challenges with BtBooster. The aptly named product gives a boost to Bt's effectiveness, in both spray form and genetically modified crops. According to InsectiGen, tests have demonstrated BtBooster's ability to increase Bt's potency by 20-fold or more. This creates several advantages for insect control. The heightened potency allows current Bt products to more effectively kill the insects they target. It also allows the development of new Bt products aimed at a wider range of pests.

What's more, the extra-potent Bt diminishes insects' ability to develop resistance to it — and farmers can use smaller amounts of Bt when it's paired with InsectiGen's product. As a result, BtBooster provides a twofold benefit for agriculture: It not only makes Bt more effective, but less costly too.

All of those advancements sprang from a happy accident — basically, a failed hypothesis that led to a scientific breakthrough.

A Path to Serendipity

"In the lab, you learn to look for 'eureka' moments," says Michael Adang, Ph.D, professor of entomology and

biochemistry and molecular biology at University of Georgia in Athens. That's exactly what he found in October 2003.

At the time, Adang sought answers to a fundamental question: What makes certain Bt toxins kill one caterpillar and not another? With several patents for genetically modified Bt plants and more than 25 years of research, Adang was already well-versed in the science of Bt. But he needed to dig deeper.

To that end, Adang and his colleagues did an experiment using fragments of an insect's receptor for Bt toxin. They took the fragments, mixed them with Bt toxin, and fed it to larvae. The researchers thought the fragments would neutralize Bt's effects and block the toxin from binding to the insect's gut. Instead, they got a startling result that defied their expectations. The receptor fragment didn't protect the insects at all — it caused them to die from lower-than-usual doses of Bt toxin.

"We thought, 'This is really unusual,'" says Adang. "At first we didn't believe it." Adang and his team — Gang Hua, Ph.D, Jiang Chen, and Mohd Amir Abdullah, Ph.D — repeated the experiment several times. When they got the same results again and again, they started believing. "We said, 'This is real.' It was a serendipitous discovery."

A Business Takes Root

To commercialize that happy accident, Adang co-founded InsectiGen in 2003 with Clifton Baile, Ph.D. With BtBooster, they envisioned a new strategy for insect control: A product that doesn't replace Bt, but augments it. "The BtBooster has no toxicity itself because it's just part of an insect protein. It bindsto the Bt, and preserves its bioactivity," says Baile, InsectiGen'sCEO. Previously, he served as a director of research and developmentat Monsanto, one of the largest agricultural biotechcompanies in the world. But he's no stranger to the struggles ofa small business. Before InsectiGen, Baile helped launch nineother biotech startups.

When InsectiGen needed to create a business plan, the not-forprofit Georgia Research Alliance helped pay for a professional to write it. Funding from the U.S. Department of Agriculture and the National Institutes of Health helped Adang conduct research to further develop the company's nontoxic protein. In 2003, InsectiGen licensed BtBooster's initial technology from University of Georgia Research Foundation, the university's technology transfer group. Since then, Adang's lab has done additional patent-worthy research for BtBooster. "We jointly own some of the patents with InsectiGen, which is a little bit unusual," says Rachael Reiman Widener, Ph.D, technology manager at the University of Georgia Research Foundation.

The company has close ties to the university; InsectiGen is currently based on campus at the university's BioBusiness Center, which serves as an incubator for faculty startups. Widener notes that not all academics are natural entrepreneurs — and that sets InsectiGen apart from other startups she's observed.

"It is not unusual to have struggles with faculty startup companies," she says. That hasn't been the case with InsectiGen. "They make it easy," says Widener. "Mike and Cliff have a good sense of what it means to run a company, versus running a lab. So we've been able to work with them without any hiccups."

Even before his BtBooster invention, Adang says the University of Georgia Research Foundation played a helpful role. "I've filed other patent applications previously, and our technology transfer group here is very faculty friendly," he says. "They're supportive of faculty that have entrepreneurial ambitions." He also appreciates the level of trust shown by the technology transfer group. "When I asked to work with a patent attorney I've known for more than 15 years, they said 'Great, go with it,'" says Adang. "They could have insisted on using a local attorney, but they didn't."

Baile echoes those sentiments regarding the technology transfer group's support. "We consider them members of the

team," says Baile, who is also a professor in University of Georgia's Departments of Animal and Dairy Science and Foods and Nutrition. "They've been very good in nourishing the commercialization activity of the company."

InsectiGen's Next Steps

Soon, the company plans to take BtBooster's commercialization a step further. It's working toward registering the product with the Environmental Protection Agency. "We've been doing field trials for several years on combinations of BtBooster with Bt biopesticides," says Adang. "I think we could have it registered in the next two or three years."

The product has already caught the attention of large companies.A subsidiary of DuPont, Pioneer Hi-Bred, is using BtBooster under a licensing agreement to develop better geneticallyengineering Bt crops. "It's the only one we have publiclyannounced, but we have other agreements with companies,"says Baile.

In its present form, BtBooster is designed to thwart agriculture infestations, but InsectiGen won't stop there. Ultimately, Adang wants to broaden the scope of insects that Bt kills — and not just pests that damage crops. His current research includes BtBooster's effect on the darkling beetle, which can transmit Salmonella in commercial poultry houses. He has other pests in the crosshairs too.

"Some of our more interesting work is trying to find a more effective way to make biopesticides for mosquito control," says Adang. He has applied for a National Institutes of Health grant to conduct field trials in this area. If he's able to curb mosquito populations with BtBooster, it could have widespread effects on world health issues by preventing the spread of lethal diseases. Malaria is one example — according to the World Health Organization, at least 1 million people die each year from malaria transmitted by mosquitoes.

Adang knows the rewards of taking a discovery from the lab to the marketplace. Each year, he helps plant that seed in students' heads by teaching a biotechnology course at University of Georgia (one of the guest lecturers the patent attorney who works on BtBooster). "I think he's really able to get the point across to students that there is another world beyond academia," says Widener.

BtBooster has officially entered that other world. It evolved from a "eureka" moment in the lab to a product that could dramatically improve pest control.

"It's very gratifying," says Adang. "But this isn't the first time I've had this experience." In 1982, he started developing technology for engineering Bt genes into plants. InsectiGen continues to build on those decades of research. With a boost in potency, Bt toxins can help reduce the damage insects do to plants, and the disease they cause in humans. The potential significance isn't lost on Adang. "It's a motivating force in my career," he says, "that you can continue to make discoveries that will have value for society."

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