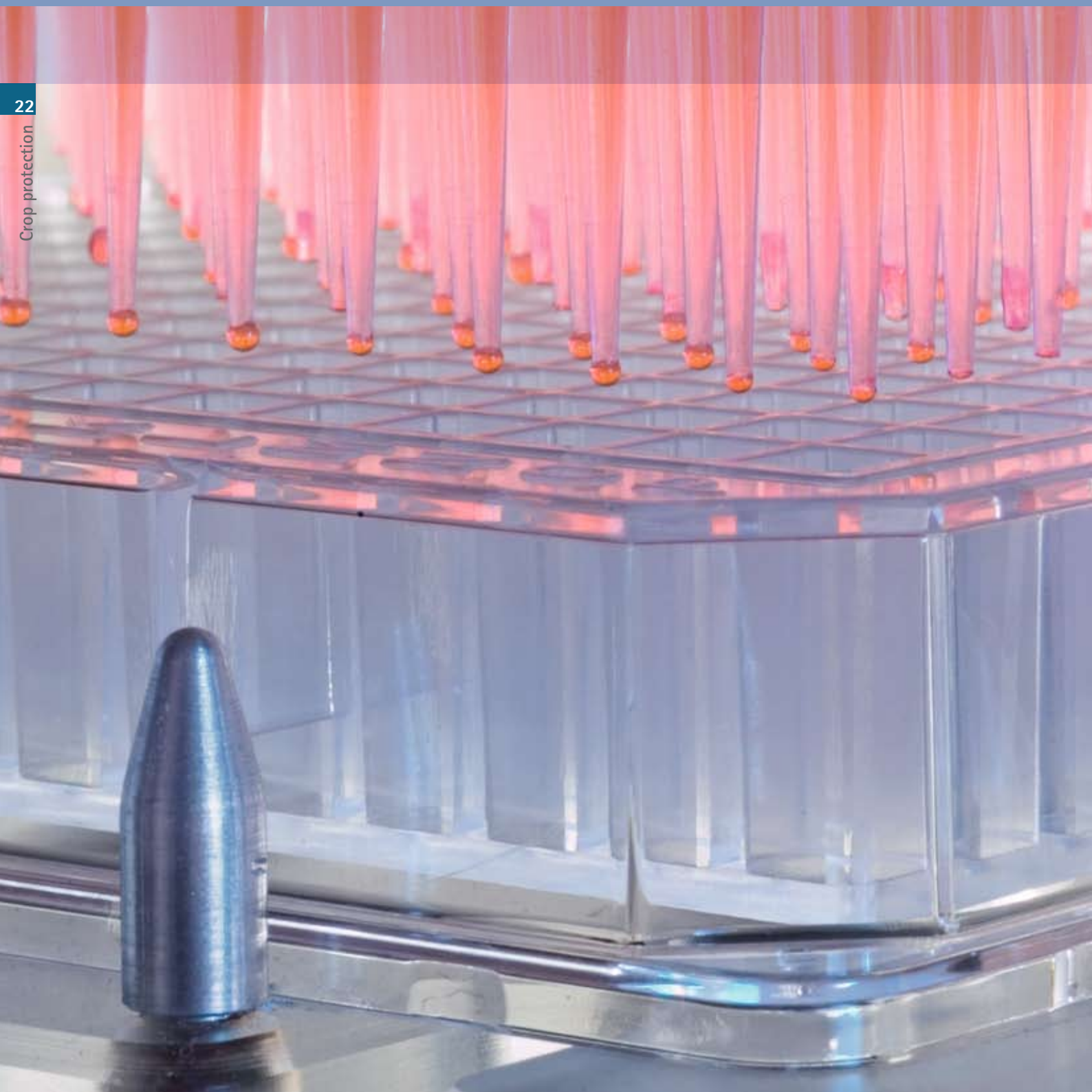


New insecticidal mechanism of action discovered

In a class of its own

22

Crop protection





Crop protection research: numerous test series were necessary before the scientific team of (left to right) Dr. Ulrich Ebbinghaus-Kintscher, Dr. Peter Lümmen, Dr. Rüdiger Fischer and Dr. Klaus Raming managed to optimize a substance that exerts a selective action against insect pests like the tobacco budworm. The pipetting robot for automated sample preparation (large photo) was an essential tool in this process.



Insect pests still cause dramatic crop damage around the world. Innovative crop protection agents are the only way to put a stop to it. Bayer CropScience has developed a substance that controls dangerous insect pests in a highly selective manner, yet is harmless to beneficial organisms. The substance's novel biochemical mode of action makes it the first in a new class of insecticide.

The Very Hungry Caterpillar in the well-known children's book eats his way through a smorgasbord of delectable foods. Much less amusing than the literary figure are its counterparts in nature, such as the tobacco budworm. Before the green caterpillar metamorphoses into a cream-colored moth, its diet includes fruit, vegetables, tea and cotton plants. Not even geraniums are safe from *Heliothis virescens*, as the insect is known by its scientific name. Its voracious appetite makes the tobacco budworm one of the most significant crop pests around. In the United States alone, caterpillars of this species decimate crops worth a quarter of a billion dollars every year.

But now, a new insecticide could get to grips with the tobacco budworm even though it has become resistant to existing crop protection agents. Bayer CropScience is currently launching a new active substance with astounding potential: flubendiamide is literally in a class of its own. It binds to a molecule in insect cells that has never been the focus of attack by any crop protection agent before. Flubendiamide is therefore

an important alternative to previous active substances, particularly since the insecticide market is dominated by only four different mechanisms of action, all of which target the transmission of nerve signals. In other words, the introduction of a novel substance class with a new mechanism would considerably expand the options available to users.

Selective effect against insects

"The substance is extremely efficient and even very small quantities are effective against insect pests," reports Dr. Klaus Raming, Head of Physiology and Biochemistry in Insecticide Research at Bayer CropScience, who is responsible for decoding new mechanisms of action. Equally important is that flubendiamide is highly selective to insects; it has no effect on vertebrates, and that includes humans.

Flubendiamide's unique mechanism of action makes it a starting point for the development of other insecticides with a similar effect on other insect species. "When it comes to crop protection

How the ryanodine receptor got its name

Ryania speciosa is a plant that can defend itself. The South American bush contains a substance with an insecticidal effect. It was discovered back in the mid-20th century, and ryanodine was introduced on the market as a broad-spectrum crop protection agent. As research demonstrated, the substance binds to a membrane-bound molecule in muscle cells, which was consequently dubbed the "ryanodine receptor". Acting as a channel, the receptor regulates the calcium concentration inside the cell. Ryanodine disrupts this sensitive process by triggering massive release of the mineral and causing severe muscle contractions. However, the effect is not limited to insect pests: ryanodine is also toxic to humans, birds and fish and therefore never became established as a crop protection agent. The search for other insecticides with an identical mode of action but higher selectivity remained fruitless for many years. But the substance class of phthalic acid diamides has now proven that the combination of high selectivity and high efficiency can be achieved by utilizing a binding location on the receptor other than that of ryanodine.

Together, researchers from both organizations decided to decode the molecular function of this promising substance. "Understanding the underlying mechanism helps us to better understand an active substance," Lümmen says. To their great surprise when working with flubendiamide, the researchers encountered an old acquaintance: the ryanodine receptor, which plays a role in the muscle contraction of insects. Numerous plant protection researchers had had their eye on this molecule for years as a potential target, but no one had yet succeeded in manufacturing the corresponding insecticide.

Muscle cell as the docking site

The reason has now become clear: flubendiamide binds not to a known location, but to another region of the ryanodine receptors where it exerts an influence on its activity. "No-one knew of the existence of another binding location," explains Dr. Ulrich Ebbinghaus-Kintscher, a specialist for physiology and electrophysiology on the flubendiamide development team. "The real breakthrough is the discovery that ryanodine receptors can actually be used as target molecules, and that the location of attack is a new one."

agents, a broad spectrum of application is always an important factor," explains Dr. Peter Lümmen, who manages the biochemistry aspects of the new substance. "And we can justifiably say that the phthalic acid diamides, to which flubendiamide belongs, have blockbuster potential."

"Flubendiamide is the product of years of chemical optimization,"

reports Dr. Rüdiger Fischer, who manages joint research work with Nihon Nohyaku, the small Japanese company which had originally discovered flubendiamide. To develop flubendiamide into a finished product and facilitate global marketing, Nihon Nohyaku went in search of a bigger, more experienced partner, which led it to Bayer Crop-Science in 2001.

Very hungry: the tiny tobacco budworm (left) causes huge damage to agriculture and gardens. Help could come from the new substance flubendiamide, which was optimized in a number of test series. DNA analysis like that carried out by Angelika Kress (right), along with many other state-of-the-art technologies, was instrumental in elucidating the insect-specific mechanism of action and helped to combat the very hungry caterpillar.



The ryanodine receptors regulate the concentration of calcium in muscle cells. The mineral is stored in specific cellular structures, whose membranes contain the ryanodine receptors. If a muscle is to contract, calcium must be released from the depot structures to the inside of the cell. In this process, the ryanodine receptors act as calcium channels.

However, under the effect of flubendiamide, the system collapses: the calcium channels remain in an open state and the entire calcium depot is released. The consequences are dramatic: the insects lose muscle control, become paralyzed and die.

All the more astounding is that human cells and those of other vertebrates don't react to the substance at all. They likewise have ryanodine receptors with the same function, but

they are built slightly differently than the channels in the insect cells. These minor differences are enough to make the substance highly selective.

Crop protection innovation with huge potential

Bayer researchers want to take advantage of these structural variations in the ryanodine receptors to develop other insecticides based on phthalic acid diamide in the future. Ideally, other phthalic acid diamides would be just as efficient and selective as flubendiamide, but they would act on other insect pests with ryanodine receptors that likewise have different structures.

"Therefore, the next step will be to optimize the chemical structure," says Fischer. "The objective is to expand the

spectrum of action of later generations of the active substance to include not only caterpillars, but also other insects, such as aphids." Adds Raming, "I can even envisage using special phthalic acid diamides in veterinary medicine one day, for example to combat lice, fleas and other house-pet parasites."

Global marketing of flubendiamide has already begun, and Raming has no doubt other substances will follow: "Thanks to their new mechanism of action, the phthalic acid diamides are a really great innovation. A discovery like this only comes along every ten years at most in crop protection."

http://clapham.tch.harvard.edu/master.php?page_type=research
This website provides background information on the function of calcium in cells.

The mechanism of action

The new substance flubendiamide (yellow) binds to the ryanodine receptors in the myofibrils in insect muscles. As a result, large quantities of calcium flow out of the sarcoplasmic reticulum (calcium depot) into the myofibrils, where it causes the myosin filaments (blue) to slide past (arrows) the actin filaments (green). The myofibrils shorten and the muscle contracts permanently. This leads to the insect's death.

