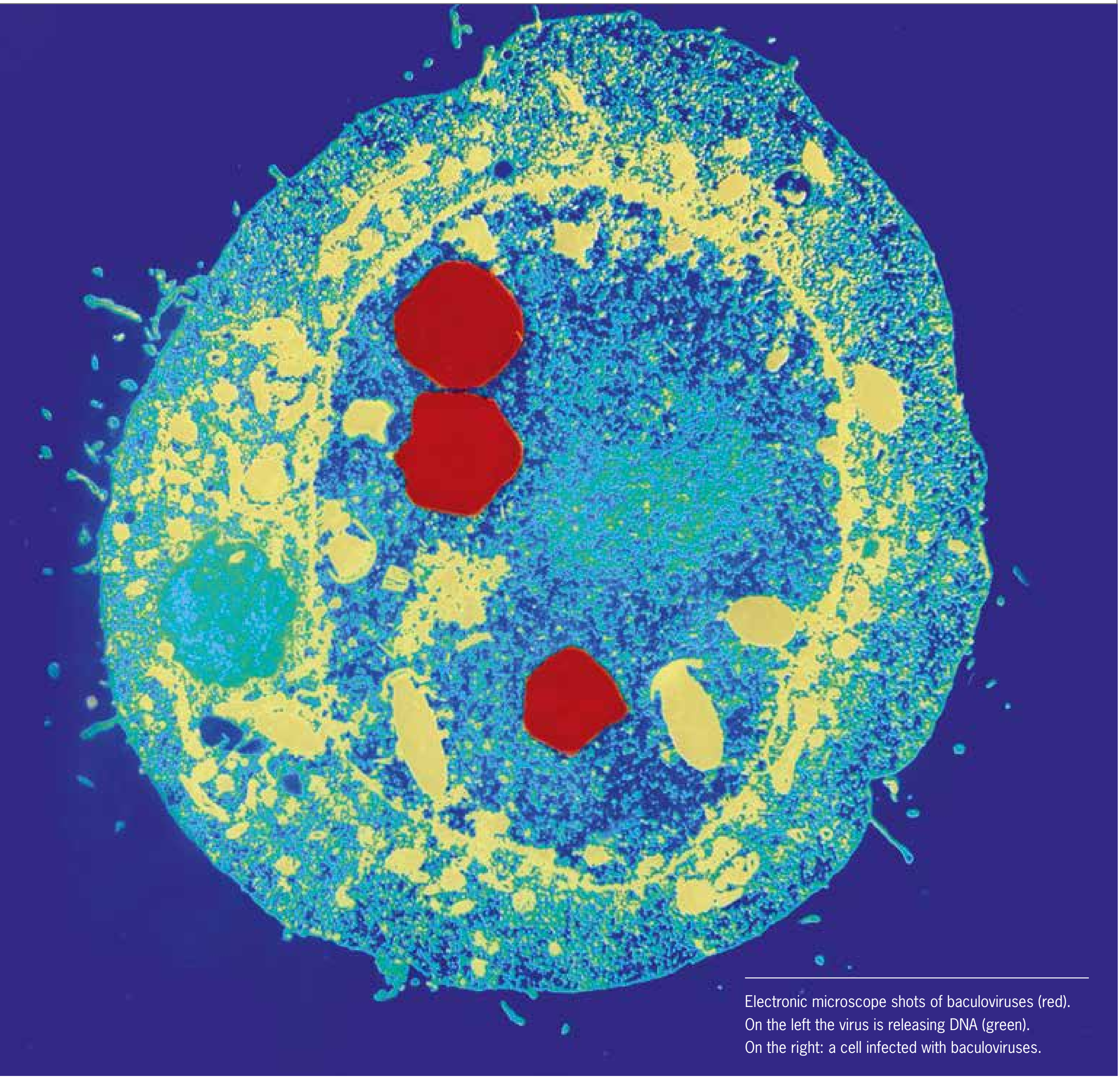
Taming viruses

Viruses are sophisticated pathogens, but virologists are now using smart tricks to make viruses do their bidding. They are using them to combat insect pests or produce vaccines for cervical cancer and chikungunya, for example.

TEXT EVELINE THOENES **PHOTOS** ANP **ILLUSTRATION** ERIK CRINS

A random day in the life of a baculovirus. Having spent days sitting on a leaf, the virus is eaten by an unsuspecting caterpillar. Its protective capsule falls off inside the caterpillar's intestines and now the virus is busy penetrating one of the intestinal cells. Once inside the cell, it makes its way to the nucleus, which is where it needs to be in order to get itself multiplied.

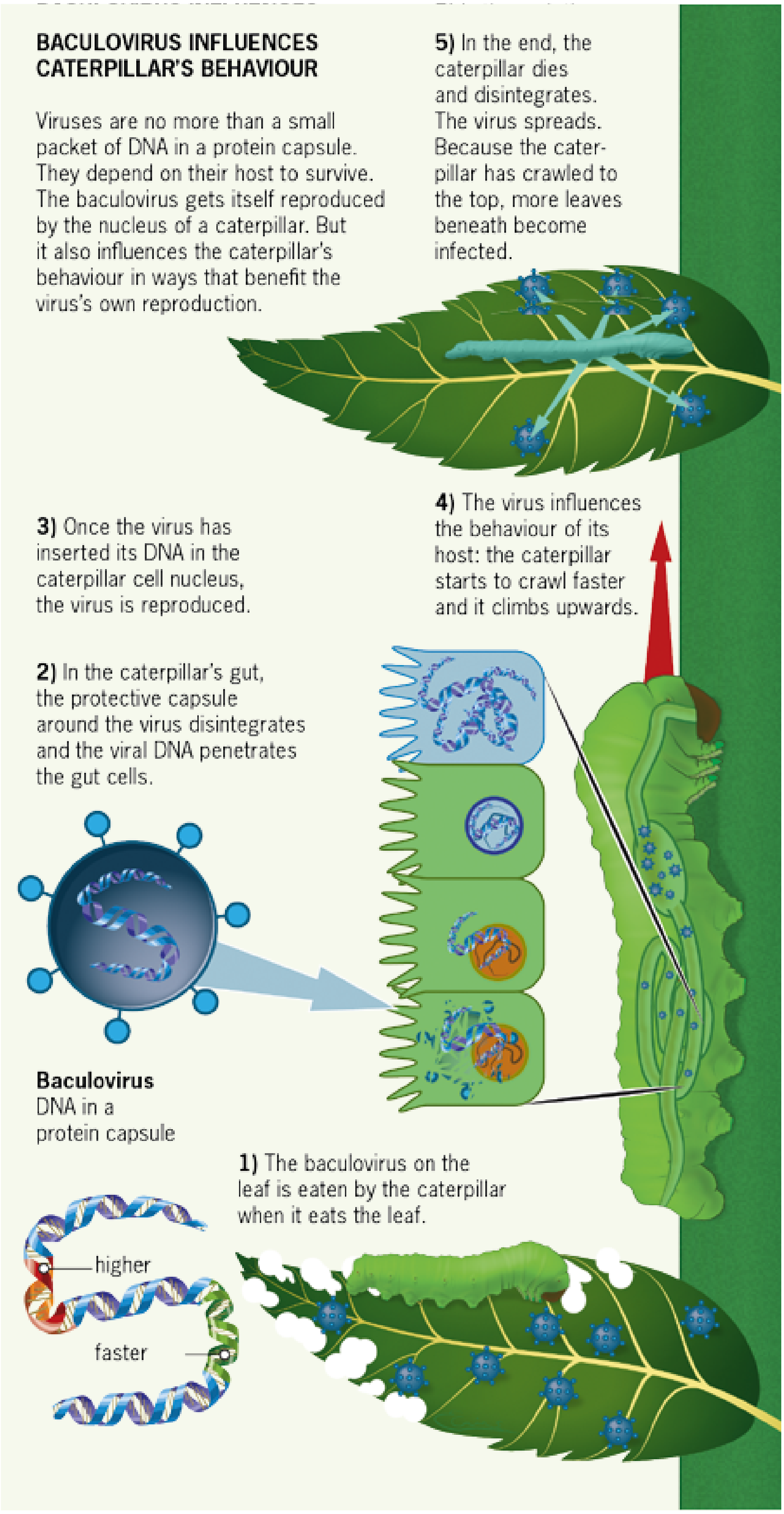


Electronic microscope shots of baculoviruses (red). On the left the virus is releasing DNA (green). On the right: a cell infected with baculoviruses.

The virus itself is not much more than some genetic material in wrapping: a small packet of DNA in a protein capsule, unable to do anything other than get itself reproduced by making use of the mini living factories in the cells of plants or animals. Baculoviruses mainly use caterpillars. Once the virus has inserted its DNA in the nucleus of a caterpillar cell, the caterpillar's enzymes automatically start to 'read' the DNA and produce the associated virus proteins, so the virus makes the caterpillar produce more virus particles, which in turn penetrate other body cells to repeat the process.

WHO IS THE MOST CUNNING?

Viruses are crafty – but so are virus researchers. In the Virology group's laboratory in Wageningen, it is the baculoviruses that do the bidding of the researchers. 'In the past few decades, biologists have come up with applications where these baculoviruses can be put to good use,' explains Monique van Oers, who has been professor of Virology at Wageningen UR since 2013. 'All viruses in the baculovirus family only infect certain insects and leave other organisms alone, which makes them ideal for use as biopesticides protecting crops against insect pests. They have been used in this way since the >



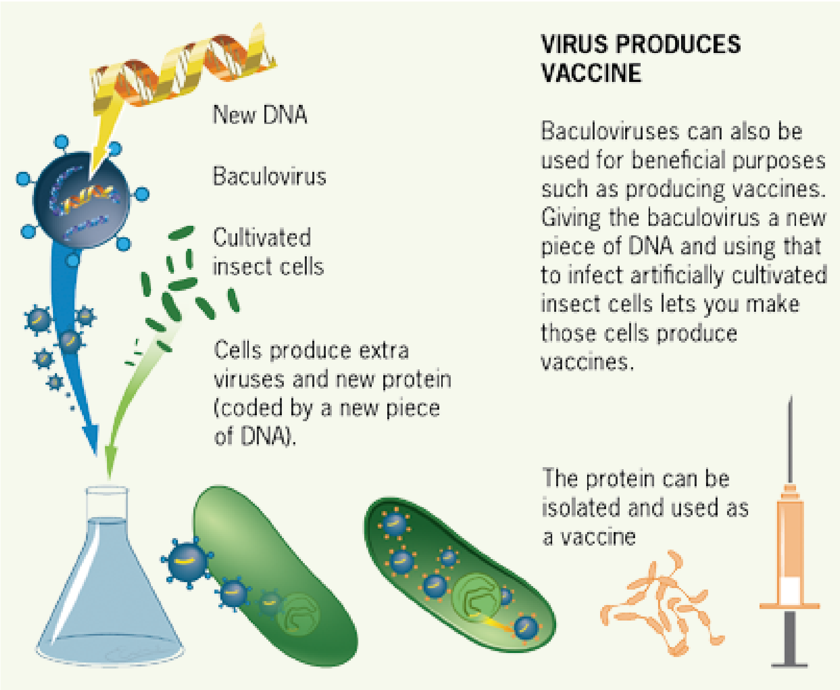
1940s, for example for combatting caterpillar damage in apples, cotton and sugar cane.' In the 1980s, researchers found a way of using these viruses in manipulating insect cell cultures. 'Giving the virus a new piece of DNA and then using that to infect the artificially cultivated insect cells lets you force those cells to produce proteins that can be used as vaccines,' explains Van Oers. According to her, this method has big advantages over conventional production methods with genetically manipulated bacteria. Bacteria are simple cells that cannot produce all types of proteins by a long way. 'Compared to them, insect cells are much closer to human cells and therefore much better able to do this,' says Van Oers. 'As long as you supply them with the right bit of DNA. And that's something that these viruses are very good at. Baculoviruses are harmless to humans, which makes this an ideal and very safe production system for medicines.'

SINT MAARTEN

There are two human vaccines on the market that are produced in insect cells using manipulated baculoviruses: a vaccine for cervical cancer and one for flu. 'Now that we have the first products for application in humans and we have proof that they work well and are safe, the expectation is that more will follow.' Scientists in Wageningen are now working on a vaccine for the chikungunya virus. Chikungunya is a nasty tropical disease causing fever and joint pain; it is transmitted from one person to another by mosquitoes. The virus was originally found mainly in Africa and Asia but at present it is a big problem in the Caribbean, including on Sint Maarten. 'So in that sense it's already on Dutch soil. Our prototype vaccine has already successfully been tested on mice and is currently being tried out on monkeys,' says Van Oers. 'If that is also a success, we hope we will able to develop it further in partnership with a pharmaceutical company.'

CATERPILLAR ARENA

Given the extensive range of applications for baculoviruses, researchers all over the world



'Baculoviruses are an ideal production system for vaccines'

want to know as much as possible about them. In Wageningen, attention is increasingly being paid to the baculovirus in its natural conditions and its interaction with the hosts that it infects. Not only does the virus apply a trick to ensure it gets reproduced, it also influences the behaviour of its host. The virus is able to make the caterpillar crawl along faster and to make it climb upwards. The caterpillar eventually ends up dying from the infection at a place far away from the original leaf where the virus exited the dead body of its previous host. This brings the virus to a new area with caterpillars that are still healthy, whose cells it can use to reproduce further.

'The further and higher the sick caterpillars crawl, the greater the leaf area contaminated with the virus as the caterpillar corpses disintegrate. Caterpillars that end up in the treetops are also picked up more easily by birds, which boosts the spread of the virus as well,' explains Van Oers. 'That is obviously good for the virus. In 2014 we showed that the crawling along faster and the climbing are caused by two different genes. Light is also an essential factor in the climbing.'

To study their movement, the lab has set up a caterpillar arena with cameras mounted on top that lets them track the caterpillars. 'We don't know yet exactly how these viruses influence their movement: whether they do something to the brain or exert an indirect influence via hormones, for example. We now want to see how the caterpillar's gene expression and protein profiles change by comparing caterpillars that have been infected with a normal baculovirus against caterpillars infected by a baculovirus in which the gene causing the hyperactivity has been removed.'

HITCHING A LIFT

In addition to the insect virus research, there are two other research areas in the Wageningen Virology group. Here too the focus is on the interactions between the viruses and either their hosts or the 'vectors': living creatures, mostly insects, with which viruses can hitch a lift. 'For instance, we are looking at arboviruses, including chikungunya, that are spread by mosquitoes and make humans or livestock sick. We also study the mechanisms plants have for resisting plant viruses, which is an important topic in crop production,' says Van Oers. Her group is also working on developing a vaccine for a viral disease in salmon. 'Given the ever-increasing numbers of farmed fish, it is only to be expected that there will be all kinds of viral outbreaks,' says Van Oers. 'Those fish live in close quarters and are sometimes under a lot of stress. Then viruses soon spread. Incidentally, you often see that viruses only really become a problem when you start having a large number of individuals of the same species living close together. Many plant viruses, for example, clearly only evolved once humans started farming and there were suddenly large numbers of the same plant growing close together.'

Van Oers thinks that the different research lines can benefit from their mutual interconnections. 'I believe we can learn an awful lot from one another. Insects often play a part in the viruses we are looking at, so the methods they use to defend themselves are interesting for all of us. The funny thing is that we are really increasingly working on the fringes of virology because we are doing a lot on the virus-host and virus-vector interactions. One of the questions we are currently focusing on is what determines whether Dutch mosquito species are capable of transmitting viruses that are tropical in origin, such as the West Nile virus and chikungunya. That is important because it lets us assess how big a risk there is of those viruses causing problems here too.' ■

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