Nitrogen fixation in the sights of the agribusinesses

Will GM microbes soon be on European fields?

Products with genetically modified microbes still play hardly any role in agriculture. But more and more companies are using genetic engineering and genome editing to develop microbial fertilizers and pesticides. Time to take a look at the developments.

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Rarely has so much money flowed into an agricultural research start-up as into Pivot Bio: the US company has received 600 million dollars in the last five years - from Microsoft founder Bill Gates and Amazon boss Jeff Bezos, among others. The fact that investors are so interested is due to Proven and Return, the two products that Pivot Bio has launched on the US market so far. Both products are fertilizers for cereals - Proven for corn, Return for millet and wheat. And both products consist of soil bacteria that fix nitrogen from the air and pass it on to the plants. What's special about them? Until now, fertilizers made from nitrogen-fixing bacteria were largely limited to vegetables such as soya, peas and beans. For cereals, however, they are a novelty. This opens up a huge market in which fertilization has so far been carried out with chemically produced nitrogen.
Another special feature of Proven and Return is that the bacteria they contain are genetically modified.

Increasing market potential for GM microbes

Products containing genetically modified (GM) microbes are still a rarity in agriculture; there are only a handful of them on the market worldwide. But this is likely to change soon. In addition to Pivot Bio, a whole range of companies have started to develop GM microorganisms for agriculture.
There are three main reasons why interest in GM microbes is growing: Firstly, thanks to technological advances, developing new strains of microbes is easier and cheaper than ever before. Secondly, a number of countries have decided in recent years to no longer regulate new processes such as genome editing as genetic engineering. As a result, the approval of GM microbes that do not contain foreign genes has also become easier and cheaper than ever before. The bacteria contained in Proven and Return, for example, could be marketed in the USA without genetic engineering approval.
The third and perhaps most important reason is that the potential market for GM microbes is constantly growing. Previously, it was small because fertilizers and pesticides consisting of fungi, viruses or bacteria were mainly used in organic farming, where GM organisms are generally prohibited. Now it is growing because politicians and society are increasingly demanding a move away from artificial fertilizers and synthetic chemical pesticides and microbial products are now increasingly being used as an alternative in conventional agriculture.
Fertilizers show just how much interest there is in the development of GM microbes. In addition to Pivot Bio, start-ups such as BioConsortia, Switch Bioworks and Quorum Bio are also active in this field, as are several corporations. One of them is Novozymes. The Danish company, which grew up producing enzymes, has also been researching microbial

agricultural products for several years. In one of its projects, the company is using genetic engineering to develop nitrogen-fixing bacteria.
Bayer also has its sights set on nitrogen fixation. In cooperation with Pivot Bio, the German multinational is working on GM strains of Bradyrhizobium. Bacteria of this species live in the root nodules of soybeans and supply the plant with nitrogen from the air. Bayer is also working with Gingko Bioworks, a leading synthetic biology company, to create GM bacteria for nitrogen fertilization in cereals. The collaboration began in 2018 with seed capital of USD 100 million.
In 2020, the world's second-largest fertilizer manufacturer, Mosaic Company, also got involved in the development of nitrogen-fixing bacteria. Since then, the US group has been supporting the start-up BioConsortia, which uses genome editing to produce bacteria for fertilizing corn and wheat. The partnership's first products are planned for 2024. One of the target countries is Brazil. The competent authority there has already certified that the company can market two preparations with foreign DNA-free GM Paenibacillus bacteria without GMO approval.
The second area in which interest in the development of GM microbes is growing is crop protection. Four products are already on the market. Nogall from Bio-Care Technology has been available for more than thirty years. The product consists of GM rhizobia, is effective against root neck gall canker in stone fruit and is approved in Australia, Turkey and the USA. As the GM rhizobia in Nogall do not contain any foreign DNA, the product is not subject to genetic engineering legislation in any of the three countries.
Also on the market are Crymax and Lepinox WDG from Certis, which have been used in fruit and vegetable cultivation in the USA since the noughties, and Jinweijun from Wuhan Kernel Biotech, which received approval in China in 2017. What the three products have in common is that they contain Bacillus thuringiensis, a soil bacterium that naturally produces insecticides. By combining toxin genes from different Bacillus strains in a single strain, the companies have each created products that produce several toxins and therefore have a stronger effect or a broader host spectrum.

Death or life: dsRNA-forming GM microbes

The number of pesticides containing GM microbes that are effective against insects is likely to increase soon, as several companies are working on such products. One of them is Pebble Labs. For the development of its products, called Directed Biotics, the US start-up is relying on a concept that is currently attracting a lot of attention: The use of GM microorganisms that form double-stranded RNA - dsRNA for short. This substance triggers the RNAi process in cells, which can be used to specifically shut down vital genes in pests. Pebble Labs is currently preparing the first release trials.
While Pebble Labs relies on the use of live GM microbes, companies such as Ajinomoto, TransAlgae and Renaissance Bioscience work with inactivated organisms. They hope that this will make it easier to get their products through the approval process, as inactivated GM microbes are not subject to the strict genetic engineering laws in many countries. The Israeli start-up TransAlgae, for example, produces dsRNA-forming microalgae and then inactivates them in a freeze dryer before bringing them to the field as a powder. The Canadian company Renaissance Bioscience, on the other hand, produces dsRNA-forming brewer's yeast, which it intends to kill with alcohol before spreading.

Some companies also have GM microbes in the pipeline to combat plant pathogenic bacteria. The US start-up Robigo, for example, wants to convert harmless bacteria with synthetic biology so that they can be used as "molecular vigilantes" against pathogenic bacteria. Cytophage and Auxergen are working on preparations with GM phages - viruses that attack bacteria. The British company Flourish is pursuing a special approach. Using a technique called Guided Biotics, it wants to develop a remedy for tomato spot blight by equipping harmless microbes with ring-shaped pieces of DNA, so-called plasmids, on which the genes for the formation of CRISPR reagents are located. Once sprayed onto infested tomatoes, the GM microbes are supposed to transfer their plasmids to the pathogenic bacteria, where the CRISPR enzyme then cuts their chromosome at the predetermined sites, thereby killing them.
In addition to fertilizers and crop protection products, biostimulants are also among the inputs for which GM microbes are being developed. Alongside US companies such as Gingko Bioworks and Elemental Enzymes, BASF is also active in this field. The German company already has a preparation on the US market. Its corn seed treatment Poncho Votivo 2.0 contains GM Bacillus thuringiensis, which break down organic substances in the root area and thus make nutrients available to the plants.

Lobbying for deregulation is underway

While GM microbes are already being used in US agriculture, the fields in Europe are still free of them. So far, only one application for placing on the market has been received in the EU. In 2005, Bio-Care Technology wanted to launch Nogall on the market, but then withdrew the application for approval - the additional requirements imposed by the authorities due to the pesticide and genetic engineering regulations at the time were too extensive for the company.
Will European fields remain free of GM microbes? It is clear that the EU market for microbial fertilizers, biostimulants and pesticides will grow as a result of the European Green Deal, which entails a reduction in synthetic products in agriculture. It is also clear that companies with GM microbes do not want to miss out on this market and are therefore working on easier access. On the product law side, the first hurdles have already been overcome: Following the revision of the Fertilising Products Regulation, EU-wide marketing of microbial fertilizers and biostimulants has been possible since 2020 and the approval requirements for products containing microorganisms have been eased in pesticide legislation in 2022. What remains to be relaxed in the eyes of companies is genetic engineering law. Lobbying for this is underway. Pivot Bio, for example, has been entered in the EU Transparency Register in 2022. EuropaBio, a lobby organization of the genetic engineering industry, is also active. It wants to achieve deregulation, particularly for GM microbes without foreign DNA, and is working towards the EU Commission submitting a proposal on this in 2024. The EU Commission's position remains to be seen. It has instructed the European Food Safety Authority (EFSA) to provide it with the basis for a regulatory proposal by the end of June 2024. The Commission's current proposal to deregulate new genomic techniques for plants shows that it could be open to a relaxation of the rules.

FOE call for moratorium on Guided Biotics

Microbes still play hardly any role in the European debate on the pros and cons of genetic engineering in agriculture. This also leaves important questions to be discussed. What risks do GM microbes pose? Are there

gaps in our knowledge that need to be filled before market launch? Are GM microbes another technofix that perpetuates industrial agriculture?
In the USA, Friends of the Earth (FOE) recently warned against the widespread use of GM microbes. The conservation organization is particularly concerned about the existing gaps in knowledge and the ease with which microbes exchange genes with each other. FOE considers Guided Biotics technology to be just as worrying as gene drive. They are therefore calling for its use to be placed under a moratorium.