The profiler

Lothar Willmitzer, a scientist at the **Max Planck Institute of Molecular Plant Physiology** in Potsdam, had never thought about the commercial application of his research. Nevertheless, he founded three companies during his career. He is particularly pleased that his research has also been able to benefit humans.

TEXT **CATARINA PIETSCHMANN**

Scientists can read the metabolism of an organism like a book. It reveals stress, diseases, environmental toxins, and nutrient deficiencies as well as which nutrients an organism needs and which medicines work in the case of illness.

In contrast to the metabolism of humans, little was known about the metabolism of plants for a long time. This is why, in 1994, Lothar Willmitzer and his colleagues at the Max Planck Institute of Molecular Plant Physiology in Potsdam-Golm, which had just been founded at the time, began to investigate the metabolic pathways of plants such as *Arabidopsis thaliana* and potato. It soon became clear just how extensive this project was. The uptake of nutrients, the formation and storage of constituents, plant growth, and seed formation are all part of the metabolism.

Even the formation of starch in a potato plant proved to be much more complicated than expected. "Once we had identified genes for starch production, we modified their activity in such a way that they were able to produce more and higher quality starch," says Willmitzer. "However, the daughter plants produced less instead of more starch." Willmitzer concluded that he would have to switch off one gene after another in order to truly understand starch metabolism.

AUTOMATED METABOLIC ANALYSIS

Countless samples of plant extracts soon covered the lab benches. Each of them was composed of different metabolic substances. To analyze them all would have been a Herculean task. "We quickly realized that we would have to automate this so we wouldn't get bogged down in routine tasks," says Willmitzer. But the chemists were skeptical. They thought that analyzing hundreds of unpurified samples in parallel would produce results that were far too inaccurate.

"We didn't want to precisely determine one substance in the sample but rather the ratio of as many substances as possible to each other," says Willmitzer. The aim was to detect the change in metabolism when a gene is switched off. Willmitzer then wanted to compare this pattern with that of other genes and thus obtain a comprehensive picture of the metabolic activity of a plant.

He called his method "metabolic profiling". He started with *Arabidopsis*. Crop plants such as potatoes, corn, or rice would follow. The initial test results suggested that the plan would work in principle. But it would take years to switch off the approx. 30,000 genes of *Arabidopsis* one by one and measure the effect.

Willmitzer thus began his second career as a company founder. It all began in 1998 with his spin-off, Metanomics. Funded by BASF and the German Federal Ministry of Education and Research, Willmitzer and four former employees developed the initial technology platform.

Before then, it was common practice to process all biochemical levels

Lothar Willmitzer is successful not only as a scientist but also as a founder of spin-offs. The companies he founded now employ around 55 people.

completely and successively: from the gene and DNA to the messenger RNA to the protein synthesis and the metabolic products. In the case of Metanomics, however, the scientists switched off a gene and then observed only the effect on the metabolic cocktail of sugars, amino acids, enzymes, and vitamins. Each sample provided a mixture of 350 different substances. Approximately 40% of the substances were completely unknown. Metanomics is now an independent subsidiary of BASF.

SERVICES FOR THE INDUSTRY

In the years to follow, Willmitzer repeatedly asked companies whether he could analyze plant metabolites for them. But services for industry are not part of the scope of a Max Planck Institute. Willmitzer therefore founded Metasysx in 2012. The company, which is located within view of the Max Planck Campus, now has around a dozen employees analyzing the metabolic profiles of plants. In addition to complete metabolic profiles, the small company also determines the fatty acid profiles of a plant, integrates genetic and protein data, and produces metabolic products as reference standards.

"Start-up companies are often very much driven by people, and developments are sometimes coincidental," says Willmitzer. For example, his Chinese doctoral researcher, Yan Li, was initially part of the Metasysx team and then returned to China. "We had considered building a laboratory there. But that wouldn't have been easy for a foreign company." But now with a Chinese pharmaceutical company as a partner, it is. Metasysx now has a subsidiary company called Metanotitia in Shenzhen. It further develops metabolic profiling for both acute and predictive diagnostics of various diseases.

Metabolic analysis for medical applications is now also becoming more important in Germany. "Metasysx also collaborates with the Charité hospital in Berlin. We hope to improve the dosage of drugs that suppress the immune system after transplantation so that the new tissue is not rejected by the body," explains Willmitzer.

MORE PRECISE DOSAGE

There is still no precise information on the quantities in which these products should be administered, so Metasysx now analyzes the metabolic profiles of blood and urine samples of patients treated with various doses. "We want to develop mathematical models in order to be able to more accurately predict the effect on individual patients."

Another joint project between Metasysx and the Charité could be the treatment of depression. "Doctors still diagnose the disease mainly by interviewing the patients. It is not possible to predict which drugs a patient will respond to. Doctors must therefore experiment with different active ingredients," explains Willmitzer. Metabolic

Arabidopsis thaliana is the model plant for plant geneticists. Even such an inconspicuous plant contains thousands of different metabolic products. These also include lipid molecules. These can be sorted based on their chemical properties (right). Each color pixel corresponds to a specific molecule type.

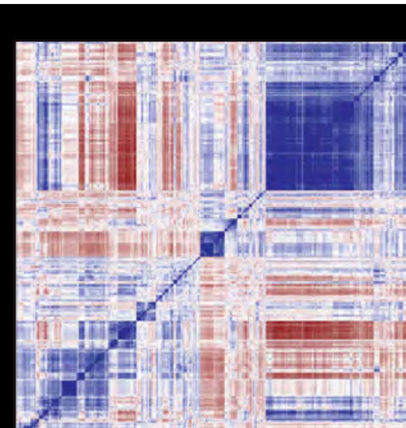

Photo: MPI of Molecular Plant Physiology; graphic: Lothar Willmitzer products in the blood reveal which active ingredient is effective in a patient. The aim is to be able to determine the right antidepressant via blood tests prior to therapy.

Another application of metabolic profiling is the development of improved herbicides. The pharmaceutical and agrochemical company Bayer initially wanted to cooperate with Willmitzer's Department at the Max Planck Institute. But Willmitzer declined. "In our field of research, everything is public. In contrast, industrial research is usually a trade secret. We would have had 20 employees who were not allowed to talk about what they do. This sort of thing is not good for the working environment." Willmitzer therefore founded Targenomix in 2013. The company analyses what exactly in a plant is triggered by pesticides.

The potato plant uses its tubers to store starch. So many genes are involved in the production of this substance, which is also important for human nutrition, that researchers can only decipher the starch metabolism only with the help of automated methods.

FOUNDER WITH HEART AND SOUL

According to Willmitzer, spin-offs face three challenges: "First, developing an idea; second, obtaining funding; and third, finding the right employees – because the success of a project depends on them." Especially in the first year after founding them, he had to put a lot of his heart and soul into his companies. "Ideally, you should then be able to gradually withdraw from the day-to-day business because the young team doesn't want the old fossil to keep showing up," says Willmitzer with a smile. Moreover, research at the Institute must continue unabated.

Three years ago, the 68-year-old chemist once again took on something completely new. He was driven by a provocative question: "Is it possible that all the small metabolic molecules with which the cells gain energy or form lipids, sugars, and amino acids also control these processes? That they are not only part of these processes but also play an important role in diseases?" Nobody had thought about that before.

But how do you obtain access to such control molecules? If they carry out these functions, they would require a partner – most likely a protein. In this case, the substances would have to occur as single molecules and be bound to a protein.

"Nobody believed us at first," says Willmitzer. But his suspicions proved to be correct. Five such protein-metabolite duos have already been found. "This approach could one day become very important. When a pharmaceutical company targets a protein for therapy, it first tests countless different compounds stored in huge molecular databases. However, if there is already a natural binding partner in the body and we know its structure, this greatly simplifies the search for active substances."

Willmitzer has also passed on this project to a younger colleague, Aleksandra Skirycz, who currently heads a research group in his Department. "But she has been offered a position in the U.S. and will take the subject with her. So, it looks like I won't have a project for my last two years here," says Willmitzer, laughing. But definitely a new idea! ◂

Photo: MPI of Molecular Plant Physiology, Josef Bergstein