High-tech replaces green fingers: Germ buds of Arabidopsis varieties are grown under standardized conditions so the functions of the various genes can be decoded.
They came up with an unusual idea and found a way to put it into practice. They provided the proof of concept – and it worked. And then they did the necessary calculations: How long would it take to switch off, individually, all of the approximately 30,000 genes found in thale cress, *Arabidopsis thaliana*, and to see how its metabolism changes as a result? Even the most optimistic projections indicated that it would take years. So now what?

In 1996, Lothar Willmitzer, Director at the Max Planck Institute of Molecular Plant Physiology in Golm, near Potsdam, found himself confronted with an awkward question: Is it really the task of a basic research institute like Max Planck to develop a high-throughput process? The answer was a clear no. The parallelization of processes is the concern of industry, he decided. And thus the idea of setting up a company was born.

What is so interesting about plant metabolism? If humans and plants have one thing in common, it is the fact that they both have rather complicated metabolic systems. The human metabolic system has been well researched, mainly because changes in this system can cause serious illnesses or, conversely, be caused by them, as in the case of diabetes.

**IF GARLIC AND VANILLA TASTED THE SAME**

In addition, the human metabolism does not have the variety of secondary compounds found in plants. Far less is known about metabolic processes of plants. To complicate matters further, there is enormous species diversity in the plant world, and the metabolites can differ significantly from species to species: some produce high-quality oils, others are rich in vitamins and flavors, while yet others mainly form sugar or starch. Which is a good thing, since plants are the primary basis of our nutrition, and life would be miserable if corn-on-the-cob, thyme, strawberries and grapefruit all tasted the same. It would be possible to tell the difference between garlic and vanilla based on their physical appearance, but not from their smell.

The consequences do not bear thinking about: the cuisine of Thailand would be the same as that of Italy. Restaurants would not exist – what for? Eating would not be a pleasurable activity, but merely a means of nutrition intake – an annoying but necessary process. Instead of grocery stores, we might have depots everywhere that we would have to stop by regularly to cheerlessly consume some nondescript pureed mush. Evolution might even have equipped us with a practical proboscis for the purpose. Fortunately, things turned out differently: a strawberry is a strawberry. And its contents are completely different in composition than those of a kernel of corn.

The nutrient content, flavor, shape, color, size and yield of a plant can be influenced through breeding. This is, however, a protracted process. Too protracted to enable the resolution of the problem of world hunger against the backdrop of the ever-increasing global population. Plant biotechnology facilitates much faster development of crop plants that are more productive, nutrient-rich, or even stress-resistant –
which means that they can thrive on barren or saliferous soils, withstand longer periods of drought, or get by with very little light.

FEISTY POTATOES DREW THE EYE TO THE BIG PICTURE

But why work through a plant’s entire genome for this? The Max Planck Institute of Molecular Plant Physiology had been established just shortly before all this happened, in 1994. Its purpose was to test the biosynthetic pathways in plants in order to understand how the formation and transport of metabolic products and their storage in the leaf, flower or fruit work. “At the time, we concentrated on the biosynthesis of starch in the potato, and identified genes that play an important role in that process,” explains Willmitzer. The researchers altered the activity of this gene in the hope that the next generation of plants would produce more and higher-quality starch. But they generated less starch and did other nonsensical things as well. But why?

“We realized that, in order to make any progress, we would first have to characterize a plant completely at the metabolic level.”

Richard Trethewey, a biochemist with a doctorate from Cambridge, who was working at the institute as a Marie Curie scholarship holder at the time and who is a co-founder of metanomics, has to laugh when he looks back at it. “The biologists in the team were enthusiastic: Fantastic! It’s amazing all
Laserrad im Fokus: Gerd Leuchs und seine Mitarbeiter polarisieren Laserlicht radial, so dass es bildlich gesprochen nur noch entlang der Speichen eines Rades schwingt. Dieses Licht lässt sich besonders scharf fokussieren.

Was aus einem Atom rauskommt, muss auch wieder reinpassen. Das radial polarisierte Licht möchten die Erlanger Forscher mit einem Parabolspiegel auf ein Atom fokussieren.

Durch einen Parcours aus Spiegeln, Linsen und anderen Instrumenten schickt Gerd Leuchs einen Laserstrahl, um das Licht für die besonders scharfe Fokussierung oder andere optische Kunststücke zu präparieren.

When particular genes are switched off, it can have an effect on the growth and flowering propensity of the plants.

The big parallel operation: In the Berlin-based biotech firm’s high-precision plant climate chambers, 10,000 plants like thale cress (Arabidopsis thaliana) can be tested simultaneously for tolerance.
Richard Trethewey, biochemist with a Cambridge doctorate and co-founder of metanomics.

Members of the metanomics team examine genetically modified thale cress plants in the greenhouse.
The planning of marketable products had to wait until phase three: the transfer of the acquired expertise to crop plants – that is, testing selected genes in corn, rice, soybeans, rape or cotton – and producing individual packages of knowledge for industrial clients.

A COMBINATION OF COURAGEOUS RISK-TAKING AND FORESIGHT

There was no question about it: this could not be done with venture capital, but required a strategic investor with staying power – a major industrial corporation that was active in the field of plant biotechnology and interested in understanding genetic functions with a view to optimizing plants. For this reason, of the eight partners initially considered, only three made it to the final round. “BASF was simply a good fit because the company produces fine chemicals, food supplements, and animal nutrition,” explains Willmitzer. Moreover, the corporation had just decided to enter the plant biotechnology market. “We told them that our technology can provide, for example, the genes that play an important role in vitamin biosynthesis in plants.”

Was it courageous risk-taking or foresight? Perhaps a combination of the two: BASF authorized an investment of 50 million deutschmarks for five years.” Then the talks with potential investors began. Willmitzer, who recognized the potential in the method early on, realized that they were still facing a very long process before the concept would actually be used commercially.

The company’s first objective had to be the development of a highly efficient technology platform. The second was the systematic analysis of the Arabidopsis genome and the development of the metabolite database. The planning of marketable products had to wait until phase three: the transfer of the acquired expertise to crop plants – that is, testing selected genes in corn, rice, soybeans, rape or cotton – and producing individual packages of knowledge for industrial clients.

High-tech behind a historic façade: The metanomics building in Berlin’s Charlottenburg Biotechnology Park.
Today, metanomics has 110 employees, a third of them scientists. The concept worked. The development of the technology platform progressed rapidly; no new equipment had to be developed, but processes and a lot of software, as most of the processes were to be automated – from cloning, extraction and analysis to feeding the comprehensive files into the database. Willmitzer, who stayed on with metanomics for a time as a consultant, adds, not without a certain pride: “After just one year, they managed to get through almost one hundred genes per week. But not with a hundred people – just one scientist working with four technical assistants!”

The number of genes that are now processed each day is not disclosed. Just this much: metanomics works in two shifts with the help of vigilant robots that send a text message if a problem arises. The analysis laboratory, in which several dozen GC-MS machines work away buzzing and humming, are generally deserted. Chemistry TAs track the work of their fully-automated colleagues on monitors in the quiet office. They enter the laboratory only for maintenance purposes and to exchange the samples.

Fifty-five thousand genes have now been tested – both by switching off existing genes and by deploying new ones in Arabidopsis. “The latter process is very interesting, as it allows useful new characteristics to be introduced into the plant. For example, the ability to activate new metabolic pathways or produce new substances,” explains Trethewey. Attention is now focused on crop plants. Why didn’t they work on corn from the outset? For practical reasons: Arabidopsis is small and easy to grow in the greenhouse and, unlike, corn, takes only a few weeks from germination to seed formation. Unfortunately, the genes in different plant species are not identical. The challenge now is to identify the crop plants’ most interesting genes from the existing data and the information provided in the relevant literature and to generate their metabolite profiles.

FROM THE BYWAY TO THE HOME STRETCH

Apart from the issue of efficiency, how does working in a company differ from working in an institute or university? Trethewey ponders the question briefly. “If we get an unexpected result, we always have to look at it in the context of our objective: are we more likely to achieve our objective now, or would it make sense to go off on a tangent with a different aim? Industry is always highly aware of such processes, but this is not always the case in basic research.” metanomics decided to go off on just such a tangent in 2003 and established metanomics Health. Metabolite profiles provide a multi-parametric and highly accurate description of the state of an organism and are of great diagnostic value. This method should therefore be ideal for use in medicine and pharmaceutical research. However,
Metabolic analysis holds enormous potential and has historically been underestimated. We are currently experiencing an absolute renaissance in medical science. Despite this, it remains a challenge to complete the cycle from scientific insight to an actual product.

Even the prudent Lothar Willmitzer did not see this potential application at the beginning.

“Not everyone reacts to a drug in the same way. For clinical tests, it would be helpful to know whether or not a subject will be among the responders,” Trethewey explains. This can be tested using a metabolite pattern in the patient’s blood or urine. The procedure is the same – only the sample preparation differs for the red and the green profiling.

“Big or small, healthy or diseased, yellow, green or speckled, the metabollic products are closest to the phenotype,” explains Willmitzer. Especially in medicine, it is important to be able to differentiate between state A and B. “And it has emerged that this can be done surprisingly well using metabolite profiles.” Together with the Charité hospital in Berlin, his Max Planck team has produced profiles of 100 kidney cancer patients – for both the tumor and healthy kidney tissue. “It was no surprise to discover that they can be clearly differentiated using the method,” he explains. However, it was astonishing that just two substances out of hundreds were sufficient to do this. And that these are substances that would never have been considered as cancer markers before. Now numerous other examples involving the use of the method can be found in medicine.

Toxicological screening is another area in which the metabolite profiling approach can be applied. Before a new substance can be authorized, its safety must be demonstrated in long-term tests, which are usually carried out on animals. According to Willmitzer, this could be done faster and more cheaply by taking a training set of 250 substances whose effect mechanisms are known, introducing them individually into human cell lines and rats, and creating a database with the metabolite profiles. “You now know which mode of action triggers which pattern. With a new substance, all you have to do is look for a similar pattern in the database and you know how it reacts in the body.”

NEW DRUGS TO MATCH THE METABOLIC PROFILE

The use of this method could also lead to significant progress in the context of everyday clinical laboratory medicine. “At present, only a few metabolites, like glucose and cholesterol, are observed in blood tests. The diagnostic validity is relatively low. But we see thousands of these compounds! If they are measured regularly, pathological changes can be identified long before they have manifested themselves. “A regular metabolite check by the family doctor? Why not? And healthy patients could be given tips on how to feel even better.

The method is now well established in science. Researchers throughout the world use it to delve deep into the system biology of various organisms. At the Max Planck Institute in Golm, it is used to track the changes in a plant’s metabolism minute by minute – from sunrise to deep in the night, at high temperatures, in frosty conditions or during periods of nutrient deprivation.

Richard Trethewey’s vision for the future also includes, among other things, new drugs that are based on a more detailed understanding of metabolism. “Metabolic analysis holds enormous potential and has historically been underestimated. We are currently experiencing an absolute renaissance in medical science. Despite this, it remains a challenge to complete the cycle from scientific insight to an actual product.”

Whether green or red profiling – the foresightedness of science and industry will pay off. As Victor Hugo said: “There is nothing more powerful than an idea whose time has come.”