Metabolic detectives: Dr. Julian I. Borissoff from Bayer HealthCare and Dr. Mark-Christoph Ott from Bayer CropScience (left to right) analyze the chemical details in the metabolism of humans, animals, plants and microorganisms to track down new targets for active ingredients.

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TRACKING DOWN DISEASES: METABOLIC ANALYSIS ENABLES NEW APPROACHES

Decoding molecular patterns

They investigate metabolic processes in humans, animals, plants and microorganisms: scientists at Bayer are using innovative methods to identify new targets for active substances and to test innovative procedures, from an artificial nose used to diagnose lung diseases through to highly effective mass spectrometry used in the development of new crop protection agents. The key to their success: precise analysis of molecular fragments called metabolites.

Molecular testing of the air from the lungs: breath analysis can detect biomarkers that are characteristic of specific diseases.

Our breath reveals our body's secrets: each time we exhale, the air we breathe out contains a large number of molecules. These metabolic products, known as metabolites, are already helping doctors to determine what diseases we have. If doctors detect nitric oxide in the breath of a patient, for example, it signifies that this person is suffering from asthma. A person's "gas fingerprint" could be of interest as a procedure to help doctors diagnose lung disease.

Using biomarkers to detect diseases

Researchers at Bayer are also using breath tests to investigate new ways of developing diagnostic procedures, monitoring the course of diseases and observing the body's response to certain active substances. "Breath analysis can be used, for example, to detect the presence of biomarkers characteristic of certain diseases. And it is non-invasive, meaning that we do not have to perform any surgical interventions on the patient's body," explains Dr. Julian I. Borissoff from Cardiovascular Research at Bayer HealthCare in Wuppertal. For example, these biomarkers could help researchers draw conclusions about metabolic activities and identify new underlying molecular mechanisms of diseases by comparing various breath patterns. Initial trials and studies to elucidate the potential of these future diagnostic tools are already under way in Bayer HealthCare's laboratories.

"The answers to many medical questions can be found not just in our breath, but in particular also in our blood, urine, saliva and tissue fluids," Borissoff explains. "All we have to know is which biomarkers, substance patterns and molecular fragments we are looking for." This search is based on the knowledge that diseases lead to metabolic changes – and evidence of these changes can be found in the metabolites. "You could say they are the body's chemical fingerprint," the Bayer scientist says. This fingerprint can provide valuable information about where in the metabolic process active substances could most effectively intervene. But although it sounds easy, it actually involves extensive research work: deciphering the metabolome, i.e. all metabolic characteristics of an organism, would mean having to analyze thousands of molecules – a mammoth task. Thanks to advances in mass spectrometry, however, it is now possible to detect a large number of different molecules relatively quickly and simultaneously. These are just some of the aspects that the metabolomics team is investigating. The researchers are part of an interdisciplinary, collaborative effort at Bayer called the Nimbus project, in which Bayer's life sciences subgroups are working together closely to share their knowledge in order to identify new approaches for new active substances.

After all, metabolic processes in humans aren't the only source of important findings. This is why the researchers at Bayer CropScience are taking a closer look at the metabolite patterns of plants, insects and microorganisms. Their goal is to determine the metabolic fingerprints that characterize, for example, very healthy plants. "Using these patterns, we can examine both the mechanisms of action of chemical agents and the effects they have on the vitality of insects, plants and microorganisms," explains Dr. Mark-Christoph Ott, Head of Bioinformatics at Bayer CropScience in Monheim.

Metabolic profiles provide an insight inside plants

The issues addressed are largely comparable with those in the field of biomedicine. The scientists are also searching for metabolites that might, for example, indicate that pests have become resistant to a specific active substance. "The molecular pattern reveals factors such as how well a plant's photosynthesis process is working and the status of its nutrient supply," Ott says. "Our goal is to identify both possible nutritional deficiencies as well as positive effects at an early stage, before the symptoms even become detectable or visible to the naked eye."

Unlike genes and proteins, metabolites serve as direct signatures of biochemical activity and are therefore easier to correlate with the phenotype (external appearance). There is a direct connection between the metabolite

Biomarkers – revealing substances

Doctors long ago recognized that biomarkers could be used to diagnose diseases. Even in ancient times, for example, healers realized that sweet-smelling urine is a sign of diabetes. Medical experts now know that glucose molecules are a biomarker for diabetes, while the presence of a peptide hormone called human chorionic gonadotropin in the urine indicates pregnancy. Blood components, concentrations of ions, enzymes and hormones and antigens are all classic examples of biomarkers in laboratory diagnostics. New molecular biology techniques also measure DNA sequences. Biomarkers can be classified into various groups: diagnostic biomarkers allow doctors to pinpoint the exact condition a patient has and distinguish it from similar conditions, prognostic biomarkers are useful for assessing the probability of a cure or how the disease will progress, and predictive biomarkers are used to determine the likelihood of a patient developing a specific condition in the future. In Alzheimer's disease, for example, it is highly likely that pathological changes occur in the brain long before other symptoms appear. Suitable biomarkers that would identify this preclinical phase and distinguish it from similar conditions would be hugely important.

Medical laboratories use samples of urine, saliva, blood and tissue fluids for diagnostic work.

profile and, for example, a disease. The metabolic processes in the tissues and cells of a large number of organisms are generally known, but there is still a lack of details at the molecular level. Recent advances in mass spectrometry allow us to measure thousands of known and unknown metabolites simultaneously. A large number of new metabolomics studies have been set up to identify previously unknown metabolic products as relevant markers for diseases and plant health. "This new knowledge can be used to characterize biological states and thus to develop new research approaches," says Ott, who is currently looking at more than a dozen biological issues from the whole world of Bayer CropScience. Together, he and his team are planning the next research steps: "In particular, we are debating which analysis methods make good sense for possible pilot studies," explains the bioinformatics specialist. Uniformity is especially important to Ott in this process. "Results such as metabolic profiles and metabolite patterns can only be optimally placed in a broader context when the underlying experimental conditions, sample preparation and measurement techniques permit comparability or when incomparable results are marked as such," Ott explains. Their focus is primarily on optimally combining the right experiments for the issues at hand, with the objective of creating a metabolite knowledge database that stores all information, links it and makes it accessible to all Bayer scientists worldwide. This extremely valuable knowledge basis will play an important role in the company's research future and will also provide scientific support for market products. The establishment of a joint metabolomics technology and data platform for Bayer Pharmaceuticals and Bayer CropScience therefore represents significant added value for both organizations. "In the future, we will be able to better compare results and arrive at those results faster and more easily. We are thus facilitating efficient sharing of knowledge and establishing analytical methods that are available to the entire team," says Ott.

"Molecular changes in the metabolic profile can be measured even before any symptoms become visible."

Dr. Mark-Christoph Ott,
Head of Bioinformatics at Bayer CropScience in Monheim am Rhein

www.research.bayer.com/metabolomics
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