

A unique rope ladder: the minimal deviations between genes are what make different people individual. The 3D model shows the atomic structure of the huge DNA molecule carrying genetic information.

BAYER RESEARCHERS ARE APPLYING DISEASE GENOMICS TO GET TO THE BOTTOM OF DISEASES

Reading genes for better therapies

Bayer researchers scrutinize the anonymized DNA of thousands of patients to find genetic differences so that they can gain a better understanding of the causes of cardiovascular diseases. The next step is to find active ingredients that can intervene in the disease processes.

Every human is unique. This individuality can be explained at least partially by differences in DNA. Each person's genetic code varies from that of the next individual at approximately ten million positions. These variations determine not only the color of our eyes or hair, but may also be responsible for our predisposition to certain diseases. An interdisciplinary group of researchers led by Dr. Kirsten Leineweber, head of the Disease Genomics Department at Bayer's Pharmaceuticals Division, is therefore searching for evidence of genetic risk factors that determine an individual's predisposition to cardiovascular disease; a complex issue that demands expertise in the most different of areas, and the team therefore comprises experts in biology, molecular and cell biology, human genetics, medicine, bioinformatics and data protection, all of whom work in Berlin, Wuppertal and Leverkusen.

Correlating patients' disease symptoms to their genes

"Our ultimate goal is to connect the phenotype – the physiological characteristics of a patient and in particular the clinical symptoms – to the genotype – the genetic profile. In this way we will be able to confirm existing knowledge and derive new hypotheses on the origins of diseases," says Leineweber. She and her expert team of genome researchers are



Dr. Kirsten Leineweber is working to identify high-risk genes that are associated with cardiovascular diseases. She and her interdisciplinary team of researchers are searching for the causes of diseases on the gene level. Their ultimate goal is to provide patients with tailor-made medicines.

not attempting to make conventional medical diagnostic tools superfluous but are rather aiming to supplement them with an additional facet. At present, the researchers are concentrating on cardiovascular diseases and kidney disorders.

"Our search for the genetic variant or variants that contribute to the severity of a disease is like the proverbial search for a needle in a haystack," says Leineweber. To improve the definition of these genetic variants, the scientists are looking for

what are termed extreme phenotypes – people who have a particularly strong or weak external characteristic. For example, elderly people who have a particularly strong cardiovascular system compared with the average in their age group may flag up protective variations that young high-risk patients lack. "In this way we can find out which genes are essential for heart function in old age or fundamentally play an important role," explains Leineweber.

Bioinformatics analysis flags up high-risk genes

The scientists are able to apply cutting-edge methods to find those variations that cause diseases among the millions of genetic variants. "We're helped by high-performance computers

99.5
percent

of human genetic information is identical.

Source: Levy et al., 2007



The laptop in the lab: bioinformatics analyses help Dr. Florian Sohler and Dr. Daniel Freitag (photo left, left to right) identify high-risk genes. Dr. Peter Staller and Dr. Bertram Weiss (photo right, left to right) develop hypotheses about the roles of these genes in cell metabolism and then verify them in the laboratory.

and statistics. That's the only way that we can correlate the heart failure phenotype to genetic markers," explains Dr. Florian Sohler, a bioinformatics specialist in the interdisciplinary team. To this end, the researchers search for gene variants that occur more frequently in a group of patients with heart problems than in a control group.

If they know the genetic marker, the question is: at what point does it inter-

vene in the disease progression? "If it changes the function of a protein, for example, we can postulate that its dysfunction plays a role in the development of the disease," says Sohler.

Confirming hypotheses with molecular biology

The next step is then to experimentally prove this hypothesis. A new tool that

the scientists are using to investigate the functionality of gene variants is genome editing. This molecular biology method can be used to specifically introduce the high-risk variant into the gene that is responsible for producing the protein that is believed to be harmful. The scientists can then investigate the physiological effects of a gene variant in a biological system.

The researchers validate their hypotheses on patients

Once the researchers have confirmed the harmful effect of the molecule in all preliminary tests, they check their hypothesis in humans. They are not looking for new active substances in these clinical trials, but rather testing the connection between phenotype and genotype in patients. In other words, they want to find out more precisely the extent to which people with the supposedly harmful gene variant differ clinically from people without this variant, for example in relation to their disease progression. Experts call this the clinical validation of a hypothesis. "After all, humans are themselves the best foundation for understanding disease processes, generating hypotheses and developing new therapeutic approaches," explains Dr. Daniel Freitag, an expert for genetic studies in Leineweber's team. The scientists analyze thousands of patients in studies like these. One of the biggest

Understanding cancer at gene level

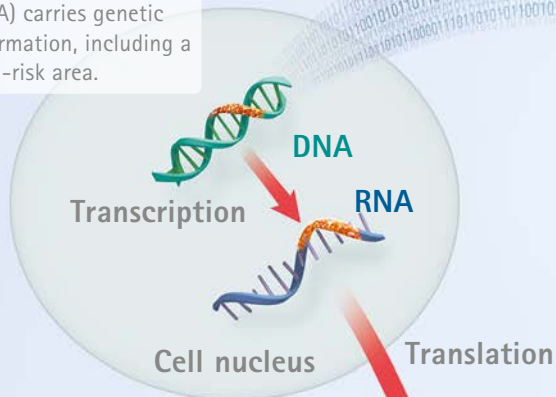
Since the early 1980s we have experimental evidence that cancer is a disease that is triggered by faulty genes. As each tumor is individual, oncologists want to use genomics to find out what distinguishes a cancer cell from a healthy body cell on the genetic level. "Such large-scale analyses became possible after the human genome was sequenced in 2001," explains Dr. Peter Staller, head of Target Validation Technologies at Bayer's Pharmaceuticals Division. Today, this technology is an important part of Bayer's research. The company's cancer drugs containing the active ingredients sorafenib and regorafenib were developed partly as a result of findings on the faulty genome of tumor cells. If the researchers know which genes trigger cancer, they can analyze which cellular processes play a role in the disease's pathogenesis. They then attempt to intervene in this process with new active ingredients. "This approach is one we are using in oncology but also in cardiovascular diseases," says Staller.

Fighting the causes of diseases in the cells

Bayer's researchers are making use of the flow of genetic information in cells to find high-risk genes so that they can then counteract the resulting negative consequences for cell metabolism with pharmaceuticals. In addition to cancer, they are concentrating primarily on cardiovascular diseases.

Flow of genetic information in the cell

Deoxyribonucleic acid (DNA) carries genetic information, including a high-risk area.



DNA is converted into ribonucleic acid (RNA) to make the information on the DNA usable. This translation likewise contains the high-risk area.

RNA serves as a chemical template for protein production. Proteins are responsible for carrying out almost all biologically important functions in cells. High-risk areas generally cause diseases on the protein level.



Leveraging disease genomics for new drugs



Bayer scientists want to find out whether people with a disease have certain harmful gene variants more frequently than healthy people. They are therefore searching through entire genomes. Using statistics and bioinformatics, the researchers can identify high-risk areas. They then check their hypotheses in experiments and clinical trials.

Dysfunctional protein



Once a harmful high-risk protein has been identified, the researchers systematically try to find a way to counteract it, for instance pharmaceutically with new active substances.



Functionally reconstituted protein



difficulties is ensuring the quality of each individual dataset. "We're conducting genome analyses, so we are particularly interested in genes. But to compare genotypes and phenotypes, what we need in particular is excellent diagnostic data," explains Professor Sven Moosmang, a clinical scientist in the Experimental Medicine

department. The researchers get these data from collaborations with hospitals. "We also review the relevance of our analyses by constantly engaging in dialog with the physicians who accompany these patients. This contact with daily clinical practice is very important to us," stresses Leineweber. Once the harmful variant of the protein

has made its way through the process and its effect has been confirmed on all levels, the researchers develop an active substance that targets precisely this cellular protein. This active ingredient is then tested again by the researchers in countless experiments – from cell cultures through to animal models. The scientists also ben-



Undersupplied heart muscle: occlusion of the coronary vessels leads to a heart attack (area in green, photo left). Dr. Dietmar Berndorff and Christiane Unger are making the results of all of Bayer's clinical trials available on a platform where all of these data can be retrieved (photo right).

enefit from the knowledge they have already assembled about the cellular function of the target molecule when it comes to designing the clinical trials.

Knowledge about genetics plays a hugely important role on all levels of the experimental procedure. "Genetics helps us to design our study groups in such a way that the participants are highly likely to respond to a new medication. We

want to positively impact the underlying disease processes in these individuals," says Moosmang. Using the participants' genetic information enables scientists to gain knowledge on risk factors and biomarkers that might be directly related to the cause and progression of a disease. Designing and conducting clinical trials on the basis of such knowledge offers immense potential. "Besides improving

the design of clinical studies, we are also at the same time marking the beginning of a paradigm shift: from the treatment of symptoms towards treatment with a clear focus on the cause of the disease," explains Leineweber.

Genomic studies like the ones conducted by Leineweber and her colleagues generate immense volumes of data. "These data remain valuable after they have been used in a study as well," says Dr. Dietmar Berndorff, expert for Biosample Management in Clinical Sciences. He is working together with an interdisciplinary, global team to set up a central platform on which the results of all studies can be archived and accessed, taking all data protection requirements into consideration.

5,800 genomes of kidney patients

The heart and the kidneys are physiologically closely linked: each one cannot function without the other. Dr. Kirsten Leineweber's team is collaborating with three university hospitals in Freiburg, Erlangen and Innsbruck in the German Chronic Kidney Disease study – GCKD for short – in which 170 kidney researchers from all over Germany are taking part. "We're getting exquisite phenotyping data on kidney failure patients from our partners," says Leineweber. The data are anonymized but they allow the researchers to monitor the disease progression of 5,800 study participants over a 4-year period. They will receive a complete set of data on the patients from their partners before the study begins, at the half-way point and at the end. "We analyze the complete genome of each patient. This will allow us to correlate the chronological sequence of the disease with genetic markers," elaborates Leineweber. She and her team are generating fundamental data about a disease that "can still be fatal despite good levels of care being available," as she puts it.

A central platform making data available worldwide

The name of the project that he is in charge of together with Christiane Unger, IT Business Partner Clinical Sciences, and which is currently in the pilot phase, is "Portal for translational data integration" or PORTIN for short. The name itself makes clear that the scientists are not setting up a new database but rather ensuring centralized access to all available genotype and phenotype patient data.

Bayer scientists will also be able to use the platform to inquire whether tissue samples with a precisely defined molecular, genetic or clinical profile are available for their ongoing investigations. Leinweber's team is likewise linking the data from its genome studies with PORTIN. "Thus we can avoid having experiments or even whole studies carried out multiple times," explains Berndorff. Once the platform has been established, new active pharmaceutical ingredients can be developed and turned into drug products more



Professor Sven Moosmang, clinical scientist in the Experimental Medicine department.

"To compare genotypes and phenotypes, what we need in particular is excellent diagnostic data."

quickly and efficiently. "We spend a lot of money on clinical trials, so we should make sure that their findings are transformed into knowledge that is available in the long term as a way of helping to optimize future studies," says Berndorff.

Compiling all relevant information: that is Leinweber's objective as well. "For many diseases, we can still only treat the symptoms. But new methods are allowing us to look much deeper into cellular mechanisms, right down to the molecular level, so that we can understand the causes of diseases." Their work could have immense medical potential. It could make it possible to make patient care as individual as the person being treated. ■

2ND "CARDIOVASCULAR-RESEARCH@BAYER" POSTDOC WORKSHOP

Up-and-coming scientists at the crossroads

The people powering academic research as Bayer's guests: 24 talented young scientists were invited by Professor Frank Eitner, department head in Cardiovascular Research at Bayer's Pharmaceuticals Division, to attend the second "Cardiovascular-Research@Bayer" postdoc workshop from April 14 to 16. "Both sides benefit from this event," explains Eitner. "The young scientists gain an insight into pharmaceuticals research at Bayer and we get to know outstanding postdocs and their ideas."

The postdocs and PhD students coming up to their doctorates presented and discussed their results in a poster session. They then left the conference center in Velbert to visit Bayer's laboratories in Wuppertal. On the last day of the workshop, the up-and-coming scientists were able to discuss real-life cases with the experts from Bayer. As such, they looked into issues that are currently in the focus of Bayer's research at this very moment. "That's my personal highlight, and the enthusiasm shown by our guests astonishes me every time," says Eitner. Many of the workshop participants were particularly and lastingly fascinated by the opportunity to search for creative solutions to current problems in pharmaceutical research. Dr. Daniel Freitag and Dr. Hana Cernecka, two of the attendees of the first workshop, now work for Bayer. Freitag, who is now conducting research in Dr. Kirsten Leinweber's team, has therefore done exactly what he formulated as his ambition at the end of the event: "I want to drive forward pharmacological research so that patients' lives can be improved or even saved."



Professor Frank Eitner and Dr. Hana Cernecka in conversation: the "Cardiovascular-Research@Bayer" postdoc workshop gives postdocs and students coming up to their doctorates an insight into industrial research. They can engage in intensive dialog with Bayer scientists at the event venue in Velbert.