Systems medicine: New opportunities in research, diagnosis and therapy
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Imprint
Foreword

Widespread diseases like cancer, cardiovascular diseases or disorders of the nervous system have one thing in common: they are the result of a complex interaction between individual genetic and physiological characteristics, the personal lifestyle and environmental factors to which the afflicted are exposed. Science is facing an enormous challenge in disentangling these interrelationships and identifying the parameters that are the cause of a disease.

This is where the groundbreaking research field of systems medicine comes into play. Systems medicine helps capture the complex biological processes of the human body accurately, comprehensively and with mathematical precision. It takes a holistic view of biological and environmental factors. This gives further insight into cause and effect with regard to the development of diseases, which may then be utilised in establishing new therapy and prevention strategies.

The Federal Ministry of Education and Research (BMBF) places enormous emphasis on systems medicine. We are therefore underpinning systems medicine with our “e:Med – Paving the Way for Systems Medicine in Germany” funding concept and via the Berlin Institute of Health, which receives BMBF funding. The various funding modules aim to encourage interdisciplinary cooperation among research groups, facilitate international networking and foster early career scientists.

This brochure serves as an introduction to the field of systems medicine, tracing the development of the systems medicine research approach and presenting the latest research into different areas of disease. Furthermore, it highlights the considerable potential of this new concept for medical research.

Prof. Dr. Johanna Wanka
Federal Minister of Education and Research
The dawn of a new medicine – piecing the system together

Systems biology aims to understand the dynamism of life at every level. To this end, researchers capitalise on the ever-increasing knowledge about genes and molecules, which determine life processes, consistently incorporating mathematical concepts and the performance capacity of modern computers in their work. Thus, in unprecedented fashion, systems biology is coming closer to unlocking the secrets of life. Systems biologists have already discovered many new findings and unexpected correlations, while many more will follow in the foreseeable future. ‘Systems medicine’ will continue to transport the systems biology approach for the benefit of mankind, applying the latest knowledge in the processes of life to facilitate a more accurate diagnosis and better treatment of illnesses.

“On the Motion of the Heart and Blood” is the title of a work published in 1628 that scarcely promises any sensational discoveries. And yet its author, William Harvey, an English physician, overturned everything about the heart that scholars of his time believed to be true. Harvey exposed the ‘seat of the soul’ as a powerful pump that keeps the blood circulating through the vessels. Not only did his findings revolutionise the way the heart and circulatory system were viewed, Harvey also gave medical science the means to treat cardiovascular diseases successfully for the first time.

Mathematics changes the history of medicine

William Harvey owed his new, pioneering insight to detailed anatomical studies, the meticulous experiments he carried out to verify his theoretical reflections – and the study of mathematics. He was the first scholar in the history of medicine to incorporate this field to an appreciable extent in understanding the processes of life. In order to refute the traditional assumption that blood is produced by the liver, Harvey determined the volume of the left ventricle and multi-
plied it by the number of heartbeats per day. Then he calculated how much blood flows through the heart in 24 hours. This amount proved to be so vast that it exceeded the production capacities of the liver. His incontrovertible dovetailing of observation, experiment and calculation silenced his critics, even though almost one hundred years would elapse before they were fully convinced.

With his unprecedented scientific approach, William Harvey succeeded in piecing together the parts that were already known but that appeared to be disconnected. He thus paved the way for modern physiology and the dawn of a new medicine.

Another scholar also adopted a similarly systematic approach. His work was to prove even more groundbreaking: Gregor Mendel. He too founded a new science, the field of genetics. Along with other disciplines like modern molecular biology and biochemistry, physics and mathematics, computer science and engineering, genetics has laid the scientific foundation for a new kind of medicine: systems medicine. It gives grounds for optimism that there will be a radical change in the prevention, diagnosis and therapy of numerous human diseases.

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The difference between systems medicine and systems biology

Systems biology aims to understand the dynamic life processes that take place in cells, tissue, organs and organisms, and to map how molecules join together in networks. To this end, it applies mathematical modelling methods to modern molecular biology.

The term systems biology was coined during the 1960s. It was originally used to refer to dynamic interactions, mathematical modelling and the simulation of biological signalling pathways.

Systems medicine aims to transfer the findings and methods of systems biology into medical science, thereby reaping benefits for patients.

The goal of systems medicine is to use the new knowledge generated by interdisciplinary research to develop new prevention strategies, diagnostics and therapeutics. Whether a person is healthy or sick depends on a number of factors, be they genetic differences, molecular changes or environmental influences. The real questions are how all these factors and systems interact and how they can be controlled.
mathematics and botany, which soon found expression in a project carried out with scrupulous care: the crossbreeding of pea plants. In the process, he followed the concepts of exact science, which holds constant as many conditions as possible in order to study how a single varying parameter changes the system.

For eight years, Mendel carried out experiments in the garden of the Augustinian monastery in Brno. He is said to have used some 10,000 plants, 40,000 flowers and 300,000 peas for the purposes of his experiments; by counting, verifying, comparing, categorising and compiling the traits of his subjects, he discovered the regularities of heredity, known as Mendel’s laws. These could only be explained by specific ‘elements’, which are passed on from generation to generation.

Since scientists at the time, including Darwin, believed that heredity was based on the obscure commingling of indeterminate parental essences, this was a revolutionary concept. The ‘particulate elements’ presented by Mendel in 1865, which are transmitted to the progeny, separating and mixing independently and whose “living interaction determines the traits that are visible to us”, are what we today call genes.

“The Mendel’s observation consisted of counting. These figures turned the hitherto merely qualitative character of biology into a quantitative science that aimed to compete with physics.”

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The human cell

The human cell is able to produce almost everything our organism needs. Most pertinent information can be found in the genetic material (DNA) in the cell nucleus.

The new biology

Subsequent generations of researchers have adopted Mendel’s approach of using experiments to reveal the secret mechanisms of life and develop them in quantitative terms, refining the method until it captures even the smallest molecules operating in the cell. Science today has solved the mystery of what genes are – sections of a chain-like molecule, referred to as deoxyribonucleic acid, or DNA for short. The hereditary molecule forms an integral part of almost every cell.

Cells are able to manufacture almost everything an organism needs. The most important products include thousands of different proteins. Life simply cannot function without them: proteins work in the cell as indispensable enzymes that are able to deconstruct and recombine the materials supplied, use them for other purposes and then dispose of them. Other proteins act as building materials or receive messages, passing them on in signalling chains into the interior of the cell. More than 100,000 different proteins perform an array of functions in the human body; nonetheless, it is still not entirely clear how all these molecules harmonise in the concert of life.
The right sequence is vital
The cell combines amino acids to form proteins, stringing them together to form a chain. The characteristics and abilities of a particular protein depend on which amino acid is located at what point in the chain. The genes determine the order – or sequence, to use the language of biochemistry – in which amino acids assemble to form a protein. Genes too are composed of smaller building blocks, known as bases. These also occur in a particular order, the base sequence. The order of the bases determines the order in which amino acids are assembled into proteins by the cell.

The correct sequence is a matter of life and death: for example, should bases be deleted, incorrectly inserted or duplicated during DNA replication, which must take place prior to cell division – the language of science uses the term mutations – the protein for which the gene is responsible (coded) cannot be produced properly. These seemingly insignificant errors at the genetic level and in the protein architecture may have grave consequences for the body, leading to diseases like cancer.

The impact of genes
Gene expression is one of the most important terms in molecular biology. Gene expression is the essential process by which the information contained in a gene is made accessible to the cell system and all subsequent organisational levels of the organism. This is because the gene is ‘merely’ the repository of biological information; by themselves, genes are incapable of passing on or expressing this information.

In order to utilise the stored data, numerous helpers are required (enzymes and other proteins), which interact in a complex chain of biochemical reactions.

With a few exceptions, all our cells carry the complete set of genetic information. However, the genes that are present in a cell are never active simultaneously: certain genes are turned on and off as required, like light switches. Thereupon, a cell begins to divide, for example, or it forms a protein product, like a hormone, that affects the metabolism of the organism. But how does this conversion of theoretical contents into concrete actions occur? In order to understand gene expression and the influence of genes on the cell, tissues and organs, and therefore on the entire body, scientists first had to learn to interpret ‘the language of genes’.

Still a source of fascination today: the double helix model of DNA structure. It was developed in the early 1950s by the American molecular biologist James Watson and the British biophysicist Francis Crick.
Gene expression and gene regulation can be studied in the laboratory using a variety of modern molecular biological methods.

The language of genes
The first ‘word’ of the genetic vocabulary was deciphered in the early 1960s. By 1965, science had decrypted the entire language of genes, the genetic code. As it turned out, a sequence of three DNA bases (i.e. three genetic letters) spell out a word; each of these three-letter words, referred to as triplets, translates into one amino acid.

It was clear from the outset that, although genes include instructions for producing a protein, they themselves are not able to link a protein together. This takes place outside the cell nucleus, in the ribosomes. But how do the signals get through to the cell’s protein factories? It was Francis Crick, who had developed the double helix model of DNA structure with his colleague, James Watson, back in the early 1950s, who then proposed a model of the information flow at the end of the same decade: first of all, the genetic information stored in DNA is transcribed using an intermediary messenger molecule. The messenger molecule extracts the information from the nucleus and delivers it to the ribosomes in the cell plasma. Crick surmised that a ‘relative’ of DNA, namely ribonucleic acid, assumes the role of messenger (messenger RNA) to convey the information, while other ribonucleic acids are responsible for analysing the signals, (transfer RNA). They are tasked with delivering amino acids according to the message. These are then linked to form a chain of amino acids at the ribosomal site and ultimately coiled onto the finished protein.

For many years, it was assumed that RNA only performed these simple services in the production of proteins. However, the world of RNA has proved to be both extensive and complex, containing vast numbers of RNA molecules – with very different tasks – about which research is only in its infancy.

Accumulated knowledge
Nucleic acid sequencing tools are fully automatic DNA reading machines. They provide information about genomes quickly and accurately, thereby opening up a completely new window onto the elementary processes of life.

Computerised databases contain billions of datasets, not just on the hereditary molecule, DNA, but also on RNA, proteins and metabolic products. These databases are an invaluable source for research. Experts refer to this search as ‘data mining’.
Gene expression and gene regulation are highly complex; despite their enormous importance, the functions carried out by RNA molecules are just one part of the process. ‘Interpreting’ the text starts at the level of DNA itself. This is carried out by special proteins, known as transcription factors, which recognise short fragments and attach to specific sequences of DNA. Thus, they are able to trigger or prevent the transcript of a gene.

And where do the transcription factors come from? Like all other proteins, they are produced by genes: certain genes are therefore responsible for proteins that regulate other genes in turn. This gives rise to a relationship between genes and proteins that is as close as it is complex.

**Data, data and yet more data**

Molecular biology – the science that aims to unravel the processes of life, right down to the last molecule – has recourse to a plethora of different methods that researchers all over the world can use to unlock the secrets of nature. Scientific progress frequently depends on technical developments. To this end, processes that reveal the base sequence of a DNA strand have proved to be especially useful. Reading or sequencing the entire genetic material, or genome, of different life forms – from bacteria right up to human beings – has been decisive for modern biology and remains so to this day.

**The Human Genome Project**

Since the mid-1980s, mapping genetic material by means of various sequencing methods has been known as genomics: genomics is science on a grand scale. This is shown by an international research project that was launched in autumn 1990 with the ambitious goal of deciphering the human genome.

The complete sequence of the human genome has only been officially available since April 2003; it is still being fine-tuned to this day. The final number of human genes was totally unexpected: researchers had initially assumed that the human genome would contain more genes than that of any other living creature. According to recent estimates, approximately 22,000 genes are responsible for proteins in the human genome – meaning that humans have fewer genes than the mouse (24,000) and scarcely more than the threadworm (19,000).

**Interpretation at different levels: genome, transcriptome, proteome and metabolome**

During the research, the increasingly apparent molecular complexity quickly made it clear that it is not sufficient to know the base sequence of DNA. The first priority is to understand how cells process and
edit genetic information. This is because sickness and health are not governed solely by the text but also by its interpretation. Moreover, as is usually the case when interpreting complex texts, deciphering the genetic text does not merely take place at one but at many different levels, which must be interconnected in order to understand the content. Termed the genome, the transcriptome, the proteome and the metabolome in the language of molecular biology, these levels are the most important molecular components of the cellular biological system.

**The first level – the transcriptome**

One important step that had to follow the sequencing of the genome is gene expression analysis, in other words, the study of what single genes, groups of genes or entire genomes actually do in a cell. The first level to be addressed in this case is the level of the transcriptome.

The transcriptome is the result of the process over the course of which single genes are transcribed into RNA molecules. Therefore, it is the total set of RNA molecules whose biological information is required for the cell at any given time. Scientists use different techniques to investigate the transcriptome, including modern RNA sequencing or microarray technology, also known as chip technology. These techniques enable researchers to analyse the expression of thousands of genes or gene segments in a single reaction.

For example, the gene expression pattern of single cells facilitates the identification of cells that are undergoing division. Furthermore, it may be an indication of how cells react to a drug. Or characteristic signatures may be discovered, according to which certain types of cancer can be divided into subgroups with a precisely defined molecular structure and referred for more specialist treatment. Other signatures make it easier to predict the progression of a disease with accuracy.

**The sum of all proteins – the proteome**

Studying the transcriptome tells scientists which genes are active in a certain cell at a given time. The second important interpretation level of the genetic text is analysing the proteome. The result is an accurate impression of the proteins contained in a cell.

Scientists use these data to compile ‘protein interaction cards’, for example, which reproduce how proteins interact within a proteome. These cards tend to focus on a small number of proteins that form nodes in a network. Some represent individual biological processes, while others tie biological processes together. This enables previously unknown molecular relationships to be visualised. Furthermore, characteristic proteome patterns may indicate changes in the body, like in blood or urine samples, that are symptomatic of illnesses. It is
hoped that doctors will be able to use these patterns as clear biomarkers, for example to diagnose prostate cancer, for the early detection of kidney diseases or as evidence that there are dangerous deposits in the blood vessels.

Biochemical profiling – the metabolome

Following the proteome, the third interpretation level in understanding the genetic text is the metabolome. The metabolome is defined as the complete collection of all metabolites present in a cell or tissue under certain conditions. The examination methods used are summarised under the heading of metabolomics or ‘biochemical profiling’.

The goal is to decipher the biochemistry of a cell or tissue that forms the basis of the different physiological conditions, whether in sickness or in health. The metabolome analysis may also be conducive to further characterising medical conditions in molecular terms and to identifying specific molecules, for example, that may serve as targets for new, targeted therapeutics.

The sum of all parts

Systems biology aims to combine all molecular information about life: the expression of a genome should no longer be considered under the aspect of single molecules but in terms of the biological systems that develop from the interaction of these molecules. For biological systems to function, certain proteins, for example, must be available in a cell at a certain time, at a certain site and in a certain quantity. A system like the human body thus depends on such fundamental factors as the synthesis rate of proteins, the correct
At the intersection of mathematics and the science of life

Experimental science in biology, physics and chemistry generally evokes visions of researchers in white coats, with black glasses and dishevelled hair, hard at work in laboratories. Nevertheless, the laboratory routine can be just as banal for scientists as it is mystifying for the layman. Scientists carry out experiments: that much is clear. But what does that involve exactly? Above all, however, what does that involve today, viewed under the aspect of modern systems biology and systems medicine?

Experimenting means putting an idea to the test. So, for example, a scientist thinks up an experiment and selects methods that enable him or her to find out more about the function of a biological characteristic, like a signal molecule, in the cell. Up to this point, biology’s traditional way of working does not differ from modern systems biology. What distinguishes the new approach in biology is the systematic involvement of other disciplines like mathematics, computer science and engineering. In this respect, computer-based analysis and mathematical modelling have accelerated developments to a tremendous degree.

Understanding biological systems as a whole
For some time, biology has had to process vast amounts of information. New methods like high-throughput technologies have since thrown up veritable mountains of data, which continue to grow day by day: these include invaluable information on the molecules that constitute life. It is now a question of digging up the hidden treasures in these mountains of data, making them accessible and reaping the benefits.

‘Systems biology’, the alliance between biology, mathematics, computer science and engineering, has set out to develop methods and programmes that will provide answers to the central questions of the life sciences. The objectives are an understanding of biological systems as a whole and the quantitative prediction of dynamic life processes. This calls for an interdisciplinary approach that takes different fields of science into account, good hardware with plenty of storage capacity – and efficient algorithms.

Instructions for computers
System biologists prefer to summarise experimental data in differential equations, mathematical formulae that specify, for example, how the amount of a signalling molecule in the cell increases or decreases and during what period this occurs. These equations are expanded into a set of complex instructions, known as algorithms, for the ‘hardware’ or computer. Thanks to
their enormous processing power, computers are excellent tools for solving numerical problems of every kind. However, they are only capable of carrying out these tasks in a meaningful way if they receive algorithms or clear ‘instructions’ that are formulated in the language of mathematics.

**Using computers creatively**

Researchers can use computers to run through scenarios or ‘models’, helping them to answer fundamental questions on the organisation of life, like: does a signalling molecule deliver its message by attaching to a receptor on the cell membrane? Does this trigger a signal chain in the interior of the cell? Which molecules are part of this chain? What happens if the signal chain is affected by other factors within the cell? Does the signalling pathway create a network with other signalling pathways? Is this network connected to other networks inside and outside the cell? Comprising computer simulation and subsequent laboratory experimentation, the complementary process builds up an overall picture of cellular interaction step by step, which increasingly accommodates the complexity of life.

**Mathematics and medicine**

Mathematics plays a major role in many different fields of medicine. One important example for how mathematics can benefit medicine is in developing new, more efficient therapeutics that have fewer side effects. To this end, systems biologists create models of individual cell functions to find molecules that play a crucial role in the disease process and that can be targeted by active substances. Based on the known molecular interactions and dynamics, computers can be used to detect and predict the mechanism of the potential drug. This can significantly reduce the otherwise extremely lengthy time needed for the development and release of new therapeutics.

**Fighting viruses with mathematics**

One example: from HIV, hepatitis to influenza, viruses are a threat to humans all over the world; new vaccinations and therapies are urgently needed. At the same time, viruses are perfect examples for demonstrating just how vital systems biology research is.

Systems biologists have developed mathematical models that map how viruses enter human cells in case of infection, how they act in the interior of the cell and the ways in which they leave the cell in order to infect other cells. This viral cycle can be replicated on the computer; moreover, it is possible to model the measures a cell uses to fight off a virus.

Using computer models and laboratory experiments in close parallel, this knowledge is pieced together to form a complex picture illustrating the interaction between the cell and the virus – allowing researchers to track which protagonist wins, when, where and why. This picture also reveals exactly where active substances would have to take effect to give the cell the competitive edge.
folding of the proteins or the enzyme degradation rate. Therefore, even the simplest biochemical processes in a cell are highly complex in actual fact; what is more, they depend on multiple factors that affect the entire system of the organism from inside or cellular processes from the outside.

In order to handle this complexity and assemble the parts to obtain a holistic view, systems biology makes consistent use of modern computers: they enable scientists to control even vast amounts of complicated data and ‘model’ complex systems, in other words to simulate the workings of the components on the computer screen. For example, computers can predict how proteins will interact or what impact the smallest molecular changes, like the mutation of a gene or the modification of a protein, will have on the biological system as a whole. The scientists subsequently verify the findings of the computer simulations with further experiments in the biological system itself (see box on “How computers help in understanding life”). The systems biologists adopt an ‘iterative’ way of working that constantly verifies results. The data and principles produced by classic experiments, whether in test-tube experiments (in vitro) or on living organisms (in vivo), are translated into mathematical models. These models form the basis for simulating biological processes on the computer (in silico). For example, using computers means that individual test parameters can be changed and results predicted. The predictions are fed back into experi-

Samples, samples, still more samples – large scale experimental studies are needed to study the genome, transcriptome, proteome and metabolome of human cells.

How computers help in understanding life

While Gregor Mendel described the shapes and colours of his pea plants, today’s research focuses on genes and proteins, molecular interaction in networks and their reciprocal effect on the environment. However, molecules are invisible to the naked eye. Researchers have to deduce their behaviour from experimental data and by means of mathematical analyses. This is where computers come into their own.

Computers can simulate natural processes, if they are given the necessary instructions (algorithms). This serves to illustrate numerous reactions and demonstrate the principles of life.

Today’s modern methods of basic biomedical research provide vast quantities of data in rapid succession. The storage, processing and analysis of data on a large scale (big data) would be inconceivable without computers.
mental tests and mathematical models, ushering in a new improvement cycle. Systems biology is thereby working its way towards a holistic understanding of biological processes, one step at a time, reproducing how they actually take place in the organism.

Thus, the linear thinking of the sequencers that was common in the past has given way to a new network mentality. Its goal is to find its way through the maze of accumulated knowledge and discover correlations because single genes, gene transcripts, proteins or metabolites are nothing but the infinitesimal strands of an incredibly complex whole, interwoven in a reciprocally interactive network and inextricably linked to the influences of the environment.

**Systems medicine – new opportunities in research, diagnosis and therapy**

Systems medicine is determined to pursue the systems biology approach for the benefit of mankind and to combine it with other methods, including modern imaging techniques like magnetic resonance imaging, for the detailed diagnosis, personalised therapy and reliable prevention of diseases. The spectrum of potential applications is enormous: a better understanding, earlier diagnosis and more targeted treatment of common illnesses like cardiovascular disease and cancer, drugs can be developed more quickly and used in a more customised way, while severe metabolic disorders will be diagnosed by their very first symptoms.

The ongoing aim is to understand the correlations between the numerous different processes in the human body, how they interact with each other and with influences in the environment. The holistic view goes hand in hand with the hope that advancing our understanding of the causes of disease and its pathogenesis will facilitate the development of new medical applications. The projects presented in this brochure have been selected as examples to give readers greater insight into the basis on which systems medicine is founded and what opportunities it offers mankind.

A complete list of the systems medicine projects that receive funding can be found online at https://gesundheitsforschung-bmbf.de/de/foerderkatalog-2435.php (only available in German).
Examples from ongoing research
Modern heart medicine: the surprisingly large influence of genes

Smoking, a high-fat diet and lack of exercise increase the risk of developing cardiovascular disease: up until now, the impact of genes had appeared to be minimal, compared with the significance of lifestyle factors. However, this view has changed. The latest clinical and research data reveal that hereditary factors play a major role in determining whether an individual is afflicted with cardiovascular disease. The underlying mechanisms of disease have not all been identified – not by a long chalk. Systems medicine aims to close this research gap.

Three words describe the heart: powerful, flexible, tireless. Without sleeping or even resting, the slight muscle – weighing just 300 grams – beats three billion times over the course of a lifetime, pumping four supertankers of blood through the 100,000 kilometre long network of veins in our bodies right through to the last cell. Yet even the strongest heart is weakened if the life-giving blood vessels, providing nutrients and oxygen, become blocked. A heart attack is the result. If a vessel supplying blood to the brain is obstructed, this leads to a cerebral infarction or stroke. These are right at the top of the statistics for the causes of death all over the world.

Myocardial and cerebral infarction almost always have a common cause: hardened arteries. The medical terms are arteriosclerosis or atherosclerosis. But how do they develop? “In the past, they were mainly attributed to lifestyle factors like smoking, a high-fat diet and lack of exercise”, says Professor Heribert Schunkert, Director of the German Heart Centre in Munich. It is now common scientific knowledge that the genes also play a substantial role. “We all have hereditary factors that encourage the development of arteriosclerosis and secondary diseases”, the cardiologist points out. This insight opens up new approaches to diagnosis and therapy.

A vascular disease and its (disastrous) consequences

A vascular occlusion starts when surplus fat particles accumulate in the inner wall of the veins. The cells of the immune system react to the invaders and attempt to ward them off with an inflammatory response. Over time, immune cells, tissue debris and fat accu-
mulate, and the inner layer of the vein becomes thickened. This leads to changes in the vascular walls, a type of plaque, that may become hardened over time. The body secures the site of the inflammation with a net of connective tissue fibres. The blood can flow freely as long as the protective cap remains stable. However, if the fibre cap ruptures, blood starts to seep in. The platelets and coagulation proteins are galvanised into action: they thicken the blood and a clot or thrombus develops. If the obstacle is too big or fails to disperse quickly enough, the blood flow comes to a standstill.

**Starting points for new drugs**
Modern bioscientific research aims to analyse this fateful series of events in greater detail – right down to the genes and the complex molecular chains of communication within the cells. Moreover, the scientific community wants to apply its new methods to shed light on how epigenetic factors, in other words, environmental influences like our diet, affect our genetic make-up. “We only think we have got it all figured out”, says Heribert Schunkert, “but the truth is, we are still barely scratching the surface”. The medical doctor and researcher goes on to explain that the rupturing of a plaque right through to the blockage of a vessel is merely the visible conclusion of a process that has much deeper molecular causes. The goal is to thoroughly explore every aspect of the molecular mechanisms that lead to arteriosclerosis.

Only by knowing all the causal connections can we hope for an early diagnosis and targeted therapy: it may be possible to find biomarkers that are reliable indicators of the disastrous process at an early stage; alternately, maybe we can identify specific molecular starting points for new, particularly effective drugs.

**Genetic variations**
In order to map the molecular networks that ultimately culminate in myocardial or cerebral infarction by means of arteriosclerosis, researchers first have to study the genetic variations that initiate this process. They bear the information for proteins, the crucial molecules that are involved in virtually all life processes. If the genes are modified, this results in proteins that are modified, both qualitatively and quantitatively – and vital signalling chains also change accordingly in the cells. This can cause diseases to develop in a variety of ways. The specific challenge for cardiovascular researchers is how to locate the gene variants that may be responsible for heart attacks and strokes among the approximately 22,000 human genes.

One method used by researchers to answer this question is as follows: the entire genome of patients suffering from cardiovascular disease is compared to the genome of healthy subjects. If certain discrepancies are detected among the patients, it may be assumed that the genetic variants are somehow involved in the development of the disease, in other words they are ‘disease-associated’.

**A slight variation with a huge impact**
In medical terms, these examinations, usually involving tens of thousands of healthy subjects and afflicted individuals, are called ‘genome-wide association studies’. Termed SNPs, the variations that researchers are looking for tend to be harmless single base sub-
EXAMPLES FROM ONGOING RESEARCH

Searching for clues – Professor Heribert Schunkert and his team research the genetic causes of cardiovascular diseases.

Institutions, millions of which are in every individual genome. “We compare these SNPs”, Professor Schunkert explains. “A variation in the frequency of these SNPs between patients and control subjects points to a site on one of the chromosomes that accommodates the genes that encourage arteriosclerosis”. Such tests generate vast amounts of data, which must be stored, compared with other datasets and evaluated. Today, bioinformatics provides great support by making enormous computing capacities available and developing dedicated programs for every line of questioning.

A molecular mystery and its solution
Ten years ago, Heribert Schunkert and his colleague, Jeanette Erdmann, a biologist from the Universität zu Lübeck began making use of genome-wide association studies to find out more about the genetic causes of cardiovascular diseases. To date, the genome comparison has enabled them to identify approximately 90 gene loci that are associated with an increased risk of a heart attack. “The more gene variants conferring risk in a genome, the higher the chance of that person being afflicted with the disease”, Heribert Schunkert explains. Taken individually, the variants only represent a small percentage of the increased risk of disease; in total, however, the genes have a huge impact.

One of the researchers’ next steps was to establish the function of the suspicious genes. The result was surprising: they found connections to traditional risk factors like high blood pressure, cholesterol, smoking and diabetes in just one third of cases – while a noticeably high number of loci were associated with inflammatory processes. “There must be disease mechanisms that we are not yet aware of”, concludes Professor Erdmann. Solving this molecular mystery would mean a tremendous opportunity for new diagnostic and therapeutic options.

Unexpected assistance from ‘heart attack families’
The researchers recently succeeded in identifying one of the hitherto unknown molecular mechanisms. They were helped by families in which a high proportion of members have suffered heart attacks. Unlike comparative association studies, this type of family studies provides direct access to the mutant gene: not only is it possible to isolate a suspicious chromosome region and designate certain ‘candidate genes’, the causative gene modifications, or mutations, can be actually tracked down.

By carrying out complex bioinformatic analyses, the researchers were able to filter out two mutant genes from tens of thousands of suspicious gene variants: CCT7 and GUCY1A3. “The fact that not just one but two genes were mutated was another surprise”, says Heribert Schunkert. Especially as it turned out that both mutant genes affect the same protein – ‘guanylyl cyclase’, which is an old acquaintance of the biochemists.
A 1 with 14 zeros – is a human being, expressed in numeric terms. The human body is composed of approximately 100 billion cells.

The nucleus of each of these cells (apart from red blood cells and blood platelets) contains a coiled strand, approximately two metres long and just two millionths of a millimetre wide: DNA (deoxyribonucleic acid), the molecule of life. The genes that decide whether we have blonde or brown hair, whether we are tall or small and the colour of our skin are sequences of the hereditary molecule, DNA.

DNA was discovered in 1869. Its structure and functioning were only established in 1953. Since then, scientists around the world have been unravelling the fascinating molecule. And constantly unearthing new secrets in the process.

Guanylyl cyclases are proteins that act as enzymes. Therefore, they form part of the extremely influential group of molecules that are responsible for countless biochemical reactions in the body. Soluble guanylyl cyclases are tasked with breaking high-energy chemical bonds and investing the energy released in cellular signalling chains. The enzyme thereby initiates vital cellular processes. Guanlyl cyclases are prompted, as it were, to perform their important function by nitric oxide. This molecule serves as an omnipresent messenger in the body. The ultimate result of these processes is a molecule named cGMP.

And now the process comes full circle: cGMP is responsible for passing on signals in the cell that relax the smooth muscles in the vascular walls. As a result, the blood vessels are switched to ‘wide’, the blood meets with lower resistance as it flows through the vessels and blood pressure drops. However, lowering blood pressure is not cGMP’s only talent. The molecule is also able to slow blood platelets down, thereby preventing overactive platelets from forming clots and blocking the vessels. All of these vital molecular processes are compromised if the two genes GUCY1A3 and CCT7 are mutated – and they work closely together.

Our diet also affects our genetic disposition and thus our risk of developing cardiovascular disease.
In the meantime, Prof. Schunkert and Prof. Erdmann have discovered how these genes cooperate: the gene GUCY1A3 and its partner form the alpha and beta subunit of guanylyl cyclase; the gene CCT7 bears instructions for assembling a protein that acts as a ‘chaperone’ and ensures the flawless performance of guanylyl cyclase. For the vital enzyme is only able to complete its task if it is assembled perfectly. By studying mice, researchers discovered that guanylyl cyclase is incapacitated if it mutates: blood clots then tend to develop quickly and are particularly common, which almost inevitably causes blood vessels to become blocked. It is extremely rare for both mutations to occur at the same time: nevertheless, this was exactly the case for the members of the ‘heart attack families’. The situation is different for a common variant in the GUCY1A3 gene, which leaves the enzyme intact but with less activity. This variant increases the risk of a heart attack by 15 percent, as Jeanette Erdmann, director of the Institute for Cardiogenetics at the Universität zu Lübeck, knows from experience, having traced the molecular mode of action. These changes occur in as many as 80 percent of the population.

The interplay of genes

Researchers now aim to identify other molecular mechanisms to improve the diagnosis of cardiovascular diseases at an early stage and maximise treatment options. In combination with lifestyle factors, understanding the ‘collective’ of the genes and the molecules for which they are responsible is a prerequisite for achieving this aim. “Counting single genes like marbles is not enough”, Professor Schunkert points out. “In actual fact, everything is interconnected in terms of function”. Disentangling these networks is another major challenge. According to Professor Schunkert, “There are certainly more possibilities for molecular interaction in the cell than there are people living on Earth. Nonetheless, I am certain that the new systems medicine approach will enable us to identify important constellations and help implement them for the benefit of our patients”.

**The process was automated** in the mid-1980s. Fluorescent versions of the bases superceded the radioactive markers. When a laser excites the dyes, they light up in different colours. Computer-controlled machines made it possible to realise large-scale projects, for example the Human Genome Project (see p. 9).

**The first rough draft of the human genome sequence** was announced at the turn of the millennium. At the time, it took about three days to determine the sequence of approximately one thousand bases. Today, modern DNA reading machines – next-generation sequencing technologies – generate as many data within a day as hundreds of Sanger sequencing tools. Nevertheless, knowing the sequence of bases in DNA is by no means synonymous with understanding what it means. This is where bioinformatics comes in by translating the genetic data collections into analysable information.
Early warning system for alcoholism

The researchers of the BMBF’s ‘SysMedAlcoholism’ project are turning the spotlight onto the molecular mechanisms of alcoholism. One of their goals is to compile genetic risk profiles that seek to predict whether adolescents – the group most frequently involved in excessive consumption – will develop alcohol use disorders in later life.

The sparkling wine bubbles seductively as it is poured into the glass, the bottle of beer that is always to hand represents freedom and herbal liqueur shots are a must at cool parties. Such are the emotive media messages, with budgets of well over €500 million being invested in advertising per year in Germany. On the other side of the scale are the sobering facts. According to the Robert Koch Institute in Berlin, 9.5 million Germans consume alcohol in amounts that pose a health risk, approximately 1.8 million are regarded as alcohol-dependent, while 74,000 people die in Germany every year as a result of alcohol abuse. As Professor Rainer Spanagel from the Central Institute of Mental Health in Mannheim emphasises, “Alcohol addiction is one of the most prevalent neuropsychiatric disorders in our society”.

As the project leader of SysMedAlcoholism (www.sysmedalc.eu), the interdisciplinary BMBF project, Professor Spanagel aims to develop methods of facilitating the early diagnosis, treatment or even prevention of alcohol addiction. Moreover, clinical studies are set to test new active substances that reduce the craving for alcohol and help avoid relapses into alcohol addiction. The scientists’ third goal is to define individual risk profiles in adolescents – the group most affected by excessive alcohol consumption and binge drinking. The profiles seek to predict the likelihood of alcohol use disorders in later life.

The molecular mechanisms of addiction and withdrawal

The question of why some people become dependent on alcohol, while others do not, remains unanswered. Without a doubt, environmental factors play a crucial role. Professor Spanagel goes on to explain; however, genetic make-up also has a significant impact. This is borne out by studies on adopted children, for example, which show that children whose birth parents were alcoholics, but who grew up in foster families without alcohol abuse, have a three to four times higher risk of becoming alcohol-dependent than other adopted children. There is not one main culprit, a single ‘drinker gene’; instead, various genes interact in complex ways with each other and with the environment.

Rainer Spanagel and his colleagues are getting to grips with the genetic base and neurobiological mechanisms of alcoholism by studying rats and mice, which can be rendered alcohol-dependent in experiments. The animal models also offer scope for examining the molecular changes occurring during withdrawal and the factors that encourage relapse. The scientists apply the systems medicine approach to their research. The findings from the experiments on animals are combined with the genetic, molecular biological and neurobiological information provided by patients; these data are then evaluated using biostatistics and mathematical models. Using this approach, they have found ample evidence of how altered genes may lead to alcoholism in conjunction with certain environmental factors.
Current figures show that 9.5 million people in Germany consume alcohol in amounts that pose a health risk. Yet why do some people become dependent on alcohol, while others do not? It is not just the social milieu that plays a role, genetic make-up also has a significant impact.

The influence of genes

One example is a defect in a gene called CRHR1. The gene is responsible for a receptor, or receiving station, for a hormone (CRH = corticotropin-releasing hormone). This is produced by the brain, triggering a signal chain within the cells, which ultimately stimulates the release of stress hormones (glucocorticoids). The study found that, under normal conditions, mice with the gene defect were occasional drinkers at most, preferring water to alcohol. However, if the animals became stressed, the mice with the gene defect drank more than three times that of the control animals. The scientists surmise that increased CRH activity could also play a part in the stress-related relapse of human patients.

A gene known as PER2 (period circadian clock 2) is also involved in regulating stress hormones. The gene is one of the hereditary factors that control the day-night rhythm. This cycle is disrupted in mice with a mutated PER2 gene. These animals drank a great deal more alcohol than healthy controls. This gene defect may also be directly comparable with human genetic mutations. “We already know that adolescents with specific mutations in the PER2 gene are heavier drinkers than their peers”, says Rainer Spanagel. It is also proven that shift workers, airline staff and other people with a disturbed circadian rhythm are more likely to suffer from problems related to alcohol.

New approaches to prevention and therapy

The researchers discovered that the brains of the genetically modified mice contained high concentrations of glutamate. Used by nerve cells to send signals, this neurotransmitter causes increased levels of excitability. The team found that the highly stimulated animals demonstrated a particular affinity for alcohol and that both the increased concentration of glutamate and the excessive alcohol consumption could be effectively treated with the drug acamprosate. Acamprosate is often prescribed in the treatment of alcohol addiction thanks to its anti-craving effect: it is thought to maintain abstinence during withdrawal and helps prevent relapses. The research team spearheaded by Professor Spanagel has since succeeded in finding out details about the drug’s molecular mode of action. The promising latest results look set to improve the drug’s efficiency, thereby protecting more patients from relapse. The researchers hope that their groundbreaking work will not just come up with new approaches to the prevention and improved drug therapy of alcoholism, but also other addictions too.
When is the right time for heart valve surgery?

Heart failure is caused by a number of mechanisms, while many factors influence the course of the disease. In the BMBF’s ‘SMART’ project in Berlin, scientists and doctors are collecting all available data and information on heart failure in a computer model. Their goal is to create an innovative cardiovascular model for predicting which treatment is most efficient for a given patient and which therapy is most likely to be successful in the long run.

If the heart is too weak to pump the blood around the body and keep the organs, tissues and cells supplied with oxygen and nutrients, doctors talk about heart failure. “Every process that causes long-term damage to the heart ultimately leads to a life-threatening heart failure”, explains Professor Titus Kühne, doctor and scientist at the Deutsches Herzzentrum Berlin. One common cause is an insufficient heart valve apparatus. The ‘Systems Medicine of Heart Failure’ research consortium seeks to demonstrate how to more clearly establish the necessity of valve replacement surgery, how to plan more personalised procedures and improve the long-term success of surgical and medical treatment concepts.

Predicting individual treatment success

Valve replacement surgery is one of the most common surgical procedures: according to figures published by the European Association for Cardio-Thoracic Surgery. Up to 70,000 heart valve operations are carried out in Europe every year. They become necessary when the heart valves no longer open or close fully due to congenital deformities, calcification, following a heart attack, as a result of infections or age-related deterioration. The cardiac muscle then steps up its efforts to keep the body adequately supplied with blood, thereby weakening the heart even further. Replacing the natural heart valve with a mechanical or biological prosthetic valve can relieve the strain on the heart and restore its pump capacity. Surgeons tend to apply the principle of “as late as possible, as early as necessary” with regard to intervention. This avoids repeated operations, at the same time preventing mild heart failure from developing into severe cardiac insufficiency and ultimately into irreversible myocardial damage. In the meantime, it is difficult to determine the right time for heart valve surgery, explains Professor Kühne. To date, this has been based on comparatively rough criteria, like the size of the heart or its pump capacity. Detailed data are sorely lacking. These data would enable individual predictions regarding the development of heart failure in a given patient’s case and at what point he or she would most benefit from a replacement of the diseased valve. The scientists in Berlin intend to make the fine data available by using a cardiovascular model that integrates all relevant data on heart failure. For the first time, the innovative model will make it possible to classify patients according to their personal attributes, identifying the required surgical and medical treatment concepts.

Virtual valve replacement

At the first level, the scientists utilise the information on the heart provided by magnetic resonance imaging, a modern imaging technique. “We observe the size of the heart and gauge how strongly it is pumping”, Professor Kühne describes the process. Up to this point, the approach still corresponds to routine diagnostics. More detailed measurements are then also added to the data, for example, the volume of blood flowing through the valve or whether there is blood turbulence behind the heart valve. However, as Titus Kühne goes on to explain, the revolutionary aspect of the process is that “in cases where we already know the size, form and function of the heart, we replace the damaged valve beforehand, on the computer”.

Not only does the virtual valve replacement enable doctors to select on-screen the valve that is the best match for the patient’s heart from the many different types available; using the computer, doctors can also simulate the heart’s reaction to the new valve and see how its pumping action will increase in the future as a result of the operation. The more data that are entered in the computer regarding the actual biological conditions, the more effective the simulation. The bioinformaticians therefore feed the computer with data obtained from the molecular characterisation of the
myocardial tissue by the experimental research scientists (Figure 2), for example, what proteins are active in the contractile cardiac muscle cell, which genes are responsible for these proteins and how the genes are regulated, in other words, switched on and off.

Integrating all this information in a holistic analysis system serves to predict the progression of the illness in a given patient, personalise the treatment according to their individual needs and improve the outcome of the therapy in the long term, thanks to the various personalisation options. The result of this process is “a highly complex cardiovascular model”, says Titus Kühne, which allows surgeons, among other things, to make a more informed decision than before regarding the right time for an operation. In just five to ten years, Professor Kühne hopes, a program could be available that would enable medical data relating to individual patients to be automatically processed and evaluated interactively – “in real-time and in the control range for a wide spectrum of patients”.

The flow in the aorta is modelled on the computer for two different heart valve prostheses. These simulations help surgeons plan heart valve operations, enabling them to select the best type of valve prior to the procedure.
The common denominator: silent inflammation is the cause of numerous diseases

Inflammation is a molecular defence mechanism maintaining the integrity of barrier functions. However, if an inflammatory response gets out of control, serious illnesses may develop. Classic examples of chronic inflammatory diseases are psoriasis or Crohn’s disease. Modern molecular biological research now associates many other illnesses with silent inflammation, from the heart attack to the stroke, even schizophrenia.

Western medicine has studied inflammation for over 2000 years. The four cardinal clinical signs established by the Roman encyclopaedist, Celsus, in his book “De medicina” are still valid today: rubor, tumor, calor and dolor – redness, swelling, heat and pain. These symptoms describe what can be directly seen and felt. Nevertheless, the true nature of inflammation was only discovered at a much later date, namely the concerted action of the immune system, which sends out its cells and neurotransmitters to ward off as early as possible any threat that might prove harmful to the body – first and foremost, the invisible myriad of microbial agents that constantly attempt to overcome the body’s defences. Extreme stimuli, like pressure, abrasion and injury, heat and cold, the sun’s rays or toxins, may also cause the body to put up vigorous resistance, i.e. to trigger its inflammation defence mechanism, albeit with temporary discomfort.

Neurotransmitters send out pain signals, alerting the body to protect the sensitive area

The more details scientists found out about inflammation, the more astonishing the biological process became. For example, a bacterium that has somehow managed to enter the body via an opening in the skin soon finds itself surrounded by molecular interceptors, i.e. antibodies. Droves of white blood cells emerge from small blood vessels in the area, following the trails laid down by signalling proteins to lead the defence cells directly to the site of infection. There they ingest the invading organisms. The external symptoms of inflammation are the side effects of the recruitment process:

More than just circumstantial evidence

Nowadays, chronic inflammation is associated with a whole range of illnesses:

- **Skin**: psoriasis and neurodermatitis
- **Bowel**: Crohn’s disease, ulcerative colitis, diverticulitis
- **Nervous system**: multiple sclerosis, Parkinson’s and Alzheimer’s
- **Lung**: bronchitis, asthma
- **Joints**: rheumatoid arthritis
- **Metabolism**: impaired glucose tolerance in diabetes
- **Gums**: periodontitis
- **Heart and brain**: heart attack and stroke due to arteriosclerosis
- **All organs and tissues**: cancer

Schizophrenia may also be caused by inflammation. Such was the outcome of a recent study carried out by the Psychiatric Genomics Consortium. Researchers had compared the DNA data of 37,000 cases and 113,000 healthy controls. In so doing, they identified 108 independent associated genomic loci, 83 of which had not previously been reported. These are assumed to be the genes that have a major impact on the disorder.

One particularly surprising finding was that a variant closely associated with schizophrenia is located in a region of the genome that is important for the immune system, primarily for triggering inflammation. Individuals who have inherited the problematic gene pattern evidently have a 20 percent higher risk of developing schizophrenia.
The inflammatory response is a series of multi-organ events taking place throughout the body, which may be the cause of a large number of very different illnesses, for example, rheumatoid arthritis.

The vessels dilate and become permeable to allow more cells to reach the site; as a result, the affected area becomes red and swollen. In order to boost metabolic activity, the cells secrete multiple signalling molecules, or cytokines, thereby raising the body temperature. While the immune cells set to work, neurotransmitters send pain signals to the body, alerting it to immobilise and protect the sensitive area.

**The spotlight is not on the individual illnesses but on the inflammation**

The complex series of events is controlled by genes, which interact with the environment in many ways: once switched on by external stimuli, they trigger the production of the different neurotransmitters, activate signalling pathways – and terminate the process as soon as the threat has been neutralised. However, if the inflammatory response is not self-terminated due to a defective control mechanism, continuing beyond what is biologically necessary to eliminate a foreign invader, this may lead to serious illnesses. These include conditions like Crohn’s disease, ulcerative colitis, psoriasis, neurodermatitis, rheumatism, asthma, periodontitis, Alzheimer’s or multiple sclerosis (see box on p. 26).

Diverse clinical symptoms of these illnesses have a common denominator: a sustained or ‘chronic’ inflammation that overshoots the mark, leading to unspecific tissue damage. However, ‘silent’ inflammation is much more common than expected and represents an underlying principle behind a heart attack, stroke or cancer. According to recent studies, even psychiatric disorders like schizophrenia may result from inflammation.

The new systems medicine approach does not focus on the individual diseases but on the root of the problem – the central process of inflammation itself. This goes hand in hand with the desire to combat diseases henceforth in a completely new and much more decisive manner: with more molecular mechanisms and metabolic and signalling pathways being identified, the number of specific starting points for new therapeutics increases. New-generation targeted therapies ensure that patients receive precise and effective treatment. It would be even better to prevent a disease from manifesting in the first place, assuming that the molecular cascades often precede macromorphologic damage by years. The goal of this early intervention is to stop the initial molecular indications of a developing disease, in order to terminate the process before it becomes irreversible and other anatomic structures are attacked and destroyed.
“The time has come to transcend traditional boundaries”
An interview with Professor Stefan Schreiber of Christian-Albrechts-Universität in Kiel

Professor Schreiber, when people talk about the new concept of systems medicine, the word ‘inflammation’ inevitably crops up. Why is that?

Professor Stefan Schreiber: That is because, by and large, the biological phenomenon of inflammation is the best example of illustrating what systems medicine is and what we hope to gain by applying modern biological research approaches.

How do you explain this?

Prof. Schreiber: Up until now, medicine has mainly focused on individual organs. This medical historical concentration on a single organ has given rise to an enormous specialisation over the last 100 years, with dermatologists treating psoriasis, asthma being referred to pulmonary specialists and rheumatologists dealing with inflammatory arthropathies. Such specialisation has many advantages from the point of view of doctors’ profound knowledge and manual ability; nonetheless, it has also developed a momentum of its own, leading to a certain reciprocal disciplinary divide. But the main problem is that medical specialisation does not reflect the biological reality. This becomes especially clear in the case of inflammation: a series of multi-organ events taking place throughout the body, which may be the cause of a large number of very different illnesses. The time has come to transcend traditional boundaries, both in terms of structures and mindset, if we want to understand how chronic inflammation can produce illnesses that appear to be totally distinct. Only then can we strike out in new directions.

With regard to mindset, what might these new directions be?

Prof. Schreiber: At a time when bioscientific research has achieved tremendous progress across the full range of its breadth, we know a great deal about the genes and proteins and signalling pathways that control the processes of life. The human genome has been deciphered and disease-related genes identified, while better and faster technologies ceaselessly accumulate ever-increasing mountains of molecular biological data. This goes hand in hand with more and more powerful computers and elaborate information technology tools; for the first time, it is possible to compile data from all over the world, then evaluate and collate them in different ways. This process throws up previously undiscovered – and often very surprising – correlations between the diseases, sometimes even their common causes. I firmly believe that we have embarked upon a process that will overturn a great deal of what was previously considered irrefutable. That is a radical paradigm shift. Only this type of change can bring about genuine innovation. Not everybody in the field has yet grasped the revolutionary aspect of the new systems medicine concept nor the opportunities it opens up – but this number is growing steadily.
Moving back to inflammation – what are the latest revolutionary findings?

Prof. Schreiber: For example, we know that people who suffer from psoriasis, Crohn’s disease or rheumatoid arthritis often go on to have a heart attack or a stroke, too. This is corroborated by numerous studies. But why is that? This calls for closer analysis. As a result, we soon arrive at one conclusion: they are all caused by inflammation – they are all interconnected. Inflammatory processes in blood vessels encourage arteriosclerosis; if a vessel of the heart subsequently becomes blocked, this culminates in a heart attack; if it affects a vessel of the brain, it triggers a stroke. Inflammation of the bowel causes Crohn’s disease and ulcerative colitis, inflammation of the skin leads to psoriasis and inflammation of the lung to asthma. The joints are also destroyed by persistent inflammation. These illnesses all exhibit extremely different symptoms; however, the underlying disease-causing process, chronic inflammation, is always the same. This is also borne out by day-to-day clinical experience. You just have to look carefully.

Can you give us an example?

Prof. Schreiber: When our Crohn’s patients come to the clinic, they complain of diarrhoea and bowel pain – but rarely report shortness of breath. However, if we then measure the patient’s lung capacity, we find that the bronchia of one in three Crohn’s patients are abnormally constricted. This may be attributed to inflammation of the respiratory tract, which is controlled by the bowel.

“Modern research shows diseases in a completely new light. This opens up innovative treatment options and new methods of prevention.”

Professor Stefan Schreiber, Christian-Albrechts-University in Kiel

And patients don’t notice this?

Prof. Schreiber: If you have up to twenty bouts of diarrhoea a day and severe abdominal pain to boot, you are not going to be taking part in a long-distance run. Patients tend not to notice their shortness of breath because their main symptoms overshadow any other symptoms. However, if a doctor wishes to fully restore a patient’s health, identifying and treating any comorbidities is imperative; to achieve this goal, he or she has to adopt a multi-organ perspective to diagnosis and address the underlying disease mechanism during therapy.

What form might this basic treatment take?

Prof. Schreiber: Once we have unravelled the inflammatory process right down to the molecules involved, we can also find active substances that single out the main molecular protagonists. One example are drugs that are already available and which block the protein known as tumour necrosis factor. This protein plays a major role in inflammation. Efforts are being made to develop other active substances that also specifically target pro-inflammatory molecules, but with fewer side effects. These go as far as the resurgence of Hildegard of Bingen’s herbal tinctures, except that their effect has now been exactly defined on the molecular level. Nonetheless, as we all know, the best illness is the one that does not manifest itself. In my
view, this is one of the greatest potentials of systems medicine – the ability to prevent chronic inflammatory diseases.

**How can this be achieved?**

**Prof. Schreiber:** To give one example: thanks to genome research, genetic patterns that indicate a patient’s risk of congenital disease can already be characterised nowadays. If we now also had opportunities for gentle intervention, these could be used in combination with the relevant genetic patterns to develop a prevention that is both effective and minimally invasive.

**What options are there for gentle intervention?**

**Prof. Schreiber:** There are safe therapies that, ideally, do not have any side effects. Perhaps certain molecularly defined food constituents, individual amino acids for example, could be suitable for use as therapeutics in reducing a genetic predisposition to inflammation of the bowel. Although these options are still a long way off, our latest studies point to possible therapeutic applications along these lines (see box on p. 31).

**What are the findings of these studies?**

**Prof. Schreiber:** We know that the microbiome of the bowel, that is to say, the community of bacteria living in our bowel, is highly sensitive to the first signs of inflammation. If we analyse in depth the changes in the microbiome that are either disease-related or the precursors of a manifestation, we may be able to find markers for an inflammatory disease at a very early stage. These markers would represent, as it were, the first dominoes in danger of toppling and triggering an irreversible chain reaction. Our goal is to identify high-risk patients at the earliest opportunity and ensure they receive effective therapy without delay. To put it another way: I’d rather not wait to treat a Crohn’s patient until the bowel inflammation is well underway and has caused extensive damage. All I can do then is chase after the inflammation with the therapeutic armoury at my disposal. Instead, I want to prevent the disease from breaking out in the first place.

**What type of prevention strategy or early intervention might there be in the future?**

**Prof. Schreiber:** We already know the genetic profile: the children of Crohn’s patients have an almost 30 percent risk of developing the same disease. If we are then able to closely monitor the children of Crohn’s patients, checking their stool and blood samples for early molecular manifestations on a regular basis, appropriate intervention would spare these children from suffering the same fate as their parents. Unfortunately, we keep seeing the same story at the clinic, with the disease being discovered much too late. The further advanced it is, the harder it is to get under control.
Reliable biomarkers are likely to be a crucial requirement.

Prof. Schreiber: Yes indeed; molecular biology will have to be a great deal more accurate in this respect. What we really need are markers that can reliably detect the existing inflammatory process at an early, asymptomatic stage. This would give rise to innovative treatments, which have to take effect before the inflammation really gets going. That is our ultimate goal. It cannot be achieved in just one, two or three steps; but it is the goal that, as a doctor, I have to set myself for the benefit of my patients. Moreover, I consider it a very real possibility that systems medicine will achieve this by joining forces with modern bioscientific research.

New approaches to therapy

Our diet affects the molecular balance of our immune system and intestinal flora. Working with his colleagues in Vienna, Philip Rosenstiel and Josef Penninger, Stefan Schreiber demonstrated this for the first time: if the body does not receive sufficient tryptophan – an amino acid that is an essential part of our daily diet – this leads to a change in the composition of the approximately 100 billion bacteria that form an extremely important community in the bowel.

Tryptophan deficiency renders the body susceptible to diarrhoea and inflammation. The genes for the enzyme ACE2 (angiotensin-converting enzyme) and the transporter B0AT1 were found to be the molecular ‘culprits’: they control the absorption of amino acids from food. When the scientists fed tryptophan derivatives to mice, i.e. they were present in high concentrations in the lower regions of the small or large intestine, the inflammatory symptoms subsided. The composition of the intestinal flora returned to normal and the mice displayed a decreased susceptibility to inflammation over the subsequent period.

Nutrients like nicotinamide may help alleviate chronic inflammatory bowel disease. Scientists now aim to demonstrate this on patients. Some day, therefore, it may well be possible to treat chronic inflammation of the bowel both effectively and gently.
Darkness and light: hot on the trail of eye diseases

The intricate association and interaction of multi-protein complexes in ultra-thin membranes determines the welfare or otherwise of photoreceptor cells in the human eye. If these proteins lose their strictly regulated patterns and rhythm, photoreceptor cells may die and the eye become blind as a result. The scientists of the ‘Dynamo’ systems medicine research consortium have succeeded in identifying a protein that may lend itself as a molecular target for drugs that can halt this devastating process.

“The eye to this day gives me a cold shudder”. Penned by none other than Charles Darwin, this statement expresses a kind of capitulation before the masterpiece of evolution. The eye generates our image of the world, for which purpose it uses light-sensitive cells, the rods and cones. The retina, the layer of tissue that lines every eyeball, contains approximately 130 million of these photoreceptors – sophisticated processing facilities for photons, which are absorbed, converted into chemical and subsequently electrical signals in a complex fashion and then transmitted to the brain.

**Cells that let us see the world**

Although the elongated rod cells are extremely sensitive to light, they cannot distinguish colours; the more compact cone cells are responsible for the perception of colour and finer details. Their striking outer segments make the rods extremely sensitive to light. These are filled with tightly packed stacks of flat membrane disks. In turn, these have abundant stores of visual pigment, a protein named rhodopsin due to its reddish-purple hue. The high concentration of visual pigment makes the cells ideal photon receptors: absorbing just a few photons is sufficient to launch a complex signal chain within the membrane disks that involves countless proteins and neurotransmitters. Over the course of these signal transduction cascades, the photons trigger a biochemical signal that is then turned into an electrical signal. This is passed on to downstream neurons within the retina, which integrate and transmit such signals to the brain in turn.

"Mutations in genes coding for rhodopsin or other proteins involved in the signal transduction of light, as well as genes involved in developing the outer segment result in severe retinal diseases that may lead to blinding retinal degenerations", explains Professor Marius Ueffing from the Department of Ophthalmology, University Hospital Tübingen. The exact molecular workings of light perception are still not fully understood. Therefore, as Professor Ueffing points out, identifying the interaction of the proteins and their tasks in the corresponding molecular networks is a top priority. The scientist goes on to explain, “Understanding of the normal physiological function and its specific failure as a consequence of a single mutation can subsequently be used to pinpoint and comprehend the effects of such pathophysiological disruptions on the entire system.” The resulting knowledge on the molecular mechanisms of disease can facilitate the development of targeted substances for future therapies.
In a worst case scenario, photoreceptor cell death means a complete loss of vision.

Simulating the proteins in a computer model
Inherited diseases of the eye that can lead to severe visual impairment at a young age include retinitis pigmentosa and Leber’s congenital amaurosis. In both cases, the photoreceptors in the retina deteriorate. The reason for the progressive degeneration: the proteins that are necessary for the functioning of the outer segment and signal conversion are unable to perform their tasks properly due to a gene defect. While carrying out their BMBF-funded research, Professor Ueffing and his partners in the ‘Dynamo’ collaborative project were able to identify a molecule that plays a part in assuring the quality of membrane proteins. The detection of abundant dysfunctional proteins generates a default signal to eliminate the affected cell. As Professor Ueffing and colleagues were able to demonstrate, this protein presents a molecular target for therapeutics that can halt these eye diseases.

Prior to this discovery, the team carried out a survey of all proteins contained in the outer segments of the rod cells. By combining the molecular and bioanalytical data generated by the survey with modelling and simulations on the computer, the scientists were able to generate hypotheses to explain how these proteins work together. The more information on this cooperation that is available, the better the proteins involved in developing the outer segments can be represented mathematically and their interplay replicated in computer models. This enables the scientists to simulate how the protein network that interacts with rhodopsin reacts to changes, for example, once one protein partner is overly abundant, defective or breaks down completely.

An inhibitor may be able to help
One important finding of the intensive relationship analysis is the function of a protein known as VCP (valosin-containing protein). “VCP is a cog in a complex molecular machine, which ensures that misfolded proteins are identified and degraded”, Professor Ueffing explains. He surmises that, in patients with a dominant form of retinitis pigmentosa, VCP is responsible for eliminating misfolded rhodopsin molecules coded by the mutated allele. However, since misfolded and correctly folded rhodopsins physically combine to dimers, intact molecules are also annihilated in the process. In summary, this disrupts the development of the outer segment. “In light of these findings, it was imperative to generate a proper VCP inhibitor”, says Professor Ueffing. Today, this inhibitor has already proven effective in saving photoreceptors from degeneration in organotypic retinal cultures and in rats with inherited retinal disease.

Teaming up with pharmacologists in a newly funded European Horizon 2020 project, Marius Ueffing and his colleagues are now hoping that their experimentally proven concept, for which they have since received a patent, can be refined in order to treat human retinal diseases.
The prognosis for lung cancer

Compared to healthy tissue, the DNA of a tumour cell usually shows a number of genetic modifications. Molecular biological studies make it possible to identify these modifications and to understand their significance for the further progression of a tumour disease. The goal is to facilitate personalised therapy, in other words, using therapeutics that are adapted to the individual molecular pattern of the cancer cells. The new systems medicine approach is now also improving the outlook for lung tumour – a type of cancer for which limited treatment options have been available to date.

In the words of Bert Vogelstein, one of the world’s leading cancer experts, “The revolution in cancer research can be summed up in one sentence. Cancer is, in essence, a genetic disease”. Back in the 1970s, cancer was still a black box; today, medical science has a reasonably good understanding of the molecular processes in tumours – often better than the causes of many other illnesses. The decoding of the human genome has gone a long way towards achieving this insight. While analysing the genome of cancer cells, scientists are now studying the impact of gene defects on the cell’s various signalling pathways and communication networks. In the process, they are hoping to discover how the molecular changes stimulate a cell to unchecked growth – and how abnormal cell reproduction can be regulated by means of suitable active substances. Experts refer to ‘targeted therapies’, as distinguished from conventional chemotherapy, a new molecularly targeted approach that aims to benefit patients as part of personalised healthcare.

Paving the way for the therapy of the future
One type of cancer that long resisted any kind of therapeutic advance is pulmonary carcinoma, one of the most common cancers in the world and the most frequent cause of cancer-related deaths worldwide. Yet the prognosis is now very different: lung cancer, largely regarded as a hopeless case, has since advanced to one of the cancers that are paving the way for the therapy of the future. Professor Roman Thomas from the Department of Translational Genomics at the University of Cologne has played a major role in this development. The scientist heads the BMBF’s ‘SMOOSE’ project, a consortium of biologists, medical professionals, chemists, physicists, mathematicians and computer scientists. The scientists are applying system-oriented techniques in order to gain extensive insight into the molecular mechanism of lung cancer cells and find points of reference for new active substances. “The process makes allowance for the genetic variations between individual patients”, explains Professor Thomas. This makes it possible to develop personalised therapy options.

Personalised therapy prolongs survival
Until now, looking at a tissue sample under the microscope has determined what type of lung cancer a patient has. Supplementary molecular biological analysis enables a more accurate diagnosis. For example, it
indicates which genes have altered in the tumour cells and how they trigger excessive growth in the cells. One prominent example of this ‘driver mutation’ is the mutated EGFR gene. It is responsible for a protein that acts as a receptor: the EGF receptor (epidermal growth factor receptor) sits like an antenna on the cell membrane and naturally receives signals that prompt the cells to start dividing. If an alteration of the EGFR gene, for example, causes too many receiving antennae to be installed in the membrane, the cell is exposed to an excess of growth signals. The abnormal growth instructions find their way into the cell nucleus via a complex molecular transmission cascade, where they crank up the cell-dividing machinery that forces the cell to divide over and over again.

Modified EGF receptors are found in approximately ten to fifteen percent of patients suffering from ‘non-small cell lung cancer’. These individuals respond to therapy with active substances that are able to block the EGF receptor and its catastrophic signal transmission. On average, patients receiving this treatment live approximately 24 months longer than those undergoing conventional chemotherapy. The researchers’ goal is two-fold: firstly, to find as many similar molecular targets as possible that might respond to therapy and, secondly, preferably to be able to offer all lung cancer patients a treatment that is adapted in line with the individual changes in each case.

The next stage of therapy
As Professor Thomas goes on to substantiate, the label of lung cancer is merely a "generic term for numerous subgroups, each with their own molecular characterisation". Using genome analysis and innovative computer algorithms, Roman Thomas and his team have pinpointed other previously unknown genetic alterations. Within the scope of the systems medicine approach, the research group places great emphasis on identifying the mechanisms responsible for the re-growth of the tumour after targeted personalised therapy, which leads to a recurrence. This represents the next stage of personalised therapy, according to Professor Thomas. For example, this could help patients who suffer a recurrence following treatment with EGFR inhibitors because the tumour cells no longer respond to therapy owing to new mutations, in other words, they have become resistant. As soon as the molecular mechanisms of resistance have been identified, the researchers intend to develop therapies that will help patients whose tumour has grown back.
The secret intelligence service of the cell: how do molecules communicate?

Thousands of interacting molecules determine the fate of a single cell. Many disciplines – from biology to mathematics and physics, right through to computer science – are needed to map the molecular signalling pathways. The combination of mathematical modelling and laboratory experiments reveals surprising details that would remain undiscovered if only conventional biological methods were used. Systems medicine applies the new basic research findings to ensure patients’ well-being.

The Nobel Prize winning physicist Erwin Schrödinger posed the question “When is a piece of matter said to be alive?” His answer was “When it goes on ‘doing something’”. A cell, the most elementary building block of all life, meets this definition without a doubt: it goes on doing something. Cells interact with their environment, they send and receive messages, they produce materials, move and proliferate. What cells do has been widely researched; but the question of how they do it, has ultimately been left unanswered, despite our detailed knowledge.

Just some ten or fifteen years ago, scientists mainly applied linear thinking to the how of life processes: a gene initiates the production of a protein and the protein does something in a certain way. Although this straightforward approach can still be found in nearly all textbooks today, it is not sufficient to describe the actual vital occurrences in a cell, which resemble a
bubbling cauldron with tens of thousands of ingredients, all interacting with each other in different ways. Neurotransmitters attach to the cell from outside, activating complex networks of molecular changes; the concentration of molecules fluctuates, reaching threshold levels and dropping again, while different chronological sequences trigger different reactions at the genetic level.

**Combining biology and mathematics**
Professor Ursula Klingmüller has been researching the dynamics of cells since the 1990s. The biologist favoured mathematical models from the outset. From a traditional perspective, systematically combining biology with mathematics is an unusual – but for Ursula Klingmüller absolutely essential – approach to understanding life processes. "Today's mathematical models may advance the life sciences in the same way the microscope did in the past", explains the biologist.

“They reveal things that would remain undiscovered if classical biological approaches only were used”.
For example, how long does a signal molecule stay in the cell nucleus in order to switch a gene on or off? Quick as a flash, Ursula Klingmüller answers “Around six minutes”. At any rate, that is the average dwell time of the STAT molecules in the nucleus. Their task is indispensable for the organism: STAT molecules induce progenitor cells to survive and proliferate, stimulating the progeny to mature into red blood cells that transport oxygen. This process must take place on an ongoing basis as fresh red blood cells are needed all the time, for instance if a bleeding wound necessitates the rapid provision of fresh supplies or because the life span of the cell specialists expires after about 120 days.

**Mathematical models visualise processes**
The scientists discovered just how long STAT molecules spend in the cell nucleus in order to perform their tasks by compiling a mathematical model. Yet is the dry theory really borne out by the teeming processes of real life? The pointer thrown up by the mathematical model was subsequently corroborated in laboratory experiments with living cells. "Without the mathematical model, we would never have discovered that STAT only stays in the cell nucleus for such a short time, affecting the genes in cycles", says Ursula Klingmüller. It was a surprise to realise that STAT molecules are only active for such a brief period and that they make multiple attempts to carry out their task during this time. The scientists had previously believed that the molecules would have to remain in the nucleus for much longer and that they approached their target in linear fashion, like a one-way street. This was not the only unexpected insight into the molecules’ commu-
unication channels. Working with ‘modellers’, their partners from physics and computer science, Ursula Klingmüller and her team discovered a whole array of other fascinating details about the cellular messaging service.

**How do molecules make decisions?**

Verifying what can be observed with accurate data is how Ursula Klingmüller defines the goal of her research. "I always found it very unsatisfying to only be able to say, a substance in the cell goes up a bit and then down a bit – I wanted to know exactly what was going on". How long does a signal molecule actually stay on the receptor, the ‘gateway’ on the surface of the cell? How does information get through the cell membrane? What passes the signal on to the nucleus and how long does transmission take?

After studying biology in Heidelberg, Ursula Klingmüller turned her attention to these questions initially at Harvard Medical School in Boston and Whitehead Institute in Cambridge (Massachusetts), the bastions of research into the phenomenon of ‘cellular signal transduction’, at that time still in its infancy.

Ursula Klingmüller now works at the German Cancer Research Centre in Heidelberg, where she is still fascinated by the question of how cells process information and how molecules contribute to the decision-making. For example, the decision that a cell has to divide and undergo a particular specialisation programme – to become a red blood cell perhaps, which is tasked with delivering oxygen to the tissues and organs of the body. Knowing the individual steps involved in cellular differentiation means also understanding how molecules sometimes make the wrong decisions and allow a healthy body to fall sick.

**Training for red blood cells**

What is the curriculum of the red blood cell specialisation programme? It starts off with the wake-up call to the progenitor cells quietly slumbering in the bone marrow, summoning them to become active and proliferate. The summons is delivered by a signalling molecule, the hormone ‘erythropoietin’ (see box). To this end, it attaches to its receptor, a protein that traverses the membrane of the progenitor cells and opens up on its surface like the leaves of a gate. As soon as the hormone arrives, certain enzymes become active in the interior of the cell: the Janus kinase (JAK). They are evidently named after the two-faced god, Janus, the guardian of gateways. The guardians notify other proteins, the abovementioned STAT molecules, whose full technical title is ‘signal transducer and activator of transcription’. The STATs advance through to the cell nucleus where, in just a matter of minutes, they activate the genes that initiate cell division and prompt the cell to adopt the development path of an oxygen carrier. Scientists refer to the JAK-STAT signalling pathway.

The individual steps on this complete pathway can be expressed as differential equations and translated into a mathematical model, which describes how single molecules and their interrelationships change over time. Theoretical models also make it possible to change different variables and try out various scenarios without fear of risk: for example, scientists can change the concentration of one intermediate product or other, or vary the speed of partial reactions, then sit back and observe at their leisure the impact of these influences on the computer screen.

This method has been used to answer many unresolved questions concerning the JAK-STAT signalling pathway, one of which had puzzled scientists for a very long time: how do the progenitor cells of red blood cells invariably manage to react appropriately to fluctuating hormone concentrations, despite the limited number of receptors on their surfaces? In other words, how come the body is always able to supply exactly the right quantity of red blood cells – neither too many nor too few and with no delay of any kind?

“Mathematical models can advance science in the same way the microscope did in the past.”

Professor Ursula Klingmüller

German Cancer Research Centre, Heidelberg
Circular communication

“If too much of the hormone floods too few receptor molecules, we would expect the saturation point to be reached very quickly. This would mean that the haematopoietic cells could no longer respond to a further increase in the hormone level”, says Ursula Klingmüller. When the scientists combined their experimental data with mathematical models in order to clarify this issue, they discovered a previously unknown intermediate stage in the communication channel.

When the hormone binds to its receptor, both are absorbed as a pair into the interior of the cell and rapidly degraded. At the same time, the cell populates its membrane with new receptor molecules, which are kept in intracellular stores. The new receptors are replenished at such speed and so precisely that the cell is able to sense incoming hormone molecules without interruption and continuously react in accordance with the hormonal message. Throughout this process, the STAT molecules’ task is to continually track how active a receptor is. Only then do STATs relay the survival signal to the progenitor cell, the prerequisite for subsequent division. “The signalling pathway is non-linear”, Ursula Klingmüller reiterates. “It is a communication cycle”.

The human body produces approximately three million new red blood cells (erythrocytes) every second. Blood formation – erythropoiesis (from the Greek erythro, meaning red, and poiesis, to make) – is stimulated by the hormone erythropoietin, or EPO for short. Having encountered the progenitor cells of the red blood cells in the bone marrow, the hormone induces progenitor cell division, which then mature into oxygen-transporting cell specialists in several stages.

The most important EPO producers are the connective tissue cells of the renal cortex. They secrete the hormone in response to low oxygen levels in the tissue. The perpetual production of short-lived red blood cells ensures that the body is kept adequately supplied with oxygen. In the event of profuse bleeding and pronounced oxygen deficiency, EPO production is first boosted and then scaled back to basic supply levels. The system is highly sensitive and flexible, adjusting the production of red blood cells to every situation.

Anaemia is caused by ineffective erythropoiesis. Genetically engineered EPO is an important medication for treating anaemia, used by doctors to prevent anaemia in dialysis and cancer patients.
Fresh hope for cancer patients
This detailed knowledge of basic systems biology research facilitates its translation into applications – systems medicine. For example, the new insight thus gained into the otherwise secret intelligence service of the cells offers hope that lung cancer therapy will be improved in the future. Once again, this entails a complex system of interrelationships: yet unravelling them opens up encouraging prospects for medical science.

Most lung cancer patients are treated with therapeutics that impede cell division. However, cytostatic drugs do not just attack the cancer cells in the lung, but also healthy blood cells. This often leads to anaemia, which causes patients to suffer unduly. In order to encourage the body to produce new blood cells and balance the anaemia, patients were given the hormone erythropoietin in drug form. However, it emerged that the tumour cells also have receptors for erythropoietin, meaning the drug does not merely stimulate the production of red blood cells but – a fatal flaw – also promotes the continued proliferation of the abnormal cells. Therefore, the former practice of treating cancer patients with erythropoietin is rarely carried out today.

It is difficult to evaluate whether medical erythropoietin does a patient more harm than good as a great many factors have a reciprocal effect in the treatment. Ursula Klingmüller and her team recently mapped this complexity in a mathematical model, which visualises whether or not tumour cells have functional receptors for erythropoietin. “Based on our latest findings, we want to establish a simple test system that makes it possible to reliably predict whether erythropoietin receptors are present on tumour cells and, if so, how many there are”, says Ursula Klingmüller. A test like this could soon allow doctors to clearly identify those patients who stand to benefit from the treatment with erythropoietin.

Plotting a path through the communication maze
Cells have many ways of processing information. They use countless molecular signalling pathways in the process – almost all of which are infinitely more complex than the JAK-STAT signalling pathway activated by erythropoietin. “The erythropoietin system is a relatively simple system but that makes it ideal for obtaining a fundamental understanding of how molecules are involved in decisions”, says Ursula Klingmüller. Once the principle is clear, we stand a chance of keeping track of ramified communication networks, like the MAP kinase pathway, which plays a major role in the development of cancer.

The MAP kinase pathway is composed of over two dozen molecules, whose convoluted interplay is still largely unknown. Nonetheless, the researchers hope that, like Ariadne’s thread, the mathematical models will guide them through the labyrinth. “In essence, models describe all signalling pathways in the cell in quantitative terms”, says Ursula Klingmüller. She hopes that, one day, all the models will be merged to form one large communications network, a roadmap describing all the molecules and interactions that are the arbiters of cell life and survival. This would also open up completely new possibilities for using suitable active substances to systematically disrupt communication chains, like those that transmit defective signals and turn healthy cells into cancerous cells.

"Models describe all signalling pathways in the cell in quantitative terms."
Professor Ursula Klingmüller, German Cancer Research Centre, Heidelberg
The profilers: analysing cancer

As part of a pilot project in Berlin, scientists are characterising tumours right down to the molecular level; in addition, they are using computer models to verify what drugs are the best match for individual patients. Systems medicine aims to address the root cause of cancer and find a cure in the process.

The patient anxiously takes a seat and faces the doctor across the desk. The laboratory report has arrived. Meanwhile, the doctor studies the results of the laboratory analysis on her computer screen. “The cells show several genetic abnormalities”, she says. “Basically, your condition is the result of a tumour that is caused by a particular molecular change”.

“What are the treatment options?” the patient wants to know. The doctor opens up the drug database and enters the results of the genetic analysis in the search field. The computer immediately displays the recommended therapy, which is personalised for both the patient and the tumour. She advises using a drug that interrupts the molecular signal chain being sustained by the carcinogenic gene at a crucial point. “Cell division will return to normal”, promises the doctor. “An additional combination of drugs, which is customised to take account of the genetic changes in your tumour cells, will subsequently cause the tumour to disappear completely; at the same time, it prevents cells from migrating and forming metastases elsewhere in the body”.

This is one possible scenario for a consultation at the doctor’s surgery in the future. Of course, the scene is too simplified to ever become reality: the biological complexity of the cells is just too great – added to the complexity of the tumour cells, which invariably develop from the body’s own cells. Nevertheless, in a nutshell, the imaginary doctor-patient consultation portrays the ultimate goal of modern cancer research:
a whole range of drugs that act in a targeted manner, offering personalised cancer therapies. This approach could turn a deadly threat into a chronic disease that can be controlled in the long term.

Hopes are now being pinned on molecular biological research, which has compiled considerable evidence over the last few decades that cancer is a genetic disease. The guiding principle of scientists around the world is: the more we know about the molecular causes, the greater chances we have of ensuring an accurate diagnosis and an effective therapy that attacks the molecular roots.

**The lost equilibrium**
Whenever a cell divides it has to replicate its hereditary material, DNA. This is a continuous process in the human body: around 50 million new cells are produced per second, like fresh blood cells, which replace the old ones as they die. Errors can creep into the genetic code with every cell division, perhaps because pollutants or damaging rays have affected the genetic material. Many of these errors will not compromise the function of the genes in any way, especially as cells have a perfectly organised molecular repair service that quickly detects and rectifies irregularities like interchanged or missing DNA building blocks. However, if a genetic modification or mutation takes place in a section of DNA that is particularly crucial for cell division, if a defect is so grave that it cannot be repaired or if so many errors have accumulated over time that the delicate genetic balance of the cell’s growth equilibrium is upset, this may lead to cancer. Hundreds of genes that are mutated in cancerous cells have since been discovered. They belong to two large categories: oncogenes, which have the potential to cause cancer and antioncogenes or tumour suppressor genes, with names like C-Myc, B-Raf, Neu, Fos, Her or p53.

The list of genes that play a role in cancer is nowhere near exhaustive. For a long time, the tools or techniques needed to complete it did not exist. Today, scientists in laboratories around the world use ‘reading machines’, or sequencers, to determine the order of the four bases obtained from tumour cell genomes. They then compare the genome of the abnormal cells with that of the patient’s healthy cells. This method reveals valuable insight into the genetic differences, which will help in developing new diagnostic and therapeutic approaches.

In the meantime, the machines’ reading speed has accelerated to such an extent that they provide large quantities of data within a short space of time. By itself, assiduously generating data would be futile without the enormous processing power of modern computers to store and compare the data, sort them in a meaning-
ful way, combine them with other experimental results and control the wealth of consolidated knowledge thus gained. “The more data we feed into the computer”, says Professor Hans Lehrach from the Max Planck Institute for Molecular Genetics in Berlin, “the more detailed and precise our tumour models become and the better we can predict the behaviour of complex biological networks, like those in tumour cells”.

Every tumour is different
The basis of every model is always the extensive molecular characterisation of a patient’s individual tumour. The computer can use these data to reconstruct cellular signalling pathways and networks, molecular interactions and feedback systems in mathematical terms, while testing which drug or what combination of active substances could prove optimal in treating a particular patient, for example. “Every patient is different and so is every tumour”, stresses Professor Peter Schlag, founding director of the Charité Comprehensive Cancer Center in Berlin. “We have to make much greater allowance for the individual type of tumour than previously, which is why we need particularly accurate computer models”.

“The genetic profile of every tumour is different – even if it appears to be the same disease. It is imperative that we use this knowledge.”

Dr. Marie-Laure Yaspo, Max Planck Institute for Molecular Genetics, Berlin

“Treat 20” – a pilot project
Dr. Marie-Laure Yaspo of Berlin’s Max Planck Institute for Molecular Genetics has extensive experience of reading genes. The French-born scientist played a prominent role in sequencing chromosome 21 as part of the Human Genome Project (see the introductory text on page 9). Now she is holding paper printouts with countless columns and coloured fields: the genetic profile of tumours.
These belong to twenty different patients, who have been diagnosed with metastasised malignant melanoma. Marie-Laure Yaspo has read the complete genome text of every single patient’s tumour cells and compared it with their healthy cells. In addition to the genome of the tumour cells, the scientist also identifies the ‘transcriptome’ – the copy of all the information stored in the DNA on messenger RNA – and the ‘proteome’, the entire set of proteins in the cell. “A vast quantity of data soon accumulates, which can only be handled by a computer because of the sheer volume”, Marie-Laure Yaspo explains.

“In future, we will no longer simply classify cancer according to groups of organs, referring to breast, bowel or prostate cancer; instead, it will be defined according to its molecular characteristics. This should enable us to treat patients in a more personalised way.”

Professor Peter M. Schlag, Charité Comprehensive Cancer Center, Berlin

For example, the scientist may find ‘deletions’, where genes have been lost; or she discovers ‘amplifications’, abnormally duplicated genes. These two typical modifications sometimes occur in tumour cells. “In some cases, we may find ten or twenty abnormally altered genes in the cancer cells”, Marie-Laure Yaspo remarks. “In other cases, we have discovered up to 300 mutations”. However, as the scientist knows from her transcriptome and proteome analyses, it is not necessarily modifications at the level of the genome that determine the fate of the cell. Every once in a while, the quantity of a gene product, a protein occurring in the tumour cell, is a hundred times greater than in a normal cell. This suggests a defect in gene regulation. “The gene itself is unaffected”, explains Marie-Laure Yaspo, “but it has been transcribed too often by the cell”. Similarly, an intact gene, whose information is essential in ensuring healthy cell life, may no longer be accessed. Molecular analysis often fails to take account of the complex level of gene regulation. However, this is precisely what is needed. As the researcher goes on to substantiate, “It is the interplay of numerous changes that determines the behaviour of a cell”.

Moving towards personalised therapy

Therefore, the scientists in Berlin enter all molecular ‘accidents’ that have taken place in the tumour cells into the computer. Then they use the model to simulate the impact of the deletion or amplification of a gene on cellular signalling pathways and networks, for example, or how feedback systems change if the cell is flooded with large quantities of a gene product. Moreover, the model allows the scientists to test how drugs affect the individual molecular circumstances or at which point on the signalling pathway an active substance should ideally intervene in order to be most effective. By using a computer, the researchers hope to be able to predict the optimal therapy for each individual patient, thereby enabling ‘personalised cancer therapy’ – treatment that corresponds to the different molecular characteristics of the tumour in each case. This approach promises to be more successful than conventional chemotherapy with cytostatic agents that tend to attack indiscriminately any body cells that undergo frequent cell division – including healthy cells. “On average, conventional therapeutics do not even help 50 percent of patients”, Hans Lehrach points out.

A change of direction

There is still a long way to go before the new systems medicine approach becomes standard clinical practice in treating the ‘model disease’ of cancer. Nonetheless,
the case study in the pilot project of a woman with a metastasised melanoma serves as a perfect example of how patients may eventually benefit from the approach. Neither conventional chemotherapy nor immunotherapy had had any effect. The molecular analysis and computer modelling indicated a modified cellular signalling path; a drug that had not previously been used in melanoma therapy, but in treating an inflammatory disease, appeared to be a good match. Permission was granted to give the drug – one of the new active substances that targets specific cellular molecules – to the patient as an off-label experimental therapy. As a result, the patient’s condition improved considerably, Peter Schlag reports. “Overall, we prevented the disease from progressing and stabilised the patient over eight months while maintaining a good quality of life”, says the medical professional. “That is a very long time for somebody at this stage of the disease”.

“We use computer models to forecast the weather, train pilots and develop new cars. Why not also use computer models to make predictions in the medical field?”

Professor Hans Lehrach, Max Planck Institute for Molecular Genetics, Berlin

The patient died after other metastases developed. The sequencing of the daughter cells showed the same genetic profile as the original tumour; however, in the meantime, a further tumour suppressor gene had been deleted and silenced genes reactivated, which cause cells to migrate and metastasise. If active ingredients were available to repeatedly strike at cancer cells by means of their catastrophic molecular changes, preventing them from dividing uncontrollably to the detriment of healthy cells, then maybe the researchers’ dream of transforming cancer into a manageable, long-term condition could someday become reality. “There is also good cause to hope that we can improve the recovery rate significantly”, Peter Schlag points out. The systems medicine approach proposes a way forward that could well be worth pursuing (see also “An opportunity to be seized with both hands” on page 46).
“An opportunity to be seized with both hands”

An interview with Professor Peter M. Schlag from Berlin’s Charité University Hospital and Professor Hans Lehrach from the Max Planck Institute for Molecular Genetics in Berlin

Professor Schlag, how would you define the term systems medicine with regard to cancer?

**Professor Peter M. Schlag:** The term is based on today’s better molecular understanding of cancer. Basic research produced the necessary premises to attain this understanding. The challenge now is to progressively incorporate the vast knowledge about the complex, uncontrolled interaction between the numerous different molecules within a tumour cell and in the surrounding tissue environment when treating cancer patients.

*In pursuit of personalised cancer therapy: Professor Peter M. Schlag, the founding director of the Charité Comprehensive Cancer Center, Berlin.*

Is every tumour really different?

**Prof. Schlag:** Almost no two tumours are completely alike. A comparison between tumour cells and normal cells usually comes up with more than one hundred, if not more, very different molecular changes. Seen in this light, every tumour is more or less unique.

What happens to all these molecular data?

**Professor Hans Lehrach:** All the data generated from a patient’s tumour are collected and used to build an accurate computer model of the tumour. The more information about the tumour is entered into the computer, the more accurate the model. It is no secret that computers are very good at handling vast quantities of data and applying them to describe the condition of a system in detail. We know how the individual components of this model interact from the findings of basic research, which also generated and analysed large amounts of data in order to discover these interactions. We compile this precise analysis of the individual parts of a particular tumour with the knowledge of how these elements interact to develop highly accurate computer models of each individual tumour.

What can these models be used for?

**Prof. Lehrach:** We test the different therapeutics that could be administered on the tumour computer model of that particular patient. To this end, we let the model run with or without a drug, for example. The computer model allows us to test the impact of different drugs and select the medication that was most effective and had the least harmful side effects in the model for use in treating the actual patient. Likewise, we can see how the tumour model changes when combinations of drugs are administered. It’s basically the same as modern development in the automotive industry, where designers also simulate what happens if the bumper is thicker or thinner, for example. In the same way, we hope to use the computer model of the tumour to help signpost whereabouts the system

“Our goal is to offer every patient a therapy that is specially tailored to their needs.”

**Professor Peter M. Schlag,**

Charité Comprehensive Cancer Center, Berlin

Our goal is to be able to offer every patient a therapy that is specially tailored to their needs. However, we are still in the very early stages of implementing this concept, which is a complicated undertaking.
needs to be changed in order to coax it to move in the right direction. It is just infinitely more complicated.

**Professor Lehrach, what do you understand by 'systems medicine'?**

**Prof. Lehrach:** On the one hand, there is this pairing of a characterisation of the initial state that is as precise as possible and, on the other, the computer model, which is able to predict how this initial state will develop in the future. As I see it that is the definition of systems medicine: the application of mathematical models to medical issues.

**What does it mean for patients?**

**Prof. Lehrach:** Genuine, possibly even revolutionary progress in the treatment of cancer. Enormous sums used to be invested in cancer research. According to some estimates, one trillion dollars have been poured into research around the world since the mid-1970s, resulting in still limited benefits for patients.

**Why is that?**

**Prof. Lehrach:** This is doubtless due to the fact that much time was spent looking for the 'silver bullet', a cancer pill that was equally effective for all patients and every type of cancer. But this is a lost cause. The biological system of cancer is just too complex. We need a different approach.

**Prof. Schlag:** I would definitely agree on that. If we continue to focus on individual molecules in experimental cancer research and rely on the 'trial and error' principle of large treatment cohorts in tumour medicine, we will not have made a great deal of progress, even ten years down the line. We need to pool our entire knowledge about cancer and a patient's specific tumour in precise biomathematical models. This is a crucial requirement, both for more outcomes-based therapeutic decision-making in the future and for developing innovative drugs and improved treatment concepts. In the past, our planning and approach was far too constrained. We need to venture a more overarching view in future. Even today, we have an enormous range of technology at our fingertips – that we do not fully exploit. And although we have accumulated vast reserves of knowledge, we have not yet tried hard enough to combine this knowledge in an interdisciplinary way. This is now a priority. Therein lies both the challenge – and the unique opportunity of systems medicine.

**Does this mean then that a molecular diagnosis and a computer model should be prepared for every patient before the start of every promising treatment?**

**Prof. Lehrach:** In an ideal world, yes. In this respect, therapy is no different to flight training, where you let the pilot try out which manoeuvres work and which cause the plane to crash; obviously, it makes sense to use a flight simulator and not a real aircraft with real passengers.

**Prof. Schlag:** Ultimately, we have to define every tumour on the molecular level, irrespective of the organ, before we can start the therapy. However, we still know nowhere near enough on the subject. First we have to gain experience, like finding out what molecular information is really relevant from a therapeutic point of view.

**Prof. Lehrach:** If we had a complete picture of the tumour and also knew exactly how drugs affect it, we should be able to build a model that simulates every aspect of the process and is invariably spot on with its predictions. It would then be possible to tell a patient, for example, this drug would be effective in your case, this drug certainly won’t be, but this combination of
drugs is promising. It is like the weather forecast. The more details I include, in other words, if I measure the temperature every minute rather than once an hour and enter this information in the computer system, the more accurate it is.

**What do we still need to make the right predictions?**

**Prof. Lehrach:** So much about tumours and their development is still unknown but we have already found out a great deal and constantly strive to learn even more. We analyse the genome, the transcriptome and the proteome of the tumour cell, and we enter every single piece of information we can get our hands on into the computer. In the future we will have increasingly precise methods, sequencing technologies for example, that are able to pinpoint the exact origin of each sequence in the tumour. So far, we have only mapped a small percentage of the rules governing the interaction of individual components, for example, which proteins interact with other proteins or the ultimate effect of the various mutations in signalling pathways and networks. Nonetheless, this will also become clear over time. Above all, however, it is a question of the funding that is available for all these tasks, which may allow us to constantly improve the models and generate increasingly accurate predictions. Even today, there is no doubt in our minds that we can make therapeutically relevant predictions for certain patients, based on molecular analyses and modelling. The medium-term goal is for computer models to become an integral part of therapy planning, thereby increasing the accuracy and success of cancer treatment.

**What hopes do you have for the future?**

**Prof. Lehrach:** That computer models will one day be used as intensively in medicine and drug development as they are in the automotive industry today. In principle, the most sensible course of action for society would be to test the systems biology approach relentlessly on a larger scale with regard to its medical application and the development of drugs. It may well be that, as a matter of principle, many only see limited opportunities for truly revolutionary transformations. However, if they come about, I am confident that the impact will be enormous.

**Prof. Schlag:** We should seize these opportunities with both hands.

“We have to define every tumour on the molecular level, irrespective of the organ, before we can start the therapy.”

Professor Peter M. Schlag, Charité Comprehensive Cancer Center, Berlin
The computed organ: mapping the virtual liver

A mathematical computer model that simulates the molecular processes in the metabolic organ – the liver – allows scientists to predict whether a drug will actually be effective.

Of all the cells in the body, hepatocytes are the most versatile: day in, day out, they deal with over 10,000 substances, either converting, synthesising or breaking them down, storing or excreting them. Mapping this astounding achievement on the computer is the objective of the Virtual Liver Network. Over 70 groups of scientists are currently working to map as many of the crucial molecules, signalling pathways and networks as possible on the computer, one step at a time. Their objective is to enable important medical applications, like predicting whether a drug would be effective for a particular patient and what side effects are to be expected. Computational models also help in detecting liver cell disorders on the molecular level and in developing new therapies.

One day more than 1,500 years ago, a young Viking began to experience the first signs of an insidious poisoning. He felt tired and listless, his skin started turning a greyish brown. The older he got, the darker his complexion became, his hair began falling out, he suffered more and more frequent convulsions in terrible agony. The slow-acting poison probably killed him before he was much older than 40, unless he succumbed to one of the other numerous ways of dying at that time.

The cause of the poor man’s affliction was iron. The cells of the small intestine absorb iron – an essential trace element – from our diet. This is regulated by a simple principle: if the body has sufficient reserves, the enterocytes stop absorbing iron; if stores are depleted, they replenish them. In the case of the Viking, this system did not function properly. As his enterocytes consistently absorbed too much iron, his body deposited the excess in his skin and liver, his pancreas, his heart, in his spleen, joints and blood vessels. The man suffered from iron overload or haemochroma-
tosis, one of the most common hereditary metabolic disorders nowadays, to which one in eight Europeans has a predisposition. The unknown young Viking was presumably the ‘founder’, as human geneticists call it: the individual who was the first to manifest this genetic defect, passing it down through the generations and over the centuries.

**A molecular error with grave consequences**

In the mid-1990s, American molecular biologists identified the genetic culprit on chromosome 6. They discovered that just one single letter distinguished it from the fully functional gene. This tiny molecular error, or point mutation, has far-reaching consequences: the amino acid tyrosine is wrongly inserted in the protein that the cell factories manufacture according to the genetic blueprint. At first glance, this appears to be nothing more than a minor biochemical variation – nevertheless, it affects the entire organism.

In 2008, the scientific team spearheaded by the biologist Martina Muckenthaler in Heidelberg succeeded in clarifying exactly how the genetic defect makes the body ill, right down to the molecular details. It turned out that the cells of the liver were using the protein that was constructed according to the genetic blueprint as a ‘sensor’. This allows them to determine whether the body has sufficient stores of iron, for example, to be incorporated in red blood cells, thereby enabling them to transport oxygen. If the amount of iron corresponds to the body’s current needs, the hepatocytes produce a hormone, hepcidin, and release it into the bloodstream. From there, hepcidin finds its way into the cells of the small intestine, inhibiting the further export of iron into the blood. However, if the gene that encourages the development of hepcidin is flawed, the hormone is produced in insufficient quantities. As a result, hepcidin is no longer able to curb the iron intake and a fatal iron overload accumulates in the body.

Over the years, basic research has revealed the workings of iron metabolism and its disorders, right down to the molecular level. This has paved the way for new approaches to therapy and exemplifies how the new systems medicine concept may lead to the desired objective: knowing about the molecular mechanisms of a disease should be conducive to systematically repairing the defects at its root. Medical science has documented many other, more common diseases of the liver and the metabolism. Here again, the goal is to understand the underlying causes of the diseases, right down to the very molecules, and find new therapies. This is the research focus of the BMBF-funded Virtual Liver Network, which has also produced important findings on iron metabolism.

**How is the liver being mapped on the computer?**

The Virtual Liver Network comprises 70 groups of theoretical and experimental scientists. The researchers aim to understand the remarkable organ and how it works in as much detail as possible. The long-term goal of the research network, which is the only one of its kind in the world, is to map a ‘virtual liver’: a com-
comprehensive mathematical model that represents the central liver processes and will enable the processes of life to be simulated realistically ‘in silico’ – using the computer. “We will not be able to map every last function of the liver on the computer”, explains Professor Ursula Kummer. “But what we can do is gradually model as many of the central signalling pathways and metabolic processes as possible that are associated with the essential incidence of disease”. By this means, the researchers hope to explain molecular dysfunctions that cause common illnesses, like hepatitis, fatty liver disease, cirrhosis or cancer of the liver, and find starting points for targeted therapies.

A weather map for the liver cell
From the outset, the biochemist Ursula Kummer has been in one of the many research groups involved in the ambitious project to map the liver and its functions on the computer. As the Professor at Heidelberg University explains, what the computers need for a realistic simulation are “as many quantitative experimental data as possible”. Ursula Kummer receives the data from her colleagues in the biological laboratory, who conduct experiments with real hepatocytes and real liver tissue. “We translate their findings into equations and draw up models that represent the biological processes in the real cell”, Ursula Kummer adds.

The subsequent ‘computer experiment’ allows individual parameters to be modified as required, thereby revealing connections that the laboratory experiment is unable to show or only with considerable effort. The systematic pairing of the biological experiment, mathematical modelling and repeated experimental verification is still a fairly recent development in the life sciences. However, it shows similar potential to the field of meteorology, where the data obtained from actual weather observations have long been entered into mathematical models to generate relatively reliable weather forecasts for the next few days.

Using a computer, Ursula Kummer has already managed to elicit important details regarding the molecular messaging system of the liver cell. How does a hepatocyte process information from a hormone messenger that ‘knocks’ on its surface, prompting it to produce a certain protein? Other molecular messengers, like calcium, subsequently become active in the interior of the cell. In the past, it had been assumed that this concentration increases and the chemical messengers transmit the hormonal signal to the command centre, the cell nucleus. For a long time, scientists conjectured that

“The mathematical modelling of complex biological processes is an essential tool in modern research.”

Professor Ursula Kummer, Heidelberg University
the messengers passed on the signal like the baton in a relay race. But then laboratory experiments indicated that this simplistic idea was not consistent with the actual biological process in the cell.

"The goal of systems medicine is to implement the new methods, thereby ensuring that patients benefit from the latest basic research findings in the not too distant future."

Professor Ursula Kummer, Heidelberg University

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**How nature encrypts information**

In the case of calcium, as it happens, the concentration does not simply increase: instead, the calcium level oscillates, in other words, it increases or decreases constantly. Accordingly, the cell does not react to consecutive sequences of events but processes the messages contained in the oscillations. "The information is contained in both the amplitude and the frequency of the concentration oscillations", says Ursula Kummer. The computer simulation of the process reveals that the function of the chemical messenger is directly dependent on this dynamism: if the scientists consistently increase the concentration of the chemical messenger and suspend the dynamism in the computer model, the cell is unable to process the information.

According to Ursula Kummer, this type of cellular message transfer is not actually that surprising. For example, the cell uses calcium to transmit very different signals. It almost defies explanation that the same messenger transports highly diverse messages by means of a simple increase in concentration. How-
ever, if the information is contained in the dynamism, it means that nature has created a mechanism that basically allows all manner of signals to be transmitted by just one messenger. Research has revealed that, apart from calcium, many other chemical messengers transmit information via oscillation or similar dynamic behaviour. Text books that continue to propagate that “Substance A increases substance B” now need to be rewritten: this simple statement has proven inadequate in understanding the processes of life.

Safe drugs

It is imperative that we recognise and take account of the complexity of cellular life, for example to predict whether a drug will have the desired effect in a specific case. "Individual factors can only provide insufficient information as to whether a drug will work on a patient", says Ursula Kummer. "A complete picture of all correlations and interactions is crucial in making these predictions".

This is the task facing Dr. Lars Küpfer, one of Ursula Kummer’s important cooperation partners in the Virtual Liver Network. At Bayer Technology Services in Leverkusen, the bioinformatician enters all experimental data on the functioning of the hepatocytes into a mathematical model. His goal is to make drugs safer. In future, for each and every patient, the computer-simulated, realistic liver functions are designed to predict whether a particular drug will be effective, the individual dose that will have to be administered and the potential side effects. As Lars Küpfer explains, these model-based methods also play a significant role in the development of completely new active substances. "The mathematical models make it possible to put the existing biological knowledge to work quickly and rationally for the benefit of the patients in the clinic".

**The remarkable workings of the liver**

**Under the diaphragm on the right** is the liver, one of the most diverse organs in our bodies. Inside are thousands of hepatic lobules, which are barely visible to the naked eye. They are made up of billions of cuboid cells, arranged in a circle around a central blood vessel.

**Approximately 2000 litres of blood** flow through the liver every day, from two sources: the heart and the digestive organs. This organisational structure makes the liver the main metabolic organ.

**One of the liver’s most important tasks** is to keep the amount of substances in the blood constant (homeostasis). To this end, the liver cells store substances until they are required by the body. For example, the hepatocytes convert glucose, the body’s most important source of energy, into insoluble glycogen and store up to 150 grams. If there is insufficient sugar in the blood, the liver cells reverse the biochemical process, breaking down their stored glycogen and releasing glucose into the bloodstream. The process is similar for vitamins, trace elements and minerals.

**Liver cells assemble amino acid building blocks** to form proteins or blood components like coagulation factors. The liver cells manufacture cholesterol from the degradation products of fats. It is essential for the nerve cells and an important precursor for hormones and bile acid, which breaks down fats.

**The liver is the body’s detoxification centre:** it breaks down blood alcohol, neutralises (most) toxins, destroys pathogens with special cells and metabolises drugs.

**Liver cells have one final talent:** if they become damaged, they are capable of almost complete regeneration.
The scientists in the ‘ColoNet’ research project are setting their sights on mutated genes and proteins in the interior of colorectal cancer cells. The project’s major objective is to improve diagnostics and open up new approaches to therapy by using science’s understanding of the molecular processes that cause cells to degenerate.

Professor Sers, in your opinion, what is special about systems medicine?

Professor Christine Sers: The focus is no longer on individual molecules; instead, it takes a holistic view of the ‘life system’. Many years ago, when I was a doctoral student, I still carried out analyses on a single molecule, referred to as a cell adhesion molecule, which causes metastases in skin cancer. But, naturally, it is not the sole cause. Systems medicine has already taken a substantial step forward: it is understood that what matters is taking a holistic view of many different components, from the molecular level right up to the level of the organ and the entire organism, in order to reach a conclusion that may be essential for a medical application. With regard to our work today, this means that we regularly come together as interdisciplinary teams to analyse the processes that take place in cells or model organisms within a certain period of time. We test the effect of a therapeutic compound on an entire network of associated interacting molecules and adapt our model systems as closely as possible to the patients’ situation.

Furthermore, the hypotheses arising from our experiments and mathematical models are regularly tested on specimens collected from the patients in order to observe the influences of hormones, the immune system or the interaction of various types of tissue.

Could you give an example of the medical application?

Prof. Sers: My colleagues and I study different cancers in a diagnostics institute. For example, an important application would be one that enables us to reliably predict, based on tissue or blood samples, whether a patient will respond to a certain therapy. Then we could give doctors firm and rational evidence on which to base their therapy decisions. Numerous disciplines have to pool their efforts in order to reach a conclusion of this kind. Technology is the first priority in obtaining verification from blood samples. We need new methods of establishing quantitative evidence of disease-specific characteristics in order to interpret the changes we see. To this end, we carry out comparisons with large medical databases, we consult specialist publications – sometimes using text analysis programmes, known as text mining – and use data from other clinical studies for reference. We can also use mathematic models to predict the impact of DNA modification and we can apply and develop fast experimental test systems, making it possible to try out different therapeutic compounds in a relatively short time.

Which disciplines are particularly important?

Prof. Sers: We regard ourselves as translational scientists, that is, as researchers who are committed to transferring results from fundamental research into preclinical development programmes and ultimately into the clinic. This calls...
for close collaboration with medical professionals who have a translational, interdisciplinary mindset, in other words, diagnosticians and practitioners in the clinic. It also takes (bio)informaticians and mathematicians who specialise in very different fields; they, too, are characteristic of systems medicine.

**What are the specific features of the systems medicine approach in your research project?**

**Prof. Sers:** Our goal is to trace the molecular networks in the interior of the cells that cause colorectal cancer. Moreover, we want to know what molecular mechanisms allow the tumour cells to survive, despite therapy or – to put it another way – to resist the effect of drugs, whether they be classic chemotherapeutics or new customised active agents. Therefore, we use computational models that mirror the complex events taking place in tumour cells while information is being processed in order to develop rational hypotheses for future courses of therapy. Another objective is to improve existing biomarkers and find new, sophisticated biomarkers that indicate which therapy will most benefit a particular patient. To give an example, we are currently reviewing combinations of markers that we hope will enable us to identify more patients who would be suitable for modern targeted therapies. To this end, we combine a genetic marker with a new epigenetic marker, that is, an indicator of modifications in the spatial structure and accessibility of the hereditary molecule, DNA.

**What does the future hold for the treatment of cancer, based on the systems medicine approach?**

**Prof. Sers:** We are exploiting the findings of the ColoNet project in our follow-up project, ‘Oncopath’, the main object of which is to draw up models for different subtypes of colorectal cancer. In other words, we are attempting to identify groups of patients whose molecular characteristics mean that they can receive personalised – and therefore effective – therapy. In future, a systems medicine approach to cancer therapy could be as follows: first of all, a patient’s tumour is extensively characterised at the molecular level and the data are fed into a mathematical model to simulate the best possible therapy. The computer eventually recommends a personalised therapy that is tailored to the individual needs of the patient. That is our vision – indeed, our hope – for the years ahead. Time will tell whether all this will come to pass. All the same, as a researcher, you always have to want more than you can accomplish in order to get anywhere at all.
The common roots of psychiatric disorders

What do depression and schizophrenia have in common? Very little, in terms of the actual symptoms. However, it is a different matter if we look at the genetic causes. IntegraMent, the most extensive collaborative project of its type in Germany to date, researches the joint molecular causes of common psychiatric disorders with the aim of significantly improving their diagnosis and therapy.

At least four million people in this country suffer from depression. Thus, the ‘deep sadness’ is Germany’s most prevalent psychiatric condition, followed by so-called bipolar disorder and schizophrenia. There is huge variation in the symptoms of the illnesses: the severely depressed suffer with low spirits and frequently contemplate suicide, people with schizophrenia primarily experience a distorted reality, delusions, confused thinking, speech and emotional disorders, while bipolar individuals undergo phases of euphoria alternating with episodes of severe depression. Until now, doctors have based the diagnosis on these readily apparent signs of illness, adjusting the treatment accordingly. However, the latest findings of genetic and molecular-biological research show that the strict differentiation of conventional diagnosis manuals is no longer adequate in acknowledging the actual underlying biological causes.

Understanding molecular causes
“`We now know that psychiatric disorders are much more closely related than previously assumed”, says Professor Markus Nöthen, director of the Institute of Human Genetics at the University Hospital of Bonn. The different illnesses and their varying severity may spring from the same genetic roots. The BMBF’s IntegraMent research project aims to unravel the molecular causes of severe depression, schizophrenia and bipolar disorder by tracing their common genetic roots and overlapping biological processes. As Professor Nöthen points out, systems medicine’s typical overview of large amounts of data, obtained from various methods, will presumably give rise to a substantially new understanding of illness. By the same token, this may also lead to substantial advantages for patients; according to Professor Nöthen, “The diagnosis can be further refined and treatment becomes more personalised”.

How does trauma affect genes?
During the first phase, the researchers are singling out the genes involved in the development of the three psychiatric disorders. To do this, they compare the genome of patients suffering from depression, schizophrenia and bipolar disorder with that of healthy subjects. If a certain genetic variant occurs more frequently among the patients, it indicates the locus of a gene that is part of the developmental mechanisms of these disorders. The scientists combine the analysis of the gene with imaging technologies (imaging genetics) to discover how the genes influence the structure and function of the neuronal cells in the brain. “For example, we want to clarify whether the genetic alterations specifically affect particular functions of the brain”, says Professor Nöthen.
At least four million people in Germany suffer from depression.

The researchers retrace how the genes change biochemical processes by conducting experiments on animals; they then analyse patients’ own stem cells to consider the impact of genetic alterations on the growth or signalling function of nerve cells. Epigenetic studies aim to shed light on how external factors, like trauma, affect the genes, potentially triggering psychiatric disorders.

**The role of mathematics**

As Professor Nöthen stresses, without bioinformatics there would be no way of linking the vast quantities of data acquired via various methods and making them available for scientific evaluation. Only by integrating these data is it possible to piece together a more complete picture – from the genes and proteins, their interaction in the cells, right through to the outer appearance – of these illnesses, which are ‘naturally’ highly complex. This also facilitates the search for targeted interventions. In future, the illnesses may even be divided into subgroups, like type A, B or C depression, which differ in terms of the underlying respective biological processes. To a greater or lesser extent, treatment has hitherto been meted out under a ‘one size fits all’ concept. This is doubtless a fundamental reason for the clinical experience that drugs have varying degrees of success, despite an identical diagnosis. In future, Markus Nöthen is hoping for a ‘precision medicine’ approach that can offer patients an effective, biology-based therapy.
Day in, day out, our immune system provides an essential service, fighting off dangerous pathogens and protecting us from many other threats. Countless immune cells act in concert to man our defences in complex ways, communicating via neurotransmitters and a multitude of molecules. Yet the immune system is not immune to ageing. Therefore, as we get older, we become more vulnerable to infection, less sensitive to vaccinations and are more likely to suffer from cancer. The scientists of the BMBF Primage project are investigating how the immune system ages in the hope of developing strategies that will allow us to retain good health into old age, with the help of our immune system.

Everybody wants to live to a ripe old age – but nobody wants to be old. Because ageing is generally associated with all types of ailments from arteriosclerosis to increased susceptibility to infections, right through to cancer. Many of the so-called geriatric diseases are attributed to the weakening of the body’s own defence systems. Nonetheless, very little is known about how the immune system ages, leaving us vulnerable to the mechanisms of illness. Under the direction of Professor Andreas Thiel from the Berlin-Brandenburg Center for Regenerative Therapies, the scientists of the BMBF’s Primage project are focusing on this issue. The researchers are particularly interested in estab-
lishing why the elderly are more susceptible to pathogens like omnipresent bacteria and viruses and why they are less sensitive to vaccinations.

**Why are vaccinations less effective in old age?**

The Berlin research team is reflecting on the reduced efficiency of the immune system by studying the influenza vaccination, which is designed specifically to protect the elderly from contracting the dangerous influenza virus. “While young people invariably develop good immunity when inoculated against influenza, the vaccination is either ineffective or not sufficiently effective in many elderly subjects”, adds Professor Thiel. “We want to get to the bottom of the difference between the immune systems of the elderly and the young”.

Weighing approximately two kilos, the immune system – a network of organs and cells distributed throughout the body – is the basis of our health. Over the course of our lives, more than a dozen different types of cells, over fifty neurotransmitters and countless recognition and regulatory molecules interact in complex ways, providing a buffer against the relentless onslaught of different infections. However, even the body’s powerful defence system can be past its prime.

**Special vaccines for the elderly**

As the immune system ages, the immune cells change. For example, the T cells and B cells, which work together in the fight against pathogens, are vitally important for the deterioration of the immune system, referred to as immunosenescence. The T cells mature in the thymus, an organ that is located behind the sternum and is approximately the size of a palm in children. The thymus gradually shrinks after puberty; in older people it only exists in a rudimentary form. Therefore, only very few T cells are produced in old age. Maturing in the bone marrow, the B cells of the immune system secrete antibodies, Y-shaped molecules, that circulate freely in the blood, intercepting infectious agents and rendering them harmless. Studies have shown that the B cells produce fewer antibodies in advanced years. This is a contributory factor in the elderly’s increased susceptibility to infections and may explain why infectious diseases are more severe and entail greater complications in older people.

As Professor Thiel explains, “Once we understand the cellular and molecular changes that cause the immune system to age, it may be possible to develop vaccines that can also induce a sufficiently potent immune response in an ageing organism”. In order to reveal the underlying mechanisms, the scientists are currently evaluating vast quantities of data and studying the correlations using modern molecular biological methods. Based on the results, the researchers hope to develop new strategies for effective vaccines, not just against the influenza virus, but also to protect the ageing organism against other, potentially life-threatening pathogens.
The wealth of systems medicine data contains enormous quantities of medical information, details on the genes, proteins and other important molecules in the interior of the cells, information obtained from tissue and blood samples or from studying the organs of the body with modern imaging technologies. All these data are archived electronically, then pooled and evaluated. It is imperative that the social, legal and ethical implications associated with the storage and use of these data be identified and discussed at an early stage. How can we ensure the protection of personalised data? What is the correct procedure for handling statistical predictions or additional, unexpected findings? The BMBF’s collaborative project on ‘Big data in systems medicine’ seeks answers to these questions.

Professor Winkler, the research project that you represent is called ‘Big data in systems medicine – normative and social aspects for doctors, researchers, patients and society’. Before we talk about the normative and social aspects, how would you define systems medicine?

Professor Eva Winkler: That is not an easy question to answer. The concept is relatively new and still not really established. In fact, one of the first goals of our project is to define systems medicine. Is it simply another term for personalised or individualised medicine? Or does systems medicine extend beyond that? At the moment, it is difficult to come up with a definition that does justice to all criteria; however, we can list some of the key components that factor in the definition and go beyond what is already known.

What are these important components?

Prof. Winkler: First and foremost, key elements are: large amounts of data, bioinformatic modelling and projection, in other words, the transfer of data and models to an enhanced understanding of disease – and ultimately to the patients, in terms of improved diagnosis and therapy in the future.

Where do systems medicine’s big data come from?

Prof. Winkler: They are mainly generated by systems-oriented technologies like the sequencing of the genome, proteome and metabolome, in other words, by the entire spectrum of modern techniques used to decipher the human genome, the complement of proteins and the metabolism of a cell; they are then synchronised with epidemiological data or clinical data on the course of the disease. These continuously evolving methods mean that new data can be collected and added to the data pool. The bioinformatic tools available today enable us to control the flood of data and analyse the information from a biological and medical point of view.

The primary objective of your research consortium is to scrutinise the ethical, legal and social aspects of systems medicine. But how can you study something for which there is no clear-cut definition?

Prof. Winkler: The social impact and normative implications follow on from the two important components of systems medicine – the collection of large, personalised datasets and bioinformatic modelling. The existing interfaces between research and clinical application are indications of the changes that are
in the offing for society and its system of values. Our research consortium is structured on three levels: the social-empirical, legal and ethical-philosophical aspects. We study the precursors of the societal changes that systems medicine will bring about from these three perspectives.

**What specific questions do you consider in the process?**

**Prof. Winkler:** It is of fundamental importance to redefine the significance of data protection and privacy in light of the systems medicine data frenzy. This is because the system-oriented approach to a patient’s molecular, genetic and clinical data raises a number of ethical and legal questions, which are unprecedented in their prominence and societal relevance. To date, data management has been governed by the principles of the specified purpose, the granting of usage-specific consent and the concept of data economy, for example. Systems medicine explicitly abandons these principles in favour of a holistic view of the individual. Another important and highly specific question is how to handle sensitive genetic data and information within individual families and what duty of consideration family members owe each other in connection with systems medicine data and findings. A further priority is how systems medicine influences perception of the role of doctors and non-medical researchers.

**What results do you hope to achieve with your research consortium in the next few years?**

**Prof. Winkler:** One short-term objective is to establish appropriate criteria that enable us to strike a balance between protecting and disclosing personal data. We also aim to bring about a more dynamic form of patient information – if we intend to collect data over the course of a lifetime from now on, we also need to keep people informed about what happens to their data during this time. Moreover, we need to ensure that any data of relevance to a patient’s health can be passed on to that individual at some point in the future, even if a great deal of time has elapsed since the data were actually collected. Basically, we are striving for viable findings that can be directly channelled into practical applications in systems medicine research and patient care. This may result in general ethical and legal manuals, in the form of guidelines for handling large quantities of medical data.
Both maintaining a healthy state and the development of disease are the result of complex, dynamic interactions – from the level of the molecular networks in individual cells right through to the interdependencies between man and the environment. Systems medicine aims to understand these connections, applying this insight to the prevention, identification and treatment of illnesses. The Federal Ministry of Education and Research (BMBF) recognised the potential of systems medicine research at an early stage. With an extensive package of measures under the umbrella of the Health Research Framework Programme, the Ministry has been funding the establishment of this new branch of research in Germany since the end of 2012.

Worldwide, experts agree that the onset of many diseases cannot be fully explained by the isolated analysis and clarification of individual components. In particular, widespread diseases like cancer, cardio-vascular or neurodegenerative disorders have complex, multifactorial causes and, more often than not, an individual course of their own. In many cases, external factors like diet, exercise and environmental conditions play a major role in their development. Then again, these factors affect individual genetic and physiological processes, thereby tipping the scales towards illness or health. Thus, a healthy human body is controlled by a finely tuned equilibrium of different factors. We need to unravel the workings of this dynamic system as far as possible in order to understand the causes of disease and use this knowledge to develop better methods of diagnosis and treatment.

As a research concept that focuses on the complex and dynamic systems of the human body, systems medicine is still in its infancy. To achieve this goal, the latest findings from the life sciences are interwoven with clinical research using information technology
tools. Systems medicine research aims to contribute to a greater understanding of molecular networks and their role in the emergence of diseases. Furthermore, this will serve as the foundation for developing new, personalised therapies.

The e:Med research and funding concept
The Federal Ministry of Education and Research has introduced the e:Med research and funding concept to promote system-oriented research into diseases and develop innovative therapy and prevention procedures. Since the end of 2012, the BMBF has earmarked 200 million euros for an initial period of eight years. The e:Med concept includes five modules. In Module I, Systems medicine research consortia, 14 research consortia currently receive funding at 42 scientific institutions in 28 cities throughout Germany and at three universities abroad. Each research consortium applies systems medicine research approaches to a specific issue that clearly relates to disease.

Cutting-edge high-throughput technologies and advances in bioinformatics now make it possible to systematically collect and analyse ever-greater medically relevant datasets at reasonable costs. While the datasets involved carry enormous amounts of information, little research has been carried out to date regarding their prognostic, diagnostic and therapeutic value in individualised medicine. In Module II: Demonstrators for an individualised medicine, funding is provided to pilot projects that show, on the basis of specific clinical research issues, how existing datasets from basic research in the life sciences can directly enhance individualised prevention, diagnosis and therapy. The focus is on ways of making data available, of usefully integrating and analysing such data, and on the iterative process of experiment, modelling and application. Of the eight collaborative projects with a total funding volume of some 18 million euros, six consortia are turning the spotlight on cancer, one project team on the functioning of the heart and one consortium on Parkinson’s disease.

Supporting the next generation of scientists within the area of systems medicine is another important aspect of the e:Med concept. Module III: Young investigators aims to attract outstanding early career medical professionals, computer scientists, mathematicians and biologists to this field, to strengthen their cooperation by means of horizontal knowledge transfer and to enhance the integration of computer science and mathematics in clinical training and research. This module supports junior research groups, junior research alliances and summer schools.

Module IV: Future-oriented and cross-cutting measures provides the necessary basis for responding flexibly to the emergence of new research topics or the need for innovation in systems medicine. It represents an interface to other BMBF initiatives and covers topics of cross-sectional significance for the advancement of this research field. In this module, the BMBF also promotes projects that explore the ethical, legal and social aspects of systems medicine.

The complete e:Med research and funding concept is available at https://www.gesundheitsforschung-bmbf.de/files/e-med_engl.pdf.

All systems medicine projects that receive funding can be found at https://gesundheitsforschung-bmbf.de/de/foerderkatalog-2435.php (only available in German).

An overview of the systems medicine research activities that receive BMBF funding are available at www.sys-med.de/en/

The BMBF also supports the further development of systems medicine at the European and international level. The focus of Module V: Internationalisation includes participation in major international research projects and European strategic research initiatives. Based on the activities and results of the EU’s PerMed project, the International Consortium for Personalised Medicine, or ICPerMed for short, was founded in November 2016, with over 30 national and regional research funding organisations and the European
Likewise supported by the EC, this initiative is first and foremost a platform for research funders who intend to invest or become involved in the fields of personalised medicine, and thus also in systems medicine, in the future. In March 2017, the members of the international consortium published a common Action Plan, which will serve as the basis for European, national and regional activities in all relevant research areas related to personalised medicine for the years ahead. Moreover, with the Coordinating Action Systems Medicine (CASyM), Germany has been spearheading the development of a Europe-wide implementation strategy (road map) for systems medicine since 2012. With 23 partners from eleven European countries, CASyM pools expertise from scientific organisations and universities, industry and pharmaceutical companies, funding organisations and project management agencies. One key instrument in implementing the results of CASyM is the first ERA-Net on Systems Medicine (ERACoSysMed) under the Framework Programme Horizon 2020 of the European Commission. The ERACoSysMed consortium is composed of 14 funding bodies from 13 countries, which have joined forces to develop a coherent research agenda, foster the networking and advancement of the European scientific community and promote transnational systems medicine projects. Launched in January 2015, ERACoSysMed published its first joint transnational call for proposals within the framework of the ERA-NET Cofund scheme in early February 2015. Nine transnational research consortia are currently being supported with a proposed funding volume of approximately 12.7 million euros, whereby German partners are involved in eight research consortia. These selected research projects, referred to as demonstrator projects, show the social and economic benefit of the systems medicine approach in a clinical setting. In early February 2017, ERACoSysMed published its second joint transnational call for proposals.

The brochure on the e:Med research and funding concept can be downloaded at https://gesundheitsforschung-bmbf.de/de/publikationen-5366.php