

DKFZ-ZMBH Alliance

German
Cancer Research Center
in the Helmholtz Association







Center for Molecular Biology of the University of Heidelberg

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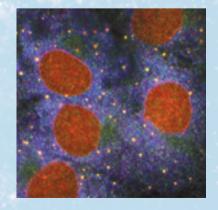
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The whole is greater than the sum of its parts.

Aristotle

Genetic information is continuously transcribed into mRNA in the nucleus (red). It is subsequently exported into the cytoplasm (blue), where it serves as the template for protein synthesis. At the end of its life time, mRNA is degraded in specific foci termed "processing bodies" (yellow).







The DKFZ-ZMBH Alliance: A Life Science Center with International Appeal

If the basic processes of life become unbalanced, a multitude of diseases threaten to strike: cancer, neurodegenerative diseases, and metabolic disorders. Even aging itself is the result of accumulating damage in the organism. The study of biological organisms – at the molecular level, the cellular level, and, at a greater degree of complexity, at the level of an entire organism – is thus a requirement for understanding health and disease. How do biological systems develop or differentiate, how are they regulated, how do they regenerate themselves, age or transform to malignancy: these are questions which form the basis of all medical understanding.

Two neighboring Heidelberg research institutes have a long tradition and first-class international reputation in the investigation of these processes. The University of Heidelberg's Center for Molecular Biology (ZMBH) was founded in 1982 with the aim of understanding biological processes at the molecular level. To this end, ZMBH employs a wide array of methods from biophysics and biochemistry, molecular and

cell biology, and genetics and bioinformatics. The German Cancer Research Center (DKFZ) has the task of systematically examining the mechanisms of cancer development and recording cancer risk factors. The results of this basic research aim to develop new approaches for the prevention, diagnosis, and therapy of human cancers. Research at the DKFZ is organized in 7 Research Programs. The focus of Research Program A at the DKFZ is on cell and tumor biology. At the center of this is the study of cellular signaling pathways that regulate differentiation, growth, and survival of healthy and neoplastic cells.

The two institutions have maintained a good relationship as neighbors, and numerous networks now link them at the project level. Both the increasing necessity for researchers to cooperate across interdisciplinary lines and the closely related aims, scientific issues, and methods prompted the decision to create an alliance between the ZMBH and the DKFZ in order to build up a new center of excellence for the molecular and cellular life sciences that will provide

initiatives for international research.

Pointing the Way for the Molecular Life Sciences

In order to be internationally successful in this era of globalized science, research programs must have a critical size. With a total of approximately 500 staff in the DKFZ-ZMBH cooperation, each of the three joint programs of the alliance has

Program

Structure, Function and Regulation of Biomolecules

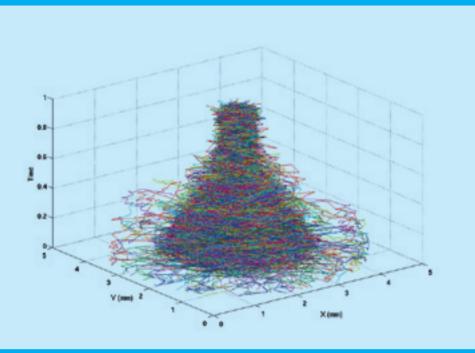
Program

Organization and Differentiation of Cells and Stem Cells

Program

Development and Regeneration, Degeneration, Aging and Cancer

sufficient personnel to broadly cover the relevant spectrum of scientific issues and provide a powerful research infrastructure. This prevents individual projects from existing in the corner, cut off from scientific exchange. The alliance is



being founded at a time when a new generation of researchers takes over at both institutions. By pursuing a strategy of jointly recruiting staff, the two institutions can focus on specific topics of research that are unique to European research.

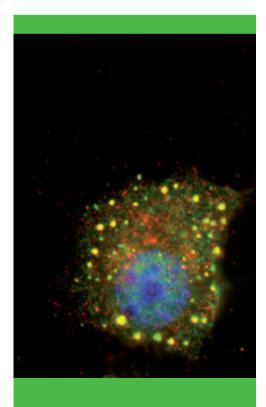
The DKFZ-ZMBH alliance provides a novel model for the cooperation between a university facility and a national Helmholtz research center. Joint management boards – scientific advisory committee, local coordinating board, directorate, and assembly of the senior scientists - are assuming responsibility for meeting the goals of the alliance in all included subunits. To promote the growing together of the two partners, research projects will be financed from a joint funding program, to which both institutions will contribute. An important step will also be to establish joint "alliance research groups".

The DKFZ already maintains a partnership with the Medical

Faculty and the Heidelberg University Hospitals in a Comprehensive Cancer Center, the National Center for Tumor Diseases (NCT) Heidelberg. This close interaction will make it easier for scientists in the alliance to collaborate with colleagues from the medical field in order to facilitate the transition of their results to the clinic. Indeed, the Medical Faculty Heidelberg has already assured the alliance of its support.

Joint Resources – Higher Performance

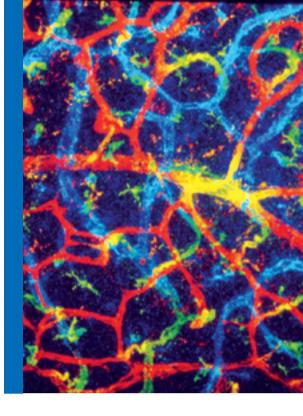
New technologies and methods of analysis enable studies to be performed in cell and molecular biology with a degree of precision previously unknown and at a level of complexity that would have been unthinkable only a few years ago. The era of dominant pipettes and test tubes is a thing of the past: the demands placed on equipment are constantly increasing, requiring the use of ever faster automated systems, analysis equipment that is sensitive enough to record even atomic details, and microscopes whose resolution is no longer limited by the wavelength of light.



To be able to play in the Premier League of the life sciences, researchers must rely on highly qualified support. Service units for protein analysis and peptide synthesis, technology platforms, high end microscopy or the personnel-intensive maintenance of a first-class animal laboratory are a major challenge for single institutions. The present alliance brings scientists and research groups together whose needs in terms of technology and services are similar. The staff of the alliance has access to the facilities of both institutions. In this way, platform technologies will be used more intensively, valuable resources will be utilized more efficiently, and expertise in the service area will benefit a greater circle of users.

Heidelberg enjoys a worldwide reputation for excellence in the life sciences. In addition to the DKFZ and the ZMBH, the European Molecular Biology Laboratory (EMBL) and the Max Planck Institute for Medical Research are located in Heidelberg. The University and the University Hospitals have first-class biomedical institutes which have been selected for special support in the excellence cluster "Cell Networks".

Top researchers from all of these institutions are among the leading scientists in their fields worldwide. The DKFZ-ZMBH alliance, which is open to working with additional partners, will make Heidelberg even more attractive for top-class experts and will help to develop this traditional campus into one of the world's leading sites for the molecular life sciences.

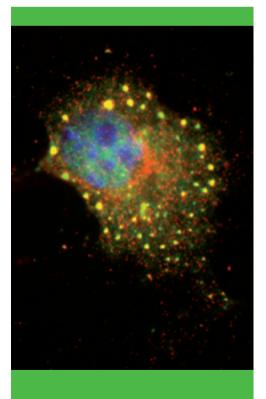


Center of Excellence for Teaching and Education

The teaching staff of the DKFZ-ZMBH alliance will assume a substantial portion of the education of Heidelberg students in molecular and cell biology. Eight professors from the ZMBH and six from Research Program



A in the DKFZ are members of the Faculty for Biosciences. A unique interdisciplinary education program in the life sciences will further increase Heidelberg's ability to attract excellent students, especially those from abroad. Another factor is the new research-ori-





ented Master's degree course "Molecular Biosciences", which is being offered in English. At the same time, we will make the alliance even more attractive by offering research professorships with limited teaching responsibilities.

Both the DKFZ and the ZMBH educate their PhD students in structured programs that offer attractive courses and guarantee supervision of individual students by a committee consisting of senior scientists. As a result of the alliance, the spectrum of this offering will be further increased. The approximately 150 PhD positions in the alliance are to be filled via joint, internationally advertised selection rounds.

By means of special junior research group programs, already established at both the DKFZ and the ZMBH, young researchers are specifically prepared for a successful academic career. The alliance will implement a joint tenure track policy to offer all successful heads of junior research groups the chance of an appointment as professor.

Anyone who relies on young scientists must kindle enthusiasm for the life sciences, even in school-age children. With the Life-Science Lab, the DKFZ already provides a comprehensive offer to talented highschool students. The ZMBH has concentrated on further education for teachers, developing molecular biological experiments for teaching in schools and offering a teacher's sabbatical. Thus, the two packages nicely complement one other and can be joined into a functionally defined unit.

Prof. Dr. Otmar D. Wiestler Chairman of the Management Board of the German Cancer Research Center

Prof. Dr. Dres. h.c. Peter Hommelhoff Rector of the University of Heidelberg

Prof. Dr. Bernd Bukau Director of the Center for Molecular Biology of the University of Heidelberg The projects on pages 6 to 23 give examples of the broad research spectrum of the DKFZ-ZMBH alliance.

Interactive Topics: Common Interests Interconnect the Three Alliance Programs

The synthesis of macromolecules, such as nucleic acids (DNA and RNA) and proteins, is a complex process. Specialized transport systems bring newly formed biomolecules to the location where they will be active. A multitude of proofreading and repair systems constantly carry out quality control to monitor for defects that are the result of errors during synthesis or environmental damage. These mechanisms also repair or, if necessary, ensure the destruction of the defective macromolecule (p. 8, B. Bukau).

The first step in a long chain of mechanisms regulating gene activity is the frequency with which a gene is transcribed. A whole series of signaling molecules, such as steroid hormones or growth factors, direct this process. Epigenetic mechanisms play a critical role, too, by shutting down specific portions of the genome if it is necessary. The fate of mRNA is another means by which gene expression can be controlled: the faster it is broken down, the less corresponding protein can be synthesized (p. 10, C. Clayton, p. 22, G. Stöcklin). Small, noncoding RNA molecules play a substantial part in this inspection stage.

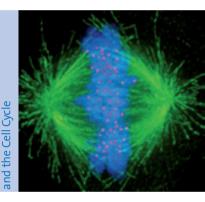
Before a cell divides, a multitude of regulatory mechanisms ensure that the genome is doubled, the chromosomes are passed on in coordinated fashion to both daughter cells, and the cell organelles are distributed appropriately between the daughter cells (p. 18, E. Schiebel). The internal or external signals that cause a cell to divide and the manner in which inappropriate coordination of this process leads to cancer can also be examined on simple model organisms such as baker's yeast or fruit flies.

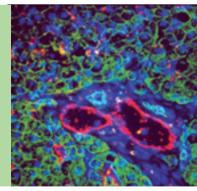
Communication is (almost) everything in life: between environment and organism, between the various structures and organs, between cells, and within the cell. The uptake and forwarding of external stimuli into the cell are fundamental prerequisites of almost all processes in life (p. 20, V. Sourjik). The control of gene activity, cell growth, and apoptosis are just some prominent examples (p. 6, H. Augustin). How all these signal cascades interact within a tissue or organ is being examined by the rapidly emerging scientific field of systems biology (p. 14, U. Klingmüller). Errors in communicating signals can finally lead to various diseases such as cancer, and signs of aging (p. 12, S. Herzig).

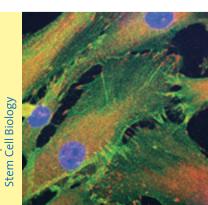
The capacity of multipotent or pluripotent stem cells to divide has evolved as a key element for the understanding of both embryonic development and cancer. This also explains the fact that the genes that control development are often cancer genes whose misregulation can lead to malignant transformation (p. 16, C. Niehrs). The exploration of stem cell biology is thus a joint task of cancer research, embryology, and regenerative biology.

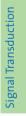
Synthesis, Transport, and Quality
Control of Biomolecules

Regulation of Genetic Activity and Epigenetics









Developmental and

Cell Division, Cell Growth

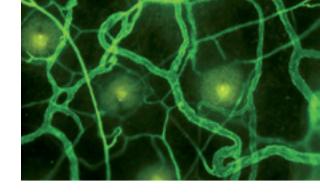


Blood and Lymph Vessels:

Supply System

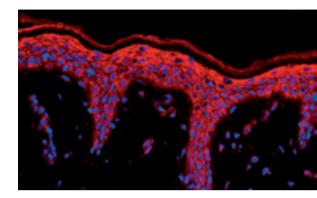
If the supply lines are not secured, any advance will fail sooner or later. This piece of military wisdom is also true of tumors. Once they have grown to a few millimeters in size, they rely on the bloodstream to supply them with oxygen and nutrition. Using special growth factors, tumors cause the endothelium – the inner lining of the vessel – of neighboring blood vessels to sprout new capillaries. This is an attractive target for cancer therapies, and a variety of agents are already being used to suppress tumor angiogenesis, i.e., the creation of new blood vessels. But while these treatments have a lifeprolonging effect in certain cancers, they fall short of the high expectations placed on them.

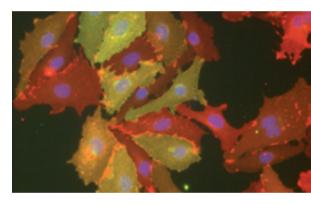
Hellmut Augustin and the staff of his department at the DKFZ are specialists in the complex interactions between tumors and endothelial cells. In the past few years, during the search for still unknown factors that the tumor uses to make contact with the endothelium, one group of growth factors has come under scrutiny, namely, the angiopoietins. One of these signaling molecules, Ang-1, causes newly created blood capillaries to mature by attracting smooth muscle cells, which are deposited on the outside of the vessels, thereby stabilizing them. Augustin's team found that Ang-2, which was discovered later, had exactly



the opposite effect, namely, the prevention of capillary maturation. This is an exciting aspect since all anti-angiogenesis treatments tested so far only work briefly until the new vessel is surrounded with muscle cells. Ang-2 offers for a first time an approach to prolonging this window of treatment and thus sensitizing tumors permanently to anti-angiogenic substances.

The body's second vascular system, the lymphatic system, also consists of endothelial cells. Tumors use the pathways of the lymphatic system for settling in other tissues, which is why the first metastases are often found in the lymph nodes surrounding the primary tumor. But whether the tumor also actively attracts lymphatic vessels – as it does blood capillaries – by stimulating growth of the lymphatic endothelial cells is still a matter of discussion. Many observations, however, point towards this. By investigating the interactions between cancer and lymphatic endothelial cells, Augustin's team aims at a better understanding of tumor metastasis. One small breakthrough has already been made: the researchers found that the surface molecule CD34 is only formed by lymphatic endothelial cells that are ready to divide and that are in tumors, in contrast to those in normal lymphatic vessels. This gives scientists for the first time a marker to identify angiogenically activated lymphatic endothelial cells. The group's next goal is to examine whether other surface molecules on activated lymphatic endothelial cells are connected with metastasizing tumor cells. This may lead to the discovery of new approaches to a specific suppression of metastasis.







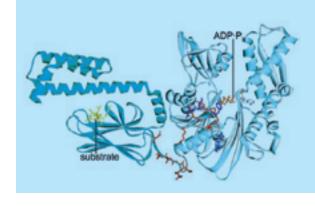
Chaperones:

The genetic blueprint of a protein provides only the information required to combine the different amino acids into a long linear polymer of perhaps hundreds of amino acids in length. However, such a polymer is incapable of carrying out its assigned molecular task without first adopting into a specific three-dimensional structure, which is determined by interactions between the amino acid side-chains. These interactions cause the polypeptide polymer to fold into helices, loops, and sheet-like structures.

While some proteins are capable of adopting their native three-dimensional conformation on their own, many proteins do not or cannot fold without the assistance of helper proteins, called molecular chaperones. Chaperones assist the polypeptide in the process of protein folding.

If a newly synthesized protein fails to fold correctly, or if an already folded protein loses its three-dimensional structure, disaster looms: unfolded or misfolded proteins have a strong tendency to aggregate. Sometimes, aggregation results in an impairment of cellular function or even cell death, as is the case in Alzheimer's disease.

Protein misfolding is a frequent event: the 3D structure of a fully folded protein is not com-



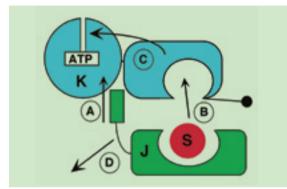
pletely stable since many proteins require a certain degree of mobility in order to carry out their functions. In addition to losing their shape in the course of their physiological function, proteins can also misfold due to age-dependent "fatigue" or due to errors in the amino acid sequence that were made during protein synthesis.

The "heat-shock response" is a well-known example of how cells respond to protein unfolding stress. Cells make a collection of "heat shock proteins" that promote protein folding in response to heat and other stimuli that induce protein unfolding. Indeed, investigations into the heat-shock response led to the discovery of chaperones.

Exactly how chaperones function is being investigated by scientists from Bernd Bukau's research group at the ZMBH. Chaperones appear to play an important cellular role since they are evolutionarily conserved in every domain of life. Thus, the insights that Bukau gains from studying the chaperones of yeast and bacteria can be used to understand how chaperones work in higher organisms such as humans. For example, Bukau's team clarified in atomic detail how the bacterial chaperone Trigger Factor may form a protective nest for newly made proteins in which the proteins can assume their native structure undisturbed by

the surrounding environment. On the other hand, another chaperone, ClpB, is involved in protein quality control. ClpB recognizes protein aggregates by binding to specific amino acids that are normally buried deep in the structure of a protein. It then pulls the aggregated protein out of the larger aggregate by drawing it through the middle of its ring-shaped structure.

However, the misregulation of chaperones can have devastating consequences. For example, tumor cells often make too many chaperones and escape regulated cell death (or apoptosis) by stabilizing their proteins. Cancer researchers have therefore set their sights on molecular chaperones as a potential target for future drugs designed to combat cancer. Because of the significant role played by chaperones in cancer and the aging process, the DKFZ-ZMBH alliance offers Bernd Bukau new opportunities to investigate novel aspects of this group of proteins.







in Trypanosomes

Confusion, impaired coordination, sleeping disturbances, and cramps are all typical symptoms of sleeping sickness. Patients stop eating, lose weight dramatically, and finally fall into the almost anesthetic-like sleep that gave the disease its name. The cause of the evil. which usually has a fatal course and is widespread in large parts of Africa and South America, are trypanosomes. These single-cell parasites are carried by the tsetse fly. If the pathogen gets into the blood, it reproduces there and later enters the infected patient's brain.

Very few medications are currently available, and they generally not only attack the parasites but are also toxic for the human body and have strong side effects. We, therefore, urgently need to develop new strategies in the fight against sleeping sickness. The first step is to precisely study the peculiarities of the pathogen. Scientists must discover which strategies the parasite uses to survive and reproduce.

Christine Clayton and her team at the ZMBH are searching for such characteristics that are typical of parasites. They know that in order for the trypanosomes to be able to exist in the tsetse fly and in humans or other mammals, they must adapt to the different conditions inside their hosts, for instance, to changing temperatures of 27°C in insects and 37°C in mam-



mals. The food available to the parasites also changes according to whether they are in humans or flies.

In order to adjust to their two different hosts, trypanosomes basically need two sets of "tools", i.e., both the proteins that secure their metabolism in the human body and those that allow them to survive in the tsetse fly. To do this, the parasites use a very special strategy. In most organisms, genes are activated when their genetic products (proteins) are needed in a certain situation. This is not the case with trypanosomes, which generally first transcribe all their genes. However, before these mRNAs can be used as construction plans for proteins, they are radically sorted out: some mRNA molecules are given the typical structures necessary for protein synthesis, while those which are useless in the current host are specifically degraded.

Clayton and her colleagues are searching for the factors that determine which mRNA molecules are broken down and which serve as matrices for the production of new proteins. A detailed understanding of the processes in mRNA breakdown might not only bring to light new targets in the fight against sleeping sickness. Cancer research might also profit, as the degradation of mRNA also plays an important role in the human organism – and possibly con-

tributes to cancer development – a question which Clayton's colleague Georg Stöcklin is investigating in the DKFZ-ZMBH alliance.





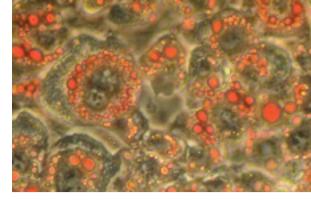


Balance

Whatever we are doing, be it lifting weights, sitting comfortably on the sofa, or just keeping our organs going at night while we are asleep, our bodies need energy to do it. This energy is provided by our food via various metabolic pathways.

The tasks of building up and breaking down energy-rich molecules must be finely adjusted since serious diseases otherwise pose a threat. This is clearly shown by the example of insulin-dependent metabolism, the object of work by the DKFZ researcher Stephan Herzig. Insulin regulates the intake of glucose molecules in muscle, fat, and liver cells. At the focus of the metabolic syndrome, which includes such disorders as diabetes, arteriosclerosis, high blood pressure, obesity, and fatty liver, is insulin resistance, in which the hormone's effect is deficient. It is not only the liver, muscles, or fatty tissue that malfunction in this situation. The macrophages, the big eater cells in the immune system, also cause problems. They cause chronic inflammation and absorb increased amounts of cholesterol. If these cells are then deposited in blood vessels, the consequence can be arteriosclerosis, heart attacks, and stroke.

In stark contrast to this is cachexia. The complete opposite in terms of clinical symptoms, it is a wasting disease charac-



terized by loss of weight and strength, which can finally lead to organ failure. It is often seen concomitant to advanced stages of tumor disease. Insulin-dependent metabolic pathways and inflammation processes are obviously involved here too. Herzig and his colleagues are investigating why disturbances in one and the same system can have such contrasting results. To this end, they are not examining each disease separately, but searching for superordinated principles, i.e., switching points where the balance of the metabolism can be pushed in one direction or the other. The DKFZ-ZMBH alliance with its numerous research groups investigating similarly complex questions, offers an inspiring environment in which to search for such system errors. Herzig and his colleagues are now trying to get to the bottom of how RIP140 and other proteins that modulate gene transcription function. They want to find out how these protein molecules differ, i.e., whether they activate or inhibit, whether they are modified differently in different syndromes, or whether they dock on in a different place. In so doing, the researchers want to understand the interplay of factors in catabolic metabolism. This will benefit not only patients with diabetes or other metabolic syndrome disorders, but also tumor patients with cancer cachexia.

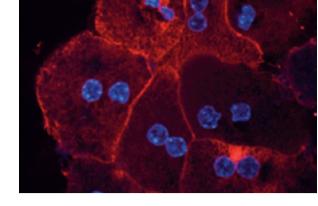


One candidate which Herzig and colleagues are watching closely is RIP140, a protein that interacts as a cofactor with socalled transcription factors and thus contributes to certain genes being transcribed – or not – as the case may be. Herzig established that the incidence of RIP140 is higher in insulinresistant, inflamed livers. It seems to play a role in the development of both fatty liver and cachexia. RIP140 also occurs in macrophages, where the DKFZ researcher presumes that it is responsible for the excessive storage of insulin and inflammatory reactions.



To know how a cell or even a whole organism functions, such as how it makes decisions on life or death, on growth or the development of special properties, one needs to keep an eye on the whole system. The investigation of individual com-

ponents and signaling pathways merely provides insight into individual biological processes. But for all life processes to run smoothly, the various participants must communicate and interact with each other – even if at first sight



they appear to fulfill completely different tasks.

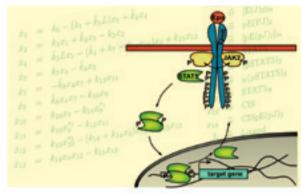
It is the task of systems biology to find out how this interaction works. To do so, this relatively recent area of study combines various biological approaches with methods from the fields of mathematics, computer science, and systems theory. Communication is thus also of the essence for successful research. The aim is to express biologists' knowledge in terms of mathematical equations and to develop models which enable computer simulation of cell processes. On this basis, it can be predicted how interactions probably take place in the cell – and the next experiments can be planned in a targeted fashion.

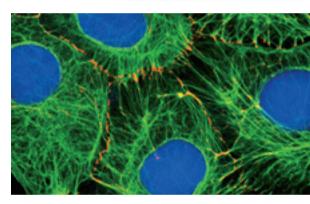
Sometimes the simulations show processes to run entirely contrary to what was expected. This is something Ursula Klingmüller has experienced herself. Her division at the DKFZ, in cooperation with partner groups worldwide, is examining various signaling pathways in the cell – including the so-called JAK/STAT pathway, which plays an important role in the proliferation and differentiation of erythrocytes, in the regeneration of hepatocytes, and in many other types of cell. JAK/ STAT is significant for cancer research too: if the regulatory pathway gets out of control, the result may be uncontrolled cell growth and cancer.

Up to now scientists had assumed that the "grow" command was passed on directly from a receptor on the cell surface via the JAK molecule to the signal transduction factor STAT. This moves into the cell nucleus and causes proliferation or specialization of the cell to take place. Thanks to systems biology models, Klingmüller and her colleagues now know that the signaling pathway runs cyclically. STAT always wanders back to JAK to receive confirmation – as it were – to continue. Discovery of this query loop has given researchers an interesting weak point with which to suppress the growth signal in cancer cells.

The scientists also recognized that cells cultured for many generations in a petri dish behave quite differently in terms of a wide variety of processes from their colleagues that have been freshly isolated from organs. For Klingmüller it seems reasonable to suppose that this is due to changes in the cell system such as are found in cancer too. Researchers expect a more detailed investigation of these deviations to give them better insight into the events surrounding cancer development.

And finally, systems biology is not just about communication between molecules: a communicative setting is necessary to inspire research success too. In the DKFZ-ZMBH alliance, sur-





rounded by colleagues analyzing biological signaling systems, Ursula Klingmüller sees herself and her team in good hands.



Master Plan

After fertilization, how does a lump of cells develop into a whole organism with specialized tissues and organs? Which signals determine where the head, arms, and legs develop? What happens if development runs out of control – do such disturbances lead to malformation or tumors? These are the questions which the developmental biologists from Christof Niehrs' team at the DKFZ want their research to answer.

Such questions can be examined well in the African clawed frog Xenopus laevis. Scientists from Niehrs' team are particularly interested in the development of the axis of head, trunk. and tail of the animal. The socalled Wnt signaling pathway plays an important role here. Its task is to regulate the expression of various genes, i.e., to decide which genetic information is transcribed and used as a construction plan for new proteins. But in order for different body parts to be able to develop with all their special characteristics, careful dosage of the Wnt protein is necessary. To achieve this, it has to be possible to block or interrupt the signaling pathway at certain times.

To solve the riddle of axis formation, it is thus necessary to identify the opponents who ensure that not too many Wnt commands are given. Niehrs discovered one important candidate for this about ten years



ago: a protein called Dickkopf that is responsible for the development of the head. Too much of it, and the tadpoles grow with oversized heads. Too little of it, on the other hand, leads in frogs and mice to heads that are too small or do not even develop at all. Dickkopf, as the scientists found, blocks the Wnt protein receptor and thus interrupts its signaling pathway.

way, Dickkopf and the Wnt signaling pathway are also involved in the development of osteoporosis.



Wnt, Dickkopf, and co. are not only significant for frogs and mice. Niehrs and his colleagues found Dickkopf in humans too, and it seems reasonable to assume that it plays a similar role here as well. And what is more: the so-called development control gene is not only active during embryonic development. It also steers cell growth and differentiation and is thus of particular medical interest. If it gets out of control, tumor formation and other diseases may ensue.

One example is multiple myeloma, a type of leukemia often associated with metastases in the bones, which leads to a significant loss of bone matter. The reason for this is that the cancer cells which have infiltrated it secrete Dickkopf protein. This adheres to the Wnt protein receptor on the surface of boneproducing osteoblasts, with the result that the cells no longer divide and thus can also no longer prevent their opponents, the osteoclasts, from destroying bone matter. In a similar

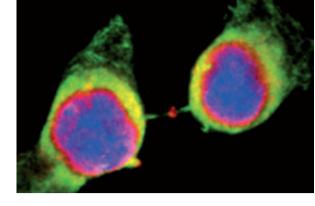


Centrosomes:

Organelles at the Center of Cell Division

"All cells arise from cells": that was how Rudolf Virchow, the Berlin doctor, formulated his cell theory in 1855. Twenty years before this, the botanist Hugo von Mohl from Tübingen had first observed division of a plant cell under the micro-

scope. In 1874, Eduard Strassburger, a botanist from Bonn, described the various stages of this process, which every schoolchild knows today from biology lessons under the name "mitosis". Mitosis designates the division of the cell nucleus in eukaryotes. Here, over the course of five characteristic phases of division, the chromosomes are split up equally between the two daughter cells. Although this process was discovered more than 130 years ago, by far not all the details are yet known of how cells successfully manage to divide so exactly



and which factors play a role in controlling this complex process.

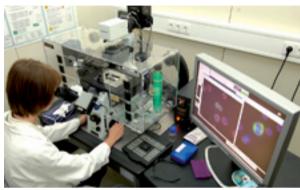
These are precisely the questions which Elmar Schiebel and his research group at the ZMBH are investigating. His preferred research object is baker's yeast, which divides by budding – so it is possible to clearly distinguish between mother and daughter cells. Schiebel is particularly interested in the function of centrosomes, which are also known as spindle pole bodies in yeast. These tiny cell organelles consist of up to 100 proteins. During cell division, the centrosomes are duplicated and move to opposing poles, from where they control the formation of the spindle apparatus. One set of chromosomes moves to the pole of the mother cell, and the other to that of the new daughter cell along these fibers, which consist of so-called microtubules.

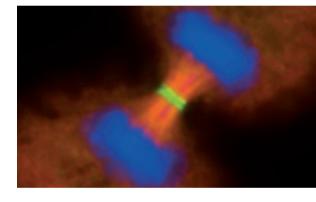
Centrosomes have an influence on when a cell divides. The tiny organelles contain proteins which regulate the cell cycle and thus determine when the next division process takes place. Schiebel wants to identify and characterize the important signalers among these.

Moreover, Schiebel has found that – at least in yeast cells – the separation of centrosomes is not a matter of chance. The

old centrosome always moves to the daughter cell, while the new one remains in the mother cell, a process termed centrosome inheritance. It has not yet been finally clarified what is behind all this. But it is interesting to note that in the division of stem cells, too, each of the two centrosomes has a preferred target. It is possible that different regulators are associated with the two organelles, which in the end leads to the mother cell retaining its stem cell status while the daughter cell, for instance, becomes a nerve cell.

The work with yeast cells is primarily basic research to help better understand the basic mechanisms of cell division. Nevertheless, detailed knowledge of these processes is also beneficial to cancer research. The components of the signaling pathway in cell division are usually very similar, regardless of whether yeast or human cells are involved. And if something goes wrong during the complex process of division, chromosomes may be unequally divided between mother and daughter cells – a phenomenon that has often been observed in tumor cells.



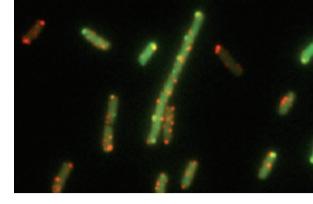




The smell of meat roasting in the oven draws us unerringly into the kitchen. Not a particular feat for humans who are well-endowed with sensory organs, a highly complex brain, and a finely adjustable locomotor system. But bacteria, the simplest of all organisms, are also capable of such an achievement.

Bacteria use a trial-and-error mechanism in this processing of stimuli known as chemotaxis. If they come into proximity with a favored source of food, such as the amino acid aspartate, they interrupt their random tumbling movement by swimming with long stretches toward the high concentration of food. If in so doing they detect a reduction in concentration, they interrupt their swimming and begin tumbling again, giving themselves a chance of happening back onto the right track.

Viktor Sourjik has spent his whole scientific career on this model, which is simple only at first sight. With his junior research group at the ZMBH, he is investigating the amount of computational power that E. coli bacteria need to process these stimuli. To recognize a gradient, the concentration of food is measured, the value recorded, and this compared with the next measurement. Within a concentration range of up to five orders of magnitude, the bacteria react to minimal devi-



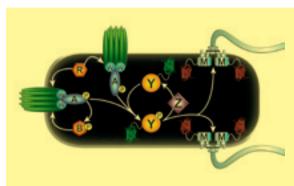
ations, i.e., those corresponding to a difference of approximately 10 aspartate molecules per cell.

The connection between the aspartate receptor on the outer cell membrane and the "motor proteins" which drive the movement of the flagella is provided by the protein CheY. If aspartate is bound to the receptor, CheY loses its phophate marker and switches the motor to "swim straight ahead". If the aspartate concentration falls, CheY regains its phosphate and signals the motor to "tumble". Further participants are proteins which "adapt" the receptor, i.e., repeatedly renew its sensitivity to signals. Using a technique that makes protein interactions visible in real time. Souriik has demonstrated how the aspartate signal in the cell is considerably amplified. This explains why only a few bound amino acid molecules suffice to trigger targeted longdistance swimming.

The chemotactic signal cascade is surprisingly resistant to disturbances such as the surrounding temperature. The system also manages to cope with the fact that the cell's synthesis apparatus delivers fluctuating concentrations of all the involved proteins. Sourjik's team quantified all the components involved in signal processing in order to simulate the whole process on the computer. The aim is to determine how

rapid and precise reactions to changes in environmental conditions are achieved with a minimal exertion of energy.

Victor Sourjik sees this simplest of all stimulus-processing systems as a basic model of signal networks in a cell. It gives us an idea of the difficulty which will be encountered in understanding the complex interactions of interconnected cells in higher organisms. The DKFZ-ZMBH alliance, with its strong focus on cellular signaling systems, provides the ideal environment to push forward into these areas.

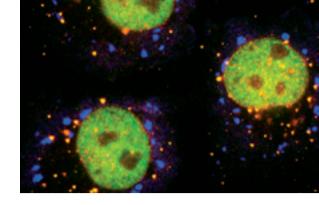




with a dation Signal

"Just-in-time production" is the magic phrase in industrial assembly lines since the unnecessary maintenance or indeed production of surplus amounts are a considerable cost factor. This management principle may possibly have been copied from nature since a cell cannot afford to waste resources on the production of surplus proteins either. But it, just as industry, must be able to react quickly to acute need. Protein synthesis is, therefore, subject to strict, multilayered regulation.

The first level of control comes into play in the production of mRNAs, the genetic copies that serve as a matrix for protein synthesis. If the need for a particular protein is, however, particularly urgent, the cell cannot wait for new copies and has to fall back on ready-made mRNAs. If the causative agent of an infection must be combated quickly, messengers of the immune system have to be released within minutes. Here is the trick: mRNA molecules are continually being produced but contain specific degradation signals consisting of the bases adenine and uracil (A and U). Under normal conditions, these signals cause the molecules to be broken down again shortly after they are produced. Only stimulation of the immune cell by, for instance, the causative disease agent stabilizes the matrices, providing the starting signal for protein synthesis.



Georg Stöcklin and the members of his junior research group at the DKFZ are concentrating their research on mRNAs with a built-in breakdown signal. The immune messengers are a suitable model system for their investigations. The lifespan of mRNA for the messenger TNF α is only 10 minutes, while in contrast RNA without an AU signal survives for many hours or days. Specific recognition proteins, such as BRF1 identified by Stöcklin, bind AU signals and initiate RNA breakdown. If the cell, however, reports acute need for an immune messenger, the AU binding proteins are inhibited by phos-phate groups, stopping the breakdown of mRNA.

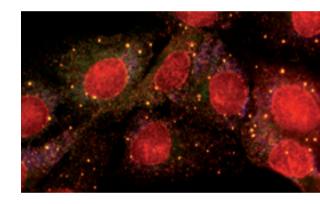
Breakdown of the mRNA molecules does not proceed indiscriminately but is concentrated in specific bodies in the cytoplasm, in so-called processing bodies. The most important enzymes are located here which, as Stöcklin has demonstrated, break down mRNAs with AU signals.

A series of observations gives reason to assume that tumor cells provide protection to particular mRNAs that code for the growth-promoting proteins, protecting them from breakdown and thus increasing the yield of these factors. To check this hypothesis, Stöcklin is systematically going through the gene activity profiles of various types of tumors. He assumes

that, in tumor cells which produce unusual levels of AU binding proteins, mRNA stabilization contributes to tumor development. This mechanism, however, still has to be proven experimentally.

Using the new possibilities of the DKFZ-ZMBH alliance, Georg Stöcklin and his research group recently moved from the DKFZ to the ZMBH where, working closely with colleagues from both institutes, he can study mRNA breakdown more comprehensively.





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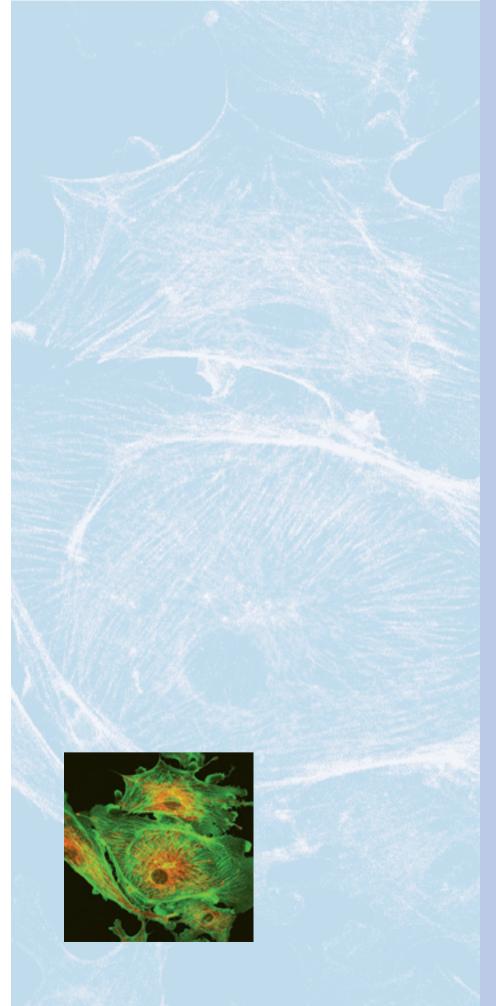
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