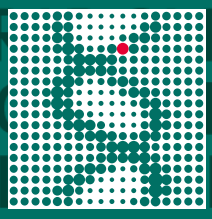


MAX PLANCK INSTITUTE FOR MOLECULAR GENETICS

The Max Planck Institute for Molecular Genetics (MPIMG) is one of the leading genome research centres in the world, and one of the largest research institutes within the Max Planck Society. Since the mid nineteen nineties, it has played a pioneering role in the sequencing of the human genome and in the clarification of genetic causes of disease. The Institute is based in Berlin, Germany.

The MPIMG has four independent, closely collaborating research departments, each headed by its own director. The individual departments focus on embryonic development, the genetic causes of mental retardation, the functional interplay of molecular networks and the mechanisms of gene regulation. In addition, an independent research group is investigating congenital skeletal malformations, and several independent junior group leaders and their teams are pursuing their own research projects. An international Scientific Advisory Board regularly verifies the quality of research at the MPIMG. The Institute has the support of a Board of Trustees with representatives from politics, industry, public society and the media.

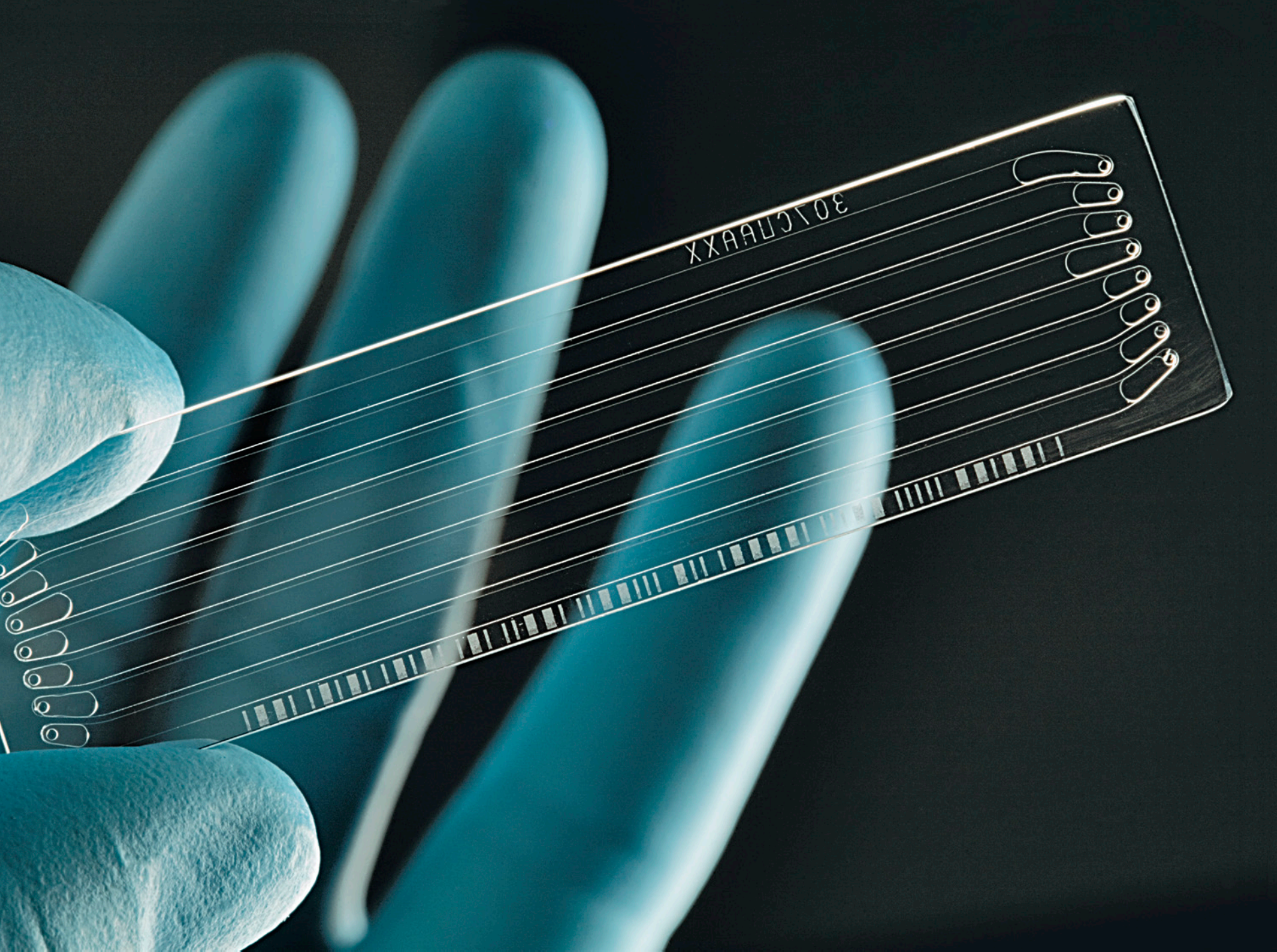
A general hallmark of the Institute is the use of cutting-edge, automated laboratory technologies that allow very fast and extensive DNA analyses, which are available for e.g. large-scale international projects. The Institute was most notably involved in the first ever sequencing of the human genome in 2000, as a member of the Human Genome Project.

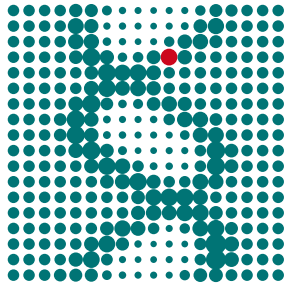
Situated in the Berlin quarter Dahlem, a location rich in scientific tradition, the MPIMG is an immediate neighbour of the Freie Universität Berlin and other institutes of the Max Planck Society. With mutual appointments and the involvement of its scientists in numerous study courses and scientific projects, the pursuits of the Institute are also closely tied with those of the Freie Universität Berlin, the Humboldt-Universität zu Berlin and the Charité – Universitätsmedizin Berlin.

In the scope of the National Genome Research Network, the MPIMG collaborates intensively with many research partners in Germany, and is involved in numerous international cooperative efforts.
The MPIMG currently employs more than 460 employees, including 125 researchers and 96 PhD students

Cover:
Amino acid sequence of the APC protein. The mutation of the gene can lead to colon tumours
(→ see reportage on page 24).

Berlin, December 2009





MAX PLANCK INSTITUTE FOR MOLECULAR GENETICS

Contents

Molecular Genetics Research in the 21st Century

In the year 2000, when former US president Bill Clinton stood before TV cameras together with genetic researchers Craig Venter and Francis Collins, it was both a media sensation and a milestone in the history of modern biology. Live from the White House, the three announced the sequencing of the human genome. This marked a fundamental change in molecular biology.

Some five decades earlier, James D. Watson and Francis Crick had presented their model of the 3-dimensional structure of DNA, a work that later earned them the Nobel Prize in Physiology or Medicine. It was around that time that the Max Planck Institute for Molecular Genetics was established in Berlin, Germany. The founding directors were Heinz-Günther Wittmann, Heinz Schuster and Thomas A. Trautner. Their work at the time focused mainly on the structure and function of ribosomes (Wittmann) and DNA replication and gene regulation in bacteria, bacteriophages and fungi (Schuster, Trautner).

In 1994, the appointment of a new generation of directors brought about a major shift in the Institute's scientific orientation. One year later, Germany – and with it the MPIMG as one of the German partners – joined the international Human Genome Project. This project started in autumn 1990 with the primary goal of sequencing the entire human genome.

At the end of the seventies, the idea of one day being able to access all three billion single components of the human genome in public online databases would have seemed like science fiction, even to leading scientists. Now, it is commonplace. There is hardly a single molecular genetic research project that does not depend upon the human genome as a basic data set. The human genome has become the researcher's tool of the trade.

Actually, the completion of the Human Genome Project marked the beginning rather than the end of an era. While the sequencing of the genome has delivered the exact sequence of the chemical DNA components A(denine), G(uanine), C(ytosine) and T(hymine), there is no message encoded in the order of A, G, C and T alone. The phrase "decoding the genome", as frequently heard in the media, is misleading.

The much more important questions are: where, in the sequence of genetic "letters", are the genes – those estimated 25,000 informational units encoding the composition of body proteins? How is the activity of these genes controlled? How does an organism with a three-dimensional structure arise from the genetic information? What errors in the flow of molecular information result in disease?

Molecular geneticists have long been pondering these questions on the functional interactions within the human genome – questions that could transform the practice of medicine in coming years, and even the general view of the organism itself. Sequencing the human genome has pushed open the door to this research, as it were, allowing

a better view of the big picture. Now it is time to step through this door and into the future.

The present departments of the Max Planck Institute for Molecular Genetics, headed by Bernhard Herrmann, Hans Lehrach, H.-Hilger Ropers and Martin Vingron, are moving in exactly this direction. Bernhard Herrmann and his team are investigating the genetic regulation mechanisms controlling embryonic development. Most remarkable is that the very same molecular signal processes in charge of maintaining normal embryonic growth can apparently lead to cancer later in life.

Hans-Hilger Ropers and his colleagues are investigating the genetic mutations that can impair brain development and lead to mental retardation. There are probably many hundreds, and quite possibly more than a thousand of different genes involved in cognitive disorders – most of which are still waiting to be discovered. The best studied is the X chromosome, on which more than 80 genes have been identified so far whose respective mutations are associated with intelligence deficits.

The researchers working with Hans Lehrach are tackling the question of how entire groups of genes and proteins interact during biological processes – an approach known as systems biology. By analyzing the many molecular interactions inside body cells, the researchers hope to be able to predict, for example, the precise effects and side-effects of anti-cancer drugs. Yet such studies can no longer be done in lab experiments alone; they now require special computer simulations.

Computational methods are a key tool in Martin Vingron's department, as well. These scientists want to know how genes are regulated – how they are turned on and off as needed. They intend to reveal this by analyzing extensive genetic databases using computational biological methods. A considerable amount of molecular biological research has long been conducted on computers.

This applies to both the interpretation and the acquisition of genetic data. By now, there are extremely fast sequencing machines available that can analyze several billion DNA building blocks in just a few days. This enormous amount of data could not be tackled without a powerful computer infrastructure. At the same time, all this is revealing the complexity of molecular biological relationships. The ability to analyze entire genomes in next to no time is allowing ever better study of the diverse interdependencies of genes, messengers, control factors and other cell components. The genes themselves are part of the molecular networks that determine the biological behaviour of body cells. Nevertheless, the genome is no "book of life" to be simply read in order to know everything there is about humans.

When Bill Clinton stood before the cameras in 2000, he adopted a rather dramatic phrase to describe the sequencing of the human genome: "Today we are learning the language in which God created life." Since then, talk about genes has tamed down considerably. One has learnt to speak of molecular genetic research in more realistic, sober terms. But that does not make it any less exciting. ●


TREPPE
1

The Organism as a Molecular System

Hans Lehrach and his team intend to deliver molecular biological computer models as a basis for personalized medicine

It is a saying we hear a lot: the whole is more than the sum of its parts. But molecular biological research has given this dictum an entirely new meaning. Biological processes – from embryonic development to heart function to the onset of high blood pressure – cannot be understood from the study of individual, isolated components alone. There is always a complex interplay of many intertwined molecular mechanisms. The organism operates as a system.

"We can already model biological systems on the computer," emphasizes Hans Lehrach, head of the Vertebrate Genomics Department. He and his group are studying how large groups of genes and proteins interact during biological processes inside the cell – an approach known as systems biology, which promises entirely new possibilities for the treatment of many diseases.

From the Single Gene to the Network

Lehrach and his colleagues have been involved in several international large-scale research projects, most notably the sequencing of the human genome. His department made a significant contribution to the sequencing of chromosome 21, for example, and was involved in decoding chromosome 3 and the X chromosome, too. The researchers also contributed significantly to the analysis of the rhesus monkey and chimpanzee genomes.

Much more important than knowing merely the gene sequence of an organism, however, is understanding the molecular information flow that builds a living system out of the genes, explains Lehrach. A specific tumour disease, for example, can involve the mutation of dozens of different genes. The individual mutations differ, at least in part, from one patient to another. Yet how does that change the biological behaviour of a tumour cell? What signal cascades go haywire, and which drug is used best in the individual case to intervene in the disease process?

The daily exchange of scientific ideas is one of the most important tools in research

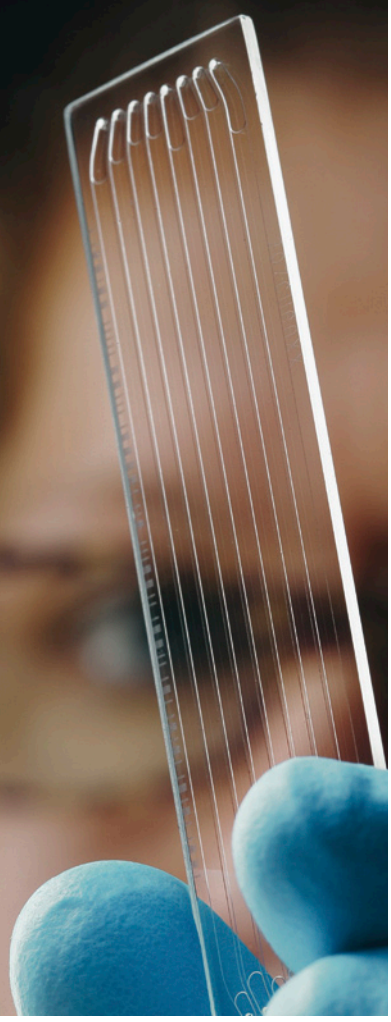
"We can already model biological systems on the computer": Prof. Dr. Hans Lehrach, Head of the Vertebrate Genomics Department.

"We want to make more precise predictions as to how a patient will respond overall to a therapy," comments Lehrach. It is already known that many drugs have been helpful to some people while they have remained ineffectual or even harmful to others. The reason for this is the molecular complexity of many diseases, the researcher explains.

In order to cope with this diversity, he and his team have developed a computer platform called PyBioS that can be used to make initial predictions of the molecular effects of drugs on the entire biological system. PyBioS automatically accesses publicly available molecular biological databases, and can thereby integrate many pieces of information about genetic and biochemical processes into a model simulation.

Tailored Tumour Therapy

In this way, Lehrach and his colleagues have studied the effects specific anti-cancer agents have on 20 different cellular signal cascades with more than 700 individual molecular components. Granted, such models will never be perfect, but the researcher is confident that they could make many treatment strategies significantly more targeted in the future. For a specific cancer patient, for example, it would be conceivable first to analyze all gene mutations and then to provide doctors with simulation software that will determine the most effective and least harmful treatment in the individual case. In principle, this scenario could become a medical reality in just a few years, Lehrach hopes.



Big Robby and his Progeny

WITH THE RISE OF ROBOTS AND LAB AUTOMATION IN THE 1990S, DECRYPTING GENETIC CODES BECAME A RACY, INEXPENSIVE PROCESS. SEQUENCING TECHNOLOGIES ARE ALREADY INTO THEIR NEXT GENERATION. A VISIT TO THE GENETICS LAB

Just a few steps through the green door, and you can already hear him quietly whining and whirring away. It is Wednesday afternoon, room 0.108 on the ground floor of the Max Planck Institute for Molecular Genetics. Big Robby is working.

"Come in," urges Richard Reinhardt, his arm swept out towards the robot line. "The facility is unique." Reinhardt heads the scientific service group Analytics at the Institute, and has summoned us to a tour of his machine farm. Big Robby – the affectionate name the researchers have given it – is one of his babies. And a trademark of the Institute.

Many ambitious research projects in recent years would have been impossible without this robot ensemble, which carries out critical DNA analysis tasks in perfect orchestration. Like a gymnast doing a handstand, a grey robot arm mounted on a sled lifts into sight in the jam-packed lab – it is the oldest part of Big Robby. And all around it is a cordon of machines; the quietly whining pipette machine shaking its chemical samples at one end, and a fridge ready for sensitive material standing standby at the other. A software program coordinates the work processes of each machine, while the grey gripper runs the samples from one to the other. And this goes on day and night.

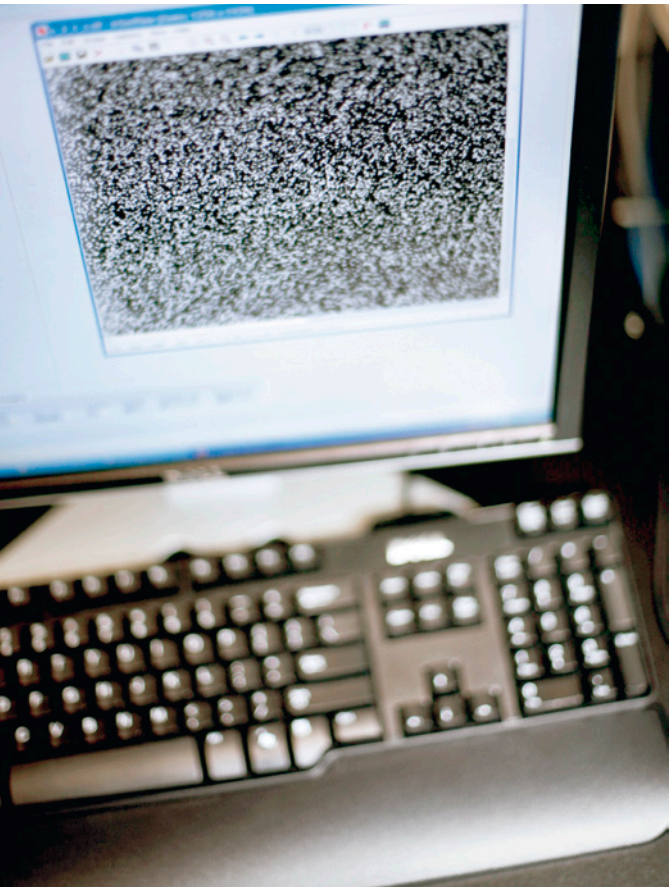
"A robot never sleeps, and never takes a smoking break either," comments Reinhardt, who remembers well the time when laboratory assistants would work, well, laboriously with pipette and test tube to accomplish what Big Robby now does in a fraction of the time, and with much greater efficiency. It was back in the nineties that Reinhardt's team together with Institute Director Hans Lehrach designed the robot line, which has undergone continual improvements ever since.

In the mid nineties, the MPI for Molecular Genetics became one of the German partners to join the international research consortium aiming at sequencing the entire human genome – a Herculean task that sparked off a veritable surge of automation in genetics labs all around the world. Ever since, Reinhardt tells us, the Institute has stood at the international peak of technological development, and you see his eyes gleam as he talks of technical things. He has always been fascinated by technical perfection. And he gets hands on wherever necessary, having tinkered with the first lab systems here at the Institute in order to create a more efficient platform for reading the genetic code – sequencing as it is properly called. Now, Big Robby has worked his way fully into the job.

View of the robot line at the Institute, which the researchers affectionately call "Big Robby".

The basic concept of sequencing is quite simple. The genetic material DNA can be "read" as a kind of molecular four-letter alphabet, the letters standing for the chemical bases A(denine), G(uanine), C(ytosine) and T(hymine). Genetic information is encoded by the order in which these letters appear. Knowing the precise DNA sequence is therefore crucial for discovering disease genes, for example, or for understanding the control of genetic activity. But in humans, this amounts to more than three billion bases.

No wonder, then, that British biochemist Frederick Sanger was awarded the Nobel Prize for developing a sequencing method in the 1970s that would later be instrumental to the Human Genome Project. His method was to cut the DNA into short fragments first and then insert these into the DNA of bacteria, which will multiply in the thousands. Then the microbes are chemically broken open, and the DNA fragments isolated by various reactions and then purified.



Message in black & white: modern genome analyses are based on the analysis of biochemically produced light signal patterns

In a third step, special enzymes synthesize molecular copies of the prepared genetic fragments. The base sequence is effectively rebuilt many times over, albeit – and this was Sanger's ingenious idea – with the reaction conditions carefully chosen so that the copy process keeps coming to a stop at different positions. This is done by incorporating a specific base as a "terminator" that has been tagged with a fluorescent dye. Each of the four bases has its own specific dye. The result of this clever reaction is a mixture of DNA fragments of different lengths, each representing a highly specific position in the sequence of interest. Since small fragments migrate faster through a gel matrix in an electric field than larger fragments, the mixture can be sorted out using electrophoresis, and the different dyes reveal which base exists at which position in the DNA.

Big Robby in fact shoulders a huge portion of the chemical reactions required for analysis. In order to isolate gene fragments from bacteria, for example, the pipette robot ceaselessly

processes nearly 400 samples at a time: these are contained in tiny indentations of a plastic plate, which is smaller than a block of chocolate and can be traced throughout the entire processing chain by barcode. Plates with prepared fragment mixtures can then be loaded into powerful capillary sequencers, which sort the DNA fragments in an electric potential field of 5,000 volts and read their fluorescence tags up to 1,200 bases long. The fastest of these machines decode more than three million bases in 24 hours – which equates to a thousandth of the human genome. "At the end of the nineties, you could still have done your doctoral thesis on that," remarks Reinhardt laconically.

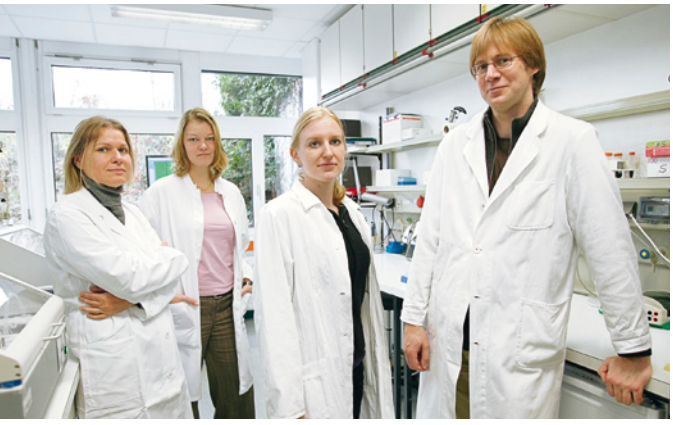
Yet, there are already new systems available that, with their enormous analytical capacity, leave even the fastest capillary sequencers far behind. These next-generation sequencers, as they are called, have captivated researchers around the world. By the end of 2009, man-high lab automation systems equipped with the latest technology will be capable of decoding 100 billion DNA bases per run. The sequencing throughput of machines quadruples every year, comparable with the performance explosion of computer processors.

"Since the nineties, we have been at the peak of technological development": Richard Reinhardt heads the scientific service group Analytics at the Institute.

Nevertheless, classic capillary sequencing will not become redundant any time soon. The method still has the advantage when decoding a complete, unknown genome or very long DNA fragments. The new high-speed sequencers, on the other hand, are unbeatable when it comes to checking already fundamentally known genetic material for subtle variations. Geneticists call this resequencing. This is what is so crucial to many medical problems today. It appears, the comparably tiny differences between the DNAs of two different humans are critical in the onset of various diseases.

The scientists at the Max Planck Institute for Molecular Genetics are therefore using this novel high-tech equipment more and more in their work. In total, the Institute has twelve such high-speed sequencers, most of which are operated in the Next Generation Sequencing service group, reports Bernd Timmermann, who is responsible for this area. Although this means the Institute counts among the smaller sequencing centres of the world, it receives requests for scientific cooperations practically every day on account of its technological infrastructure. The innovative technologies were developed in recent years by various firms and research groups. The method is based on various biochemical reaction cascades, which the Swiss Roche Group and the two Californian companies Applied Biosystems and Illumina now offer in the form of integrated lab machines.

The new method revolves around a basic principle similar to that of Frederick Sanger's classical method, in that molecular copies of tiny gene fragments are created. However, the process runs on several million DNA fragments at once, and in a condensed space. The Illumina method, for example, adheres to a thumb-sized glass plate somewhere between ten and a hundred million different DNA fragments, which are all reconstructed in parallel by special enzymes. A sensitive optical system detects each newly added base using a specific fluorescence signal, and stores the information in an image file. Within days, a parallel sequencer collects data on several billion bases, where several terabytes of data are accumulated – more than ten times as much as a typical modern PC can store on its hard drive.



"We receive requests for scientific cooperations every day": Bernd Timmermann with his colleagues from the Next Generation Sequencing service group.

As it is, the Institute has more than doubled the storage capacity of its computer farm

With plastic plates the size of chocolate blocks, around 384 samples can be analyzed in one go.

Trend towards new technologies: Ralf Sudbrak coordinates the Institute's participation in the 1000 Genomes Project, an international project for researching individual genetic differences.

just to be able to use the supersequencer more intensively. The new sequencing systems are not only fast. They are also cheap to run. One main reason for this is the high degree of miniaturization. The lab machines are like chemical minilabs, in which only teensy quantities of reagents and enzymes are consumed. That saves money. While the Sanger technique allows you to sequence around 1,000 DNA bases for 50 cents, next-generation methods will sequence up to 500,000 bases.

Most experts estimate it will probably soon be possible to read the entire genome of an individual person for less than 1,000 euros. It is foreseeable, then, that there will soon be private customers wishing to sequence their own DNA.

It is already clear, however, that the new technologies are changing genetic research. "Our project has reached a scale we could not have envisioned," explains Ralf Sudbrak, who coordinates the participation of the Max Planck Institute for Molecular Genetics within the international 1000 Genomes Project. Sudbrak is a slim man in a comfortable jacket and jeans. He sits in his office on the first floor, flipping through his documents.

In this international research project, the entire genome from at least 1,000 people of different ethnic origin shall be analyzed, says Sudbrak. "The logistics are extreme." Already during the eight-week pilot phase in 2008, the Berlin team led by Hans Lehrach sequenced as many DNA bases as had been decoded in the entire Human Genome Project worldwide though year-long efforts.

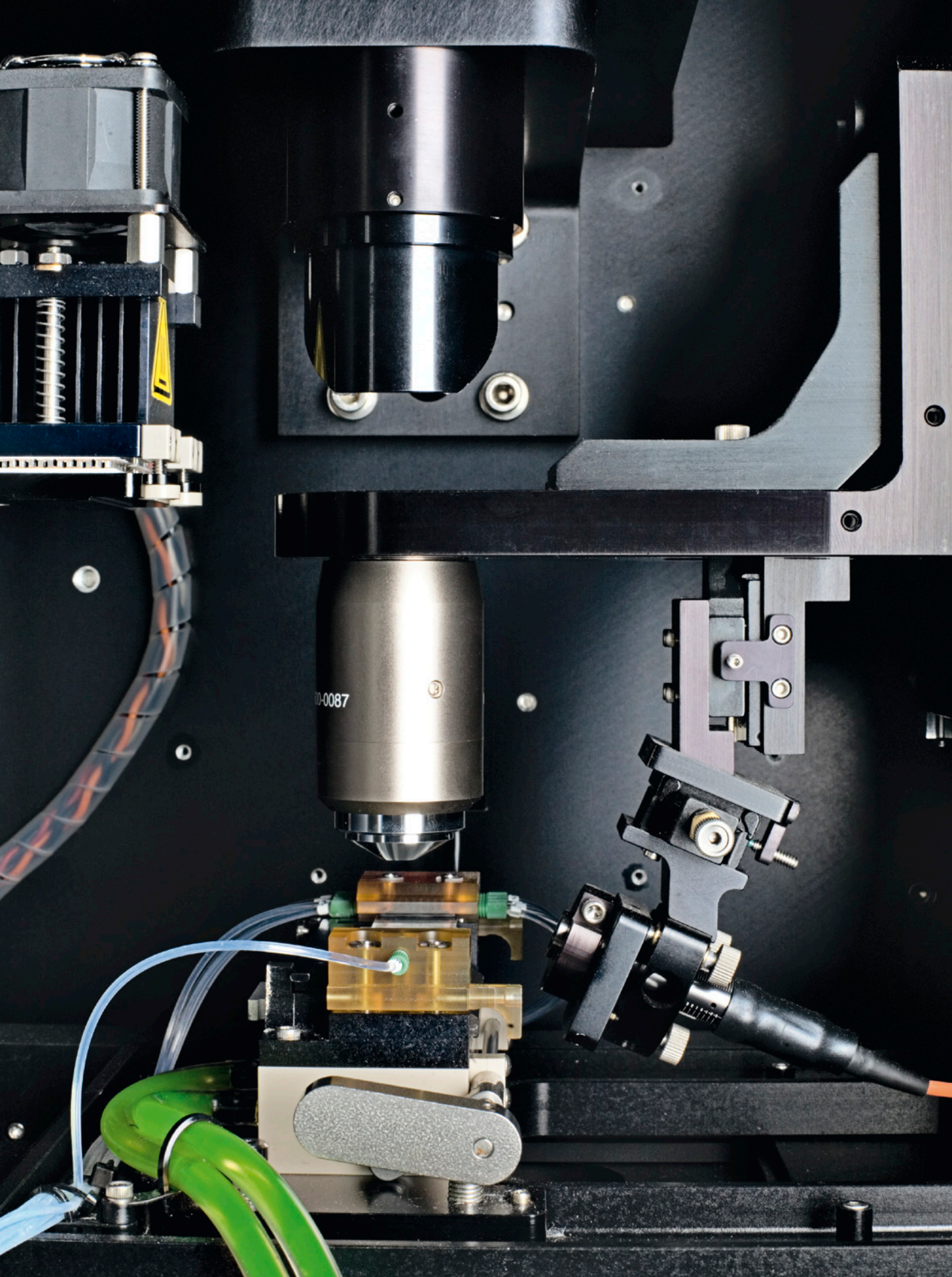
While any two individuals differ by less than one percent of their DNA, it may well be precisely these subtle differences that decide whether one person is especially susceptible, say, to heart disease or diabetes. The aim of the 1000 Genomes Project is to create a detailed catalogue of these genetic variations by the end of 2010, in order to scrutinize it in later studies for links to common diseases, says Sudbrak.

Even now, innovative concepts are already being devised in Hans Lehrach's department for using the new sequencing capabilities for personalized medicine. "We intend to use the genetic data to

With next generation sequencers, it may soon be possible to read the entire genome of an individual person for less than 1,000 euros.

View inside a high-speed sequencer. An optical system records fluorescence signals from the genetic sample material.

make very precise predictions of the course of the disease and to find the optimal therapy for individual cancer patients," says Lehrach. The genomes of thousands of tumour patients and the mutated DNA of their tumours will be sequenced in an international collaboration over the next few years. "This will help doctors to adapt their treatment to the individual patient," Lehrach adds. To him, personalized medicine research has long been more than just a future prospect. ●



The Development of the Embryo

Bernhard Herrmann and his team are investigating how body formation is controlled

The speed is as astounding as the precision. A fully formed embryo arising from a fertilized egg cell is one of the most fascinating phenomena of biology. "I wanted to know how it actually works," comments Bernhard Herrmann, head of the Developmental Genetics Department and a pioneer in the field. He and his group belong to the international leaders in deciphering the genetic regulatory networks that control trunk formation in mammals. Basically: how does the embryo grow in length?

Essentially, there are three parts to a vertebrate embryo: the head is followed by the trunk and the tail. The first to appear is the head; the trunk only gradually forms by stepwise elongation of the anterior part. Typical of this process are new tissue segments that arise at regular intervals – the "somites". These later develop into the spinal column and skeletal muscles, among other structures.

To the Beat of the Genetic Clock

This building principle dates back more than 450 million years, back to the beginnings of vertebrate evolution, Herrmann reports. By stringing ever new somites together, organisms of just about any length could form, such as dinosaurs or snakes. Today, we know that somite formation is precisely controlled. In the chicken embryo, for example, a new somite forms every 90 minutes at a certain stage of development.

It is obvious that this clockwork-like precision requires finely tuned control mechanisms – and Herrmann's team has already decoded some of them. The researchers work on mouse embryos, but the results are almost entirely analogous to humans, Herrmann explains. It turns out, for example, that a signal protein called Wnt3a acts as a kind of master-regulator of embryonic trunk development. Wnt3a is produced mostly at the posterior end of the embryo, in what is known as the caudal bud. This signal source causes numerous other de-

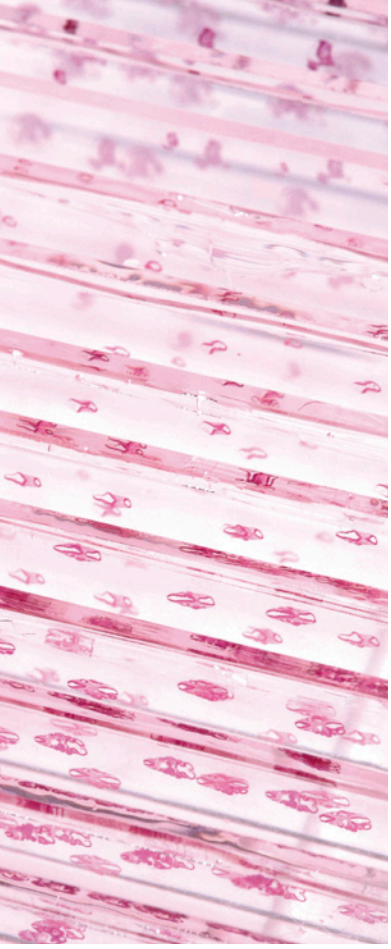
Very similar genetic programmes are followed during embryonic development to those in the onset of tumours: the research group in discussion.

"I wanted to know how embryonic development actually works": Prof. Dr. Bernhard Herrmann heads the Developmental Genetics Department.

velopmental genes to be switched on and off in the neighbouring tissues, and leads to progressive segmentation and differentiation in the embryo from head to tail. If these signal networks are disrupted, abnormalities in the vertebral column are the result. The worst case is an interruption of trunk development and death of the embryo.

Permanent Signaling leads to Cancer

Very similar control mechanisms also come into play in the formation of extremities, which arise from the trunk at short delays, and even in the formation of organs, teeth, mammary glands and hair follicles, Herrmann adds. What is even more striking is that genetic programs, that control trunk formation in the embryo, are in fact reactivated at the onset of tumours and their metastases in the adult organism. "In many tumours, signal processes occur that are very similar to those in the embryo," Herrmann explains. Of course, there is one crucial difference, in that the genetic control mechanisms are strictly controlled and temporally coordinated in the embryo, but manage to escape this control in the development of cancer. A special tumour research group in Herrmann's department is studying precisely how this happens. ●



Legacy from Prehistory

FINELY TUNED GENETIC NETWORKS CONTROL THE DEVELOPMENT OF AN EMBRYO INTO A DEFINITE FORM. IN THE ADULT ORGANISM, HOWEVER, THE SAME MECHANISMS CAN LEAD TO CANCER. SCENES FROM A RESEARCH PROJECT

Are they sea horses? It could be tiny sea horses that Ralf Spörle holds in his hands. Delicately swimming beings with impressive heads and elegantly bent tails. They are a snapshot of a prenatal transformation.

"All mammalian embryos must go through this stage," says Spörle, whether man or mouse. Spörle is a zoologist, and he knows more about the anatomy of the developing organism than just about anyone at the Max Planck Institute for Molecular Genetics. At his workplace on the ground floor are a computer and a microscope. Spörle has studied, catalogued and photographed thousands of mouse embryos according to scientific standards – a unique collection of data that should help to elucidate even the secret of the human embryonic development.

With a skilful grip, Spörle has already removed four mouse embryos from the tube in his hands, and placed them under his high-power optical microscope. Details of the shimmering bodies can be studied by stereomicroscopy: under the voluminous head is an as yet shapeless organ – the heart. Behind these are the disc-like segments of the trunk, the so-called somites, which taper off into a delicate tail end. Even the buds for the front and hind legs are already distinguishable in subtle pink.

"A human embryo at the corresponding developmental stage would look almost identical," comments Spörle. The mouse embryos he is studying are eight and a half to eleven and a half days old, and thereby at half their prenatal time. Mouse pregnancy lasts about three weeks. The mice are mated in the Institute's animal facility, and the embryos taken from the womb at the appropriate time. Most of the organs are established and already undergoing differentiation, which is controlled by a diversity of genetic signals.

The scientists from the Developmental Genetics Department analyze this process systematically. As the first step, the researchers employ special molecular probes with which they can detect the genetic activity in the tissues by a colour reaction. The embryonic tail, for example, lights up as a strong purple under Spörle's microscope. This is the evidence that one of the developmental genes they were seeking was active at precisely this stage in the immature body.

"We are interested in the genetic basis of a central developmental process," Lars Wittler adds. He has just sat down in the brightly furnished department lounge a couple of doors further down. Wittler and his group are studying the formation of the trunk, which takes place in the mouse embryo from the ninth to the eleventh day of pregnancy. During this period the segments appearing as disc-like

Genetic mechanisms of prenatal development can be studied from early developmental stages of mouse embryos and are analogous for humans.

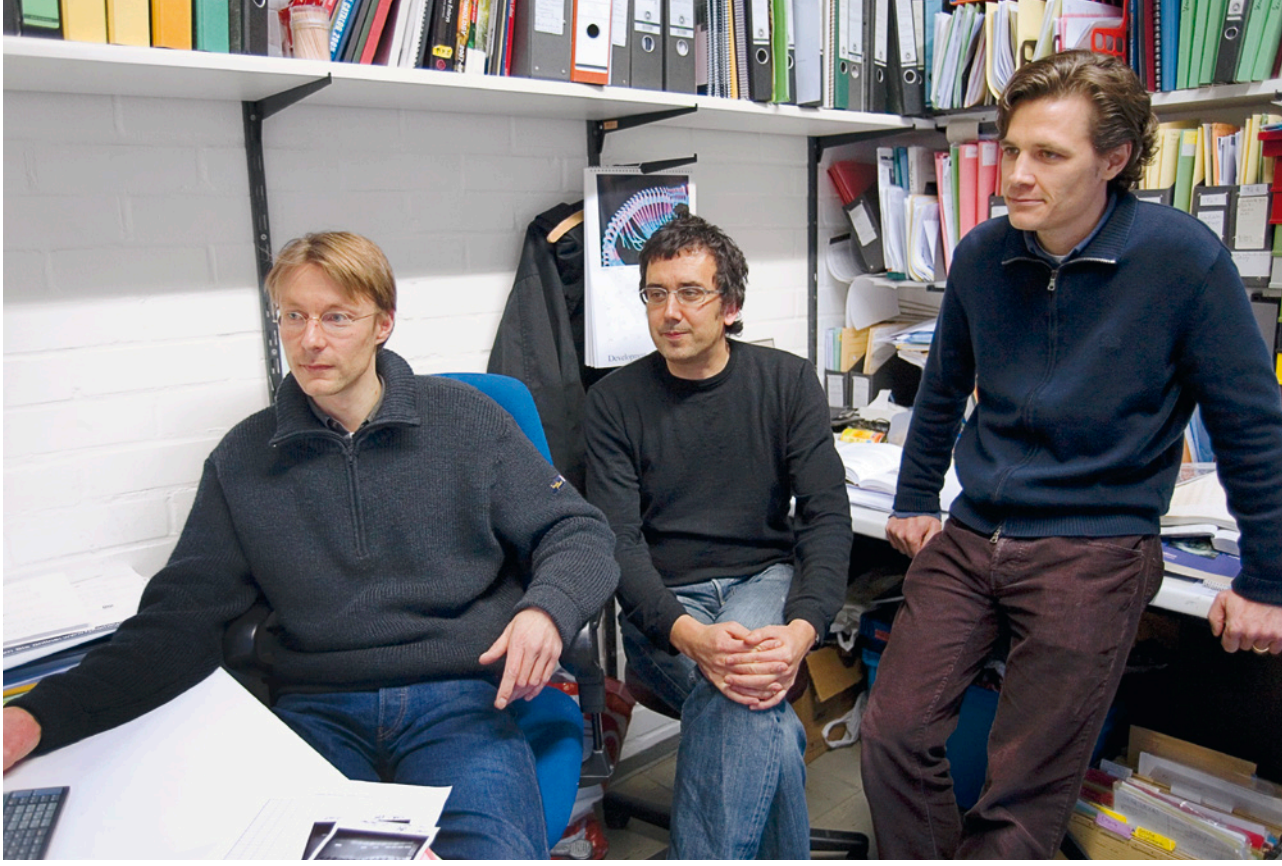
"All mammalian embryos must go through this stage – including human."

segments under the microscope, known as somites, are generated at regular intervals in time. These later develop into the spinal column and skeletal muscles.

It has long been known that the embryo only develops a properly-formed trunk if very specific genes are switched on and off according to a strictly controlled spatial and temporal pattern. This dynamically changing gene activity can be followed even in living embryos by using fluorescent marker proteins.

Now, Wittler and his colleagues intend to decode the entire developmental genetic network and its coordinated signal transduction chains. Ideally, explains Wittler, this would allow them to create a kind of complete molecular genetic scenario of trunk formation – and with it a representative model of embryonic development overall. What happens, for example, when a certain developmental gene is defective or its function is blocked? Which genes are high up in the network hierarchy, and therefore indispensable for the survival of the embryo, and what faults in the signal transduction chains could possibly be compensated? How does the precise temporal sequence in the formation of the body axis come about?

Archive of the first days: a mouse embryo halfway through the three weeks of pregnancy.



Wittler lists the methods required for analysis. The activity of thousands of genes and control molecules from embryonic tissue samples is studied. Afterwards, the experimental data is analyzed by special computational methods. One of the most important results is that a signal molecule named Wnt3a acts as a kind of master-switch for trunk development. Wnt3a is produced mainly in the tail end of the embryo and, in concert with several other signal pathways, controls the segmentation that leads to the typical formation of the body axis.

One of the most remarkable findings, however, is that the Wnt signaling cascade is involved in more than just embryonic development. The same mechanism can also lead to cancer. "All essential signaling pathways of embryonic development are also important at the onset of tumours," states Markus Morkel. He is the tumour specialist of the department, and sits at his lab post, bent over a piece of mouse intestine. Morkel immediately starts to explain. Basically, a tumour forms because embryonic developmental programmes are switched on permanently by genetic mutations – and thereby run out of control. What determines normal growth according to a meticulously regulated pattern in the early developmental history of the embryo can end in chaotic, rampant tissue growth in the adult organism.

Looking through Morkel's microscope, one sees many tiny nodules in the finger-length, yellowish strip of tissue from the intestine.

"We are interested in the genetic bases of a central developmental process": Researchers Lars Wittler, Markus Morkel and Martin Werber (from left).

Analysis of embryonic trunk formation: a special colour reaction (red areas) highlights the activity of certain developmental genes.

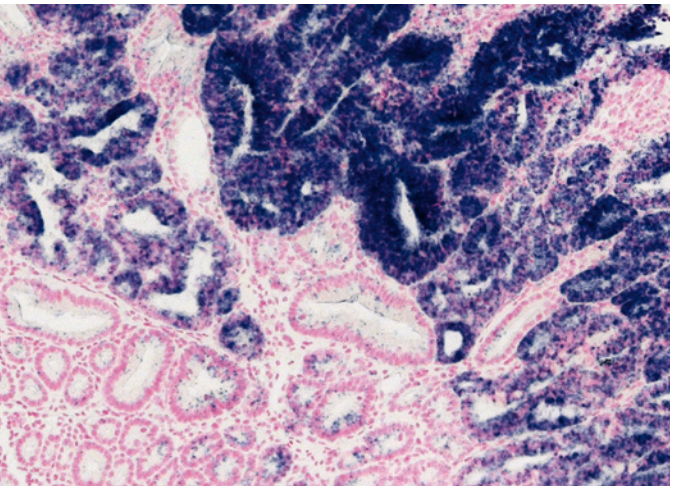
These are precursors of malignant tumours. The tissue comes from a mouse in which the so-called APC-gene is mutated, explains Morkel. Exactly this mutation causes a deregulation of the Wnt signaling cascade.

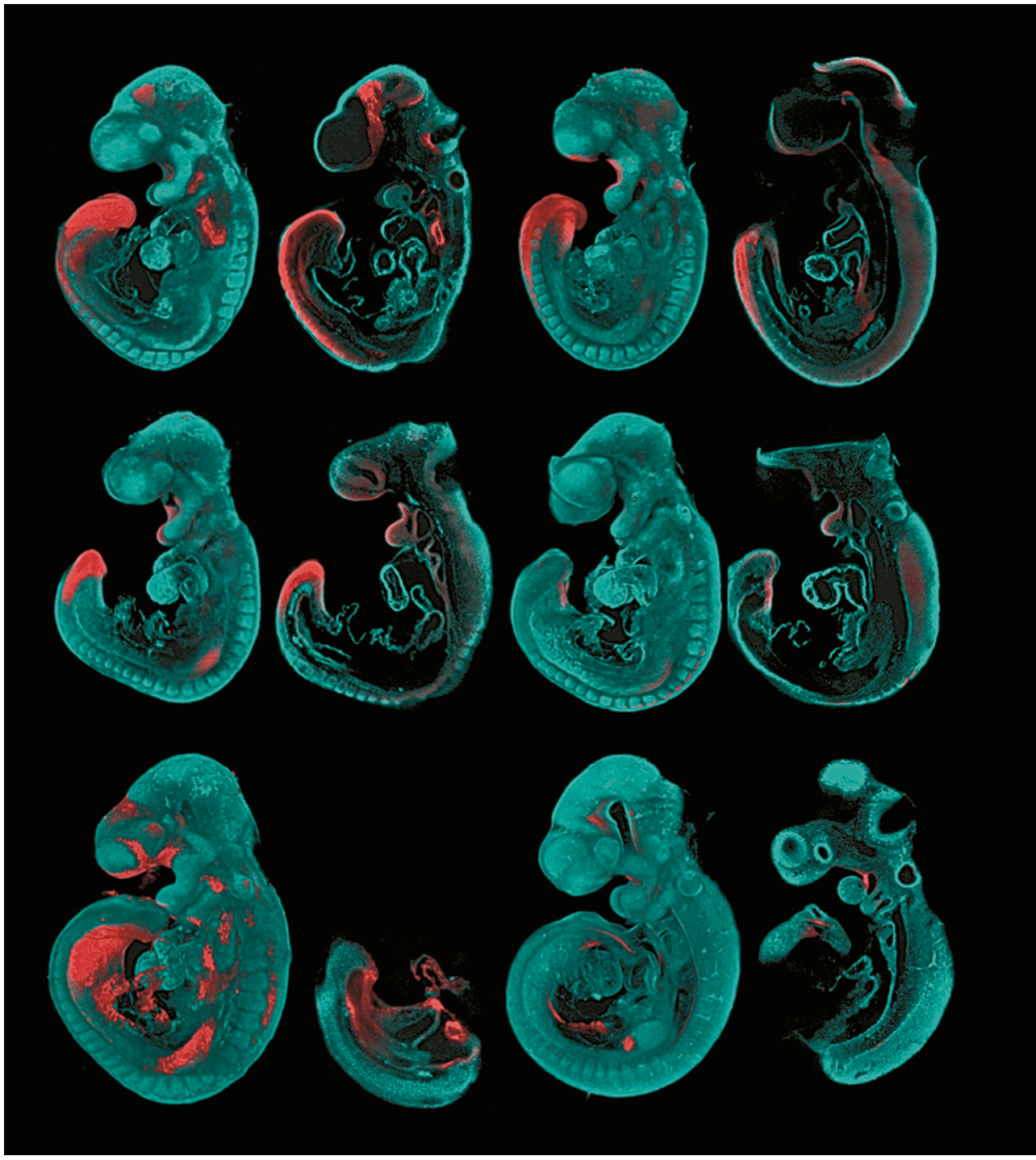
It is a fact well known that the hereditary APC mutation predisposes not only mice but also humans to the formation of extensive colonic tumours, so-called adenomas. While adenomas are benign in themselves, they can sometimes transform into a dangerous cancer.

One critical step in this process is that the tumour cells begin to grow aggressively, and to form metastases. In such situations, the cells effectively revert to that particular primitive embryonic state, in which the embryo still exhibits no discernable form and most resembles a flat disc. This is the stage, at which certain cells migrate into a new layer of tissue beginning to form inside the embryonic disc, from which the somites later arise. The cells gain their ability to migrate by signals from the Wnt cascade – and this can happen later on again in a tumour. The prognosis darkens as soon as tumour cells break loose from a locally limited lump and spread throughout the body.

"Cancer cells use the genetic repertoire of the embryo, as it were, to the detriment of the adult organism," comments Morkel. The research into developmental genetic mechanisms will also lead to a better understanding of tumour growth – and could therefore be the key to new approaches in cancer therapy.

Tissue section from a colon tumour. The Wnt signaling pathway, a central genetic mechanism of development, plays a key role in the formation of tumours. The blue coloration indicates gene activity.

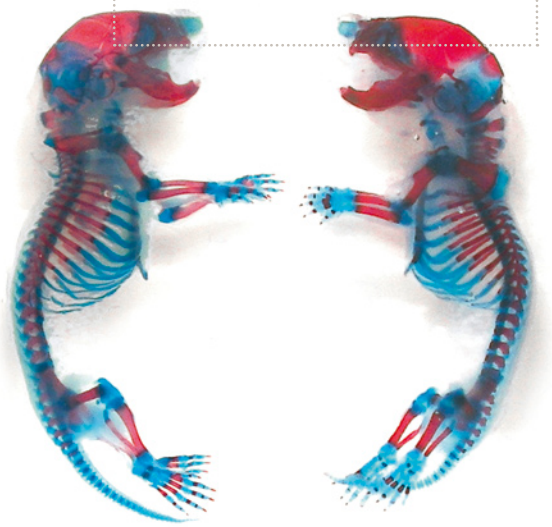




Developmental Errors in the Skeleton

Stefan Mundlos's research group is investigating the causes of congenital malformation

Studying skeletal malformations: staining of prepared cartilage (blue) and bone (red) of newborn mice allows a first estimation of the severity of a genetic defect.



The human skeleton is like a building set with many little pieces. It is assembled from more than 200 bones, about half of which belong to the hands and feet alone. Sometimes however, skeletal development in the embryo can become disordered. Some people are born with an additional finger, while the fingers of others are too short, for example. Even whole bones can be missing, or joints do not exist and bone elements are therefore fused together.

"While each individual of these disorders is rare, skeletal anomalies overall are the most common congenital malformations of all," Stefan Mundlos emphasizes. Together with his team, he is studying the molecular mechanisms that lead to congenital malformations of the skeleton.

In the last few years, Mundlos and his colleagues have been able to trace various hand malformations back to disfunctions in a molecular regulation cascade. Signal molecules called "bone morphogenetic proteins" (BMP) play a significant role in this. If certain BMP effects are diminished or augmented, the result can be shortness of fingers or fusing of finger bones.

Relief for Comminuted Fractures

Such molecular genetic insights allow not only a better understanding of congenital malformations, but could also be helpful in the treatment of complicated bone fractures. BMPs are already used to stimulate bone healing in the case of comminuted fractures. This could be made significantly more effective if tailored drug molecules were developed that could intervene more directly in the underlying signal cascades, Mundlos argues.

In fact, many processes of embryonic skeletal formation and the regeneration of bones in adults progress very similarly. This might even apply to widespread diseases such as osteoporosis or arthrosis, which belong to the most common ailments of the elderly. Mundlos and his colleagues

are studying genetically related forms of osteoporosis, which, in very rare cases, can lead to bone degradation already in newborn infants. By now, the scientists have already discovered several of the responsible genes. They hope their findings will yield in new approaches for osteoporosis therapy for the elderly.

Close Relationship between Research and Practice

The team working with Mundlos is cooperating closely with medical practitioners of the Charité - Universitätsmedizin Berlin. Mundlos heads the Institute of Medical Genetics of the Charité, where patients with genetic diseases and their families get support and genetic advice. Among other things, Charité experts perform an anticipatory (predictive) diagnostic investigation. This allows them to estimate, for example, the chances of another disorder a family with a handicapped child will be facing on their next pregnancy, or whether relatives of a cancer patient run the risk of the same affliction. For many people concerned, the answers are of existential importance for their future lives and family planning.

"With the new methods of genome analysis, our options for making predictions are increasing enormously," Mundlos emphasizes. "At the same time, however, the demand for advice is also rising." The direct cooperation between the Max Planck Institute for Molecular Genetics and the Charité-Universitätsmedizin Berlin provides optimal conditions for practical application of molecular genetic insights to the benefit of patients, says Mundlos. ●

Prof. Dr. Stefan Mundlos heads the research group Development and Disease.

In the Animal House

THE INSTITUTE'S LABORATORY ANIMALS ARE ITS GREATEST TREASURE. THEY MUST BE PROVIDED THE BEST POSSIBLE CONDITIONS AT ALL TIMES. A TOUR AMONG MICE

Ludger Hartmann has already been waiting. We have hardly reached the flat building nestling up against the hill behind the Max Planck Institute for Molecular Genetics in the milky winter light, when he opens the door upon the first ring. Hartmann gives quick explanations, handing out plastic shoe covers. Then we enter the brightly lit interior of the building.

More than 10,000 mice live here in ten different rooms. They are a closely guarded treasure.

"The animals' value can hardly be measured in dollars and cents," says Hartmann. He is responsible for their special care. Hartmann, who grew up in the country and has already brought one or two calves into the world, is now a veterinary specialist for laboratory animals and molecular biology, a distinctive figure who, together with his team, developed the recently built animal house into the state-of-the-art research animal facility it is today. As we enter, he explains the concept of the building, pointing at a floor plan: on one side of the brightly lit central corridor are laboratories, offices, tearooms and two large sculleries with their gleaming silver machines. Here, more than three thousand cages a week are emptied of old straw, cleaned and refilled. On the other side of the corridor is the animal area, screened off by sterilization airlocks. Around 250 genetically engineered mouse strains are among them, most of the mutants unique in the world. Soon, promises Hartmann, we will be entering the innermost section of the animal house.

There are not only mice at the Max Planck Institute for Molecular Genetics. Down in the animal house basement, for example, are thousands of zebrafish swimming in blue shimmering aquariums. Because their embryos grow rapidly and are translucent up until their larval stage, they are especially suitable for biological studies of development. Some research groups also work with fruit flies, worms or sea urchins bred in various other labs at the Institute. In the past, there were even sheep and rabbits kept in wooden sheds. They produced antiserums for protein research. The history of modern biology is equally a history of laboratory animals.

The mouse stands out among them for several reasons. Being a mammal, it is genetically very close to humans. It reproduces very rapidly. It can, like all rodents, live under very different conditions, and accordingly under laboratory conditions. All in all, the mouse is an ideal model for molecular genetic research – and is often indispensable as a laboratory animal. “Naturally, everyone reacts against the idea of animal testing, including me,” Hartmann points out, broaching the subject even before we get a chance to question him about it. He knows how delicate the matter is. But if we want to understand the genetic causes of cancer or heart disease, we simply could not do so without a suitable model organism, Hartmann adds. He now stands at the bookshelf in his office, which bears scientific works on the mouse, its diseases and its genetic manipulation.

The Institute’s animal house is one of the most advanced research animal facilities of its kind in Germany.

By making specific interventions in mouse embryos, for example, animal strains can be bred in which a certain gene is put out of action, or its function is modified. The consequences of such mutations can then be systematically studied in the transgenic mouse strains. On a very small minority of animals, this may be done by taking blood samples or performing surgeries under anaesthetic, for example.

Of course, government animal protection authorities prescribe explicit requirements for such experiments, emphasizes Hartmann. In Berlin, a separate, special application must be submitted before every animal test. This application must not only explain what insights are expected to be gained from the experiment, but also whether the animals could suffer and how this can be prevented or at least minimized. The general living conditions of the mice, such as the size of their cages, are also regulated by law.

The welfare of the animals is, at any rate, one of the fundamental prerequisites for a molecular genetic research laboratory, of which the experts are well aware. It can take an entire year to establish a

"The animals' value can hardly be measured in dollars and cents": Ludger Hartmann, head of the animal facility, is a specialized veterinarian for laboratory animal science and molecular biologist.

transgenic mouse strain, for example, and it would be a disaster if they were to subsequently perish in the animal house.

Just as importantly: scientific experiments have little to no significance if the lab animals live under bad conditions. Infectious diseases, stress or even temperature fluctuations can change organ functions and the behaviour of the animals, and distort the test results.

The whole point of the animal facility is to avoid precisely that – and to ensure standardized keeping conditions for all mice. The air humidity, for example, must be kept at a constant 50 to 60 percent by regulated vapour generators. It is known that animals feel best at these humidities. A light-regulating computer makes sure the inside of the house follows the normal day-night cycle, without which the mice would not mate. Dreaded rodent germs such as hepatitis viruses, salmonella and even gastrointestinal worms are fended off by a whole barrage of measures protecting the animal colonies. The damage caused by an epidemic in the animal house would be immeasurable.

A sophisticated ventilation system maintains a constant positive pressure inside the room. That way, no pathogen-carrying air currents can penetrate from outside. Every animal cage also has its

The researchers must have model organisms if they are to research the genetic causes of cancer or heart disease, for example. These are frequently mice or zebrafish.

Like a surgical operating theatre, the domain of the 10,000 mice is a technologically controlled site.

own ventilation, which would prevent an infection from jumping from one box to the next. All objects that make it into the animal premises – food and straw for the animals, laboratory equipment, laptops, pens – are sterilized beforehand with steam or hydrogen peroxide. Like a surgical operating theatre, the animals' domain is a technologically controlled site.

From the brightly lit foyer of the animal facility, one has to take the small side door to the personnel airlock to get inside. Green, sterile protective clothing is ready and waiting. Through the airlock and a few steps to the right, we meet Maria Pohle. Her dark eyebrows stand out against the white mask pulled over her mouth and nose. Pohle is just lifting one mouse after the other into clean cages, gripping the dark brown rodents by the base of the shiny, pink tail, their insensitive part.

Maria Pohle is 25, animal caretaker, and maintains one of the ten mouse rooms here in the animal house. More than 500 special cages rest in high shelves, most with two to three occupants. A quiet chattering can be heard.

"When I come into the room in the morning, I can tell the mice are awake," describes Pohle. In the course of the day, however, the nocturnal rodents settle down and become quieter. The soft music that plays from radios in all animal rooms serves mainly to habituate the mice to a certain degree of background noise, says Pohle. Otherwise, they would be too frightened by the caretakers' actions.

Every day, Pohle checks on the welfare of the mice, looks for newborn offspring, cleans the cages and distributes water and food. Some strains are sensitive and require special food; others are characterized by sluggishness; others still are wild and jump half a metre high if one does not open their cage calmly and gently. Yet Pohle would generally not recognize the animals individually. There are simply too many.

In any case, the mice here look entirely normal. While there may, for example, be a genetically engineered strain with excess toes – serving the research into congenital skeletal malformations in humans –, most transgenic animals, like the unmanipulated, so-called wild type strains that are also bred here, are inconspicuous in their outward appearance, and can only be distinguished by their ear marks and coloured cards on the cages. These identify the sex, date of birth and ID number of the parents, and also carry codes such

as “C5” – which indicates a modification on chromosome 5. The details are meticulously stored in a mouse management software program with which the scientists can manage and check on the animals online.

As one approaches the mouse cages, they scurry to the back. “Mice are flight animals,” says Pohle. Their behaviour is basically predictable. The animals start to realize their biological programs, as soon as the right stimulus comes along. Mating behaviour, for example, is determined to a high degree by chemical cues, so-called pheromones, in the urine and even in the tear fluid of the male.

Every afternoon, Maria Pohle and her colleagues bring together certain males and females. The next morning, the female animals are examined for the typical mucous plug in the vaginal opening that forms in mice after copulation. This way, the success of the pairing and the age of the developing embryos can be supervised. Some embryos are taken from the womb before birth at a specific stage for developmental genetic studies.

The afternoon pairings with subsequent pregnancies, however, are only the standard model of propagation in the animal facility. “In some cases, the offspring are carried by surrogate mothers,” comments Ludger Hartmann, who had waited at the entrance to the animal section, and now points to two microscopes in a small room. Here, foreign embryos can be introduced into female mice.

Animal caretaker Maria Pohle looks after one of the ten mouse rooms. Two to three occupants reside in each of the over 500 special cages.

Several thousand zebrafish live in aquariums in the animal house basement. Because their embryos grow rapidly and are translucent up until their larval stage, they are highly suitable for studies of development.

This method is imperative in particular when researchers wish to work with transgenic strains from other research teams. Some mice came in from Stanford University a couple of days ago, and next week we are expecting animals from Hong Kong and Singapore, Hartmann tells us. The foreign mice will not be simply integrated into the animal facility – there is too great a risk of introducing an infection. Instead, they are first kept and paired in quarantine, much like when breeding in agriculture, Hartmann explains. Next, they remove the embryos and implant them in the oviducts of especially well-growing females from their own house. This intervention is done under anaesthetic. Any stress for the mouse could complicate the pregnancy.

These days, Hartmann reports, many teams have stopped sending live animals, and started directly sending frozen embryos instead. A laboratory network funded by the EU – the European Mouse Mutant Archive– even preserves the sperm and embryos of important mouse mutants systematically, in order to facilitate the exchange of transgenic strains within the international research community. Likewise, Hartmann and his colleagues have already stored the sperm or embryos of around one hundred of their 250 transgenic strains in liquid nitrogen. This deep-frozen material is, so to say, a backup of the valuable animals, says Hartmann.

We are quickly ushered from the embryo transfer room. The tour stops here. Back at the personnel airlock, Ludger Hartmann lastly explains where the protective clothing can be returned to; a handshake, and moments later, we are back on the other side of the airlock.

With a gentle click, the door to the innermost sanction of the animal facility falls shut, and we step out into the milky light of the winter afternoon. ●


Albino
* 26.08.08
neue Stufe: 22.09
-"- : 24.10.08
Aquarium: 3.12.08
aus Becken # 2/5
* 26.08.08
aus Becken
5/2
* 26.08.08 Alb.

Genetic Causes of Mental Retardation

Hans-Hilger Ropers and his colleagues are investigating why cognitive defects occur

The development of the human brain is regarded as a mystery par excellence. But what is responsible when it is impaired? About 0.4 to 0.5 percent of the population in Western industrialized countries – in Germany around 400,000 people – have an IQ below 50, and are considered severely mentally retarded. Most of these cases have a genetic cause.

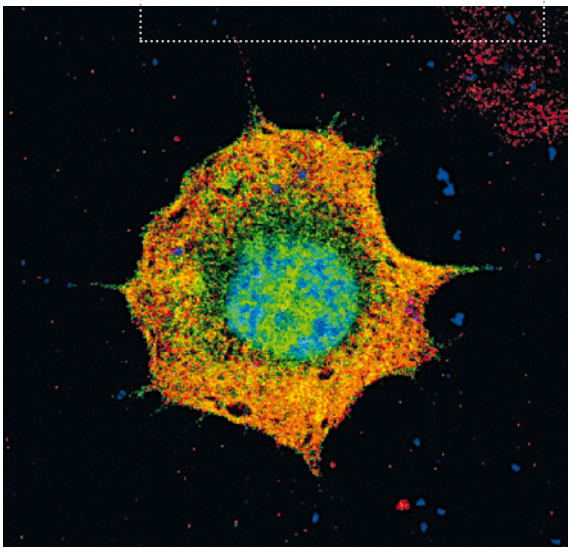
"Mental retardation is one of the biggest unsolved problems in medical care," stresses Hans-Hilger Ropers. He heads the Human Molecular Genetics Department, which is one of the leading groups working on cognitive disorders worldwide. "We have only just begun to understand the molecular basis of intelligence disorders since the middle of the nineteen nineties," says Ropers.

Boys Have It Worse

One starting point for their research was the long known fact that boys are more frequently mentally impaired than girls are. This difference could in part be explained by a higher general susceptibility of male foetuses and newborns. But there is also an obvious genetic cause. Girls have two X chromosomes, whereas boys have only one – so any damage to this chromosome cannot be compensated for and will more often lead to a disorder in boys.

There are in fact more than 80 X chromosomal genes known to date that could cause mental retardation, Ropers reports. He and his colleagues were directly involved in the discovery of 31 of these genes. In total, there are probably up to 200 genes residing on the X chromosome that are associated with impaired intelligence, scientists estimate. There could even be over 1,000 more disease genes on the remaining chromosomes, which have only very recently been studied intensively for any correlation with cognitive disorders. Even a single defect among these genes can lead to a serious intelligence deficit.

View inside a nerve cell: the exact position of polyglutamine-binding protein 1 (PQBP1) in the cell can be detected by coupling a green fluorescent dye to it.



"The brain is dependent on the proper function of thousands of genes": Prof. Dr. H.-Hilger Ropers, Director of the Human Molecular Genetics Department.

There is a simple reason as to why so many different mutations can lead to mental retardation: the brain, one of the most complex organs, is dependent on the proper function of thousands of gene sequences. In particular, dysfunctions that negatively affect the fine structure of the neuronal contact points (synapses) could cause mental retardation. Cruder anatomical anomalies, on the other hand, are the exception.

Drugs Against Intelligence Deficits

In order to explain the causes of intelligence deficits, Ropers and colleagues are working closely with numerous European teams as well as with scientists from Iran, India and Pakistan. The families are significantly larger there, and consanguineous marriages much more frequent than in western countries. Certain hereditary impairments therefore occur more often, which makes searching for the genetic causes easier.

One of the aims is to find preferably all genetic defects that could lead to mental retardation, says Ropers. That way, better genetic advice could be given to the families concerned. One key to this are the new sequencing technologies used within the scope of a large-scale project funded by federal means for the systematic search for mutations in these families. Thanks to the novel methods, a universal diagnostic test for all candidate genetic mutations will be available in just a few years.

Furthermore, deciphering the function of these genes could also provide new options for therapy, Ropers adds. In animal studies, it has already been tested whether brain function can be normalized in case of fragile X syndrome, one of the most common forms of congenital mental retardation. Ropers considers it highly probable that at least some cognitive disorders will be able to be alleviated with drugs in future. ●

Gene Hunting

MENTAL RETARDATION CAN RESULT FROM HUNDREDS OF DIFFERENT GENE DEFECTS. PINNING THEM DOWN IS A HERCULEAN TASK. LOGBOOK OF A HUNT FOR GENETIC CLUES

There is one day in the spring of 2006 that Vera Kalscheuer will probably never forget. The molecular biologist had flown to Maastricht at seven in the morning, where her Dutch colleague was already waiting with coffee and rolls. The researchers then drove out to the patient family: the two sick brothers, the healthy brother and the healthy sister.

They were to discuss their genetic heritage that day.

"The encounter made a formidable impression on me," Kalscheuer recalls. She is a slim woman of 50, with dark hair and sports shoes. At her office in the Human Molecular Genetics Department of the Institute, she sits in a blue swivel chair holding the open folder containing the history of the Dutch patients. The details of the visit come back to her vividly as she talks. Back then, the biographical, human dimension of her molecular genetic research was fully appreciable and undisguised.

Over several generations, the Dutch family had inherited a genetic defect that leads to mental retardation. Kalscheuer's team had to pin it down. Professionals refer to such a search through the genome for the precise cause of a disease as "gene hunting". This can be a tedious search for a needle in a haystack – or a surprising story of discovery.

With a research group of ten, Institute Director Hans-Hilger Ropers and his co-worker Vera Kalscheuer picked up the trail. From pedigree analyses of families with affected children, it was already known that a certain type of mental retardation affects only boys. It was an obvious conclusion that this involved a mutation on the X chromosome. This is because girls have two X chromosomes while boys have only one. As a result, damages cannot be compensated for in boys, so disorders are more likely to develop.

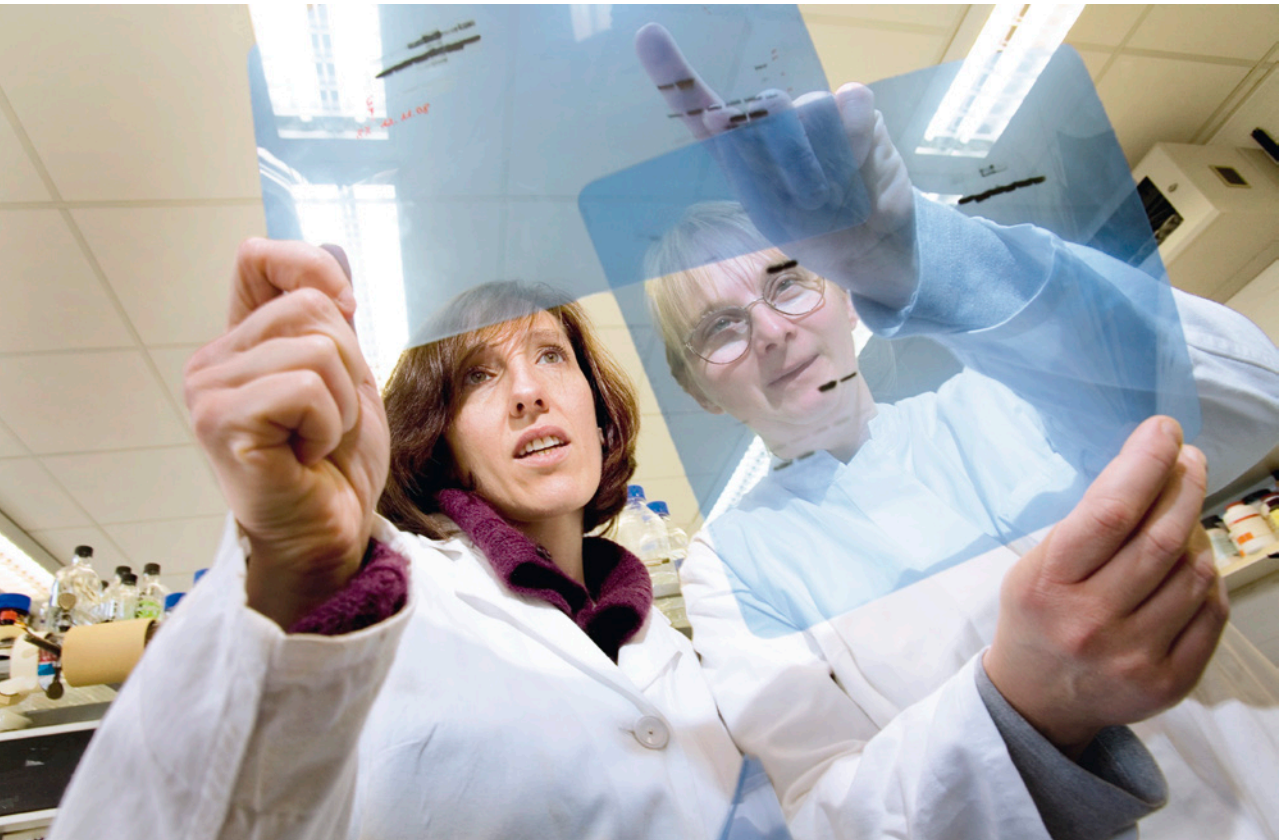
Over several generations, a genetic defect had been passed on in the family that leads to mental retardation. This genetic heritage had to be researched.

Presently, it is assumed that hundreds, or probably even more than a thousand, different genes in the entire genome can impair the development of the brain, and thereby result in congenital mental retardation. There are probably somewhere around 200 such genes residing on the X chromosome; more than 80 have already been discovered in the last few years.

Anyone who goes from Kalscheuer's office into the neighbouring laboratory will be given a good idea of the persistence this search requires. In the large room, bright neon lamps hum on the ceiling. Littering the lab benches are pipette holders and countless bottles with all kinds of chemical buffer solutions.

"We also had a lot of luck, of course," Kalscheuer admits. It took the researchers nearly a year to compare the DNA extracted from blood samples of affected families, to pinpoint suspicious sections on the X chromosome, and then to decode the exact genetic mutations. Finally, they found mutations of the same gene on the short arm of the X chromosome in all affected members of five patient families. One of these families was the clan from the Netherlands.

"Look," says Kalscheuer, pointing to a densely printed poster in the corridor outside her office, which summarizes the former research



It took nearly a year for the researchers to circle suspicious segments on the X chromosome: Luciana Musante and Astrid Grimme with the results of a Western blot, a frequently used biochemical analysis method.

results in numbers and graphs. There are in fact various types of mutation in the gene in question, called PQBP1, explains Kalscheuer. In some cases, certain DNA components were lacking, in others they were inserted in surplus. Depending on the kind of change, the consequences ranged from merely a slight impairment to severe retardation with additional cardiac defects. Other genes would also apparently modify the effects of a PQBP1 defect, the researcher adds. Even two people with an absolutely identical mutation would therefore not necessarily suffer from the same limitations.

The older sick brother was already over 50 when Kalscheuer and her colleague visited him. He had long been living together with his younger brother in a home for the handicapped near Maastricht. A couple of years ago, he had still played football with friends, "but I'm not so fit now," he said, smiling a little impishly.

Kalscheuer, who speaks Dutch, was able to ask questions, and to stand up to the family's questioning, too. While both brothers had difficulty articulating, they were capable of having a simple conversation – and were also happy for the many visits, relates Kalscheuer. "It was basically like a kind of family reunion." The healthy brother of the two took the opportunity for a family visit, as did the healthy sister, who promptly riddled Kalscheuer with questions. Could it be

"I could do research on any gene or protein – but this is about the destinies of individual patients": group leader Vera Kalscheuer.

The cause of the impairment was ultimately found to be an unusual sequence segment (shown here in red) in the PQBP1 gene on the short arm of the X chromosome.

that she had also inherited the damaged X chromosome from her mother, and passed it on to her now adult daughter? Would she in turn have handicapped children? And should she be tested for that gene mutation?

The chances of a newborn boy being handicapped are fifty/fifty if the mother carries the defect on one of her X chromosomes. "I personally would always want to know," says Kalscheuer. In fact, most families positively welcomed the opportunity for a definite diagnosis. Yet Kalscheuer also understands when people prefer not to know, and refuse the gene test.

Meanwhile, the team at the Max Planck Institute is already investigating exactly what biochemical consequences a PQBP1 mutation has in the brain cells. One hypothesis is that the function of the nerve contact points, the synapses, is impaired, reports Kalscheuer. "The most tantalizing question is of course: will there be a therapy?" The old dogma that mental deficiencies, due to only the finest changes in nerve cells, are not treatable per se, is long regarded obsolete. Meanwhile, animal studies have demonstrated that the Fragile X syndrome for example – one of the most common forms of congenital mental retardation – can be attenuated by MPEP, a substance that works in the brain. Since the syndrome has definite parallels to the PQBP1 defects at a molecular level, it is quite possible that new drugs could be developed against the latter as well, stresses Kalscheuer.

Research into genetic causes of diseases can be a tedious search for a needle in a haystack – or a surprising story of discovery.

The possibility of creating entirely new prospects for treatment through molecular biology has always fascinated her, Kalscheuer adds. "I could of course do research on any gene or protein, or anything – but this is about the destinies of individual patients, the mental development of children." While talking, she has closed the folder with the history of the Dutch brothers again. No, says Vera Kalscheuer still with the same meditative smile, she has no children of her own; the good lord did not permit, so to speak. Then she stands up to bid farewell: a woman who is a researcher in heart and soul. That is what drives her work. ●

TGCCTCCTGAGCGTAGTCCAGTTACTTTCAGGCTCGGGGAGTG
AAGGCCTCGTTGAGAGAAGGTCTCATTCGGTGTTTTGGGAAGA
GAGTCGTGTGGGCCCAGGTATCGTAGCGGCGACACGAGAGA
GACGGGCGGTGTGACAGCCTTCCACTACCTGCAC
GAGTGTATTGGTAACGTTGGGGTCTGTCTGCTATCAGCTATGCCG
CTGCCCGTTGCGCTGCAGACCCGCTTGGCCAAGAGAGGCATCCT
CAAACATCTGGAGCCTGAACCAGAGGAAGAGATCATTGCCGAG
GACTATGACGATGATCCTGTGGACTACGAGGCCACCAGGTTG
GAGGGCCTACCACCAAGCTGGTACAAGGTGTTCGACCCTTCCTG
CGGGCTCCCTTACTACTGGAATGCAGACACAGACCTTGTATCCTGG
CTCTCCCCACATGACCCCAACTCCGTGGTTACCAAATCGGCCAAG
AAGCTCAGAAGCAGTAATGCAGATGCTGAAGAAAAGTTGGACCG
GAGCCATGACAAGTCGGACAGGGGCCATGACAAGTCGGACCG
CAGCCATGAGAAACTAGACAGGGGCCACGACAAGTCAGAC
CGGGGCCACGACAAGTCTGACAGGGATCGAGAGCGTGGCTATGA
CAAGGTAGACAGAGAGAGAGAGCGAGACAGGGAACGGGATCGG
GACCGCGGGTATGACAAGGCAGACCGGGAAGAGGGCAAAG
AACGGCGCCACCATCGCCGGGAGGAGCTGGCTCCCTATCCCAA
GAGCAAGAAGGCAGTAAGCCGAAAGGATGAAGAGT
TAGACCCCATGGACCCTAGCTCATACTCAGACGCCCCCGGGG
CACGTGGTCAACAGGACTCCCCAAGCGGAATGAGGCCAA
GACTGGCGCTGACACCACAGCAGCTGGGCCCCTCTTCCAGCAG
CGGCCGTATCCATCCCCAGGGGCTGTGCTCCGGGCCAATGCA
GAGGCCTCCCGAACCAAGCAGCAGGATTGAAGCTTCGG
CCTCCCTGGCCCTGGGTTAAAATAAAAGCTTTCTGGTGATCCTG
CCCACCAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

The Institute's Junior Researchers

Four junior researchers with independent workgroups are investigating the effects of nutrients on gene activity, the structure and interplay of proteins and the causes of degenerative diseases in the brain

Scientific discussions all over the place: everyday scene from the Institute.

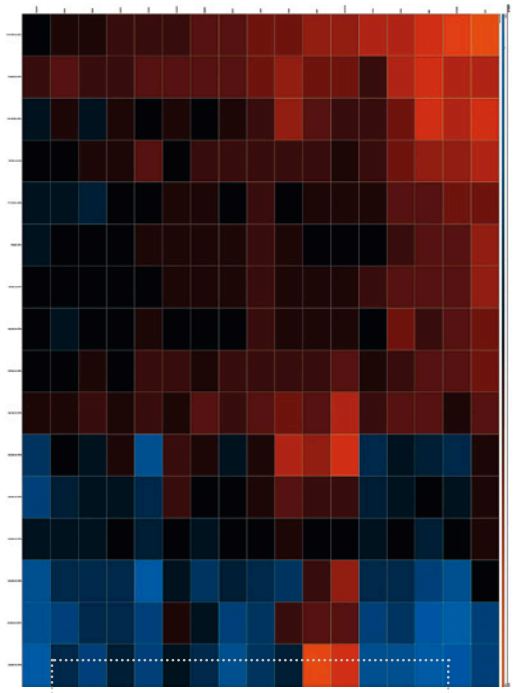
They are a trademark of many Max Planck Institutes: the independent junior research groups. Equipped with their own budget, highly talented young scientists can pursue a research topic over several years with their own teams, and simultaneously build up their research career. The position of a junior research group leader is analogous to that of a junior professor at university. In total, there are four junior research groups at the Max Planck Institute for Molecular Genetics.

The Influence of Diet on Genes

What effects do natural products, and in particular nutrients, have on genes? This is the question that Sascha Sauer's group intends to explain. His junior research group Nutrigenomics and Gene Regulation is investigating whether – and how – natural products can influence gene activity. One of their main interests is the fundamental analysis of genetic regulation of metabolic processes. "After all, it is about finding out which compounds or potential food additives could be useful for preventing diseases," explains the biochemist. To find this out, some ten thousand naturally occurring substances are being tested whether they bind to so-called transcription factors in body cells. These molecules can directly activate genes. A transcription factor known as PPARγ, for example, causes certain genes for glucose metabolism and transport to be switched on in fat cells. In fact, the diabetes drug Rosiglitazone activates PPARγ very efficiently and thereby normalizes the blood sugar level. Yet the drug also has undesirable side effects such as weight gain.

Now, Sauer's team has identified a number of effective edible substances from certain, sometimes exotic, plants. They could be a more compatible alternative for treating metabolic disorders, and for regulating blood sugar. The team is currently studying whether the herbal substances

also interfere with other genetic signal cascades and metabolic pathways. Through such analyses, Sauer and colleagues want to create molecular genetic expression profiles for potential nutrients, which could be suitable for preventing and treating metabolic disorders.



Genetic expression pattern: certain nutrients can turn specific genes on or off.

Dr. Sascha Sauer heads the junior research group Nutrigenomics and Gene Regulation.

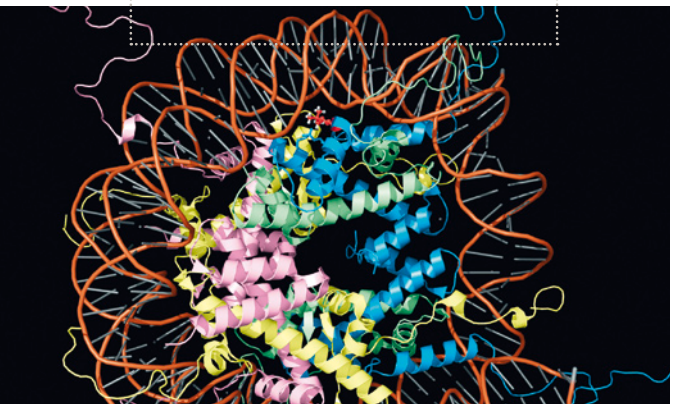
Dr. Michael Lappe heads the junior research group Bioinformatics /Structural Proteomics.

The 3D Structure of Proteins

Bioinformatician Michael Lappe is pursuing a different research goal. He heads the junior research group Bioinformatics/Structural Proteomics, currently investigating the 3D structure of proteins.

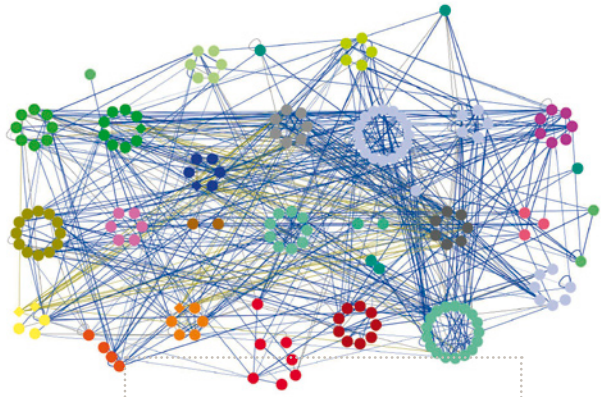
In principle, proteins are different length chains of various amino acids strung together like pearls on a string. Their exact sequence is encoded in genes. The tricky question, however, is how does a three-dimensional, biologically functional protein arise from a linear chain of amino acids? "We know that the chain usually folds up in a matter of seconds," explains Lappe. But until now, there have only been few cases in which the exact 3D structure has been predicted from scratch on the computer.

Computer simulations are an important tool for deciphering the spatial structure of proteins.



In order to solve this "folding problem", Lappe and his team first analyzed already known protein structures. What emerged were typical contact patterns of which amino acids interact particularly often with other components of the chain, and thereby form the specific structure of the protein molecule. From this information, the researchers developed a clever computer process by which, at its present stage, the fully folded form of any amino acid sequence can be modelled on screen.

Since the majority of structures of human proteins – of which there are probably more than a hundred thousand – are still undeciphered to date, the procedure is of great importance. Such computer models form the basis for the design of tailored drugs that attach specifically to certain protein structures, says Lappe. Furthermore, the 3D data can help to understand many biological processes that are based on spatial protein-protein interactions.



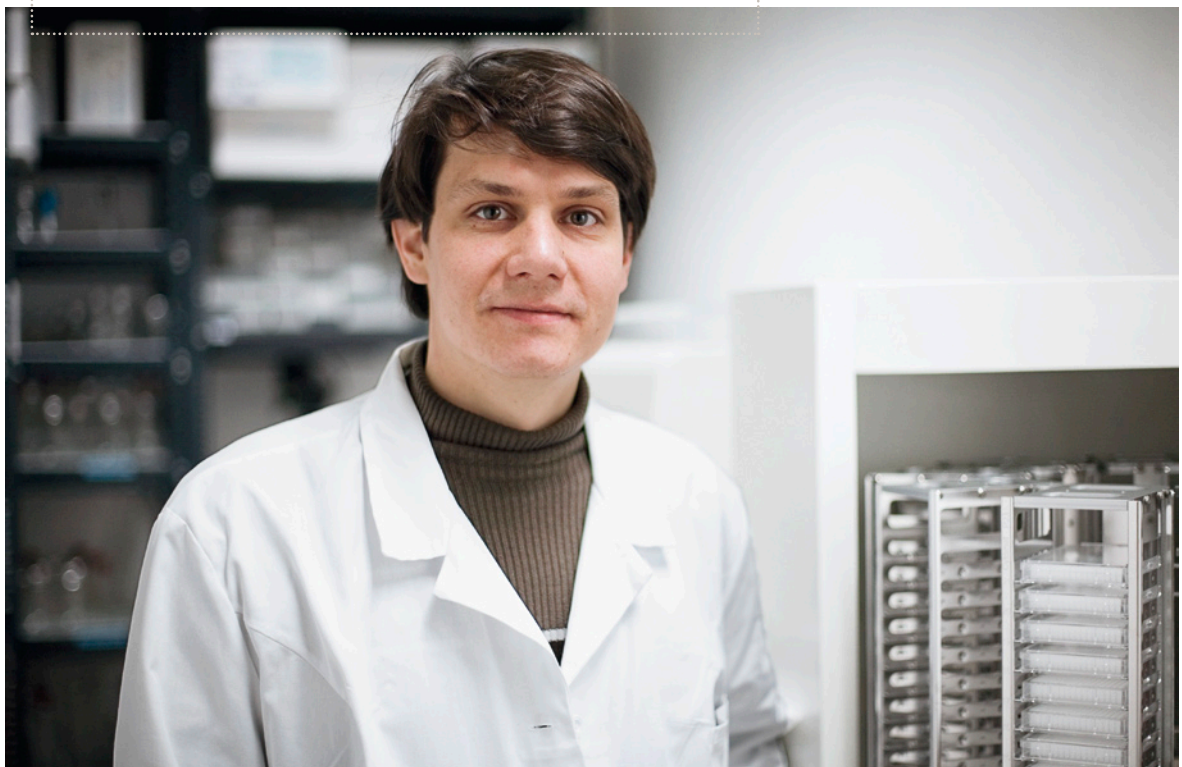
Complex interactions between proteins can be analyzed using graphical network maps.

In the Web of Proteins

Ulrich Stelzl is working in the same field, but he is primarily concerned with experimental laboratory methods. His junior research group Molecular Interaction Networks intends to find out how the many human proteins come into contact and communicate with one another inside the cell.

This is tested on thousands of genetically modified yeast cells that each carries a gene for a specific human protein. As two cells merge, special detection methods can determine whether the two human proteins couple together. “Using this method, we can distinguish 100,000 to 200,000 potential interactions,” emphasizes Stelzl. It was not long ago that such an order of magnitude was still unfeasible. In fact, the analysis of protein networks allows a considerably greater understanding of many biological processes and disease mechanisms, stresses the scientist. These protein interactions make it easier to understand how the programme of a cancer cell changes, for example, which could improve early disease recognition. Another example are studies of the protein huntingtin. Huntington’s disease in humans (“St. Vitus’s dance”) is a condition in which characteristic, probably toxic deposits form in certain regions of the brain. As network analyses now suggest, this process accelerates due to the interactions between huntingtin and other previously unsuspected interaction partners. These interactions still need to be investigated more closely, but it is conceivable that knowledge of these protein interactions will present entirely new options for intervening in the disease process.

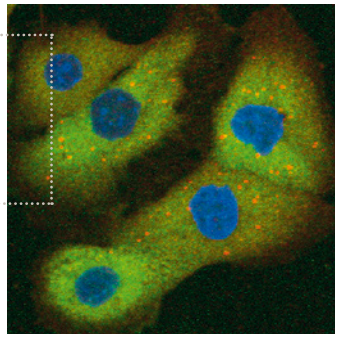
Dr. Ulrich Stelzl is head of the junior research group Molecular Interaction Networks.

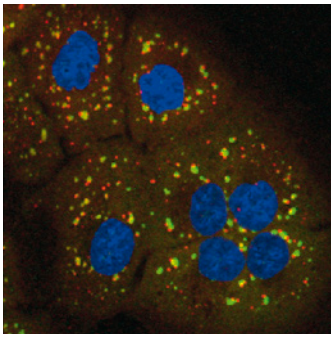


Dr. Sylvia Krobitsch heads the junior research group Neurodegenerative Disorders.

Degenerative Processes in the Brain

Sylvia Krobitsch's research points in a very similar direction. The biologist heads the junior research group "Neurodegenerative Disorders". These are diseases that lead to a continuous loss of certain nerve cells. They include Alzheimer's and Parkinson's disease, as well as Huntington's disease and the so-called spinocerebellar ataxias (SCA), which are associated with movement defects. "We are trying to identify common molecular mechanisms for these diseases," Krobitsch says.





Ataxin-2 (green) is highlighted with special dyes. Under stress conditions, the cells form tiny granules, in which the protein is localized.

She and her colleagues are concentrating especially on SCA type 2, in which a protein called ataxin-2 is implicated. The protein is a component of tiny, granular cell structures known in technical jargon as "stress granules". They serve as a protective mechanism of cells against various stresses.

What makes it especially interesting is that ataxin-2 also seems to play a part in other SCA types and in Huntington's disease. Apparently, some neurodegenerative disease processes could overlap at the molecular level, explains Krobitsch. She hopes that related treatment strategies against the degenerative diseases will be derived from this knowledge in the future. ●

People from all around the world are brought together in the lab by a common interest.

Computer Models of Genetic Regulation

The researchers working with Martin Vingron are using computational molecular biological methods to study how genes are switched on and off

An important amount of molecular biological research takes place at the desk and on computers for quite some time: Work scene from the research department.

Even now that the entire human genome has been sequenced, the crucial question remains: How are genes regulated? Every cell in the body has all of the 25,000 or so genes, but only some of these genes are ever active in each cell. Different genetic information is required in the brain than in the liver, for example, and many of the gene sequences that are switched on in the two-week old embryo are already silenced again in the newborn child.

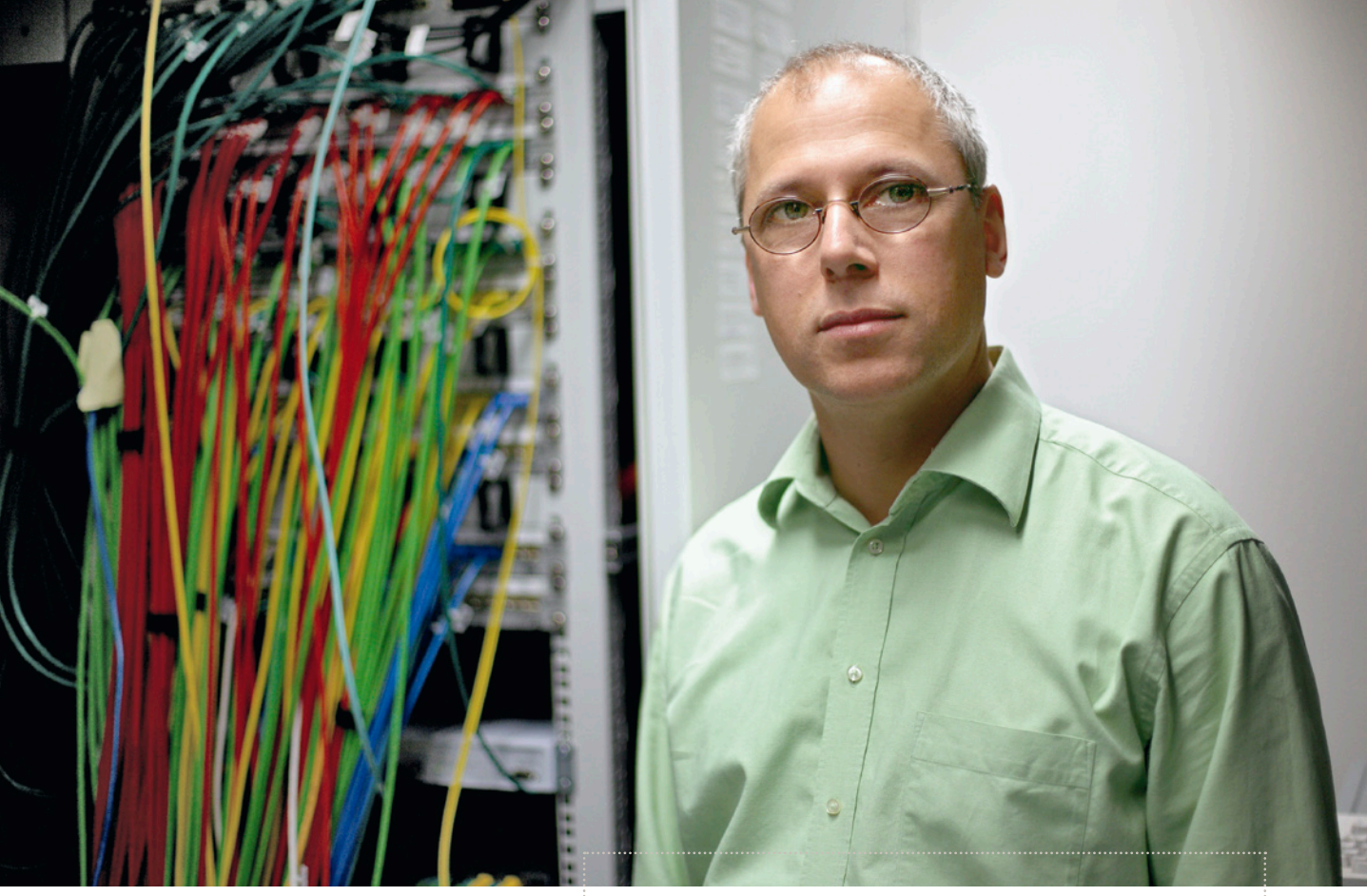
"The regulation of genes is one of the most exciting fields of research at present," states Martin Vingron, head of the Computational Molecular Biology Department. His group is using computer analyses to study those only fragmentarily understood mechanisms by which genes are switched on and off. It is about the "command structure of the genome" as the mathematician says.

Crunch Question: Who is Controlling Whom?

Vingron and his colleagues are directing their attention mainly to so-called transcription factors. These special control molecules dock onto the starting point of a gene, and can thereby initiate or stop the genetic reading process (transcription). During transcription, the genetic information is copied from the DNA into a molecular transcript, called RNA. Cells then build specific proteins from the RNA. In this way, transcription factors directly influence protein metabolism – and with it the biological function – of all kinds of body cells.

What makes the matter especially interesting is that many transcription factors can bind not only to one single binding site in the DNA, but also to several binding sites. They can also be involved in regulating several genes. Conversely, it appears that one and the same gene is sometimes controlled by numerous factors.

These interactions lead to decidedly complex regulation networks – and this is where computational molecular biology comes into play. Vingron

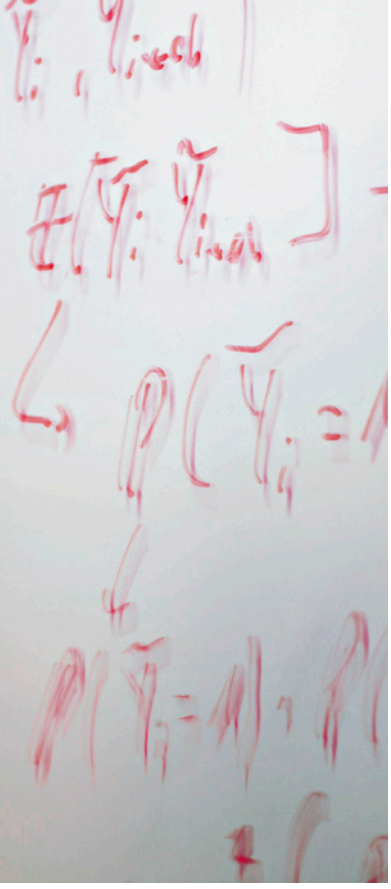


"The regulation of genes is one of the most exciting fields of research": Prof. Dr. Martin Vingron, Head of the Computational Molecular Biology Department.

and his colleagues, for example, have developed special computer programs with which the entire human genome, with its three billion or so DNA components, can be searched through from comprehensive databases for unknown binding sites. And, vice versa, the researchers can use mathematical models to predict what control molecules will most probably occupy known binding sites. The scientists intend to use such analyses, for example, to gain a better understanding of the faulty genetic regulations involved in complex congenital cardiac defects.

Game of Options: Hungry or Satiated?

One principal advantage of virtual methods is that they can even exploit areas that are inaccessible in lab experiments. The millions of years of evolution of molecular structures, for example, can hardly be traced in the laboratory, but they can very well be modelled with bioinformatic methods, explains Vingron. For the most part, however, computer and laboratory methods have complemented each other in genetic research. One example are the group's investigations about the different regulatory networks that are switched on in well fed and in starving yeast cells. "With computer models, we can capture the different regulatory options that well fed and hungry cells have," says Vingron. The hypotheses derived from this can in turn be verified in the lab.



Researchers of the Heart

CONGENITAL CARDIAC DEFECTS ARE SOME OF THE MOST COMMONLY OCCURRING MALFORMATIONS – AND ARE PROBABLY DUE TO A DISRUPTED GENETIC FINE TUNING IN THE EMBRYO. WITH COMPUTATIONAL ANALYSES OF THEIR GENETIC CAUSES, IT MAY EVEN BE POSSIBLE SOME DAY TO CULTIVATE HEALTHY HEART TISSUE.

Silke Sperling is 37 and is the woman for affairs of the heart at the Max Planck Institute for Molecular Genetics. This is not on account of Lola-Sophie, her beautiful baby, who Sperling at times brings to work with her. No, it's because the young researcher is interested in the innermost workings of the organ. She says: "You have to understand the heart at a molecular level." If so, then there is a good chance that sick hearts will one day be able to be healed.

Tuesday, 11:30 AM. Sperling has given us some of her time to talk. In her office are a couple of bookshelves, a desk with a silvery laptop, and a blackboard with a postcard stuck on it, from a friend perhaps. It reads: "Films that go to the heart".

Sperling has always been fascinated by the heart. Already on the twenty third day of pregnancy, it begins to beat inside the embryo; it is the first functioning organ. To begin with, it resembles a rhythmically pulsating tube, which is later tied into a bow, and finally becomes a refined system with four hollow chambers – the two atria and the two ventricles. It is a miracle-like transformation process.

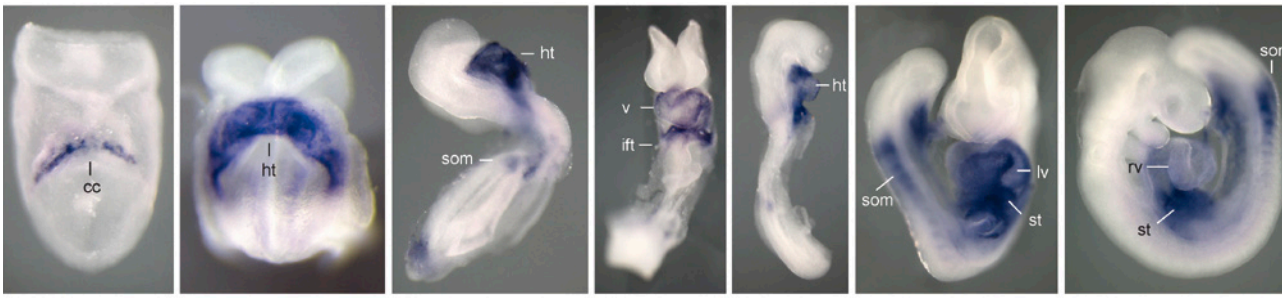
And it can go wrong. After all, one out of every hundred babies born on earth has a cardiac defect, says Sperling. The spectrum ranges from small holes in the cardiac septum to complex malformations such as the so-called tetralogy of Fallot (TOF), in which the entire heart anatomy is basically disarranged and, unlike in normal circumstances, both ventricles pump blood into the body's arteries.

“You have to understand the heart at a molecular level”: Workgroup head Silke Sperling, pictured with her baby in the Institute’s library.

With an operation at an early childhood age, most patients can lead a largely normal life, says Sperling. The question is, however: due to what genetic modifications do the malformations arise in the first place? And how does the heart manage to adapt, at least for a certain length of time, to the tasks it was not at all intended to do? Only in a minority of cases can cardiac defects be explained by a single gene mutation, Sperling stresses. Her hypothesis is rather that they are due to an interplay of very different genes – the fine tuning in the molecular networks, as she describes it.

"To date, we still can't understand the full complexity," admits Sperling. But, of course, that is precisely her goal. Born in Saxony, Germany, when she came to Berlin in 1989 – "I was 18 and stood on the wall as it fell" – the way was cleared for a medical study in the western part of the city, then later study and research in the USA, and then a job at the Deutsches Herzzentrum Berlin (German Heart Institute Berlin). Finally, she moved to the Max Planck Institute for Molecular Genetics, where she and her group began to analyze tissue samples from children with cardiac defects. The first step in the analysis of far more than a hundred malformed hearts was to determine the activity of the thousands of genes of each in the lab. They

"The analysis of millions of data is no trifle": Bioinformatician Utz Pape.



Series of mouse embryos: The blue staining marks the activity of the control molecule DPF3 in the developing heart region.

essentially had to contemplate the entire genetic kaleidoscope – and to find those flaws that occasionally steer the development of the embryonic heart in the wrong direction.

In short: They had to analyze millions of data. "That's no trifle," comments Utz Pape, a smart man of 28 who has just come back from lunch, and has made himself comfortable in the department library's black leather sofa. And he is fully entitled to, for he just recently completed his doctorate in bioinformatics with top marks. Pape was one of the first participants in a highly prestigious PhD programme for young bioinformaticians, the International Max Planck Research School for Computational Biology and Scientific Computing. The Max Planck Institute for Molecular Genetics together with the Freie Universität Berlin established this programme a few years ago. It has long been clear that molecular biological research could no longer cope with its giant sets of data without its own computational methods, let alone analyze them.

So it was with the Heart Project, too, on which Sperling's group is working together with scientists of the Computational Molecular Biology Department, and in which Pape was responsible for essential analytical steps. With the help of computer algorithms, the researchers discovered that a specific group of genes was excessively or insufficiently active in each different case of cardiac malformation. In a way, the changes in the heart's anatomy reflect characteristic genetic activity patterns. In the case of TOF, for example, it could be some hundreds of genes that together lead to the entangled condition of the heart.

The exiciting question is, then: how do you explain the fact that such a large number of genes apparently act together in a coordinated fashion in the onset of cardiac defects? One obvious hypothesis was that the genes concerned are controlled by the same so-called transcription factors. These control molecules can bind to specific sequences (binding sites) of the DNA – such as CCTAATATGG – and thus switch on a neighbouring gene. If several genes act as a functional network, then all of them would have to have the same binding sequences for control molecules located nearby.

The scientists followed up precisely this idea – and found what they were looking for. It turned out, for example, that four different transcription factors are of particular importance in the case of TOF: each one of them is involved in controlling hundreds of genes. That means, like molecular puppet masters, they hold together large parts of the genetic network that dominates the anatomy of the malformed heart.

"Naturally, we are particularly interested in these hotspots in the networks," comments Sperling. In the meantime, her group has identified another control molecule, called DPF3 in short, that is even involved in the regulation of some thousands of genes. Until now, Sperling says, it had been completely unknown that the DPF3 protein plays any part at all in cardiac defects. However, as experiments on zebrafish have since shown, normal heart development is blocked if DPF3 is missing entirely. Furthermore, heart cells of considerably weakened muscular strength are formed. Conversely, elevated concentrations of DPF3 lead to a strengthening of the heart muscle – a molecular mechanism by which the heart can apparently compensate for excess stress.

These very effects could in future be selectively imitated by novel drugs, Sperling speculates. This could very possibly facilitate the treatment of heart weaknesses. An even more audacious vision is that, thanks to the insights into heart development, entirely new heart tissue could be grown. Various research groups are already intensively pursuing the "tissue engineering" approach, which could deliver a kind of tissue plaster for people with heart defects, or even for countless infarct patients. The reproduction of heart tissue in the lab is still proving difficult. Yet, it is not unlikely that analysis of the genetic networks in the heart will well and truly advance this process. ●

An audacious vision for lab work: to understand the functioning of the organism in its full complexity.

Profile: The Max Planck Institute for Molecular Genetics

Employees

The Max Planck Institute for Molecular Genetics (MPIMG) has 463 employees, including 125 scientists and 96 PhD students. Foreign researchers make up 42 percent, and foreign PhD students 25 percent.

Funding and Third Party Funds

Since the mid nineties, the MPIMG has developed into the fifth largest institute of the Max Planck Society (MPG). The primary funding is from the means of the MPG, added to which are third party funds that nearly double the budget provided by the MPG. These funds, predominantly from the Federal Ministry of Education and Research, the European Union and the Deutsche Forschungsgemeinschaft, go exclusively into research work. They fund posts for researchers, technical employees and PhD students, as well as resources.

Support of Junior Scientists

The promotion of young, talented scientists is a central theme at the Max Planck Institute for Molecular Genetics. A large number of students finish their education by doing research at the Institute, where the scientists working here supervise bachelor, masters, diploma and doctoral theses. 96 PhD students are presently working at the Institute. In 2004, the MPIMG together with the Freie Universität Berlin established the International Max Planck Research School for Computational Biology and Scientific Computing. Since 2008, all PhD students at the Institute have also been able to participate in an in-house graduate programme. The Otto-Warburg Laboratory of the MPIMG offers young top scientists from Germany and abroad the opportunity to pursue their own research goals with their own workgroup (independent junior research group) over a long term.

Collaboration with Berlin Universities

The MPIMG collaborates closely with Berlin universities on many scientific projects. A director and a research group leader were appointed jointly with the Charité-Universitätsmedizin Berlin; the other directors hold honorary professorships at the Freie Universität Berlin. Scientists of the MPIMG are involved in university teaching, including the preclinical training of medical students, in the study courses of bioinformatics, biology, biochemistry and molecular medicine, at the Berlin-Brandenburg School for Regenerative Therapies and at the International Max Planck Research School for Computational Biology and Scientific Computing.

The Max Planck Society

The Max Planck Society (Max-Planck-Gesellschaft) for the Advancement of Science e.V. is an internationally leading scientific organization. It presently maintains 76 institutes and 3 additional research facilities in Germany. Three institutes and several branches are located abroad. Max Planck Institutes perform basic research in the interest of the general public in the sciences, the arts and the humanities, with the aim of concentrating focus onto excellent research in specific research fields. This complements the work done at universities and other research facilities. More information is provided at http://www.mpg.de. ●


PyMOL>

Imprint

ISSUER
Max Planck Institute for Molecular Genetics
Ihnestraße 63–73
14195 Berlin

T/F +49 (0)30-8413-0/1388
E-Mail: info@molgen.mpg.de
www.molgen.mpg.de

CONCEPTION AND COORDINATION
Dr. Patricia Marquardt, Dr. Giovanna Morelli, MPIMG

TEXT
Dr. Martin Lindner, Berlin

PHOTOGRAPHY
Edgar Zippel, Berlin
www.edgarzippel.de

SCIENTIFIC ILLUSTRATIONS
Max Planck Institute for Molecular Genetics

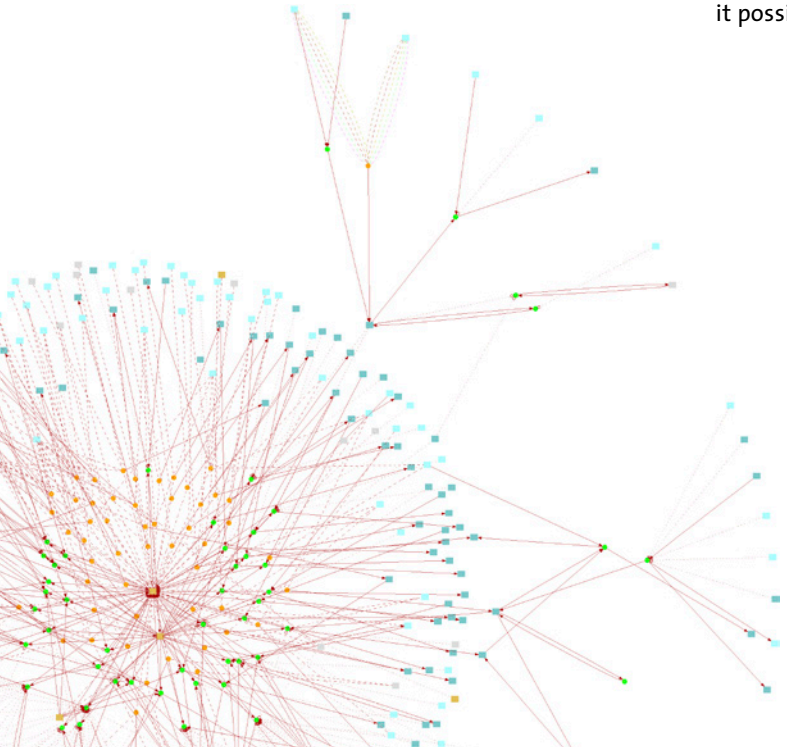
GRAPHIC DESIGN
Stephan Fiedler, Berlin
www.stephanfiedler.eu

COLOUR SEPARATION
Licht & Tiefe, Berlin

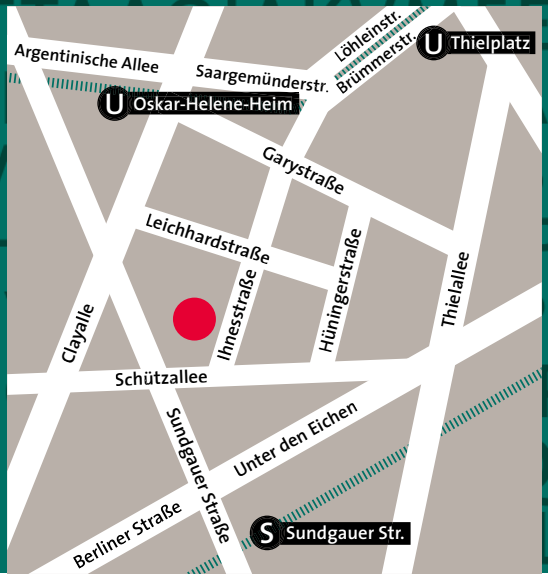
PRINT
Medialis Offsetdruck GmbH, Berlin

COPIES
3.000

Special thanks go to all employees who spared us a moment of their precious time, and have thus made it possible to complete this brochure.



Network of interacting cellular components made available in public databases. By consolidating many individual pieces of information, models are created that allow predictions of an organism's reaction to external influences, such as drugs (modelled in PyBioS).



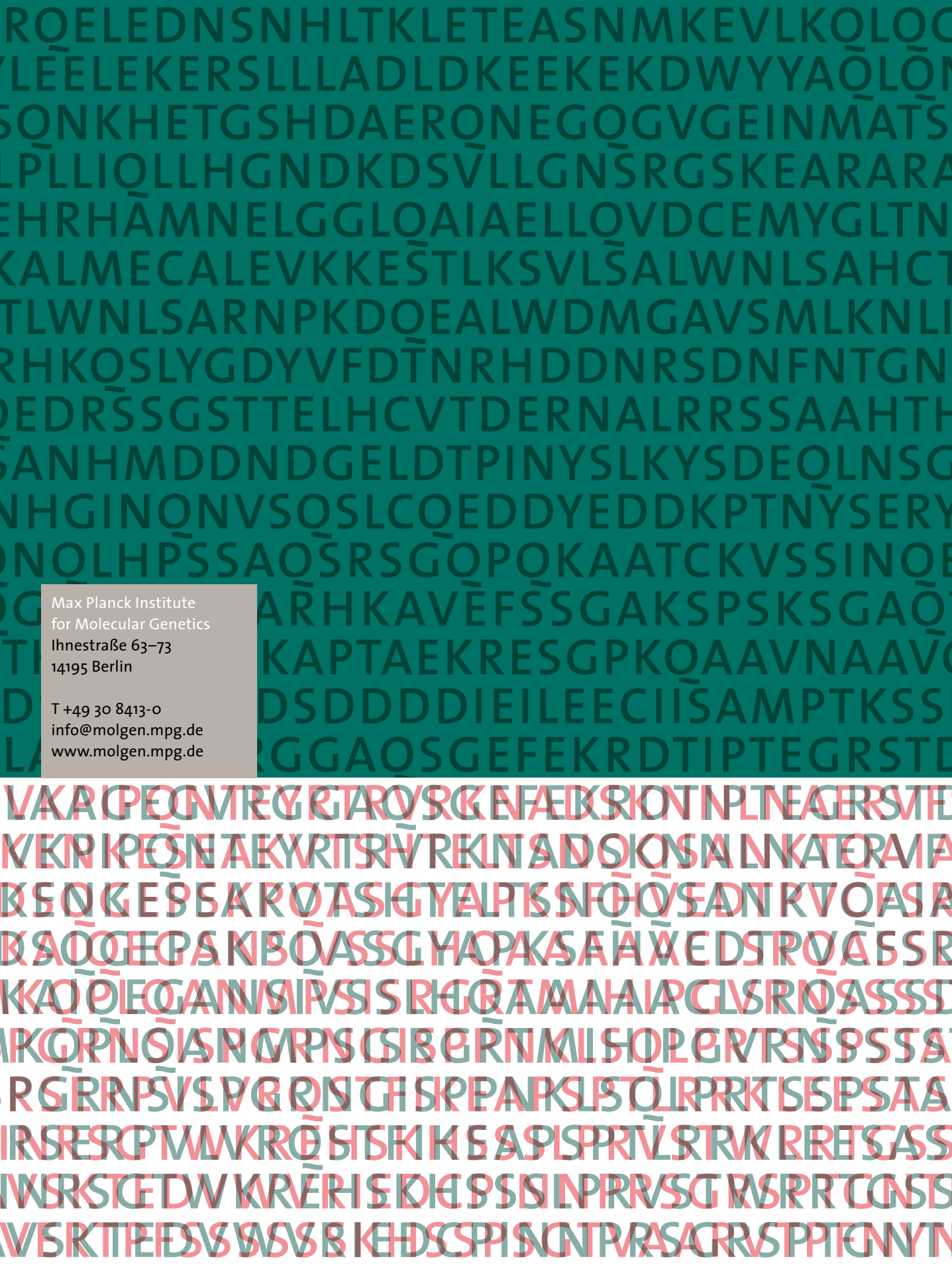
Underground / U-Bahn U3
→ Oskar-Helene-Heim or
→ Thielplatz

Urban rail system / S-Bahn S1
→ Sundgauer Str.

Bus 110, M11
→ Bitscher Str.

Bus 115, 285, X10
→ Schützallee or
→ Leichhardtstr.

Bus 101, M48
→ Holländ. Mühle or
→ Winfriedstr.



Max Planck Institute
for Molecular Genetics
Ihnestraße 63–73
14195 Berlin

T +49 30 8413-0
info@molgen.mpg.de
www.molgen.mpg.de