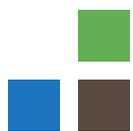


EMBL



UniversityHospitalHeidelberg



**MMPU**

Molecular Medicine Partnership Unit

Today's research for tomorrow's medicine

**Molecular Medicine Partnership Unit**

A pioneering joint venture between the Medical Faculty of the University of Heidelberg and the European Molecular Biology Laboratory



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*The MMPU is a collaboration between two renowned institutes located in Heidelberg, Germany. The cover image represents the city's iconic "old bridge" against a backdrop of highly magnified cells and tissues.*

## The Molecular Medicine Partnership Unit (MMPU)

The Molecular Medicine Partnership Unit is a collaboration between two institutions with world-renowned expertise in the life sciences and medicine: the European Molecular Biology Laboratory (EMBL) and the Medical Faculty of the University of Heidelberg. Its primary aim is to speed the transformation of remarkable ongoing discoveries in the biomedical sciences into applications that can be used for the development of personalized medicine strategies.

Founded in 2002, the MMPU currently comprises five international research teams, jointly headed by a principal investigator from each organization and staffed by medical doctors, research associates, post-doctoral fellows, PhD students and technicians from both institutions. In this unique and stimulating setting, basic and clinical researchers work side-by-side to discover the molecular mechanisms that underlie common diseases. The MMPU is co-directed by Prof. Andreas Kulozik from the Angelika-Lautenschläger Hospital for Children and Adolescents at the University of Heidelberg and by Prof. Matthias Hentze from EMBL, and is housed in the Otto-Meyerhof-Zentrum on the Medical Campus of the University of Heidelberg.

### Three elements are essential in the MMPU's approach

- a focus on important classes of diseases that makes optimum use of scientific expertise and clinical knowledge
- a combination of clinical and molecular knowledge with the most sophisticated technologies and methodologies
- the participation of scientists with a commitment to creativity and success



*“A translational approach to biomedical research will speed up new discoveries, allowing patients to benefit from research findings sooner.”*

*Andreas Kulozik, Co-Director MMPU*



*“Molecular Medicine provides great opportunities both for medicine and for basic science: medicine will benefit by achieving a deep molecular understanding of important diseases and basic science will gain important models to understand key biological processes.”*

*Matthias Hentze, Co-Director MMPU*



*In the MMPU, basic and clinical researchers work side by side to understand the fundamental mechanisms behind a number of serious, widespread diseases.* ►

*For MMPU collaborators, the road to understanding disease begins and ends with patients.*



## The MMPU within a changing paradigm of medical research

Medicine and the molecular life sciences spring from different traditions that are only now coming together in a unified approach to human health. Modern medicine arose when scientists learned that microorganisms cause infectious diseases and discovered ways to combat them using vaccines and drugs such as antibiotics. But today the major killers in industrialized nations – and increasingly the developing world – stem from defects within our own cells. Treating them will require a deep understanding of how genes, proteins, and other molecules contribute to disease, and new safe methods of altering their activity in patients.

This approach follows decades of systematic work in laboratories to discover molecules and learn their functions. Until recently, it has been difficult to observe how the elements of complex biological

systems interact to transform a healthy cell into a diseased one, or vice versa. But the past decade has seen a boom in the development of new technologies capable of analyzing processes at the level of cells and organisms.

Genome projects have provided a complete catalogue of the genes of humans and many other organisms; microarrays and proteomic platforms yield a census of all the molecules active in a cell or tissue and can be used, for example, to compare their behaviour in states of health and disease, or their response to drugs or other treatments. Sophisticated imaging and screening techniques have automated the search for molecular functions and substances that can be used to manipulate them. The new science of bioinformatics and systems biology integrates all of this information into models that can be used to search for new

drug targets, or predict the likely effects of a treatment.

“Molecular medicine” aims to draw together laboratory and clinical research in a new approach based on an understanding of the basic mechanisms that cause disease. Achieving this vision requires bringing together two cultures with different approaches to questions of health and disease, and different systems of education and working styles. The MMPU’s strategy relies on the formation of close-knit teams involving a basic and clinical researcher and their groups, encouraging the use and development of innovative technologies, and providing new types of training for the next generation of “physician-scientists”.



## The MMPU approach: From the bedside to the research lab and back again

The MMPU builds on existing, well-established research and clinical groups, drawing them into collaborative teams and offering several types of practical support as they take a unified approach to disease processes. MMPU groups have unrestricted access to a complete range of some of the most powerful and innovative services and facilities available in the world, housed within the University of Heidelberg network of institutes and clinics and the EMBL. This includes a number of core facilities with state-of-the-art technologies, screening platforms, a range of established animal models for human diseases, tissue samples and data from patients at various stages of a disease, access to clinical trials, etc. A number of innovative methods and technologies have been developed within the teams themselves, a process which is strongly encouraged within the MMPU.

MMPU teams bring together medical doctors, clinical researchers, molecular biologists, physicists, chemists, engineers, computer scientists and other specialists from across the world to solve challenging biological problems that are typically difficult to address in any single clinical or laboratory setting. Support is offered to research projects on the basis of excellence.

Such multidisciplinary teams are likely to become the standard in biomedical research in the future, which will require a new generation of “physician-scientists” who are trained to work on translational themes. The MMPU offers hands-on practical training through the University’s Medical Faculty degree track as well as through a dedicated interdisciplinary teaching seminar series aimed at students preparing for Master’s, Bachelor’s, PhD and

MD degrees. EMBL also provides affiliation for MMPU members to the EMBL International PhD Programme (EIPP) and the EMBL Interdisciplinary Postdocs (EIPOD) programme, while the Medical Faculty provides access to its Postdoc Fellowship Programme. These formal structures are complemented by international conferences, courses, seminar series and other events in which partners can keep abreast of developments in their field. The MMPU also hosts public research days, organized twice a year, aimed at communicating the exciting discoveries coming from the collaboration to the wider scientific and medical communities.



## The Partners

The MPMU is a partnership between EMBL and the Medical Faculty of the University of Heidelberg, drawing together a growing staff of currently more than 50 experts recruited from across the world.

The European Molecular Biology Laboratory, dedicated to basic research in the molecular life sciences, is internationally recognized as one of the world's foremost research institutions. Established in 1974, EMBL is funded by public research monies from 20 European member states, and associate member state, Australia, and comprises almost 100 independent groups covering the spectrum of molecular biology. Groups work either at the Main Laboratory in Heidelberg, or at one of four outstations located across Europe. In addition to its world-class research activities, EMBL provides a renowned training programme for PhD students and postdoctoral fellows and offers vital services to scientists in the member states. It has widely recognized expertise in developing new instruments and

methods in the life sciences and has an active technology transfer pipeline to translate discoveries into applications that benefit society.

The Medical Faculty of the University of Heidelberg, founded in 1386, forms part of one of the oldest and most distinguished academic institutions in Europe. The Faculty fosters close links between research labs and hospital wards, permitting the swift implementation of newly acquired knowledge from clinical studies. Its practically oriented modern teaching methods and systematic encouragement of young researchers makes it one of the leading institutions for medical research and training in Germany. In 2007, the Medical Faculty was officially recognized by the German federal and state governments as part of its "Excellence Initiative". The Medical Faculty provides MPMU researchers with full access to its facilities, offers the laboratory space for the MPMU and funds scientists through its postdoc fellowship programme.



*The EMBL Advanced Training Centre on the EMBL campus*



*The Otto-Meyerhof-Zentrum on the Medical Campus of the University of Heidelberg*

*“The Medical Faculty of the University of Heidelberg and EMBL share a long tradition of excellence in medical and basic research. By channeling their expertise through the MMPU, they have created one of the world’s foremost centres with remarkable potential to make real advances in finding treatments for disease.”*

*Claus R. Bartram, Dean of the Medical Faculty of the University of Heidelberg*

*“The MMPU successfully bridges the gap between basic and clinical research. In order to devise new effective therapies and diagnostic tools we first need to obtain a thorough understanding of the molecular mechanisms of disease. In the MMPU biologists and medical scientists combine their complementary expertise and work hand-in-hand to pursue this goal.”*

*Iain W. Mattaj, Director General of EMBL*

## MMPU research themes

### Disease prevention by mRNA volume and quality control

Diseases of mRNA metabolism

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### Breathing fresh air into chronic lung diseases

Cystic fibrosis/Chronic airway disease

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### The hunt for molecular signposts of cancer

Pathogenesis of colorectal cancer and development of novel approaches for early detection, diagnosis and prevention

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### Managing the body’s supply of iron

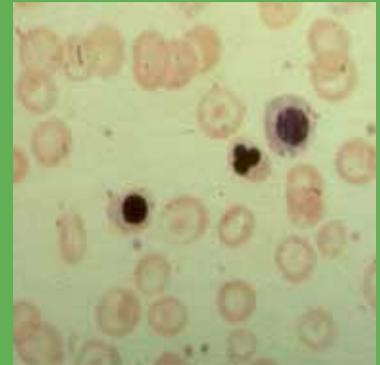
Iron homeostasis in health and disease

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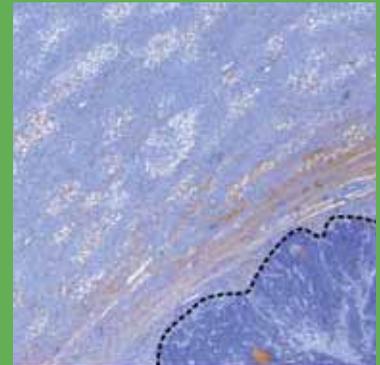
### Keeping cholesterol in check

Cell biology and disorders of cholesterol homeostasis

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*Carriers of beta-thalassemia are healthy if NMD is active, but if it is inactive, they suffer abnormalities in red blood cells (depicted above) and other serious symptoms.*



*A metastasis (bordered by the dotted line) invades healthy liver tissue in an image obtained through prothrombin immunohistochemistry.*

◀ **Matthias Hentze, MD**

*Associate Director and Group Leader,  
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**Andreas Kulozik, MD, PhD**

*Director of the Department of  
Paediatric Oncology, Haematology and  
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## Disease prevention by mRNA volume and quality control

### Diseases of mRNA metabolism

The scientific collaboration between Matthias Hentze and Andreas Kulozik, which stretches back over a decade, was the original inspiration for the establishment of the MMPU. This successful partnership between a basic researcher and a clinician has become a model for the other MMPU teams. The work of their team has led to important new discoveries related to blood diseases and revealed fundamental new aspects of the basic biology of cells that are applicable to a much wider range of diseases.

Currently the team is focusing on common diseases such as haemoglobin disorders, thrombosis, inflammation and childhood cancer. Many of these health problems can often be traced to the loss of a crucial protein, changes in the amount that is made, or the production of defective versions. Matthias, Andreas and their colleagues have traced some of these problems to the way messenger RNAs are processed as the cell attempts to translate them into proteins.

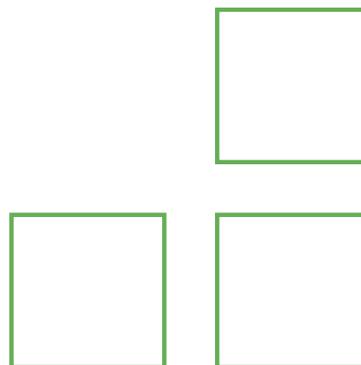
Cells often exercise quality control and destroy faulty mRNA molecules before they can do harm. For example, nonsense-mediated decay (NMD) often breaks down mRNAs before they are used to make proteins. This process depends on extra information in an mRNA that is not translated into protein. A sequence called a stop codon tells the cell where an mRNA's protein-encoding information ends. Mutations in genes often put a stop codon too early in the molecule, which activates NMD. This may cause the mRNA's destruction and the loss of an essential molecule;

if it does slip through, it may be produced in a shortened form that ends up doing more harm than if there were no protein at all.

NMD detects misplaced stop codons by recognizing protein tags that have been attached to mRNAs. Matthias and Andreas have discovered that various combinations of these tags send the mRNAs down alternative processing pathways, with different outcomes. This results in different dosages of proteins and explains why some patients suffer a more severe form of a disease or respond differently to treatments than others with the same mutation. To demonstrate this, the team had to develop the first method to measure the overall activity of NMD. As a result, they successfully proved the principle in cystic fibrosis, and they suspect that a similar process is at work in a number of other diseases.

A second major project also involves extra information in mRNAs. The work began with a clinical study to find the gene responsible for a hereditary form of thrombosis. It revealed that patients have a mutation in the prothrombin gene which subtly increases levels of the protein in their blood and greatly increases their risk of thrombosis.

The mutation affects a region in the untranslated tail end of prothrombin mRNA; the team discovered that this region acts as a sort of volume control. Over a long period of evolution, the volume of the signal has been tuned down in the prothrombin gene of humans and many other species.



The mutation removes the control, leading to abnormally high amounts of prothrombin messenger RNA and protein.

Even healthy people need higher levels of prothrombin than the mRNA would normally yield. This led to the discovery of a second signal that counteracts the first by promoting higher prothrombin levels. A delicate balance between the two signals determines how much protein is produced. The signal is activated by stress factors, such as inflammation and tumour invasion, and thereby contributes to a variety of pathological conditions. The team's findings highlight how subtle changes in gene expression can have serious consequences for disease and point to the importance of analyzing small changes. The researchers have confirmed that the combination of signals occurs in a number of other molecules. It is another new mechanism that seems to explain the origins of several diseases, and may provide a starting point for the development of new types of therapies.



## Breathing fresh air into chronic lung diseases

Cystic fibrosis/Chronic airway disease

Breathing is something most of us take for granted – but for the millions of people across the world who suffer from chronic lung diseases, shortness of breath can be a matter of life and death. Cystic fibrosis, for example, remains the most common lethal genetic disease, and chronic obstructive pulmonary disease is now the fourth leading cause of death worldwide. Through a unique combination of work with patients and animal models, innovative microscopy techniques and chemistry, the labs of Marcus Mall and Carsten Schultz are developing new tools to diagnose and monitor some of these diseases, gaining insights into underlying mechanisms that are essential in the search for new treatments.

The main focus of the team has been cystic fibrosis, caused when patients inherit a defective form of a gene called CFTR. This affects a layer of tissue called the epithelium that lines airway surfaces in the lungs. Normally this layer should be coated with a thin layer of liquid, but for that to happen, the epithelial cells need to absorb and secrete salt and water in a coordinated fashion. The genetic problem affects a channel in the cells' membranes, causing them to release chloride ions very inefficiently and to absorb too much sodium. As a result, a thick layer of mucus forms and creates an environment that sets the stage for chronic inflammation and bacterial infection. Patients with cystic fibrosis are usually diagnosed in their early childhood and often don't survive to reach middle age.

As a clinical researcher at the Children's Hospital of the University

of Heidelberg, Marcus provides clinical care for patients suffering from cystic fibrosis and other lung diseases. His lab developed a mouse model of cystic fibrosis lung disease which contains a defective version of ENaC, an ion channel protein that causes the epithelial cells of the airway to absorb too much sodium. This draws off the fluid present on the airway surfaces and imitates the symptoms of cystic fibrosis. Carsten, a chemical biologist at EMBL, has developed small compounds that can slip into cells and alter these systems to modulate the activity of the ion channels and thus improve the hydration of the airway surfaces. Lately, his group has been designing fluorescent probes to monitor systems within cells that control the behaviour of ion channels.

People with cystic fibrosis often develop pulmonary inflammations that cause the destruction of the small, sac-like alveola and emphysema. (Emphysema is also frequently triggered by the continued inhalation of cigarette smoke and other chemical irritants.) One of the team's projects is to understand the link between inflammation and the development of emphysema. Their recent work has focused on the activity of a molecule called macrophage elastase (MMP12), which is secreted by alveolar macrophages in the lung in response to inflammations.

MMP12's normal function is to break down proteins in the matrix that surrounds cells, often changing the architecture of a tissue. In 2002 another lab discovered that it is hyperactive in inflammations of the

lungs of smokers. This promotes the destruction of the walls of the alveoli and thus very likely contributes to the development of emphysema. But it has been hard to get a direct look at MMP12's activity.

The team accomplished this by designing a set of probes that give off a fluorescent signal when MMP12 becomes active on the surfaces of cells, observable under the microscope. When they used this tool to examine tissue taken from mice with acutely inflamed lungs, they discovered that MMP12 was much more active than normal. The next step is to confirm this finding in human samples, so they are adapting the method to measure MMP12 activity in cells from patients with cystic fibrosis and other chronic lung diseases. Since the procedure is non-invasive and is carried out using cell samples, they hope that it can be used to diagnose inflammatory pulmonary conditions and monitor disease progression in the clinical setting. This would provide physicians much earlier with the information they need to treat patients before the lungs are damaged and emphysema starts to develop.

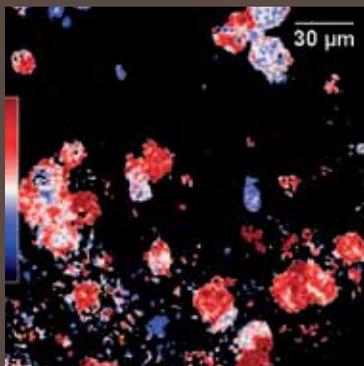
MMP12's position on the cell surface could make it an ideal candidate as a drug target. The probes are allowing the team to study how the behaviour of the protein changes over the course of the disease. They are also providing a tool to search for small compounds, first in mice and hopefully in humans, which can tune down its activity. That's a first crucial step in creating a drug that can control inflammation and emphysema in cystic fibrosis and other chronic lung diseases.

**Marcus Mall, MD** ▶

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**Carsten Schultz, PhD**

Interdisciplinary Group Leader and  
Senior Scientist, EMBL

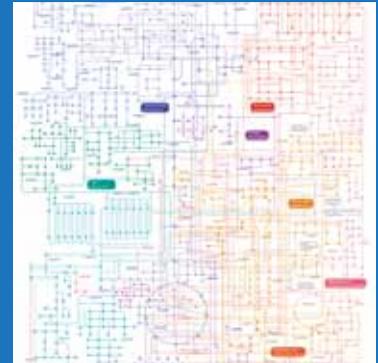


MMP12 is overactive in cells in a mouse model of cystic fibrosis. Here, fluorescence microscopy reveals the activity of MMP12 on macrophages by cleaving a synthetic reporter molecule on the surface of cells from bronchoalveolar lavages.

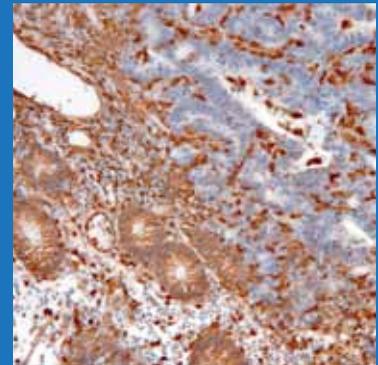


X-ray images of the chest of cystic fibrosis patients reveal the development of lung disease.





*Bioinformatics comprises a set of powerful tools which enable researchers to compile and interpret vast amounts of information about diseases. The results often reveal new targets for drugs and may lead to the design of new diagnostic tools.*



*Colorectal cancer tissue stained to detect expression of HLA class II antigens*

◀ **Peer Bork, PhD**

*Group Leader and Senior Scientist,  
EMBL*

**Magnus von Knebel Doeberitz,  
MD, PhD**

*Director of the Department of  
Applied Tumour Biology, Institute of  
Pathology, University of Heidelberg  
and Group Leader Cooperation  
Unit Cancer Early Detection, DKFZ  
Heidelberg*

## The hunt for molecular signposts of cancer

Pathogenesis of colorectal cancer and development of novel approaches for early detection, diagnosis and prevention

What makes healthy cells lose control of the normal programmes that guide their differentiation and start down a path toward becoming cancer? In most cases, researchers believe, the cause is an accumulation of changes in their genomes, mainly mutations in important genes. Every cell accumulates mutations when it divides, through chance or the influence of environmental factors such as carcinogenic chemicals. Evolution has given our cells protective mechanisms to detect most of the mistakes and repair them, or to commit suicide in a process called apoptosis, if the damage can't be repaired. Even so, enough mutations slip past the controls to make cancer a leading cause of death worldwide. Magnus von Knebel Doeberitz and Peer Bork are engaged in a hunt for molecular signposts of the disease – particularly in colorectal cancer – that could be used to diagnose it at early stages and treat it more effectively.

As cells accumulate mutations, their genomes usually become unstable, often making it likely that more mistakes will occur at a faster pace. Mutations affecting one type of cellular control, called the DNA mismatch repair system, occur predominantly in regions that have repeats of a single letter of the genetic code – like a key that has become stuck on a computer, repeating the same character over and over. Cancers that develop in this way are called microsatellite unstable or MSI tumours.

Magnus and Peer have compiled a database of the human gen-

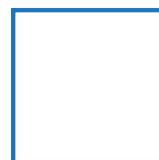
ome that lists all the regions with repetitive DNA sequences. Based on this information, they scan for patterns that appear uniquely in cancer cells of a specific type and therefore might be used to detect them. They have established a bioinformatics model that predicts the frequency at which a mutation is likely to occur in any particular position in the genome that contains long, repeated DNA sequences. They found that specific sites undergo unusually high rates of mutations, suggesting that they are functionally relevant and promote tumour development. The method revealed novel target genes involved in colorectal cancer development. Moreover, they have set up a unique model for a hereditary form of colorectal cancer known as Lynch syndrome.

The scientists have discovered new links between several genes and the probability that a tumour will take a malignant turn or the likelihood that therapies will succeed. This information may be useful in the design of new diagnostic tools and in coming up with treatment plans for individual patients. Now they are extending their analysis to shorter repeats in the genome and epigenetic alterations, such as the methylation of gene promoter regions, in hopes of finding more genes and mechanisms that underlie the early steps of cancer formation.

A mutation often leads to a molecule with unusual characteristics; sometimes it is visible on the surfaces of cells. That might call it to the attention of the immune system and offer a potential handle for therapies. For

example, during their refinement in the cell, many proteins are glycosylated – coated with sugars. Magnus and Peer discovered altered patterns of glycosylation in MSI tumours, and they are now using high-throughput technologies to try to identify them systematically. This may yield another way to distinguish different types of tumour cells from healthy tissue.

If the immune system can recognize mutated proteins, or be trained to do so, it might be possible to develop vaccines that target tumours. Another of the group's projects aims to train white blood cells called T cells – major players in immune responses – to detect specific mutated proteins and eliminate the cells on which they are expressed. The group demonstrated that the strategy works with tumours grown in cell culture, so a clinical trial has been designed to test these so-called frameshift antigens as vaccines. Phase I/II of the trial, scheduled to begin in 2010, aims to determine whether the vaccines have any toxic side effects, and what dosage may be necessary to successfully treat patients' tumours.





## Managing the body's supply of iron

### Iron homeostasis in health and disease

As life evolved, it had to cope with the presence and abundance of elements such as iron in the environment. Iron plays a crucial role in living systems: It drives chemical reactions within cells, captures oxygen in our lungs and carries it in red blood cells, and is used to combat bacteria and other parasites. The amount is crucial: Either too much or too little iron can lead to serious diseases. How the body maintains this balance has been the subject of years of study by Martina Muckenthaler and Matthias Hentze. They have developed creative new methods and used a wide range of technologies to probe the causes of iron-related disorders, along the way uncovering fundamental cellular processes that contribute to many other diseases.

Our bodies extract a small amount of iron from foods such as red meat, poultry, fish and beans as they leave the stomach and enter a section of the small intestine called the duodenum. But the body uses most of its iron by recycling what is already there. Martina and Matthias have helped prove that a complex network of interactions throughout the body monitors global amounts of iron, makes adjustments that tell duodenal cells when to absorb more or less, and regulates how much is released from storage.

A molecule called Hfe plays a central role in iron regulation. Mutations in its gene cause the iron overload disease hereditary haemochromatosis (HH), which is the most common genetic disorder in the Western world: one-eighth

of us carry the relevant mutation, and one in every 250-300 people inherit two defective copies of the gene, leading to symptoms of the disease. The team helped prove that Hfe's presence in liver cells is required for the proper production of a molecule called hepcidin, a hormone that blocks the release of iron from cells. Without hepcidin, too much iron enters the bloodstream and the body becomes overloaded. Previously most researchers looked to the duodenum itself for the key to the body's regulation of iron; this discovery proved HH to be a 'liver disease' and highlighted the key role of this organ in iron metabolism.

A central theme of the group's research is to understand the functions of the hepcidin hormone and the factors that influence its production and release. In a collaboration with Michael Boutros' lab at the German Cancer Research Center, the team is using the powerful approach of blocking the activity of specific genes across the entire genome using molecules called small interfering RNAs (siRNAs). If a particular siRNA disrupts hepcidin synthesis, this is a good hint that its target gene may be involved in the regulation of systemic iron levels – which can be confirmed through other experiments. Using this approach, the group has already discovered one factor (called SMAD7) that normally suppresses hepcidin expression. In the longer term, knowledge of the molecules that influence hepcidin levels will be useful in identifying existing drugs or discovering new ones that can be used in the treatment of iron disorders.

Cells release iron through channels in their membranes made from a protein called ferroportin, mainly found in cells of the liver, small intestine, and blood cells called macrophages. Hepcidin binds to this gate-like molecule to control how much of it is present on the cell surface: rising levels of hepcidin lower the number of iron transport channels and reduce iron levels in the blood. The lab is also using the new siRNA method and modern microscopy techniques (in collaboration with Rainer Pepperkok's lab) to discover how it does so. This might allow them to learn to control the behaviour of the channel with drugs or other substances.

Recently scientists have discovered that cells produce vast numbers of small microRNAs that naturally block the activity of genes. Defects in these molecules have been linked to a number of diseases. Martina, Matthias and their colleagues suspected that they also play a role in the regulation of iron levels, but it has been hard to find miRNAs and study their effects. The team has developed an innovative technology called miChip which can monitor miRNAs. The scientists are particularly interested in studying miRNAs in mouse models that replicate iron diseases in humans. Their search has revealed that an miRNA specifically produced in the liver (miR122) controls hepcidin production. The miChip technology can also be used to clarify the roles of miRNAs in other diseases, and the team has entered into a number of collaborations with other laboratories worldwide to do so.

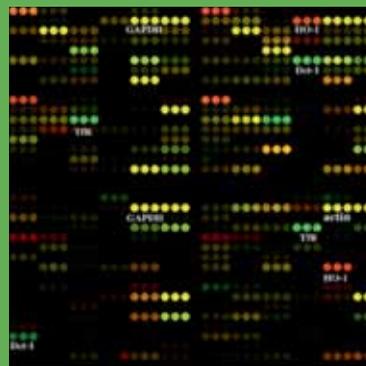


◀ **Matthias Hentze, MD**

Associate Director and Group Leader,  
EMBL

**Martina Muckenthaler, PhD**

Head of the Molecular Medicine  
Laboratory, Department of Paediatric  
Haematology, Oncology and  
Immunology,  
Angelika Lautenschläger Hospital  
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University of Heidelberg



The "iron chip" reveals differences in gene expression patterns between cells taken from healthy patients and from those suffering from iron-related diseases.



The team's investigations of hereditary haemochromatosis have revealed a central role for the liver in regulating the body's uptake of iron.



## Keeping cholesterol in check

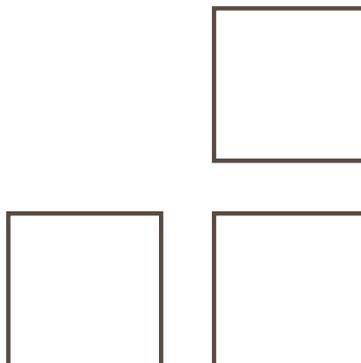
### Cell biology and disorders of cholesterol homeostasis

Doctors constantly advise us to get enough exercise and follow a diet low in fatty foods and high in fruits and vegetables. Not doing so can lead to an accumulation of cholesterol in the blood, a major risk factor in two diseases that are leading causes of death in the Western world: atherosclerosis and coronary heart disease. MPMU collaborators Heiko Runz and Rainer Pepperkok are trying to get a handle on these diseases by studying the body's cholesterol and the factors that regulate its production, uptake and metabolism.

Despite a bad reputation, cholesterol is not always harmful; it plays an important role in vital processes in the body such as digestion and the synthesis of hormones and vitamins. Most cholesterol is produced in the liver, but we also get some through our diets. For it to do its job correctly, cholesterol from either source must be taken up from the bloodstream and metabolized by cells. This process is normally tightly regulated by a network of proteins inside cells, but under certain conditions, the system can become dangerously unbalanced. The team combines the expertise of Heiko, a human geneticist who has worked on diseases related to the storage and release of cholesterol, and Rainer, a cell biologist who uses cutting-edge light microscopy techniques to study the transport of cholesterol and other molecules through the cell.

Their current work includes searching for genes and cellular processes involved in hypercholesterolemia, Niemann-Pick Type C

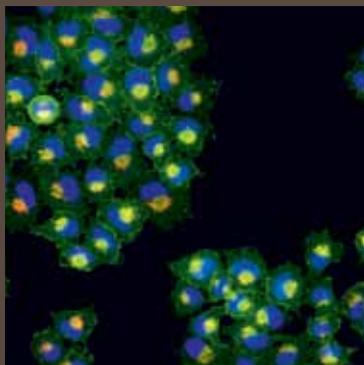
(NPC) disease, and other cholesterol-related disorders. One project aims to identify genes that may contribute to raising levels of cholesterol in the blood. The researchers first monitored the cells' genomes to discover genes that were being activated or silenced when cells were exposed to low levels of cholesterol. Once they had a list, they tested the function of these genes using a powerful technique called RNA interference (RNAi). This method is based on small RNA sequences called siRNAs that are inserted into the cell, blocking the production of proteins from specific genes.



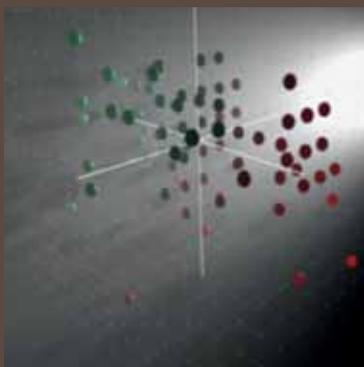
To discover the functions of the genes they found, they used innovative technology developed by Rainer's group at EMBL. The method allowed them to expose cells to many different siRNAs at once and monitor the effects under the microscope. It permitted the parallel analysis of several hundred genes, leading to the identification of 20 genes that had not been previously associated with cholesterol metabolism, but are likely to have an important effect on balancing levels of the molecule.

In further studies they identified a role for one of these genes in NPC disease, a rare inborn condition that is caused by mutations in the genes NPC1 or NPC2. Infants' cells are unable to transport cholesterol and other types of fatty molecules, resulting in inefficient metabolism and dangerous accumulations of these molecules within the cell. This eventually leads to death through the degeneration of a patient's nervous system and liver. Using their new screening method, the researchers are currently searching for genes that help to restore the faulty transport mechanism and that may serve as targets in the development of a treatment.

Ultimately they hope that their studies will open new avenues to design targeted therapies for cholesterol-related diseases, for example by finding small molecules that can affect genes involved in cholesterol metabolism. They have already identified some promising targets and will soon test them in animal models.



The team uses automated high-throughput microscope studies of fluorescent molecules to observe crucial components of cholesterol metabolism. The image shows cholesterol (green), a lysosomal marker (red) and cell nuclei (blue).



3D-visualization of multiparametric data from RNAi-screening for novel cholesterol regulators

**Heiko Runz, MD** ▶

Group Leader Molecular Metabolic Disease Unit, Institute of Human Genetics, University of Heidelberg

**Rainer Pepperkok, PhD**

Team Leader in Cell Biology and Cell Biophysics Unit and Head of Advanced Light Microscopy Facility, EMBL





## Getting involved in the MMPU

Whether you are a student setting out on a career in the life sciences, a postdoc looking for a new challenge, an experienced researcher interested in applying your scientific knowledge to questions related to human health, a physician looking to learn more about the molecular basis behind a disease – or if you simply want to know more about the exciting research being conducted on the diseases studied by our groups, the MMPU has something for you.

### For MD and PhD students ...

The MMPU provides extraordinary opportunities for highly talented, motivated students who wish to make the most of a career in the biomedical sciences. MD and PhD students may join the MMPU through the University of Heidelberg's Medical Faculty degree track or through the internationally renowned EMBL International PhD Programme (EIPP).

### For postdocs ...

Postdoctoral researchers may join the MMPU through a number of well-established postdoctoral programmes, including the EMBL Interdisciplinary Postdocs (EIPD) Programme and the Postdoc Fellowship Programme of the Medical Faculty of the University of Heidelberg.

### For established scientists ...

EMBL and the Medical Faculty both have active Visitors Programmes that allow experienced researchers interested in collaborating to join MMPU teams to share their knowledge, perform joint experiments, acquire new skills and learn specific techniques.

### For physicians ...

The MMPU also offers possibilities for medical doctors who would like to explore the fundamental mechanisms underlying a disease within the research spectrum of the MMPU, for ex-

ample searching for genes that contribute to a disease, or finding new targets for drugs based on an understanding of a biological process.

### For the wider scientific and medical communities ...

The MMPU hosts public research days, organized twice a year, aimed at communicating the exciting discoveries arising from the partnership to a wider audience.

For more information on how to get involved in MMPU activities, contact us at:

[info@mmpu.de](mailto:info@mmpu.de)

[www.klinikum.uni-heidelberg.de/Molecular-Medicine-Partnership-Unit-MMPU.101349.0.html](http://www.klinikum.uni-heidelberg.de/Molecular-Medicine-Partnership-Unit-MMPU.101349.0.html)

[www.embl.de/research/partnerships/mmpu/index.html](http://www.embl.de/research/partnerships/mmpu/index.html)

*The MMPU would like to thank the following organizations which, in addition to the core funding provided by EMBL and the University of Heidelberg, provide generous funding for research projects: Ara Parseghian Medical Research Foundation, Bundesministerium für Bildung und Forschung, Deutsche Forschungsgemeinschaft, Dietmar Hopp Stiftung, European Commission, European Research Projects on Rare Diseases, Fondation Leducq, Fritz Thyssen Stiftung, Manfred Lautenschläger Stiftung, Mukoviszidose e.V..*

#### **Credits**

*Written and edited by Sarah Sherwood, Barcelona and Russ Hodge, Berlin*

*Layout and design by Sybille Sukop, Medienzentrum / Unternehmenskommunikation Stabsstelle des Universitätsklinikums und der Medizinischen Fakultät Heidelberg Leitung, Markus Winter [www.klinikum.uni-heidelberg.de/medien](http://www.klinikum.uni-heidelberg.de/medien)*

*Photography by Hendrik Schröder and Markus Winter Medienzentrum Marietta Schupp, Photolab, EMBL and iStockphoto*

*Cover design by Petra Riedinger, OIPA, EMBL*

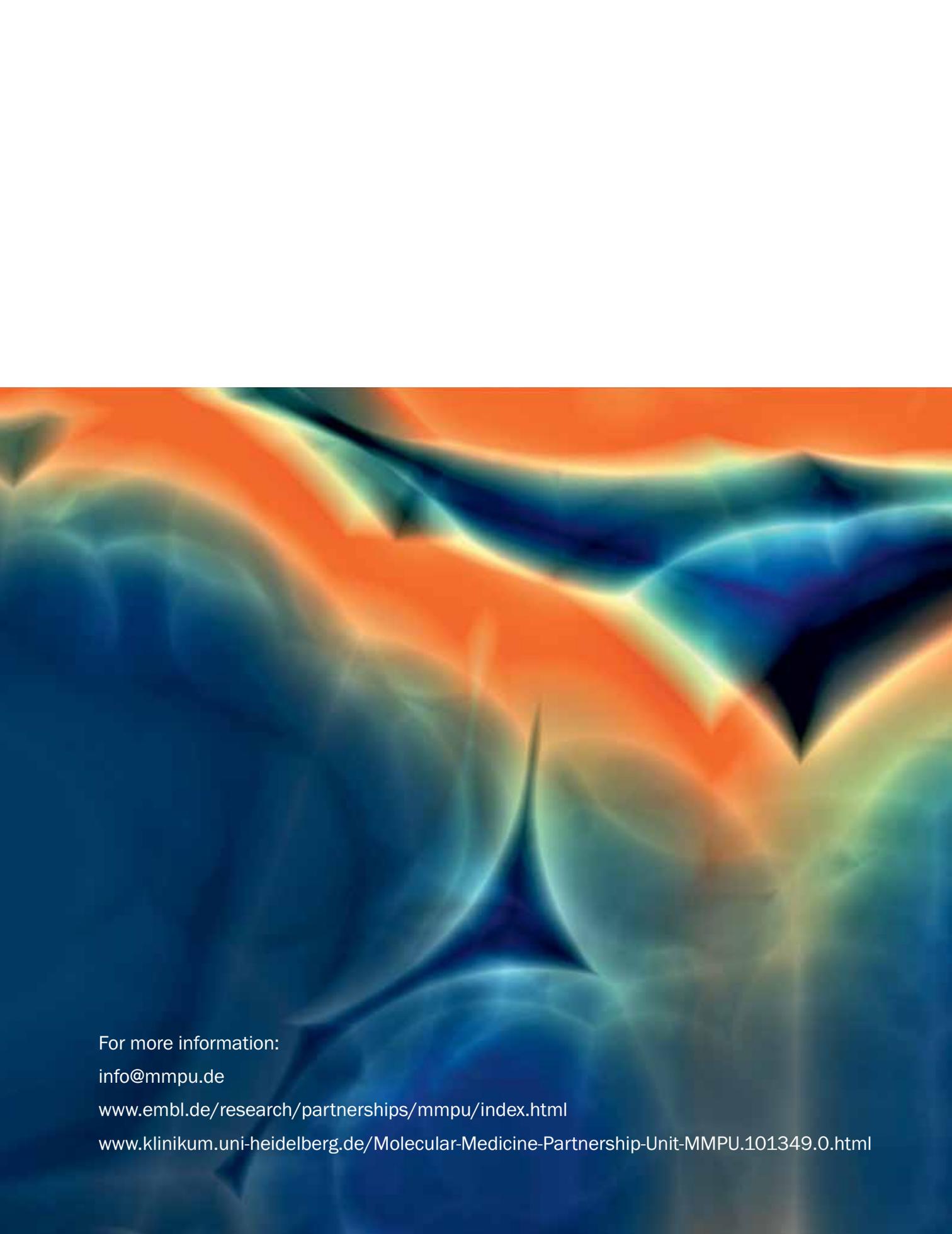
*MMPU 'cubes' by Leo Burger, Workshop, EMBL*

*Project coordination by Britta Schläger, Kobris, Sandhausen*

*Printed by Nino Druck GmbH, Neustadt/Weinstraße*

*Published for the Molecular Medicine Partnership Unit by the Medical Faculty of the University of Heidelberg and the European Molecular Biology Laboratory (EMBL)*

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