DZHK
DEUTSCHES ZENTRUM FÜR
HERZ-KREISLAUF-FORSCHUNG E.V.

DZG DEUTSCHE ZENTREN
DER GESUNDHEITSFORSCHUNG

German Centre for Cardiovascular Research (DZHK)

ANNUAL REPORT

2014

The DZHK is the largest research institution for cardiovascular diseases in Germany.
Our goal is to promote scientific innovation and to bring it quickly into clinical application and to patient care in order to improve the prevention, diagnosis and treatment of cardiovascular diseases.

Contents

Preface

Diseases of the cardiovascular system are still the no. 1 cause of death in Germany, even though cardiovascular medicine has made a lot of progress in recent decades. That this progress is not reflected at a larger scope in reduced numbers of those who are sick is, above all, owed to the change in demographics: people are getting older, thus resulting in an increase of chronic diseases such as cardiac insufficiency or aortic valve stenosis. At the same time, the basic provision with standard treatments such as medications that lower blood pressure and cholesterol inhibitors has reached a high level in Germany. A lot of people can prevent severe cardiovascular diseases well this way. Emergency care in case of a myocardial infarction and sudden cardiac death is also at a high level, which has resulted in an enormous increase of the chances of survival. Due to these counter-trends, there are, however, still approx. 1.5 million inpatient treatments per year in Germany due to cardiovascular diseases. Cardiovascular diseases do, by far, cause the highest disease costs.

We, as German Centre for Cardiovascular Research, are clearly tasked with combining basic research and clinical research so that patients can benefit more quickly from research results (translation). The work of our Centre in the reporting year 2014 is modelled after this task. Corresponding to their individual strengths, our seven partner sites have achieved excellent results in basic research. Within the DZHK, we have developed structures that allow for quickly picking up these results and developing them further into treatments or diagnostic procedures suitable for practice. At the core of these structures are our flexible research funding and our selection processes for the funding that are based on internal and external experts. These structures and processes enable us to sponsor only the best and most promising preclinical and clinical studies and projects and to quickly react to scientific innovations.

In 2014, we were able to achieve an extraordinarily important step: researchers and physicians from 17 university-medical institutions agreed on uniform standards for conducting clinical studies. A large share of future projects in the area of clinical research is based on these standards and on the clinical-scientific infrastructure built on them. Some of these studies have already been started and we are waiting full of anticipation for the results.

Last but not least, our Centre has grown together into a true community in the past year. Many excellent scientists from all over Germany have contributed to a joint research strategy and invested time and ideas in cooperative projects and structures. Thank you very much for this to all! We are convinced: translation can succeed this way only.

Thomas Eschenhagen
Chairman of the Board

Gerd Hasenfuß
Board Member

Thomas Sommer
Board Member

German Centre for Cardiovascular Research (DZHK)

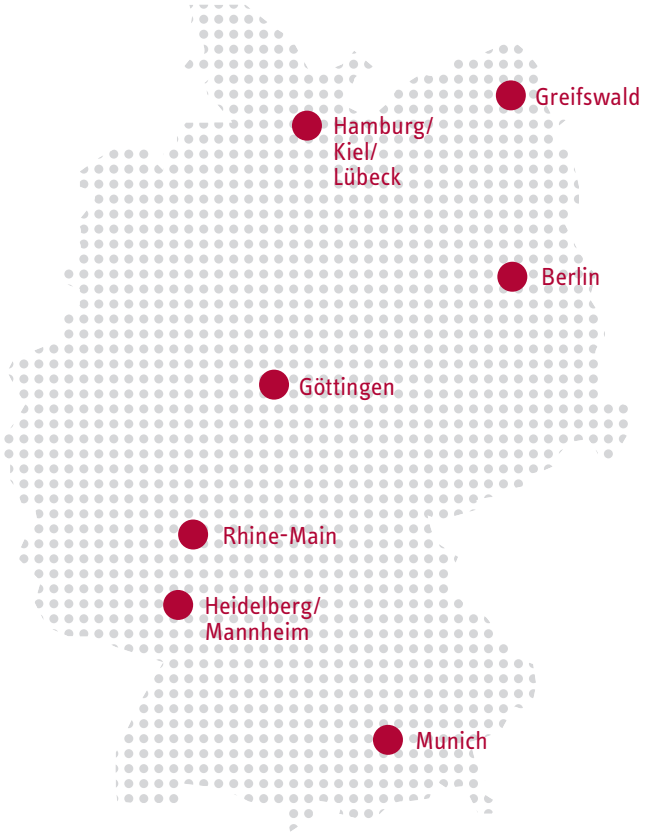
The DZHK combines basic research with clinical research, thereby bringing research results to patients more quickly.

The German Centre for Cardiovascular Research (DZHK) – a German Centre of Health Research

The German Centre for Cardiovascular Research (Deutsches Zentrum für Herz-Kreislauf-Forschung) is among the six German Centres of Health Research (DZG) that are dedicated to the improvement of the prevention, diagnosis and treatment of endemic diseases. It was founded in 2011 upon the initiative of the German Federal Ministry of Education and Research (BMBF) and is funded jointly by the federal government (90 percent) and the governments of those German states in which member institutions are headquartered (10 percent). The goal of the six German Centres of Health Research is to quickly bring results from basic research to clinical application.

Mission and goals of the DZHK

The DZHK focuses on translating new approaches in cardiovascular research as rapidly as possible into clinical practice in order to improve the diagnosis, prevention and treatment of cardiovascular diseases. This mission is of utmost clinical and health economic importance because in the future, the incidence of cardiovascular disease will increase further as a result of the rising incidence of metabolic disorders (obesity, diabetes) and due to demographic change. In order to be able to implement this mission, the DZHK unites excellent basic researchers and clinical researchers from seven sites in Germany. It promotes the cooperation between them with the goal to develop synergies and to thereby accelerate the process of translation.



Above all, it invests its funds in previous weak spots of the translation process. This is ensured through a coordinated research strategy and specific funding instruments.

Important topics and developments

In 2014, the DZHK for the most part completed its developmental phase. The year was all under the concept of further developing the funding instruments for the flexible funds. In the context of the 2013 strategy debate, these funds were increased from 35 to 55 percent of the total budget. The DZHK has streamlined its structures and defined a total of four areas of funding: preclinical research, clinical research, training & mentoring, scientific exchange.

In these areas, there are more funding instruments with corresponding funding guidelines. The processes have all been established by now. The Clinical Study Group (CSG) and Translational Research Group (TRG) panels, which were established in 2014, play an important role in these processes.

Excellent result in midterm evaluation

The developmental phase of the DZHK also was the topic of the first midterm evaluation in June 2014 which provided for an excellent result. The international panel of reviewers attested the DZHK a very good start and efficient structures. The translational strategy of the DZHK was considered innovative and internationally competitive. The reviewers praised, above all, the infrastructure for clinical studies that the DZHK created within a short period of time as well as the provision of funds for cooperations with external partners and the industry.

A unique nationwide treasure of cardiovascular data in Germany

In 2014, the DZHK for the most part concluded the development of its central infrastructure for clinical studies. All member institutions can now uniformly record and centrally store the data of the clinical studies, registries and cohorts funded by the DZHK. This way, a unique nationwide treasure of cardiovascular data in Germany is created in the long term which allows for additional research approaches above and beyond the purpose of the individual studies. The multi-year and laborious process of the harmonisation of processes and IT infrastructures was possible only due to the long-term funding that the DZHK receives. The infrastructure for clinical studies of the DZHK had its baptism by fire in December 2014 with the inclusion of the first patient in the TORCH registry at the Heidelberg/Mannheim site (also, cf. Chapter 4).

Potential for synergies – the Cardiological Competence Networks

In 2014, the General Assembly of Members of the DZHK made the decision to fund the three Cardiological Competence Networks for four years with a total of 7.3 million euros, starting 2015. The DZHK perceives a potential for cooperation and synergies in the area of guideline-relevant studies, in particular with the Competence Networks for Atrial Fibrillation and Cardiac Insufficiency. With the Competence Network for Congenital Cardiac Defects, an important area of research is added that previously had not been represented strongly in the DZHK. The financing by the DZHK allows for the continuation of already existing studies, registries, cohorts and biomaterial databases of the Competence Networks.

Joint activities of all DZG

In the reporting year, the DZHK played a leading role in the organisation of joint activities of the DZG. It organised two meetings of the DZG speakers at which the DZG, among other things, developed a draft regarding benchmarks for translation. In addition, the DZG appeared jointly in public. For this, the DZHK organised a workshop regarding the topic of translation at the World Health Summit in October in Berlin featuring international experts, as well as a parliamentary evening of the DZG which took place in Berlin in February 2015. Both events were extremely successful. Due to the positive feedback, the DZG agreed upon continuing and further intensifying joint activities in public relations. As such, an event in Brussels is planned and the DZG will also appear jointly again at the World Health Summit 2015.

Photo: © WHS

In the presence of the Secretary of State of the Federal Ministry of Education and Research, Dr. Georg Schütte (2nd from the left), representatives of the DZG discuss new approaches for translation with foreign experts at the World Health Summit in Berlin.

Science – Focus on translation

Since diseased heart cells cannot regenerate, DZHK researchers are trying to cultivate artificial heart tissue in the laboratory (Tissue Engineering).

Research strategy

The DZHK is focussing on the research of three main topics that are of particular importance to patients and to the health system: prevention and treatment of myocardial infarction, prevention and customised treatment of heart failure and prevention of sudden cardiac death. In order to expedite translation, the DZHK is focussing with its research strategy on select phases of translation that are particularly challenging or have only been worked on very little to date: late preclinical projects, early clinical studies, guideline-relevant studies.

Funding in competition

In 2014, the research strategy was officially adopted in the General Assembly of Members and it constitutes the foundation for the further development of the funding instruments and of the structures of the DZHK. It also includes the decision that, starting 2015, more than half of the funds of the DZHK are to flow into translational and predominantly cooperative projects that are modelled after the research strategy (in the founding phase of the DZHK this ratio was still reverse: 35 percent cooperative funds, 60 percent partner site funds). Scientists of the DZHK can apply for these “free” funds with project applications. The awarding of the funds is solely based on the scientific excellence and the translational chances of success of the submitted projects. This competitive procedure allows for the promotion of the best scientific approaches and for the implementation of the joint strategy in the spirit of a successful translation. By the end of 2014, five clinical studies and one preclinical research

project were approved this way. In addition, we fund numerous smaller cooperation projects in the context of Shared Expertise (cf. Chapter 4) with flexible funds.

Partner site projects

Successful translation requires the generation of new ideas that can be brought into clinical application. The partner site funds flow into long-term projects that serve the search for starting points for new treatments and diagnostic procedures. Each partner site is investing these funds corresponding to its individual strengths. As such, the projects are a type of "breeding ground" for the translation. The partner site funds are, in essence, spent in three categories: DZHK procedures, scientific infrastructures such as biobanks and scientific projects with a translational perspective. Research highlights from this area can be found in Chapter 5.

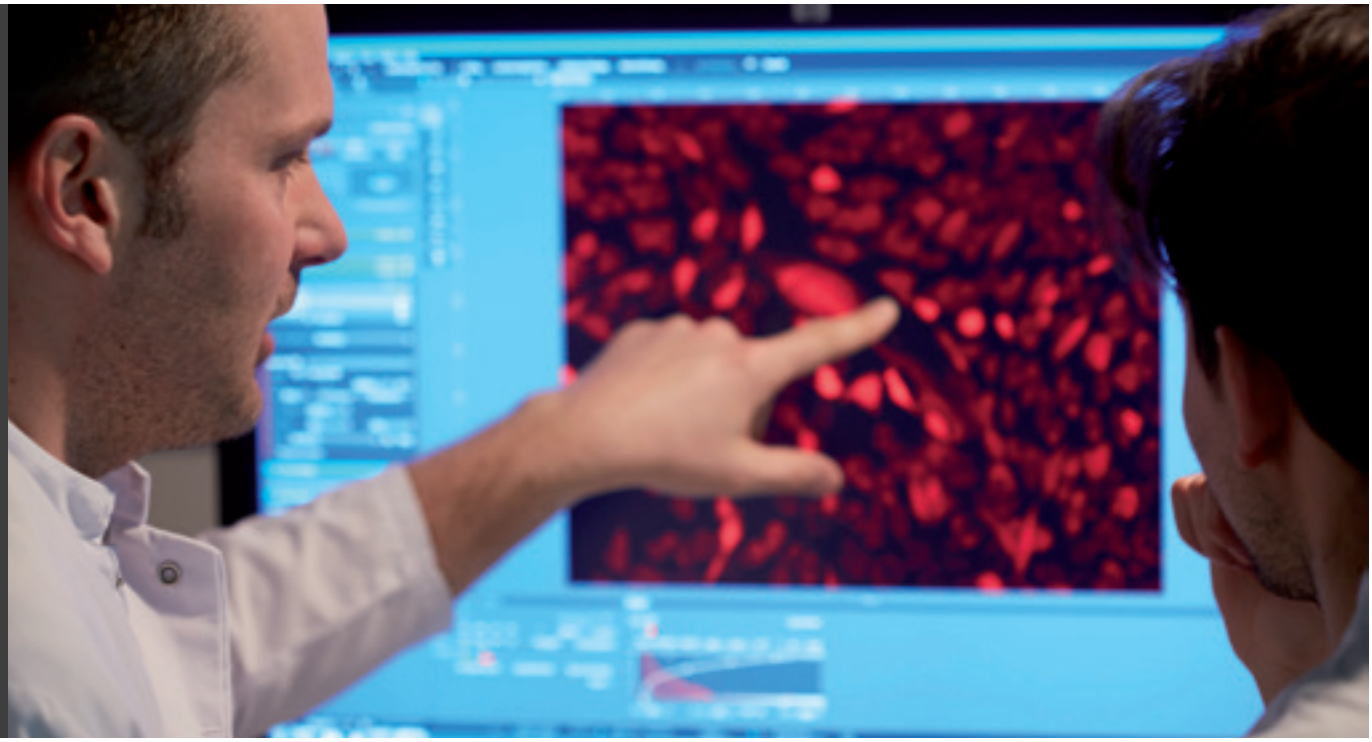
Distribution of partner site projects by topic

Category	Partner sites	Projects
OMICs technologies & biomarkers	6	26
Molecular mechanisms of cardiovascular diseases	6	24
Imaging	6	14
Prevention & epidemiology	5	11
Clinical research	4	7
Induced pluripotent stem cells, tissue engineering, cell therapy	5	12
Arrhythmia research	4	8
Late translation, large animal models	4	5

What are OMICs?

"OMICs" refers to technologies with which the whole of the biological structure or processes that exist in cells, tissues or whole organisms can be examined. The processes refer to sub areas of biology that end with the syllable "omics". This can be the whole of gene sequences (genomics), the composition of proteins (proteomics) or of metabolites (metabolomics). From the systematic, statistically processed comparison of the omics patterns in different groups, for instance healthy control groups vs. sick groups, or young vs. old groups of people, conclusions regarding disease mechanisms can be drawn. Omics studies generate, as such, new hypotheses that can be checked in experimental or clinical studies. They play an increasing role in biomedicine and, in particular, also in the research of the DZHK.

Preclinical research



The preclinical research in the DZHK is concentrated on the last steps that are necessary before a new method can be tested on patients for the first time.

Target structures found in basic research must be checked for their suitability as a therapeutic agent and must be developed further for this before they can be used in the clinic. This is done in animal models and in human cell models. To develop such models anew and adjust them for different treatment approaches is an important step in translational research. In order to test new therapies in large animal models or in first clinical studies on patients, therapeutic agents such as viral vectors, microRNAs or stem cells do, furthermore have to be manufactured on a large scale. These are not standard processes. Highly specialised laboratories within the DZHK handle this task which presupposes a huge research and development expenditure. The DZHK is setting a strategic focus on application-oriented preclinical research and has therefore, in this area, developed four lines of funding with flexible budgets: High Risk High Volume Late Translational Projects, experimental cooperations by means of Shared Expertise, experimental cooperations with external partners and experimental cooperations with the industry.

High Risk High Volume Late Translational Projects (HRHV)

This line of funding was newly established in 2014. The projects are located in the area of late preclinical research and represent a central element in the DZHK research strategy. They are based on the proof of concept in an animal model and include the last steps before initial application in human beings. Members

of the DZHK are thus provided with the opportunity to further develop innovative preclinical projects with a concrete perspective for a clinical application. They receive financial support for the last research steps that are necessary before testing in human beings is allowed for the first time for a new therapeutic or diagnostic principle. At this point there are often bottlenecks in academic research and the industry does not yet become active in this early phase. The funds are allocated within the DZHK in competition. Starting 2015, the DZHK is making available 3 million euros per year for the projects.

Translational Research Group (TRG)

To ensure that the translational projects are following the DZHK research strategy and have a realistic chance of success, the DZHK established the Translational Research Group (TRG) in 2014. Not only are academic researchers represented in the TRG, but also experts from biotechnology companies and technology transfer institutions as well as biostatisticians. More than half the members are external. The TRG examines the respective applications and provides consulting and support to the applicants, for instance regarding aspects of commercialisation and in terms of questions regarding statutory approval. With all this, the TRG bundles and expands the know-how for the development of new therapeutic principles within the DZHK. In August 2014, the first 13 HRHV applications were submitted to the TRG. The TRG recommended to fund the project "Development of miR-92a inhibitors for the treatment of cardiovascular disease", handed in by Stefanie Dimmeler, partner site Rhine-Main.

Development of miR-92a inhibitors for the treatment of cardiovascular diseases

Duration: 2015 to 2016

Budget: EUR 398 thousand in 2015;
EUR 738 thousand in 2016

Goal: Based on own preliminary works that show that miR-92a inhibitors can improve cardiac function after infarction, the safety and optimisation studies necessary for an application in human beings are to be carried out in the context of the application. For this, the composition of the microRNA inhibitors is to be optimised and the necessary pharmacological and toxicological examinations are to be performed.

Participating scientists: Stefanie Dimmeler, Andreas Zeiher, Angelika Bonauer, Ariane Fischer, Rhine-Main

Collaborations within DZHK: Christian Kupatt, Rabea Hinkel, Munich

Members of the TRG

Mat Daemen (University of Amsterdam)

Heimo Ehmke (Universitätsklinikum Hamburg-Eppendorf, Hamburg/Kiel/Lübeck)

Michael Gotthardt (Max Delbrück Center for Molecular Medicine, Berlin)

Tim Jessen (Evotec, Hamburg)

Ralf Krappa (Medigate, Hamburg)

Ulf Landmesser (Charité – Universitätsmedizin Berlin)

Stephan Lehnart (University Medical Center Göttingen)

Harald Petry (uniQure, Amsterdam)

Kurt Ulm (Technische Universität München)

Martin Ungerer (advanceCOR GmbH, Munich)

Cooperations by means of Shared Expertise

The cooperations by means of Shared Expertise have been proving themselves already since 2012. With this line of funding, small experimental cooperation projects are made possible. In this, the idea is: excellent scientific abilities, specialised knowledge and infrastructure of one DZHK partner are easily made available to DZHK partners at other partner sites in a transparent, uncomplicated fashion.

Top 10 of the most frequently utilised Shared Expertise

Shared Expertise	Partner site	Number of users until 31 Dec 2014
Genomics/Proteomics	Berlin	12
Generation and cardiovascular phenotyping of transgenic rats	Berlin	10
Vascular Proteomics	Rhine-Main	8
AAV Vector Platform	Heidelberg/ Mannheim	7
OMICs Platform	Munich	7
MicroRNA-Array platform	Hamburg/ Kiel/Lübeck	5
Cardiomyocyte and Engineered Heart Tissue Phenotyping	Göttingen	4
NextGeneration Sequencing Platform (Heidelberg)	Heidelberg/ Mannheim	4
Stretch	Hamburg/ Kiel/Lübeck	4
Experimental and Therapeutic Stem Cell Bank and Stem Cell Phenotyping	Göttingen	3

Typical Shared Expertise are animal models, vector and OMICs technologies as well as stem cell based models of human diseases. Through the funding of cooperation by means of Shared Expertise, the DZHK wants to intensify the cooperation between partner sites and make available to the DZHK researchers the whole spectrum of experimental expertise within the DZHK. Due to the fact that the users choose the Shared Expertise best suited for them, a competition within the DZHK is initiated. This avoids that infrastructures of the same type are procured or set up with DZHK funds at different DZHK partner institutions. To Young DZHK members, in particular, these smaller projects provide the opportunity to gather first experiences with independent research work. As such, in the reporting year, 11 Young DZHK members were applicants or co-applicants of a Shared Expertise project. In 2014, the partner institutions of the DZHK offered 118 Shared Expertise. 46 cooperations by means of Shared Expertise were carried out between the sites (2013: 68).

Cooperations with external partners

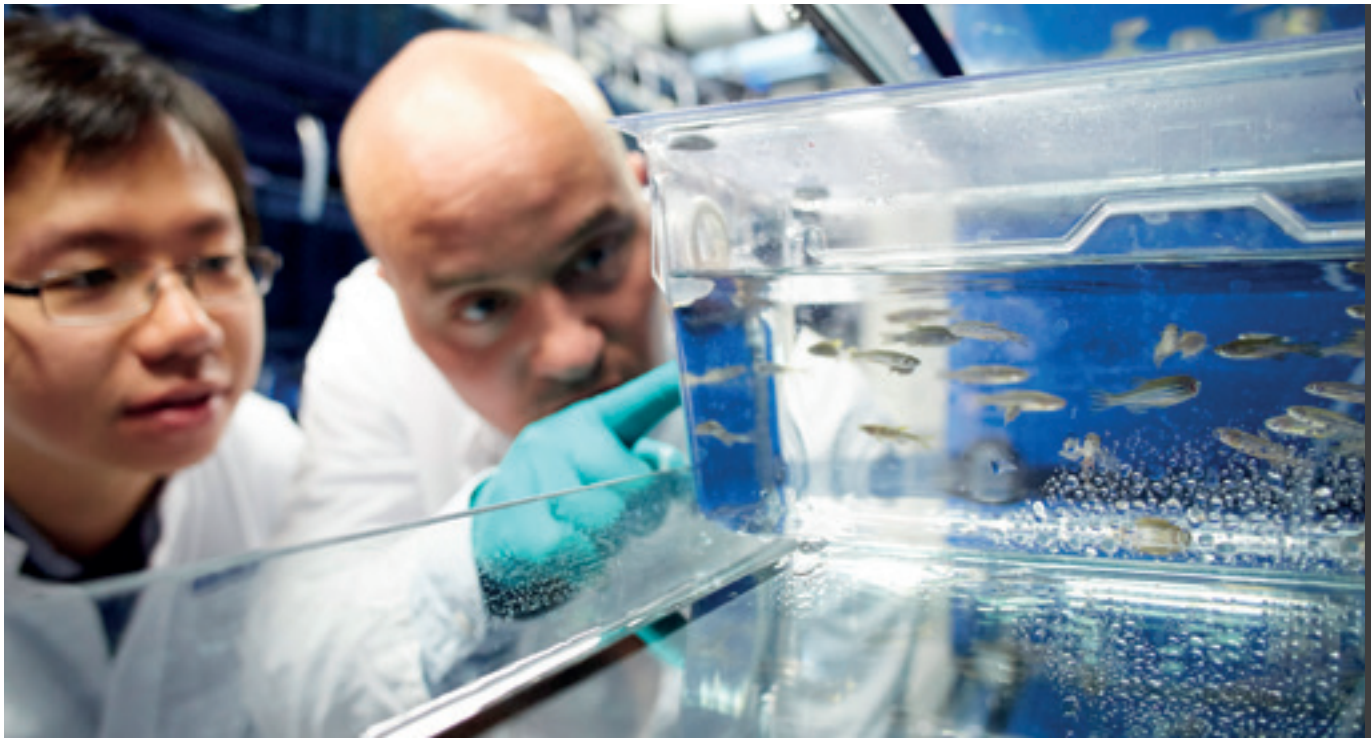
This line of funding is explained in Chapter 8.

Industry cooperations

This line of funding is explained in Chapter 8.

Goals for 2015

HRHV projects constitute the heart piece of preclinical research within the DZHK; they are intended to close decisive gaps in the translation process. We do, therefore, want to approve at least three additional projects in this area. Shared Expertise enables partners of different sites to quickly and unbureaucratically carry out smaller experimental cooperation



Zebrafish serve as model organisms in cardiovascular research and are offered within the DZHK as Shared Expertise.

projects. The results of such projects can be the prerequisites for larger projects. On the other hand, the cost/benefit ratio of the administrative effort is not good in case of very small projects. Here, a good compromise has to be found. We are therefore striving to maintain the number of cooperations by means of Shared Expertise in 2015 at the level of 2014. These projects are particularly suited as first independent research works of young scientists. Therefore, in 2015 even more applications should be submitted by Young DZHK members.

Goals for 2015 at a glance

- **Approval of three additional HRHV projects**
- **Approval of 40 – 50 Shared Expertise projects (average value EUR 20 – 25 thousand)**
- **Successful completion of 40 Shared Expertise projects**
- **Share of young scientists in Shared Expertise: 30 percent**

Clinical research

Clinical studies constitute a focal point in the research strategy of the DZHK.

Photo: © DZHK

Clinical studies are the last and deciding step before a treatment can be utilised in the routine care of patients. Therefore, clinical research is a strategic focal point of the DZHK. All 17 clinical member institutions are participating in the studies, registries and cohorts of the DZHK. Furthermore, external clinics are also urged to include patients in DZHK studies. A comprehensive harmonisation process carried out within the DZHK allows for the uniform collection, recording and storage of the patient data and biomaterials in each of these studies. The collection of data and biomaterial being created this way has the potential to long-term develop into Germany's most important resource for cardiovascular clinical research projects.

Clinical research within the DZHK

Clinical research can take different paths. The DZHK funds clinical studies, registries and cohorts. Registries collect data regarding the courses of diseases and treatments of patients. With the help of such data, researchers can track down the causes of diseases and optimise treatments. Cohort studies investigate, above all, which external factors within a select group of people have an influence on the pathogenesis or course of a disease. In clinical studies, ultimately the effectiveness and tolerance of a treatment or a diagnostic procedure are being tested on healthy or sick subjects. In order for a treatment to receive approval for the patient, it must pass several phases of clinical studies. With its flexible funds, the DZHK is funding, in particular, such clinical studies that, to date, constitute a weak spot in the translation chain in the area of cardiovascular research and which are particularly challenging: early clinical studies and guideline-relevant studies.

Early clinical studies

This area encompasses a wide spectrum of rather small, science-driven studies. This includes first-in-

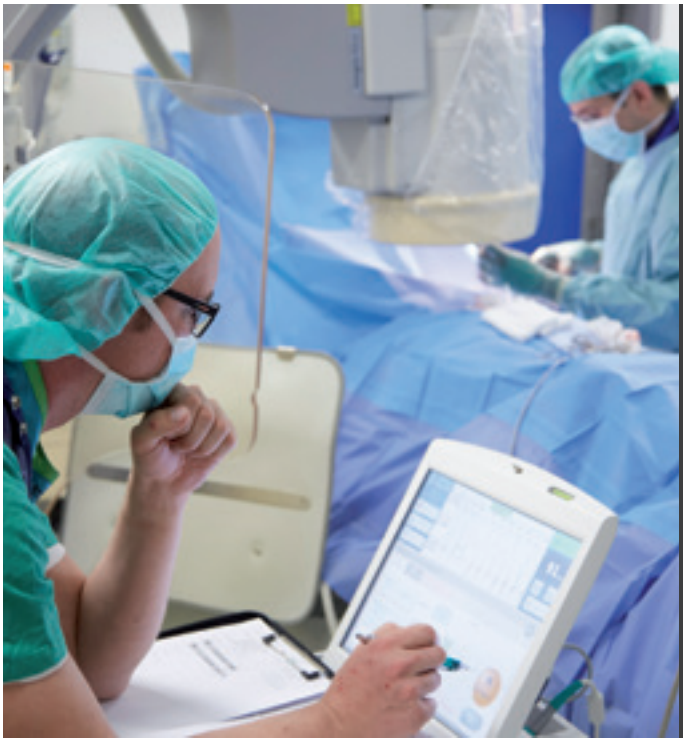
man studies which test the dosage and tolerability of a new therapeutic agent. Pharmacogenetic studies examine how the genetic makeup of a patient influences the reaction to a medication or in which way the medication is being metabolised and what side effects it has. Biomarker studies examine whether certain markers in the blood or urine allow for the prediction of the response to a treatment or allow for a better control of a treatment.

The testing of medications already established in other areas of medicine for cardiological diseases allows for new insights into disease mechanisms and can open up new areas of application. Imaging studies belong in this area, e.g. when it is to be investigated how biomarkers that predict the chances of recovery of the cardiovascular tissue after an infarction can be detected in imaging processes.

Guideline-relevant studies

These are studies that lead to a change of practical treatment recommendations. An example for this is the comparison of the different already approved therapeutic procedures that can only be performed by an independent, publicly funded facility such as the DZHK. Another example is the testing of known drugs for new indications (repurposing studies), or the testing of strategies for the utilisation of pacemaker and cardiac support systems and also of other new treatment methods.

The DZHK studies are investigator-initiated trials (IIT) which are also ordered out of interest by other clinics and which are predominantly carried out with public funding. As a rule, these are early clinical studies in a phase in which the industry is not yet participating or the topics that are not of sufficient interest to the industry. In case of these studies, the responsibility of the sponsor is borne by the respective clinical facility



All 17 clinical partner institutions of the DZHK will include patients in the DZHK-funded clinical studies.

at which the applying, scientifically-interested clinician is working and which then – after successful proposal of the study project at the DZHK – receives the funding. In the carrying out of his or her study, the clinician then receives support from an academically-oriented competence centre for clinical studies which, for example, takes care of the administrative handling or performs the independent monitoring.

On-going clinical studies, registries and cohorts

In 2014, two more clinical studies, registries and cohorts were added to the three selected for funding in 2013. These are fully funded, guideline-relevant studies that will start 2015. In addition, in 2014 a clinical study was included in the DZHK partial funding and two more were associated without any DZHK funding. Association means: already fully funded clinical studies in which at least two DZHK partner institutions are participating can apply for the status "DZHK-associated" if the goals of the study comply with the research interest of the DZHK. The DZHK association shows that the DZHK is providing non-material support to the study and, for example, wants to promote the recruiting into the study by means of its network.

Imaging processes can also be the topic of clinical studies within the DZHK.

Clinical studies that were started and/or prepared in 2014:

TransitionCHF: cohort study regarding asymptomatic, restricted cardiac output and development of a heart failure or of a symptomatic myocardial insufficiency; Gerd Hasenfuß, Rolf Wachter, Frank Edelmann, Göttingen; no. of patients planned: 1,500; registration at ClinicalTrials.gov: NCT02323750; start of recruiting: December 2014

TORCH: translational registry for cardiomyopathies; Hugo Katus, Heidelberg/Mannheim, Wolfgang Hoffmann, Greifswald; no. of patients planned: 2,300; registration at ClinicalTrials.gov: NCT02187263; start of recruiting: December 2014

VAD: comparison between early and, where applicable, emergent implantation of a cardiac support system in patients on the waiting list for heart transplantation; Volkmar Falk, Christoph Knosalla, Berlin, Gerd Hasenfuß, Tim Friede, Göttingen; no. of patients planned: 500; registration at ClinicalTrials.gov: NCT02387112; start of recruiting: 2015

Fully financed clinical studies selected in 2014 for funding (starting 2015):

TOMAHAWK: immediate unselected coronary angiography versus delayed triage in survivors of out-of-hospital cardiac arrest without ST-segment elevation; Steffen Desch, Holger Thiele, Hamburg/Kiel/Lübeck; no. of patients planned: 498

FAIR–HF2: intravenous iron in patients with systolic heart failure and iron deficiency to improve morbidity & mortality; Stefan Anker, Göttingen, Mahir Karakas, Hamburg/Kiel/Lübeck; no. of patients planned: 1,200

2014 associated clinical study, partially financed by DZHK:

ISAR-REACT 5: Ticagrelor versus Prasugrel in patients with acute coronary syndrome – a randomised clinical study; Adnan Kastrati, Stefanie Schüpke, Munich; no. of patients planned: 4,000; registration at ClinicalTrials.gov: NCT01944800

2014 associated clinical studies without DZHK funding:

CULPRIT-Shock: prospective, randomised, multicentre study for comparison of an immediate interventional opening of multiple coronary vessels by means of balloon expansion with a treatment of only the infarction-causing vessel and a potential later treatment of other bottlenecks in patients in cardiogenic shock after acute myocardial infarction; Holger Thiele, Lübeck; no. of patients planned: approx. 700; registration at ClinicalTrials.gov: NCT01927549

FIX-HF-5C: assessment of the safety and effectiveness of the OPTIMIZER® system in patients with moderate to severe cardiac insufficiency and an ejection fraction between 25 and 45 percent; Gerd Hasenfuß, Göttingen; no. of patients planned: 230; registration at ClinicalTrials.gov: NCT01381172

First patients recruited

On December 1, 2014, the first patient of a DZHK study at the Heidelberg University Hospital was included in the TORCH registry. In the next two years, the registry for cardiomyopathy will collect data and biomaterial of 2,300 patients from all over Germany whose cardiomyopathy was not caused by a cardiac infarction but rather has other causes. The data of the registry is intended to help in the identification of disease-related molecular changes in the samples of the patients. With this knowledge, researchers can then develop new therapies and diagnostic procedures.

Each clinical study has a study centre that drives the clinical-scientific handling and ensures the data quality. The study centre of the TORCH registry consists of the clinical-scientific project centre at the Heidelberg University Hospital and the data and quality centre at the Institute for Community Medicine of the Greifswald University Hospital.

With the first patient inclusion, the central study infrastructure of the DZHK commenced its regular operation (cf. Chapter 6). On December 19, the first patient in Göttingen was also included in the TransitionCHF cohort. The cohort pursues the question how it can be predicted at what point a restricted cardiac output without symptoms is turning into a manifest disease. A total of 1,500 patients are planned.

In addition to the 17 clinical institutions of the seven DZHK partner sites, more clinics across Germany will include patients in the two studies.

On December 1, 2014, Joachim Fiebig was welcomed as the first patient of the TORCH registry at the Heidelberg University Hospital (from left to right): Myriam Wittek, study nurse, Prof. Hugo A. Katus, medical director, PD Dr. Andreas Dösch, attending physician, PD Dr. Claudia Seyler, scientific employee.

Clinical Study Group (CSG)

In 2014, the DZHK established the Clinical Study Group (CSG). The CSG includes the CSG Steering Committee and the CSG staff. The CSG Steering Committee supervises the clinical studies and is serving in a consulting role in the selection and execution. In 2014, it convened four times and reviewed 14 (1st Call) and 10 applications (2nd Call), respectively, for clinical studies in a two-stage process. Of these, two studies from the first call were accepted for funding and three more studies of the second call were asked to submit complete applications.

In the reporting year, we have started with the hiring of study doctors and study nurses at our 17 clinical partner institutions (CSG staff). The CSG staff is responsible for the coordination of the clinical studies on-site and, in particular, has the task of pushing the recruitment of patients.

Quality training

For persons who are working on-site in the multicentre clinical studies TORCH and TransitionCHF, we have carried out two quality training sessions in Berlin in 2014. The training sessions were aimed at employees of all included centres. The attendees were informed of the goals and the organisation of the clinical studies within the DZHK. Among other things, they learned the handling of our secuTrial data acquisition system and became familiar with the Standard Operating Procedures (SOP) and the patient consent forms.

Clinical-scientific infrastructure

In the reporting year, the development of the clinical-scientific infrastructure for clinical studies, registries and cohorts within the DZHK was pursued with great vigour. The development of a central data management (ZDM) consisting of the DZHK trusteeship office and

Members of the CSG Steering Committee:

Stefan Anker (University Medical Center Göttingen, Göttingen)

Martin Borggrefe (University Medical Centre Mannheim, Heidelberg/Mannheim)

Tim Friede (University Medical Center Göttingen, Göttingen)

Eva Herrmann (University Hospital Frankfurt, Rhine-Main)

Adnan Kastrati (German Heart Centre Munich, Munich)

Hugo Katus (Heidelberg University Hospital, Heidelberg/Mannheim)

Ulrich Kintscher (Charité – Universitätsmedizin Berlin, Berlin)

Julinda Mehilli (Hospital of the Ludwig-Maximilians-Universität München (LMU))

Matthias Nauck (University Medicine Greifswald, Greifswald)

Burkert Pieske (German Heart Institute Berlin (DZHB), Berlin)

Holger Thiele (Universität zu Lübeck, Hamburg/Kiel/Lübeck)

Karl Wegscheider (Universitätsklinikum Hamburg-Eppendorf, Hamburg/Kiel/Lübeck)

Andreas Zeiher (University Hospital Frankfurt, Rhine-Main)

DZHK data management for clinical data as well as the development of a structure for the DZHK biobanking were jointly with the adoption of uniform Standard Operating Procedures (SOPs) and the adoption of the usage regulation and of the ethics concept the prerequisites for the first patient inclusion. For additional information regarding the clinical-scientific infrastructure for our studies, cf. Chapter 6.

Goals for 2015

In our two lines of funding, "Early clinical studies" and "Guideline-relevant studies", a total of four new study applications are to be approved for funding. The VAD study will start with patient recruiting in 2015. The goal for 2015 is, furthermore, for all 17 clinical partner institutions of the DZHK to include patients in our on-going studies. In addition, in 2015 we also want to entice external study centres to participate in our clinical studies and to recruit patients. The hiring of the members of the CSG staff should be completed 2015.

Photo: © DZHK

Goals for 2015 at a glance

- **Approval of four new study applications in the two programs**
- **Start of VAD recruitment**
- **All 17 clinical partner institutions are recruiting patients**
- **Inclusion of at least 500 patients**
- **Initiation of at least two external study centres that recruit patients into DZHK studies**
- **CSG staff completely hired**

Scientific excellence – Research highlights 2014

How cardiovascular diseases happen – the cardiovascular continuum

Typically, cardiovascular diseases follow a pattern, the so-called cardiovascular continuum. It starts with **risk factors** such as being overweight, lack of movement and unhealthy eating. This leads to increased blood lipid concentrations, deposits in the vessels (plaques) and hypertension, through which the coronary heart vessels can coarctate **(atherosclerosis).** As a result, the cardiac muscle is subjected to reduced blood circulation; this is referred to as **coronary heart disease.** If the plaques tear off, blood clots form and close off the coronary vessels which results in myocardial infarction. Said infarction is lethal in approx. 40 percent of the cases, however, more and more people are surviving it. But in most cases the heart has sustained damage from it, heart cells die off and scar tissue is generated. If a relevant part of the heart tissue is damaged, the remaining cardiac muscle cells must work harder permanently and are overburdened. They increase in size (hypertrophy) in order to provide the necessary pumping power. This **remodelling of the cardiac muscle cells** and the scarring promote cardiac arrhythmia which is the main cause for sudden cardiac death. The remodelling processes cannot compensate long-term for the decrease of the pumping power of the cardiac muscle, heart failure occurs for which there is no cure to date. In case of most severe heart failure, the patient needs a new heart and is placed on the waiting list for a heart transplantation.

Genetics and environmental factors

The course and severity of classic cardiovascular diseases depends on a mix of genetic and environmental factors which is why the research of the **genetics of cardiovascular diseases** plays an important role at the DZHK. A number of heart diseases does not follow the cardiovascular continuum but rather has predominantly **genetic causes.** These rather rare diseases, which instead often take quite a dramatic course, are also being researched at the DZHK.

High-ranking publication of results

In this annual report, we would like to introduce research results from the DZHK on the following pages that start at different spots of the cardiovascular continuum. In 2014, they resulted in high-ranking publications which furthermore were each crowned “Paper of the Month” of the DZHK or were nominated for it.

Focus: Risk and prevention

How can one best prevent cardiovascular diseases from occurring or from getting worse? These questions are at the centre of prevention research. In addition to the classic risk factors such as being overweight, smoking and lack of movement, researchers are searching for additional factors that have an impact on the occurrence and course of cardiovascular diseases – and are finding something in the process. Noise and stress can, for instance, be held responsible for the occurrence of cardiovascular diseases. DZHK researchers at the partner site Rhine-Main have now zeroed in on another candidate: vitamin D.

Moving about in the sun and fresh air can prevent vascular diseases.

Photo: © PT DLR / BMBF

Vitamin D lets vessels grow

A U.S. study published in 2014 suggests a connection between vitamin D deficiency and the risk of a disease of the coronary vessels. According to the study, in 70 percent of the people with such a disease, a vitamin D deficiency was present. DZHK researchers from the partner site Rhine-Main were now able to reveal a mechanism how vitamin D promotes the new formation of blood vessels.

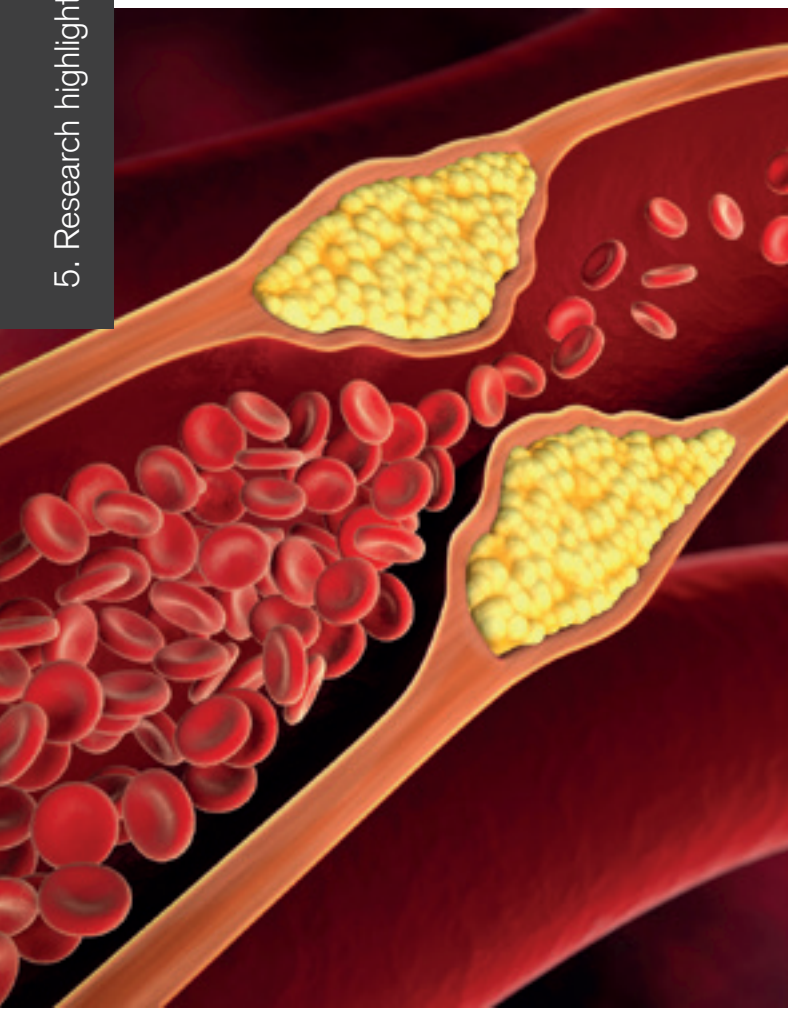
They observed that the intake of vitamin D in humans increased the amount of regeneration-activating cells circulating in the blood. At the same time, they were able to prove in a mouse model that the administration of low doses of the active vitamin D hormone accelerated the healing of blood vessels. It was possible to completely normalise with this the severely restricted formation of new vessels in case of, for example, diabetes.

According to the researchers, the vitamin D hormone increased vessel regeneration by increasing the production of a very important signal molecule in the cell. This protein called hypoxia inducible factor (HIF1) is responsible for the formation of a multitude of important regenerative tissue hormones. The scientists arrived at the conclusion that an administration of vitamin D should be tried in patients with restricted vessel regeneration – such as in diabetics – in order to prevent consequential damages such as cardiac infarctions and cerebral infarctions.

PAPER OF THE MONTH 9/2014 (NOMINATED):
Vitamin D Promotes Vascular Regeneration. Wong, M. S., Leisegang, M. S., Kruse, C., Vogel, J., Schurmann, C., Dehne, N., Weigert, A., Herrmann, E., Brune, B., Shah, A. M., Steinhilber, D., Offermanns, S., Carmeliet, G., Badenhoop, K., Schroder, K. & Brandes, R. P. *Circulation,* (2014).

Focus: Angiostenosis (Atherosclerosis)

In atherosclerosis, deposits form in the inner wall of the vessel which lead to chronic inflammations and coarctate the vessels. This can lead to the formation of blood clots that impede or even completely block the flow of blood which can trigger a cardiac infarction or a cerebral infarction. Researchers are looking for opportunities to stop this process in order to prevent coronary heart disease and myocardial infarction this way.



DZHK-researchers have discovered a principle by which damaged vessels can be repaired again.

How microRNA are repairing vessel walls

Atherosclerosis develops, above all, where the function of the endothelial cells, the innermost wall layer of the vessels, is disrupted. If, for instance, the blood flow ratios are disrupted and thereby increase the cholesterol values a stress reaction occurs at the vessel's interior wall with cell death but also with an increased growth of endothelial cells. The body has mechanisms to repair these damages to the vessel's wall again. DZHK researchers at the partner site Munich were able to show for the first time that two microRNAs are involved in this repair activity. microRNAs are very short sections of RNA that significantly contribute towards regulating the activity of genes.

The researchers found out that miR-126-5p is suppressing the formation of a protein that prevents endothelial cells from regenerating. If not enough miR-126-5p is present in the vessels, this protein becomes active and the vessel's walls cannot be repaired. The researchers were able to show in the mouse model that the administration of miR-126-5p reduced the progression of atherosclerosis. With this, the researchers may have discovered a new therapeutic principle for the protection against atherosclerosis.

A patent has already been filed for the development of the therapeutic application and is to be pursued further in the context of the DZHK and in cooperation with biotechnology companies.

PAPER OF THE MONTH 3/2014:

MicroRNA-126-5p Promotes Endothelial Proliferation and Limits Atherosclerosis by Suppressing Dlk1. Schober, A., Nazari-Jahantigh, M., Wei, Y., Bidzhekov, K., Gremse, F., Grommes, J., Megens, R. T., Heyll, K., Noels, H., Hristov, M., Wang, S., Kiessling, F., Olson, E. N. & Weber, C., *Nature Medicine 20*, 368–376 (2014).

Focus: Coronary heart disease

Coronary heart disease is a circulatory disorder of the cardiac muscle that occurs as a result of coarctated coronary vessels. If the cardiac muscle does not receive enough oxygen, the affected person feels pain in the chest, the so-called angina pectoris symptoms. In translation, angina pectoris means "tightness of the chest" or "tightness of the heart". Typically, the cause of coronary heart disease is an atherosclerosis of the coronary vessels.

Blood test for angina pectoris

In case of an unstable angina pectoris, the coronary vessels coarctate so that the cardiac muscle is subject to insufficient blood circulation. The result are the typical chest pains. Just as in case of a cardiac infarction, it is of particular importance that the patient receives a vasodilating treatment as soon as possible so that the cardiac muscle does not sustain permanent damage. Nowadays, a cardiac infarction can be diagnosed very early and sensitively with the troponin test. For chest pains of unknown origin that may hint at angina pectoris no such clinical test exists to date.

Researchers at the DZHK partner sites Hamburg/Kiel/Lübeck and Rhine-Main have now identified a set of microRNAs that may potentially ease the diagnosis of an unstable angina pectoris in patients with chest pains. In daily clinical practice, it is difficult to distinguish these pains from other chest pains. "Unstable" angina pectoris means that the pains are occurring for the first time or are getting worse.

MicroRNAs are involved in a lot of cardiovascular diseases and circulate in the blood. The researchers found eight microRNAs that were elevated in patients with unstable angina pectoris. They do, therefore, suggest to utilise these as a biomarker set for the detection of an unstable angina pectoris. Such a biomarker set could contribute towards protecting patients from a looming myocardial infarction by quickly having the correct treatment performed, such as the dilation of the constricted vessel. Patients whose chest pains have other causes would be spared this procedure.

The researchers now want to test the suitability of the microRNA set in a larger patient collective in the real clinical environment.

PAPER OF THE MONTH 4/2014:
Assessment of MicroRNAs in Patients with Unstable Angina Pectoris. Zeller, T., Keller, T., Ojeda, F., Reichlin, T., Twerenbold, R., Tzikas, S., Wild, P., Reiter, M., Czyz, E., Lackner, K. J., Munzel, T., Mueller, C. & Blankenberg, S. *Eur Heart J 35,* (2014).

Physicians must be able to decide very quickly whether chest pains are an indication of a coronary heart disease, or whether there are other causes.

Focus: Treatment of coarctated coronary vessels

If coronary vessels are coarctated or even obstructed, they must be opened up again immediately so that the cardiac muscle receives a sufficient supply of blood. In cardiology, this is done with catheter-based methods, for instance by dilating the vessel with a small balloon (balloon angioplasty) or through the insertion of a stent. During the treatment, the patients receive medications such as aspirin which are intended to prevent their platelets from sticking together and to prevent blood clots (thromboses) from blocking off the vessels again.

Aspirin effect can predict risk

Not all patients respond equally well to the administration of aspirin for inhibiting the conglobation of platelets. In a registry study, DZHK scientists of the partner site Munich have examined whether a correlation existed between the response to aspirin and the risk of death or a stent thrombosis in the subsequent year. For this, they have analysed the data of approx. 7,000 patients who had undergone a catheter procedure on the heart. During the procedure, these patients, among other things, received aspirin. It was determined to what extent aspirin actually led to an inhibition of platelet activity. Accordingly, a high platelet activity is equivalent to a low response to aspirin.

The researchers put the value for the platelet activity in correlation to whether the respective patients were befallen by the events of death or stent thrombosis in the subsequent year. They found out that patients with high platelet activity had a significantly higher risk of dying or suffering a stent thrombosis. Since the platelet activity with aspirin is easy to measure in daily clinical practice, this biomarker can be used as an additional indicator for which patients are at particular risk of suffering a cardiovascular event again.

The effect of aspirin can predict whether patients are at risk of suffering additional severe cardiovascular events.

The researchers suggested to add the value of platelet activity under aspirin to the already existing, established prognostic biomarkers in order to achieve an improved risk assessment for this patient collective.

PAPER OF THE MONTH 10/2014:

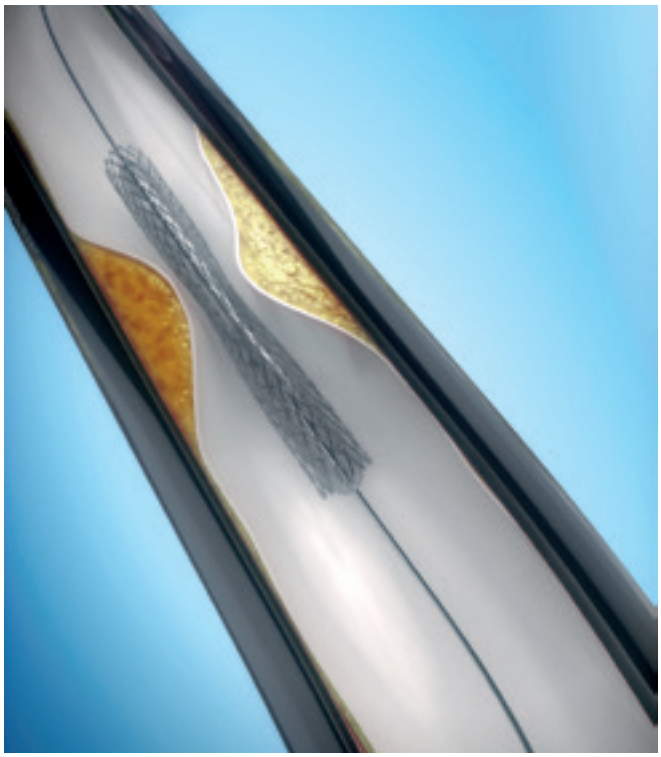
Aspirin Treatment and Outcomes after Percutaneous Coronary Intervention: Results of the Isar-Aspi Registry. Mayer, K., Bernlochner, I., Braun, S., Schulz, S., Orban, M., Morath, T., Cala, L., Hoppmann, P., Schunkert, H., Laugwitz, K. L., Kastrati, A. & Sibbing, D. *Journal of the American College of Cardiology 64*, 863-871, (2014).

Focus: Treatment of angiostenosis by means of stent

If coronary vessels are coarctated, a stent can be inserted to keep them open permanently. In this, it can happen that the vessel is slowly closing up again at the spot where the stent was placed, due to increased growth of connective tissue. Such a restenosis is the most common complication after the insertion of a stent.

So that vessels do not close up again

An international team of researchers under the leadership of DZHK researchers from the partner site Hamburg/Kiel/Lübeck has discovered a mechanism that is, to a considerable degree, responsible for the renewed coarctation of arteries. Subsequent to vessel injuries, for instance when inserting stents, an inflammatory reaction occurs. As a result, the smooth muscle cells in the arterial wall temporarily change into a state that is characterised by rapid cell division and reduced cellular death (apoptosis). This state only exists temporarily, but it is responsible for the vessels growing again.



A constricted vessel is dilated with a stent. However, quite often it closes up again.

Photo: © CLIPAREA.com – Fotolia.com

The researchers found a mitochondrial key protein that regulates this early phase. They inhibited this protein and were thereby able to counter the narrowing of the arteries. These new mechanisms were not only described in cell culture and in the small animal model but have already been tested in the large animal model. With this, basic research has found a target that can lead to new substances that could be used in the clinic for the prevention of angiostenosis. It is important that the inhibition of the mechanism does not disrupt the relining of the vessels with an endothelial layer (re-endothelialisation); this is of great importance for the healing of the vessels.

In addition to 15 scientists of the Universitätsklinikum Hamburg-Eppendorf (UKE), scientists from USA/Stanford, Sweden/Stockholm, Spain/Salamanca and Germany/Lübeck were also involved. A clinical DZHK study regarding this is in the planning stages at the Hamburg/Kiel/Lübeck partner site.

PAPER OF THE MONTH 5/2014:

Dichloroacetate Prevents Restenosis in Preclinical Animal Models of Vessel Injury. Deuse, T., Hua, X., Wang, D., Maegdefessel, L., Heeren, J., Scheja, L., Bolanos, J. P., Rakovic, A., Spin, J. M., Stubbendorff, M., Ikeno, F., Langer, F., Zeller, T., Schulte-Uentrop, L., Stoehr, A., Itagaki, R., Haddad, F., Eschenhagen, T., Blankenberg, S., Kiefmann, R., Reichenspurner, H., Velden, J., Klein, C., Yeung, A., Robbins, R. C., Tsao, P. S., Schrepfer, S., *Nature*, (2014).

Focus: Remodelling processes in the diseased heart

Permanent hypertension as well as constrictions at the heart valves or at the aorta mean very heavy labour for the heart. If this burden is compensated for via excessive muscle growth, chronic cardiac insufficiency all the way up to heart failure may be the result.

Inhibition of calcineurin could be treatment for cardiac insufficiency

The enzyme Calcium/Calmodulin-dependent kinase II (CaMKII) is a protein kinase that adds phosphate groups to other molecules (phosphorylation) and this way influences the activity of these molecules. The enzyme calcineurin is a phosphatase which conversely splits phosphate groups off of other molecules (dephosphorylation) and, this way, also influences the activity of molecules.

The role of both molecules for cardiac diseases has been researched in depth in the last 20 years. There are numerous indications that both CaMKII as well as calcineurin, which are both activated by calcium-dependent mechanisms, are important key enzymes in the occurrence and progression of chronic cardiac insufficiency. There are, however, also contradictory findings regarding whether it is merely the experimental over-activation of this enzyme that is inducing the disease process or whether the activation of the enzymes that exist in the cardiac muscle cells is sufficient to induce it.

Researchers of the Heidelberg/Mannheim partner site, for the first time, used a new mouse-genetic model in which all CaMKII genes that exist in the heart were switched off so that no more CaMKII activity in the cardiac muscle cells was detectable. This way, it was possible to determine which target molecules are specifically phosporylated by CaMKII. It was found, among other things, that CaMKII induces the phosphorylation of calcineurin and thereby inhibits calcineurin. In the hearts of mice without CaMKII activity, accordingly an activation of the calcineurin contained in the cardiac muscle cells was observed. This led to a growth of the cardiac muscle. The new, surprising insight is that the calcineurin-induced growth of the cardiac muscle led to an improved function and to fewer abnormal remodelling processes after a stress of the heart. Based on these findings, the researchers concluded that the inhibition of CaMKII but not the inhibition of calcineurin is a promising approach for the treatment of chronic cardiac insufficiency.

Patients with severe heart failure are severely limited in their functional capacity.

PAPER OF THE MONTH 8/2014:

The Cardiac Camkii Genes Delta and Gamma Contribute Redundantly to Adverse Remodeling but Inhibit Calcineurin-Induced Myocardial Hypertrophy. Kreusser, M. M., Lehmann, L. H., Keranov, S., Hoting, M. O., Kohlhaas, M., Reil, J. C., Neumann, K., Schneider, M. D., Hill, J. A., Dobrev, D., Maack, C., Maier, L. S., Grone, H. J., Katus, H. A., Olson, E. N. & Backs, J. Circulation, (2014).J. *Circulation*, (2014).

Focus: Research of genetic causes in cardiovascular diseases

Be it atherosclerosis, myocardial infarction or heart failure – occurrence and course of cardiovascular diseases depend on a mix of genetic and environmental factors. Therefore, researchers are searching for typical genetic changes in those who are sick. The knowledge of which genes are involved in which diseases allow for better prevention and can lead to new therapies and individual treatment approaches.

Genetic map for dilated cardiomyopathy

In dilated cardiomyopathy (DCM), the left ventricle is severely expanded and the pumping power of the heart is diminished. DCM is therefore one of the most common causes of heart failure. In approx. half of all cases there is a familial accumulation which can be caused by a multitude of different genetic mutations.

With Next Generation Sequencing (NSG), a large number of patients can be examined for characteristic genetic changes.

Photo: © DZHK

DZHK researchers from the Heidelberg/Mannheim partner site have – in the context of the international INHERITANCE consortium – for the first time examined a large patient group (n=639) by means of Next Generation Sequencing (NGS). With NGS, the base sequence of very large amounts of DNA can be sequenced with a high throughput in a very short period of time. The researchers examined the patient samples for 84 known genes that have been associated with DCM. In this, they also found that the genetic differences between the participating countries were relatively small.

In approx. half of the patients, the researchers found genetic changes (mutations) that were already described as known which will make the interpretation of genetic testing easier in the future. One surprise was that in DCM patients it was often possible to also identify mutations of other cardiac muscle diseases which is currently being investigated in additional DZHK studies.

The consortium for the first time applied a highly standardised and quality-controlled NGS to a large DCM patient collective. With the recorded data, researchers will, in the future, be able to more closely examine, for instance, the connection between genetic mutation and clinical picture. The goal is to, at some point, be able to have a custom treatment for DCM corresponding to its genetic causes.

PAPER OF THE MONTH 9/2014 (NOMINATED):
Atlas of the Clinical Genetics of Human Dilated Cardiomyopathy. Haas, J., Frese, K. S., Peil, B., Kloos, W., Keller, A., Nietsch, R., Feng, Z., Muller, S., Kayvanpour, E., Vogel, B., Sedaghat-Hamedani, F., Lim, W. K., Zhao, X., Fradkin, D., Kohler, D., Fischer, S., Franke, J., Marquart, S., Barb, I., Li, D. T, ., Amr, A., Ehlermann, P., Mereles, D., Weis, T., [...] Katus, H. A. & Meder, B. *Eur Heart J,* (2014).

Focus: Gene therapy for rare cardiac disease

Some severe cardiac diseases clearly have genetic causes. If this is a single disease-causing gene, it can be replaced with a healthy gene by means of gene therapy. In an ideal case, the cells permanently integrate the gene, the treatment lasts a lifetime, and the patient is healed. To date, there is only one approved gene therapy in human medicine which is aimed at a congenital lipometabolic disorder.

Successful gene therapy in mice with congenital heart disease

Approx. one in five hundred people is born with a genetic defect of the cardiac muscle. This defect can lead to a situation where the muscle wall of the left ventricle is thickened – the so-called hypertrophic cardiomyopathy (HCM). The heart cannot pump as well and has a tendency towards cardiac arrhythmia. In young, athletic people, HCM is the most common cause of sudden cardiac death.

A particularly severe form of HCM, from which newborns are already suffering, leads to death within the first year of life. HCM can be triggered by different genetic defects. In each case, the structure and function of proteins of the sarcomere are impacted, which are those proteins that are responsible for the tensing and relaxing of the cardiac muscle. To date, HCM cannot be healed. The patients receive medications that alleviate the symptoms of the disease. In case of severe forms, only a heart transplantation helps.

Young mice can be healed from a severe form of cardiomyopathy with a single application of a gene therapy agent.

DZHK researchers from the Hamburg/Kiel/Lübeck partner site have now, for the first time, tested in the mouse model a promising approach for a gene therapy of HCM. For their tests, they selected mice that were suffering from newborn-HCM. This severe form of HCM is caused by a very frequent change in the gene for cardial myosin-binding protein-C (cMyBP-C). With the help of a transport vehicle common in molecular biology, a benign virus envelope, the researchers inserted the correct genetic materials targetedly into the cells of the cardiac muscle. The diseased, one day old mice received a single dose of the therapeutic gene. Over a period of up to 34 weeks after the treatment, the researchers examined the morphology and pumping characteristics of the mice hearts. These differed hardly at all from healthy hearts.

In addition, the researchers were able to prove that the cardiac muscle cells produced approx. two thirds of the healthy cMyBP-C protein, whereas these cells produced only ten percent before the treatment. The findings provided the researchers with cause for optimism; they now want to apply the results to human beings.

PAPER OF THE MONTH 12/2014:

Mybpc3 Gene Therapy for Neonatal Cardiomyopathy Enables Long-Term Disease Prevention in Mice. Mearini, G., Stimpel, D., Geertz, B., Weinberger, F., Kramer, E., Schlossarek, S., Mourot-Filiatre, J., Stoehr, A., Dutsch, A., Wijnker, P. J., Braren, I., Katus, H. A., Muller, O. J., Voit, T., Eschenhagen, T. & Carrier, L. *Nature communications 5*, 5515, (2014).

Scientific infrastructure within the DZHK

On the campus of the University Medical Center Göttingen, a new MRI building was built in 2014, in which real-time MRI research is to be carried out in the context of the DZHK.

The scientific infrastructure within the DZHK was developed in 2014 in different contexts: the DZHK partner sites invest part of their DZHK site funds into scientific infrastructure, for example into large equipment and biobanks. But some partner sites have also created extra building capacities for the DZHK research that could be financed through other sources. And last but not least, in 2014, the central infrastructure for clinical research was developed within the DZHK which, in addition to devices, software and know-how, also includes regulations.

New laboratories for the DZHK

In Göttingen, a new MRI building was erected in 2014, which was fi nanced by the university. In said building, studies are being carried out with the real-time MRI developed by Göttingen DZHK PI Jens Frahm. The Göttingen partner site is investing a significant share of its DZHK site funds into research that is to bring the new MRI method into clinical application. For this research, the new infrastructure is providing the best prerequisites. Furthermore, another research and laboratory building is to be erected at the partner site, funded by the university.

At the Heidelberg site, the analysis centre “Analysezentrum III” was opened, a modern laboratory and analysis building that now houses the cardiologists and cardiovascular researchers of the DZHK site. The building was, to a great degree, financed by the Klaus Tschira Foundation. The placement of the different working groups in one building promotes the close and interdisciplinary cooperation as well as the intense exchange of the DZHK working groups.

High-quality devices for preclinical and clinical projects

Corresponding to the research strategy of the DZHK, the partner sites have – in 2014 – invested part of their site funds in equipment that is needed for carrying out preclinical research projects and clinical studies. As such, at two partner sites, each, the most modern echocardiography equipment for patient exams and small animal exams was procured. In the context of clinical research, the DZHK will collect biomaterials from patients. For this, the partner sites, in part, have to modernise and expand their capacities for the storage and logistics of biomaterial samples. In addition, analysers for biomaterials were procured, such as fluorescence activated cell sorters, and the sequencing platforms were expanded.

Central infrastructure for clinical research

The more uniform and the more reliable data from clinical studies is, the more value it has for current and future research projects. For this reason, the DZHK has created joint regulations, standards and ancillary regulations for its multicentre studies as well as a central IT infrastructure. Of great importance in this is the consistent compliance with current data protection regulations and ethical standards. Only this way it can be assured that all data and biomaterials are gathered, processed and archived in the same form and fashion that is absolutely compliant with respect to ethics and data protection.

The harmonisation process started 2012 and in late 2014 reached another important milestone with the inclusion of the first patient into the TORCH registry. The uniform clinical-scientific infrastructure of the DZHK allows for combining data from different DZHK studies and analysing it time and again with new scientific goals. This way, a unique nationwide “treasure trove” of cardiovascular data in Germany is created over the years, in which also future researchers can search for causes and treatment options for cardiovascular diseases using methods not yet known today.

In addition to the IT infrastructure, the clinical-scientific infrastructure also includes rules and regulations that are geared towards the uniform gathering and utilisation of data and samples. The following elements currently constitute the clinical-scientific infrastructure of the DZHK:

Central data management (ZDM)

The central data management (ZDM) of the DZHK officially commenced regular operations in December 2014 with the first patient inclusion. It consists of the trusteeship office of the Greifswald University Hospital and the data management at the Department of Medical Informatics of the University Medical Center Göttingen.

The personal data of a patient from a DZHK study is initially transmitted to the trusteeship office via an encrypted connection and is replaced with a pseudo-

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nym there. Under this pseudonym, the clinical data of a study is stored and archived in a special web-based data entry software (secuTrial) in the data maintenance at the Department of Medical Informatics in Göttingen. The pseudonymity is a data protection requirement since only this way it can be ensured that nobody can connect the personal data of a patient with said patient's health data. The trusteeship office also manages the declarations of consent of the patients.

Standard Operating Procedures (SOP) ensure that the examination of study patients is carried out in the same way at all sites.

Standard Operating Procedures (SOP)

For clinical examinations, the DZHK has developed a total of eight Standard Operating Procedures (SOP) to date. They stipulate in which way clinical data is to be gathered. It is only this way that the data is subsequently usable for cross-centre and even cross-study analyses. In 2015, additional SOPs for the gathering and storage of biomaterials will be added.

Usage regulation and ethics concept

All clinical studies that are primarily funded by the DZHK are required to adhere to the central and harmonised rules of the DZHK. The patients have to transfer the ownership of and/or usage right to the data and biomaterials to the DZHK. This way, the DZHK can retain the meta data and raw data for potential secondary utilisations and can ensure access to the samples long-term for additional research purposes.

An important step in 2014 was the adoption of the uniform usage regulation for data and samples from DZHK studies. The usage regulation was coordinated in a comprehensive process involving all (back then) 28 partners of the DZHK and was agreed upon unanimously in the General Assembly of Members. It is available for download on the Internet so that interested external study centres can also inform themselves of the regulations at the DZHK. Serving as basis for the application of the usage regulation is a joint ethics concept of the DZHK which provides the template for the ethical principles of the DZHK studies.

Collection of biomaterial

In addition to diagnostic and therapeutic data, all clinical studies that take place within the DZHK will also collect biomaterials such as blood, urine, or tissue. Within the DZHK, the biomaterials are stored decentralised, which means that each partner site is equipped with its own biomaterial storage. Just as with the clinical data, to make the comparison of the biomaterials of different sites possible, an approach that is as uniform as possible is necessary in the collection, further processing and storage. Just as with the clinical data, this is regulated by SOPs.

Biomaterials that were obtained in the context of DZHK studies are stored decentralised.

In the reporting period, the members of the DZHK have decided to create a joint so-called basic biobanking collection for the benefit of medical research, in particular for cardiovascular research. This means that all DZHK studies, in addition to the biomaterials that they require, also collect a set of biomaterials that is the same for all studies. This collection allows for cross-study research with these materials.

For the recording and administration of the biomaterial data, a technical system, a so-called laboratory information [management] system (LIMS) is necessary. The purchase was approved in 2013 by the General Assembly of Members. In the reporting period, biobanking-specific processes and requirements were defined and coordinated as well as compiled in a directory of services which constitutes the basis for an international putting out to tender to external service providers. The studies that have already started initially begin without such a system while implementing a transitional solution. In the planning and implementation of the transitional solution care was taken to implement the fundamental principles of the long-term DZHK biomaterial collection.

Data protection concept

In 2014, the DZHK created an overarching data protection concept for the central data management (ZDM). It was presented to the Technology, Methods and Infrastructure for Networked Medical Research (TMF) “Data Protection” working group and received a positive vote.

Image data management

In clinical studies within the DZHK, among other things medical images are generated such as in case of MRI or echocardiography. These are to be captured perspectively in a joint image data management system (BDMS). To establish such a cross-centre system is a very complex challenge and requires technical, logistical, scientific and financial considerations. In 2014, the imaging experts of the DZHK developed an initial concept for such a BDMS and presented it to the General Assembly of Members. The adoption of the concept and the start of the implementation will take place in 2015.

Goals for 2015

In order to be able to utilise the central infrastructure for clinical research under optimal conditions, the individual partners must also have access to uniform technical equipment. Therefore, we are striving for equipping all clinical DZHK partners in 2015 with the necessary infrastructure such as uniform analytical and diagnostic equipment and uniform equipment for

In the future, image data obtained in clinical studies is to be managed with a central image data management system.

biobanking. For this, an investment program was established in late 2014 already. In this context it is also planned that the clinical partners set up uniform "phenotyping units" which are uniform examination rooms. In addition to contributing to the standardisation of the phenotyping of patients of the DZHK studies, this also contributes to an increased visibility of the DZHK, since these rooms and/or units will be very clearly marked as belonging to the DZHK.

In 2015, we will establish a Use & Access Committee which is to oversee the handing out of the data for research purposes. For this, the approval and data hand-out processes in the transfer partner site must be defined. For the LIMS, the contract with a service provider should be concluded in 2015 and the implementation should start. Another goal for 2015 is to convert all documents regarding the clinical studies to English so that we can integrate international partners into our studies without a problem.

Goals for 2015 at a glance

- **DZHK research building at the Göttingen partner site completed (financed with funds of the university)**
- **Uniform minimum standards of equipment of the clinical study centres of the DZHK established**
- **Phenotyping units set up**
- **Use & Access Committee established**
- **Decision made for a laboratory information management system**
- **All documents for clinical studies also available in English**

Cooperation and scientific exchange within the DZHK

Translation can only succeed when experts of different disciplines and institutions are acting in concert.

Translation requires cooperation, both across partner site boundaries as well as across disciplines. The DZHK has therefore created structures and funding measures for the funding of internal cooperations. But in 2014 the DZHK also entered into cooperations with different external partners (cf. Chapter 8).

Board of Directors and RCC

The triumvirate Board of Directors of the DZHK convenes twice a month at the main office; the chairman of the Board, Thomas Eschenhagen, is in Berlin every week. The most important panel within the DZHK is the Research Coordinating Committee (RCC). Members of the RCC are partner site spokespersons, members of the Board, representatives of member institutions and individual scientists who represent specific subject areas. In 2014, it was embodied in the bylaws that the spokesperson of the Young DZHK may also be represented in the RCC and has a voting right. First and foremost, the RCC discusses structural and research strategy questions. In 2014 the preparation of the DZHK midterm evaluation and the setup of the Translational Research Group (TRG, cf. Chapter 3) and of the Clinical Study Group (CSG, cf. Chapter 4) were at the centre of the meetings. Additional panels of the DZHK can be found in the chapter “Facts and Figures: Committees and Governance”.

Project groups

As a result of the 2013 strategy discussion, the DZHK has transitioned toward replacing disease-related program groups with topic-oriented project groups. The

project groups are time-limited cooperatives of DZHK scientists; they do not have a budget of their own. In 2014, ten project groups founded themselves that dealt with topics such as prevention and nutrition, myocarditis in children and adults, replacement of heart tissue by means of tissue engineering, or DNA-based and RNA-based treatments. The project groups serve to generate ideas within the DZHK and to prepare projects to a point where they result, for example, in larger translational research projects or clinical studies. For these, applications can then be submitted in the context of the flexible funds. The establishing of project groups is decided upon by the Board of Directors based upon corresponding applications. Project groups approved by the Board of Directors are listed on the Intranet and can utilise the DZHK video conference platform as well as bill travel costs for meetings via the DZHK.

Symposia, lectures, congresses

DZHK symposia are an internal, cross-site instrument of scientific exchange regarding DZHK-relevant topics that we introduced in the second half of 2014. In 2014, two symposia were funded:

- Aortic valve insufficiency: Myocardial fibrosis as marker and as target, November 6, 2014, Berlin (30 attendees from five DZHK sites)
- Receptors, G Proteins and Integration of Ca2+ Signaling in the Cardiovascular System, 2. – 22 November 2014, Berlin (150 attendees from all DZHK sites)

External attendees were allowed at the first two symposia, too. Starting 2015, the internal exchange within the DZHK will be a clear focus of this instrument. Ideas for symposia are introduced in the RCC and discussed there under research strategy perspectives. The RCC then decides on which symposia are going to be held; attendance, by now, is possible only for DZHK members – aside of select external speakers. For scientific events of a DZHK member facility there is the option to invite a presenter for a DZHK lecture (2014: 7). Typically, this is a scientist from another DZHK site. This instrument increases the visibility of the DZHK within the member institutions and the exchange across sites.

DZHK Retreat and Young DZHK Retreat

In 2014, the DZHK Retreat took place for the second time, this time September 25-27 in Braunlage (Harz Mountains). The DZHK Retreat was preceded by a one-day retreat for the Young DZHK. The DZHK Retreat is the most important instrument for the exchange with the DZHK beyond executive committees. The number of attendance requests significantly exceeded the 160 spots offered. After the strategy of the DZHK had been the main topic of discussion at the 2013 retreat, the reporting year featured a comprehensive program of scientific presentations and workshops that was modelled after the DZHK research strategy.

In addition to scientific exchange, the retreat also contributes towards DZHK members growing together into a true community.

Photo: © DZHK

During the retreat, representatives from biotech companies reported on their concrete experiences with translation.

One highlight was the panel discussion regarding practical examples for successful translation. For this, we were able to attract representatives of young biotech companies who, for instance, reported on the hurdles to and conditions of success of translation based on the example of the market introduction of the first gene therapy for a lipometabolic disorder. At the focus of the scientific program were current research topics such as microRNA as potential new therapeutic agents, prevention, imaging, OMICs technologies, gene therapy, arrhythmia, epidemiology, as well as clinical studies. In her much recognised keynote presentation regarding the topic of gene regulation, Eileen Furlong, PI at the European Molecular Biology Laboratory (EMBL), impressively illustrated how important the understanding of fundamental molecular processes is for considerations regarding translation.

The Young DZHK Retreat was independently conceptualised by members of the Young DZHK and was organised with the support of the main office. 55 young scientists attended the Young DZHK Retreat. Condition for attendance was that the attendees submit an abstract for a poster or a presentation. With kind support of Bayer AG, it was possible to present a DZHK poster prize to the best three scientific presentations. The award winners then had the opportunity to present their research at the beginning of the main retreat and this way effected an exciting start. The Young DZHK Retreat was a great success and contributed considerably to the networking of the DZHK young scientists from different sites and disciplines. It will therefore become a fixed staple within the DZHK.

The DZHK scientists and young scientists are wishing for the retreat to alternatingly take place in the surrounding area of the DZHK sites in the future. This was the result of a 2014 survey in which 375 people participated. As a result, Potsdam (Berlin), Bad Aibling (Munich) and the Baltic Sea region (Greifswald) were specified as retreat sites for 2015 to 2017.

Scientific exchange in the laboratory

In the context of the training program (cf. Chapter 9), members of the Young DZHK can apply for a

The Young DZHK Retreat took place for the first time in 2014 and was a great success.

Photos: © DZHK

time-limited research stay at another DZHK partner site. The goal is to learn new laboratory and analysis methods and to integrate them into one's own research work. In 2014, the DZHK funded 18 of these exchanges within the DZHK (2013: 19). Additional exchanges took place with external laboratories.

Internal communications

The internal newsletter of the DZHK, published in monthly issues, informs all people involved in the DZHK (PIs, DZHK scientist, members of the Young DZHK, partner site managers, employees of the administration of partner institutions) of calls for tender, deadlines, scientific events, the Paper of the Month and other news and by now features approx. 1,000 recipients.

In 2014, the Intranet of the DZHK grew further and is also supporting administrative processes with new features. Since 2014, users have been able to submit registrations online for internal events such as the retreat, symposia and workshops and also for congresses with external attendees. This saves a lot of work and is very user-friendly. The tool was already utilised for the retreat and the two symposia in 2014. Eventually, this area is also to be expanded for the submission of application in the context of the training program.

The Internet-based video conference system of the DZHK is also enjoying increasing popularity. It is being utilised for regular meetings of the main office with the site managers, but also by project groups, the scientific advisory board, the central data management and panels of assessors. During the period of April 2014 to April 2015, 357 meetings with a total of 1,555 participants were conducted.

Goals for 2015

In this area, the primary focus is on filling new instruments of scientific exchange with life. Internal symposia are intended to shift even more towards the character of internal think tanks regarding scientific and cross-discipline issues. During the symposia, the status quo within the DZHK is to be presented and new research collaborations are to be initiated based thereupon. As a result, DZHK project groups could for instance be created or Shared Expertise offered. Project groups have similar goals, but regarding a somewhat more restricted topic.

From the latter, applications for preclinical or clinical projects within the DZHK or even applications for projects with third party funding are to result in 2015, if possible.

In 2015, the internal communications are to be improved in such a way that the funding processes and administrative processes, which are increasingly becoming more and more complex and comprehensive, become more transparent and – where possible – get the red tape cut. Rendering the funding guidelines more uniform and leaner is intended to serve this purpose just like FAQ on the Internet and the user-friendly visualisation of processes based on flowcharts.

Goals for 2015 at a glance

- **Carried out at least three DZHK symposia**
- **Project groups have provided concrete results (applications for DZHK projects or projects with third party funding)**
- **Designed funding processes more transparently and clearer**

External cooperations

For translation, the joining of forces of the most diverse disciplines and institutions is indispensable. Therefore, the DZHK has embodied cooperations with external partners in its research strategy and reserved ten percent of its funds for these cooperations. The external cooperations take place in the three major areas of research of the DZHK, preclinical research, clinical research and promotion of young scientists.

Research cooperations with external partners

With the Shared Expertise, the DZHK makes its whole expertise in the area of preclinical research available to all DZHK partners. Furthermore, scientists of the DZHK can cooperate with external partners, subject to similar regulations if their expertise does not exist within the DZHK. Both partners receive funds from the DZHK for the joint project. In the reporting year, 13 applications for cooperation with external partners were assessed positively within the DZHK. The cooperation project had, among other things, the goal to identify new target molecules for therapy development or to validate in animal models molecules that had already been examined. But biomarker studies and OMICs analyses were performed, too.

Cooperations in clinical research

In clinical research, the DZHK is highly motivated and even dependent on cooperating with external centres. Most studies can only reach the necessary number of patients if external partners include patients in DZHK studies. In case of the VAD study prepared in 2014, for example, which involved the transplantation of a cardiac support system, all of Germany's 30 transplantation centres were willing to include patients in order for the number of 500 patients to be reached. The TransitionCHF cohort study is cooperating with the working group of leading cardiological hospital doctors, Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte e.V. (ALKK), in order to also be able to recruit patients in local hospitals.

In addition, external partners can associate with their studies at the DZHK. The DZHK association shows that the DZHK is providing non-material support to the study and, for example, wants to promote the recruiting into the study by means of its network. In 2014, we have associated two studies of DZHK partner institutions that were already funded by third parties. These studies, in turn, sometimes have international partners. This way, the DZHK is networked worldwide with the clinical research scene and is visible above and beyond the confines of the sites and the borders of Germany.

In clinical research and in the development of the central data management and the DZHK biobanking, the DZHK cooperated closely with TMF – Technology, Methods and Infrastructure for Networked Medical Research. In the area of biobanking, in particular, a regular exchange with the responsible parties for the biobanks and IT of other German Centres of Health Research and of the German Biobank Node (GBN) is taking place which is to be intensified further.

Industry cooperations

The transfer of new diagnostic or therapy principles into clinical practice often is possible only with the

support of industry partners. For the search for suitable active ingredients by means of high throughput screening or for the optimisation of target structures all the way to clinical studies, the pharmaceutical industry and biotechnology companies feature unique prerequisites and competencies. Therefore, the DZHK has made it its goal to enter into strategic partnerships with industry partners.

We are in negotiations with an industry partner in which we are advised and supported by the Ascenion technology transfer firm. Above and beyond that, we are also interested in cooperating with additional partners. Questions of intellectual property (IP) must be negotiated and regulated thoroughly in such cooperations.

Series of joint workshops with the German Cardiac Society (DGK)

Since 2013, the DZHK has held the series "Fundamentals of Cardiovascular Research" jointly with the DGK; in autumn 2014, such a workshop took place already for the sixth time in cooperation. The DGK organises two workshops each during its spring and fall conference; in the summer, a workshop designed and organised by the DZHK takes place in Berlin at the DZHK main office. This cooperation brings DZHK young scientists together with other young scientists and increases the visibility of the DZHK in the cardiovascular scene.

Cooperations with Deutsche Herzstiftung

The DZHK is cooperating with the German heart foundation Deutsche Herzstiftung, in particular when it comes to educating and informing patients. The heart foundation has done excellent work in this area for decades. We have therefore decided to not establish a medium of our own for patient education. However, in order for interested patients to be able to find out what is topical in cardiovascular research, we have started to report on DZHK research topics in the patient magazine of the heart foundation, "Herz heute (Heart Today)". In addition, approx. 30 primarily clinically active DZHK PIs are on the scientific advisory board of the heart foundation. They are integrated into the patient consultation hours of the heart foundation that take place on a regular basis, and they respond to inquiries online and by phone.

Goals for 2015

We will intensify our external cooperations in 2015. In clinical research, we want to begin to also involve external centres in DZHK studies. From the integration of the competence networks, we hope for an integration of external centres that recruit patients into our clinical studies. We are aiming for concrete negotiations regarding a cooperation agreement with an industry partner for late 2015.

Goals for 2015 at a glance

- **Initiation of at least two external study centres that recruit patients into DZHK studies**
- **Draft contract of a structured cooperation with an industry partner**

Promoting junior researchers – The Young DZHK

Attendees at the 1st Young DZHK Retreat in Braunlage in September 2014.

Translation needs young people who dedicate themselves to this task and who can combine clinical and experimental knowledge. This is why the promotion of junior researchers is of such great significance in the DZHK. While in 2013 only approx. 34 applications by young scientists in the training program were submitted, in 2014 these already amounted to more than 180.

The Young DZHK

In 2013, all measures aimed at early career researchers of the DZHK as well as the officially registered young scientists were combined under the label Young DZHK. In 2014, the number of Young DZHK members has more than doubled in comparison to 2013 (2014: 387, 2013: 149).

In order to be able to better represent the interests and needs of young, translationally working researchers, the young scientists already started to establish structures of their own within the DZHK in 2013. Since 2014, the PostDoc representative body has been an official panel within the DZHK, which is also embodied in the bylaws. The spokeswoman from the Hamburg/Kiel/Lübeck partner site, Dorothee Atzler, has been a voting member in the Research Coordinating Committee since 2014; Jan Haas from the Heidelberg/Mannheim partner site is vice spokesman. The group consists of two PostDocs per DZHK partner site.

Dorothee Atzler, spokeswoman of the PostDoc representative body

Jan Haas, vice spokesman of the PostDoc representative body

The DZHK has established a comprehensive program for the promotion of young scientists. It supports young scientists who decide on a career in translational cardiovascular research.

Photo: © DZHK

In 2014, the young scientists organised a retreat of their own for the first time which took place one day before the DZHK Retreat in September in Braunlage (also, cf. Chapter 7). In addition, the PostDoc representative body suggested in 2014 to establish a program for the promotion of excellence for post-doctoral young scientists and physicians within the DZHK, in addition to the measures of the training program. In cooperation with the main office, the group developed five modules for this (re-integration grant, rotation grant for physicians, research grant (release from teaching), PostDoc start-up grant, DZHK junior research group), which were adopted in 2014. The excellence program is going to start 2015 with the first calls.

Furthermore, the Young DZHK members are initiating a workshop series of their own. Here, they want to pick up topics which are suggested and selected by the young scientists within the DZHK themselves since they are not yet sufficiently reflected in the continuing education offers to date. The workshop series will start 2015 with workshops regarding the topics of "Applied Regression Modeling" and "Scientific Grant Writing".

Training program of the DZHK

In 2014, a particularly high number of young scientists took advantage of the option to present their results at high-ranking congresses and conferences and were granted a travel grant for this (2014: 106, 2013: 12). In the context of the mobility program of the DZHK, young scientists can go to a laboratory of a partner institution in order to learn or apply a method. The program promotes the scientific exchange and the networking of the DZHK partner institutions. In addition, young scientists can also visit external labo-

ratories, which was predominantly the case in 2014. Of the 51 approved applications, 19 young scientists went to DZHK laboratories and 32 to external laboratories. In 2014, too, medical students who work for at least one year full-time on their doctoral thesis were promoted with a DZHK doctoral scholarship (2014: 25; 2013: 13).

Mentoring program

In March 2014, the first annual group of the DZHK mentoring program started with twelve participants. The mentoring is geared towards young physicians, scientists and science managers. The goal is to make the young scientists from cardiovascular research fit for a leadership role. Preferably, applicants are approached for whom reconciling family and professional demands poses a particular challenge. In workshops customised to their needs, the mentees can learn soft skills and in coaching sessions they can prepare for challenging situations in professional leadership positions. In a survey, all mentees interviewed assessed the program with very good to good.

According to the survey, they benefitted in particular from the expansion of their professional network and from the improvement of their communication skills. In September 2014, the call for applications started for the second annual group which will begin in March 2015.

Further elements in the promotion of young scientists are the Young DZHK Retreat and the joint workshop series with the German Cardiac Society (DGK). They are described in the chapters “Cooperation and scientific exchange within the DZHK” and “Cooperation with external partners”.

Goals for 2015

The Young DZHK is composed dynamically, young scientist regularly switch institutions early in their career in order to develop themselves further. This must also be reflected in the turnover rate of the Young DZHK members which we have to track. The measures for the promotion of excellence will be spelled out for the first time in 2015 and the first promotions are to be awarded to qualified young scientists. Furthermore, in the year ahead, medical students who dedicate at least one year full-time to their doctorate will be sponsored with scholarships.

Goals for 2015 at a glance

- Document a turnover rate of at least ten percent in the Young DZHK
- At least 20 doctoral scholarships for physicians
- Award five PostDoc start-up grants
- Award five rotation positions
- Establish at least one junior research group

Photo: © DZHK

The DZHK in public

In April, the DZHK – for the first time – appeared with a booth of its own at the Annual Conference of the German Cardiac Society in Mannheim.

In 2014, the DZHK increasingly pursued media relations activities; we distributed 13 press releases (2013: 4). The DZHK media relations activities led to coverage in reputable newspapers and/or magazines such as the Standard, the taz or Focus, as well as to publication on Internet portals and to inquiries from the press. In cooperation with other publishers, we were able to achieve that contributions regarding the DZHK were published in "Herz heute (Heart Today)", in the BMBF newsletter Health Research and in the World Health Summit Yearbook 2014.

In 2014, the DZHK – for the first time – appeared with a booth of its own at the Annual Conference of the German Cardiac Society (DGK) in Mannheim in April. This was a great success and increased the visibility of the DZHK within the German cardiovascular scene.

In the program, the DZHK was represented with three sessions of its own.

Restructurings and the realignment of the strategy necessitated a relaunch of the DZHK website which went online at the end of 2014. Now, the area of clinical research is represented adequately, too. Located here is an overview of all currently ongoing clinical studies of the DZHK, including contact information and recruiting figures. The number of website visitors increased from 23,000 in 2013 to 35,000 in the reporting year.

The symposia sponsored by the DZHK received an area of their own on the DZHK homepage and were advertised with flyers with the DZHK corporate design. Registrations were carried out via the registration tool

on the DZHK Intranet. In 2014, the DZHK financially supported two congresses that were organised by a DZHK member facility and touched on the areas of research of the DZHK. The congresses listed the DZHK with logo as sponsor and held special DZHK sessions in the program. Both contributed towards increasing the visibility of the DZHK within the cardiovascular research landscape. In 2014, the DZHK – in a leading role – organised two events with a public impact for the DZG, a workshop featuring international experts regarding the topic of translation at the World Health Summit in Berlin in October, as well as a parliamentary evening of the DZG which took place in Berlin in February 2015. Due to the positive feedback of these events, the DZG agreed upon continuing and further intensifying joint activities in public relations. As such, an event in Brussels is planned and the DZG will also appear jointly again at the World Health Summit 2015.

Goals for 2015

In 2015, the DZHK will – jointly with the Cardiological Competence Networks – have a larger booth at the DGK Annual Conference. In addition, a brochure regarding the promotion of young researchers within the DZHK is to be published in 2015.

We are also planning on increasing the visibility of the DZHK at the sites. For this, the DZHK institutions at the sites are to be better equipped with signs. In addition, DZHK professors will be provided with a guideline indicating how they can direct more attention to their special professorship within their institution. The international visibility of the DZHK is also to be increased; for this, we want to develop a concept in 2015. Furthermore, we want to explore additional media formats such as videos in order to increase the popularity of the DZHK in further target audiences and in order to be able to better utilise the distribution options of social media. In the area of clinical research, we want to provide detailed information on the Internet for patients who participate in our studies.

The DZHK, jointly with the other DZGs, wants to position the group of the German Centres of Health Research as one of the most important players in German health research. For this, we will develop a concept for a DZG research magazine and suggest it to the other DZGs.

Photo: © DZHK

Goals for 2015 at a glance

- **Brochure regarding DZHK promotion of young researchers published**
- **Visibility of the DZHK at partner institutions (DZHK professorships and DZHK projects on website, signage) increased**
- **DZHK video series launched**
- **Patient information for study participants is online**
- **Concept for DZG research magazine created**

Benchmarks

Translational research can only be successful when it combines strong basic research with clinical research.

How can the success of translational research be assessed? Ever since its founding, the DZHK has been discussing this question jointly with the other German Centres of Health Research (DZG). To date, internationally, there are no generally applicable benchmarks for the success of translational research, either. Common research benchmarks, such as high-ranking publications are only of peripheral relevance to research institutions with a translational or clinical alignment since these are not capable of measuring progress from a patient's point of view.

The DZHK is therefore proposing benchmarks here that seem, at a minimum, to be applicable to translational cardiovascular research. We are quite aware that some of them might turn out to be unsuitable and will continue the process of benchmark development. Also, at this Benchmarks point, we cannot yet support the benchmarks with facts since we did not capture this information systematically in the past. However, we have started to do so now.

Level A – Prerequisites for successful translation

1. Physician scientists

Translation requires people who carry it out at the interface between practical medicine and research. Therefore, the number of physician scientists who published at least one scientific paper as first author during the reporting period may be a suitable benchmark.

Additionally, a differentiation can be made under which DZHK-specific prerequisites the publication occurred:

- Scientists with DZHK-financed positions
- Financing through DZHK programs (e. g. mobility program, cooperation by means of Shared Expertise, partner site funds, excellence program)

2. Documented cooperations between partner sites

Translation is an interface process; it can only be successful if different partners work together. We therefore suggest the number of cooperations in the context of Shared Expertise, the number of publications with at least two DZHK authors of different partner sites and the number of cooperative project groups and/or the frequency of the meetings as a benchmark.

3. Documented communication with regulatory authorities

In order for new therapies to be able to reach patients, they must comply with statutory provisions. To identify them and take them into consideration already in the research process is possible only through the integration of and close contact with the corresponding offices. Therefore, the communication and cooperation with them is indispensable and may serve as a benchmark.

4. Documented cooperation with the industry

When a treatment has proven its efficacy and safety, it needs a partner who brings it to market. To effect an optimal transition here, the cooperation with industrial partners should start already at a very early research phase. Such cooperations may therefore constitute a suitable benchmark.

5. Cooperative structures

Quality (type) and quantity (frequency of utilisation) of these structures in the area of clinical research allow for drawing conclusions as to how successful the translation within the DZHK is. We have established and/or are in the process of establishing the following structures and regulations within the DZHK: central data management, trusteeship office, ethics concept, laboratory data management system, image data management system, usage regulation. Efficiency and degree of realisation of these structures can be utilised as benchmark.

Quantifiable are: number of Standard Operating Procedures (SOPs), number of documented utilisa-

tions of biomaterials of the DZHK, number of documented utilisations of data from the clinical studies of the DZHK.

6. High-ranking publications

Translation is possible only based upon new insights from basic research. These are reflected in high-ranking publications. The number of such publications (all, impact factor greater than 10) is therefore a supplemental indicator for successful translation.

7. Pre-clinical projects and clinical studies

Only when research projects systematically have individual steps of the translation chain as their content, can the process be ultimately successful. The number of translational projects may therefore serve as a benchmark. In the context of its research strategy, the DZHK is focusing on the following research projects:

- Number of new or improved cell and animal models
- Number of on-going late preclinical studies (large animal models, dose-response examinations, pharmacokinetics)
- Number of on-going clinical studies that are financed or primarily financed by the DZHK
- Number of published clinical studies
- Performance of the clinical studies
  - Start-up time (time from the confirmation of funding to the first patient inclusion)
  - Recruiting
  - Time until publication (from end of study)

Level B – mid-term successes in translation (< 5 years)

- Number of published studies that show the effect of a new principle
- Number of first-in-man studies
- Number of successfully tested new treatments/ diagnostics
- Economic success (this includes spin-offs or licensing to companies)

Level C – long-term successes in translation

- Number of guidelines that where changed due to DZHK studies
- New therapeutic and diagnostic principles that were developed by DZHK researchers and made it into clinical application
- Number of patients who were treated in accordance with new therapeutic or diagnostic principles
- Economic savings due to new therapeutic or diagnostic principles

Goals for 2015

The benchmarks are initially specifically tailored to the DZHK. We want to further discuss with the other DZG which generally applicable benchmarks are suitable for translational research and arrive at a final result, here. In 2015, we will start to systematically capture and analyse the data regarding the aforementioned benchmarks.

Goals for 2015 at a glance

- **Discussion with the other DZG regarding the benchmarks completed**
- **First collection of the DZHK benchmarks for 2014 completed**

BMBF initiative "German Centres of Health Research"

The German Centres of Health Research constitute new research structures for fighting the great endemic diseases.

As in the past, the number of people who suffer from or are newly falling ill with endemic diseases such as cancer, cardiovascular diseases, metabolic diseases, infectious diseases, lung diseases, or neurodegenerative diseases is giving cause for concern. To create optimal research conditions to fight endemic diseases is a central concern of the German Centres of Health Research (DZG). These Centres were founded in the years 2009 to 2011 upon the initiative of the German Federal Ministry of Education and Research (BMBF) in order to optimise the so-called translation process from research result to application in patients, i.e., to bring new medical research results into application faster and to improve the prevention and treatment of endemic diseases. They are funded jointly by the federal government (90 percent) and the German states (10 percent), in 2014 with funds in the amount of more than 225 million euros. In 2015, these funds will increase once more significantly to 280 million euros.

At the focus of the research works are, among other things, an improved prevention and diagnosis all the way to concept for individualised treatments that are jointly aimed at an optimal care of patients. This long-term funding sustainably strengthens the high innovation potential of health research at the science location Germany.

A total of 41 sites with more than 100 partner institutions constitute the six German Centres of Health Research in the areas of neurodegenerative diseases, diabetes, infectious diseases, cardiovascular diseases, lung diseases and cancer.

Advisory bodies featuring internationally high-ranking experts accompany the work of the DZG to ensure that the Centres are and remain active at the top of the scientific progress. Additionally, at regular intervals, external international panels of assessors evaluate the Centres with respect to scientific excellence and strategic alignment; for the DZHK, this took place in 2014 (cf. Chapter 1).

Ever since their founding, the German Centres of Health Research have been working together closely, both scientifically and administratively. In 2014, the DZHK was the leader in organising this cooperation. (cf. Chapter 1).

Finances and staff

Finances

In 2014, the DZHK had available EUR 14,632 thousand in new funds and a carry-over from 2013 in the amount of EUR 4,842 thousand. Funds in the amount of EUR 16,112 thousand were utilised. For comparison: in 2013, there were EUR 12,337 thousand in new funds, a carry-over from 2012 in the amount of EUR 1,694 thousand, withdrawn were EUR 9,387 thousand.

The outflow of funds, therefore, significantly improved in comparison to 2013; relative to the new funds, it was at 110 percent in 2014 (2013: 73 percent). The creation of a joint financial controlling by the DZHK main office, funding management and partner site management, the supplementation of partner site management with additional clerk positions and the offer to the partner sites to increase projects for one-time purchases necessary from a scientific point of view were decisive for this.

The funds of the DZHK are provided jointly by the federal government (90 percent) and by those German states in which the member institutions of the DZHK are headquartered (10 percent). For the preparation of the year-end financial statement of the association, Schomerus & Partner Berlin (tax advisers, attorneys at law, auditors) was contracted.

In the reporting year 2014, the DZHK **funding management office** (FMM) at the Max Delbrück Center for Molecular Medicine continued to pass on funds for project funding to 26 of the 33 [1] partner institutions of the DZHK. This was in addition to the passing on of funds to a steadily increasing number of external cooperation partners (eleven in 2014). In cooperation with the main office, the processes for the implementation pertaining to grant law of the DZHK concept of competitive funding offers were optimised and expanded. In total, 454 projects were funded in 2014 (2013: 292 projects).

For a more in-depth inspection of the proof of utilisation, 13 of the 292 projects from 2013 were selected and checked, six of them by means of on-site inspection.

Staffing costs/material costs/investment resources of the DZHK in EUR thousand

- Staffing costs: 7,407
- Material costs without investments: 3,666
- Investments: 2,199

Staffing costs/material costs/investment resources of the association/main office in EUR thousand

- Staffing costs: 480
- Material costs without investments: 313
- Investments: 16

1 The DZHK e.V. has 28 members. Additionally, there are four Max Planck Institutes as partner institutions and the main office of the DZHK e.V.

Number of staff financed by the DZHK categorised by the respective German state in which the member facility has its headquarters (with main office and funding management office).

DZHK-Personal 2014	BE	BW	BY	HE	HH	MV	NI	RP	SH	GSt.	FMM	Total
Number of staff (as of 31 December) VZÄ	20,45	28,41	19,50	15,72	8,76	19,83	20,45	6,50	10,50	8,50	7,15	165,77
Number of staff (as of 31 December) heads	28,00	39,00	25,00	25,00	14,00	31,00	32,00	7,00	14,00	10,00	9,00	234,00
of those male	9,00	13,00	12,00	8,00	5,00	10,00	14,00	2,00	3,00	1,00	1,00	78,00
of those female	19,00	26,00	13,00	17,00	9,00	21,00	18,00	5,00	11,00	9,00	8,00	156,00
Number of scientific staff members (FTEs)	10,20	21,22	12,70	7,09	5,09	12,09	13,85	2,00	6,50	3,80	2,00	96,54
Number of scientific staff members (heads)	16,00	27,00	18,00	11,00	8,00	18,00	22,00	2,00	9,00	4,00	2,00	137,00
of those male	6,00	11,00	10,00	4,00	3,00	7,00	13,00	2,00	2,00	0,00	0,00	58,00
of those female	10,00	16,00	8,00	7,00	5,00	11,00	9,00	0,00	7,00	4,00	2,00	79,00
Number of non-scientific staff members (VZÄ)	9,25	6,19	5,80	8,63	1,67	7,74	5,60	4,50	3,00	4,70	5,15	62,23
Number of non-scientific staff members (heads)	11,00	11,00	6,00	14,00	4,00	13,00	9,00	5,00	4,00	6,00	7,00	90,00
of those male	2,00	1,00	1,00	4,00	1,00	3,00	0,00	0,00	1,00	1,00	1,00	15,00
of those female	9,00	10,00	5,00	10,00	3,00	10,00	9,00	5,00	3,00	5,00	6,00	75,00
Number of DZHK professorships (FTEs)	2,00	2,00	3,00	1,00	2,00	2,00	3,00	1,00	1,00	0,00	0,00	17,00
Number of DZHK professorships (heads)	2,00	2,00	3,00	1,00	2,00	2,00	3,00	1,00	1,00	0,00	0,00	17,00
of those planned	1,00	1,00	2,00	1,00	0,00	2,00	2,00	1,00	0,00	0,00	0,00	10,00
of those filled	1,00	1,00	1,00	0,00	2,00	0,00	1,00	0,00	1,00	0,00	0,00	7,00
of those male	1,00	1,00	1,00	0,00	1,00	0,00	1,00	0,00	0,00	0,00	0,00	5,00
of those female	0,00	0,00	0,00	0,00	1,00	0,00	0,00	0,00	1,00	0,00	0,00	2,00

BE: Berlin, Berlin partner site (Berlin and Brandenburg, Brandenburg 2014 without DZHK personnel)
BW: Baden-Wurttemberg, Heidelberg/Mannheim partner site
BY: Bavaria, Munich partner site
HE: Hesse, Rhine-Main partner site
HH: Hamburg, Hamburg/Kiel/Lübeck partner site
MV: Mecklenburg-West Pomerania, Greifswald partner site
NI: Lower Saxony, Göttingen partner site
RP: Rhineland-Palatinate, Rhine-Main partner site
SH: Schleswig-Holstein, Hamburg/Kiel/Lübeck partner site

There was an increased cash balance in only one project which was balanced out under a simultaneous interest payment. At the FMM, as of December 31, 2014, the DZHK funded 7.15 FTEs, which were distributed across nine people and the tasks of management, scientific inspection, inspection of applications and proofs of utilisation, controlling and office management.

Personal

In 2014, as of December 31, 165.77 full-time equivalents (FTEs) and/or 234 "heads" were financed from DZHK funds. This also included 10 employees of the DZHK main office and 9 employees of the funding management office.

In 2014, the gender distribution was as follows:

- of all employees financed by the DZHK, 66.6 percent women and 33.3 percent men;
- of scientific staff members, 57.7 percent women and 42.3 percent men;
- of DZHK professorships, 28.6 percent women and 71.4 percent men.

Principal Investigators (PI), DZHK scientists, Young DZHK members

In addition to the scientists funded by the DZHK, Principal Investigators (PIs) are of central importance to the DZHK. In most cases, the PIs are not funded by the DZHK but introduce their ideas and their expertise in the cooperation within the DZHK and as such form the basis of our success. In the reporting year, the DZHK had 138 PIs. PIs are appointed by the partner sites and confirmed by the General Assembly of Members. Each site features a maximum of 20 PI spots wherein there are additional spots for each DZHK professor working at the partner site.

In order to map people to the DZHK, we introduced – already in 2013 – the two statuses "Young DZHK member" and "DZHK scientist". Both statuses have to be applied for. Prerequisites are a defined engagement within the DZHK and the option of assignment to a DZHK PI working at a partner facility. In the reporting year, the DZHK had 195 DZHK scientists (2013: 130) und 386 Young DZHK members (2013: 149).

Photo: © DZHK

Scientific achievements

Publications 2014	Number 2014 (2013)
DZHK affiliation	**368** (255)
DZHK acknowledgement	**36** (7)
First authorship of a DZHK-PI	**11** (21)
Last authorship of a DZHK-PI	**130** (103)
In cooperation with other DZHK site (PI)	**40** (17)
Journals by Nature Publishing Group[1]	**11** (10)
Journals by Cell Press[2]	**4** (3)
NEJM, Lancet, JAMA	**9** (2)
Circulation, Circ Res, EHJ, JCI, JACC	**51** (51)

1 includes Nature, Nat Med/Nat Cell Biol/Nat Immunol/Nat Genet
2 includes Cell, Cell Metabolism, Cell Stem Cell, Molecular Cell

Publications

In September 2012, the DZHK already developed rules for a joint DZHK affiliation and a DZHK acknowledgement. Here, we are presenting the figures of the corresponding publications and as an example the "Paper of the Month" from the reporting year 2014. A complete list of the publications with DZHK affiliation and/or DZHK acknowledgement can be found on the Internet at: http://dzhk.de/forschung/publikationen

The DZHK Board of Directors selects virtually every month a **Paper of the Month** which subsequently is announced in the DZHK newsletter and is published on the Internet via the DZHK website.

February 2014: Disruption of Vascular Ca2+-Activated Chloride Currents Lowers Blood Pressure. **The Journal of Clinical Investigation 124, 675-686 (2014)** (DZHK authors: Seniuk, Ehmke)

March 2014: MicroRNA-126-5p promotes endothelial proliferation and limits atherosclerosis by suppressing Dlk1, **Nature Medicine 2014, doi:10,1038/nm.3487** (DZHK authors: Schober, Weber)

April 2014: Assessment of microRNAs in patients with unstable angina pectoris, **European Heart Journal, doi: 10,1093/eurheartj/ehu151** (DZHK authors: Zeller, Keller, Wild, Münzel, Blankenberg)

May 2014: Dichloroacetate prevents restenosis in preclinical animal models of vessel injury, **Nature (2014), doi:10,1038/nature13232** (DZHK authors: Deuse, Zeller, Eschenhagen, Blankenberg, Reichenspurner, Schrepfer)

June 2014: The beta-hydroxybutyrate receptor HCA2 activates a neuroprotective subset of macrophages,

Nature Communications (2014), doi:10,1038/ ncomms4944 (DZHK authors: Müller-Fielitz, Offermanns, Schwaninger)

July 2014: Silencing of CCR2 inmyocarditis, **European Heart Journal, doi:10,1093/eurheartj/ ehu225** (DZHK authors: Leuschner, Meder, Katus)

August 2014: The Cardiac CaMKII Genes Delta and Gamma Contribute Redundantly to Adverse Remodeling but Inhibit Calcineurin-Induced Myocardial Hypertrophy, **Circulation, doi:10,1161/ CIRCULATIONAHA. 114,006185** (DZHK authors: Lehmann, Hoting, Maier, Katus, Backs)

September 2014: Essential role of sympathetic endothelin A receptors for adverse cardiac remodeling, **PNAS, doi: 10,1073/pnas.1409026111** (DZHK-authors: Lehmann, Spiger, Wieland, Katus, Backs)

October 2014: Aspirin treatment and outcomes after percutaneous coronary intervention: results of the ISAR-ASPI registry, **doi: 10,1016/j. jacc.2014.05,049,** (DZHK authors: Bernlochner, Schulz, Morath, Schunkert, Laugwitz, Kastrati, Sibbing)

November 2014: Cardiac myocyte-secreted cAMP exerts paracrine action via adenosine receptor activation, **doi: 10,1172/JCI74349,** (DZHK authors: Ahles, Dendorfer, Engelhardt)

December 2014: Mybpc3 Gene Therapy for Neonatal Cardiomyopathy Enables Long-Term Disease Prevention in Mice. **Nature communications 5, 5515, (2014).** (DZHK authors: Mearini, G., Stimpel, D., B., Weinberger, F., Kramer, E., Schlossarek, S., Braren, I., Katus, H. A., Muller, O. J., Eschenhagen, T. & Carrier, L.)

Spin-offs

At the DZHK partner site Heidelberg, InoCard GmbH was founded as a spin-off of the Heidelberg University Clinic in December 2013. The biotech spin-off of the DZHK PIs Patrick Most and Hugo Katus pursues the goal of developing a novel gene therapy against myocardial insufficiency. The biological principle of the gene therapy is based on the protein S100A1 which is capable of regenerating the pumping power of the diseased cardiac muscle. The founding of the company was based on preliminary works of a DZHK project at the Heidelberg University Clinic.

With the Dutch biotech firm uniQure NV, a partner for the biotechnological development of S100A1 technology could be won in 2014. The most recent partnership with Bristol Myers Squibb now secures the clinical development with a worldwide operating biopharmaceutical company.

Goals for 2015 at a glance

- **Increase the scientific output of the DZHK and, in particular, the number of cooperative publications**
- **In total, a minimum of 400 publications with DZHK affiliation**
- **A minimum of 150 publications with DZHK authors as first or last author**
- **A minimum of 50 publications with PIs from at least two sites**
- **A minimum of 70 publications with DZHK young scientists as first author**
- **A minimum of 60 publications with an impact factor greater than 10**

Personalia, prizes and awards

Award winners of the poster prize of the Young DZHK Retreat on September 25, 2014: **Ilka Mathar,** *Heidelberg/Mannheim;* **Christian Müller,** *Hamburg/Kiel/Lübeck;* **Claudia Noack,** *Göttingen.*

PD Dr. med. Konstantinos Stellos, Frankfurt University Clinic, Medical Clinic III/Cardiology and Institute for Cardiovascular Regeneration in February received the Else Kröner Memorial Scholarship of the Else Kröner Fresenius Foundation which pays EUR 200,000.

Prof. Dr. Stefan W. Hell, Max Planck Institute for Biophysical Chemistry in Göttingen, in May received the Kavli Prize as one of the worldwide highest awards, paying USD 1 million. The prize was awarded in recognition of his research results regarding overcoming the diffraction limit of optical microscopes.

Prof. Dr. Sonja Schrepfer, University Heart Center of the Universitätsklinikum Hamburg-Eppendorf (UKE), was in July awarded with the Innovation Prize of German Higher Education Medicine, valued at more than EUR 10,000, for her insights regarding a new mechanism that plays an important role in the healing of damaged vessel walls.

Prof. Dr. Vera Regitz-Zagrosek, Director of the Institute of Gender In Medicine (GiM) of the Charité and spokeswoman of the DZHK site Berlin, was in October honoured with an honorary doctorate of the Innsbruck Medical University for her outstanding contributions in the area of gender medicine.

Prof. Dr. Martin Borggrefe, University Medical Centre Mannheim, received the Silver Medal of the European Society of Cardiology (ESC) for his multi-year active participation on the Board of the ESC, last as Vice President International.

Dr. Reinier Boon, Institute of Cardiovascular Regeneration of the Goethe-University Frankfurt am Main, in December received the ERC Starting Grant of the European Research Council (ERC) in the amount of EUR 1.5 million, based on the research of the last years and the strong expertise of the Rhine-Main site with respect to the investigation of non-coding RNAs.

Prof. Dr. Stefan W. Hell, Max Planck Institute for Biophysical Chemistry, in December received the Nobel Prize in Chemistry for the invention of superresolution fluorescence microscopy. His method enables researchers to take a look at the molecular inner workings of cells and to identify structures that are smaller than the wavelength of visible light.

DZHK professorship appointments within the reporting period:

On September 1, 2014, the Göttingen site appointed **Stefan Anker** (previously Berlin) as DZHK W3 Professor for Innovative Clinical Studies at the University Medical Center Göttingen. He is active in the area of clinical studies and, in addition, deals with cachexia (severe emaciation) that often occurs in patients with severe cardiac insufficiency.

Also since September 2014, **Holger Gerhardt** (previously: Vascular Biology Laboratory, London Research Institute, UK) has been W3 Professor at the Charité – Universitätsmedizin Berlin and senior group leader at the Max Delbrück Center for Molecular Medicine. The professorship is funded by the DZHK and by the Berlin Institute of Health – BIH. Gerhardt's focal points are the density and arborisation of blood vessels and their adaptation to metabolic processes which – if these processes are misdirected – can have an impact on cardiovascular and metabolic diseases.

Stefan Anker

Holger Gerhardt

Tanja Zeller

Tanja Zeller, from the Hamburg/Kiel/Lübeck site, started the DZHK professorship "Genomics and System Biology" at the Hamburg-Eppendorf University Clinic (UKE) on October 1, 2014. The focal point of her research is the identifi cation of molecular biomarkers in the area of cardiovascular diseases. For this, the workgroup of Tanja Zeller combines molecular cellbiological and bioinformatics-statistical methods with genetic and clinical epidemiology into system-medical approaches.

Committees and governance of the DZHK

The General Assembly of Members of the DZHK is making all important strategic decisions.

The **Board of Directors** convenes regarding the strategic alignment of the DZHK and represents the Centre externally. During the reporting period, it met 19 times at the main office in Berlin. Thomas Eschenhagen, spokesman of the Board, was at the main office one day per week.

The **Research Coordinating Committee (RCC)** convened ten times at the main office in 2014. All sites are represented within the RCC. The RCC is a committee that advises and prepares the General Assembly of Members, but can also be considered as an "expanded Board of Directors".

The **General Assembly of Members** is the topmost organ of the association and convened twice in 2014. In the General Assembly of Members, all fundamental decisions are made regarding strategic alignment, changes to the structure of the association, acceptance of new DZHK-PIs and the business plan and investment plan of the Centre. In 2014, the General Assembly of Members re-elected the Board of Directors for the years 2014 to 2017 (Thomas Eschenhagen, Gerd Hasenfuß) and newly elected (Thomas Sommer as successor to Walter Rosenthal), respectively.

The international and high-calibre filled **Scientific Advisory Board** in 2014 convened once in Berlin and another time via video conference in order to advise the DZHK regarding its scientific alignment and its development.

The **Commission of Donors (KdZG)** convened twice; it is the Centre's committee for exchange with the donors, meaning with the BMBF and the ten German states where partner site headquarters are located. In strategic as well as essential financial, organisational and personnel questions, the Board of Directors and the General Assembly of Members are required to obtain the approval of the Commission of Donors.

In the **main office,** a staff of ten including the managing director were working (8.5 FTEs as of 31 December 2014) in the reporting period. The work of the main office is focussed on supporting the Board of Directors in coordinating the scientific work within the DZHK. In the reporting period, this included, in particular, the

- Organisation of all selection processes and assessment processes in the areas of preclinical research, clinical research and training program
- Development of new funding guidelines for High Risk High Volume Late Translational projects, guidelines for relevant clinical studies and for early clinical studies as well as the revision of the funding

guidelines for the training program and the development of new funding guidelines for "promotion of excellence measure" (e. g. young scientist group leaders and committees and governance of the DZHK rotation positions)
- Organisation of the mentoring program
- Coordination of the joint project regarding central data management and execution of the sub-project for this assigned to the main office (preparation of the development of a laboratory information [management] system and of an image data management system)
- Preparation and organisation of the first meetings of the Steering Committee of the Clinical Study Group (CSG) and of the Translational Research Group (TRG)
- Development and coordination of the documents for the DZHK midterm evaluation
- Organisation, preparation and post-processing of any and all committee meetings
- Development of a financial controlling jointly with the funding management office and the site management
- Media relations and public relations as well as internal communication of the DZHK (cf. Chapter 10)

The employees of the main office and of the funding management office constitute the central part of the DZHK administration. It is supplemented by the seven decentralised site managements in which typically one scientist with half a position funded by the DZHK (science manager) is working and since 2014 one clerk is funded by the DZHK with a full position. The staff in the funding management office, in the site management and in the main office have worked together closely and well in 2014, including in the context of 44 weekly video conferences and six meetings. Jointly, they constitute the science administration of the DZHK.

The DZHK main office in the reporting year 2014 (from left to right): Isa Hauke, Katharina Eulenburg, Christine Vollgraf, Christiane Heiß, Birgit Wilms, Stephanie Lesser, Annett Grützmacher, Joachim Krebser, Anna Pannier

Photo: © DZHK

Donors of the DZHK

- Federal Ministry of Education and Research (BMBF)
- Baden-Wurttemberg
- Bavaria
- Berlin
- Brandenburg
- Hamburg
- Hesse
- Mecklenburg-West Pomerania
- Lower Saxony
- Rhineland-Palatinate
- Schleswig-Holstein

Partner sites

Vera Regitz-Zagrosek
Site spokeswoman

Roland Hetzer
Vice site spokesman

Carola Schubert
Site manager

DZHK partner site Berlin

Site spokeswoman: Vera Regitz-Zagrosek, Director of the Institute of Gender in Medicine (GiM), Charité – Universitätsmedizin Berlin

Vice site spokesman: Roland Hetzer, German Heart Institute Berlin

Partner site manager: Carola Schubert, Charité – Universitätsmedizin Berlin

Site clerk: Patrick Cochanski, Charité – Universitätsmedizin Berlin

Partner institutions at the Berlin DZHK site

- Charité – Universitätsmedizin Berlin
- Max Delbrück Center for Molecular Medicine in the Helmholtz Association (MDC)
- German Heart Institute Berlin
- Federal Republic of Germany, represented by the Federal Ministry of Health, represented by the Robert Koch Institute (RKI)
- German Institute of Human Nutrition (DIfE) Potsdam-Rehbrücke

Research focus within the DZHK

At the centre of research at the Berlin site is the research of cardiac muscle diseases, vascular diseases and metabolic diseases. A research focus exists in identifying epigenetic and genetic biomarkers, developing new imaging processes and analysing the impact of gender, age, ethnic affiliation and lifestyle on the development of cardiovascular disease. There is a close networking of the Berlin DZHK site with the DFG special research area “Sex differences in cardiovascular protection and maladaptation” as well as the DZHK-funded Competence Network Congenital Cardiac Defects. The basic research of the site was strengthened in the reporting period through the procurement of a small animal echogram device in the context of the 2014 scale-up program. Furthermore, the stem cell platform at the MDC was significantly improved through new devices from the scale-up program. In the area of preclinical research, in 2014 a total of 21 Shared Expertise (SE) were offered, of which five were utilised at other sites. From this, seven cooperations with other sites resulted. In an additional seven cases, the Berlin site utilised the Shared Expertise offered by other sites. In the area of clinical research, the VAD study centre at the DHZB was expanded further and the clinical personnel for the four clinical institutions at the site was recruited and hired. In the reporting year, the site was able to win four new high-ranking cardiovascular researchers who also are or are intended to be PIs within the DZHK (Volkmar Falk, Burkert Pieske, German Heart Institute Berlin; Ulf Landmesser, Charité – Universitätsmedizin Berlin; Holger Gerhardt, Max Delbrück Center for Molecular Medicine).

Wolfram H. Zimmermann
Site spokesman

Eberhard Bodenschatz
Vice site spokesman

Axel Kaul
Site manager

DZHK site Göttingen

Site spokesman: Wolfram H. Zimmermann, Head of the Department of Pharmacology, University Medical Center Göttingen

Vice site spokesman: Eberhard Bodenschatz, Director of the Max Planck Institute for Dynamics and Self-Organization

Site manager: Axel Kaul, University Medical Center Göttingen

Site clerk: Sylvia Vann, University Medical Center Göttingen

Partner institutions at the Göttingen DZHK site

- Georg-August-University Göttingen and University Medical Center Göttingen
- Max Planck Institute for Biophysical Chemistry (MPIbpc)
- Max Planck Institute for Dynamics and Self-Organization
- Max Planck Institute of Experimental Medicine
- German Primate Center

Research focus within the DZHK

The research focus of the Göttingen site is cardiac insufficiency research with the topics of "Mechanisms of the transition of clinical asymptomatic mycardial insufficiency" as well as "Cardiac regeneration in case of cardiac insufficiency". In the area of preclinical research, six Shared Expertise from Göttingen were utilised by other sites in 2014. From this, nine cooperations with other sites resulted. In an additional five cases, the Göttingen site utilised the Shared Expertise offered by other sites. In the area of clinical research, the site coordinated the TransitionCHF cohort study and was – jointly with the Berlin site – responsible for the coordination of the VAD study. Jointly with the Greifswald site (trusteeship office) and the DZHK main office, Göttingen is responsible for the "Central Data Management" for clinical DZHK studies. The construction of an MRI centre with 2,400 square meters at the German Primate Center was completed and two new, powerful MRI scanners (Siemens Prisma 3T and Bruker BioSpec 94/30 9.4 T) were installed. In 2014, the cardiac catheter laboratory was in the construction phase, the relocation of the cardiac catheter system is planned for the second half of 2015. An electronic laboratory journal for the coordination of a decentralised biobank for induced pluripotent stem cell models from patients and healthy subject was established; it was piloted at the partner sites Göttingen and Hamburg and is intended to go into application DZHK-wide in 2015. On December 10, 2014, Stefan Hell, Göttingen DZHK PI, received the Nobel Prize in Chemistry for his invention of STED microscop

Stephan B. Felix
Site spokesman

Ulrich John
Vice site spokesman

Stefan Groß
Site manager

DZHK site Greifswald

Site spokesman: Stephan B. Felix, Director of the Internal Medicine Clinic, University Hospital Greifswald

Vice site spokesman: Ulrich John, Director of the Institute of Social Medicine and Prevention, University Hospital Greifswald

Site manager: Stefan Groß, University Hospital Greifswald

Site clerk: Anne-Kathrin Beiersdorf, University Hospital Greifswald

Partner facility at the Greifswald DZHK site

- University Hospital Greifswald

Research focus within the DZHK

The execution of population-based epidemiological and clinical studies with comprehensive cardiovascular phenotyping, research regarding the prevention of cardiovascular diseases, high-throughput OMICs analyses, telemedicine, biobanking as well as data management/analysis are a particular expertise of the Greifswald site. In the area of preclinical research, a total of nine Shared Expertise (SE) were offered in 2014. In the area of clinical research, the Greifswald site is integrated in the development of a cross-site scientific DZHK infrastructure in the area of patient data management and biobanking. In the area of infrastructures for clinical research, the trusteeship office of the central data management (collaborative project jointly with the Göttingen site and the DZHK main office in Berlin) has been established in Greifswald. For this, a corresponding infrastructure for the administration of the personal data of the study subjects was set up in 2014. For the TORCH study, the site started the patient management in 2014; in addition, the basic and study biobanking for the whole DZHK was set up and coordinated by the Greifswald site in 2014. At the end of 2014, the Greifswald University Hospital was right at the verge of including patients in the first clinical studies of the DZHK as including study center.

Thomas Eschenhagen
spokesman

Norbert Frey
site spokesman

Gabriele Huhn
Site manager until the end of 2014

DZHK site Hamburg/Kiel/Lübeck

Site spokesman: Thomas Eschenhagen, Director of the Institute of Experimental and Clinical Pharmacology and Toxicology, Universitätsklinikum Hamburg-Eppendorf

Vice site spokesman: Norbert Frey, Director of the Clinic of Cardiology and Angiology, University Medical Center Schleswig-Holstein

Site manager: Gabriele Huhn, Universitätsklinikum Hamburg-Eppendorf (as of 1/1/15: Doreen Stimpel, Universitätsklinikum Hamburg-Eppendorf)

Site clerk: Monika Glimsche, Universitätsklinikum Hamburg-Eppendorf

Partner facility at the Hamburg/Kiel/Lübeck DZHK site

- Universitätsklinikum Hamburg-Eppendorf
- Christian-Albrechts-Universität zu Kiel
- Universität zu Lübeck
- Asklepios Klinik St. Georg

Research focus within the DZHK

In their scientific work, the groups involved at the Hamburg/Kiel/Lübeck site concentrate on the research of genetic risk factors and biomarkers of cardiovascular diseases, the regenerative and biomedical utilisation of pluripotent stem cells and tissue engineering, molecular mechanisms of pathological hypertrophy as well as on the research and individualised treatment of cardiac insufficiency, in particular of genetically caused cardiomyopathies. In the area of clinical research, the site, in 2014, successfully applied for the two new, multicentre clinical studies FAIR-HF (iron therapy in case of cardiac insufficiency, jointly with the Göttingen site) and TOMAHAWK (regarding invasive diagnostics after reanimation); their start is planned for 2015. In the area of preclinical research, 25 Shared Expertise (SE) were offered in 2014, of which seven were utilised by other sites. From this, nine cooperations with other sites resulted. In an additional five cases, the Hamburg/Kiel/Lübeck site utilised the Shared Expertise offered by other sites. With an automated measuring booth for artificial heart tissues from human iPS cells, the DZHK is providing a unique method for target validation and for screening of medicines. In addition, the European Screening Port (Fraunhofer Institute, Hamburg), is – as an external partner – offering to the DZHK a professional high-throughput medicine screening platform in a non-commercial context.

Hugo A. Katus
Site spokesman

Martin Borggrefe
Vice site spokesman

Tanja Weis
Site manager

DZHK site Heidelberg/Mannheim

Site spokesman: Hugo A. Katus, Medical Director of the Internal Medicine Department III, Heidelberg University Hospital

Vice site spokesman: Martin Borggrefe, Director of I. Medical Clinic, University Medical Centre Mannheim

Site managerin: Tanja Weis, Heidelberg University Hospital

Site clerk: Matthias Knüll, Heidelberg University

Hospital Partner facility at the Heidelberg/Mannheim DZHK site

- Heidelberg University
- Heidelberg University Hospital
- University Medical Centre Mannheim
- German Cancer Research Center (DKFZ)
- European Molecular Biology Laboratory (EMBL)

Research focus within the DZHK

The research of hereditary and inflammatory cardiomyopathies is the scientific focus of the Heidelberg/Mannheim site. In the context of a translation pipeline, the cardiomyopathies are being worked on scientifically from genetic and molecular diagnostics all the way to innovative molecular therapy concepts. For this, genetic, epigenetic and electrophysiological analyses, image-producing diagnostics, ps-iPS as well as model systems of cellular systems for the functional analysis of molecular signal paths are utilised. Methodological platforms (Next Generation Sequencing, AAV platform, zebrafish platform, platform for human-relevant disease models) are available to the whole DZHK, just as a modern fully-automated biobank with automated sample processing. In the area of clinical research, Heidelberg/Mannheim coordinates the setup of the TORCH cardiomyopathy register. In the area of preclinical research, 21 Shared Expertise (SE) were offered in 2014, of which five were utilised by other sites. From this, five cooperations with other sites resulted. In an additional seven cases, the Heidelberg/Mannheim site utilised the Shared Expertise offered by other sites. As an important infrastructure development, the new laboratory building “Analysis Center III” in Heidelberg was moved into in 2014, which provides the DZHK with approx. 1,300 square meters of new laboratory and usable floor space. In this context, new institutions for zebrafish and mouse models, for the Next Generation Sequencing, as well as a fully automated biobank for more than one million biosamples were implemented at the same time.

Stefan Engelhardt
Site spokesman

Christian Weber
Vice site spokesman

Sandra Rauser
Site manager

DZHK site Munich

Site spokesman: Stefan Engelhardt, Director of the Institute for Pharmacology and Toxicology, Technische Universität München

Vice site spokesman: Christian Weber, Director of the Institute for Prevention and Epidemiology of Circulatory Disorders, Ludwig-Maximilians-Universität München

Site manager: Sandra Rauser, Technische Universität München

Partner institutions at the Munich DZHK site

- Technische Universität München (TUM)
- Hospital of the Ludwig-Maximilians-Universität (LMU) München
- Ludwig-Maximilians-Universität Munich (LMU)
- German Heart Centre Munich (DHM)
- Klinikum rechts der Isar (MRI)
- Helmholtz Zentrum Munich – German Research Center for Environmental Health
- Max Planck Institute of Biochemistry (MPIB)

Research focus within the DZHK

The scientific focus at the Munich site is on the identification of new therapy targets as well as the development of innovative and optimised processes for the treatment of cardiovascular diseases. In this, the whole medical translation chain from basic research via experimental studies, the examination of clinical sample all the way to the carrying out of clinical studies is mapped. In the area of clinical research, a project at the Helmholtz Zentrum München supports the harmonisation of the ethics applications for the clinical studies, registries and cohorts of the DZHK. For the partially funded DZHK study ISAR-REACT 5 of DZHK PI Prof. Adnan Kastrati (German Heart Centre Munich), patients are continuously being recruited at the participating domestic and international clinics; approx. one third of the planned recruiting volume was achieved by the end of 2014. In the area of preclinical research, 20 Shared Expertise (SE) were offered in 2014, of which eight were utilised by other sites. From this, eleven cooperations with other sites resulted. In an additional seven cases, the Munich site utilised the Shared Expertise offered by other sites.

Andreas Zeiher
Site spokesman

Stefanie Dimmeler
Vice site spokeswoman

Angelika Bonauer
Site manager

DZHK site Rhine-Main

Site spokesman: Andreas Zeiher, Director of Medical Clinic III, Universitätsklinikum Frankfurt

Vice site spokeswoman: Stefanie Dimmeler, Director of the Institute of Cardio-vascular Regeneration, Universitätsklinikum Frankfurt

Site manager: Angelika Bonauer, Universitätsklinikum Frankfurt

Site clerk: Alexander Schwarz, Universitätsklinikum Frankfurt

Partner institutions at the Rhine-Main DZHK site

- Goethe-Universität Frankfurt
- Max Planck Institute for Heart and Lung Research, Bad Nauheim
- Kerckhoff Clinic, Bad Nauheim
- Johannes Gutenberg University Mainz (JGU)

Research focus within the DZHK

The research focus of the Rhine-Main site is on the identification of epigenetic markers and mediators of cardiovascular diseases in order to stimulate the repair and regeneration of vessels and cardiac muscle tissue therewith. In 2014, it was possible to show that the Oncostatin-mediated invasion of macrophages affects cardiac regeneration. In additional basic research studies it was possible to identify non-coding RNAs of different lengths that influence the function of endothelial cells and regulate the survival of cardiomyocytes. At the Mainz University Medical Center, the first interim analysis point was reached with the 1,000th study participant in the MYOVASC cohort study regarding cardiac insufficiency, carried out as a site project (year end N=1,350). The study with multiple phenotyping and comprehensive biobanking is the starting point for numerous translational research projects that are now in the analysis phase. At the Kerckhoff Clinic, furthermore, for the first time a detailed analysis of the population of macrophages in the blood of patients after a cardiac infarction was performed which provides a significant new contribution to the identification of cellular biomarkers after a cardiac infarction. In the area of preclinical research, a total of nine Shared Expertise (SE) were offered in 2014, of which four were utilised by other sites. From this, six cooperations with other sites resulted. In an additional 15 cases, the Rhine-Main site utilised the Shared Expertise offered by other sites. Also in the preclinical area, the application submitted by Stefanie Dimmeler for a “High Risk High Volume Late Translational Project” with the title “Development of miR-92a inhibitors for the treatment of cardiovascular disease” convinced and was granted at the end of 2014 – DZHK-wide as the first one in this line of funding.

Member institutions

New partners in the association

In the reporting period, the number of association members increased from 24 to 28. The most recent members in the DZHK e.V. are the University Medical Center Göttingen, the German Institute of Human Nutrition Potsdam-Rehbrücke (DIfE), the Asklepios Kliniken Hamburg GmbH and the Ludwig-Maximilians-Universität München (LMU).

Member institutions by German states where site headquarters are located

Baden-Wurttemberg
- German Cancer Research Center (DKFZ)
- European Molecular Biology Laboratory (EMBL)
- Klinikum Mannheim GmbH
- Heidelberg University
- Heidelberg University Hospital

Bavaria
- German Heart Centre Munich
- Klinikum rechts der Isar (MRI)
- Hospital of the Ludwig-Maximilians-Universität (LMU) München
- Max Planck Institute of Biochemistry (MPIB)
- Technische Universität Munich (TUM)
- Helmholtz Zentrum München German Research Center for Environmental Health (HMGU)
- Ludwig-Maximilians-Universität München (LMU)

Berlin
- Charité – Universitätsmedizin Berlin
- German Heart Institute Berlin DZHK
- Max Delbrück Center for Molecular Medicine in the Helmholtz Association
- Bundesrepublik Deutschland, represented by the Federal Ministry of Health, represented by the Robert Koch Institute (RKI)

Brandenburg
- German Institute of Human Nutrition (DIfE) Potsdam-Rehbruecke

Hamburg
- Universitätsklinikum Hamburg-Eppendorf (UKE)
- Asklepios Klinik St. Georg

Hesse
- Goethe-Universität Frankfurt
- Kerckhoff Clinic, Bad Nauheim
- Max Planck Institute for Heart and Lung Research, Bad Nauheim

Mecklenburg-West Pomerania
- University Medicine Greifswald

Lower Saxony
- German Primate Center, Göttingen
- Max Planck Institute for Biophysical Chemistry (MPIbpc), Göttingen
- Max Planck Institute for Dynamics and Self-Organization, Göttingen
- Max Planck Institute of Experimental Medicine
- Universität Göttingen
- University Medical Center Göttingen

Rhineland-Palatinate
- Universitätsmedizin der Universität Mainz

Schleswig-Holstein
- Universität Kiel
- Universität zu Lübeck

Acronyms

BDMS	Image Data Management System
CSG	Clinical Study Group
DZG	Deutsche Zentren der Gesundheitsforschung
DZHK	German Centre for Cardiovascular Research
FMM	Funding Management Office
HRHV	High Risk High Volume Late Translational Projects
KdZG	Commission of Donors
LIMS	Laboratory Information Management System
PI	Principal Investigator
RCC	Research Coordinating Committee
SE	Shared Expertise
SOP	Standard Operating Procedure
TRG	Translational Research Group
ZDM	Central Data Management

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