



DZHK
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HERZ-KREISLAUF-FORSCHUNG E.V.

DZG DEUTSCHE ZENTREN
DER GESUNDHEITSFORSCHUNG

German Centre for Cardiovascular Research

ANNUAL REPORT



2016

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.

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Preface

Today, modern cardiovascular medicine is already capable of preventing the worst when it comes to diseases like myocardial infarction, atrial fibrillation or defective cardiac valves. However, cardiovascular diseases cannot yet really be cured. People affected must ordinarily take medication permanently or depend on supportive systems. Thus, in a steadily aging population, the number of people with a restricted quality of life will grow as well. With a life expectancy of 80 years, we spend an average of 10 years being ill. Cardiovascular diseases account for the largest share of these lost years.

For this reason, the German Centre for Cardiovascular Research (DZHK) is intensively searching for solutions to improve the diagnosis and therapy of cardiovascular diseases. Today, these solutions can no longer be found by one research facility alone, instead, the expertise of a great range of specialists from all over Germany is needed. The DZHK has thus been uniting experts from basic and clinical research over the last five years. This allows us to pursue a research strategy in which translation, i.e., the translation of results derived from basic research into clinical application, is the focus.

In the reporting year, the German Council of Science and Humanities (Wissenschaftsrat) was also able to convince itself that this is a laudable and promising approach. In its statement published in July 2017 on the hearing of the six German Centres of Health Research (DZG) in the autumn of 2016, the Council recommended the full continued funding of the DZG and, in addition to this, distinct legal-administrative improvements in order to simplify governance and research funding of these research structures unique in Germany.

For us, as the DZHK, this recommendation of the highest scientific advisory board of the Federal German Government is a tremendous incentive to pursue our objectives further: We want to be able to cure diseases such as heart failure or atrial fibrillation; and for those for which we cannot find a cure, we want to reduce the stress of the affected patients to a minimum – so that people have a better quality of life.

We thank all the employees of our partner institutions for their dedicated work in 2016 and the financial sponsors and cooperation partners for their support.



Thomas Eschenhagen
Chairman of the Board
of Directors



Gerd Hasenfuß
Board Member



Thomas Sommer
Board Member

The DZHK – Focus on Translation



Mission and Goals

The German Centre for Cardiovascular Research (DZHK) has a clear mission: We want to develop new therapies and diagnostic procedures for the benefit of people who are suffering from cardiovascular diseases. This can only be accomplished if we succeed in rapidly and purposefully translating the results from basic research into clinical application (translation). This mission is of utmost clinical and health economic importance, because in the future the incidence of cardiovascular diseases 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 partner 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, the DZHK invests its funds in previous weak spots of the translation process. This is ensured with a coordinated research strategy and specific funding instruments.

Strategy

Researching three major topics which are of particular importance to patients and the health care system is the focus of the DZHK:

- Prevention and therapy of myocardial infarction
- Prevention and individualised therapy of heart failure
- Prevention of sudden cardiac death

In order to study these diseases, the DZHK introduced innovative clinical and preclinical research programmes, for which it reserves a large part of its annual budget.

Among these programmes are major cross-institutional clinical studies, cohorts and biobanks, as well as sophisti-

cated projects bordering basic research and clinical application that prepare a treatment's first-time use in humans. In addition, all DZHK researchers have the opportunity to benefit from the special knowhow of a partner from another institute within the scope of small bilateral projects and also prepare larger cooperations in this manner.

Allocating a part of its funds competitively belongs to the DZHK's strategy. These funds are not distributed directly to the partner sites. Instead, scientists of the DZHK partner sites may apply for funding for specific projects in various funding lines. Selection is made using competitive procedures with structured evaluation processes.

A strategic goal of the DZHK is to spend more than half of its respective annual budget on competitive or flexible purposes. Their share of the 2016 DZHK annual budget reached roughly 30 percent and will further increase in future years (cf. also Chapter 2). The four areas of the DZHK in which competitive funds exist are preclinical research (Chapter 3), clinical research (Chapter 4), promotion of young scientists (Chapter 6) and scientific exchange (Chapter 7).

The DZHK – a German Centre of Health Research

The German Centre for Cardiovascular Research (DZHK) is among the six German Centres for 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 for Health Research is to quickly bring results from basic research to clinical application.

More information:

www.dzhk.de/en/dzhk/

www.dzhk.de/en/research/

Where do we stand?

In the reporting year, its fifth business year, the DZHK has moved from the construction phase into a steady-state working phase. Its structures and promoting instruments are established and effective. This is shown by the fact that the DZHK has spent its annual budget of about 41 million euros almost completely for the first time thanks to the successful execution of numerous selected projects in previous years.

The current clinical studies of the DZHK have transitioned into routine operation, while the TORCH DZHK1 Register was able to recruit the 1,000th patient in the reporting year. The register, which collects the data and biological material of patients with myocardial diseases, exemplifies the multicentre approach of DZHK studies particularly well: Only 30 percent of TORCH patients come from the Heidelberg study centre, the remaining 70 percent are from the study centres of the other 16 DZHK partner institutions.

Three clinical studies that started in 2015 were able to recruit the first patients in 2016, and further major studies and projects were launched in 2016 including 3 High Risk High Volume projects and 3 clinical studies. New studies and projects are in the pipeline as well: 11 studies and four HRHV projects were being reviewed in late 2016 and will thus await funding decisions in early 2017.

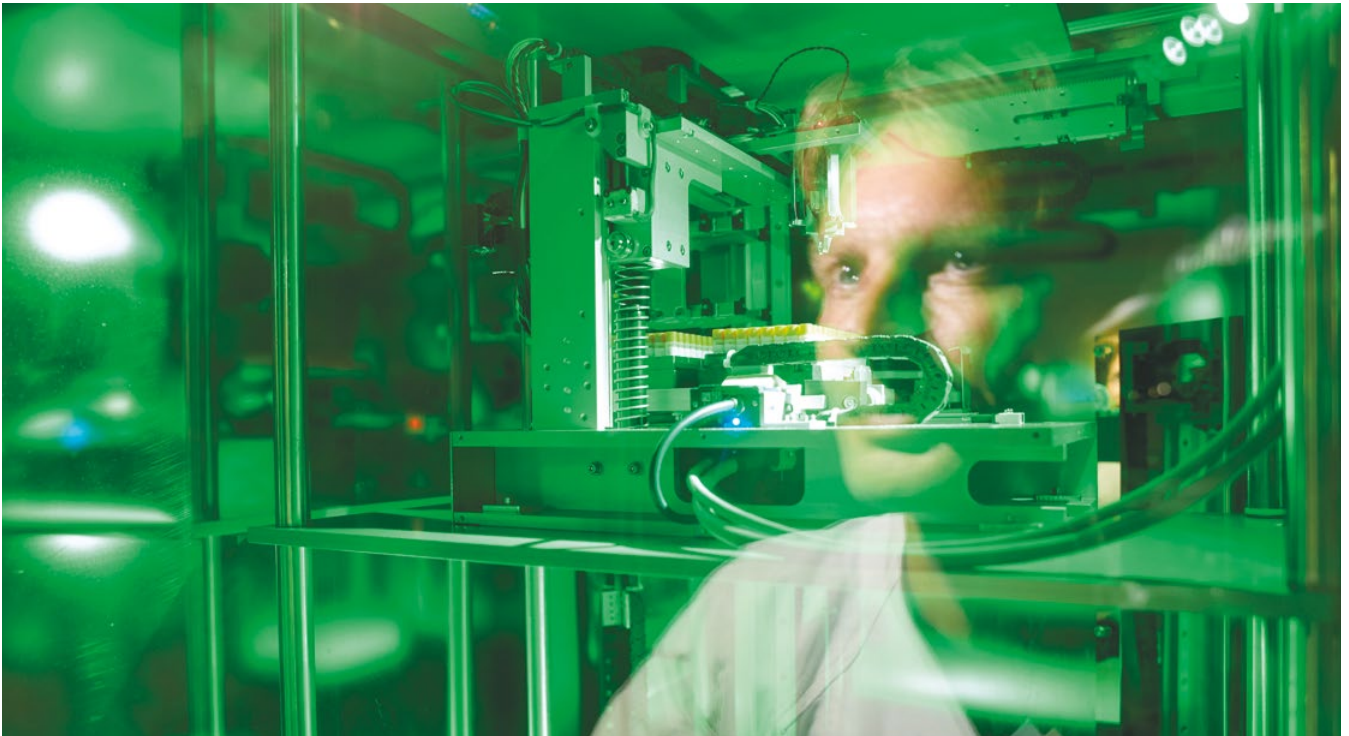
A positive sign was also set by the DZHK with its staff survey at the end of the year: About 50 percent of the approx. 1,300 scientists registered at the DZHK took part in the online survey comprising 46 questions.

Apart from this appreciated high rate of participation, another figure also reveals the excellent functioning of the DZHK network: Nearly 80 percent of the sample stated that the DZHK plays an important role for their research and personal career (see also Chapter 7).

Research at the DZHK is more successful than average. This becomes evident in the number of scientific publications (approx. 1,700 papers with DZHK affiliation or acknowledgement), and even more so in the excellent mean citation rate, i.e., the attention these publications have obtained in the field (data derived from the online database SciVal at the end of 2016).

The DZHK is obtaining more and more international connections and is also popular as a model for translational research. The board executives thus regularly present the DZHK at meetings and conferences, e.g., at the Netherlands Heart Institute in Utrecht in 2016. In the reporting year, DZHK researchers submitted applications in a concerted action in the cooperative programme of the European Research Area Network on Cardiovascular Diseases (ERA-CVD). Among the first 14 projects approved for the whole of Europe, DZHK researchers were immediately successful seven times. Further international cooperations exist in clinical studies and in junior scientist promotions.

Research at the Partner Sites



Partner Site Projects

In 2016, the DZHK invested approx. 60 percent of its funds in 110 scientific partner site projects (including investments, compare below). The projects are often committed to issues of basic research, however, they might also be concerned with clinical studies, investments for major equipment systems, or financing of DZHK professorships. With these projects, the DZHK increases the scientific power of its partner institutions, for which reason the focus of the projects greatly vary. For example, the partner institutions have a focus on subjects like imaging techniques, prevention, epidemiology, microRNAs, genome analyses, artificial heart tissue, vascular diseases or cardiac arrhythmias. In the scope of their site projects, clinicians are committed to finding solutions to very specific clinical problems, e.g., how they are related to stent implantations, heart transplantations or the diagnosis of myocardial infarction.

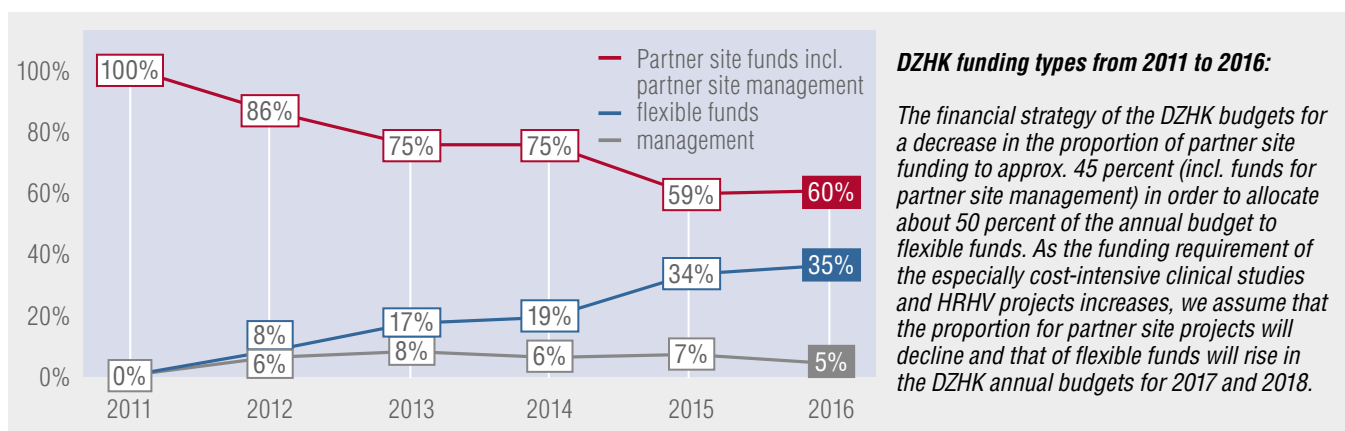
The basic researchers at the partner institutions take a closer look especially at the molecular alterations of cells and tissues which are essential to cardiovascular diseases. They search for biomarkers, i.e., measurable molecular or physiological alterations that are characteristic of a specific disease. Or they browse the human genome for indications of genetic causes of cardiovascular diseases. If the researchers postulate hypotheses on the basis of their experiments at a molecular or cellular level, they subsequently test them in a small animal model for verification. This also frequently happens within the scope of partner site projects, but also in Shared Expertise cooperations (Chapter 3).

The partner site projects are scientifically very successful, evidenced by the fact that they accounted for 644 publications in the year 2016 (cf. also Facts and Figures).

In addition, they provide the basis of preclinical and clinical research (Chapters 3 and 4) at the DZHK, which are financed with flexible funds.

Please find an overview of all DZHK partner site projects in the new internet-based project database at:

<https://dzhk.de/ressourcen/projekt Datenbank/>



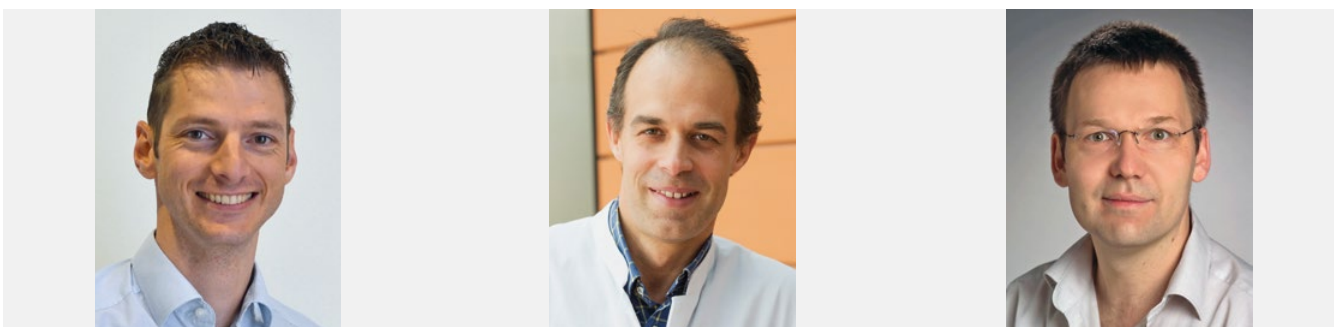
DZHK Professorships

The DZHK professorships are a part of the partner site projects. They are appointed by the partner sites for strategically important topics. At the close of 2016, the DZHK had 14 professorships, three of which were added in 2016. Until, 2018 a total of 22 DZHK professorships are planned.

DZHK professorships at the sites since 2012

Name	Title of Tenure	Since	Site
Anker, Stefan	Innovative Clinical Trials (W3)	Sep. 2014	Göttingen
Backs, Johannes	Cardiac Epigenetics (W3)	2012	Heidelberg/Mannheim
Boon, Reinier	RNA Biology (W2)	Mar. 2016	Rhine Main
Erdmann, Jeanette	Integrative and Experimental Genomics (W3)	2012	Hamburg/Kiel/Lübeck
Gerhardt, Holger	Experimental Cardiovascular Research (W3)	Sep. 2014	Berlin
Gori, Tommaso	Vascular and Myocardial Interactions (W3)	Sep. 2016	Rhine Main
Hansen, Arne	Cardiac Tissue Engineering (W1)	2012	Hamburg/Kiel/Lübeck
Kararigas, Georgios	Translational Gender Research, Focus on Heart Failure (W1)	Nov. 2015	Berlin
Luther, Stefan	Imaging and Numerical Simulations (W2)	Feb. 016	Göttingen
Nagel, Eike	Clinical Imaging (W3)	Jan. 2015	Rhine Main
Söhnlein, Oliver	Vascular Immunotherapy (W2)	2013	Munich
Uecker, Martin	Real-Time MRI (W2)	Sep. 2015	Göttingen
Zeller, Tanja	Genomics and System Biology (W2)	Oct. 2014	Hamburg/Kiel/Lübeck

The following professors were newly appointed in 2016:



Reinier Boon of the Goethe University Frankfurt took up the DZHK professorship (W2) for "RNA Biology" in May 2016. He is researching the role of non-coding RNAs and their potential therapeutic application. A special focus is on analysing the role of non-coding RNAs in the aging process of the cardiovascular system. The object of this work is to develop new RNA-based therapeutic approaches for cardiovascular diseases.

Tommaso Gori was appointed as DZHK professor (W3) for "Myocardial and Vascular Interactions" at the University Medical Centre Mainz in September 2016. His research focuses on interventional cardiology, invasive imaging and endothelial function. The planned projects comprise smaller mechanistic studies, health-care provision research, multicentre registers and clinical studies, as well as participation in three major cohort studies.

Stefan Luther of the Max Planck Institute for Dynamics and Self-Organisation in Göttingen is the DZHK professor (W2) for "Imaging und Numerical Simulation" since 2016. The main focus of his research is the development of new imaging measurement methods and computer models of the heart. With them, he investigates mechanisms which contribute to cardiac arrhythmias. The aim of his work is to develop new methods to stop life-threatening cardiac arrhythmias gently and without pain.

Committee:

Group of DZHK professors

In the reporting year, the DZHK professors established themselves as a committee. They took over responsibility for the organisation of the scientific programme for the DZHK Retreat for the first time and have regularly conferred with each other during this time – also in cooperation with the PostDoc representatives of the Young DZHK. To increase their participation in the DZHK, they hold bimonthly video conferences. The spokesperson and deputy spokesperson are both members of the RCC. In addition to the annual meetings at the DZHK Retreat, the DZHK professors have agreed to visit a research facility once a year to thus further intensify the exchange.

Investment Programme 2014–2017

In its start-up phase, the DZHK granted a total sum of 20 million euros for the extension of partner site-specific research infrastructures, in addition to the roughly 45 percent of each annual budget that is permanently budgeted. Distributed over four years, whereby 2016 was the year of maximum funding, the partner sites were able to invest in large pieces of equipment they urgently needed. Another essential aim of the programme was to harmonise and modernise the clinical research infrastructure at all 17 clinical partner institutions. This was necessary for the strategic concept of uniting data and biological samples from DZHK clinical studies in a centralised collection and making them available to all researchers for scientific analysis at a later date.

A joint research highlight of the DZHK was financed with funds of the investment programme, i.e., the OMICs Resource Project, pursuing the primary objective of generating whole genome sequences and a variety of RNA sequences from a population-based aggregate of six cohorts resident in Germany, which will serve as a "healthy" control resource for genotypes and transcriptomes of various diseases (cf. also Chapter 9).

In addition, further "project arms" were financed at certain partner site projects in 2016 and 2017. Personnel and material costs were hence temporarily increased to explore an additional aspect.

The following investments were made in the scope of the investment programme 2014–2017:

Large equipment over ~100,000 € (excerpt)

- BD LSRFortessa flow-through cytometer (Munich)
- Thrombo Microscopy – Zeiss laser scanning microscope (Munich)
- FUJIFILM VisualSonics Vevo Imaging System (München)
- Aliquoting robot incl. decapper and rack scanner (for the integration of this aliquoting robot into the fully automatic lab

- line at the UMG Central Laboratory) (Göttingen)
- IVIS lumar system for the detection of bioluminescent cells (Göttingen)
- Scanning ion-conductance microscope (Hamburg/Kiel/Lübeck)
- Confocal Microscope Zeiss LSM 800 (Hamburg/Kiel/Lübeck) with Airyscan (Hamburg/Kiel/Lübeck, Rhine Main)
- Cryoprep for the preparation of small sample amounts and den chromatographic system for an improved separation of peptides (Rhine Main)
- Mass spectrometer Q exactive plus standard MS system (Rhine Main)
- Analytics for highly sensitive gene expression analyses on single-cell level (Greifswald)
- Hybrid mass spectrometer Synapt (Greifswald)
- Abberior 4-channel STED super resolution microscope (Berlin)
- Plastiflow and ViCaVaBi-Live (Berlin)
- HyperSwitch with microscope, CELLigence cardio ECR and cell counter Contess in the project HD-KAME-1 (Heidelberg/Mannheim)

Harmonised infrastructure for clinical research (excerpt)

- 17 examination rooms for DZHK studies (1 room per institution)
- 17 Schiller ECG units (1 ECG unit per institution)
- Various rack scanners /hand scanners for DZHK biobanking (LIMS)

Goals for 2017

- The appointment of two further DZHK professors
- The purchase of all instruments approved in the scope of the 2016/17 investment programmes
- The outflow of 100 percent of the site project funds freshly approved for 2017

Preclinical Research



Preclinical research in the broadest sense comprises all research work which takes place before clinical research. More specifically, we see it as research that bridges the gap between basic research and the first clinical trials. This stage generally constitutes a weak spot in the translational research chain which is the reason why the DZHK gives it special attention.

We count numerous partner site projects and, in particular, Shared Expertise cooperation projects with internal and external partners as preclinical research. These cooperations enable DZHK researchers to draw upon the entire spectrum of experimental expertise within and outside of the DZHK which they need for smaller preclinical projects. In 2016, the DZHK invested 3.8 million euros of its flexible and competitive funds in preclinical research.

High Risk High Volume Late Translational Projects (HRHV)

HRHV projects are primarily focused on topics in late preclinical research. They comprise research work which immediately precedes the first application of new therapies or diagnostic methods in humans (first-in-man) or provides the necessary foundations for it. These might consist of toxicological or dose-finding studies, the generation of human-relevant animal models, or the reproduction of the proof of concept in a large-animal model.

In the reporting year, the DZHK invested 2 million euros in HRHV projects.

In 2016, three project applications were submitted under this funding line, three applications received a research grant recommendation after evaluation by

the Translational Research Group (TRG) and external evaluators – two projects of which were launched in the reporting year.

HRHV projects approved and/or started in 2016:

Gene therapy for neonatal sarcomeric cardiomyopathies: towards first-in-patient

Duration: from 2016 to 2018

Budget: 447,000 €

Aim: One of the most frequent causes of cardiomyopathy in newborns are homozygous or complex heterozygous mutations of the MYBPC3 gene which encodes the cardiac myosin-binding protein C, a protein belonging to the sarcomere. These congenital cardiomyopathies may rapidly turn into systolic heart failure and in serious cases result in death within the first year of life. Recently, we demonstrated a long-term prevention of the disease using MYBPC3 gene therapy in a homozygous Mybpc3-targeted knock-in mice, which genetically mimic human neonatal cardiomyopathies.

In the absence of any treatment options except heart transplantation, gene therapy is a realistic treatment option for this subset of infants with severe and fatal neonatal cardiomyopathy. Our goal is to establish MYBPC3 gene therapy in a large animal model (pig) and thus move another important step closer to clinical application. Such a porcine model, which carries bi-allelic truncating MYBPC3 mutations and displays the cardiac phenotype of the cardiomyopathy in newborns, is not yet available. It will be generated using CRISPR/Cas9-technology, somatic cell nuclear transfer and embryo transfer. Once the porcine model has been successfully developed, the AAV9-mediated, cardiac-specific MYBPC3 gene transfer will be applied. If it turns out to be as successful as in mice, this therapy may perhaps be applied to the little patients in the foreseeable future.

Involved scientists: Lucie Carrier, Hamburg/Kiel/Lübeck

Collaborations in the DZHK: Guilia Mearini, Hamburg/Kiel/Lübeck; Angelika Schnieke, Christian Kupatt, Rabea Hinkel, Eckhard Wolf, Munich

IPSC-EHT transplantation for cardiac repair – towards first-in-patient

Duration: from 2016 to 2021

Budget: 1.4 million €

Aim: The mortality rate of patients with end-stage heart failure is high, while treatment options are very limited. The availability of cardiomyocytes, which are obtained from induced pluripotent stem cells, makes it possible to culture artificial heart muscles, which can be used in allogenic transplantation. It was demonstrated in a guinea-pig myocardial infarction model that the engineered heart tissue (EHT) grows on ailing hearts and improves cardiac function. This project intends to determine the minimal effective dose/size of the engineered heart tissue, and study the growth of artificial cells and the size of the engineered heart tissue. Lastly, the trials will be repeated using a porcine animal model.

Involved scientists: Thomas Eschenhagen, Arne Hansen, Hamburg/Kiel/Lübeck

Collaborations in the DZHK: Hermann Reichenspurner, Gerhard Adam, Hamburg/Kiel/Lübeck; Eckhard Wolf, Rabea Hinkel, Christian Kupatt, Munich





Generation and functional characterisation of macrophage cell lines from yolk sac precursors

Duration: from 2017 to 2019 (not yet started)

Budget: 257,000 €

Aim: The tissue macrophages in adult organs, including those of the cardiovascular system, mostly originate from embryonic precursors located in the yolk-sac. However, existing macrophage cell lines mostly derive from peripheral blood mononuclear cells or leukemic cells. Available macrophage cell lines are therefore insufficient to study tissue macrophage functions under culture conditions. The project's goal is to generate a cell line of bona fide yolk sac-derived macrophage progenitors which can be expanded and differentiated into tissue macrophages. The functions of the macrophages of various origin are to be characterised and compared *in vitro* and *in vivo*.

Involved scientists: Christian Schulz, Munich

Collaborations in the DZHK: none

In addition, two of the three projects released for grant acceptance in 2015 (cf. also Annual Report 2015, p. 14) started in 2016:

- Transapical mitral-valve stent implantation without using a heart-lung machine, Georg Lutter, project start: 1 Jan. 2016
- Low-energy defibrillation of ventricular fibrillation in pigs as an animal model for heart failure, Stefan Luther, project start: 1 Jan. 2016
- *In vivo* characterisation of the chemokine receptor CXCR4 to detect an inflammation in atherosclerotic plaques by means of PET/MR, Markus Schwaiger, still under assessment because of issues pertaining to grant law.

For the last-mentioned project, the legal approval of the grant faced difficulties, because of complex questions regarding intellectual property rights and compliance with issues of grant law, the reason for which there have been delays.

Interview with Professor Stefanie Dimmeler

The researcher reports on the HRHV project "Development of miR-92a inhibitors for the treatment of cardiovascular disease". It is the first project in this funding line and started in 2015.

■ What were the important results of your project in 2016?

We were able to chemically optimise our substance to inhibit the micro-RNA92a in a way that we were able to find a candidate which possesses an exceptional biological efficacy but only a low toxicity. Around the middle of the year, we then had a consultation appointment at the Federal Institute for Drugs and Medical Devices (BfArM), where you get advice regarding what still needs to be done before the substance can be used in humans, which is ultimately our goal.

■ How did you achieve this?

First, we had to present our proof-of-concept study. The experts there then estimated whether enough data were

available to suggest that there could be a potential benefit for patients. In addition, we presented the trials with which we were planning to test the toxicity and requested their opinion on whether they are sufficient for us to continue with the next steps. BfArM evaluated both as comprehensive and sufficient.

■ What are your next steps?

After our appointment with BfArM, we planned the third work package which resulted in an expansion and prolongation of the project. It consists above all of final toxicological tests in various animal models. If these tests are successful, nothing else stands in the way of testing the substance in healthy control subjects.

Committee:

Translational Research Group

The TRG supports the DZHK in building expertise in the area of late translational research. It audits and evaluates applications for HRHV projects and gives recommendations for the applications' eligibility for funding to the Board of Directors and the RCC. In addition, it advises applicants on regulatory affairs, property rights and aspects of commercialisation.

The members of the TRG were appointed for the first time by the General Assembly of Members in the autumn of 2014. The term of office of the DZHK internal members Stephan Lehnart, Heimo Ehmke, Michael Gotthardt and Ulf Landmesser ended after two years. All four were reappointed by the General Assembly in the autumn of 2016. In 2016, Harald Petry resigned as external TRG member. Jérôme Van Biervliet was appointed as a new external member. He has comprehensive experience in the field of business development at the interfaces between academic research, enterprises and investors. The TRG convened for three sessions in the reporting year.

Scientific Cooperations by means of Shared Expertise (SE)

In this funding line, the DZHK partners provide each other with laboratory methods and other scientific expertise mainly derived from the field of preclinical research. This way the knowhow of individual DZHK partners will benefit other DZHK partners. In 2016, 66 cooperations with Shared Expertise were approved. As usual, the selection of the projects proceeded at the partner sites.

In the reporting year, 21 Young DZHK members (32 percent) were applicants and 6 were co-applicants of SE projects. In 2015, the number of Young DZHK members among the applicants was still at 17 (22 percent). The average project costs amounted to 42,820 euros. The TOP 10 of Shared Expertises were requested in about 41 percent of the applications in 2016.

Variations compared to previous years are small. Similar to previous years, innovative technologies which are not widely available are especially in demand.

Cooperations with External Partners

Certain expertises needed by DZHK researchers can only be found outside the DZHK. For this reason, similar to cooperations with Shared Expertise, there is the funding line called "Cooperations with external partners". These are small bilateral projects that belong to preclinical research. In 2016, 21 (2015: 30) cooperation projects with external partners were approved. Application eligibility was also extended to Young DZHK members. Since the foundation of the DZHK, we have conducted a total of 84 of such cooperations, nearly 2.3 million euros went to external partners working in science.

TOP 10 of the most frequently utilised Shared Expertise

SE	Name of Shared Expertise	Since	Partner Site	Uses applied in 2016	Uses since 2012
SE006	Genomics/proteomics	Sep. 12	Berlin	5	25
SE028	AAV vector platform	Sep. 12	Heidelberg/Mannheim	5	20
SE001	Generation and cardiovascular phenotyping of transgenic rats	Sep. 12	Berlin	2	17
SE041	OMICS platform	Sep. 12	Munich	3	10
SE031	Next-generation sequencing platform	Sep. 12	Heidelberg/Mannheim	2	9
SE056	Vascular proteomics	Sep. 12	Rhine Main	1	9
SE019	Experimental and therapeutic stem cell bank and stem cell phenotyping	Sep. 12	Göttingen	2	8
SE063	MicroRNA array platform	May 13	Hamburg/Kiel/Lübeck	1	7
SE092	Primary cardiac fibroblasts	Mar.14	Hamburg/Kiel/Lübeck	3	6
SE057	Cardiometrics	Jan. 13	Hamburg/Kiel/Lübeck	2	6

Cooperation partners in the scope of the DZHK funding line "Cooperations with external partners" since 2013

Institution	Number of cooperations	total
Hannover Medical School	10	181,255
Saarland University Medical Center	5	217,617
Julius Maximilian University Wurzburg	4	69,186
University Hospital Essen	4	98,404
University Hospital Munster	4	106,317
Albert Ludwig University Freiburg	3	118,737
Heinrich-Heine-University Düsseldorf	3	106,397
Justus Liebig University Gießen	3	118,750
Philipps University Marburg	3	67,615
University Hospital Aachen	3	68,500
University Hospital Tübingen	3	105,550
Fraunhofer Institute of Molecular Biology and Applied Ecology	2	53,100
Friedrich-Alexander-University Erlangen-Nürnberg	2	68,950
Herz- und Diabeteszentrum NRW, Bad Oeynhausen	2	67,500
Max Planck Institute for Molecular Biomedicine	2	40,750
Technical University of Dresden	2	51,500
University of Bielefeld	2	37,750
University Potsdam	2	60,480
University of Regensburg	2	60,000
University Hospital Regensburg	2	41,290
German Cancer Research Center in the Helmholtz Association	1	12,733
Free University of Berlin	1	20,000
Heart Center Leipzig - University Hospital	1	12,138
University of Applied Sciences Darmstadt	1	31,173
Competence Centre for Social Services IIT at the University of Bielefeld	1	19,760
Leibniz Institute for Analytical Sciences - ISAS - e.V.	1	66,080

Ludwig-Maximilians-Universität München	1	8,330
Medical Faculty of the University Hospital Magdeburg	1	11,008
Ozgene Pty Ltd, Bentley, Australia	1	46,803
The National Metrology Institute of Germany (PTB)	1	20,000
University of Bonn	1	27,600
Technical University of Berlin	1	28,000
University of Leipzig	1	8,000
University of Ulm	1	28,500
University of Cologne	1	12,562
University of Lübeck	1	20,000
University Heart Center Freiburg, Bad Krozingen	1	20,000
University Hospital of Gießen and Marburg	1	67,179
University Hospital Cologne	1	20,000
University Hospital Leipzig	1	73,800
University Hospital Ulm	1	19,923

Achievements in 2016

- ✓ The HRHV project started in 2015 was successfully developed until the first BfArM briefing
- ✓ The three HRHV projects approved in 2015 were started
- ✓ Three additional HRHV projects were brought to grant release
- ✓ Further increase of the percentage of Young DZHK members in Shared Expertise projects
- ✓ Funding line "Cooperation with external partners" opened up to Young DZHK members and DZHK researchers (hitherto only for DZHK PIs)

Goals for 2017

- Brief web presentation of the HRHV projects
- Accelerated selection procedure for HRHV projects
- Increase application numbers for HRHV projects
- Internal evaluation of Shared Expertise projects

Clinical Research



4.1. Clinical Studies

In its research strategy, the DZHK determined that the focus of clinical studies supported with flexible funds shall be set on guideline-relevant studies and early clinical studies.

Patients benefit directly from guideline-relevant studies, as they mostly compare established treatment and diagnostic methods, thus enabling the optimal treatment for certain diseases or patient groups to be determined. With FAIR-HF2-DZHK5 and DEDICATE-DZHK6, two major and important guideline-relevant DZHK studies were in a stage of intensive preparation in 2016. These studies have the potential to improve the treatment of patients with cardiac insufficiency and cardiac valve diseases all over the world.

Early clinical studies test innovative therapeutic approaches in a smaller group of patients and give insight into the mechanisms of actions. If they are successful, further clinical studies can explore the suitability of the new therapies for use in many patients. The study SMART-MI-DZHK9, for example, investigates whether a small implantable monitor may protect myocardial infarction patients from an impending cardiac rhythm disorder.

In the reporting year, the largest sum of flexible and competitive funds went into the area "Clinical Research" with 6.2 million euros. This area is also a great challenge for administration. One figure makes this quite clear: 107 project applications for clinical studies have been received by the main office since the two funding lines "Early Clinical Studies" and "Guideline-relevant Studies" started in 2013.

Before the end of 2016, the DZHK had selected a total of 17 DZHK studies for funding, 9 of which had already begun (TORCH-DZHK1, TransitionCHF-DZHK2,

VAD-DZHK3, TOMAHAWK-DZHK4, FAIR-HF2-DZHK5, APPROACH-ACS-AF-DZHK7, SPIRIT-HF-DZHK8, SMART-MI-DZHK9, CAVA-AD-HF-DZHK10) and six were actively recruiting in the reporting year. The remaining studies were in a state of administrative approval.

Committee:

Clinical Study Group (CSG) Steering Committee

The group, composed of clinical researchers, basic researchers and biostatisticians of the DZHK, met four times in the reporting year in order to discuss 21 brief applications, 9 of which were early clinical study applications and 12 guideline-relevant study applications, and 15 full applications. During the work sessions ideas on how to improve recruitment in clinical DZHK studies and the reasons and initial solutions for the long study preparation periods within the first years of the DZHK were discussed.

The agenda and the results of these work sessions were communicated to the DZHK community in form of short protocols on the Intranet. Moreover, one application for DZHK association of a clinical study was received and evaluated.



DZHK Studies*

Acronym	Disease/ treatment / diagnostics	Study type*	Responsible PIs (site)	Study participants (planned)	Subjects recruited
TORCH-DZHK1	Myocardial diseases	Register	Katus (Heidelberg), Hoffmann (Greifswald)	2,300	1,418
TransitionCHF-DZHK2	Heart failure	Cohort	Hasenfuß, Wachter, Edelmann (Göttingen)	1,500	232
VAD-DZHK3	Severe heart failure, heart transplantation	GrS	Falk, Knosalla (Berlin), Hasenfuß, Friede (Göttingen)	500	9
TOMAHAWK-DZHK4	Cardiac arrest	GrS	Desch, Thiele (Lübeck)	558	1
FAIR-HF2-DZHK5	Heart failure and iron deficiency	GrS	Karakas (Hamburg) Anker (Göttingen)	1,200	-
DEDICATE-DZHK6	Aortic valve stenosis	GrS	Blankenberg, Seiffert (Hamburg/Kiel/Lübeck)	1,600	-
APPROACH-ACS-AF-DZHK7	Acute coronary syndrome in combination with atrial fibrillations	GrS	Wakili, Massberg (Munich)	400	40
SPIRIT-HF-DZHK8	Heart failure	GrS	Pieske, Edelmann (Berlin)	1,300	-
SMART-MI-DZHK9	Sudden cardiac death after myocardial infarction	ECS	Bauer, Kääh, Massberg (Munich)	400	29 (+ 57 registry)
CAVA-ADHF-DZHK-10	Heart failure	ECS	Thiele, Jobs (Hamburg/Kiel/Lübeck)	352	-
Ex-VAD-DZHK11	Exercise with a ventricular assist device	ECS	Edelmann, Pieske, Halle, Falk (Berlin, Munich)	66	-
Decipher HFpEF-DZHK12	Heart failure, MRI	ECS	Nagel (Rhine Main)	170	-
DYNAMIC-MR-DZHK13	Cardiac valve insufficiency, mitral valve reconstruction	ECS	Pieske (Berlin)	150	-
CTSN-TR-DZHK14	Mitral valve insufficiency	GrS	Falk (Berlin)	400	-
CLOSURE-AF-DZHK16	Atrial fibrillations	GrS	Landmesser, Endres, Boldt, Skurk, Pieske (Berlin) Eitel, Thiele	1,586	-
HFpEF-stress-DZHK17	Heart failure	ECS	Schuster (Göttingen)	70	-

DZHK-associated studies

SFB/TR19plus	Myocarditis	Cohort	Felix (Greifswald)	5,001	71
ISAR-REACT 5	Acute coronary syndrome	GrS	Kastrati, Schüpke (Munich)	4,000	2,958
CULPRIT-Shock	Myocardial infarction with cardiogenic shock	GrS	Thiele (Lübeck)	706	596
FIX-HF-5C	Heart failure	GrS	Hasenfuß (Göttingen)	140	n/s
Revacept-PCI in CAD	Coronary heart disease	ECS	Kastrati, Massberg	330	-

***Study type** GrS > Guideline-relevant study
ECS > Early clinical study

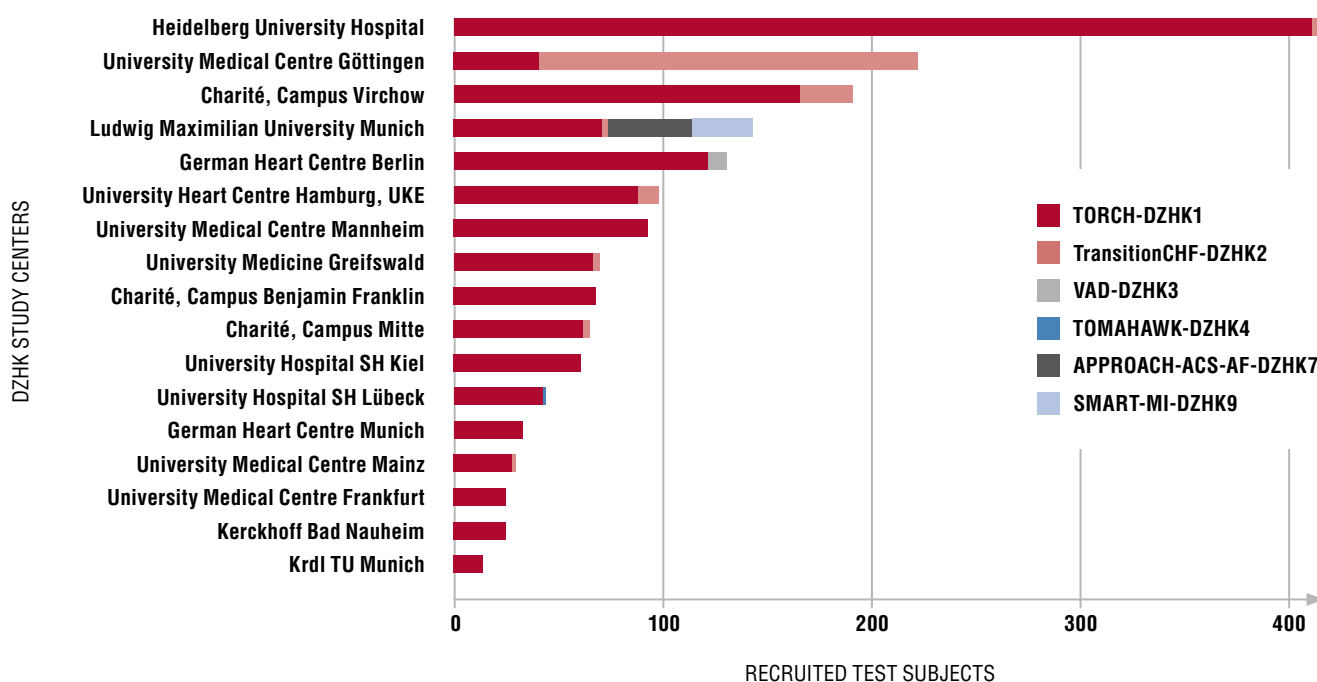
* The studies of the Competence Networks are shown in the table on page 48.

Patient Recruitment

In the reporting year, our greatest concern in the area of clinical research was how well patients are recruited in DZHK multicentre clinical studies. Up to the end of 2016, a total of 1,865 patients were enrolled in six DZHK studies (end of 2015: 671). Three studies began recruiting in 2016, three already in 2015. The TORCH-DZHK1 register (started in 2014) was able to enrol the 1,000th patient in the summer of 2016 and is thus the DZHK study with the highest number of patients. By end of the year, the register recruited 1,400 patients, i.e., more than half of the 2,300 patients planned.

For each of the six multicentre studies, further clinical DZHK partner sites were initiated as study centres and thus declared themselves ready to enrol patients. So far, the respective centre of the principal scientific

investigator, i.e., the centre of the researcher who designed and applied for the study, has recruited by far the most patients. The recruitment figures of the other – up to 16 centres per study – enrolling DZHK centres stayed more or less clearly under the target figures. Although this problem also exists in many other multicentre studies, we take it very seriously and have started an internal process which intends to elucidate the reasons and develop measures for improvement. Thus, the recruitment figures will be presented at each RCC session and compared with success scores and discussed. Furthermore, the clinical staff financed by the DZHK (see below) will be intensively concerned with the improvement of the recruitment performances at all centres. We assume that the delayed recruitment is a result of starting difficulties and are very optimistic that we will achieve an obvious improvement as early as 2017.



Recruited participants per study /per DZHK study centre

Clinical staff

The clinical staff of the DZHK is composed of study physicians and study nurses /orderlies and study coordinators, respectively. These roughly 30 individuals are financed by the DZHK in order to support the realisation of the clinical DZHK studies at the partner institutions. One duty of the clinical staff is to coordinate the enrolment of patients in the clinical DZHK studies locally. In the reporting year, clinical staff funding was extended until the end of 2018. The group convened in the summer for a major work meeting, during which the clinical staff members from each of the partner sites introduced themselves, current news from the field of clinical research at the DZHK was reported, followed by discussion rounds on biobanking, the use of the central scientific infrastructure for clinical studies of the DZHK, specific study contents and experiential reports about contacts with patients.



Clinical staff meeting in Berlin, August 2016.

Dovetailing Clinical and Preclinical Research

In the reporting year, the DZHK discussed its opportunities of establishing closer interrelations between preclinical and clinical research. As a translational research centre, we see this as a special mission; it was also suggested by our Scientific Advisory Board.

For this reason, a strategy discussion was held on this subject in the RCC of April 2016.

The CSG Steering Committee subsequently decided as follows (protocol excerpt):

"When it comes to strengthening connections between preclinical and clinical projects, in the future, every guideline-relevant study application shall have to answer the question whether contact points for reverse translation exist." This means that applicants of clinical studies shall already outline mechanistic subprojects in their study applications. Such projects complement the clinical issue, for example, by questioning the molecular foundations of clinical effects and may be starting points for further clinical innovations. A corresponding point for describing subprojects has been integrated into the clinical study application documents.

Proband Information Platform PIP

Patients participating in DZHK studies have given their broad consent allowing their data and biological samples to be used for other projects of cardiovascular research beside the actual study purpose. On ethical grounds, it is therefore appropriate that study participants are comprehensively informed about the research projects and the results which are based on their data. The DZHK has therefore installed a Proband Information Platform (PIP) online in the reporting year. At first, it provides information on the procedure, content and contact persons of the DZHK studies. Later on, research results and planned research projects will be displayed here, too. The DZHK is a pioneer with an information platform of this kind and does more than legal provisions demand. For PIP inquiries and preparation, the main office contacted 41 self-help groups on the list of the German Heart Foundation. We asked them questions about the information needed by patients who (want to) participate in clinical studies. The answers were included in the PIP concept.

 pip.dzhk.de

Achievements in 2016

- ✓ Four new study applications were approved in both programmes (seven new funding contracts for studies were issued in 2016)
- ✗ 2,500 patients recruited (75 percent achievement)
- ✓ Clinical staff has formed as a group, spokesperson selected (prepared, election of spokesperson in January 2017)
- ✓ All 17 clinical DZHK partner institutions and at least three external centres recruit patients

Goals for 2017

- Achieve recruitment goals for TORCH-DZHK1 (2,300 patients)
- Complete recruitment for Culprit-SHOCK study
- Decrease the average study preparation time (from funding contract to the enrolment of the first patient) to six months
- Record 1,400 patients in the Central Data Management System in 2017

4.2. Scientific Infrastructure for Clinical Studies

The DZHK has established a central scientific infrastructure for its multicentre studies. In it, all data and samples from patients derived from DZHK studies (2016: six and one associated project SFB/ TR19plus, which continues to follow a cohort of a Collaborative Research Centre on myocardial inflammation) are compiled and stored in accordance with unified standards. The data collection accruing in this way makes it possible to process research projects that reach beyond the actual subject of a study. In the reporting year, data derived from a total of 1,865 patients were recorded within the clinical-scientific infrastructure of the DZHK.

The components of the infrastructure are interlinked by IT technology and also by their contents, and therefore work very closely together (the single components are presented on page 24). Coordination and optimisation processes are therefore of great significance in the work of the single components. In the reporting year, the clinical-scientific infrastructure organised nine training and kick-off events for new and already started studies and for the involved centres. This chapter will briefly outline the development of the most important components of the clinical-scientific infrastructure in the reporting year.

A general description of the structures can be found on the DZHK website.

More information:

- ➔ www.dzhk.de/en/research/clinical-research/clinical-infrastructure/



Components of the Clinical-Scientific Infrastructure

Internal Web Portal: Study Preparation and Execution

Before patients can be enrolled in a DZHK study, the main study centre as well as each enrolling centre must fulfil the necessary conditions. For this purpose, a lot of communication between the main study centre, other enrolling centres, study personnel and the structures of the clinical-scientific DZHK infrastructure is necessary. In order to make all necessary communication and coordination processes quick and transparent, the DZHK established an internal web portal for study preparation and execution in the reporting year. It contains documents, forms, check lists, FAQs and flow charts for every phase and aspect which is of relevance to a clinical DZHK study. The portal and the information it contains are continually updated and adjusted.

Collecting and Archiving Data and Biological Samples:

Ethics Project

Conducting clinical studies in a research alliance raises numerous ethical questions, which the DZHK is addressing in the scope of its Ethics Project in Munich. As early as 2014, the project's employees had already developed a central ethics concept for "Clinical Research" that regulates basic questions for all the studies of the DZHK. The concept was revised after the initiation of the first studies. The second version of the ethics concept submitted in the reporting year now includes additional aspects which have emerged from study work. The project collaborates closely with the other components of the clinical-scientific infrastructure of the DZHK and supports the studies in their dialogue with the local ethics commissions, whenever needed.

Independent Trusted Third Party

When a patient file is created, the Independent Trusted Third Party in Greifswald receives the person identifying data and converts them into pseudonyms. They manage the electronic administration of the patients' declarations of informed consent. In 2016, the Trusted Third Party also compiled cost calculations for 48 clinical study applicants for potential services within the scope of the study, as these services must be budgeted by the applicants in advance. Furthermore, the Trusted Third Party was involved in the tendering procedure for the Image Data Management System (IDMS) and the implementation of the Laboratory Information Management System (LIMS). In the reporting year, the Trusted Third Party worked together with Data Handling to further improve the technical communication of the systems. A monthly feedback report informs the study centres about open questions and problems relating to the administration of the informed consent declarations.

Data Handling

Data Handling in Göttingen stores and manages the clinical data of all DZHK studies in pseudonymised form. In the reporting year, Data Handling activated new study databases for TOMAHAWK-DZHK4, APPROACH-ACS-AF-DZHK7 and SMART-MI-DZHK9. In addition, they worked on the bilingualism of the systems. All modules, forms and SOPs (standard operating procedures) are now also available in English. This ensures that international partners can also participate in DZHK studies, which is planned in particular for the studies FAIR-HF2-DZHK5 and SPIRIT-HF-DZHK8.

Biobank and Laboratory Information Management System (LIMS)

The organisation of the DZHK biobank is decentralised. This means that the samples remain at the site of the partner institutions.

It comprises samples from both basic DZHK biobanking and study biobanking. Each DZHK study collects samples for basic biobanking according to standard specifications, whereas study biobanking is specific to each study. In the reporting year, biological samples from 1,653 people were collected.

The data pertaining to all biological samples are documented in the new Laboratory Information Management System (LIMS). LIMS enables the standardised registration of biological samples and the associated data in a web-based software. The DZHK partner institutions can prepare the tubes for taking the biological materials themselves, since LIMS issues the necessary labels. This saves time and resources and assures a standardised documentation of the acquisition and processing of biological materials in conformity with data protection as well as a unified quality of the stored biological samples in conformity with SOPs.

In the reporting year, LIMS was successfully tested at the three pilot sites the University Medical Centre Greifswald, the University Hospital Eppendorf and the Charité – Universitätsmedizin Berlin (Campus Virchow). Before, the software was specifically adjusted to the DZHK and the DZHK infrastructure in cooperation with the manufacturer and the IT Department of the University of Greifswald, the DZHK main office and the three pilot sites.

The technical operation of the system took place at the IT department of the University Medical Centre of Greifswald.

Next year, gradually all DZHK partner institutions shall be equipped with the new web-based DZHK-LIMS.

Image Data Management System (IDMS)

Image data have a huge informative value when it comes to the characterisation of a cardiovascular disease and are therefore often a part of clinical studies at the DZHK. Imaging methods can make typical morphological and functional alterations visible, which may serve as biomarkers. In the reporting year, the DZHK therefore acquired a central Image Data Management System. The EU-wide tender took place in the first half of 2016, and it was accepted in the third quarter. The system shall be ready for operation by mid-2017. The image data of the clinical studies will then be centrally stored at the data centres of the service provider, from where they can be retrieved for evaluation and research purposes. The evaluation of the images is done with so-called core labs, i.e., specialised evaluators that ensure the images are evaluated in accordance with unified standards. The results are thus more significant than they would have been had various evaluators been involved. The web-based system permits the integration of any group (worldwide) as a core lab.



IDMS team during the tender presentation in Berlin, June 2016.

The Use of Data and Biological Samples:

Beside the initiators of the DZHK clinical studies, other scientists may make (secondary) use of the data. By doing so, the DZHK wants its data to be available to many scientific issues. The DZHK Use & Access Policy regulate who may use the data and how.

Transfer Office

The Transfer Office organises the transmission of data and biological samples after the Use & Access Committee (U&AC) (cf. box on the right) has given its approval to a user request. Furthermore, it also provides the tools needed to technically support the Use & Access process. Like Data Handling, the Transfer Office is located in Göttingen. In the reporting year, the Transfer Office established the processes for the use of data collected in DZHK studies together with the U&AC. These includes application procedures and proceedings for the technical integration of the various infrastructure components into the data recovery process. In addition, the Transfer Office established a "Data Catalogue" (cf. Chapter 9) that shows which data are available at the DZHK without actually displaying them. Next year, this system shall be complemented with a "Feasibility Explorer", which gives potential data users profound insight into the DZHK's data inventory.

Committee:

Use & Access Committee (U&AC)

The Use & Access Committee gives recommendations whether applications submitted by scientists for using the DZHK's collection of data and biological samples should be approved. The U&AC started its operations in January 2016 with a constitutional meeting, where a spokesperson and two deputy speakers were elected. The U&AC cooperates closely with the Transfer Office and in the reporting year established numerous processes regulating the use of the DZHK's collection of data and biological samples. In the reporting year, the central topic of the U&AC's work was on the design of a publicly accessible "Data Catalogue" which describes the registered DZHK study data stored in the Central Data Management System. In late summer 2016, the first usage notification of a DZHK researcher was submitted and the U&AC gave a recommendation to the applicant in the prescribed period of ten weeks according to the DZHK Use & Access Policy.

Achievements in 2016

- ✓ Decision made in favor of an image data management system
- ✓ Clinical-scientific infrastructure now also available in English
- ✓ Inventory of data and samples were made available externally
- ✓ Systems established for Use & Access and first request accepted

Goals for 2017

- At least half of the clinical DZHK institutions shall use LIMS
- First studies document image data using IDMS
- Implementation of the Feasibility Explorer
- Numerous usage applications for data and sample received and processed

Scientific Highlights and Publications

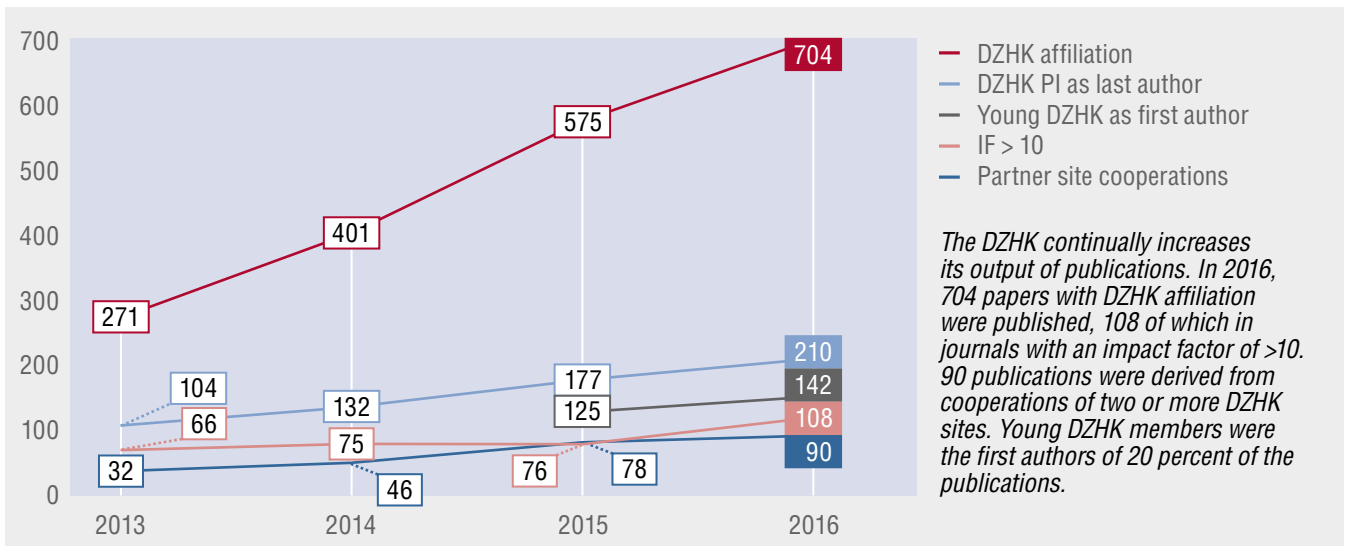


Research at the DZHK is more successful than average. This becomes evident in the number of scientific publications – most of which originate from partner site projects. Smaller bilateral or trilateral cooperations (Shared Expertise projects and cooperations with external partners) increasingly result in scientific publications. At the end of 2016, the online database SciVal counted nearly 1,700 papers with DZHK affiliation or acknowledgements; the number of publications per annum increases continually.

Please find more information about publications in the "Figures and Facts" section of this report.

Goals for 2017

- More than 700 publications with DZHK affiliation
- More than 100 publications with an impact factor >10
- More than 90 cooperative publications



Paper of the Month 2016

Every month, the DZHK's Board of Directors selects a paper of the month which is then communicated by the DZHK Newsletter and published on the DZHK website online.

January

Critical Role of Rage and Hmgb1 in Inflammatory Heart Disease. Bangert, A., Andrassy, M., Muller, A. M., Bockstahler, M., Fischer, A., Volz, C. H., Leib, C., Goser, S., Korkmaz-Icoz, S., Zittrich, S., Jungmann, A., Lasitschka, F., Pfitzer, G., Muller, O. J., Katus, H. A. & Kaya, Z. Proceedings of the National Academy of Sciences of the United States of America 113, E155-164, (2016).

February

Foxo1 Couples Metabolic Activity and Growth State in the Vascular Endothelium. Wilhelm, K., Happel, K., Eelen, G., Schoors, S., Oellerich, M. F., Lim, R., Zimmermann, B., Aspalter, I. M., Franco, C. A., Boettger, T., Braun, T., Fruttiger, M., Rajewsky, K., Keller, C., Bruning, J. C., Gerhardt, H., Carmeliet, P. & Potente, M. Nature, (2016).

March

Intestinal Congestion and Right Ventricular Dysfunction: A Link with Appetite Loss, Inflammation, and Cachexia in Chronic Heart Failure. Valentova, M., Von Haehling, S., Bauditz, J., Doehner, W., Ebner, N., Bekfani, T., Elsner, S., Sliziuk, V., Scherbakov, N., Murin, J., Anker, S. D. & Sandek, A. *European heart journal*, (2016).

April

Coding Variation in *Angptl4*, *Lpl*, and *Svep1* and the Risk of Coronary Disease. Myocardial Infarction, G. & Investigators, C. A. E. C. *The New England journal of medicine* 374, 1134-1144, (2016).

May

Essential Role for Premature Senescence of Myofibroblasts in Myocardial Fibrosis. Meyer, K., Hodwin, B., Ramanujam, D., Engelhardt, S. & Sarikas, A. *Journal of the American College of Cardiology* 67, 2018-2028, (2016).

June

Myoscape Controls Cardiac Calcium Cycling and Contractility Via Regulation of L-Type Calcium Channel Surface Expression. Eden, M., Meder, B., Volkens, M., Poomvanicha, M., Domes, K., Branchereau, M., Marck, P., Will, R., Bernt, A., Rangrez, A., Busch, M., German Mouse Clinic, C., Hrabe de Angelis, M., Heymes, C., Rottbauer, W., Most, P., Hofmann, F. & Frey, N. *Nature communications* 7, 11317, (2016).

July

Circulating Micrnas Strongly Predict Cardiovascular Death in Patients with Coronary Artery Disease-Results from the Large Atherogene Study. Karakas, M., Schulte, C., Appelbaum, S., Ojeda, F., Lackner, K. J., Munzel, T., Schnabel, R. B., Blankenberg, S. & Zeller, T. *European heart journal*, (2016).

August

Distinct Genetic Architectures for Syndromic and Non-syndromic Congenital Heart Defects Identified by Exome Sequencing. Sifrim, A., Hitz, M. P., Wilsdon, A., Breckpot,

J., Turki, S. H., Thienpont, B., McRae, J., Fitzgerald, T. W., Singh, T., Swaminathan, G. J., Prigmore, E., Rajan, D., Abdul-Khalik, H., Banka, S., Bauer, U. M., Bentham, J., Berger, F., Bhattacharya, S., Bu'Lock, F., Canham, N. et al. *Nature genetics*, (2016).

September

Adenosine-to-Inosine Rna Editing Controls Cathepsin S Expression in Atherosclerosis by Enabling Hur-Mediated Post-Transcriptional Regulation. Stellos, K., Gatsiou, A., Stamatelopoulos, K., Perisic Matic, L., John, D., Lunella, F. F., Jae, N., Rossbach, O., Amrhein, C., Sigala, F., Boon, R. A., Furtig, B., Manavski, Y., You, X., Uchida, S., Keller, T., Boeckel, J. N., Franco-Cereceda, A., Maegdefessel, L., Chen, W. et al. *Nature medicine*, (2016).

October

Axial Tubule Junctions Control Rapid Calcium Signaling in Atria. Brandenburg, S., Kohl, T., Williams, G. S., Gusev, K., Wagner, E., Rog-Zielinska, E. A., Hebisch, E., Dura, M., Didie, M., Gotthardt, M., Nikolaev, V. O., Hasenfuss, G., Kohl, P., Ward, C. W., Lederer, W. J. & Lehnart, S. E. *The Journal of clinical investigation*, (2016).

November

Cardiac Repair in Guinea Pigs with Human Engineered Heart Tissue from Induced Pluripotent Stem Cells. Weinberger, F., Breckwoldt, K., Pecha, S., Kelly, A., Geertz, B., Starbatty, J., Yorgan, T., Cheng, K. H., Lessmann, K., Stolen, T., Scherrer-Crosbie, M., Smith, G., Reichenspurner, H., Hansen, A. & Eschenhagen, T. *Science translational medicine* 8, 363ra148, (2016).

December

Oral Thrombin Inhibitor Aggravates Platelet Adhesion and Aggregation During Arterial Thrombosis. Petzold, T., Thienel, M., Konrad, I., Schubert, I., Regenauer, R., Hoppe, B., Lorenz, M., Eckart, A., Chandraratne, S., Lennerz, C., Kolb, C., Braun, D., Jamasbi, J., Brandl, R., Braun, S., Siess, W., Schulz, C. & Massberg, S. *Science translational medicine*, (2016).

Research Highlights

Myocardial Infarction – Specific Genes Provide Protection

Some people have a built-in protection against myocardial infarction. Special genetic features ensure that the level of lipids in their blood serum is very low. The genetically anchored mechanism could serve as a model to prevent myocardial infarction using drugs.

Two out of a thousand people have a modified gene which indirectly accelerates the decomposition of certain blood serum lipids, the so-called triglycerides. Like LDL cholesterol, these lipids increase the risk of cardiovascular diseases and myocardial infarctions. The amount of triglycerides in the blood is genetically determined, but it is also influenced by dietary factors. These lipids are found especially in foodstuffs of animal origin such as meat or dairy products.



Certain genes accelerate the decomposition of blood serum lipids.

The gene was discovered by the researchers of a major international consortium led by Professor Jeanette Erdmann (DZHK Hamburg/Kiel/Lübeck site) and Professor Heribert Schunkert (DZHK Munich site). In a genome-wide association study lasting four years, the scientists analysed 13,000 different genes of 200,000 myocardial infarction patients and healthy control subjects. The researchers were looking for alterations which have an impact on the risk of getting a myocardial infarction.

They found a gene which affects the decomposition of triglycerides. It contains the blueprint for a protein named angiotensin-like 4 or ANGPTL4 for short. This protein normally slows down the activity of lipoprotein lipase. Lipases are enzymes that degrade lipids. A rare variant of ANGPTL4 does not possess this decelerating property and allows the activity of the lipoprotein lipase to fully develop: It decomposes more triglycerides and thus lowers the risk of myocardial infarction.

The researchers now intend to develop drugs to neutralise the effects of the ANGPTL4 gene, which may lower the risk of a myocardial infarction. This has already been successful in animal trials. Monkeys who had received a neutralising antibody against ANGPTL4 displayed drastic serum lipid decreases. This allows the scientists to hope that similarly acting antibody products may soon be successfully applied to human patients as well.

This work was done in the scope of the international research alliance "Myocardial Infarction Genetics and CARDIoGRAM Exome", in which 15 DZHK researchers from two partner sites were involved. It was co-financed with partner site funds and a DZHK rotation grant.

Coding Variation in Angptl4, Lpl, and Smp1 and the Risk of Coronary Disease. Myocardial Infarction, G. & Investigators, C. A. E. C. The New England journal of medicine 374, 1134-1144

Congenital Heart Defects – Three New Genes Discovered

An international consortium with the involvement of the DZHK and the Competence Network for Congenital Heart Defects has discovered three new genes which play a role in the development of congenital heart defects. The results also help the genetic counselling of affected families.

In the scope of an international study, the researchers analysed the genetic information of children with congenital heart defects. They noticed that some children displayed developmental retardation and a peculiar face shape. The researchers were able to find the common cause for these phenomena: three genes were responsible for hitherto unknown alterations.

The modified genes appeared spontaneously, they were therefore not transmitted by the parents. "The parents of the affected children now know the reason for the disease and that there is not necessarily a greater risk for further siblings," says Dr Marc-Phillip Hitz of the DZHK partner site Hamburg/Kiel/Lübeck, one of the first authors of the study. This result is exemplary for an important finding of this study: Most of the so-called syndromic heart defects, i.e., those associated with additional physical malformations, appear for the first time. This means that both parents are not carriers of the pathogenic mutation.

A different situation exists whenever the heart defects appear without any additional symptoms of disease, the so-called nonsyndromic heart defects. They make up approx. 90 percent of all heart defects. They are far more often hereditary than previously assumed, the study reveals. Often both parents possess a few rare genetic modifications, although they do not have any heart defects or any serious heart defects themselves. If a child inherits the modified genes from both of its parents, the combination might result in a serious heart defect.* In the future, these parents could take a genetic test predicting the probability of another child being affected.



The cause of heart defects occurring without other symptoms of disease is mostly hereditary.

The researchers analysed a total of 4,000 people – affected children and their parents – applying a method called exome sequencing. It examines only the part of the DNA which contains the blueprints for proteins in the body, the so-called exome.

Samples from Germany, England, Belgium Saudi Arabia, and Canada were incorporated in the study. In summary, the results help to improve genetic counselling and diagnostics of individuals with syndromic and nonsyndromic heart defects.

*The HRHV project of Lucie Carrier "Gene therapy of familial hypertrophic cardiomyopathy" (cf. p. 13) seeks to develop a treatment for such congenital heart defects.

Distinct genetic architectures for syndromic and nonsyndromic congenital heart defects identified by exome sequencing, *Nature Genetics*, 2016.

Atherosclerosis – Therapy with Less Side Effects

The molecule cathepsin G only occurs on the walls of arteries, where it causes inflammations. This property makes it a candidate for a treatment of atherosclerosis with low on side effect – the team of DZHK Professor Oliver Söhnlein from the DZHK Munich partner site discovered.



White blood cells, leukocytes, are substantially involved in the development of atherosclerosis.

Atherosclerosis – also often referred to as vascular calcification - is an inflammatory disease affecting the arteries. Also involved are white blood cells, leukocytes. In the course of atherosclerosis, they are attracted by messenger substances and induce an inflammation process in the wall of the artery. This initiates further reconstructive processes in the vascular wall which ultimately lead to the formation of dangerous plaques.

The attraction of leukocytes is an important process in all inflammations in the body. However, there is a crucial difference between acute, inflammations probably caused by infection and atherosclerosis: In case of acute inflammations, the inflow of leukocytes is important for healing, whereas in atherosclerosis it exacerbates the course of the disease.

The researchers therefore asked whether there are molecules which specifically attract leukocytes in atherosclerosis, but not in other inflammations. They came across the protein cathepsin G. It belongs to the family of proteases, i.e., enzymes that degrade proteins. In isolated human arteries, they were able to prove their existence on the surface of arteries using luminescent antibodies, however, not in veins. Arteries are large vessels that supply the organs such as the heart and kidneys with oxygen-rich blood.

The researchers demonstrated that cathepsin G attracts leukocytes by using knockout mice – animals unable to produce this protein. When these animals contracted atherosclerosis, considerably less leukocytes aggregated in their arteries than in normal atherosclerotic mice.

Distinctly less plaque had also formed in the arterial walls of the knockout mice.

According to the researchers, cathepsin G only occurs in in arteries, because of the shear forces which are higher in arteries than in veins. First, the shear forces activate a certain type of white blood cell which then increasingly releases cathepsin G. Second, the protein is involved in the organisation of integrins which ensure that the leucocytes withstand the high shear forces in the arteries.

For the first time, the discovered mechanism gives us the opportunity to selectively inhibit inflammation processes in the arteries. This would leave other inflammations, which older people with atherosclerosis also often have, unaffected – a crucial criterion for an atherosclerosis treatment with only minor side effects.

Cathepsin G Controls Arterial But Not Venular Myeloid Cell Recruitment, *Circulation*, dx.doi.org/10.1161/CIRCULATIONAHA.116.024790

Healing Heart Failure – with Artificial Heart Tissue from the Laboratory

Strips of heart muscle cultured in the laboratory grow on diseased hearts of guinea pigs and improve their heart function. DZHK researchers now want to apply this very promising method to humans.

In the heart of humans, a myocardial infarction usually destroys cells that never regenerate. This makes the heart less productive in the long run, thus a heart failure develops. A team led by Professor Thomas Eschenhagen and Dr Florian Weinberger of the DZHK Hamburg/Kiel/Lübeck site succeeded in replacing dead heart tissue in guinea pigs with human heart tissue cultured in the laboratory. They used guinea pigs because, compared to all other small animals, their hearts are most similar to those of humans. The tissue grew on and the cardiac efficiency of the animals improved by up to 30 percent.

From pluripotent stem cells – reprogrammed human body cells – the researchers cultured strips which they sewed onto the heart like patches. Such pieces of tissue have the advantage of not washing out, which often happens, for example, with cell suspensions, which other groups



Heart tissue cultured in the laboratory improves the pump performance of guinea pig hearts.

use in their trials. This is because, if immature pluripotent stem cells enter the body, they could form tumours.

Control experiments with tissue strips that do not consist of heart-muscle cells were also supposed to rule out that a stabilisation of the heart muscle by any kind of tissue could increase cardiac performance. The hearts of animals thus treated, however, did not work better.

The twitching strips from the laboratory have their own rhythm and only once ultimately returned to beat with the original heart did they perform at full capacity. In order to reach this electrophysiological coupling, the tissue was sewn onto healthy tissue above and below the scar. The researchers were indeed able to observe this coupling in a variety of other animals.

There still are some steps that need to be taken before this method can be used in humans. Whether and how many cells are washed out and how much tissue is needed must be investigated precisely. There is also still uncertainty about the best time for treatment. The researchers do not yet know if it is better to put on the patches shortly after injury or once the heart lesion has already become chronic. And finally, the trials must be reproduced in larger animals, e.g., pigs, whose cardiovascular system is even more similar to that of humans.

For these steps, the group received DZHK funding for a HRHV project in 2016..

Cardiac repair in guinea pigs with human engineered heart tissue from induced pluripotent stem cells. Florian Weinberger et. al., *Sci. Transl. Med.* 8, 363ra148 (2016)

Bioresorbable Stents – It's the Width that Counts

Bioresorbable stents used to widen coronary arteries seem to have nothing but advantages. They eventually dissolve and the artery retains its elasticity. Only the somewhat increased thrombosis incidence rate after implantation still puzzles cardiologists. DZHK researchers from Mainz were now able to solve the problem.

In case of a myocardial infarction or a coronary heart disease, an artery supplying the heart with blood is either constricted or occluded. Cardiologists then widen the artery with a small balloon and implant a small scaffold, something that looks like an interior corset that prevents the artery from clogging up again. So far, these scaffold structures, so-called stents, have been made of metal and remain inside the body for a lifetime. For about four years now, stents have also been made of a bioresorbable material – mostly lactic acid – which dissolves after a period of 6-18 months.

By that time, the artery has usually restabilised and can respond to various functional requirements with its usual elasticity, whereas arteries containing metal stents remain permanently rigid.

Due to these advantages, cardiologists are now increasingly using bioresorbable stents. However, compared to conventional stents, physicians observed an elevated risk of thrombosis, i.e., the formation of a clot that occludes the artery.



The risk of thrombosis associated with bioresorbable stents can be reduced by applying the right surgical method.

"These stent-induced thromboses are very dangerous, which is why we want to do something about it," says Professor Gori.

In a study including 1,300 patients, DZHK-researchers at the University Medical Centre Mainz discovered that the elevated numbers of thromboses could be reduced by modifying the operation technique. "Thromboses decrease if we widen the stent to a minimum degree during its implantation," says Gori. The exact measurement is 2.4 millimetres. "This implantation technique decreased the risk of thrombosis to 73 percent, which is comparable with that of metal stents." Additional widening did not reduce the risk any further.

The researchers also discovered the reason for the increased thrombosis risk: the struts of the bioresorbable stents are thicker than those made of bare metal. If the resorbable stent is not widened enough, i.e., less than 2.4 millimetres, the struts are so close to each other that the vascular wall is almost completely covered. The increased contact with the foreign body activates the platelets at this site where upon they begin to form clots – thrombosis is immanent. According to the researchers, the last remaining disadvantage of bioresorbable stents can be overcome by the right surgical technique – to the benefit of the patients.

This work was done in the scope of the DZHK professorship of Professor Tommaso Gori of the Rhine Main site.

Bioresorbable Coronary Scaffold Thrombosis. Multicenter Comprehensive Analysis of Clinical Presentation, Mechanisms, and Predictors. *J Am Coll Cardiol.* 2016;67(8):921-931. doi:10.1016/j.jacc.2015.12.019

Promotion of Young Scientists – the Young DZHK



The promotion of young scientists in the field of translational cardiovascular research belongs to the most important objectives pursued by the DZHK. In the reporting year, the DZHK therefore provided 1.5 million euros for the promotion of young researchers. In addition, the DZHK supports the Young DZHK, the self-organised union of all young researchers of the DZHK. The Young DZHK counted 824 members at the end of the reporting year.

Young scientists at the DZHK may submit applications for a total of ten funding lines particularly devised for them. The measures of the training sector are basically addressed to all Young DZHK members, whereas the promotion of excellence measures are reserved for post-doctoral scholars. In addition, cooperations with Shared Expertise and cooperations with external partners

(Chapter 3) are also open to Young DZHK members. In clinical studies, the Young DZHK members may act as co-applicants. Beyond this, they have the chance to join project groups (Chapter 7). Of the 103 project group members in the reporting year, 10 percent belonged to the Young DZHK.

Another career option addressed to young medical scientific researchers are the physician posts financed by the DZHK with its central funds at all of its 17 clinical member institutions in order to support recruitment in DZHK studies (Clinical Staff, cf. also Chapter 4.1). Finally, the DZHK is working on the development of a Clinician Scientist Programme which is especially adapted to the needs of researching physicians.

Committee:

PostDoc Committee

The PostDoc Committee of the Young DZHK convened four times in the reporting year, the spokesperson or her representative took part in the monthly session of the Research Coordinating Committee and the meeting of the Scientific Advisory Board. Apart from organising and executing the annual Young DZHK retreat, the most important issues in 2016 were planning two Young DZHK workshops and consolidating cooperations with other national and international junior scientist networks. On the national level, cooperation with the AG38 (German Chapter of Young Cardiologists of the ESC) of the German Cardiac Society was intensified and a joint session was held at the Spring Meeting 2016 in Mannheim.

On an international level, cooperation with young researchers of the American Heart Association was improved. The spokesperson of the Young DZHK has been a member of the ATVB Early Career Committee since 2016. In the course of the audit of the German Centres for Health Research (DZG) carried out by the Scientific Advisory Council, the spokesperson took over the part of introducing the DZHK junior scientists.

Training Programme

The number of funding measures which in the broadest sense serve the purpose of scientific exchange among young scientists that were applied for has once again increased in the reporting year relative to the previous year (participation at high-ranking conferences, mobility programme, attending external workshops).

A total of 17 applications were received by the mentoring programme in its fourth year, 14 participants were selected. The year starts in March 2017. Almost all participants in recent years stated that intensive networking had been a special advantage of the mentoring programme. In order to develop this further, we have started mentoring alumni activities.

In 2016, the first Mentoring Alumni Newsletter was published and the planning of an alumni meeting in the summer of 2017 has started. We postponed the elaboration of a coordinated further development concept for

the mentoring programme until 2017. However, it has already been decided that the fifth mentoring year, which is to start in 2018, will be held in English. To develop the programme as much as possible to the benefit of its users, in the reporting year we began to carry out before and after queries about individual modules and also about the entire programme.

Funding measures for Young DZHK members derived from the Training Programme 2016 (in parentheses 2015):

Travel grants for high-ranking conferences	211 (180)
Doctoral scholarships	23 (31)
Mobility programme	38 (24)
Attendance of external workshops	67 (24)
Mentoring (call 2016)	14 (14)

In the reporting year, the Young DZHK organised a Young DZHK Retreat (cf. Chapter 7) on its own for the third time. In addition, the Young DZHK organised and held a scientific workshop:

- Large animals in basic cardiovascular research, 20–21 Oct. 2016 in Hamburg
Organisers: Katharina Scherschel (Hamburg / Kiel/ Lübeck), Martin Bahls (Greifswald)



Excellence Programme

In the reporting year, a similar number of young scientists as the year before were promoted. The number of applicants was also comparable, whereby the number of applications and funding quota strongly depended on the respective funding module.

The funding quotas in 2016 were as follows (a maximum of five grants can be awarded to each call for proposals):

- Rotation grant: 5/11 projects (2015: 6/8)
- Research grant: 2/3 (2015: 1)
- Reintegration grant: 3/3 (2015: 0/0)
- Postdoc start-up grant: 5/24 (2015: 10/63)

In 2016, the DZHK announced a call for proposals for two DZHK junior research group leaders for the second time. This time, only three applications were received. As a result, no junior research group was awarded. In order to acquire more eligible applicants, the funding measure will be revised in 2017.

Promotion of Excellence in 2016

Name	Institution	Funding Line*	Title
Jedrzey Hoffmann	Hospital of the Johann Wolfgang Goethe University	Pds	Identification of ischemic heart disease-regulated T-cell lncRNAs
Lorenz Lehmann	University Hospital Heidelberg	Pds	YY1 associated factor 2 (Yaf2) as an epigenetic regulator of the cardiac cell cycle
Konstantin Stark	University Hospital Munich	Pds	Myocardial HMGB1 as mediator of increased atherosclerosis and thrombosis in the post-myocardial infarction period
Constanze Schmidt	University Hospital Heidelberg	Pds	Specific K2P channel remodeling in atrial fibrillation and heart failure-implications for therapy
Xingbo Xu	University Medical Centre Göttingen	Pds	The role of long non coding RNA in gene-specific promoter methylation during cardiac fibrogenesis
Maik Drechsler	University Hospital of Munich	Pds	The role of formyl peptide receptor 1 (FPR1) and DAMPs in myocardial infarction
Toshiya Sugino	Max Planck Institute for Heart and Lung Research	Pds	Regulation of endothelial FOXO signaling by deubiquitinating enzymes

Promotion of Excellence in 2016

Name	Member Institution	Funding Line*	Titel
Alexander Teumer	University Medical Centre Greifswald	Pds	Epigenome-Wide Association Study on Platelet Count and Platelet Volume
Michelle Collins	Max Planck Institute for Heart and Lung Research	Pds	Elucidating the cellular mechanism driving asymmetric patterning of the cardiovascular system
Shabana Din	University Hospital Heidelberg	Rig	Role of the Myeloid Cell Compartment in Cardiac Hypertrophy
Simone Martini	University Hospital Schleswig-Holstein/Campus Kiel	Rig	Epigenetics of cardiac hypertrophy
Stephanie Tennstedt	University of Lübeck / University Hospital SH Campus Lübeck	Rig	From GWAS hits to novel treatment targets
Alexandra Klaus-Bergmann	Max Delbrück Center for Molecular Medicine in the Helmholtz Association	Rig	REMODEL/ AIM5/ The role of YAP/TAZ signaling in retinal angiogenesis
Christian Fork	Hospital of the Johann Wolfgang Goethe University	Resg	Characterisation of the PHF8 splicing target sHLA-G
Nadine Althof	Charité – Universitätsmedizin Berlin	Resg	Molecular aspects of the antiviral activity of ISG15 in CVB3-induced myocarditis
Lorenz Lehmann	University Hospital Heidelberg	Rotg	Enhancer regulation in metabolic cardiac stress
Marc Daniel Lemoine	University Hospital Hamburg-Eppendorf	Rotg	Electrophysiological characterisation of a HCM-causing ACTN2 mutation in human iPSC-cardiomyocytes
Uwe Raaz	University Medical Centre Göttingen	Rotg	Arterial stiffness in type 2 diabetes: Therapeutic potential of microRNA miR-29b
Hendrik Sager	German Heart Centre Munich	Rotg	Therapeutic targeting of the NLRP3-inflammasome in atherosclerosis
Konstantin Stark	University Hospital Munich	Rotg	Antibodies as central mediators of thrombosis and hemostasis

***Funding lines:** Pds > Postdoc start-up grant
Resg > Research grant

Rig > Reintegration grant
Rotg > Rotation grant

Achievements in 2016

- ✓ Exemption from teaching and return after family leave was publicised more in order to receive more applications
- ✓ After two application rounds summary was drawn on how the measures are requested
- ✗ Mentoring programme was further developed
- ✓ Publication of a Mentoring Alumni Newsletter

Goals for 2017

- Launch of a Clinician Scientist Programme
- Revision of the funding measure for the junior research group
- Revision of the reintegration grant
- Mentoring programme prepared in English

Scientific Exchange and Cooperation at the DZHK



More than 200 researchers from the DZHK took part in the fourth DZHK Retreat in Bad Aibling.

DZHK Retreat and Young DZHK Retreat

From 15 to 17 September, the scientific annual meeting – the DZHK Retreat – took place for the fourth time. This time, the Munich partner site hosted the retreat and more than 200 researchers convened in Bad Aibling / Chiemgau. The members of the Young DZHK once again met one day before.

For the first time, the scientific programme of the 2016 meeting was drafted by the DZHK professors who constituted the programme committee. To do this, they invited the entire DZHK community to make suggestions on topics and conferred closely with the spokespersons of the Young DZHK PostDoc Committee. The result was a programme that not only took into consideration the proposals of the DZHK members, but also integrated the

junior scientists into the main programme more strongly in particular. Consequently, an open poster exhibition was held on the first evening, during which the participating members of the Young DZHK had the opportunity to present their scientific work.

The posters were on display throughout the entire time of the Retreat. In addition – a further novelty – at least one lecture by a young researcher was included in each session. As every year, the three keynotes were a further highlight of the Retreat. Fady Malik of Cytokinetics, Inc. in San Francisco; Eva Prescott of the University of Copenhagen; and the Director of the Max Delbrück Centre for Molecular Medicine in Berlin, Martin Lohse, held exciting lectures which inspired much discussion and exchange. The three parallel workshops were dedicated to the motto "how-to", allowing the participants to

choose from the topics CRISPR/Cas9 Genome Editing, Imaging and Optogenetics, as well as Modelling Cardiovascular Disease. There was no separate industry session this year, however, representatives from Siemens Healthcare GmbH and Metanomics Health GmbH were invited to hold lectures.



Junior scientists at the Young DZHK Retreat present their results in poster sessions and lectures.

The Young DZHK Retreat was organised as it had been the year before. Thus, seven scientific sessions were held, distributed over a period of one and a half days. Two lectures and two poster prizes were awarded and conferred at the end of the main retreat with kind courtesy of Bayer AG and FUJIFILM VisualSonics Inc. Furthermore, there was a session on infrastructural topics in which in addition to the mentoring programme, Central Data Management (ZDM), the ethics project of the DZHK, and quality management with reference to TORCH were also presented. The junior scientists were able to win Filip Swirski of the Harvard Medical School and Esther Lutgens of LMU Munich as keynote speakers.

The project groups act autonomously and without a budget provided by the DZHK, however, they may draw on administrative support from the main office, e.g., for organising video conferences or reimbursements of travel expenses. The project groups report that there is a close exchange between basic researchers and clinical scientists.

The Retreat was also used to make connections and exchange views outside the actual programme. The DZHK professors, partner site managers, representatives of the OMICs Resource Project and the Use & Access Committee held their own additional meetings. Furthermore, the RCC and the General Assembly of Members met prior to the start of the Retreat in Bad Aibling.

Project Groups

A total of 15 project groups existed at the end of the reporting year. New project groups founded in 2016 were "Imaging" and the "Clinical Study Group Competence Network for Heart Failure". Project groups are loose associations of DZHK scientists from all partner sites who initiate future projects on the basis of their mutual exchange and develop corresponding funding applications. In this case, especially the funding module cooperation by means of Shared Expertise is utilised. However, in the clinical sector, the project groups also submitted applications for early clinical studies and guideline-relevant studies last year. In addition to phone and video conferences, the project groups also organised their own meetings and symposia. In 2016, the project group "Imaging" was responsible for the organisation of the only DZHK symposium held in that year entitled "Imaging/Biomarkers in Cardiovascular Disease and Big Data in Biobanking". In addition, it was involved in the organisation of the 2nd Berlin Symposium on Cardiac Imaging held under the auspices of the DZHK.

As part of an international research group, the members of the project group "Genetics of Congenital Heart Diseases" significantly contributed to the Paper of the Month August 2016, which appeared in Nature Genetics. A variety of other publications resulted from the work of the project groups. The project group "Imaging" also coordinates the image data management of the DZHK and is currently working on a database which intends to make the imaging expertise of the individual DZHK partner sites visible.

The project groups act autonomously and without a budget provided by the DZHK, however, they may draw on administrative support from the main office, e.g., for organising video conferences or reimbursements of travel expenses. The project groups report that there is a close exchange between basic researchers and clinical scientists.

Symposia and Conferences

In the scope of its scientific exchange funding lines, the DZHK promotes its own internal events such as the DZHK symposia, but also external congresses and conferences which are organised by a member institution of the DZHK.

In comparison to co-financed conferences, DZHK symposia are addressed exclusively to members of the DZHK (PI, DZHK scientists and members of the Young DZHK). The goal is to create an internal exchange platform and thus promote networking across the various sites. Symposia are submitted to the RCC or proposed by the RCC itself. This ensures that the topics are in line with the overall scientific strategy of the DZHK.

Three symposia and three co-financed conferences to be held in 2017 were applied for and approved in the reporting year. In October 2016, the DZHK double symposium "Imaging-/Biomarkers in Cardiovascular Disease and Big Data in Biobanking" took place in Frankfurt/Main.

Internal Communication

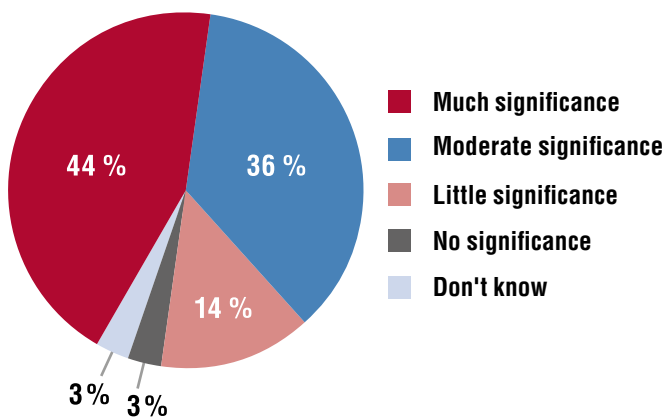
In the reporting year, we revised all our funding guidelines as well as all pertaining forms. The application documents were numbered for better assignability, uniformly formatted and are now also available in English. They can be retrieved over a matrix from a central site on the intranet. The documents are subject to a three-monthly updating cycle, important changes of content are communicated in the DZHK-internal newsletter.



In October, we carried out a survey among all scientific employees registered at the DZHK for the first time. The online survey contained a total of 46 questions relating to funding instruments, committees and governance, communication and networking, and personal integration into the DZHK. 49.9 percent of the invited 1,276 employees took part in the survey.

Employee survey:

For my work and my personal career, the DZHK has ...



Fifty percent (629) of the scientific employees of the DZHK took part in the internal survey in October 2016.

This is a very gratifying result for a decentralised organisation which is not the direct employer. Also satisfying is the fact that 80 percent stated the DZHK plays an important role for them.

The surveyed employees predominately expressed positive opinions about the instruments for research and promotion of young researchers, work done by the committees, and communication within the DZHK. For example, 90 percent were of the opinion that Shared Expertise projects are able to make specific competences of one site available to all the others.

Regarding clinical studies, 82 percent stated that they are suited to advance cooperation within the DZHK, and 76 percent believed that clinical studies would promote translation. However, it also showed that employees know too little about some measures and that the transparency of selection processes could be improved.

An 88-page overview containing the results was published on the DZHK intranet and partial results were also brought to the knowledge of the German Council of Science and Humanities in the scope of the hearing of all DZG members. The survey will be further evaluated over the course of 2017 and the evaluations will be to some extent broken down at partner site level. Results of the survey will also merge into the optimisation and improvement processes on board and on main office level.

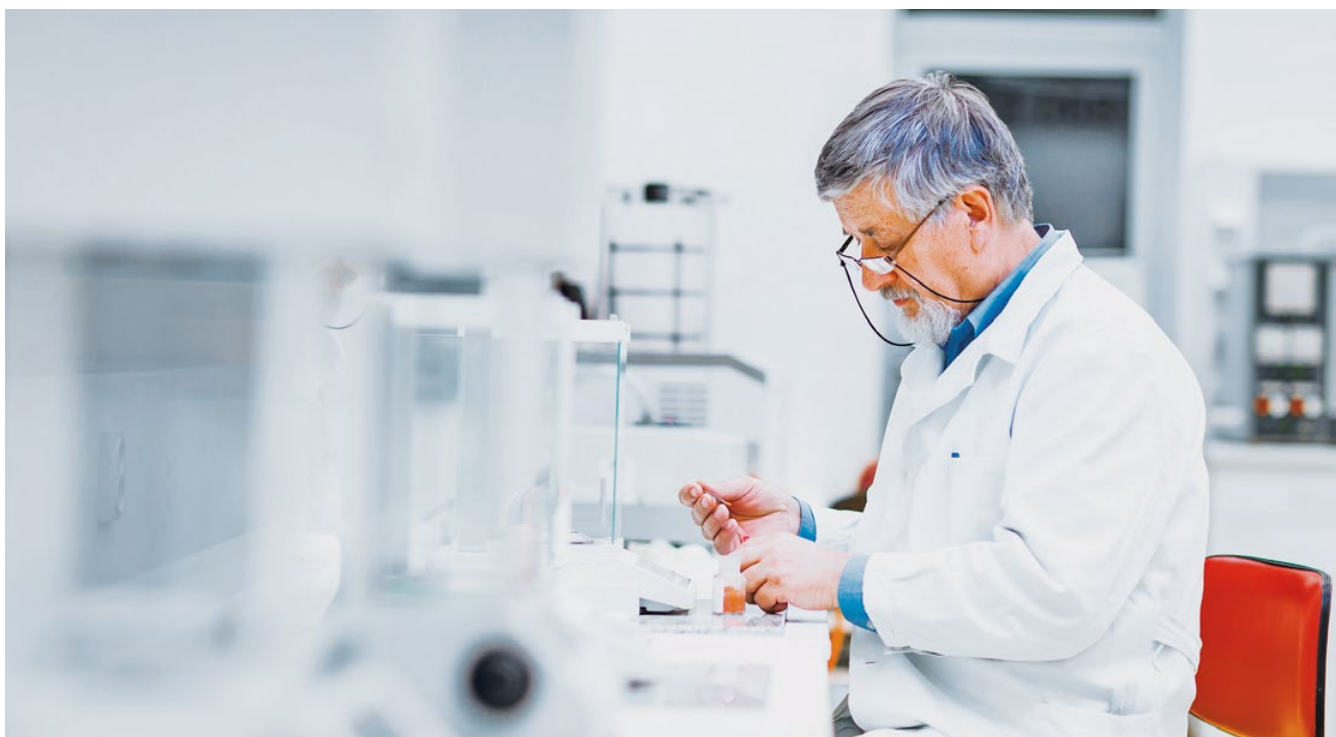
Achievements in 2016

- ✓ Project group work produced concrete results
- ✗ At least two DZHK symposia carried out
- ✗ Number of Retreat participants increased
- ✓ Revision of funding guidelines finalised

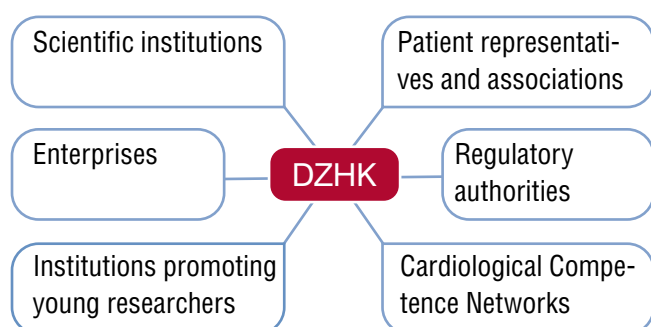
Goals for 2017

- 5th DZHK Retreat with increased participant satisfaction
- Number of Retreat participants increased
- At least two DZHK symposia carried out
- Administrative simplification of DZHK symposia
- Project group work produced concrete results

Cooperations with Partners outside the DZHK



Successful translation has many fathers and mothers. It is therefore natural for the DZHK to cooperate with external partners that play an important role in the translation process. We identified the following groups or areas as being important to translation and will explain these cooperations in more detail:



External Cooperations with Science

Preclinical Research

The DZHK engages more and more in international cooperations. In the reporting year, DZHK researchers submitted applications in a concerted action to the cooperative programme of the European Research Area Network for Cardiovascular Research (ERA-CVD). Among the first 14 projects approved for the whole of Europe, DZHK researchers were immediately successful seven times. For 2017, it is also planned for the DZHK to engage in a joint tender with the British Heart Foundation (BHF) and the Dutch Heart Foundation (DHF), pursuing the goal of supporting a major transnational project annually with a funding amount of approx. 5 million euros for a 5-year period. A special funding line for cooperations with external partners exists for preclinical research. It is described in Chapter 3.

Clinical Research

In the scope of its clinical studies, the DZHK cooperates with university hospitals all over Germany. They recruit patients in clinical trials and receive a patient fee in return.

Until the end of 2016, five external clinical partners recruited patients in the fully financed studies of the DZHK. Further 14 external hospitals were initiated as study centres. We assume that they will begin recruiting patients by 2017.

External clinics initiated as study centres for DZHK studies are

- Klinikum Coburg II. Medical Hospital (Cardiology, Angiology, Pneumology)
- University Medical Centre Regensburg
- University of the Saarland, Homburg/Saar
- Heart Centre Leipzig
- University Hospital Tübingen
- Municipal Hospital Karlsruhe, Medical Clinic IV
- Asklepios Klinik St. Georg Hamburg
- Helios Heart Centre Wuppertal
- Municipal Hospital Munich – Klinikum Neuperlach Neuperlach
- University Hospital Jena, Hospital for Heart and Thorax Surgery
- Asklepios Center Langen
- Krankenhausgesellschaft St. Vincenz mbH Limburg
- Hannover Medical School, Hospital for Cardiology and Angiology / Hospital for Heart, Thorax, Transplantation and Vascular Surgery
- Klinikum Lippe Detmold
- Heart and Diabetes Centre NRW - Bad Oeynhausen
- RWTH University Hospital Aachen, Hospital for Thorax, Heart and Vascular Surgery
- Heart Centre, University of Freiburg-Bad Krozingen, Hospital for Heart and Vascular Surgery
- University Medicine Erlangen, Heart Surgery Clinic
- University Hospital of Gießen and Marburg, Hospital for Heart and Thorax Surgery

In addition, the DZHK supports ten clinical trials and registers of the Cardiological Competence Networks (cf. page 47).

With the German Cancer Research Center (DKFZ), the DZHK entered into a cooperation in the scope of its 1,000 genome project (OMICs Resource). The DKFZ will sequence the genomes of 1,000 healthy control persons which will then serve as the foundation of clinical research projects (cf. Chapter 9).

In the reporting year, a close cooperation was agreed with the Dutch Interuniversity Cardiology Institute - Netherlands Heart Institute (ICIN-NHI) for the use of data and samples in the scope of clinical trials, shall be developed in 2017. In addition, the DZHK will fund two clinical trials (SCREEN-AF, CTSN-TV) which will be carried out and financed together with the National Institute of Health (NIH) and the Canadian Cardiothoracic Surgical Trials Network (CTSN).

Patients and Participants

The integration of this target group is very important for the DZHK's intention to conduct research for the benefit of the patients. This is done, i.e., in the scope of guideline-relevant, fully financed DZHK studies. Here, applicants must already consider the perspective of patients in their study applications. In the DZHK funding guideline for guideline-relevant studies it reads: "Patient participation: How were the patients' needs, goals, and preferences considered in developing the main question and in defining the endpoints? Have patient representatives/patient advocacy groups been involved?"

For the studies FAIR-HF2-DZHK5 and DEDICATE-DZHK6, the German Heart Foundation wrote a letter in support of the study and an individual promotion in preparation of DEDICATE. The chairman of the board of the

German Heart Foundation, Professor Thomas Meinertz, is also a member of the DEDICATE steering committee.

Moreover, we already cooperate with the German Heart Foundation, whose target group is mainly patients and patient associations, in matters relating to patient inquiries. We are receiving more and more inquiries from patients who tell us about their personal problems and seek advice. We refer them to the patient office hours of the German Heart Foundation and draw their attention to the pertinent information offered by the Heart Foundation. We seek to develop our cooperation with the Heart Foundation further as far as patients are concerned and we are planning a meeting at board level to take place in 2017. It shall cover, i.e., how the enrolment of patients in clinical trials, registers and cohorts of the DZHK could be improved.

In the reporting year, we launched the Proband Information Platform (PIP) online in order to keep the participants of our clinical trials updated with respect to research purposes and study results (cf. Chapter 4.1 for more information). The feedback from patient organisations and self-help groups have been incorporated into the concept.

Cooperations with Industry

A part of late preclinical projects (HRHV projects – cf. Chapter 3) as well as many clinical studies have industry partners who share the intellectual property rights and provide medication or instruments free of charge.

In addition, the DZHK carried out two major tenders in the reporting year for the operation of its Laboratory

Information System (LIMS) and the Image Data Management System (IDMS) (cf. also Chapter 4.2). These tenders were awarded to the companies Kairos GmbH and Deutsche Telekom Healthcare and Security Solutions GmbH. These companies provide the technical basis for the purposes the DZHK needs. However, these are not standard solutions. The respective products will be adapted to DZHK requirements and further developed in a cooperative process.

Industry partners in the scope of site projects, HRHV projects and clinical studies

- IHF GmbH - Institut für Herzinfarktforschung, Ludwigshafen
- advanceCor GmbH
- Bristol-Myers Squibb (BMS)
- Eli Lilly and Company
- Medtronic Bakken Research Center
- miRagen Therapeutics (from HRHV funding line)
- Monitoring Services Munich
- Pfizer
- Rapid Biomedical
- Sanofi
- Siemens Healthcare
- TomTec
- Vifor Pharma Ltd., CH-8152 Glattbrugg



Cooperations with industry in the scope of publicly funded research projects are subject to strict European regulations in order to prevent state subsidies distorting the competition. For example, if a company owns a patent for an active substance, the value of this patent can rise when a study proves the efficacy of the substance. This would mean that the company gains a competitive advantage. We have therefore developed a declaration for the various types of intellectual property. It provides an informative basis regarding what needs to be considered in the respective cooperation agreements closed between companies and the DZHK partner institution.

External Cooperations for the Promotion of Young Scientists

Three workshops were held again in 2016 in cooperation with the German Society for Cardiology (DGK): "The Fundamentals of Cardiovascular Research". The DGK organised two workshops during its spring and autumn meetings. In the summer, a workshop planned and organised by the DZHK took place at the DZHK main office in Berlin. The aim of the programme was to offer clinical

scientists a curriculum similar to what life scientists encounter in research training groups and is oriented towards translation in the field of cardiovascular medicine.

These were the DGK-DZHK workshop topics:

- Vascular biology, 30 March 2016
- Stem cell biology – relevance to cardiovascular basic research, 6 June 2016
- Cardiac insufficiency – Mechanisms, 7 October 2016

Regulatory Authorities

An applicant for the late translational HRHV projects has sought advice from the Paul Ehrlich Institute (PEI) in Langen for submission of an application. The information obtained merged into the application and project design and represented an important step towards realising the project. In the context of another study project, consulting the PEI is planned again, depending on the results obtained at the end of project.

Clinical studies of the Cardiological Competence Networks partially funded by the DZHK (DZHK-associated studies)

Acronym	Disease/ Study goal	Study type	Competence network	Number of participants (planned)	Recruitment status
AFNET-EORP	Atrial fibrillation and clinical treatment	Register	AFNET	3,500	3,500
AXAFA – AFNET 5	Atrial fibrillation, anticoagulation with NOACs, catheter ablation	Guideline-relevant study	AFNET	630	516
EAST – AFNET 4	Atrial fibrillation and stroke prevention	Guideline-relevant study	AFNET	2,745	2,789
DIAST-CHF	Heart failure	Cohort	KNHI	1,400 (number of 10-year follow-up examinations)	1,041
KNHI – TP 9a	Myocarditis	Guideline-relevant study	KNHI	120 (number of 10-year 39 follow-up examinations)	39
KNHI – TP 9b	Heart failure	Guideline-relevant study	KNHI	650 (number of 10-year follow-up examinations)	650
CIBIS-ELD Trial	Beta-blockers in seniors with heart failure	Guideline-relevant study	KNHI	500 (number of follow-up examinations)	455
NRAHF	Congenital heart defects	Register	KNAH	(open)	51,150
INH-Studie	Chronic heart failure	Guideline-relevant study	KNHI	400 (number of follow-up examinations)	247
NOAH-AFNET 6	Atrial fibrillation, stroke prevention	Guideline-relevant study	AFNET	3,600	65

Scientific advice from BfArM also took place in the scope of a project study. The information obtained from BfArM merged into the planning of the trials belonging to the yet outstanding work packages (cf. Interview p. 15).

The Cardiological Competence Networks

Since 2015, the DZHK has been funding selected studies and structures of the Cardiological Competence Networks (cf. table above for studies funded). Main topics are guideline-relevant studies on heart failure and atrial fibrillation as well as the promotion of the National Register for Congenital Heart Defects. The Competence Networks reported after two years of DZHK funding in the RCC on "Where do we stand?" and "What do we

want?" In addition, the interim evaluation of the Competence Network for Congenital Heart Defects has been submitted. The reports of the interim evaluation representing the half-time status of DZHK funding will be discussed by the RCC at the start of 2017.

Of the ten partially DZHK-funded and DZHK-associated studies of the Cardiological Competence Networks, five studies are in the recruitment stage (AFNET-EORP, AXAFA – AFNET 5, EAST – AFNET 4, NOAH – AFNET 6, NRAHF) while 5 studies are compiling data in the follow-up stage (DIAST-CHF, KNHI - TP 9a, KNHI - TP 9b, CIBIS-ELD Trial, INH study).

Competence Network for Congenital Heart Defects

The DZHK has been funding the Competence Network for Congenital Heart Defects (KNAHF) since 2015. The National Register for Congenital Heart Defects (NRAHF) is the core project of the collaborative research effort supported by the cardiological professional associations DGPK, DGK and DGTHG. The NRAHF supports research activities all over world with its powerful database infrastructure. In the summer of 2016, the NRAHF registered the 50,000th patient. NRAHF's own biobank also comprises 50,000 gene and tissue samples. The KNAHF thus disposes of one of the largest research bases in the field of congenital heart defects.



In 2016, the National Register for Congenital Heart Defects registered its 50,000th patient.

Acting in a continuous exchange with patient and parent associations, organised in the action alliance Congenital Heart Defects, the KNAHF supervises clinical, epidemiological and genetic studies on congenital heart defects of all age groups and on cardiovascular diseases acquired during childhood. The nationwide association of physicians and scientists plans and realises these studies.

Project-related, the NRAHF compiles the respective database and ensures legal security and quality of data and samples.

Also in 2016, together with the DZHK, KNAHF realised research projects which have already found their way into guidelines and hence into clinical practice. Thus, based on the biological data of children with complex congenital heart defects and their parents, researchers were able to identify three new genes involved in the development of certain heart defects (cf. also page 31). This research success was realised by an international consortium under the auspices of the Wellcome Trust Sanger Institute in Cambridge and in cooperation with paediatric cardiological departments in Berlin, Erlangen, Freiburg, Homburg, Kiel and Leipzig, among which were also DZHK researchers. Genetic counselling of families benefits directly from these results.

In the future, a lot will depend on the successful prevention, diagnostics and treatment of congenital heart defects and on the transfer of knowledge into the field of acquired cardiovascular diseases. The significant worldwide increase of patient numbers in both areas requires multicentre research on a permanent basis which moves the interests and needs of individual patients deliberately into the focus of medical and scientific action. KNAHF, sponsored by the German Heart Foundation, the Fördergemeinschaft Deutsche Kinderherzzentren e. V, and the Friede-Springer-Herz-Stiftung, will therefore dedicate itself to research and its effectual translation in the future in an even more broadly networked context under the roof of the DZHK.

www.kompetenznetz-ahf.de/en/home

Competence Network for Atrial Fibrillation

In the Competence Network for Atrial Fibrillation e.V. (AFNET), scientists and physicians from clinics and medical practices from all over Germany work together in order to improve treatment for patients with atrial fibrillation in Germany, Europe and in the United States by means of coordinated research. To this end, AFNET conducts science-initiated clinical studies and registers at a national and international level.



Echocardiography in a patient with atrial fibrillation.

In 2016, the DZHK continued financing the three international studies EAST – AFNET 4, AXAFA – AFNET 5 and NOAH – AFNET 6, in which AFNET bears the overall responsibility as the sponsor, and the nationwide patient register AFNET-EORP. Beside measures to enhance patient recruitment and support a study-specific bio-bank, parts of the AFNET infrastructure were funded, in particular, the project management of the branch office in Münster.

The AFNET-EORP register (treatment of atrial fibrillation in Germany) and the EAST – AFNET 4 study (early rhythm-retaining treatment) reached their recruitment goals in March 2016 and at the end of 2016, and are now in the follow-up observation stage. The AXAFA –

AFNET 5 study (anticoagulation during catheter ablation) enrolled more than 80 percent of the planned patients by the end of 2016 and will likely reach its recruitment goal in the first half of 2017. In June 2016, the first patient was enrolled in the newly started NOAH – AFNET 6 study (anticoagulation in atrial high-frequency episodes).

The current AFNET studies were not only funded by the DZHK, but also supported by joint activities, e.g., by an AFNET symposium chaired by the DZHK at the annual conference of the German Cardiac Society. AFNET cooperates with the DZHK in the planning and execution of the new CLOSURE-AF study on left atrial appendage occlusion in cases atrial fibrillation, initiated in 2016 by members of DZHK headed by Professor Ulf Landmesser (Berlin) with the co-PIs PD Dr Ingo Eitel (Lubeck) and PD Dr Leif-Hendrik Boldt (Berlin). AFNET is involved in project management and filling positions in committees. At present, regulatory preparations for starting the study are in progress.

In addition, AFNET conducts further clinical studies in which it acts as sponsor and is also involved in national and international studies and projects.

In March 2016, the registered association Competence Network for Atrial Fibrillation e.V. established a scientific council that supports the Board of Directors with competences in law and business management.

 www.kompetenznetz-vorhofflimmern.de/en/home



Heart failure is not yet curable, thus the mechanisms must be explored intensively in the laboratory and in patients.

Competence Network for Heart Failure

The studies of the Competence Network for Heart Failure (KNHI) funded by the DZHK were initiated in the period from 2004 to 2005. They comprise important phenotypes of the clinical heart failure syndrome (systolic and diastolic heart failure) as well as groups with patients at risk of developing heart failure. Funding from the DZHK enables further substantiation of the KNHI study results and a more exact evaluation of the long-term health effects of an adjusted therapy. Approx. 2,500 follow-up examinations were completed by the end of 2016.

In 2016, the Board of Directors of the DZHK approved the foundation of a KNHI project group in which members of the DZHK are also represented. This group will serve as a platform for initiating new DZHK studies in the future.

Concurrently, the KNHI is involved in the DZHK study TransitionCHF as a study centre. The application for ethical approval was given a positive opinion by the ethics commission of the University of Würzburg at the end of 2016, and the initiation of the Würzburg centre is planned for the beginning of 2017. The network of cardiologists "Heart Failure Bavaria", with which the KNHI closely collaborates, is to be included in the recruitment of patients.

Besides, the KNHI created a CodeBook to the Basic Clinical Dataset (BCD) for interested scientists to view on the DZHK website. Using the BCD was obligatory in all 22 KNHI projects.

The minimum dataset requires a standard format of the parameters and facilitates a unified data review for plausibility and consistency. This is the requirement for conducting cross-study evaluations of special issues. The first evaluation ideas have already been sent to the administrative office of the KNHI. Beside the CodeBook, the comprehensive databases of KNHI studies and biomaterials (DNA, serum, EDTA) are available to researchers for evaluation purposes.

www.knhi.de/en/

Achievements in 2016

- ✘ Development of framework conditions for individual cooperations with industry in the scope of HRHV projects and clinical trials
- ✘ Payment of patient fees to external hospitals for recruitment

Goals for 2017

- Development of framework conditions for individual cooperations with industry in the scope of HRHV projects and clinical trials
- Payment of patient fees to external hospitals for recruitment
- Competence Network Atrial Fibrillation: completion of AXAFA – AFNET 5 and AFNET-EORP recruitment

Further Resources and Research Infrastructures



The DZHK wants to inspire cooperations and create synergies within the centre and beyond. In addition, redundancies shall be avoided. In this chapter, we will therefore present central research infrastructures and data collections which are directed towards internal researchers, but can also be consulted and partially used by external researchers. All offers are either already available online or are in preparation. Specific resources available at the partner sites will be presented in the respective partner site reports.

- ▶ Shared Expertise
- ▶ Data Catalogue
- ▶ Durrer Catalogue
- ▶ OMICs
- ▶ DZHK SOPs
- ▶ Stem Cell Database
- ▶ Project Database (by 2017)

Shared Expertise

Since 2012, the DZHK summarises under the term "Shared Expertise" specific know how and specific laboratory methods of the DZHK partner institutions. All DZHK researchers may use Shared Expertise in the scope of bilateral small research projects. A total of 155 Shared Expertises were offered in the reporting year, hence 15 more than in the previous year. A survey for DZHK members in the reporting year revealed that Shared Expertise cooperations is among the most used and known support options within the DZHK.

www.dzhk.de/en/research/preclinical-research/shared-expertise/

Data Catalogue

All basic data and biological samples collected in DZHK studies were presented in a Data Catalogue launched on the DZHK website in June 2016. The purpose of the Data Catalogue is to describe in detail the basic data and biological samples contained in the scientific infrastructure (basic biobanking) of the DZHK. With this catalogue, researchers can decide whether they wish to submit a usage application for using the DZHK collection of data and biomaterials.

🔗 www.dzhk.de/en/resources/data-manual/



OMICs

The OMICs Resource Project ("1,000 Population-based Genomes") evolved from the investment programme (cf. Chapter 2). To ensure the success of the overall project, a preliminary study with the aim of harmonising the samples derived from the various cohorts to ensure optimal comparability and coordinating processes in order to minimise error sources was done first. With a successful harmonisation of the samples and processes, the preliminary study was successfully completed in 2016.

A comprehensive and constructive follow-up discussion of the preliminary study results and the planning of the main study took place at the DZHK Retreat in autumn. As far as the main study is concerned, the cohorts sent all samples to the laboratories in Munich (RNA) and Heidelberg (DNA) for standardised sample preparation for DNA and RNA sequencing before the end of the reporting year. The samples now await actual sequencing.

DZHK SOPs

SOPs (standard operating procedures) are standardised work instructions used in clinical research in order to harmonise processes. The DZHK has developed eight clinical, two biobanking and four process SOPs for its clinical studies. The latter SOPs were added in 2016 or were significantly updated. In particular, they serve the purpose of standardising the processes at the interface between patient recruitment and Central Data Management. It therefore concerns how exactly data should be entered or what should be done in case of a recall. The DZHK has made its SOPs publicly accessible online. Thus, other centres may use them as a model template, which in fact has already been the case. It has already produced overlaps with the SOPs of the other German Centres for Health Research (DZG), particularly in the field of biobanking, which could be a first step towards harmonisation across the boundaries of the DZG.

🔗 <https://dzhk.de/ressourcen/sops/>



Stem Cell Register

The Biobank Register contains data pertaining to the induced pluripotent stem cells existing at the DZHK. The datasets can be filtered according to various features and thus allow researchers to make targeted requests to use the cells. At the end of the reporting year, the register contained 166 datasets from the Göttingen, Hamburg and Munich sites.



More datasets from other sites shall be added. Use requests have been received from working groups in Göttingen and Munich.

<https://dzhk.de/en/resources/stem-cell-registry/>

Project Database (from 2017)

Over the course of the reporting year, the DZHK built a web-based project database containing all scientific projects (except for projects which had ended prior to 2016). Research topics of the DZHK are thus made transparent. Target groups are equally the public and the DZHK researchers themselves who are thus given a new opportunity to find cooperation partners. Yet the database also provides the Board of Directors, the main office and the supervisory committees of the DZHK with an important search tool.

<https://dzhk.de/ressourcen/projektdatenbank/>

Goals for 2017

- OMICs resource: complete the whole genome and RNA sequencings
- OMICs resource: start processing generated raw data
- Publication and semiannual update of the project database on the Internet

The DZHK in the Public



In the reporting year, public relations focused on "Clinical research". The press office of the DZHK supported the clinical studies in their public relations activities. Upon request, the studies received their own logos and own websites as subdomains under www.dzhk.de.

We developed a template for the study websites based on the design of the DZHK website and thus giving it a high recognition value. The subdomains are hosted on the same server as the DZHK website and can be made available to the studies at no extra cost. The study websites below were launched in 2016:

- 🔗 <https://smart-mi.dzhk.de/>
- 🔗 <https://approach.dzhk.de/>
- 🔗 <https://fair-hf2.dzhk.de/>
- 🔗 <https://tomahawk.dzhk.de/>
- 🔗 <https://vad.dzhk.de/>

For the start of each new clinical study we published a press release. In order to keep the patients of our clinical studies informed we also developed a Proband Information Platform launched at the end of 2016 (cf. Chapter 4.1).

We released videos II and III of the series "Elevating Science" in German and English. A fourth video was in preparation. All videos had been accessed 1,840 times in total before the annual report closed. In the reporting year, the DZHK participated for the first time in the "Long Night of Sciences" in Berlin. DZHK researchers from the Max Delbrück Center led visitors through a walkable model of the heart and answered questions about cardiovascular research.

We produced flyers and online programmes for the scientific symposia and workshops organised by the DZHK.

In the reporting year, we contributed to the following conferences with a booth:

Meeting/Conference	Date/Place	In cooperation with
45 th Annual Meeting of the German Society of Thoracic and Cardiovascular Surgery (DGTHG) and the 48 th Annual Meeting of the German Society of Paediatric Cardiology (DGPK)	13 - 16 February Leipzig	Competence Network for Congenital Heart Defects
82 nd Annual Meeting of the German Cardiac Society (DGK)	30 March - 2 April Mannheim	Cardiological Competence Networks
122 nd Congress of the German Society of Internal Medicine	9 -12 April Mannheim	German Centres of Health Research
16 th GAIN Annual Meeting (German Academic International Network)	9 - 11 September Washington, D.C.	-

Preparation for the first DZHK Conference for Translational Medicine was the main focus of the DZHK public relations work at the end of 2016. We created a conference logo, a conference homepage, a programme flyer and advertised for the event with a press release amongst other things. Since the conference took place in 2017, it will be discussed in more detail in the next annual report.

In 2016, we published 13 press releases which led to a variety of articles and internet publications. Excellent research results stood at the centre of the press releases; for example, excerpts from the Paper of the Month. Next year, we intend to increase the number of press releases and always publish them in English as well.

The number of website visits ("sessions") stayed roughly consistent (45,700; 2015: 45,300). However, the average usage time per session increased from 3:08 to 4:03 minutes, what we appreciate and attribute to the extended content of the DZHK website. Thus, various data collections were added under the menu heading "Resources", as were the subdomains for clinical studies and the Proband Information Platform (PIP).

Together with the other DZG centres we pressed ahead with the preparations for the DZG Magazine to the extent

that the tenders for the external service providers can take place at the start of 2017. Our cooperation with the DZG in publishing the magazine will be regulated by a cooperation agreement which was elaborated and signed in the reporting year.

Achievements in 2016

- ✓ A comprehensive Proband Information Platform (PIP) established
- ✓ Marketing of the DZHK clinical studies
- ✓ Production of two or three YouTube videos
- ✗ Project database of major DZHK projects online
- ✓ Initiation of approaches to address a broad public

Goals for 2017

- Increase of the public awareness of the Proband Information Platform (PIP)
- Publication of at least 24 press releases per year
- Publication of all press releases also in English
- Intensification of social media activities
- Project database of scientific DZHK projects online
- Increase of press responses

Committees and Administration



Board of Directors

The Board of Directors manages the DZHK strategically and operatively and represents the Centre externally. It is elected by the General Assembly of Members for a period of office lasting three years and in the reporting year was composed of Thomas Eschenhagen, University Medical Centre Hamburg-Eppendorf (UKE) as Chairperson of the Board, Gerd Hasenfuß, University Medical Centre Göttingen, and Thomas Sommer, Max Delbrück Center for Molecular Medicine in the Helmholtz Association. The Board of Directors usually convenes twice a month, during the reporting year the Board met 16 times altogether.

Research Coordinating Committee (RCC)

In the RCC, the Board of Directors, the partner site spokespersons and the representatives of the member institutions as well as the representatives of the Young DZHK exchange views on all principle DZHK topics. In addition, the RCC makes a wide range of important decisions, including the majority of funding decisions. This committee is authorised – since 2016 in a more formal fashion than has previously been the case – by the accordingly revised business statutes of the DZHK and a long-term decision taken by the General Assembly of Members. The RCC meets once a month and permits the presence of several permanent guests who represent significant DZHK activities, e.g., Central Data Management. It can be considered as an extended Board of Directors or a small General Assembly of Members, but

it also has the character of a DZHK parliament. The most important RCC issues in 2016 were accompanying discussions and funding decisions for clinical studies and High Risk High Volume projects, strategic discussions on the prolongation of partner site projects, discussions on the development of a curriculum for a Clinician Scientist Programme, and elaborate reports of the three Competence Networks funded by the DZHK (Competence Network for Congenital Heart Defects, Competence Network for Atrial Fibrillation, Competence Network for Heart Failure).

General Assembly of Members

The highest organ of the DZHK e. V. is the General Assembly of Members, which convenes twice a year at the main office in Berlin. It is composed of the representatives of the 28 member institutions of the association. All members of a partner site have a common voice in the General Assembly of Members. The General Assembly of Members establishes the guidelines for the work of the association and decides on issues of fundamental significance, e.g., about the strategic orientation, changes to the structure of the association, acceptance of new DZHK PIs, and the business plan and investment plan. In 2016, it extended the four clinical infrastructure projects: data management, independent Trusted Third Party, IT coordination/Laboratory Information System, and ethics, as well as the 2016/17 top-up programme and a revision of the bylaws.

Scientific Advisory Board

The association is supported by a Scientific Advisory Board (SAB) consisting of internationally renowned experts in the field of cardiovascular research. The Scientific Advisory Board advises the Board of Directors and the General Assembly Members on all scientific and programmatic issues. It convenes once a year chaired by Garret FitzGerald and supports the DZHK in continuously defining its strategy more precisely.

In 2016, SAB members highly commended the DZHK and its development. The three most significant recommendations made in the session were:

- More "T1 science", hence real translation (late preclinical and early clinical studies)
- Developing stricter recruitment rules for clinical studies together with principal investigators
- Further strategic development and extension of the junior scientist promotion

Commission of Donors (KdZG)

The Commission of Donors assists the DZHK in securing exchange with the donors. Donors of the DZHK are the German Federal Government and the governments of the federal states in which the headquarters of the member institutions are located. Each donor posts one representative in the commission. The chair of the commission is the representative of the German Federal Government. In strategic as well as essential financial,



Meeting of the Scientific Advisory Board in January 2016 at the main office in Berlin.

organisational and personnel matters, the Board of Directors and the General Assembly of Members are required to obtain the approval of the Commission of Donors. In 2016, the commission convened once at the DZHK main office and once at the DZHK Munich site. Topics focused on in these meetings were: discussions on a potential modification of the funding procedure of the DZG and on key figures of DZHK development, decisions on the establishment of a downstream compensation mechanism and on joint proportionate financing of the fund management of all member federal states, as well as an adoption of the 2017 business and investment plan and the medium-term financial planning for the years 2018–2020.

Donors of the DZHK are:

- German Federal Ministry of Education and Research (BMBF); Baden-Württemberg; Bavaria; Berlin; Brandenburg; Hamburg; Hesse; Mecklenburg-Western Pomerania; Lower Saxony; Rhineland-Palatinate; Schleswig-Holstein
- 90 percent of the DZHK funds are provided by the German Federal Government and 10 percent by those federal states in which the headquarters of the member institutions are located.

These committees are described in the respective chapters:

- » Translational Research Group (TRG)
- » Clinical Study Group (CSG) – Steering Committee
- » Use & Access Committee (U&AC)
- » Group of DZHK professors
- » PostDoc Committee of the Young DZHK

DZHK Administration

The employees of the main office, the Funding Management Department and the seven partner site management offices constitute together the scientific administration of the DZHK.

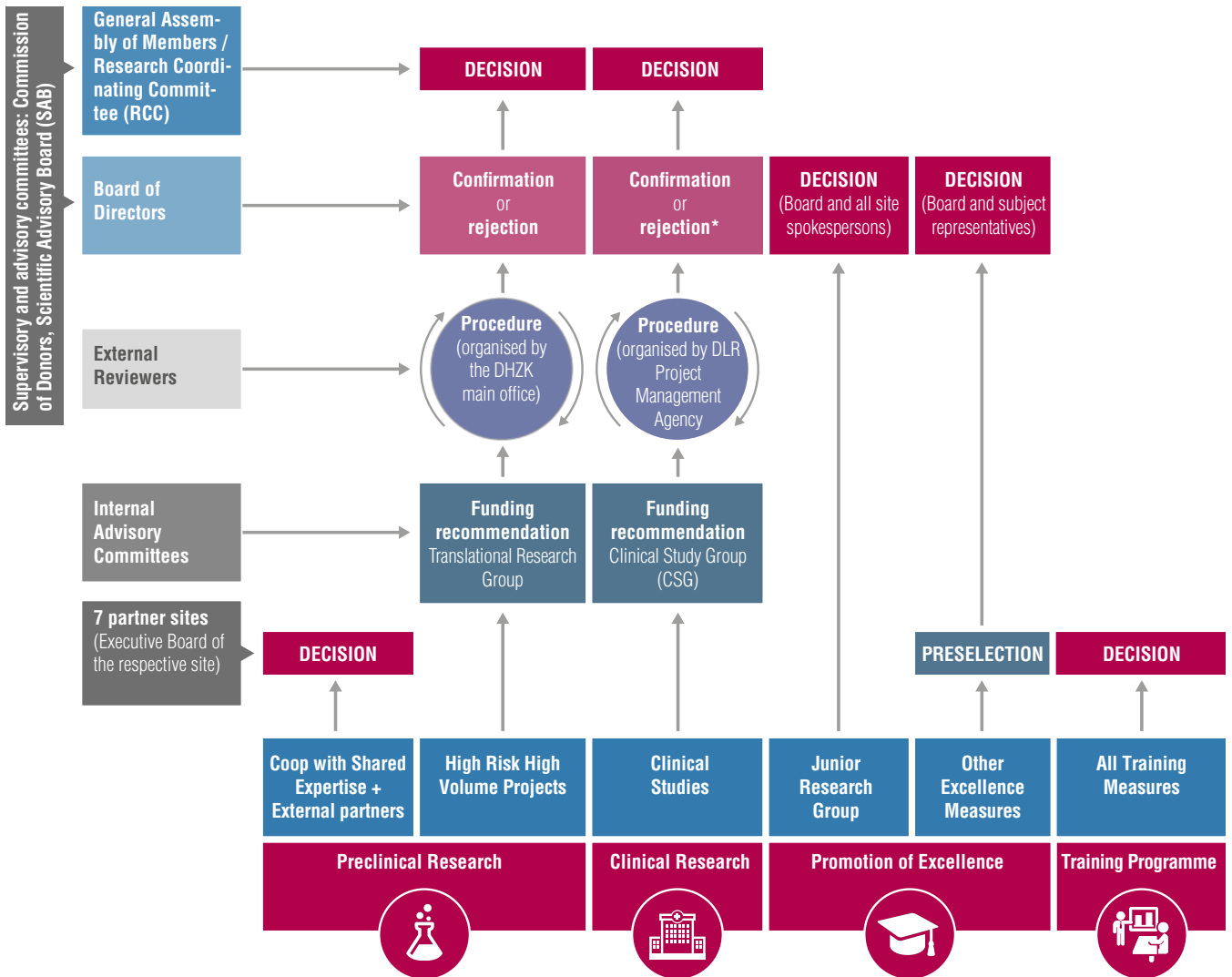
In 2016, their collaboration was once again close and cooperative, including within the scope of 39 weekly video conferences and three face-to-face meetings held either at the partner sites or the main office of the DZHK. In addition to the exchange on the respectively current DZHK-funding procedures and all administrative operations from filing applications to business reporting, a particular focus in 2016 of the joint work was set on the revision and standardisation of all funding guidelines.

Main Office

In the reporting year, 15 employees including the managing director were working in the main office (12.23 FTE as of 31 Dec 2016). The main office primarily supports the association's Board of Directors in coordinating the scientific cooperation in the DZHK. In the reporting year, this included in particular:

- Organisation of regular calls as well as the selection and evaluation of procedures in the three cooperative areas: preclinical research, clinical research, and promotion of young scientists
- Organisation of the mentoring programme
- Preparing the connection of the first pilot sites to the Laboratory Information System and managing the cooperation between central clinical-scientific infrastructure and DZHK studies
- Preparation of the 1st DZHK Conference on Translational Medicine
- Answering cardinal questions and compiling facts and documents in the scope of the hearing of the German Council of Science and Humanities
- Preparation and execution of the 2016/2017 top-up programme
- Controlling the flow of funds together with the Funding Management Department and the partner site management offices
- Organisation, preparation and follow-up for all committee sessions
- Press and public relations as well as internal communication of the DZHK

Procedural organigram of the DZHK for making funding decisions



*By Selection Board (2 board members, 2 SAB members, 2 CSG-representatives)

Funding Management Department

The Funding Management Department (FMM) as part of the Max Delbrück Center for Molecular Medicine in the Helmholtz Association (MDC) is entrusted with the administrative realisation of the funding of the DZHK partner institutions and external cooperation partners. It is authorised to review applications on compliance with grant legislation as well as to inspect the use made of the funds in accordance with the DZHK provisions and the conditions of grant use of the German Federal Ministry of Education and Research (BMBF). The Funding Management Department also compiles the controlling reports for the sites in order to support them in with an effective budget management.

In the reporting year 2016, the FMM was responsible for forwarding funds for project funding to 28 of the 32 partner institutions of the DZHK. The five partner institutions to which the FMM did not forward any funds are: Robert Koch Institute (because it is a governmental research facility), the University of Göttingen (funds only go to the University Medical Centre Göttingen, which is a member itself), University of Heidelberg (funds only go to Heidelberg University Hospital, which is a member itself), the Max Planck Institute for Experimental Medicine Göttingen (no funding so far), the Max Delbrück Center for Molecular Medicine in Berlin-Buch (no "forwarding" of funds). In addition, contributions are made to an increasing number of external cooperation partners, amounting to 70 in 2016 (44 in 2015), among which the three Competence Networks are funded. Altogether, 634 projects were funded in the reporting year (2015: 679 projects).

The FMM was extended by a fourth position in the request review in November 2016 and thus now counts 11.6 FTE or 13 employees as of 31 Dec 2016, which are assigned to the tasks of management, scientific evaluation, review of applications and confirmation of use, controlling and secretariat.

Partner Site Management

In 2016, as a rule, one part-time employed scientist financed by the DZHK (partner site manager) and one full-time administrator financed by the DZHK worked at each of the seven decentralised partner site managements. At the end of 2016, we began to increase this staffing ratio successively by an additional half-time position for a scientist in order to manage the distinctly increased science-related tasks. The partner site managements are the interfaces between the scientific projects, partner site spokespersons, third-party funding administrations, human resources departments, the deans of the research offices, the legal departments, the main office and the FMM. The site managements coordinate all activities of the partner sites. They organise partner site retreats, PI meetings and the work of the site's board of directors. In addition, each one carries out decentralised finance controlling for its respective site and coordinates the application and reporting system. They develop the procedures and processes at the DZHK together with the main office and Funding Management Department.



Partner site managements are interfaces between the scientists on site, the DZHK main office and the Funding Management Department.

Indicators for the Success of Translational Research



Indicators for the Success of Translation

Indicator	Definition	2016 (2015)
Short and medium term indicators		
1. Physician Scientists	Percentage of scientifically employed (licenced) physicians among the 1,300 researchers registered at the DZHK	51 % (n.s)
2. Cooperations between partner sites	a. Number of Shared Expertise projects (year)	66 (79)
	b. Number of publications with at least two DZHK authors from different partner sites	90 (78)
	c. Number of current major multicentre projects (recruiting DZHK studies and HRHV) (31 Dec.) in which multiple DZHK partner sites are involved	7 (3)
	d. Number of cooperative project groups (31 Dec.)	16 (13)
	e. Number of visiting scientist sojourns at other DZHK partner sites (year)	10 (9)
3. Communication with regulatory authorities	Consultation appointments (e.g., PEI, BfArM) in the scope of recruiting DZHK studies, HRHV projects and partner site projects (year)	2 (2)
4. Cooperation with industry	Cooperations with industrial partners in the scope of recruiting DZHK studies, HRHV projects and partner site projects (31 Dec.)	17 (8)

Indicators for the Success of Translation

Indicator	Definition	2016 (2015)
Short and medium term indicators		
5. Cooperative structures in clinical research	a. Type (quality) of cooperative structures (31 Dec.)	Central Data Management (ZDM) with data administration and Third Party Trust, stem cell register, central ethics project
	b. Number (quantity)	
	- of patients registered in the ZDM (31 Dec.)	1,913 (679)
	- SOPs (31 Dec)	15 (15)
	- use applications/notifications for data and image materials (year)	0/1 (0)
	- approved use applications /notifications (year)	0/0 (0)
6. High-ranking publications	DZHK publications in high-ranking journals, Impact factor >10 (year)	108 (76)
7. Preclinical projects and clinical studies	a. Number of HRHV projects and recruiting DZHK studies (31 Dec.)	11 (4)
	b. Publications resulting from HRHV projects and clinical studies (year)	1 (0)
Long term success criteria		
8. Altered medical guidelines	Number of guidelines which were altered as a result of DZHK studies or Competence Network studies (total)	0 (0)
9. New therapeutic or diagnostic principles	Number of new therapeutic or diagnostic principles which were developed in the scope of DZHK projects and were translated into clinical applications (total)	0
10. Patients treated according to new therapeutic or diagnostic principles	Number of patients who were treated according to new therapeutic or diagnostic principles developed by DZHK researchers (total) (measurability is questionable)	0

Comments regarding the Table:

- *Definition of DZHK studies: financed with competitive/flexible funds; predominately financed by the DZHK; study uses the Central Data Management of the DZHK*
- *All indicators are related exclusively to projects which are financed with DZHK funds; no indicator is related to the research of DZHK member institutions financed otherwise. For simplified documentation, the indicators 2a, 2c, 2e, 5, 7 and 8 refer exclusively to competitive/flexible DZHK funds and not to DZHK partner site projects*

The German Centres for Health Research

Researchers and physicians from all over Germany joined forces in the six German Centres of Health Research (DZG) so that patients can benefit from the results of research studies more quickly. They united in order to fight major endemic diseases, such as diabetes, cardiovascular diseases, cancer, neurodegenerative diseases, infections and lung diseases.

For, although an increasing number of people recover from cancer diseases and increasingly fewer die of cardiovascular diseases, the six major endemic diseases are still the cause of much suffering and very high healthcare costs—in Germany, one-hundred billion euro per year. Due to the ageing population, the incidences of people with dementia, diabetes, heart failure, cancer or lung diseases are still on the rise. Resistant strains of bacteria are becoming a threat in hospitals, infectious diseases still take the lives of many people, especially in developing countries.

Further successes in therapy and diagnosis are no longer to be achieved single-handedly by individual research groups. Instead, more effective structures are needed in which all significant partners cooperate in a process of translation—university physicians and researchers from non-university institutes, the pharmaceutical industry, regulatory bodies, politics and patient association.

Along with the German Centres for Health Research, the German Ministry of Education and Research started to establish such effective structures in 2009. A main objective is to optimise the translation process from research result to patient application, i.e., bringing new medical research results into application more quickly to improve the prevention and therapy of endemic diseases.

A total of over 90 sites with more than 120 universities, university hospitals and non-university research facilities now constitute the six German Centres for Health Research.

From 9 to 12 April 2016, the DZG appeared together for the first time at the Annual Meeting of the German Society for Internal Medicine (DGIM) in Mannheim and presented themselves with a common stand. In symposia under the auspices of the DZG, the latest research results were presented, e.g., relating to immunotherapy in oncology (DKTK), obesity and lipid metabolism (DZD), heart failure therapy (DZHK), new dangerous infectious diseases (DZIF), and the individualised therapy of obstructive lung diseases (DZL).

In October 2016, the DZG held a workshop in the scope of the World Health Summit for the third time. The subject was "Data Warehouse Systems as a Basis for Precision Medicine".

DZG DEUTSCHE ZENTREN
DER GESUNDHEITSFORSCHUNG

Facts and Figures

Associated Institutions

The number of 28 associated members remained constant in the reporting year. Together, the association members represent 32 member institutions, which are shown in the figure below along with their respective geographical sites.



Member Institutions by German states where headquarters are located

Federal State	Institute
Baden-Württemberg	German Cancer Research Center (DKFZ) European Molecular Biology Laboratory (EMBL) Klinikum Mannheim GmbH University Heidelberg University Hospital Heidelberg
Bavaria	German Heart Centre Munich (DHM) Klinikum rechts der Isar (MRI) Hospital of the University of Munich (KMU) Max Planck Institute for Biochemistry (MPI) Technical University Munich TUM) Helmholtz Center Munich – German Research Center for Health and the Environment (HMGU) Ludwig-Maximilian University Munich (LMU)
Berlin	Charité – Universitätsmedizin Berlin German Heart Centre Berlin (DHZB) Max Delbrück Center for Molecular Medicine in the Helmholtz Association (MDC) Federal Republic of Germany as represented by the Federal Ministry of Health as represented by the Robert Koch Institute (RKI)
Brandenburg	German Institute for Human Nutrition Potsdam-Rehbrücke (DIfE)
Hamburg	University Hospital Hamburg-Eppendorf (UKE) Asklepios Klinik St. Georg
Hesse	Goethe University Frankfurt Kerckhoff Klinik GmbH, Bad Nauheim Max Planck Institute for Heart and Lung Research, Bad Nauheim
Mecklenburg-Vorpommern	University Medical Centre Greifswald
Lower Saxony	German Primate Center Göttingen Max Planck Institute for Biophysical Chemistry, Göttingen Max Planck Institute for Dynamics and Self –Organization, Göttingen Max Planck Institute for Experimental Medicine, Göttingen University of Göttingen University Medical Center Göttingen
Rhineland-Palatinate	University Medical Centre Mainz
Schleswig-Holstein	University of Kiel University of Lübeck

Facts and Figures

Finances and Staff

Finances of the DZHK

In the reporting year of 2016, the DZHK had at its disposal for the second time the full annual funding amount promised since its foundation of about 41 million euros of new funds plus a carry-over from 2015 totalling 14,072,000 euros (2014: 3,444,000 euros). Of this sum, funds amounting to 39,847,000 euros were drawn (2015: 30,393,000 euros).

The DZHK has thus spent nearly one-third more funds in absolute figures than in 2015. Nevertheless, 15,314,000 euros could not be spent. These funds were carried over to 2017. In relative terms, the outflow of funds based on the respective new funds (annual budget without the carry-over from previous years) amounted to 108 percent in 2014, 74 percent in 2015, and 97 percent in 2016. The outflow of funds was not higher in 2016, primarily because clinical studies and projects involving the clinical infrastructure were delayed.

Reasons for this are to some extent real delays resulting from the complexity of multicentre studies, but also to some extent the lack of experience at the time these projects were applied for and approved – the required funds had not been distributed realistically over the years of the respective project periods. We have learnt from this and in the future we will approve funds for clinical studies more towards the end of the project term. The remaining funds which did not flow out are allocated to partner site projects and all other funding lines of the DZHK; reasons for this include delayed investments and temporarily vacant positions.

Due to the huge number of newly started projects, we hope to increase the outflow of funds considerably again in 2017 and thus starting to reduce the funds carried over from previous years. The DZHK is now clearly "overplanned" — more projects have been approved for the coming years and are in a state of planning than for

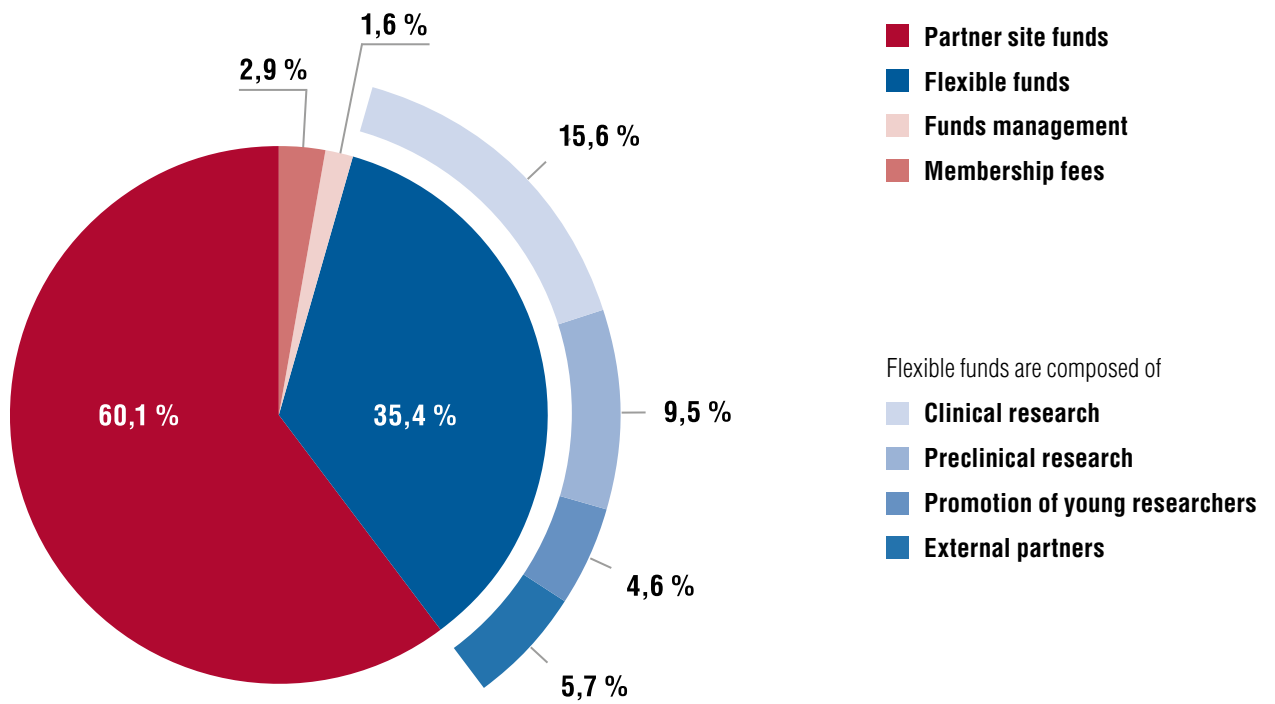


which we actually have funds. The transition from the phase of being concerned about a sufficient outflow of funds to a phase of having to economise with scarce funds will present a great challenge to funds management, main office and the partner site managements in 2017 and 2018.

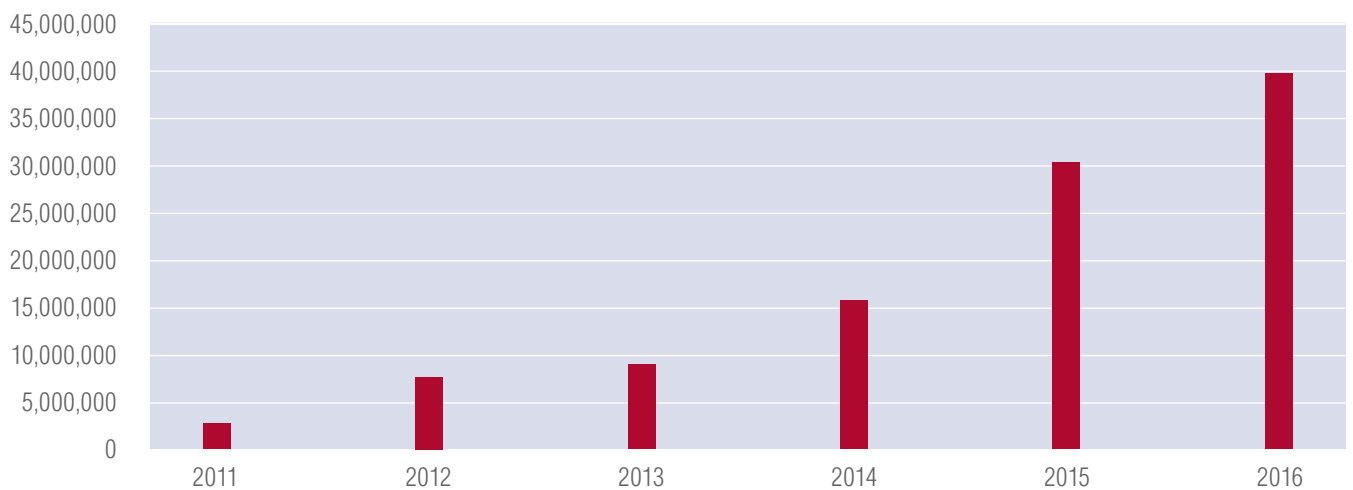
The drawn (expended) funds in 2016 amounting to 39,847,000 euros were allocated as follows:

- **Partner site funds:** 23,926,000 euros
- **Flexible funds:** 14,123,000 euros (among which are 6, 214,000 euros for clinical research, 3,806,000 euros for preclinical research, 1,831,000 euros for the training programme, and 2,272,000 euros for external partners (including Competence Networks with 1,943,000 euros and cooperations with externals with 329,000 euros))
- **Membership fees:** 1,167, 000 euros (predominately contributions for the business office budget of 2017 amounting to 1,104,000 euros, to some extent also contributions for the business office budget of 2016)
- **Funding Management Department:** 631,000 euros

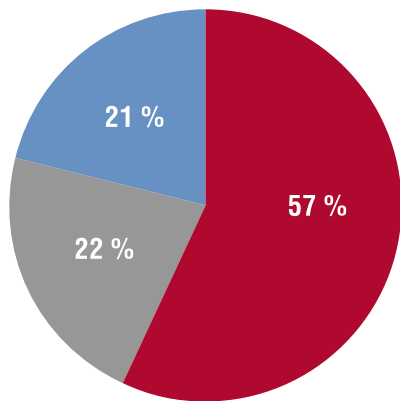
Allocation of DZHK funds expended in 2016 to areas of planned funding



Expended DZHK funds 2011–2016



Staff, material and investment funds of the DZHK in euros



- **Staffing costs: 22,854,000** (2015: 16,707,000)
- **Material costs: 8,587,000** (2015: 8,174,000)
- **Investments: 8,406,000** (2015: 6,593,000)

DZHK Main Office Budget

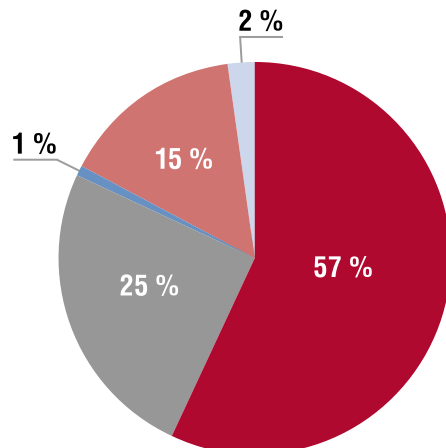
In 2016, the budget of the main office of DZHK e.V., which is financed by membership fees, amounted to 1,071,000 euros (2015: 998,000 euros). Of this total, 1,048,000 euros were membership fees and 24,000 euros were carried over from the budget year 2014 to 2016.

983,000 euros (2015: 958,000 euros) of which were expended; the miscellaneous revenues amounted to 9,000 euros. The General Assembly of Members of the DZHK shall decide on the use of the resulting surplus amounting to 97,000 euros in September 2017.

Schomerus & Partner Berlin (tax counsellors, attorneys, financial auditors) were commissioned to prepare the annual financial statement of the association.

Staffing, material and investment costs of the main office

- **Staffing costs: 558,000 euros** (2015: 518,000 euros)
- **Material costs: 243,000 euros** (2015: 248,000 euros)
- **Investments: 10,000 euros** (2015: 29,000 euros)
- **Public relations: 151,000 euros** (2015: 142,000 euros)
- **Contributions (TMF e.V.): 20,000 euros** (2015: 20,000 euros)



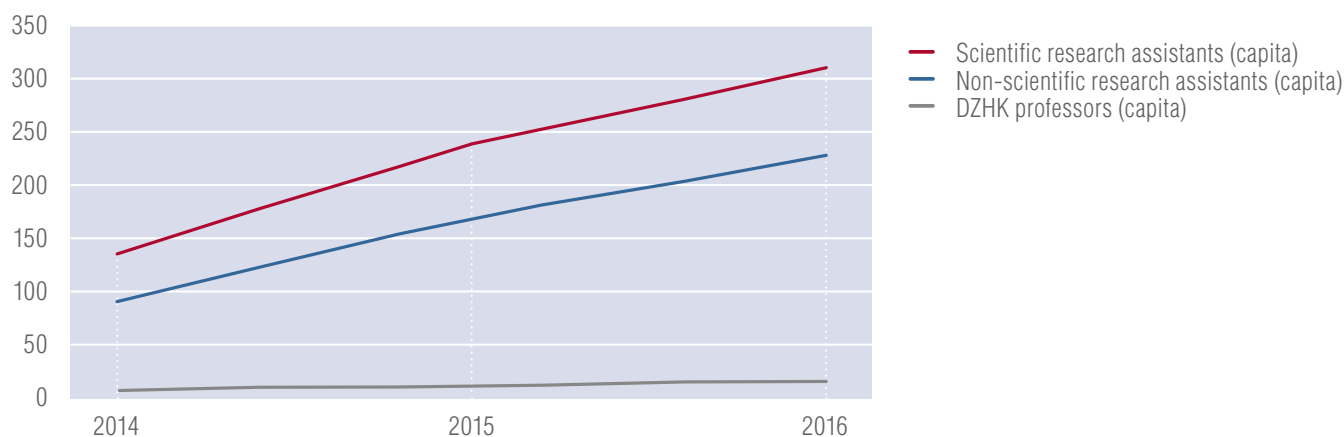
Staff

As of the reporting date, 31 December 2016, **403.58** (2015: 286.50) full-time equivalents (FTE) or **532** (2015: 415) persons or "capita" were financed by DZHK funds. Among them were also 15 employees of the DZHK main office, 13 employees in fund management and 23 employees in the Competence Networks.

Number of employees financed by the DZHK 2014–2016

	2014	2015	2016
Number of employees (as of 31 December) FTE	165.77	286.5	403.58
Number of employees (as of 31 December) capita	234	415	532
of which are male	78	130	165
of which are female	156	285	367
Number of scientific research assistants (FTE)	96.54	154.39	220.76
Number of scientific research assistants (capita)	137	237	307
of which are male	58	98	139
of which are female	79	139	168
Number of employees who are not scientific research assistants (FTE)	62.23	122.11	168.82
Number of employees who are not scientific research assistants (capita)	90	168	227
of which are male	15	26	27
of which are female	75	142	200
Number of DZHK professors (FTE)	7	10	14
Number of DZHK professors (capita)	7	10	14
of which are male	5	8	12
of which are female	2	2	2
For information only: additionally planned professorships	0	14	9

Development of DZHK employees 2014 - 2016

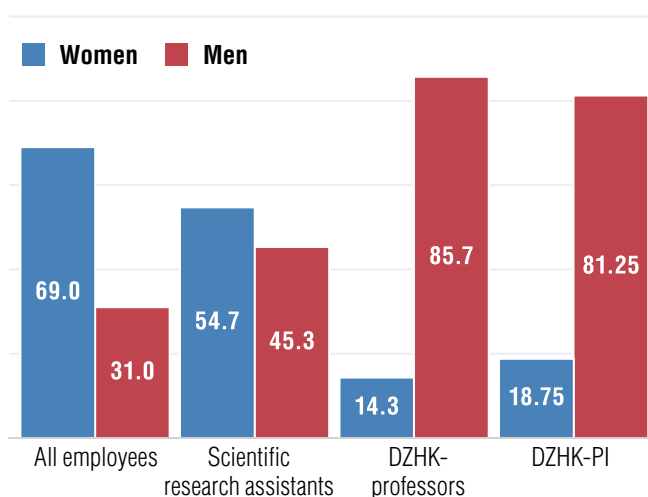


Results of the PI third-party funds survey 2016

	Participants' survey 105/140 PIs	Extrapolation 140/140 PIs
Total staff (full-time equivalents - FTE)	597.6	796.8
Professorships	7.0	9.3
C4/W3	4.0	5.3
C3/W2	3.0	4.0
Scientific personnel (FTE)	429.1	572.1
Physicians	36.4	48.5
of which are clinical scientists	27.8	37.1
Non-medical scientists	387.7	516.9
of which are Junior Research Group leaders	13.9	18.5
of which are postgraduates	193.7	258.3
Non-scientific staff members (FTE)	166.5	222.0
Nursing staff	5.3	7.1
Technicians	100.3	133.7
Administration	17.9	23.9
Other	35.3	47.1

The question being raised by the German Council of Science and Humanities, we asked all DZHK PIs how many third-party funded positions (excluding DZHK-funded positions) they had at their institute or clinic with an evident thematic reference to the DZHK (cf. Table above). 105 of 140 DZHK PIs answered to this query and collectively stated nearly 600 full-time equivalents. Extrapolated to the entire DZHK, this is equivalent to nearly 800 full-time equivalents covered by third-party funds in the thematic field of the DZHK at the end of 2016. In addition, there are DZHK-funded positions (compare Table on page 70) and basically financed positions (not registered).

Gender Distribution at the DZHK in percent



Principal Investigators (PI), DZHK Scientists, Young DZHK Members

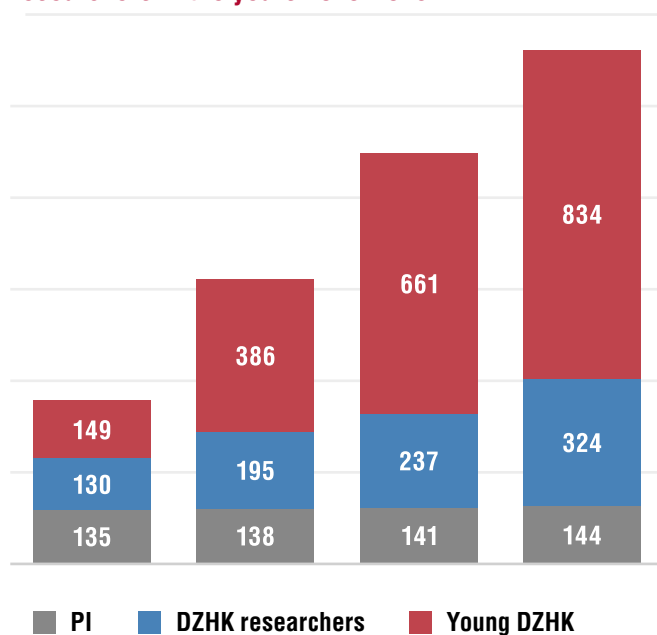
Apart from the DZHK-funded researchers, the principal investigators (PI) are of central significance to the DZHK. In most cases, PIs are not financed by the DZHK, however, they bring their ideas and their expertise into the cooperations with the DZHK and thus provide the basis of our success. The DZHK had **144** PIs in the reporting year (2015: 141). PIs are appointed by the partner sites and confirmed by the General Assembly of Members. Each partner site disposes of a maximum of 20 PI positions, whereby additional places are available at the partner site for each DZHK professor appointed with DZHK funds.

In the reporting year 2016, the following three new PIs were confirmed by the General Assembly of Members:

Stefan Luther (Göttingen, simultaneously DZHK professor), **Reinier Boon** (Rhine Main, simultaneously DZHK professor) and **Tommaso Gori** (Rhine Main, simultaneously DZHK professor).

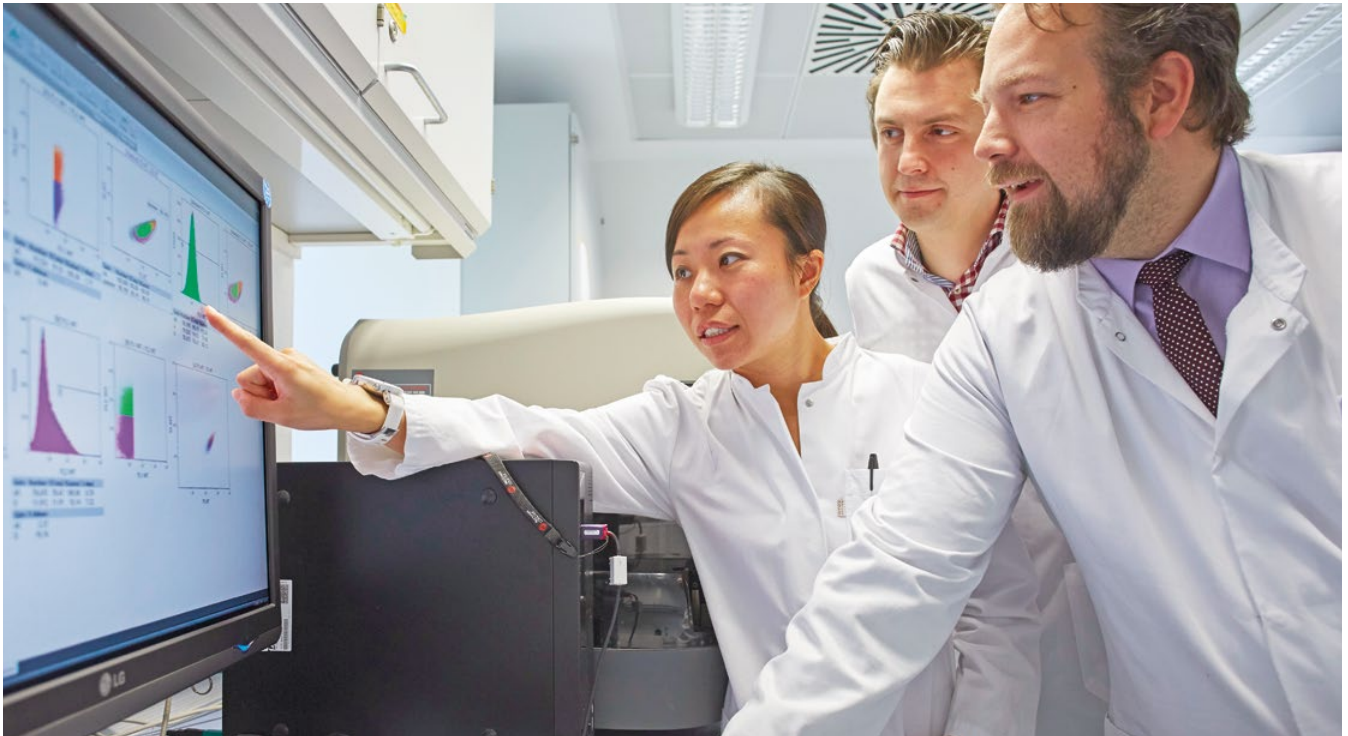
In order to classify researchers who are not PIs, there are two statuses: "Member of the Young DZHK" and "DZHK Researcher". Both statuses need to be applied for. Requirements are a defined commitment in the DZHK and an allocation to a DZHK-PI working for a partner institution. In the reporting year, the DZHK had **324** DZHK researchers (2015: 273) and **834** Young-DZHK members (2015: 661).

Development of PI, DZHK researchers and Young DZHK researchers in the years 2013-2016



Facts and Figures

Scientific Achievements, Prizes and Awards



The DZHK has had rules for a joint DZHK affiliation and a DZHK acknowledgement since 2012. Here, we present the figures of the corresponding publications (cf. Chapter 5). A complete list of publications with DZHK affiliation or DZHK acknowledgement is available online at:

🔗 <https://dzhk.de/en/forschung/publikationen>

In addition, every month the DZHK Board of Directors selects a Paper of the Month, which is subsequently mentioned in the DZHK Newsletter and published on the DZHK website online (cf. page 28).

Publications in 2016

	Number 2016 (2015)	
DZHK affiliation	670	(536)
DZHK acknowledgement	34	(38)
First authorship of a DZHK PI	28	(38)
Last authorship of a DZHK PI	210	(174)
First authorship of a Young DZHK	142	(126)
Cooperation with another DZHK site (= PI of ≥ 2 sites)	90	(78)
Journals of the Nature Publishing Group	31	(15)
Journals of the Cell Press	8	(6)
NEJM, Lancet, JAMA	8	(6)
Circulation, Circ Res, EHJ, JCI, JACC	56	(49)
Science	5	(1)

Prizes, Grants, Personalia

Name	Prizes, Grants, Personalia
Dr Michael Kreußer (Heidelberg)	Forßmann-Preis
PD Dr Renate Schnabel (Hamburg)	ERC Consolidator Grant of the European Research Council
Prof Dr Lucie Carrier (Hamburg)	Presidency of the International Society for Heart Research European Section (2016-2020)
Prof Dr Thomas Eschenhagen (Hamburg)	Presidency of the International Society for Heart Research International (2019-2022)
Prof Dr Jeanette-Schulz-Menger (Berlin)	First president of the Society for Cardiovascular Magnetic Resonance, the largest association for heart MRI
Prof Thomas Wieland (Mannheim)	Held the Honorary Award Lecture on Basic Science at the 82 nd Annual Meeting of the German Cardiac Society
Prof Dr Vasilis Ntziachristos (Munich)	ERC Advanced Grant of the European Research Council amounting to 2.49 million euros over five years for his project PREMSOT
Dr Hendrik B. Sager (Munich)	Uta and Jürgen Breunig Research Prize 2016 of the German Heart Foundation and the German Society of Internal Medicine
Prof Christian Weber (Munich)	ERC Advanced Grant; for his project "PROVASC; Cell-specific vascular protection by CXCL12/CXCR4" he received a grant amounting to 2.5 million euros
Dr Constanze Schmidt (Heidelberg)	Oskar-Lapp Research Prize 2016
Prof Johannes Backs (Heidelberg)	"Outstanding Investigator Award" of the International Society of Heart Research (ISHR)
Prof Ziya Kaya (Heidelberg)	Franz Maximilian-Groedel Research Prize of the DGK
Prof Didier Stainier (Bad Nauheim)	ERC Advanced Grant of the European Research Council amounting to 2.5 million euros over five years
PD Dr Sophie Van Linthout (Berlin)	Core member of the ESC 'Working Group on Cellular Biology of the Heart'
Prof Sabine Steffens (Munich)	ESC Outstanding Achievement Award 2016
Prof Dr Michael Gotthardt (Berlin)	Inauguration of W3 professorship for "Experimental and Translational Cardiology" at the Charité – Universitätsmedizin Berlin
Annelie Blumrich (Berlin) und Christian Müller (Hamburg/Kiel/Lübeck)	Winner of the Best Lecture Prize at the Young DZHK Retreat on 14-15 September
Susanne Schlick (Göttingen) and Franziska Rathjens (Göttingen)	Winner of the Best Poster Prize at the Young-DZHK Retreat on 14-15 September
Prof Dr Matthias Endres (Berlin)	Member of the National Academy of Sciences Leopoldina
Dr Christian-H. Heeger (Munich)	Hugo-von-Ziemssen – Poster Award 2016
Prof Christian Weber (Munich)	Listed as worldwide leading expert in the field of atherosclerosis
Prof Dr Ulrich Dirnagl (Berlin)	Berlin Science Award of the Governing Mayor of Berlin 2016
Prof Dr Jens Frahm (Göttingen)	Induction into the Hall of Fame of German Research
Dr Uwe Raaz (Göttingen)	Young Investigator Award of the DeGAG
Prof Dr Stefanie Dimmeler (Frankfurt am Main)	Member of the Scientific Council of the Berlin Institute of Health

Facts and Figures

Partner Sites



DHZB – German Heart Centre Berlin

Partner site Berlin

Partner site Spokesperson: Vera Regitz-Zagrosek, Director of the Institute for Gender Research in Medicine (GiM), Charité – Universitätsmedizin Berlin

Vice Partner site Spokesperson: Holger Gerhardt, Max Delbrück Center for Molecular Medicine in the Helmholtz Association

Partner site Management: Carola Schubert (Partner site Manager), Mariam Abou-Saleh (Partner site Clerk), Charité – Universitätsmedizin Berlin

Partner Institutions at the DZHK Berlin site

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

Research Focus within the DZHK

The focus of the member institutions at the Berlin site is the clinical and translational investigation of cardiac insufficiency, vascular and metabolic diseases as well as gender aspects in hospital, research and academic teaching (Charité). Researchers at the MDC are primarily concerned with basic research and translational research in the area of genomics, vascular biology, molecular cardiology and myocardial function, whereas the focus of the DHZB is on surgery in cases of cardiac insufficiency, transplantation and assistance systems as well as cardiovascular diseases in children. The RKI and DIfE (Federal State of Brandenburg) also belong to the member institutions where researchers are concerned with epidemiological studies and with the subjects of nutrition and metabolism. With the 2016/2017 top-up programme, four new partner site projects were added (MDC/Bader, DIfE/ Grune, Charité/Pieske and Stangl), as well as six projects with new project arms and/or investments. The following investments in particular will significantly strengthen the Berlin site in the future on the level of basic research and clinical research. At Charité, a CCR-multi-user-facility has been created with a cardiovascular Drosophila lab, a seahorse analyser and a FACS cytometer for cardiovascular basic research. At the MDC, the STED microscope purchased in the investment programme of 2015 was equipped with new additional hardware and software. In the area of clinical research, in addition to the recruitments of studies already in progress, funds for four new clinical studies with study centres located in Berlin were successfully raised and are close to starting recruitment. In November 2016, Christoph Knosalla was appointed to the W2 professorship "Surgical Therapy of Heart Failure" at the DHZB.



German Primate Center in Göttingen

Partner site Göttingen

Partner site Spokesperson: Wolfram H. Zimmermann, Director of the Institute for Pharmacology at the University Medical Centre Göttingen

Vice Partner site Spokesperson: Eberhard Bodenschatz, Director of the Max Planck Institute for Dynamics and Self-Organisation

Partner site Management: Axel Kaul (Partner site Manager), Sylvia Vann (Partner site Clerk), University Medical Centre Göttingen

Partner Institutions at the DZHK Göttingen site

Georg August University Göttingen; University Medical Centre Göttingen (UMG); Max Planck Institute for Biophysical Chemistry, Max Planck Institute for Dynamics and Self-Organisation; Max Planck Institute for Experimental Medicine; German Primate Centre

Research Focus within the DZHK

The research focus of the DZHK Göttingen site is cardiac failure research with the subjects "Mechanisms of the transition from clinical asymptomatic myocardial weakness to symptomatic heart insufficiency as well as heart regeneration in case of cardiac insufficiency". In 2016, the focus of clinical research was set on the intensified, successful recruitment of patients for the clinical DZHK studies TransitionCHF and TORCH and the initiation of additional study centres for TransitionCHF. The funds for two further DZHK-funded studies, i.e., SCREEN-AF and HFpEF-STRESS, was successfully raised. A High Risk High Volume project entitled "Low-Energy Termination of Ventricular Fibrillation in a Porcine Heart Failure Model" was successfully initiated and will run until the end of 2018.

The 2016/2017 top-up programme was used in order to:

- establish an intervention laboratory including a heart catheter unit at the MRI imaging centre at the German Primate Center (DPZ). GOE MD4 DPZ: Cardiac insufficiency regeneration.
- strengthen the infrastructure for cellular imaging and arrhythmia modelling in the new DZHK heart research building, i.e., by purchasing a high-resolution LSM confocal microscope. GOE MD5 UMG: Arrhythmia modelling and control.
- elevate the performance of the stem-cell unit by additional laboratory equipment and staff recruitment. GOE SI 1 UMG: Stem-cell bank. The near-completion of the Heart Research Building (laboratory space: 950 m², office space: 350 m²) took place in 2016. The research focus intensified by this new construction lies in the application of physical methods (imaging and modelling) in cardiac medicine. The working groups led by S. E. Lehnart, S. Luther, W. A. Linke as well as the working groups of the newly-appointed professors for heart surgery, I. Kutschka, and molecular pharmacology, N. Voigt, will move into the Heart Research Building in 2017.



University Medical Centre Greifswald

Partner site Greifswald

Partner site Spokesperson: Stephan B. Felix, Director of the Department of Internal Medicine at University Medical Centre Greifswald

Vice Partner site Spokesperson: Ulrich John, Director of the Institute for Epidemiology and Social Medicine at University Medical Centre Greifswald

Partner site Management: Stefan Groß (Partner site Manager), Anne-Kathrin Beiersdorf (Partner site Clerk) [since 1 Jul. 2017: Susanne Franck], University Medical Centre Greifswald

Partner Institutions at the DZHK Greifswald site

University Medical Centre Greifswald

Research Focus within the DZHK

Special expertise of the Greifswald site is in conducting population-based epidemiological and clinical studies with comprehensive cardiovascular phenotyping, research on the prevention of systolic and diastolic cardiac

insufficiency or dilative cardiomyopathy, high-throughput multi-OMICs analyses, telemedicine biobanking and data management/analysis of large patient cohorts. In 2016, the 2015 investment programme was completed with the furnishing of a weight training room and the purchase of exercise machines. Furthermore, a central study ECG storage will be purchased. Three additional projects could be initiated in the scope of the 2016/2017 top-up programme (starting in August/September) and respective additional posts for scientists were filled. In the HOMEX HF pilot study, in progress since 2014, further participants were enrolled and an interim analysis shall take place soon. Moreover, the one-year follow-up of the IBEKO study was completed. The University Medical Centre Greifswald is involved as an enrolling study centre in the clinical DZHK studies TORCH, TransitionCHF, Culprit-SHOCK and soon also in TOMAHAWK (initiation in the first quarter of 2017), SMART-MI (initiation in the first quarter of 2017), APPROACH-ACS, SPIRIT-HF, and CLOSURE-AF. Patients have been enrolled in Culprit-SHOCK since 2014, and in TORCH and TransitionCHF since 2015. In the scope of the ESC-EORP register for cardiomyopathies, a total of approx. 90 patients have been enrolled since 2015. In the field of clinical research, the Third Party Trust of Central Data Management (collaborative project together with the Göttingen site and the main office in Berlin) is established in Greifswald. The site also takes over patient management in the TORCH study. Furthermore, the Greifswald site coordinates DZHK basic and study biobanking and operates the laboratory Information System of the DZHK. The tenure procedure for a W2 professorship in "Molecular Cardiology" has nearly been completed and the appointment will be made in the second quarter of 2017. In addition, a PostDoc start-up grant was obtained by a young researcher from Greifswald in the scope of the DZHK excellence programme.



Asklepios Klinik St. Georg

Partner site Hamburg/Kiel/Lübeck

Partner site Spokesperson: Thomas Eschenhagen, Director of the Institute for Experimental Pharmacology and Toxicology at University Hospital Hamburg-Eppendorf

Vice Partner site Spokesperson: Norbert Frey, Director of the Cardiology and Angiology Clinic at University Hospital Schleswig-Holstein

Partner site Management: Doreen Stimpel (Partner site Manager), Monika Glimsche (Partner site Clerk), University Hospital Hamburg-Eppendorf

Partner Institutions at the DZHK Hamburg/ Kiel/Lübeck site

University Hospital Hamburg-Eppendorf, Christian Albrecht University Kiel, University of Lübeck, Asklepios Klinik St. Georg

Research Focus within the DZHK

The four partner institutions at the site combine their individual expertise to pursue the joint goal of finding the potential causes of cardiovascular diseases and the development of new treatment concepts. In particular, the scientific focus is on the identification of genetic risk factors and biomarkers of cardiovascular diseases, stem cells and tissue engineering as well as mechanisms and therapies of congenital and acquired myocardopathies. In 2016, the site linked its basic research disciplines with clinical research even more.

Together with partners of the DZHK, innovative therapy approaches with concrete perspectives for clinical application are being tested (gene and heart muscle replacement therapy) at the UKE in the scope of two projects approved in 2016 of the High Risk High Volume Late Translation (HRHV) funding line. The site is currently conducting four clinical studies on important cardiological issues fully funded by the DZHK. In Hamburg, the guideline-relevant DEDICATE study received its funds release in 2016 and patient enrolment has been prepared for FAIR-HF2. In Lübeck, the first patient for TOMAHAWK was recruited in 2016 and cooperation agreements for the early clinical study CAVA-ADHF were finalised. In the scope of the 2016/2017 top-up, the spectrum of experimental methods was extended by various investments and the locally shared scientific infrastructure was further consolidated. Currently, the DZHK funds three professors at the site (Professor Jeanette Erdmann, Lübeck; Professor Arne Hansen and Professor Tanja Zeller, both Hamburg). The tenure procedure for a further DZHK W2 professorship at Campus Kiel is being finalised.



Heidelberg University Hospital

Partner site Heidelberg/Mannheim

Partner site Spokesperson: Hugo A. Katus, Medical Director of the Department of internal Medicine III of the Heidelberg University Hospital

Vice Partner site Spokesperson: Martin Borggreffe, Director of Medical Clinic I of the University Hospital Mannheim (since May 2017: Thomas Wieland, University Medical Centre Mannheim)

Partner site Management: Tanja Weis (Partner site Manager), Claudia Marquart (Scientific Project Manager), Matthias Knüll (Partner site Clerk) [Sep. 2016-Dec. 2016: Tanja Schaaf, since March 2017 Ines Schneider], Heidelberg University Hospital

Partner Institutions at the DZHK Heidelberg/Mannheim site

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

Research Focus within the DZHK

The scientific focus of the Heidelberg/Mannheim site is the research of genetic and inflammatory cardiomyopathies. By means of a translation pipeline, cardiomyopathies are being worked on scientifically from genetic and molecular diagnostics all the way to innovative molecular treatment concepts. For this, genetic, epigenetic and electrophysiological analyses, imaging diagnostics, ps-iPS cells as well as model systems of cellular systems including zebrafishes, mice and rats, all the way to the human-relevant porcine model are being used for the functional analysis of molecular signalling pathways and the identification of new diagnostic and therapeutic targets. Methodical platforms (next-generation sequencing, AAV platform, zebrafish platform, platform for human-relevant disease models) are available to the entire DZHK, just like a modern fully automated biobank with automated sample processing.

DZHK funds equipped the clinical facilities in Mannheim and Heidelberg with innovative echocardiography scanners.

In addition, a production line based on the baculovirus insect cell expression system for the AAV platform as well as a modern laboratory information management system compatible with the DZHK meta-LIMS has also been implemented for Heidelberg's CardioBiobank. In clinical research, particularly noteworthy is the patient recruitment of the TORCH Register coordinated by the Heidelberg site. More than 1,600 patients from 20 centres were enrolled. The Heidelberg/Mannheim site was involved in seven other DZHK studies as an enrolling centre and is among the leading clinical centres in the DZHK when it comes to the recruitment of patients. The DZHK professorship "Functional Genomics of Cardiomyopathies" could not be filled and was postponed for the time being.



LMU – University Hospital Großhadern

Partner site Munich

Partner site Spokesperson: Stefan Engelhardt, Director of the Institute for Pharmacology and Toxicology of the Technical University of Munich

Vice Partner site Spokesperson: Christian Weber, Director of the Institute for Prophylaxis and Epidemiology of Cardiovascular Diseases at Ludwig Maximilian University Munich

Partner site Management: Sandra Rauser (Partner site Manager), Sissy Künzel (Partner site Clerk), Technical University of Munich

Partner Institutions at the DZHK Munich site

Technical University of Munich (TUM); Hospital of Ludwig Maximilian University of Munich (KUM); Ludwig –Maximilian University Munich (LMU); German Heart Centre Munich (DHM); Klinikum rechts der Isar (MRI); Helmholtz Centre Munich – German Research Centre for Health and the Environment (HMGU); Max Planck Institute for Biochemistry (MPI)

Research Focus within the DZHK

The scientific focus at the Munich site ("Munich Heart Alliance", MHA) is the identification of new therapy targets and the development of innovative and optimised processes for the treatment of cardiovascular diseases. In this, the entire medical translation chain is represented. In the context of clinical research, ethics applications are being harmonised in a project of the Helmholtz Centre Munich, while the University Hospital Munich is one of four DZHK sites involved in the Central Image Data Management System for clinical studies. The study centres of the partially DZHK-funded studies "ISAR-REACT 5" and "Revacept-CAD" are located at the German Heart Centre Munich, the study centres for "APPROACH-ACS-AF", "SMART-MI" and for the "AFNET-EORP Register for Atrial Fibrillation" are at the University Hospital Munich. The early clinical study "Ex-VAD" conducted in cooperation between the cardiovascular hospitals in Berlin and the Klinikum rechts der Isar was released for funding by the RCC. In preclinical research, three HRHV projects obtained funding in 2016, another project was approved for funding by the RCC.

At the Klinikum rechts der Isar, the Junior Research Group led by Professor Lars Mägdefessel started their work and the Review Panel for the DZHK Promotion of Excellence approved two grant applications for rotation support and the PostDoc start-up funding of young DZHK researchers in Munich. Two meetings with lectures and poster presentations on the status of Munich's DZHK projects supported scientific exchange and the connection of research activities at the site in 2016 as well. So far, one DZHK professorship (Professor Söhnlein) is being funded in Munich, the procedures of two others were in progress in 2016 and appointments are expected in 2017.



Johannes Gutenberg University Mainz

Partner site Rhine Main

Partner site Spokesperson: Andreas Zeiher, Director of the Cardiology Department of the University Hospital Frankfurt

Vice Partner site Spokesperson: Stefanie Dimmeler, Director of the Institute for Cardiovascular Regeneration of the University Hospital Frankfurt

Partner site Management: Angelika Bonauer (Partner site Manager), Alexander Schwarz (Partner site Clerk) [since Oct. 2016: Julia Dahlhaus], University Hospital Frankfurt

Partner institutions at the DZHK Rhine Main site

Goethe University Frankfurt; Max Planck Institute for Heart and Lung Research, Bad Nauheim; Kerckhoff-Klinik, Bad Nauheim; Johannes Gutenberg University Mainz

Research Focus within the DZHK

The research focus of the Rhine Main site is the identification of epigenetic markers and mediators of cardiovascular diseases in order to stimulate the repair and regeneration of vessels and cardiac muscle tissue. Another focus is the identification therapeutic influence of non-coding RNAs in the cardiovascular system as well as the identification of biomarkers and the improvement of cardiovascular imaging. In this context, the site project "Biomarker Research Group" at the Kerckhoff-Klinik was able to enrol the 12,000th patient. First evaluations on secondary prevention based on a partial cohort of more than 4,500 patients will be presented for the first time soon.

In the scope of the MyoVasc cohort study in Mainz, the three-year observational study started in January 2016; the first randomised participants were enrolled in the study in June 2016. Preparations for genotyping the biological material of the first 2,000 participants have already begun. As far as the Frankfurt partner site project "RNA Therapeutics" is concerned, several long non-coding RNAs (lncRNA), which play a role in the pathophysiological processes in the cardiovascular system, were identified. The group directed by Professor Brandes demonstrated among other things that the lncRNA MANTIS regulates the function of endothelial cells. Furthermore, Professor Dimmeler's preclinical High Risk High Volume project "Development of miR-92a Inhibitors for Treatment of Cardiovascular Diseases" received a good evaluation and was therefore extended. Additional preclinical studies in conformity with GLP and genotoxicity experiments have been planned and initiated. The W3 professorship "Vascular and Myocardial Interactions" in Mainz has now been filled by Professor Tommaso Gori, and the W2 professorship "RNA Biology" in Frankfurt by Professor Reinier Boon. Both groups started working in 2016.

Acronyms

AFNET	Arterial Fibrillation Competence Network
IDMS	Image Data Management System
CSG	Clinical Study Group
DZG	German Centres for Health Research
DZHK	German Centre for Cardiovascular Research
FMM	Funding Management Department
HRHV	High Risk High Volume Late Translational Projects
KdZG	Commission of Donors
KNAH	Competence Network for Congenital Heart Defects
KNHI	Competence Network for Heart Failure
LIMS	Laboratory Information and Management System
PI	Principal Investigator
RCC	Research Coordinating Committee
SE	Shared Expertise
SOP	Standard Operating Procedure
TRG	Translational Research Group
U&AC	Use & Access Committee
ZDM	Central Data Management
✓	Goal reached
✓	In progress
x	Goal not reached

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Reference for use of gender equitable language:

In the interest of better readability and lack of space feminine forms will not always be mentioned separately in this publication. Of course, these terms refer to female as well as male persons.

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