



DZHK

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



**FASTER TRANSLATION OF RESEARCH
FINDINGS INTO PATIENT CARE**

New Approaches to Cardiovascular Research



THE DZHK – NEW STRATEGIES FOR SUCCESSFUL CLINICAL RESEARCH

Cardiovascular medicine has made great strides in recent decades. Due to effective medications and treatments that have been in use for many years, patients live longer, and their quality of life has improved. Notwithstanding this remarkable progress, cardiovascular diseases remain the number one cause of death in Germany and worldwide. New approaches are needed to improve life expectancy and the quality of life of those affected. Such new approaches may already exist in basic research, but they rarely find their way into clinical practice.

The reasons for this are manifold and varied. It is intrinsically difficult to further improve effective treatments. Cardiovascular diseases usually have a chronic course, and treatment is life-long. Drugs must therefore be safe and have few adverse side effects. Their long-term effectiveness in mainly elderly patients can only be inadequately studied in existing animal models. In addition, there is much evidence that the one-for-all treatment protocols – standard in cardiovascular medicine – have reached their limits of improvability. Thus, further progress requires greater individualisation.

And finally, the structures in academic institutions and in industry are not ideal for the efficient translation of basic research results to clinical practice. The increasing financial pressure that clinics are experiencing also impacts experimental research in academic medicine.

In view of these factors, the Federal Ministry of Education and Research (BMBF) has initiated the founding of the German Centre for Cardiovascular Research (DZHK) – one of six German Centres of Health Research (DZG).



Findings from the DZHK key research areas are implemented into innovative preventive and treatment approaches.

LINKING INDIVIDUAL STRENGTHS

In medical research – as in other fields of science – one of the great challenges of science policy, both internationally and nationally, is to create successful cooperation in consortia. By establishing the German Centres of Health Research (DZG), founded upon the initiative of the Federal Ministry of Education and Research (BMBF), Germany is embarking on a unique approach in which the federal and state governments are investing substantial additional resources.

The DZHK as a model

The DZHK serves as a model for how outstanding scientists connect and form a network in a transparent process and thereby develop common research strategies and new strengths. The DZHK is characterised by a balance of large national and bilateral cooperative projects. It builds on intensive cooperation between university and non-university centres and strengthens the partner sites. This creates new perspectives for a new generation of translational clinicians and scientists.

All this follows the overriding objective to further improve the quality of life and prognosis of patients with cardiovascular



The "Cardiac Imaging" programme of the DZHK serves as a technology platform for the entire network.

disease through innovation. Over the medium term this will, in fact, lead to a new "translational space" in cardiovascular research.

Mission and Objective

TRANSLATIONAL RESEARCH – IMPORTANT FOR HEART PATIENTS AND THE HEALTH SYSTEM

The DZHK focuses on translating new approaches in cardiovascular research as rapidly as possible into clinical practice in order to improve the diagnosis, prevention and treatment of cardiovascular diseases. This mission is of utmost clinical and health economic importance because in the future, the incidence of cardiovascular disease will increase further as a result of the rising incidence of metabolic disorders (obesity, diabetes) and due to demographic change.

The research activities of the DZHK focus on three main topics which are particularly important for patients and for the health system:

- ▶ Prevention and treatment of heart attack
- ▶ Prevention and individualised treatment of cardiac insufficiency
- ▶ Prevention of sudden cardiac death

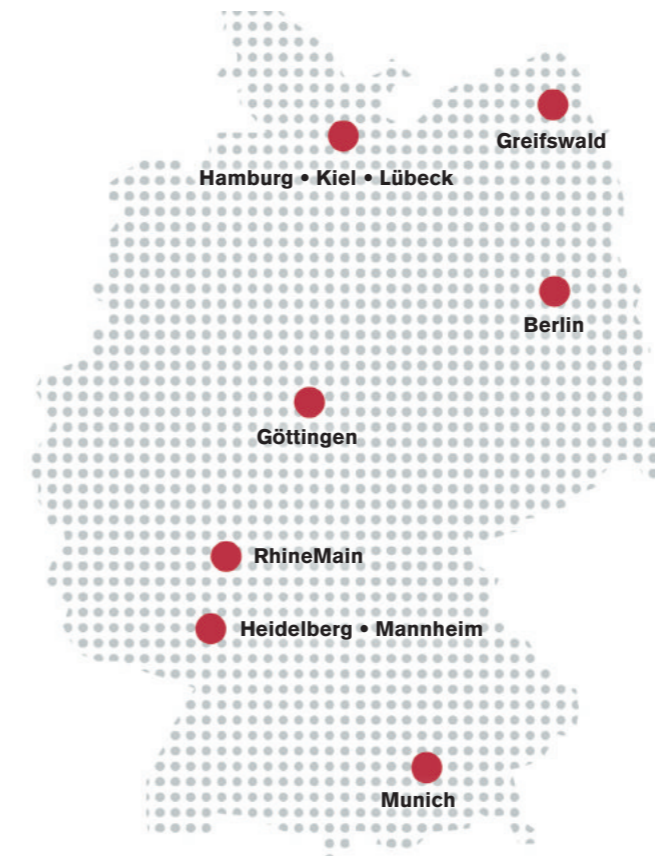
Structure and Characteristics

EXCELLENT INSTITUTIONS

Because of its size, structure and networking, but due also to the combination of excellent basic research and clinical research, the DZHK is the number one among the German cardiovascular research institutions.

27 partners in 7 locations

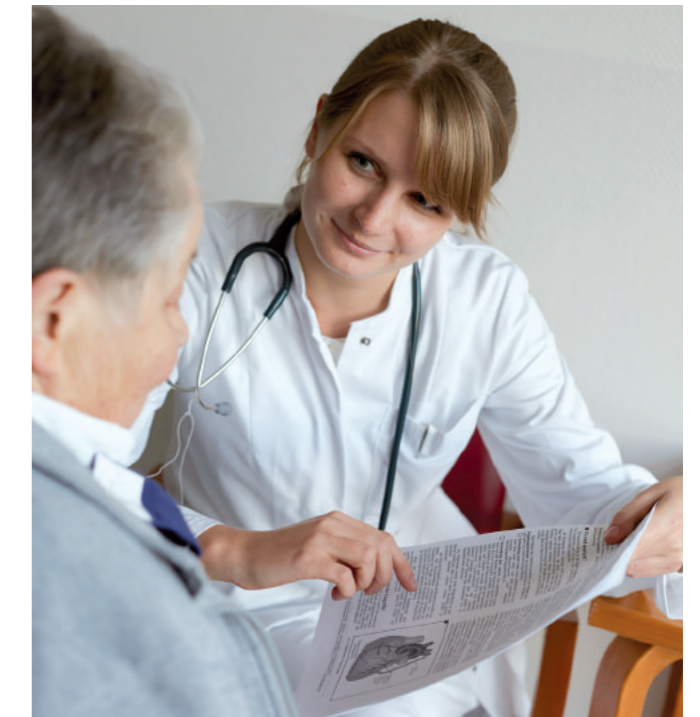
The DZHK consists of 27 partner institutions in 7 locations that were selected in an international peer review process. Members of the DZHK represent the entire spectrum of cardiovascular research at an internationally competitive level. The partner institutions include 14 university hospitals and universities as well as centres of the Helmholtz Association, the Leibniz and Max Planck Institutes and one ministerial research institution of the Federal Government.



All institutions of the seven DZHK partner sites:
dzhk.de/1/partner-sites

Each of the institutions contributes its special expertise to the DZHK, both in the area of basic research, particularly in the identification of new drug targets, and within the scope of clinical studies.

In addition, the DZHK is closely connected with the German Society for Cardiology (DGK) and other external research partners in the cardiovascular field.



The DZHK is creating structures to ensure that even greater numbers of patients can be enrolled in clinical studies in the future.

Access to patients

Access to patients is especially valuable for a translational research institution. Therefore, in the near future more than 50 university teaching hospitals in Germany will include patients in DZHK studies in addition to the 14 university hospitals that are already participating in the DZHK. This is an ideal foundation for translating research results into daily clinical practice. In this respect, the DZHK is superior to local research networks that lack these structures to recruit large numbers of patients. Moreover, the DZHK differs from nationwide clinical networks such as the competence networks in that it includes strong basic research in addition to the clinical research at the partner sites.

SELECTED STEPS OF TRANSLATION

The so-called bench-to-bedside path leading from initial findings in basic research to new cardiovascular treatments is long and arduous. This process, known as translation, involves many individual research steps. However, translational research can also take the reverse path, from bedside to bench, in which experiments are planned on the basis of observations and studies carried out in the clinics. With its scientific strategy, the DZHK focuses on selected stages of the translational research process that are particularly challenging and so far have been undertaken only sparingly (see fig.).

Late preclinical studies

Clinically relevant target validation is the basis for the first clinical studies on humans. This area includes:

- ▶ the establishment of clinically relevant animal models of cardiovascular diseases and the testing of new therapeutic methods in such models
- ▶ human cell models
- ▶ large-scale production of therapeutic drugs, such as viral vectors, microRNAs or stem cells

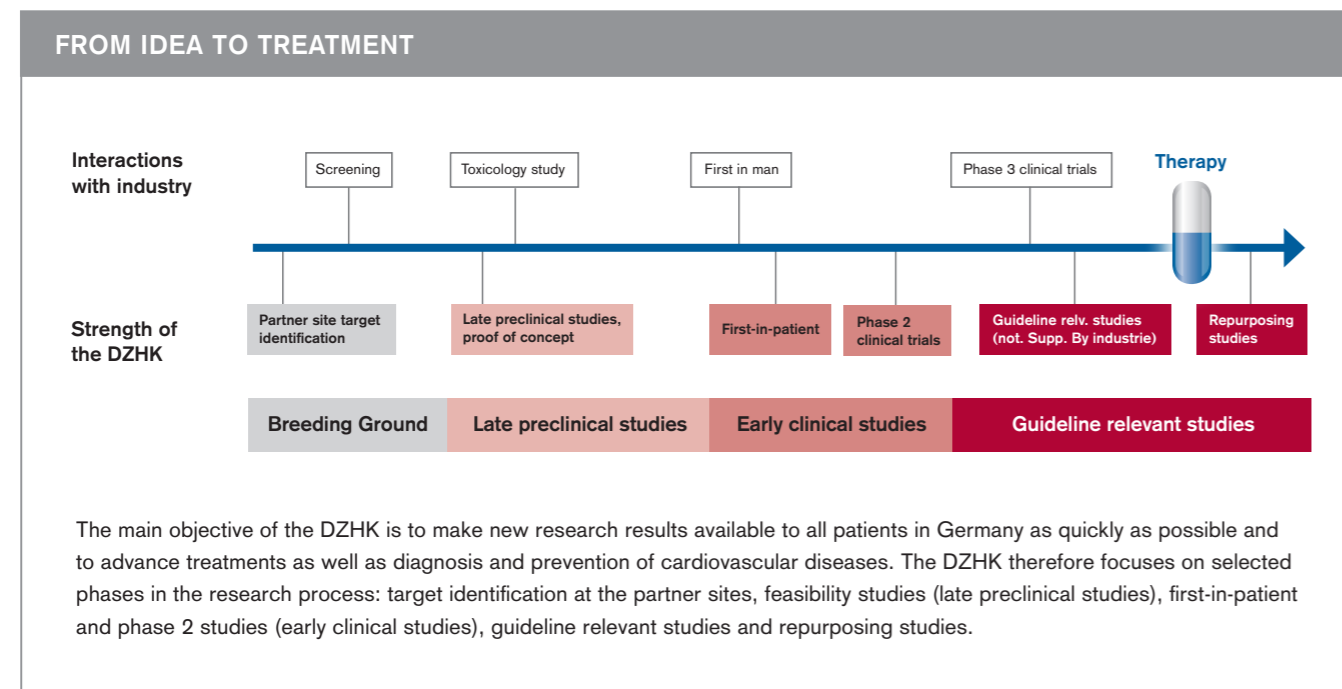
Early clinical studies

This area includes:

- ▶ first-in-patient studies
- ▶ early clinical studies, which may include investigation of pharmacogenetics and biomarkers
- ▶ imaging studies

Guideline relevant studies

These are studies that lead to a change of practical treatment recommendations. Examples are the comparison of existing therapeutic procedures and the testing of known drugs for new indications (repurposing studies), and the comparison of pacemaker and cardiac support systems and other new treatment methods.



In various projects, DZHK researchers elucidate the causes of heart diseases such as heart attack or genetically determined heart failure. For this purpose, they isolate the hearts of diseased mice and can thus investigate the function of cells and tissues in detail.

ADDED VALUE THROUGH FLEXIBLE STRUCTURES

Successful translation requires new ideas and discoveries, as well as structures that support the various steps of the translational value chain. Therefore, the DZHK invests in innovative, translational structures and strengthens the existing excellence in cardiovascular basic research as a breeding ground for translational concepts.

Equally important, translational research requires the interaction and exchange between different players. And it needs people trained to work at the interface between experimental basic research and clinical research – to work in a translational space. The DZHK has the opportunity to create such a space.

New structures – support of clinical studies

Clinics rarely have appropriate structures for multicentre studies. The DZHK seeks to improve this situation by various means.

This includes the establishment of a Clinical Study Group (CSG), which selects, carries out and monitors DZHK studies. The CSG has a steering committee consisting of researchers experienced in clinical studies and a coordinator based in the main office. The CSG also has staff based at the 14 university hospitals participating in the DZHK; these are doctors and nursing personnel employed by the DZHK within the scope of the studies.

Centralised data management, a trusteeship office, a biobank system and rules for the use of and access to study data have already been established to facilitate national cooperation and long-term data access.

Each year the DZHK allocates more than 14 million euros from its flexible research budget for these structures and for the conduct of clinical studies.

Faster results – investment in translational concepts

While academic structures currently in use promote new discoveries in basic research, they do not promote the systematic development of new therapy concepts.

The DZHK therefore finances so-called “Shared Expertise” at the partner sites (including the use of animal models established at the partner sites, stem cell-based models of human diseases as well as omics technologies). These are scientific infrastructures and methods that are used in different steps of the translational chain. DZHK scientists can use the Shared Expertise of other partner sites within the scope of their DZHK research.

The DZHK will also establish a Translational Research Group (TRG), which shall advise and support a limited number of large translational research projects in the initial phase. Its tasks also include aspects of commercialisation, the assessment of translational research proposals and the preparation of decis-



Clinical studies are a main focus in the DZHK in order to provide the best therapeutic and diagnostic procedures for patients. A uniform platform established by the DZHK ensures that as many patients as possible are enrolled in the studies under identical conditions. Furthermore, comparisons of large numbers of patient data enable conclusions to be drawn about the mechanisms of a disease.

COOPERATIVE INITIATIVES WITH FLEXIBLE BUDGETS

Usually in an association, the entire funds for several years in advance would be allocated to the respective partners. Although these funds may be well invested, the association itself would only have limited strategic control over their use. The DZHK, by contrast, has reserved more than half of its funds for genuine common projects of the partners, so-called “Cooperative Initiatives”. The ideas for these projects are conceived in the DZHK – and the DZHK also decides which projects will be funded. Not every partner has to benefit from this in the same measure or according to a fixed scheme; good ideas and the ability to excel in cooperation prevail. This competitive procedure enables the DZHK to allocate funds flexibly, to promote the best scientific approaches and to implement a common strategy.

ions in the DZHK bodies. Along with this, the TRG combines and expands the knowledge base for the development of new therapy principles within the DZHK.

The DZHK has reserved a flexible annual budget of more than 6 million euros for this structure to support preclinical translational research, to promote Shared Expertise and for individual, large-scale translational research projects.

Opportunity for young scientists – career path for translational research

Effective translational research requires young researchers interested in specialising in this field. Until now, young doctors have opted for careers in medical care or in basic research. There has not been a specific career path for translational or clinical research.

To remedy this, the DZHK is launching a training programme with a focus on training clinicians and scientists in those areas which are neglected by the current curricula. In addition, the

DZHK offers young scientists many opportunities such as exchange programmes or scholarships. In the YoungDZHK young scientists organise themselves as a group and thus create a framework for networking and scientific exchange.

A flexible budget of approximately 2 million euros a year is available for the different modules of the training programme.

Foundation for ideas – basic research at the partner sites

Important new therapy concepts are rarely discovered as such. Rather, as a rule they develop from research projects that seek to elucidate fundamental biological principles and their role in the disease process.

Therefore, the DZHK also invests in the basic research of cardiovascular diseases. Here a particular strength of the DZHK becomes evident – the internationally recognised expertise of its partners in cardiovascular basic research. This is funded at the partner sites through third-party grants

of the German Research Foundation (DFG), the European Union (EU), the Federal Ministry of Education and Research (BMBF), the Leducq Foundation and other donors, and by the basic funding of the universities, which however is becoming increasingly inadequate.

The DZHK funding for site projects enables the partners to strengthen their local infrastructure in three areas, in accordance with the DZHK strategy:

- ▶ through the establishment/appointment of new professorships in areas of high relevance for cardiovascular research
- ▶ through the purchase of new research equipment
- ▶ through the funding of scientific and technical personnel



In the laboratory, DZHK researchers cultivate human myocardial cells from pluripotent stem cells. These cells and the thus derived artificial heart tissue serve as model for various heart diseases and further experiments. Beyond this, the researchers' aim is to be able to repair diseased hearts with artificial tissue.

The scientific programmes of the partner sites and their interconnectedness are the basis for the identification of new therapeutic principles. Through the central DZHK structures these are then translated to clinical applications. Both the DZHK studies and the DZHK partner site projects are subject to review by external evaluators.

This "Breeding Ground" of the DZHK has an annual budget of more than 16 million euros.

Organisation and Financing

COMBINING AUTONOMY AND EFFECTIVE COORDINATION

Association and Board of Directors

The DZHK is organised as an association (e.V.) whose statutes allow the partner sites a high degree of autonomy and participation in the General Assembly of Members (one vote per site). Key issues of strategic importance are decided in this assembly. In return, all DZHK members commit to actively participate in the DZHK bodies, to comply with fundamental DZHK rules at their site and to implement the overarching DZHK strategy. The Board of Directors comprises Thomas Eschenhagen (spokesperson), Gerd Hasenfuss and Walther Rosenthal. The Board of Directors represents the DZHK and develops its strategy.

Scientific cooperation

The scientific cooperation takes place in various committees and working groups. The DZHK pursues a bottom-up approach. Ideas for early and late translational projects as well as for other DZHK studies can originate from individuals, institutions, partner sites and organs of the DZHK association.

Two "Disease Groups" represent a broad DZHK communication platform to exchange and develop new ideas. Time-limited project groups that pursue a defined objective are a second key element. This objective can be, for example, to develop and carry out a translational project or a clinical study, a registry or a cohort.

The Clinical Study Group (CSG) and the Translational Research Group (TRG) provide support for clinical studies and/or preclinical translational projects.

The Research Coordinating Committee (RCC) is the central and strategic decision-making body in the DZHK. It develops ideas, is concerned with issues related to the DZHK strategy and prepares decisions for the General Assembly of Members.

The Scientific Advisory Board advises the DZHK on scientific and structural issues.

Main office

Although the DZHK has a decentralized, federal and democratic structure, the Berlin-based office has developed into the key coordinating office. Here, for example, regular meetings of the DZHK groups take place. Already in the second year after the founding of the DZHK, staff members specialised in each of the major DZHK tasks work in the office.



One aspect of the DZHK strategy – intensive exchange at all levels.

In the course of establishing a well-connected coordinating office, a DZHK team spirit has developed. The office staff assists the Board of Directors in matters of public relations, in strategic discussions, in the development of support programmes, in the administration of clinical studies and in the establishment of a scientific infrastructure.

Finances and budget allocation

The DZHK is funded jointly by the federal government and nine state governments. The federal share amounting to 90 per cent of the total funding is financed by the Federal Ministry of Education and Research. Each DZHK partner institution receives the remaining 10 per cent from its respective state. The ten sponsors are organised in the Commission of Donors.

The federal funds are provided through a funding management office, which is based at the Max Delbrück Center for Molecular Medicine (MDC).

The DZHK receives institutional funding. This funding will increase incrementally to 41 million euros in 2015 and thereafter will benefit from a fixed annual increase, which has been guaranteed for the German Research Centres. 55 per cent of the DZHK budget (EUR 22.6 million in 2015) is allocated for clinical studies, preclinical translation and the promotion of young talent. The sites as Breeding Grounds for new ideas receive 40 per cent (EUR 16.4 million in 2015). A maximum of 5 per cent will be provided for the central administration and management (up to EUR 2 million in 2015).



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