

DZD German Center for Diabetes Research

DZD10 YEARS # DIABETES RESEARCH

Research for a Future without Diabetes



Preface

The objective of the German Center for Diatant foundations for innovative methods of betes Research (DZD) is to bring the results of prevention and treatment. Furthermore, with research from the laboratory to the patient as offers of further training, for example in our quickly as possible (translation) in order to bettwo-day research schools, we have succeeded ter prevent and treat diabetes and thus avoid in attracting talented young scientists to the secondary diseases. The DZD was founded ten field of diabetes research. years ago, on June 24, 2009, upon the initiative of the German Federal Ministry of Education Over the past ten years, the DZD has developed and Research. More than 400 experts from into a nationally and internationally recognized various disciplines, including basic researchers, institution in translational diabetes research. epidemiologists, health care researchers and This would not have been possible without the clinicians are working together in the DZD on outstanding achievements of all those involved and the support of the federal and state govnew stratified prevention and therapy concepts. ernments. In the future, our research activities The research work of the DZD not only contribwill continue to be centered on people in order to ensure that the individual patient can benefit from our research results as quickly as possible.

utes to the understanding of the pathogenesis of the metabolic disease, but also lays impor-



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Glass

Dr. Astrid Glaser **DZD** Managing Director

Diabetes – A Growing Threat

ullet

16% of deaths are associated with type 2 diabetes. (Source: DD7/D7D)

Every seconds a person in Germany is diagnosed with diabetes. (Source: DDZ. RKI)

In 2040, it is estimated that 12 million Germans will have diabetes. (Source: DDZ, RKI)

2 out of 3 people with diabetes are of working age (age 20 - 64). (Source: IDF)

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People in cities have a 40% higher risk of developing diabetes than people living in rural areas.

(Source: German Health Report 2019)

Secondary diseases of diabetes



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Brain 2 to 4-fold increased risk of stroke. Dementia and Alzheimer's can also be consequences. **Depression:** Increased risk of depression.





Heart Cardiac death is the main cause of diabetes-related deaths (33% of all heart attacks).

Eyes Diabetic retinopathy (30% of new cases of blindness).

10 % of the total expenditures of the statutory health insurance funds flow into the care of people with type 2 diabetes. (Source: DDZ/DZD)





Kidneys Diabetic nephropathy (40% of renal



Nerves Diabetic neuropathy (frequent lower limb



Depression Increased risk of depression.



Translational Diabetes Research -From Bench to Bedside

A future without diabetes – that is the ambitious goal of the DZD.

In order to realize this vision, the DZD bundles the expertise of leading German research institutions and universities in the field of metabolic and diabetes research. The aim of this close collaboration is to accelerate translation so that patients benefit more quickly from new findings from basic research. The special added value of the DZD is based on its broad technical expertise, the collaboration of basic researchers, clinicians, epidemiologists and health care researchers across departments



Prevention of diabetes



Non-alcoholic Fatty Liver Disease (NAFLD)



Insulin action and resistance in the brain



Beta Cell/Islet Protection and Regeneration

and institutions, as well as its state-of-the-art research infrastructures.

What influence do liver or brain have on diabetes? # How do environmental factors such as diet affect the activity status of genes?
How can beta cells be protected? # What other diseases are associated with diabetes?

In order to investigate these questions, the DZD focuses on the following research topics:



Multicenter Studies – Research in Networks

The DZD has set up multicenter clinical studies to develop precise prevention and therapy measures, i.e. the right treatment for the right patient group at the right time (precision medicine). The Germany-wide cooperation in the research network makes it possible to initiate large-scale studies and to recruit the necessary number of participants. In total, more than 5,000 people have already participated in the studies.

The DZD is conducting studies on the prevention and treatment of type 1 diabetes and type 2 diabetes, gestational diabetes and secondary diseases as well as on the treatment of

The DZD has set up multicenter clinical studiesfatty liver in diabetes and on insulin resistanceto develop precise prevention and therapyin the brain. The studies are conducted at upmeasures, i.e. the right treatment for the rightto ten study locations.

Initial results are already available. The studies show that there are different subtypes of prediabetes and diabetes. Not every subtype has the same risk of developing diabetes or serious secondary diseases. In new studies, the DZD is now contributing to the development of interventions and therapies tailored to the individual subgroups in order to prevent or at least delay the onset of the metabolic disorder and its complications.





German Diabetes Study GDS DELL

Combined Active Treatment of Type 2 Diabetes with NASH COMBAT T2 NASH DZD-

. . . .

Prediabetes Cohort

Prediabetes Lifestyle Intervention Study PLIS

Innovative Infrastructures for Excellent Research

State-of-the-art technology platforms are a prerequisite for successful translational biomedical research. This is why the DZD specifically strengthens the expansion of research infrastructures for key technologies at the DZD locations and establishes central service facilities.

These include preclinical models, genotyping and phenotyping, epidemiological cohorts, high-throughput screening platforms and a GMP laboratory for tissues and cells for transplantation. In addition, central service facilities of the DZD - such as clinical trial management, biosample and data management or the Core Unit Computational Biology – provide an

ideal basis for high-quality and cost-effective research on scientific questions. Multicenter studies, cohorts, long-term epidemiological studies, preclinical models, genotyping and phenotyping provide valuable health data. The DZD has launched the data management project DZD Connect in order to better analyze this information across locations and make it available to scientists. Artificial intelligence shall be used to facilitate pattern recognition in order to investigate relationships between complex data sets more quickly.



Central study

Infrastructures for translational research

Computationa biology

Data management



DZD NEXT – Promoting Talented Young Scientists

DZD NEXT trains innovative and internationally competitive young diabetes scientists. Through high-level programs, events and courses, DZD NEXT provides a sustainable basis for future careers in science and makes Germany attractive as a science location for talented young researchers.

The annual highlight is the DZD Diabetes Research School for doctoral students, postdocs and physicians active in research. During the two-day research school, renowned diabetes researchers give an insight into their current research work, and the 80 international participants present their own projects on posters.

The training program of DZD NEXT provides specialized knowledge for translational research. DZD NEXT also fosters early interdisciplinary contacts, especially between young physicians and scientists in medical research. The close cooperation with the programs of the graduate schools of the DZD partners complements the range of offerings in management, leadership and communication. A funding program for projects of young DZD scientists enables them to take first steps toward scientific independence and supports them in establishing a professional national and international network.

DZD NEXT cooperates successfully with international organizations such as the Danish Diabetes Academy, Lund University Diabetes Centre Sweden and Ciberdem in Spain. Local training offerings are open to partner organizations. These joint events offer ideal platforms for networking.

With these opportunities, DZD NEXT supports young DZD talents in building a professional and international network and in establishing themselves as excellent scientists in translational diabetes research.



Founding of the DZD 2009

2011

- Use of KORA/EPIC data for the German Diabetes Risk Score (DRS)
- Start of DZD NEXT
- Interactive pavilion at the Year of Science Research for Our Health
- Opening ceremony of the 6 German Centers for Health Research

2012

- Start of the multicenter studies PLIS and PREG o-
 - Biomarker for T2D (patent granted) o-
 - Start of DZD grants o-
- Establishment of the DZD Clinical Trials Platform

2010

- German Diabetes Study (GDS) becomes multicenter study
- Launch of IMI-IMIDIA (European consortium for type 2 diabetes)
- Opening of the DZD office in Munich
- Implementation of structures and governance
- Lo Scientific Advisory Board of the DZD appointed

2014

Flattop (Fltp) biomarker for beta On cell maturation (patent pending)

- Excellent evaluation by O
- Launch of the French-German o-Diabetes Academy
- Admission of associated partners

2013

School

Partner at EIT Health o-

• First transplantation of an

First DZD Diabetes Research

Establishment of DZD Research

Coordination Board

in T1D patient

encapsulated artificial pancreas

-• Polyagonists for the treatment

2015

- of overweight/obesity (patent pending)
- New receptor for insulin-like growth factors (patent pending)
- Establishment of Core Unit **Computational Biology**
- Integration of the Diabetes Mellitus Competence Network

2016

- Proof of epigenetic o inheritance of diet-related obesity and diabetes
- Start of collaboration with the Danish Diabetes Academy

Start of the diabetes prevention study POInT o-

DZD10 YEARS **#** DIABETES RESEARCH

2018

- EMLiFa study completed o-
- Start of multicenter study Dopamine o-Genetics (DAG))
- microRNA inhibitors for the treatment of O metabolic diseases (patent pending)
- Start of cooperation with LUDC (Sweden) Oand Ciberdem (Spain)
 - Second French-German Conference oon Diabetes Research
 - Development of a national い diabetes information portal

2019

2017

• PLIS multicenter study completed

• Positive assessment of the DZG by the German Science Council

• First xenotransplantation without immunosuppression

-O Method for the purification of endoderm and pancreatic endoderm cells generated from human embryonic stem cells (patent pending)

- Method for determining the risk for the development of type 1 diabetes (patent pending)

- Restructuring of focus areas of research into translational academies
- Development of knowledge and data management DZD Connect
- Lo Partner in Sanofi I Award Program



Research Spotlights

The research work of the DZD not only helps to better understand the development of diabetes, but also lays important foundations for innovative prevention and treatment strategies.

Determine your own diabetes risk

The DIFE - German Diabetes Risk Score[®] (DRS) (drs.dife. de) provides important information on the individual diabetes risk. With the help of the DRS, adults can determine their personal risk of developing type 2 diabetes within the next five years. In addition, the online test also shows individual ways of reducing the risk - for example through lifestyle changes. Diabetes Research and Clinical Practice 2014

Immunotherapy for type 1 diabetes

The autoimmune disease type 1 diabetes usually begins with a misdirected immune reaction against insulin. DZD experts are working on a method of desensitization to prevent the onset of the disease in children with increased genetic risk. A daily dose of insulin powder trains the body to tolerate its own insulin. The procedure is currently being tested in the randomized, controlled double-blind POInT study. JAMA 2013 | Nature Communications 2016

Biomarker for type 2 diabetes

Type 2 diabetes does not develop from one day to the next. Patients go through longer stages, in which the metabolism begins to change. DZD researchers have been able to identify metabolites and proteins in the blood that serve as biomarkers for these processes. **Diabetologia 2016 | Diabetes 2019**

Research Spotlights

Lifestyle is inheritable

Not only the genetic code itself influences the risk of diabetes. Lifestyle can also influence the extent to which certain genes are read and their information is implemented (epigenetics) - even over generations. The DZD also showed that diet-induced obesity and diabetes are transmitted epigenetically to the offspring, both via egg cells and via sperm. An epigenetic modification promotes obesity and fatty liver disease, both of which are related to type 2 diabetes. Nature Genetics 2016 | Diabetes 2017

Discovery of new candidate genes for diabetes

Metabolic diseases such as diabetes and obesity are a global problem. In addition to lifestyle and environmental factors, many different genes are responsible for their development. The DZD has identified more than 50 new genes associated with metabolism. The genes have common regulatory elements and are believed to form a network.

Nature Communications 2018 | Human Molecular Genetics 2018



Gestational diabetes affects the fetus

Gestational diabetes affects the unborn child. DZD stud-A research focus of the DZD is the protection and regeneration of islet cells. Important insights are provided ies show that gestational diabetes slows down the fetal brain response after the mother's meal. These children by the unique biobank which contains samples from may already have insulin resistance in the brain in the the human pancreas. From these samples, researchers womb, which could increase the likelihood that the child isolate the pancreatic islets containing the insulinwill develop obesity and type 2 diabetes later in life. producing beta cells. Promising approaches are re-DZD researchers are now investigating whether this can generative processes in which beta cells are generated be prevented by changing mothers' lifestyles. from stem cells. Researchers at the DZD are working on exploiting these endogenous reserves and were able to The Journal of Clinical Endocrinology and Metabolism 2015 identify the protein flattop as a biomarker that enables the differentiation of the two variants of beta cells # "Artificial" pancreas (insulin-producing cells and immature "reserve" cells that divide more frequently). A facility for the appli-In type 1 diabetes and in the advanced stage of type 2 cation-oriented production of beta cells from human diabetes, the insulin-producing beta cells in the pancreas pluripotent stem cells is currently under construction. are destroyed. The DZD is working on an artificial pan-Nature 2016 | Diabetologia 2018

creas in which the beta cells are surrounded by a special teflon membrane that allows hormones and nutrients to pass unhindered but prevents contact with the body's own immune cells. The great advantage of the system is that there is no need for drugs to suppress the immune system.

PNAS 2017 | Nature Scientific Reports 2018

Beta cells from the lab

Polyagonists to treat obesity

Polyagonists can open up new approaches in the treatment of type 2 diabetes. DZD experts have developed a new drug candidate – an active compound that mimics the combined effects of the three hormones GLP-1, GIP and glucagon. In the animal model, the polyagonist not only drastically reduced blood glucose levels, appetite and body fat, but also improved cholesterol levels and calorie burning and reduced fatty degeneration of the liver. The first drug candidates are already in the clinical phase. DZD researchers are currently working on further polyagonists, among other things, to improve glucose metabolism and cholesterol levels as well as to reduce body weight and fatty degeneration of the liver. Science Translational Medicine 2013 | Cell 2016

Brain - mastermind of metabolism

Studies conducted in recent years show that the brain is an insulin-sensitive organ. A number of brain regions react to insulin, for example regions that are important for food intake, metabolism and memory. Among other things, the DZD was able to show that altered reactions in the brain are involved in the development of wholebody insulin resistance. These findings could open up new therapeutic approaches.

Nature Neuroscience 2013 | Nature Reviews Endocrinology 2015 | Cell 2018

Diabetes and fatty liver

About one in three adults in industrialized countries has a diseased fatty liver. This also increases the risk of developing type 2 diabetes. The accumulation of fat in the liver favors a disturbance of the blood glucose metabolism. The liver cells produce an increased amount of hepatokine fetuin-A. The protein binds to insulin receptors of muscle and fat cells and thus contributes to insulin resistance. DZD studies have shown that the three parameters fetuin-A levels, fatty liver status and fatty acid levels in particular indicate an increased risk of diabetes. Studies show that severely overweight patients with non-alcoholic fatty liver disease show a significantly increased activity of mitochondria in the liver.

As fatty liver inflammation (NASH) progresses, mitochondrial performance decreases and oxidative stress increases. This is due to the fact that the liver first burns more excess fat in the early stages of obesity. Even a single high-fat meal can damage the metabolism and pave the way for fatty liver and diabetes. The DZD is starting clinical trials to investigate how type 2 diabetes and NASH can be treated in combination. **Nature Reviews Endocrinology 2013 | The New England Journal of Medicine 2014 | Cell Metabolism 2015 | Journal of Clinical Investigation**

2017 | The Lancet Diabetes & Endocrinology 2018 | Nature 2018

Diabetes subtypes

Type 2 diabetes is a disease with very heterogeneous manifestations. There is not "the" type 2 diabetes, but rather different subtypes. Studies from Scandinavia show that there are different clusters with differing courses of disease progression. These groups were confirmed by the German Center for Diabetes Research (DZD) in analyses of the German Diabetes Study (GDS). Patients suffering from certain subtypes have a high risk of diabetic complications.

Type 2 diabetes does not develop from one day to the next. Patients often go through longer preliminary stages in which the metabolism already begins to change (prediabetes). Current studies of the DZD show that already in prediabetes there are distinct subgroups that respond differently to lifestyle interventions. Studies indicate that not every prediabetic has the same high risk of developing diabetes later on. Rather, there is a high-risk group: test persons suffering from fatty liver with insulin resistance or an insulin secretion disorder are very likely to develop manifest diabetes. The Lancet Diabetes & Endocrinology 2019

DZD in Dialog

From the ivory tower to practice: The DZD informs patients, doctors, politicians and decision makers at public events and congresses about current research progress, exchanges information with professional societies and patient organizations and works together with associations and international scientific organizations.

Diabetes information services, easy-to-understand videos, extensive websites, newsletters, social media – the DZD provides information via numerous channels on the widespread disease diabetes, causes of metabolic diseases, current research results and the development of innovative prevention and therapy approaches. In order to enable experts and the public to participate in the latest research results, the DZD also utilizes direct, on-site exchange at congresses, symposia, health and patient days. There, interested individuals can talk to the scientists and receive first-hand information.



Research in a Network

In line with its mission, the DZD supports close networking and short communication channels between the DZD partners and external research groups - nationally and internationally. This continuous, open exchange between different research areas and partners not only enables the development of innovative research approaches, but also the more effective implementation of new insights from the laboratory into practice.

The DZD actively contributes to medical research networks across Germany. It works closely with the other German Centers for Health Research (DZG), the Robert Koch Institute (RKI) and the German Diabetes Association (DDG). In addition, partners of the DZD are involved in the National Cohort Health Study, the largest German population-based cohort study for research on major diseases. On an international level, the DZD cooperates with leading organizations in the field of diabetes research.

The healthcare industry is an important cooperation partner of the DZD. By involving all members of the value chain in the development of new medical products, the DZD makes optimal use of existing resources and can quickly transfer research results into practice.

Partners in the DZD

The German Center for Diabetes Research (DZD) is one of the six German Centers for Health Research (DZG). It brings together experts in the field of diabetes research and interlinks basic research, epidemiology and clinical application.

Members

German Diabetes Center Düsseldorf Speaker: Prof. Dr. Dr. h.c. Michael Roden

German Institute of Human Nutrition Potsdam-Rehbrücke (DIfE) Speaker: Prof. Dr. Annette Schürmann

Helmholtz Zentrum München - German Research Center for Environmental Health Speaker: Prof. Dr. Dr. h.c. mult. Martin Hrabě de Angelis

Institute for Diabetes Research and Metabolic Diseases of Helmholtz Zentrum München at the Eberhard-Karls-University of Tübingen-Speaker:

Prof. Dr. Dr. h.c. mult. Hans-Ulrich Häring



Paul Langerhans Institute Dresden (PLID) of Helmholtz Zentrum München at the University Hospital Carl Gustav Carus of TU Dresden Speaker: Prof. Dr. Dr. Michele Solimena

Further partners

Associated partners of the DZD are diabetes research groups at the universities of Heidelberg, Cologne, Leipzig, Munich and Schleswig-Holstein. In addition, further project partners are part of the DZD.

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