DZD
German Center for
Diabetes Research

DZG DEUTSCHE ZENTREN
DER GESUNDHEITSFORSCHUNG

German Center for Diabetes Research

Annual Report

2020

VISION

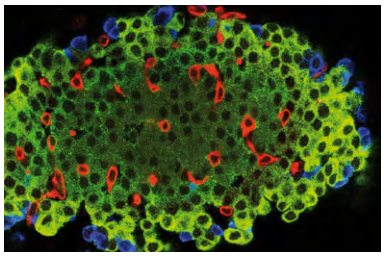
Research for a future without diabetes

MISSION

The mission of the DZD is to discover and develop innovative, precise strategies for the prevention, early detection and treatment of individuals with prediabetes or diabetes.

Our goal is to improve quality of life and reduce diabetes-related comorbidities, complications and premature mortality.

Highlights and Publications/ Research Successes



Research Program DZD Academies

Research Infrastructures

TOGETHER FASTER FROM BENCH TO BEDSIDE

Health research is currently facing great challenges: Although the COVID-19 pandemic must be contained as quickly as possible, the growing threat of other common diseases such as diabetes must not be neglected. It is also very important to keep an eye on widespread diseases. Studies show that people in Germany gained weight during the lockdowns because of a lack of exercise and an unhealthier diet, among other factors. Being overweight, not exercising enough, and eating too much unhealthy food can contribute to the development of common diseases such as type 2 diabetes. Even before the pandemic, experts predicted that more people would develop diabetes in the coming years, and that the numbers could rise from nearly 8 million at present to as many as 12 million in 2040.

In order to counteract this development, new effective prevention measures and innovative forms of treatment are needed. The German Center for Diabetes Research (DZD) combines the expertise of Germany's leading research institutions and universities in the field of metabolic and diabetes research in order to develop precise approaches to the prevention, diagnosis, and treatment of diabetes. The aim of the close interdisciplinary and cross-site collaboration is to accelerate translation so that people can benefit more quickly from new findings from basic research.

In the past year, the DZD has achieved some decisive milestones. For example, in the preliminary stage of diabetes (prediabetes), six different subtypes, each of which have a different risk of developing the metabolic disease and serious secondary diseases, have been identified. In 2019, DZD researchers had identified different diabetes subtypes with different risks for complications in the German Diabetes Study. These results are important steps towards precision medicine.

Prof. Dr. Dr. h.c. mult.
Martin Hrabě de Angelis
DZD Board of Directors

Prof. Dr. Dr. h.c. mult.
Michael Roden
DZD Board of Directors

Prof. Dr. Dr. Michele Solimena
DZD Board of Directors

Prof. Dr. Annette Schürmann
DZD Speaker

Prof. Dr. Andreas Birkenfeld
DZD Speaker

Dr. Astrid Glaser
DZD Managing Director

Digitalization is a central topic at the DZD. In order to make better use of the valuable health-related data that multi-center studies, cohorts, and long-term epidemiological studies, among others, provide us with, we have established the Bioinformatics and Data Management unit DZDconnect. With the help of new innovative information technologies such as graph technologies, Artificial Intelligence (AI), and Machine Learning (ML), we can connect and analyze data from different sources. This allows us to explore the common disease of diabetes in a new dimension.

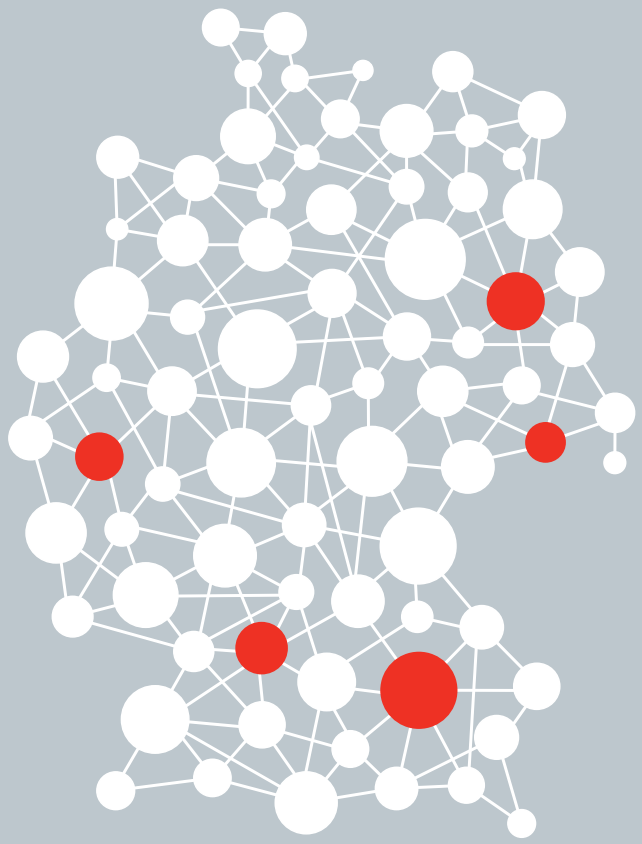
Promoting talented young scientists and attracting them to translational diabetes research is an important concern of the DZD. We are therefore continuously expanding our DZD NEXT Program and offering joint activities with international organizations. In 2020, we offered the International DZD Diabetes Research School as a webinar. The event was attended by 170 early-career scientists interested in diabetes and metabolism research.

Another focus of the work of the DZD is to provide the population with comprehensive information about diabetes. Last year, the national diabetes information portal diabinfo.de went online. At diabinfo.de, interested parties find reliable and scientifically proven information on the topics of prevention and living with diabetes.

The focus of our work is always human beings. Our goal is to prevent diabetes, improve the quality of life of people with diabetes, and prevent diabetes-related complications and premature mortality. The current annual report shows what possibilities and opportunities the collaboration of basic and clinical research open up and provides an overview of our research priorities and successes.

DZD AT A GLANCE

> 400 Scientists in the DZD work together on an interdisciplinary basis.



22 Prizes and awards in 2020 for DZD researchers, including two ERC Starting Grants and one ERC Consolidator Grant.

European Research Council

The DZD is a national center with five partners, five associated partners, and six project partners.

&

> 188,000 Samples in biobanks.

> 5,100

People are participating in multicenter clinical studies of the DZD.

In seven main research areas, the DZD investigates the most pressing questions in diabetes research.

478 Publications (2020) in peer-reviewed journals.

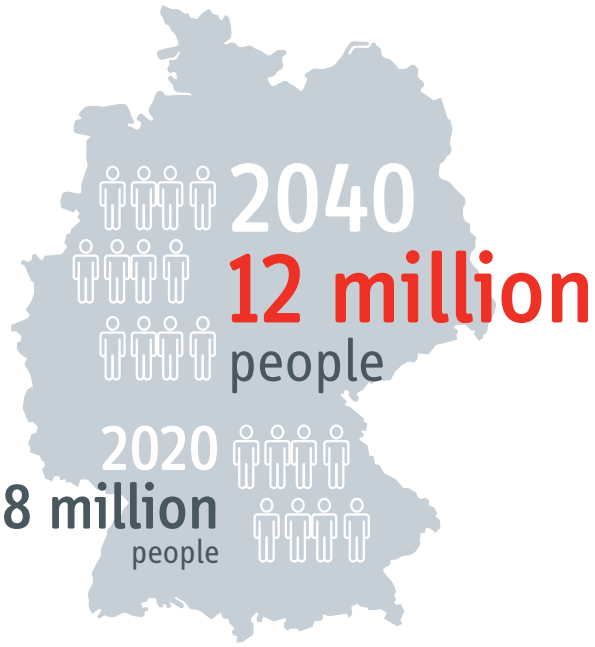
22 Articles in print and online media per week about the DZD and its partners.

150 talented young scientists take advantage of the DZD NEXT program for young scientists.

TRANSLATIONAL DIABETES RESEARCH

A future without diabetes – this is the ambitious goal of the German Center for Diabetes Research (DZD). *In order to realize this vision, the DZD combines the expertise of the leading German research institutions and universities in the field of metabolic and diabetes research. The goal is to bring the findings and results of diabetes research from bench to bedside as quickly as possible (translation).*

Diabetes mellitus is a chronic metabolic disease and can affect people of any age. In Germany, almost 8 million people suffer from the disease. Approximately 373,000 people suffer from type 1 diabetes – including about 32,000 children and adolescents under the age of 18. About 95% of diabetes patients have type 2 diabetes. The number of cases is on the rise: Every year, up to 600,000 people are diagnosed with diabetes mellitus for the first time. By 2040, up to 12 million people could suffer from the metabolic disease.



About eight million people in Germany (2020) have diabetes. If the trend continues, it is expected that ***up to 12 million people*** *may suffer from it by* ***2040****.*

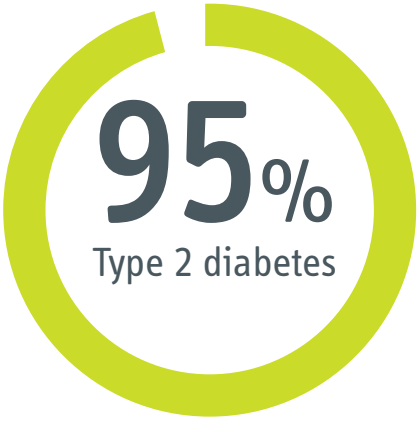
Interdisciplinary collaboration – researching together

These dramatic figures illustrate how urgently new effective prevention measures and innovative forms of treatment are needed. In the DZD, more than 400 experts from different disciplines such as basic research, epidemiology, health services research, and clinical practice are working together to counteract this diabetes epidemic. The aim is to decipher the complex process of diabetes development and to discover new, precise prevention, and therapy concepts – i.e., the right treatment for the right patient group at the right time. Here, the DZD has achieved important research progress: Among other things, subtypes of prediabetes and type 2 diabetes have been identified (see page 12). These are the first important steps towards precision medicine.

Diabetes can lead to various serious complications. In order to avoid or delay such consequences, it is important to identify which patients are at high risk for complications and to develop new therapeutic approaches. Using genetic, cell and biological, as well as precinical model systems techniques, researchers are elucidating the molecular mechanisms of diabetes. New genes associated with diabetes have been identified, and epigenetic and biochemical regulatory pathways have been elucidated. In large population studies, the DZD is investigating the effects of environment, lifestyle, and genes on the development of diabetes. New biomarkers that could improve the diagnosis of diabetes have already been found.

Recent studies show that the brain plays an important role in the development of both type 2 diabetes and obesity. DZD researchers investigate the connection between brain and metabolism. Another focus is to stop the destruction of beta cells or to replace them. DZD researchers are also discovering, validating, and further developing new active ingredient candidates and targets for innovative drugs.

In the field of type 1 diabetes, the aim is to decipher the mechanisms that lead to the development of the autoimmune disease as well as to identify markers that enable early diagnosis and develop therapies to prevent type 1 diabetes.



*About **95%** of diabetes patients have type 2 diabetes.*

Main research topics (Academies) include:

- Prevention of type 2 diabetes
- Complications of diabetes
- The influence of genetics and epigenetics on the development of diabetes
- Causes and treatment of non-alcoholic fatty liver disease
- Insulin action and resistance in the brain
- Protection and regeneration of beta cells
- Preventing the autoimmune disease type 1 diabetes

Promoting young talent

With its own program for the promotion of young talent, the DZD contributes to the training of internationally competitive young researchers. DZD NEXT offers young talents from medicine and natural sciences special programs and courses that teach important aspects of translational diabetes research. These include the international Diabetes Research School and DZD NEXT Young Talent Program as well as DZD Awards and research grants (see page 44).

Actively communicate and inform

Through numerous scientific articles in international and national journals as well as lectures and poster presentations at professional congresses, the DZD informs physicians, diabetes advisors, and researchers about the current results of its translational research.

The work of the DZD also focuses on providing comprehensive information about diabetes and diabetes prevention. That's why the national diabetes information portal diabinfo.de – a quality-checked and independent internet service covering all aspects of diabetes mellitus – was established. The information on **www.diabinfo.de** is aimed at people with diabetes and people at particular risk of diabetes as well as their families. The diabetes information portal also provides information for professionals.

*Up to **600,000 new cases of** type 2 diabetes every year.*

600,000
New cases

Facts about the DZD

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

Founding members and partners in the DZD are:

- German Diabetes Center (DDZ), Düsseldorf
- German Institute of Human Nutrition (DIfE), Potsdam-Rehbrücke
- Helmholtz Zentrum München
- Institute of Diabetes Research and Metabolic Diseases of the Helmholtz Zentrum München at the University of Tübingen
- Paul Langerhans Institute Dresden of the Helmholtz Zentrum München at the Carl Gustav Carus University Hospital and the Medical Faculty of TU Dresden (PLID)

Five associated partners at the universities in Heidelberg, Cologne, Leipzig, Lübeck, and Munich as well as project partners expand the spectrum of expertise of the DZD.

Foundation: 2009
Funding: 90% via federal government (BMBF), 10% via participating federal states

www.dzd-ev.de

HIGHLIGHTS OF 2020

DZDconnect awarded: The project "Graphs to Fight Diabetes" of the DZD has won a bytes4diabetes Award 2020.

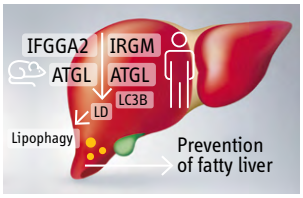
Public health: Evaluation of the Fr1da study suggests screening of children for islet cell autoantibodies to significantly reduce diabetic ketoacidosis (Ziegler et al., JAMA).

Fr1da

COVID*Graph: The DZD is participating in the construction of the COVID-19 Knowledge Graph in which publicly available information on COVID-19 as well as datasets from genome and molecular biology databases are linked and presented in a descriptive manner.

COVID-19 and common diseases: Fighting the COVID-19 pandemic and major diseases at the same time: A balancing act for biomedical scientists (Zeggini et al., Cell).

NAFLD: Additional genetic cause for non-alcoholic fatty liver disease discovered (Schwerbel, et al., Journal of Hepatology).



January · February · March · April · May · June

diabinfo
Das Diabetesinformationsportal

"diabinfo.de" goes online: The new National Diabetes Information Portal informs the public, patients, and professionals about diabetes prevention and therapy in an evidence-based and industry-independent manner.

Restoration of beta cell function: New drug combination restores beta cell function in animal model – potential for diabetes remission (Sachs et al., Nature Metabolism).

Novel in-situ platform unveiled: Even in early stages of type 2 diabetes, beta cell function declines (Cohrs et al., Cell Reports).

Brain and metabolism: Brain insulin sensitivity is linked to adiposity and body fat distribution (Kullmann et al., Nature Communications).

Transcriptional memory: Cells pass on metabolic transcriptional memory to their progeny (Bheda et al., Molecular Cell).

ERC Starting Grants: Maria Rohm and Michael Menden receive ERC Starting Grants. The award for young researchers is endowed with up to € 1.5 million.

DZD Diabetes Research School: Successful launch as an online format with six top speakers and 179 young talents from around the world.

New diabetes marker: Epigenetic changes precede the onset of diabetes (Ouni, M. et al., Diabetes).

Awards: DZD scientist Jens Brünning receives the Ernst Schering Prize 2020 and is honored by the European Association for the Study of Diabetes (EASD) with the EASD/Novo Nordisk Foundation Diabetes Prize for Excellence.

Virtual DDG Autumn Conference: DZD contributes with lectures and presents, among other things, diabinfo.de. Several DZD researchers are honored with awards and grants.

Virtual World Diabetes Day: About 8,000 interested people take part in the online event with medical lectures also from DZD researchers or view the videos of the event.

Fatty liver: DZD researchers decipher how protein protects against liver fat (Xu, et al., Liver International).

1st virtual DZD Community Meeting: Successful launch of the new online format to inform all DZD researchers about news and current research results.

July

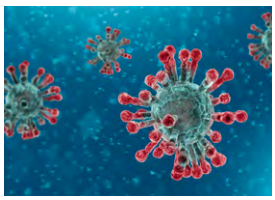
August

Biomarkers: Risk of diabetes complications increases with elevated levels of NT-proBNP (Birukov, et al., Diabetes Care).

Genetic cause: Protective mechanism for insulin resistance discovered in the brain (Schriever, et al, J Clin Invest).

September

October



COVID-19: Screening for SARS-CoV-2 antibodies in the Fr1da study shows a sixfold higher SARS-CoV-2 exposure rate in children in Bavaria (Hippich et al., Med).

November

December

Prediabetes subtypes: Six subphenotypes that differ in disease progression, diabetes risk, and development of complications identified (Wagner et al., Nature Medicine).

Risk factors of diabetes: Study shows link between long-term air pollution, obesity, and neuropathy (Herder et al., Environmental Health Perspectives).

TRANSLATIONAL RESEARCH FOR A FUTURE WITHOUT DIABETES

Subtypes detected in prediabetes. *In people with pre-type 2 diabetes, there are subtypes that differ in disease development, risk for type 2 diabetes, and development of complications. The new classification should help to reduce the risk of disease through targeted prevention.*

Diabetes does not develop from one day to the next. Often, people go through a longer preliminary stage of diabetes (prediabetes) in which blood glucose levels are elevated but they are not yet sick. Until now, it has not been possible to predict which patients will develop manifest diabetes and have an increased risk of complications or who will have only a harmless form of slightly higher blood glucose levels with no significant risk. A team of DZD researchers used cluster analysis to discover six distinct subgroups of people with prediabetes at different risk for diabetes and secondary diseases.

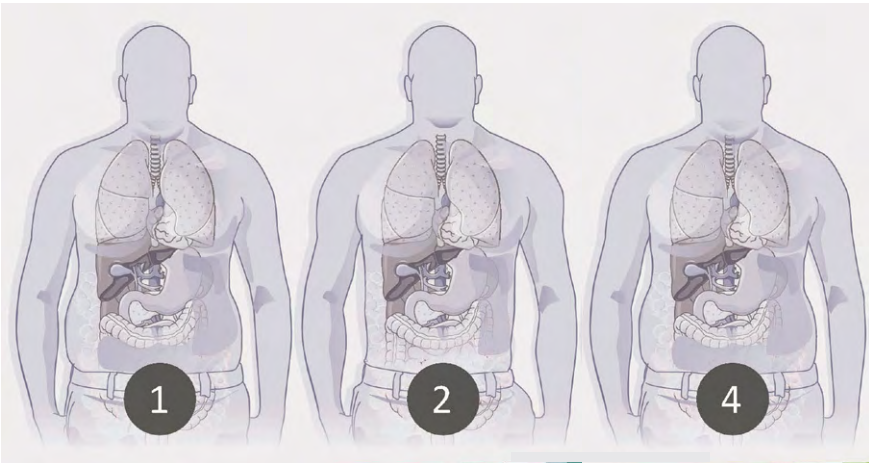
Prediabetes: Six different subtypes identified

The team studied the metabolism of people with prediabetes who were still considered healthy. The nearly 900 women and men came from the Tübingen Family Study and the Tübingen Lifestyle Program Study and have been intensively studied over the past 25 years. These extensive surveys provided the scientists with information on the type and amount of sugar and fat molecules in the blood, the fat content of the liver, and the distribution of body fat as well as the expression of certain genes that are crucial for the development of diabetes. These data were subjected to cluster analysis. **Summary: Based on certain characteristics, six clearly distinguishable clusters can be regarded as subtypes of prediabetes.**

Three of the newly identified subtypes (Clusters 1, 2, and 4) are characterized by a low risk of diabetes, while the remaining three (Clusters 3, 5, and 6) are characterized by an increased risk of diabetes. Representatives of Subtypes 1 and especially Subtype 2 are considered healthy and have a low risk of developing complications. Subtype 4 is made up of overweight individuals whose metabolism is still relatively healthy.

The other subtypes are associated with an increased risk of diabetes or serious secondary diseases: People classified as Subtype 3 produce too little insulin and are therefore at high risk of developing diabetes. People with Subtype 5

In people with prediabetes, there are six clearly distinguishable subtypes (clusters) that differ in disease development, risk for diabetes, and the development of complications. Three of the newly identified subtypes (Clusters 1, 2 and 4) are characterized by a low risk for diabetes and complications; the remaining three (Clusters 3, 5 and 6) are characterized by an increased risk.



have a pronounced fatty liver and also a high risk of diabetes because their bodies are resistant to the blood sugar-lowering effect of insulin. Individuals with prediabetes of Subtype 6 have a significantly higher risk of kidney damage – even before their diabetes becomes apparent. Mortality is also higher in this group.

But can the classification into six prediabetes subtypes be confirmed in other cohorts? In order to investigate this, the researchers extended the procedure to nearly 7,000 subjects in the Whitehall II cohort in London, where they also identified the six subtypes of prediabetes.

Step towards precision medicine

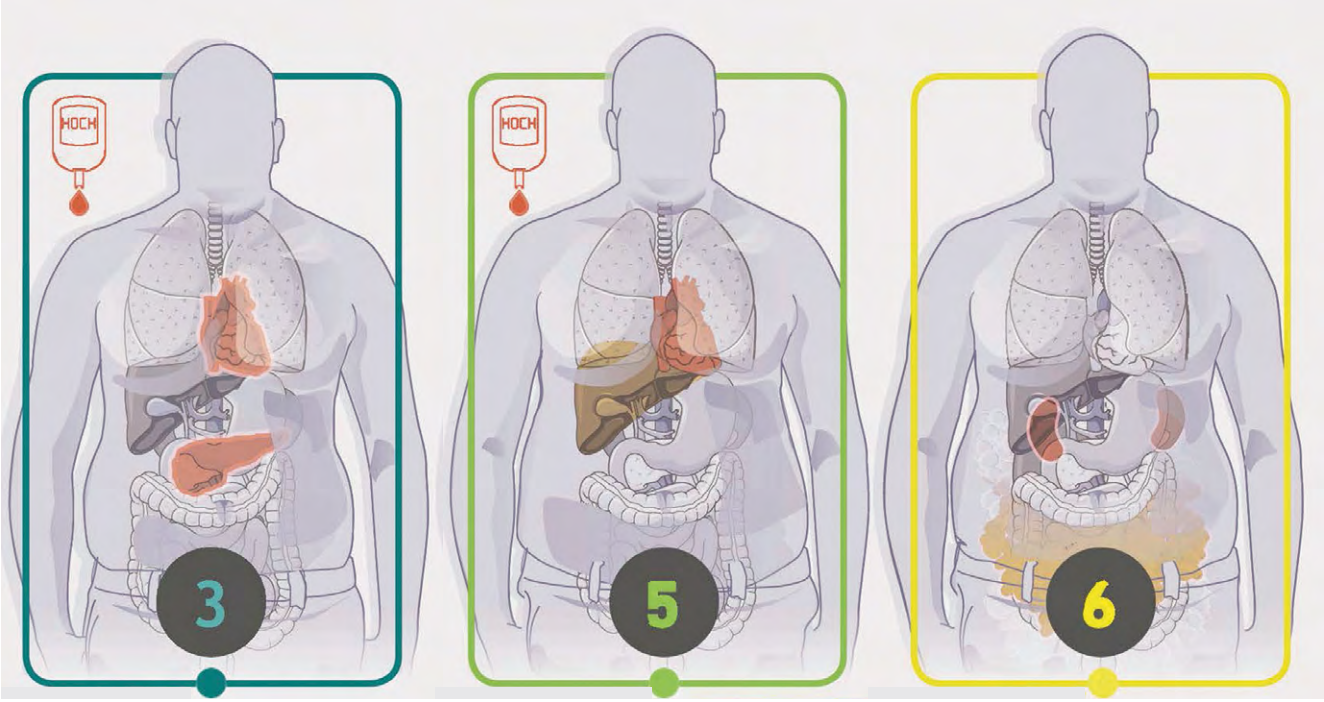
"By classifying people into subtypes, we will be able to assess more accurately than before whether someone is at low or high risk for diabetes or kidney disease. In the future, we want to develop prevention strategies so that people with a high risk can positively influence the further progression of their metabolic disorder," explains Robert Wagner from the Institute of Diabetes Research and Metabolic Diseases of the Helmholtz Zentrum München at the University of Tübingen.

The DZD intends to investigate how this can best be achieved in several hundred individuals who embody Subtype 3 or 5 and are at high risk of developing diabetes. To this end, men and women with prediabetes of subtype 3 and 5 will soon be recruited as subjects at the DZD study centers in Berlin, Düsseldorf, Dresden, Heidelberg, Cologne, Leipzig, Lübeck, Munich, and Tübingen. Half of the study group will fast at certain times, and the other half will receive a classical diet. The new study will help develop precise prevention and treatment strategies for people at high risk of diabetes.

More targeted prevention and treatment

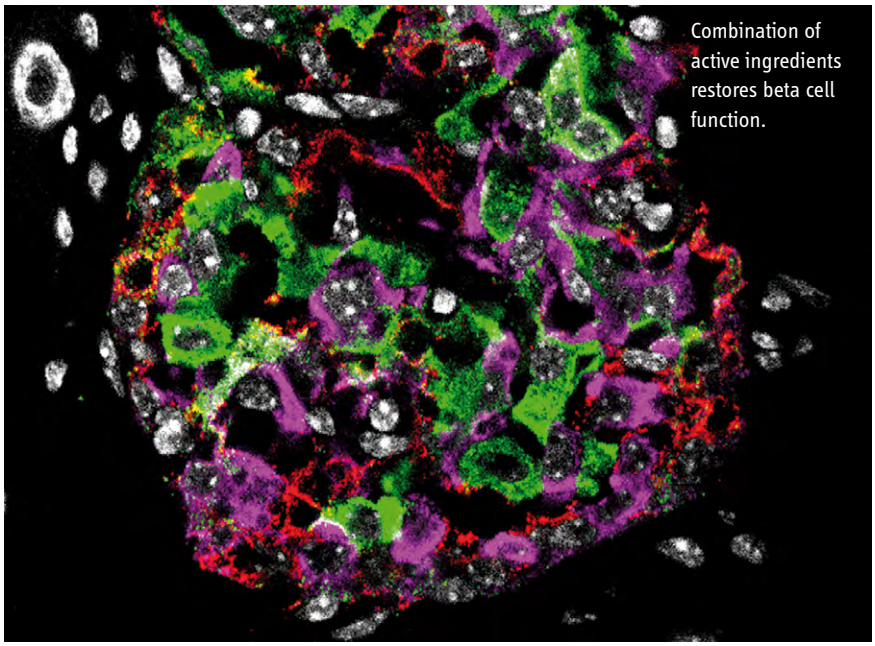
An important goal of the DZD is to find the right treatment for the right patient group at the right time. Last year we reported that DZD researchers had identified different diabetes subtypes with different risks for complications in the German Diabetes Study. These results and the recent discovery of subtypes in the pre-stage of type 2 diabetes are important steps towards precision medicine in diabetes and its complications.

Original publication: Wagner, R et al.: Pathophysiology-based subphenotyping of individuals at elevated risk for type 2 diabetes. Nature Medicine, DOI: 10.1038/s41591-020-1116-9



BETA CELL FUNCTION CAN BE RESTORED

One of the causes of diabetes *is the dedifferentiation of insulin-producing beta cells (i.e. loss of cell identity). In an animal model, a research group was able to restore beta cell function with the help of a new drug combination.*



Combination of active ingredients restores beta cell function.

Under certain conditions, beta cells revert to a less differentiated state, thereby losing their identity and most of their functions. As studies by the DZD show (p. 15), beta cell dysfunction is a hallmark of diabetes development. Previous therapies have not been able to stop the process. A research group has now succeeded in inducing redifferentiation and restoring beta cell function through a new combination therapy.

The group worked on a mouse model with streptozotocin-induced diabetes. The toxin kills insulin-producing beta cells and triggers severe diabetes. However, when the researchers injected several low doses of the toxin, some beta cells survived. These beta cells were dedifferentiated. Using the model, the scientists tested various active ingredients to see whether or not the function of the dedifferentiated beta cells could be restored.

Successful drug combination GLP-1/estrogen and insulin

The result: The administration of a conjugate of glucagon-like peptide-1 (GLP-1) and estrogen (provided by Novo Nordisk) and a long-acting insulin is particularly effective. This resulted in better success than treatment with the individual active ingredients. This was evident in both the normalization of blood glucose (glycemia) and glucose tolerance and the increase in pancreatic insulin content and beta cell numbers. This opens new avenues for potential mitigation of diabetes.

Even at high doses, the new active ingredient combination GLP1/estrogen did not trigger systemic toxicity in animal tests – a prerequisite for possible future clinical studies. Initial studies also show that the active ingredient combination is also effective in human beta cells: GLP-1/estrogen – but not GLP-1 or estrogen alone – have been shown to increase beta cell function in human cells, even when pancreatic islets are exposed to cytokine stress, a condition that impairs beta cell function.

"This is the first study to demonstrate beta cell redifferentiation through a targeted pharmacological intervention," says Prof. Dr. Heiko Lickert, director of the Institute of Diabetes and Regeneration Research at the Helmholtz Zentrum München and one of the coordinators of the DZD Academy on Beta Cells.

Original publication: Sachs, S. et al.: *Targeted pharmacological therapy restores β-cell function for diabetes remission.* Nature Metabolism, DOI: doi.org/10.1038/s42255-020-0171-3.

MALFUNCTION OF BETA CELLS CHARACTERIZES DIABETES DEVELOPMENT

***Even at an early stage of type 2 diabetes pathogenesis**, the function of insulin-producing beta cells deteriorates. The number of beta cells is unchanged at this stage.*

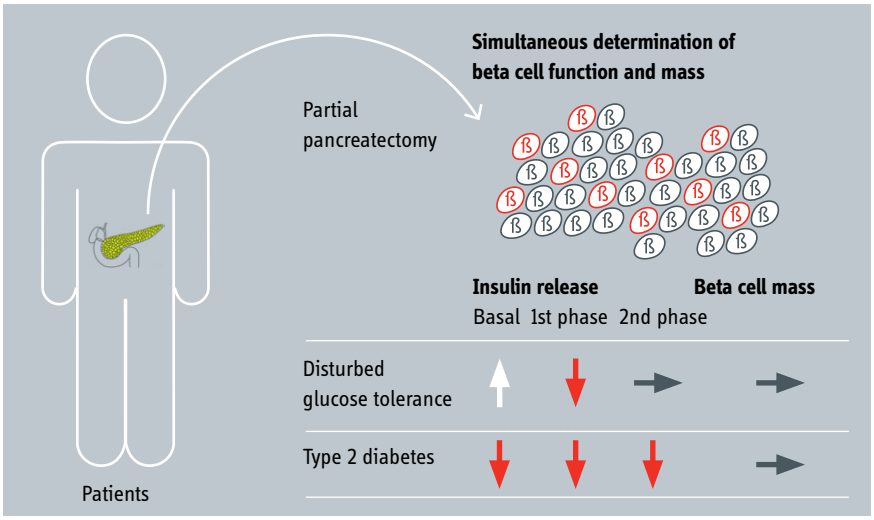
Type 2 diabetes is characterized not only by insulin resistance but also by the pancreas producing less insulin. Until now, however, it was unclear whether the inadequate insulin levels during the development of the disease were due to beta cell dysfunction or the loss of beta cell mass. In order to gain new insights, DZD researchers used a novel *in situ* platform to study the human pancreas in diabetes pathogenesis.

The group used freshly harvested pancreatic tissue for their studies in order to analyze the function of beta cells in their original organ environment and to determine beta cell volume. The tissues studied were from donors who had been metabolically phenotyped prior to removal of the pancreas. The study included people without diabetes (ND), people with impaired glucose tolerance (IGT), and people with type 2 diabetes (T2D), thus representing the entire developmental spectrum of T2D pathogenesis.

After preparing 120 µm thick tissue sections, glucose-induced insulin secretion was quantified under near-physiological conditions in the tissues of the subjects, and 3D cell morphology was examined in parallel on adjacent sections. With this new *in situ* approach to human pancreatic tissue sections, it was possible for the first time to simultaneously study beta cell mass and function and correlate these with the diabetes status of the patients.

"Our data show that beta cells exhibit significant functional deterioration and depletion even at early stages of T2D pathogenesis, when subjects have impaired glucose tolerance but are not yet diabetic. In contrast, the number of beta cells of the examined tissue remains unchanged at this stage of the disease progression," says Prof. Dr. Stephan Speier from the DZD partner Paul Langerhans Institute Dresden (PLID). "Our results thus suggest beta cell dysfunction as an initial feature of diabetes development."

Original publication: Cohrs, CM et al.: *Dysfunction of Persisting ß Cells Is a Key Feature of Early Type 2 Diabetes Pathogenesis Cell Rep.* DOI: doi.org/10.1016/j.celrep.2020.03.033



The study used pancreatic tissue sections from metabolically phenotyped subjects undergoing pancreatectomy in order to assess beta cell pathogenesis in the development of type 2 diabetes. They show beta cell dysfunction as an early hallmark of type 2 diabetes pathogenesis, which manifests as increased basal and absent insulin secretion in the first phase, although the beta cell mass is preserved. Source: PLID

INSULIN ACTION IN THE BRAIN DETERMINES FAT DISTRIBUTION IN THE BODY

Insulin action in the brain determines not only the success of a lifestyle intervention but also where fat is stored in the body.

How unhealthy body fat is depends mainly on where it is stored. If fat accumulates in the abdomen, this is particularly unfavorable. There, the fatty tissue releases numerous messenger substances that can affect blood pressure and trigger inflammation, among other things. On the other hand, when fat accumulates on the buttocks, thighs, and hips, it has no known negative effects on health.

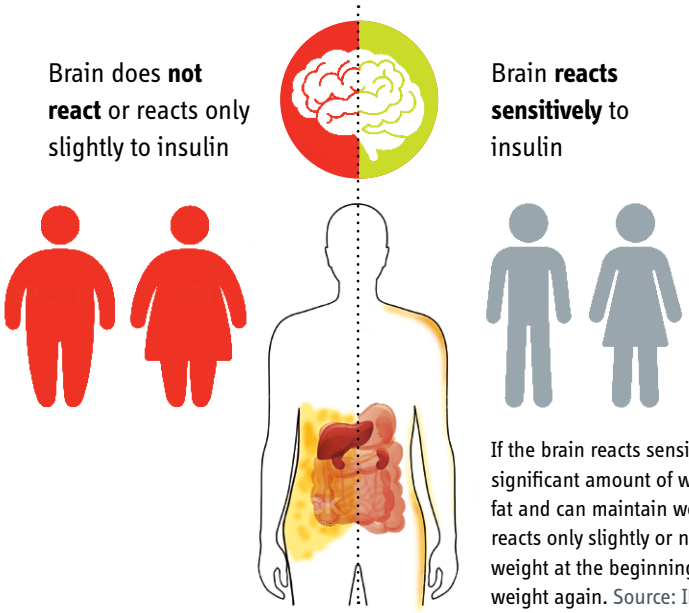
However, it is still unclear why fat is not stored in the same place in all people. Studies in the Tübingen Lifestyle Intervention Program suggested that the influence of insulin in the brain may play an important role here. If the brain was sensitive to the hormone, people lost significant weight and developed a healthier fat distribution. How the insulin sensitivity of the brain affects body fat distribution and weight in the long term was investigated by DZD researchers in a long-term study. Over a nine-year period, they studied 15 people in whom brain insulin sensitivity was determined before they began a 24-month lifestyle intervention.

High insulin sensitivity in the brain associated with reduction of abdominal fat

This showed that insulin action in the brain determines not only body weight but also the distribution of fat in the body. If the brain reacts sensitively to the hormone, you lose significant amounts of weight, reduce unhealthy belly fat, and can maintain your weight in the long term. Individuals with brain insulin resistance showed modest weight loss only during the first nine months of the program. After that, body weight and abdominal fat increased significantly again.

“Our study reveals a new and central mechanism that controls fat distribution in humans,” says Prof. Dr. Martin Heni of the DZD partner Institute of Diabetes Research and Metabolic Diseases of the Helmholtz Zentrum München at the University of Tübingen (IDM), summarizing the results. Because abdominal fat not only plays a role in the development of type 2 diabetes but also increases the risk of cardiovascular disease and cancer, the study results may also open up new approaches for therapeutic options beyond metabolic diseases.

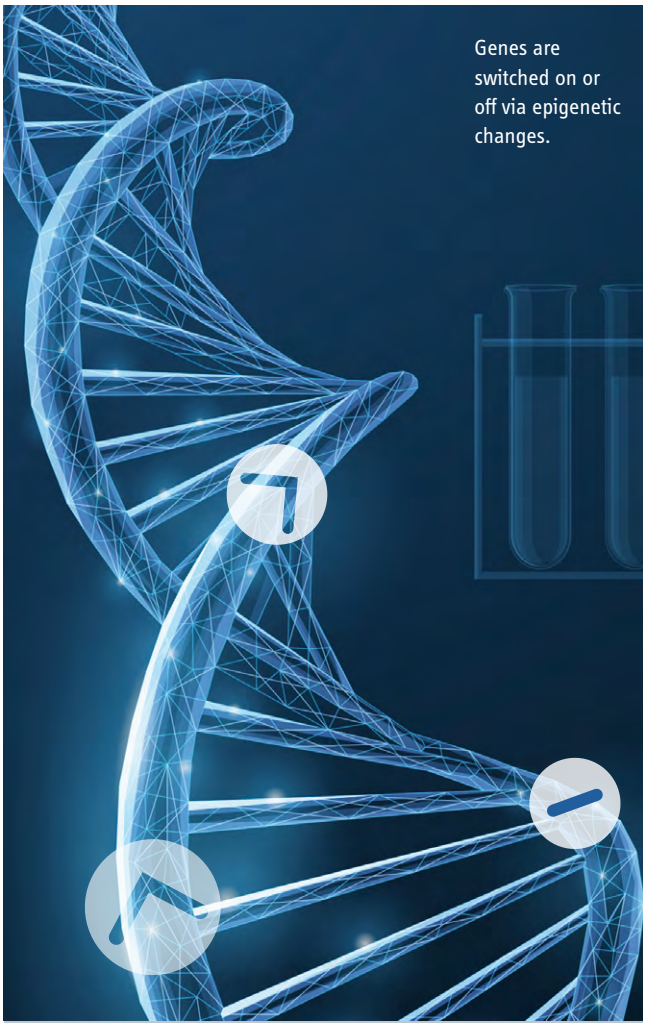
Original publication: Kullmann et al.: *Brain insulin sensitivity is linked to adiposity and body fat distribution*. Nature Communications, DOI: doi.org/10.1038/s41467-020-15686-y



If the brain reacts sensitively to the hormone, you lose a significant amount of weight, reduce unhealthy abdominal fat and can maintain weight in the long term. If the brain reacts only slightly or not at all to insulin, you only lose some weight at the beginning of the intervention and then gain weight again. Source: IDM

EPIGENETIC CHANGES PRECEDE THE ONSET OF DIABETES

***Epigenetic changes in the pancreatic islets of Langerhans can be detected** in affected individuals several years before the diagnosis of type 2 diabetes. These findings could help develop further diagnostic markers for type 2 diabetes.*



Genes are switched on or off via epigenetic changes.

In order to prevent the development of type 2 diabetes, it is important to identify people with an increased risk of the disease at an early stage. The DZD investigated the extent to which the development of the metabolic disease is associated with epigenetic changes in the cells of the islets of Langerhans in the pancreas. Epigenetics is the study of how the properties of genes are controlled without changing the DNA sequence itself. Like a kind of switch, methyl groups or other biomolecules can turn the activity of genes on or off. According to current research findings, lifestyle can also lead to epigenetic changes in genetic material.

The research team led by Prof. Annette Schürmann and Dr. Meriem Ouni identified nearly 500 candidate genes that showed early changes in DNA methylation and expression patterns in the islets of Langerhans in animal models with an increased risk of diabetes. It then tested which of these changes was also detected in humans before diabetes was diagnosed.

Potential new diagnostic markers for type 2 diabetes

To do this, the team looked for similar epigenetic changes in blood cells from subjects in the EPIC-Potsdam study (270 controls and 270 incident type 2 diabetes cases at an average of 3.8 years before diagnosis). Epigenetic modifications associated with subsequent diabetes diagnosis were revealed in 105 genes. Many of these changes are also seen in the islets of Langerhans of type 2 diabetes sufferers.

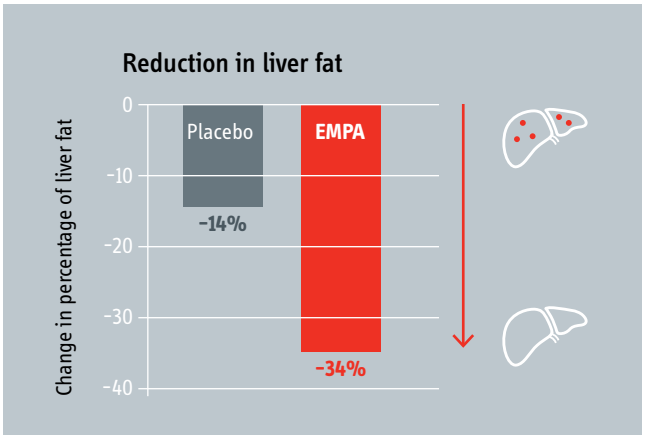
"Our findings may help to use some of these changes as diagnostic markers for type 2 diabetes," says DZD speaker Prof. Dr. Annette Schürmann of the German Institute of Human Nutrition (DIfE).

The researchers now want to investigate whether unfavorable DNA methylation patterns can be corrected by diets or certain drugs. They also want to test whether the identified markers differ in the different diabetes subtypes.

Original publication: Ouni, M. et al.: *Epigenetic Changes in Islets of Langerhans Preceding the Onset of Diabetes.* Diabetes, DOI: doi.org/10.2337/db20-0204

EMPAGLIFLOZIN: HOW THE LIVER GETS RID OF FAT

Recent studies show that the anti-diabetic drug empagliflozin can effectively reduce liver fat levels in type 2 diabetes. The compound could be used as a support for the treatment of non-alcoholic fatty liver disease in individuals with diabetes.



In patients with type 2 diabetes with short disease duration and good metabolic control, empagliflozin effectively reduces fat in the liver.

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in the Western world and among the leading causes of liver failure and liver transplantation. People with type 2 diabetes are particularly affected. About 70 percent of all individuals with type 2 diabetes have NAFLD, and up to 20 percent develop clinically significant fibrosis (abnormal proliferation of connective tissue in the liver with progressive loss of function). NAFLD is associated not only with increased risk of cardiovascular disease but also chronic kidney disease and diabetic neuropathy as well as increased mortality. These risks increase further in the presence of concomitant NAFLD and type 2 diabetes. To date, there is no generally accepted drug treatment recommendation for non-alcoholic fatty liver.

Therefore, several DZD sites conducted a clinical study to investigate the effects of the drug empagliflozin (EMPA) on liver fat content in subjects with type 2 diabetes and good metabolic control as well as short disease duration. The antidiabetic drug empagliflozin is one of the SGLT2 inhibitors and ensures that more glucose is excreted from the blood via the urine by inhibiting the transport protein SGLT2 – which is used in the kidneys to recover glucose from the urine.

EMPA lowers liver fat in well-controlled type 2 diabetes

The results of the clinical study show that empagliflozin can effectively reduce liver fat in type 2 diabetes and also induce some weight loss (through increased caloric excretion in the form of glucose via the kidneys). “The findings provide additional information that the drug lowers uric acid concentrations in the blood and increases levels of the adipose tissue hormone adiponectin. This results in improved adipose tissue function and fat metabolism in the liver,” explains Dr. Sabine Kahl of the DZD partner German Diabetes Center in Düsseldorf. Thus, the weight loss that occurs with empagliflozin treatment contributes to the reduction in liver fat content. Adiponectin-mediated mechanisms may also play an independent role here. Empagliflozin may thus contribute to the early treatment of non-alcoholic fatty liver in people with type 2 diabetes in clinical practice.

Original publication: Kahl, S, et al.: *Empagliflozin Effectively Lowers Liver Fat Content in Well-Controlled Type 2 Diabetes: A Randomized, Double-Blind, Phase 4, Placebo-Controlled Trial.* Diabetes Care. DOI: https://doi.org/10.2337/dc19-0641

EARLY DETECTION TEST FOR TYPE 1 DIABETES

Screening for islet autoantibodies makes it possible for the first time *to diagnose the disease before the first symptoms of type 1 diabetes appear (pre-symptomatic stages).*

Type 1 diabetes is the most common metabolic disease in children and adolescents – with sometimes life-threatening consequences. In order to be able to treat type 1 diabetes at an early stage, it is important to detect the disease as early as possible. For this purpose, appropriate diagnostics in childhood are necessary. This can help to prevent dangerous metabolic derailments (diabetic ketoacidosis) as well as the development of serious complications such as cardiovascular diseases or kidney damage.

In the Fr1da study, researchers led by Prof. Anette-Gabriele Ziegler from the DZD partner Helmholtz Zentrum München used the world's first early detection test for type 1 diabetes and studied its effects. From 2015 to 2019, they tested 90,632 children aged two to five years across Bavaria for the presence of auto-antibodies against insulin-producing beta cells (islet auto-antibodies).

Diagnosis via islet auto-antibodies

Pre-symptomatic type 1 diabetes can be diagnosed with the detection of at least two islet auto-antibodies in the blood. The presence of these antibodies indicates that the body's immune system is attacking the insulin-producing beta cells of the pancreas – the cause of type 1 diabetes. These antibodies can be detected in the blood years before the first symptoms of the disease appear.

Using a novel approach, the research group classified the children who had antibodies in their blood into three stages: Stage 1 (normoglycemia), Stage 2 (dysglycemia), and Stage 3 (clinical type 1 diabetes). This classification allows for individualized progress monitoring and treatment of the children.

Prevent diabetic ketoacidosis

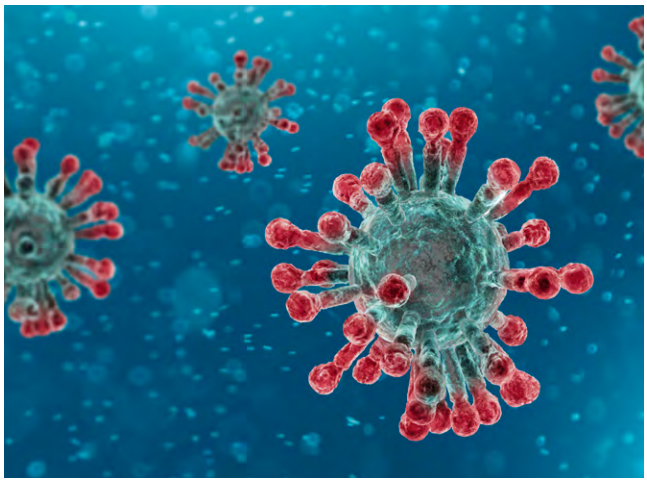
Examination of the 90,632 children revealed pre-symptomatic type 1 diabetes in 280 children (0.31%). Of these 280 children, 24.9% developed clinical type 1 diabetes (Stage 3). Because families were informed and sensitized about the risk in advance, dangerous metabolic derailment was avoided in most cases. Only two children developed diabetic ketoacidosis.

The results suggest that an early detection test may prevent progression from pre-symptomatic type 1 diabetes to dangerous diabetic ketoacidosis. The study thus provides the basis for formulating new guidelines for diagnostic procedures and discussing recommendations for the inclusion of screening in the catalog of benefits for standard preventive care.

Original publication: Ziegler, A. et al.: *Yield of a public health screening of children for islet autoantibodies in Bavaria, Germany.* JAMA, DOI:10.1001/jama.2019.21565

CORONAVIRUS SARS-COV-2 AND DIABETES

***The German Center for Diabetes Research** is involved in various research initiatives and studies on the SARS-CoV-2 coronavirus. A special focus is on COVID-19 and diabetes.*



Medical research and clinical care are particularly challenged in combating the SARS-CoV-2 pandemic. Together with the other German Centers for Health Research (DZG), the DZD has supported the search for suitable drugs for the treatment of COVID-19. The DZD is also participating in the establishment of the Lean European Open Survey on SARS-CoV-2 Infected Patients (LEOSS) case registry. Clinical data from patients with SARS-CoV-2 infection are collected there. All DZG cooperate in the project initiated by the German Society for Infectious Diseases together with the German Center for Infection Research – with the respective focus on cancer, cardiovascular, metabolic, infectious, pulmonary, and neurodegenerative diseases. For example, questions can also be investigated as to whether and how pre-existing conditions influence the course of the disease. The DZD has compiled key diabetes data that will be collected in LEOSS and is participating in patient recruitment at partner sites. One goal is to determine how obesity and diabetes affect the progression of the disease.

Evaluations of recent studies already show that severe obesity, diabetes, and elevated blood glucose levels increase the risk for severe courses of COVID-19. The DZD has established a COVID registry to investigate the impact of prediabetes and diabetes on mortality.

More infections in children than known

Area-wide antibody tests against the new coronavirus SARS-CoV-2 can help to obtain realistic values about the frequency of infection with the pathogen. Researchers from the "Fr1da plus" screening study, which tests children in Bavaria for early-stage type 1 diabetes, have tested blood samples from the study for the presence of antibodies to SARS-CoV-2. The result: In Bavaria, significantly more children were infected with SARS-CoV-2 coronavirus than reported – six times as many during the first wave and three to four times as many during the second wave (between October 2020 and February 2021).

COVID*Graph and diabinfo.de: Making knowledge visible

In the COVID*Graph project, publicly available literature sources, patent specifications for COVID-19, and datasets from genome and molecular biology databases will be linked and graphically displayed in a Knowledge Graph. The goal is to help researchers quickly and efficiently navigate the diverse data on COVID-19. The DZD data and knowledge management team is one of the lead partners in the project. Because people with diabetes have a higher incidence of severe complications from SARS-CoV-2 infection, DZD researchers are expanding data integration technology to include diabetes-related data.

It is also important to provide targeted information to people with diabetes. The national diabetes information portal diabinfo.de has therefore set up a special page on "Diabetes and Coronavirus", where, among other things, frequent questions on the subject are answered.

These are just a few examples of how the research of the DZD is helping to combat the pandemic. The DZD will continue to work on this in 2021.

PRIZES AND PUBLICATIONS

*The **interdisciplinary and translational approach of** the DZD also led to excellent scientific achievements in 2020.*

Publications
This is demonstrated by the high number of publications in renowned journals. Last year, there were 478 publications in peer-reviewed journals. The complete lists of DZD publications can be found at:
www.dzd-ev.de/en/latest/featured-papers

Prizes, awards, and honors

Award winners	Awards
Prof. Dr. Jens Brüning, Cologne	Novo Nordisk Foundation Diabetes Prize for Excellence (EASD); Ernst Schering Prize
Prof. Dr. Carolin Daniel, Munich	Nils-Ilja-Richter Award 2019, IUIS Early Career Research Prize in Vaccinology
Mohamed Elhadad, Munich	Paul Dudley White International Scholar Award
Dr. Louise Fritsche, Tübingen	Hellmut Mehnert Project Funding
Dr. Sofiya Gancheva, Düsseldorf	Silvia King Prize
Prof. Dr. Reinhard Holl, Ulm	DDG Gold Badge of Honor
Prof. Dr. Martin Hrabě de Angelis, Munich	IMPC Award of Excellence
Dr. Alexander Jarasch, Munich	bytes4diabetes Award
Dr. Sabine Kahl, Düsseldorf	Promotion Award 2020 of the Dr. Eickelberg Foundation for Biomarker Research
Dr. Natalie Krahmer, Munich	Novo Nordisk Future Leader Award (EASD)
Prof. Dr. Heiko Lickert, Munich	Werner Creutzfeldt Prize
Dr. Michael Menden, Munich	ERC Starting Grant
Manuela Neuenschwander, Düsseldorf	Stephan Weiland Prize 2020
Dr. Meriem Ouni, Potsdam-Rehbrücke	Silvia King Prize
Prof. Dr. Paul Pfluger, Munich	ERC Consolidator Grant
Dr. Maria Rohm, Munich	ERC Starting Grant
Prof. Dr. Matthias Tschöp, Munich	EMBO Membership
Oana Patricia Zaharia, Düsseldorf	Sponsorship Award of the DDG
Prof. Dr. Dan Ziegler, Düsseldorf	Hans Christian Hagedorn Project Funding
Elric Zweck, Düsseldorf	Menarini Project Funding

INFLUENCE OF GENETICS AND EPIGENETICS ON THE DEVELOPMENT OF DIABETES

Coordination: Annette Schürmann, Johannes Beckers, Martin Hrabě de Angelis

Obesity, insulin resistance, and type 2 diabetes (T2D) *are caused by an interplay of genetic, epigenetic, and lifestyle factors.*

In order to identify new candidate genes for diabetes, DZD researchers in the International Mouse Phenotyping Consortium (IMPC) studied metabolic functions of mouse models, each of which lacked a precisely selected gene. They were thus able to identify 974 genes, the loss of which has effects on glucose and fat metabolism. By matching with genomic data collected in humans, 23 genes appeared to play a role in diabetes in humans. In a second approach, the genomes of five mouse strains (Collective Diabetes Cross, CDC) with different diabetes risk were mixed by crosses, the offspring were examined with regard to their genome, body weight, glucose concentration, and various metabolic parameters, and 15 new disease genes were identified, including by means of bioinformatic analyses. Most of these are also relevant in humans.

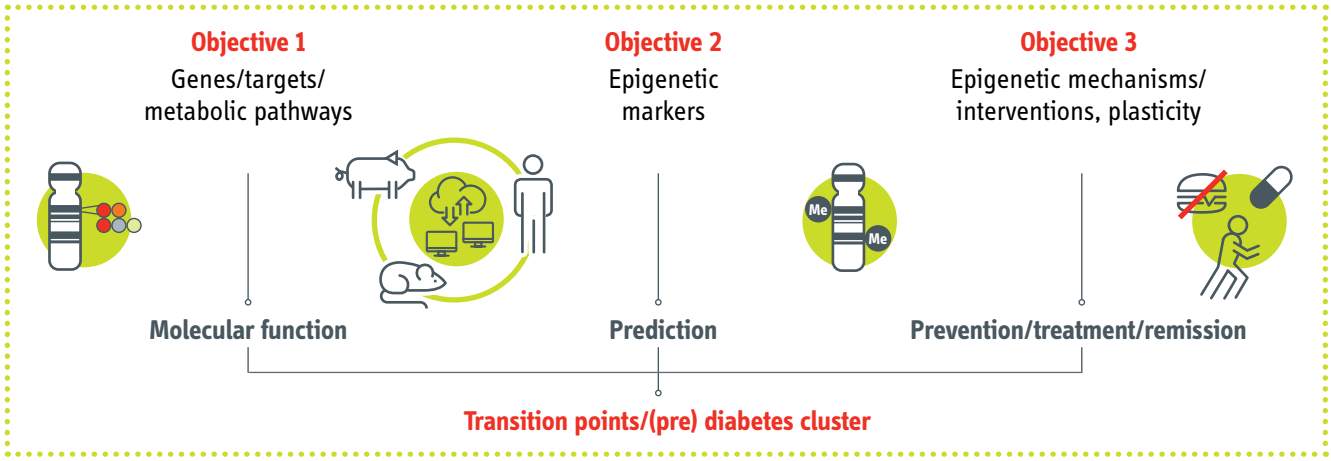
New candidate genes

Further investigation is currently underway to determine the functions of the genes identified by the overlay of IMPC or CDC and human data. One example is the Notch ligands Delta-like 1 (DLL1) and DLL4, which are specifically expressed in beta cells. Their loss in adult beta cells improves glucose tolerance. Glucose-stimulated insulin secretion and hyperglucagonemia are increased. On the other hand, the overexpression of the intracellular domain of DLL1 induces the opposite effects.

Based on the CDC, researchers at the DZD have discovered new genes that play a role in the development of fatty liver. The genes IRGM, Ifgga2 and Ifgga4 are responsible for the production of regulatory proteins of the family of immunity-related GTPases in humans and in mice; these counteract fat accumulation in the liver. However, a genetic modification leads to the production of fewer of these proteins.

Genome-wide association studies (GWAS) showed that the DUSP8 gene is associated with T2D. DZD research suggests that in men, a genetic variant of the gene may impair the brain's response to the hormone insulin, thereby increasing the risk for T2D.

Genes appear to play only a minor role in weight reduction through lifestyle interventions in children with overweight or obesity. This is the result of a DZD study. Examination of approximately 1,200 children during an inpatient lifestyle intervention program identified only five single nucleotide



Other members of the Academy

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polymorphisms (SNPs) significantly associated with a reduction in body weight in response to lifestyle intervention.

Epigenetic changes

But it is not only the genetic code itself that influences the risk of diabetes. Various DZD studies have shown that lifestyle alters the activity state of genes (epigenetics). Last year, the DZD was able to demonstrate that epigenetic changes in the pancreatic islets of Langerhans can be detected in affected individuals several years before the diagnosis of T2D. These findings could help develop further diagnostic markers for type 2 diabetes (see page 17).

DZD researchers have already shown in animal models that parental lifestyle influences the phenotype of the offspring through epigenetic mechanisms. Research in 2020 suggests that there are other transgenerational mechanisms. The results are expected to be published in 2021.

Treatment of epigenetic disorders

Research into treatments for epigenetically induced disorders is an important aspect of the Academy. DZD researchers have identified changes in DNA methylations that affect the activity of genes in skeletal muscle of obese individuals after bariatric surgery and which contribute to improved insulin sensitivity. It is important to clarify which other non-invasive interventions elicit comparable epigenetic effects. To be able to study this and to analyze the reversal of epigenetic transmission of obesity and hyperglycemia across generations, the DZD is working on establishing a suitable mouse model.

Physical exercise increases glucose uptake in skeletal muscle and improves glycemic control. A key regulator of transcription of the glucose transporter HDAC5. Lower HDAC5 levels contribute to exercise-mediated improvement in insulin sensitivity.

Achieved

- Identification of epigenetic changes in islets of Langerhans before the onset of T2D. (potential new diagnostic markers for T2D).
- New gene functions discovered: DLL1- and DLL4-mediated Notch signaling is essential for adult pancreatic islet homeostasis. IRGM or Ifgga2/4 induce lipophagy and decrease fat storage in the liver.
- Project start to build a mouse model for reversing the epigenetic transmission of obesity and hyperglycemia across generations.

Objectives for 2021

- Identification of additional genes relevant to metabolism and clarification of their molecular function.
- Identification of new factors for intergenerational inheritance.
- Start of investigation of differences in microRNAs and DNA methylation patterns in prediabetes clusters as well as in the SIDD and SIRD diabetes clusters.
- Data analysis of epigenetically inherited markings.

● Target achieved
○ Ongoing project

PROTECTION AND REGENERATION OF BETA CELLS

Coordination: Michele Solimena, Heiko Lickert, Annette Schürmann

***In type 1 diabetes as well as in the advanced stages of type 2 diabetes, the insulin-producing beta cells are lost** or no longer function properly. To date, there is no way to halt or reverse the progression of beta cell loss. The DZD is working on methods to better protect beta cells or to restore or replace them.*

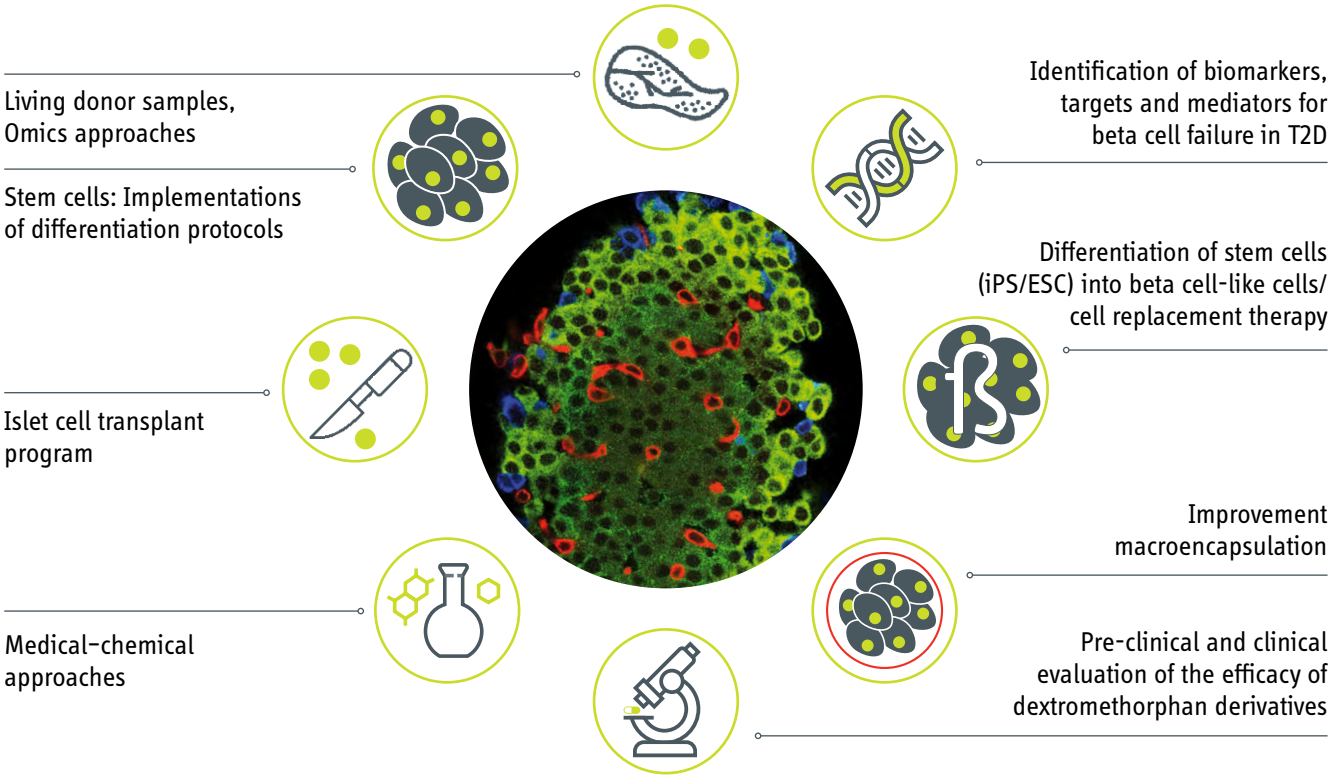
To this end, the DZD is investigating molecular mechanisms that lead to beta cell failure and working on improved protocols for the differentiation of stem cells into beta cell-like cells as well as on new approaches to beta cell or islet cell transplantation. It also conducts research on pharmacological therapies to protect, restore, or regenerate functional beta cell mass.

Unique biobank for pancreatic tissue

In order to gain insights into the mechanisms responsible for the progression of type 2 diabetes, the DZD is establishing the "Human Islet Biobank". This will collect pancreatic tissue and blood samples from metabolically characterized living donors who have undergone total or partial pancreatic removal. Various research projects are already working with the samples collected in the biobank in order to use them to gain new insights, particularly into the pathogenesis of type 2 diabetes.

Regeneration of beta cells

With the help of samples from this biobank, among others, the DZD was able to show for the first time last year that the function of insulin-producing beta cells deteriorates in an early phase of type 2 diabetes pathogenesis (see page 15).



Other members of the Academy

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Volker Burkart
Ünal Coskun
Anthony Gavalas
Jantje Gerdes
Felicia Gerst
Anne Grapin-Botton
Tilman Grune
Eckhard Lammert
Barbara Ludwig
Nikolay Ninov
Henrik Semb
Stephan Speier
Susanne Ullrich
Thilo Welsch
Eckhard Wolf

A new combination of active ingredients may be suitable for counteracting this dedifferentiation of beta cells. Researchers at the DZD demonstrated for the first time in mice with chemically induced T1D that the combination of GLP-1 and estrogen allows for redifferentiation and a restoration of beta cell function. This opens up new avenues for possible diabetes remission (see page 14).

Beta cell replacement therapy

The DZD is working on different approaches to better protect beta cells or to restore or replace them. One approach is based on regenerative processes in which insulin-producing beta cells are generated from stem cells. For example, DZD scientists improved an *in vitro* protocol for differentiating pluripotent stem cells into beta cells with better glucose regulation and insulin production. This is an important step towards beta cell replacement therapy.

Transplants and artificial pancreas

Another way to restore the body's own insulin production is to transplant a functioning pancreas or its islet cells. Despite significant progress in this field, the shortage of donor organs and the need for permanent immunosuppression limit the possibilities of transplantation. Researchers at the DZD are therefore also working on the development of an artificial pancreas, a 'bioreactor'. The bioreactor contains healthy functional islet cells that independently measure blood glucose levels and produce insulin with precision.

Pharmacological therapies

Studies show that the active ingredient dextromethorphan protects islet cells of the pancreas and can lower blood sugar. The DZD is working to modify dextromethorphan so that it can produce antidiabetic and beta cell-protective effects without affecting the central nervous system. An initial goal in this project was achieved, and two U.S. patents granted for such molecules.

Achieved

- Identification of beta cell dysfunction as an early hallmark of the pathogenesis of type 2 diabetes.
- Restoration of beta cell function by a combination of drugs in animal models.
- Publication of an improved *in vitro* protocol for the differentiation of pluripotent stem cells into beta cells with better glucose regulation and insulin production.
- Genetic modification of pigs: Islet cells locally inhibit the immune system. The long-term goal is to make xenotransplantation possible.
- Publication of study results identifying signaling pathways altered by the hepatokine fetuin-A in beta cell differentiation.

Objectives for 2021

- Transcriptomic and epigenetic mapping of pancreatic islets and beta cells for glucose tolerance.
- Elucidation of beta cell differentiation and maturation mechanisms.
- Further expansion of the islet cell transplantation program.
- Identification of novel targets to increase beta cell insulin sensitivity.
- Optimization of the active ingredient dextromethorphan (DXM) to prevent diabetes progression without side effects on the brain.
- Screening islet cells from humans with COVID-19 for SARS-CoV-2 infection.

● Target achieved ○ Ongoing project

AUTOIMMUNE DISEASE TYPE 1 DIABETES

Coordination: Carolin Daniel, Anette-Gabriele Ziegler, Ezio Bonifacio

T1D

Type 1 diabetes is an autoimmune disease that occurs primarily in childhood and adolescence. *The goal is to better understand the underlying mechanisms of the disease and thus develop therapies that target the immune system to correct immune deficiencies and prevent the destruction of beta cells in the pancreas.*

Type 1 diabetes (T1D) is an autoimmune disease in which the body's immune defense system forms auto-antibodies and destroys insulin-producing cells. T1D Academy research includes healthy state, pre-symptomatic T1D (detection of autoantibodies without symptoms), and early stages of symptomatic disease.

Risk markers and subtypes of type 1 diabetes

The team has already developed a genetic risk score and introduced it into different population screenings in Europe. In addition, comprehensive risk assessments for auto-antibodies are performed in genetically susceptible children. Evaluations of the Fr1da study show that screening children for auto-antibodies can help prevent diabetic ketoacidosis (see page 19).

In the current COVID-19 pandemic, the resources of the T1D Academy are also being deployed beyond its proper field of research. For example, established T1D studies for children have been and are being used to screen samples for antibodies to SARS-CoV-2 as well. Two recent studies addressing immune mechanisms have demonstrated the importance of early changes in T cells and their contribution to the development of autoimmunity against islet cells.

In order to study human T1D pathogenesis and understand pancreatic heterogeneity, the team established a platform for human pancreatic tissue sections. A proof-of-concept study has now demonstrated that human pancreatic tissue sections are suitable to investigate the underlying cellular mechanisms of T1D in an *in situ* setting and to provide a detailed profile of the pancreatic pathology of each donor.

Development of immunomodifying therapeutic strategies

Regulatory T cells (Tregs) prevent excessive immune responses in healthy individuals. However, in autoimmune diseases such as T1D, they are limited in function. Two recent studies demonstrated the importance of early changes in T cells and their involvement in the development of islet cell autoimmunity. This suggests a potentially causative role of early Treg plasticity and instability in immune activation and progression.

Markers for T1D risk and subtypes
- Pre-symptomatic disease
- Subtypes
- Heterogeneity of the pancreas

Development of immune modifying therapy strategies
- Mouse models
- New targets and mechanisms

Influence of environmental risk factors
- Viral infections
- Inflammations

Other members of the Academy

Reinhard Holl
Karsten Kretschmer
Nikolay Ninov
Teresa Rodriguez-Calvo
Michele Solimena
Stephan Speier

In addition, by analyzing the underlying mechanisms of autoimmunity, potential targets for future immune-modifying therapeutic approaches were identified, and new mouse models were developed for the pre-clinical testing of these strategies.

Influence of environmental risk factors on the immune system

Environmental triggers for T1D include early viral infections and maternal T1D. DZD researchers study how immune cells and beta cells are altered in early childhood. Models include the interaction between immune cells and beta cells in the zebrafish and mouse pancreas during early postnatal development, the effects of coxsackievirus B infection on beta cells, early childhood immunity in the offspring of mothers with and without T1D, and innate immune aging in infant immune cells.

Studies on cells from genetically vulnerable children confirmed the link between viral infections and autoimmunity. In addition, various metabolic and mitochondrial stresses that may occur during infection have had wide-ranging effects on T cells.

Previous findings indicate the presence of an interferon (IFN) signature in T1D; this is capable of inducing chronic inflammation and impairing beta cell function. Last year, it was shown that the expression of type 1 interferon response markers is associated with immune infiltration and viral infection in T1D. The results are expected to be published in 2021.

Achieved

- Evaluation and publication of the Fr1da study (screening of more than 90,000 children in Bavaria for auto-antibodies): Detection of at least two islet cell auto-antibodies in the blood is useful for diagnosing presymptomatic T1D and may help prevent diabetic ketoacidosis as well.
- Screening for antibodies to SARS-CoV-2 in the Fr1da study showed that about six times more children in Bavaria were infected in the first wave of the pandemic than was originally reported.
- Identification of T cell-specific immune mechanisms in early stages of islet autoimmunity.
- Investigation of beta and alpha cell function in pancreatic tissue sections from young organ donors revealed the expression of interferon response markers in islet cells in donors with T1D.

Objectives for 2021

- Identification of age-related risks for islet cell autoimmunity in children at increased genetic risk.
- Continuation of the investigation of test samples from the Fr1da study for antibodies to SARS-CoV-2.
- Preparation of the Fr1da study in Saxony: Screening for presymptomatic T1D

● Target achieved ○ Ongoing project

INSULIN ACTION AND RESISTANCE IN THE BRAIN

Coordination: Hubert Preißl, Jens Brüning, Cristina García Cáceres, Martin Heni

The brain plays an important role in the development of obesity and type 2 diabetes. *The DZD is investigating the connection between brain and metabolism. Research spans the entire lifespan – from the fetus to the elderly.*

The brain is the most important control organ for behavior, cognition, and metabolism. The Academy is working to unravel the causal interaction of brain and peripheral organs in order to discover the specific brain-related pathomechanisms of diabetes and define transition points of impaired brain processes specifically in (pre)diabetes subtypes.

Academy members have access to state-of-the-art neuroimaging tools for animals and humans. The Academy focuses on the following main objectives:

1. The identification of the progression of brain insulin resistance during the pathogenesis of diabetes.
2. The elucidation of glia/neuron interactions and neurocirculations involved in CNS metabolic control and the clarification of their clinical significance in humans.
3. Deciphering of the pathophysiological link of diabetes with cognition and major complications such as neurodegeneration and psychiatric disorders.

Effects of insulin resistance in the brain

Insulin action in the brain influences where fat is stored in the body. If the brain is sensitive to the hormone, people not only lose more weight but also show a healthier fat distribution; this is because less unhealthy visceral fat (belly fat) is stored. Insulin sensitivity also affects the distribution of body fat in the long term (see page 16). There is also increasing evidence that inflammation in the hypothalamus contributes to obesity-associated insulin resistance in this area.

Genetic causes

However, genetic causes may also predispose a patient to the development of insulin resistance in the brain. DZD researchers have found that in men, a genetic variant of the gene DUSP8 impairs the response of the brain to the hormone insulin and can thus increase the risk of type 2 diabetes.

But peripheral insulin sensitivity also has an influence on the brain. Research shows that insulin resistance in the body promotes cognitive decline, specifically in the area of memory. Treatments of diabetes that improve insulin sensitivity may therefore delay or even prevent cognitive decline in patients with diabetes.

Interaction of the maternal metabolism with brain development in the fetus

It is not yet known when insulin sensitivity changes in the brains of overweight people. However, important decisions could be made at a very early stage. Human development – physiological, metabolic, and cognitive – begins *in utero*. In basic science studies, the DZD investigates how exactly maternal nutrition can influence the behavior of offspring later in life.

Preliminary results show that when nursing mice were fed high-fat diets during the suckling period, certain circuits in the young that suppress appetite did not mature properly. Recent studies have also shown that a high-fat diet in nursing mice the suckling period also induces a long-lasting change in gene expression in the brain of the offspring.

Other members of the Academy

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Sofiya Gancheva
André Kleinridders
Stephanie Kullmann
Rachel Lippert
Soyoung Park
Paul Pfluger
Sebastian Schmid
Sophie Stecolorum
Marc Tittgemeyer
Eckhard Wolf

Altered brain response in the pathogenesis of diabetes

Causes

Mechanisms of diabetes-related changes in neurons and astrocytes.

Fetal origins of diabetes.

Consequences

Mapping of neurocircuits for CNS-dependent control of overall metabolism.

Treatment of insulin resistance in the human brain

Astrocytes and neurons

There are still many unanswered questions about the interaction between brain and metabolism. Research suggests that essential metabolic and behavioral processes are regulated not only by neural pathways but also by other cell types in the brain (e.g., astrocytes). DZD researchers showed that these react to insulin and leptin and thus actively control the uptake of sugar into the brain. These cells can also develop insulin resistance – with unfavorable effects on the whole organ.

But another cell type also seems to play an important role: Studies show that short-term feeding of mice with a high-fat diet activates certain neurons (PNOCARC neurons). If these neurons are removed, the mice eat less and are protected from obesity.

Achieved

- Research shows that brain insulin sensitivity is associated with obesity and body fat distribution.
- Identification of genetic causes of insulin resistance in the brain.
- Continuation of the recruitment of subjects for the Dopamine Action on Metabolism Depending on Genetic Heterogeneity (DAG)-Study. Because of the Corona pandemic, recruitment has not yet been completed.

Objectives for 2021

- Investigation of the effect of empagliflozin on hypothalamic insulin sensitivity in people with prediabetes.
- Investigation of the role of astrocytes in the control of brain energy metabolism in physiological and dietary obesity.
- Generate of astrocyte-specific knockout mouse lines.
- “Brain and Diabetes” special issue in Frontiers in Endocrinology (Editors: Preissl/ García Cáceres/Lippert).

Target achieved

Ongoing project

DIABETES AND NON-ALCOHOLIC FATTY LIVER DISEASE

Coordination: Michael Roden, Andreas Birkenfeld, Norbert Stefan

Obesity, insulin resistance, and type 2 diabetes *increase the risk of non-alcoholic fatty liver disease (NAFLD) and other complications. However, too much fat in the liver also has a negative effect on glucose metabolism and may contribute to the development of T2D. The DZD is investigating the link between NAFLD and T2D.*

NAFLD is now the most common liver disease in Western countries – and the trend continues to rise. In Germany, about 18 million people suffer from NAFLD; of these, about 3.3 million have non-alcoholic steatohepatitis (NASH). NAFLD is a concomitant and secondary disease of T2D – more than 70% of all people with T2D also have NAFLD. On the other hand, people with NAFLD have an increased risk of developing not only advanced liver diseases (e.g., cirrhosis and liver cancer) but also cardiovascular diseases and T2D.

Identification of biomarkers

In order to improve risk stratification, DZD researchers are working to identify biomarkers as well as genetic and epigenetic factors. This should enable the diagnosis of NAFLD at an early stage and thereby halt or even reverse further progression of the disease. DZD researchers demonstrated that the variant of a gene is related to the recently described diabetes Subtype of severe insulin-resistant diabetes (SIRD), which is associated with an increased risk of fatty liver disease. They also characterized specific epigenetic modifications and miRNA expression profiles in NAFLD.

Identification of mechanisms

Another focus is to identify mechanisms that contribute to the pathogenesis and progression of NAFLD and its co-morbidities. Last year, DZD researchers identified a new mechanism that may contribute to the pathogenesis of NAFLD. The genes IRGM, Ifgga2, and Ifgga4 are responsible for the production of regulatory proteins of the family of immune-associated GTPases in humans and in mice; these counteract fat accumulation in the liver. The proteins increase the specific breakdown of fat in the liver (lipophagy) (see page 22). However, in humans as well as in mice with fatty liver, the transcription of the genes is impaired.

Treatment of fatty liver

The DZD is researching drug approaches for the treatment of fatty liver disease. In a randomized Phase 4 study, the SGLT2 inhibitor empagliflozin (EMPA) led to a greater reduction in liver fat content of T2D patients than placebo (see page 18). In the past year, the DZD has continued to prepare the COMBAT_T2_NASH study. The multicenter study will evaluate the effect of treatment with the GLP1 receptor agonist semaglutide and empagliflozin or empagliflozin monotherapy compared with placebo on NASH in T2D (see also multicenter studies). COMBAT_T2_NASH received regulatory approval, and 23 study sites were recruited.

Special diets help reduce liver fat

New treatment concepts also rely on weight loss and dietary approaches. Several randomized controlled studies have already demonstrated the potential of dietary changes to reduce liver fat content. In particular, a high-protein, low-calorie diet can melt harmful liver fat – and do so more effectively than a low-protein diet. DZD researchers demonstrated the efficacy of a high-protein diet in lowering liver fat content prior to bariatric surgery.

Other members of the Academy

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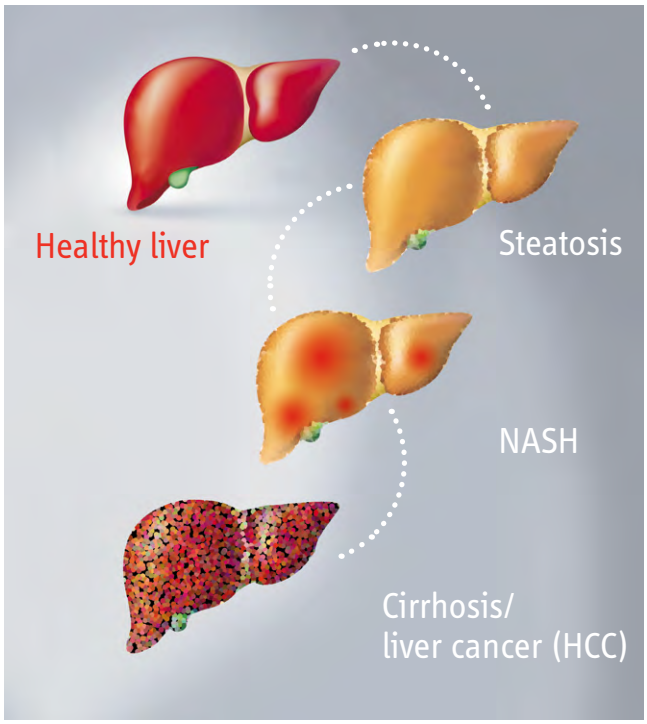
Thomas Laeger
Andreas Peter
Andreas Pfeiffer
Annette Schürmann
Anja Zeigerer

1 Identification of biomarkers to improve NAFLD risk stratification and/or screening in (pre)diabetes.
2 Identification of the major pathogenetic pathways of NAFLD in (pre)diabetes.
3 Testing of lifestyle and pharmacological treatment concepts of NAFLD in (pre)diabetes.



NAFLD refers to a spectrum of liver diseases from steatosis to steatohepatitis (NASH) to fatty liver cirrhosis.

Achieved

- Discovery of the association of the PNPLA3 risk allele (G) with the SIRD diabetes cluster, which is associated with an increased risk of NAFLD.
- Identification of murine Ifgga2/4 (human IRGM) as an inhibitor of fatty liver development (NAFLD).
- Establishment of study coordination and quality management in accordance with ICH-GCPE6 (R2) for the COMBAT_T2_NASH study.
- Receipt of approval from the regulatory and ethics committee to conduct COMBAT_T2_NASH and successful recruitment of 23 study sites.
- Studies in animal models conducted in parallel with the COMBAT _T2_NASH studies demonstrated that the active ingredient liraglutide improved steatosis as well as the expression of inflammation- and fibrosis-related genes.

Objectives for 2021

- ○ Start of the COMBAT_T2_NASH study.
- ○ Beginning studies of the role of autophagy (mitophagy, lipophagy) and its induction in the prevention and treatment of NAFLD.
- ○ Start of the implementation of TM6SF2 and PNPLA3 genotyping for future NAFLD risk assessment in the clinical setting.

● Target achieved ○ Ongoing project

PREVENTION OF TYPE 2 DIABETES

Coordination: Andreas Fritsche, Sofiya Gancheva, Andrea Icks, Matthias Schulze

***People with prediabetes** differ in their blood glucose metabolism and show different courses: 5 to 10 out of every hundred of these people develop diabetes each year, while others have normal blood glucose levels again. The DZD is working to identify the different subtypes and develop precise prevention for them.*

The Prevention Academy has two overarching goals:

1. Understand mechanisms and evaluate treatment options which reduce the risk to develop diabetes. Determine response or nonresponse to diabetes prevention.
2. Transfer of individualized early detection and prevention of diabetes to the health care system and general population.

In order to achieve these goals, researchers are investigating fundamental mechanisms essential to prevention processes, testing them in clinical studies, and conducting health services research on the implementation of prevention in public health.

Prediabetes subtypes identified

Until now, it was not possible to predict whether people with prediabetes would develop the metabolic disease and be at risk for serious complications or would just have a harmless form with slightly higher blood glucose levels. However, reliable classification into high- and low-risk individuals for type 2 diabetes (T2D) is crucial for targeted prevention of the metabolic disease.

Here, the DZD has achieved an important breakthrough: Six clearly definable subtypes (clusters) were identified in a cohort of 900 individuals. The results were validated in the Whitehall II cohort (see also page 12).

The DZD is also conducting several studies in order to identify pathomechanisms and predictors of diabetes. For this purpose, large-scale prospective cohort studies (EPIC-Potsdam, KORA, NAKO Health Study) are also evaluated in the DZD. Thus, new predictors of type 2 diabetes (e.g., circulating proteins, plasma glycans, and lipids) were found.

With the German Diabetes Risk Score (DRT), adults can easily and straightforwardly determine their individual risk of developing type 2 diabetes within the next five years. The

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DRT model has now been extended to include the blood glucose parameter HbA1c, and the model has been validated in a nationally representative study (GNHIES98 cohort). The Academy is also working on an expanded model for cardiovascular risk prediction. In addition, the DIRIKO online study examined how different forms of risk communication about the DRT affect risk perception and willingness to change behavior.

In a claster-randomized trial, DRT was used in addition to routine Check-up 35 in primary care practices. This showed that the DRT helps identify people at high risk for T2D.

Implement diabetes prevention in the public health system

In examining the cost-benefit ratio of diabetes prevention, thresholds from the DRT indicating increased risk were evaluated. Here, lifestyle intervention was shown to be cost-effective in individuals with a five-year risk of diabetes of at least 5% when the risk score and blood glucose levels were used in combination to identify this high-risk group. A well-established decision analytic diabetes model was adapted for economic evaluation in the German population. For this purpose, German data on costs of illness and the risk of complications of diabetes were analyzed. Work is currently underway to implement diabetes prevention in routine German care. DZD representatives are involved in the advisory board for the educational campaign of the BZgA as well as in diabinfo.de. There, the diabetes risk score is an important component.

In order to make the new research results better known among diabetologists, a special issue of the professional journal “Der Diabetologe” was designed on the topic of prevention.

Achieved

- Identification of six subtypes of prediabetes and publication of the results.
- Preparation of an intervention study in risk subphenotypes of patients with prediabetes and diabetes (IFIS).
- Identification of novel diabetes risk factors by examining (omics) biomarker profiles in cohort studies (EPIC, KORA).
- Expansion of diabetes risk score for cardiovascular disease (partially achieved).
- The PLIS (long-term follow-up) study provided evidence for risk-stratified prevention.
- Establishment of a DZD-COVID-19 registry to study mortality in prediabetes and diabetes.

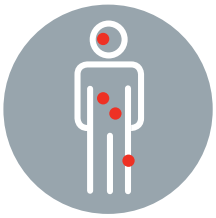
Objectives for 2021

- Start of the IFIS study (Intermittent Fasting to Improve Insulin Secretion).
- Analysis of patient needs and preferences.
- Planning of an intervention study (SGLT2- inhibition in addition to lifestyle intervention in risk subphenotypes with prediabetes).
- Investigation of the role of diabetes and diabetes prevention in the progression of COVID-19.

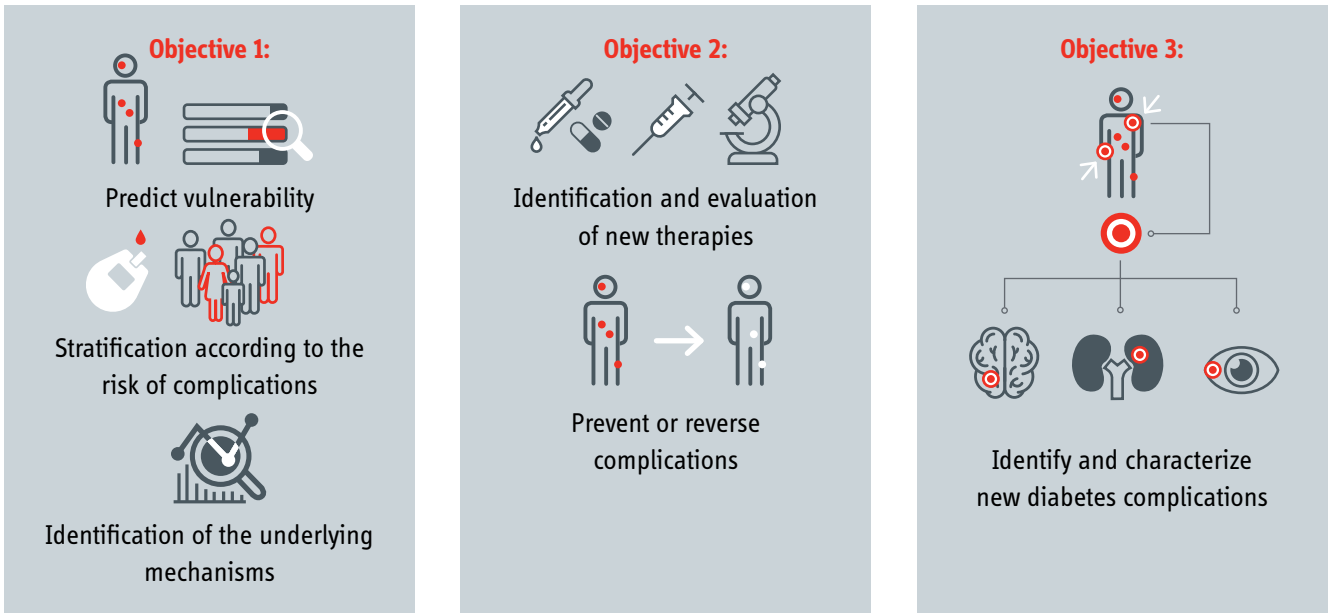
● Target achieved
○ Ongoing project

COMPLICATIONS OF DIABETES

Coordination: Stephan Herzig, Annette Peters, Dan Ziegler



***Vascular disease, eye disease, kidney dysfunction, stroke, heart attack** and occasionally cancer – diabetes can lead to various serious secondary diseases. The DZD is researching new ways to prevent, improve treatment of, or even cure complications of type 1 and type 2 diabetes.*



The conventional distinction into only two common types of diabetes (type 1 and type 2 diabetes) does not adequately reflect the multiple causes and different effects of impaired glucose metabolism. The discovery of diabetes subtypes, which also differ in the risk of secondary diseases, creates an important basis for more precise prevention and treatment of complications.

The DZD is working to decipher the metabolic processes underlying diabetes subtypes that contribute to the development of complications. In addition, the DZD regularly examines subjects in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam cohort and the Cooperative Health Research in the Augsburg Region (KORA) cohort in order to update the glycemic status of subjects, collect biological samples, and gather information on risk factors and diabetes-related complications.

New risk factors for complications

Last year, the DZD discovered several new biomarkers for complications. Circulating peptide NT-proBNP is a classic diagnostic and prognostic marker for heart failure. However, higher plasma NT-proBNP levels measured before the diagnosis of diabetes also increase the risk of microvascular and macrovascular complications.

Studies in the “German Diabetes Study “(GDS) found that in individuals with recent-onset type 2 diabetes (T2D), higher plasma levels of specific lipid metabolites are closely associated with cardiac autonomic dysfunction. This may indicate that an impaired lipid metabolism plays a role in the early development of cardiac autonomic neuropathy in T2D.

A consortium of five cohort studies and the KORA study identified several metabolites associated with renal func-

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tion in T2D as well as with the occurrence of chronic kidney disease in individuals with hyperglycemia and/or normal glucose tolerance.

In a translational approach, DZD researchers demonstrated an association between systemic concentrations of magnesium and methylglyoxal (a highly reactive molecule) and the risk of distal sensorimotor polyneuropathy (DSPN). These findings support the role of oxidative stress in the development and progression of diabetic neuropathy and reveal a potential new pathogenetic mechanism.

For several years, air pollutants have been discussed as risk factors of T2D and its (mostly also obesity-associated) comorbidities. DZD research shows that air pollution increases the risk of developing DSPN in obese individuals.

New therapies to prevent complications

In order to be able to better treat diabetes and to better prevent diabetes complications, the DZD is working on new pharmacological therapies. The researchers are combining different hormones into a single highly potent active ingredient. These new active ingredient candidates not only improve blood glucose levels but also reduce weight and body fat significantly more than previously available therapies. They are currently being investigated in phase 2 and 3 clinical studies.

The DZD is also investigating the therapeutic influence of fasting therapies on diabetes-related functional disorders and long-term complications. The researchers compare different fasting protocols and create a comparative picture of all proteins in different organs. In 2020, several studies on intermittent fasting were completed.

Identification of new complications

Diabetes can also lead to secondary diseases that are not among the “classic” complications associated with diabetes. These include lung or liver fibrosis and cancer. However, the mechanisms underlying these associations are still not known. A new study showed that in diabetes, DNA repair is impaired; this can eventually lead to fibrosis. Restoring the ability to repair DNA not only stops progression but can even reduce inflammation and fibrosis.

Achieved

- ◉ Discovering new biomarkers and risk factors for complications in diabetes using machine learning.
- ◉ Set-up and start of proof-of-principle studies for new therapeutic fasting protocols and combination therapies.
- ◉ Role of DNA damage and repair in the pathogenesis and regression of organ fibrosis identified.

Objectives for 2021

- ○ Completion of the fasting-mimicking ketogenic diet study (a six-month fasting period followed by a three-month period of “normal healthy lifestyle” and start of analysis).
- ○ Identification of biomarkers for polyneuropathy (DSPN) and publication of results.
- ○ Investigation of the effect of the hormone GIP in the regulation of body weight and food intake.
- ○ Pre-clinical validation of novel RNA therapeutics.

◉ Target achieved
○ Ongoing project

MULTICENTER STUDIES

Coordination: Michael Roden, Andreas Birkenfeld

In order to develop precise prevention and therapy measures, *i.e., the appropriate treatment for the right patient group at the right time (Precision Medicine), the DZD is conducting large clinical multicenter studies. More than 5,100 subjects have already participated in the studies.*

The DZD is working on studies on the prevention and therapy of type 1 and type 2 diabetes, gestational diabetes, complications, the treatment of fatty liver in diabetes, and insulin resistance in the brain. The multicenter studies are being conducted at up to 10 study sites in Germany. In addition, monocentric, investigator-initiated trials (IITs) are conducted at study sites.

DZD platform for clinical studies

The studies are coordinated via the DZD platform for clinical studies; this is located at the head office of the DZD. The aim of the standardized unit is to continuously improve compliance and data quality in the clinical studies of the DZD by supporting the study directors in the coordination and administration of the studies. In 2020, five web-based meetings were held with the Clinical Study Board in order to discuss and finalize protocols for the new DZD multicenter studies and harmonize the standard operating procedures (SOPs). In 2020, important preliminary work was done to establish a core data set. The goal is to further improve standardized data collection across studies and facilitate data comparability, usability, and quality. The DZD Clinical Study Board consists of at least two representatives from each study site and is chaired by Prof. Michael Roden and Prof. Andreas Birkenfeld.

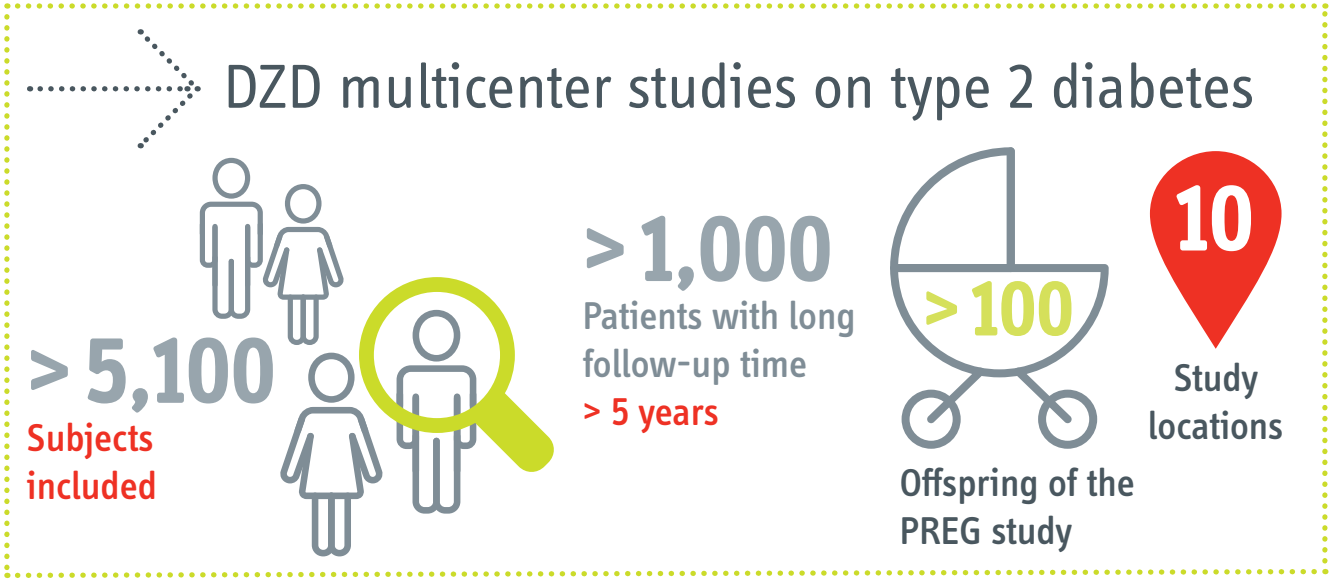
Diabetes prevention study (PLIS, Follow-up)

In the completed multicenter Prediabetes Lifestyle Intervention Study (PLIS), the DZD set itself the goal of developing personalized preventive measures. For the PLIS study, 1,145 patients were recruited. To scientifically follow up this valuable cohort, the follow-up of the study participants was extended to a long-term observation over a period of 12 years after the intervention. There have already been 250 subjects perceiving the 6-year follow-up.

Study on complications

(German Diabetes Study, GDS)

Patients with newly diagnosed type 1 or type 2 diabetes will be followed for 10 years in this study. In this way, warning



Study physicians

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Gesine Flehmig
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Sabine Kahl
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Stefan Kopf
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Andreas Lechner
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Sebastian Schmid
Peter Schwarz
Norbert Stefan
Julia Szendrödi
Ingo Weigmann
Anette-Gabriele Ziegler

signs of later complications can be detected at an early stage, and all approved therapy methods can be compared with each other in parallel. The influence of hereditary factors on the course of the disease is also being investigated. At the end of 2020, 2,050 subjects were enrolled; 650 had already presented at the five-year follow-up and 170 at the 10-year follow-up. Recruitment was expanded to 2,500 subjects.

German Gestational Diabetes Study (PREG)
Gestational diabetes (pregnancy diabetes) affects women who are first diagnosed with a glucose metabolism disorder during pregnancy. In most cases, diabetes disappears after birth. However, those affected have an increased risk of developing type 2 diabetes later. In this study, pregnant women with and without gestational diabetes will be followed up for 10 years in order to detect precursors of diabetes at an early stage and offer preventive measures. The goal is to recruit 800 women at the beginning of pregnancy. By the end of 2020, 73% of the recruitment target had been reached.

DAG study
The brain has a decisive influence on eating behavior and thus on body weight. Here, the reward system (dopaminergic system) in particular plays a crucial role. But certain genes also influence our body weight. An important risk gene influences the reward system in the brain. The study will investigate whether this gene alters the action of dopamine in the brain. This study is being conducted in four study centers throughout Germany. The study included 85 subjects.

COMBAT_T2_NASH: The study will evaluate the efficacy of modern antihyperglycemic drugs in T2D patients with NASH in order to determine new treatment strategies.

IFIS-Studie: The study investigates the influence of interval fasting on insulin secretion (Intermittent Fasting to Improve Insulin Secretion).

Achieved

- Despite massive constraints because of the Corona pandemic, 96 subjects were recruited for GDS, PREG, and DAG.
- Design of the multicenter study (Combined Active Treatment in Type 2 Diabetes with NASH) completed. Approval of the study by the Ethics Committee and the Federal Institute for Drugs and Medical Devices (BfArM). Because of the Corona pandemic, the start of recruitment was delayed until 2021.
- Design of the IFIS (Intermittent Fasting to Improve Insulin Secretion) multicenter study completed. Because of the Corona pandemic, the start of recruitment was delayed until 2021.

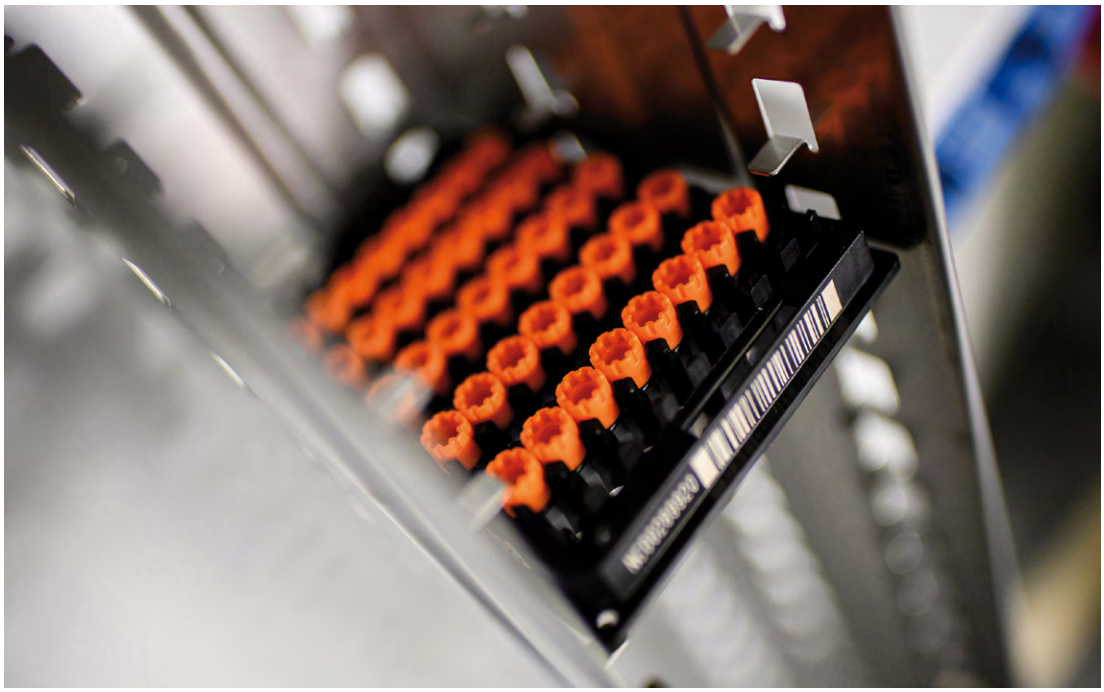
Objectives for 2021

- Approval of the IFIS by ethics committee.
- Recruitment start of the multicenter studies COMBAT_T2_NASH and IFIS.
- Continuation of recruitment for all GDS, PREG, and DAG studies.
- Definition of a basic dataset for DZD studies.

- Target achieved
- Ongoing project

CENTRAL PLATFORMS

State-of-the-art technological platforms are a prerequisite for ***successful translational biomedical research****. For this reason, the DZD is specifically strengthening the expansion of research infrastructures for key technologies at the DZD sites and establishing central service facilities.*



Sample rack with up to 96 individual tubes containing biosamples.

Access to state-of-the-art research infrastructures is central to the success of the translational research strategy of the DZD. These include pre-clinical models, genotyping and phenotyping, epidemiological cohorts, clinical studies and biobanks, high-throughput screening platforms, and imaging infrastructures. The DZD infrastructures are available to all DZD researchers.

Pre-clinical models

A deep understanding of the pathology of diabetes in humans and animal models is essential for the development of new therapeutic concepts.

- German Diabetes Mouse Clinic: Standardized mouse models focusing on metabolic disorders and diabetes research.
- Large animal models: Pig model for the translation of research results to humans.
- Zebrafish as a model for the development and regeneration of islets.

Infrastructures for translational research

In the DZD, the successful translation of research results and the development of new therapies is supported by diverse infrastructures and central platforms:

- Clinical study platform: Central study and data management of the DZD clinical studies (see also page 36).
- DZD Imaging Unit: Whole-body MRI, localized MR-spectroscopy, functional and quantitative MRI of the brain, and fetal magnetoencephalography and related techniques for newborns and children combined MRI/PET brain imaging.
- Cohorts: Large population studies (cohort studies) provide evidence on the influence of genes, environment, and lifestyle (KORA and EPIC-Potsdam studies with 18,000 and 27,500 subjects, respectively). Epidemiologic cohort studies serve as the basis for data and samples on diabetes. The DZD prediabetes cohort includes more than 8,100 patients.

- DPV register: This diabetes patient history record contains data on more than 640,000 patients.
- High-throughput screening platform.
- GMP facility: Laboratories in accordance with the GMP (Good Manufacturing Practice) standard enable the preparation of cells and tissues for clinical use (e.g., transplantation).

Genotyping and phenotyping

Modern technologies enable detailed coverage of the genome, proteome, and metabolome. This allows molecular signatures of diabetes and associated changes during the disease to be determined. Physiological parameters (phenotype) are recorded with the aid of powerful imaging techniques. Here, the DZD has a platform of imaging methods for the pre-clinical and clinical areas (DZD Imaging Unit).

DZD Biobank

The DZD has well-established biodatabases such as the PLIS Biobank (149,000 samples), the GDS Biobank (30,000 samples), PREG Biobank (9,000 samples) and the Pancreatic Islet Biobank (750 samples). The central DZD Biobank is currently being established as a valuable resource for future DZD diabetes and metabolism research.

Computational Biomedicine Group

In addition to DZD data management (see page 40), the Computational Biomedicine Group strengthens bioinformatics and data analysis in the DZD. Dr. Michael Menden has headed the Group since 2019. He is an independent junior group leader at the Institute of Computational Biology (ICB) of the Helmholtz Zentrum München and an ERC Starting Grant awardee in 2020.

The Computational Biomedicine Group is working to establish AI and advanced computational analyses in the DZD. The goal is to help make greater use of the huge potential of bioinformatics and AI in diabetes research. It also focuses on training the next generation of diabetes researchers in AI, data handling and visualization, basic statistics, and ML.

The Computational Biomedicine Group is a focal point for DZD researchers (e.g., to enable research projects with AI). In recent years, several joint research projects have already been implemented. For example, the Computational Biomedicine Group was involved in five DZD publications, among others. The group is currently working with DZD researchers on innovative systems biology and ML methods in order to better predict risk for peripheral neuropathies and painful neuropathy based on multi-omics characterizations.

Furthermore, signaling pathways and mechanisms will be identified that underlie the degeneration and regeneration of beta cells. The Computational Biology Core Unit also creates an important link to established bioinformatics and statistics core facilities of the ICB.

DZD Online Tools

The DZD has developed its own algorithms for genetic analysis. These are available free of charge as an open science resource to the scientific community (miR-QTL scan and graphical representations of Quantitative Trait Loci, QTL).

Achieved

- Concept of the DZD Biobank submitted to the Ethics Committee.
- Start of the development of a DZD core data set.
- Data management of PLIS relaunched.

Objectives for 2021

- Positive vote of the Ethics Committee for the DZD Biobank.
- Finalization of the DZD core data set.
- Development of advanced systems biology and ML methods to predict risk for peripheral and painful neuropathy.

Target achieved

Ongoing project

DZDCONNECT – HOLISTIC DATA INTEGRATION

***MRI scans, blood values, clinical studies, biosamples, genetic analyses** – the DZD collects numerous data from a wide variety of sources. In order to better analyze this information across sites and make the data available to researchers, the DZD has established a data and knowledge portal.*

Diabetes mellitus is one of the very well researched widespread diseases. Yet its complex interplay of causes, accompanying circumstances, and consequences still puzzles scientists. At the DZD alone, more than 400 researchers are investigating the risk, development, progression, and treatment options of the complex metabolic disorder diabetes from different angles. This produces a wide variety of data that varies widely in terms of research base, discipline, species, and data type. In order to be able to explore the emergence of the disease together, it is important to make these unstructured data versatile and to store them in reusable form and make them accessible (FAIR principles – **F**indable, **A**ccessable, **I**nteroperable, **R**euseable).

Integrate additional data sources

Data management at the DZD faces the challenge of preparing the diverse data obtained. The objective here is to make them readily available to all scientists at the DZD across all sites in accordance with data protection guidelines. In addition to the internally acquired data, important external sources for diabetes research will be integrated into the data pool and made more accessible. These include biomedical literature databases (e.g., PubMed), gene and protein databases, and standardized databases on diseases and metabolic processes.

Network and evaluate data

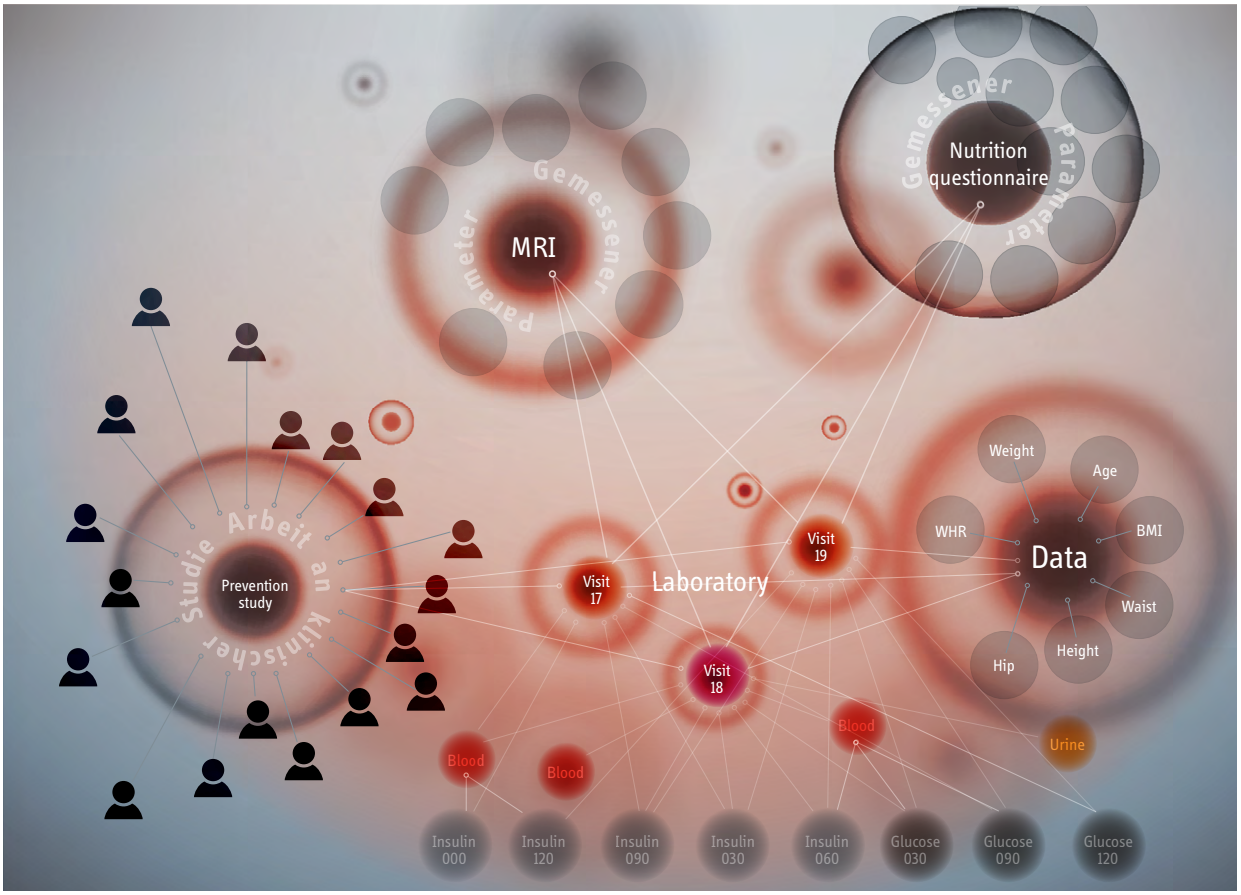
Because there are many and at the same time strongly networked Data, a graph database system has turned out to be the ideal form of storage. With the graph database DZDconnect, the DZD provides its researchers with a knowledge graph that integrates all relevant internal and external sources with a focus on linking data points. DZDconnect is based on the innovative graph database technology Neo4j.

Unlike the common relational databases, a graph stores the knowledge
gained not in individual tables or lists but rather as a knowledge network in which different sources are seamlessly connected.

Quick search

Thanks to the graph structure, DZDconnect can not only be searched quickly but also offers the possibility of establishing new connections. Patterns can be recognized and similarities identified. A specially trained algorithm can make heuristic predictions and provide clues to future relationships. This can play a key role, especially in the context of evidence-based prevention. Previously hidden patterns can thus be uncovered in the future: Why do some people get diabetes and others don't? What role do genes, diet, exercise, and environmental factors play? Linking different datasets can provide fundamentally new answers here and help researchers to discover subtypes of diabetes or new markers for a precursor of the metabolic disease.

In recent years, considerable progress has been made in translational research and in the treatment of people with diabetes mellitus. Linking this knowledge and making it jointly usable is one of the great challenges of the future – and the motivation behind the knowledge graph DZDconnect.



Achieved

- Integration of literature databases and biomedical data into the Knowledge Graph and better access to the information (Natural Language Processing, NLP).
- 35+ articles (not peer-reviewed) in prestigious journals such as Forbes Magazine, Digital Health, HIMSS, Journal for Clinical Studies, Ärzteblatt, Zdnet, and Linux Magazine.
- Winning the bytes4diabetes Award for the project “Graphs to Fight Diabetes”.
- Co-initiator of COVID*Graph (Opensource), a non-profit collaboration of research, software development, data science, and medicine that provides tools to quickly and efficiently navigate the COVID-19 datasets. (April 2021 COVID*Graph became part of HealthECCO).

Objectives for 2021

- ○ Preparation of the installation of bridgehead(s) at additional DZD partners.
- ○ Transfer of clinical data into a clinical database system with implementation of interactive dashboards and automated analysis of raw data.
- ○ Merging of data from pre-clinical models and clinical data.
- ○ Use of COVID*Graph established procedures and data for the DZD.
- ○ Establishment of the DZG overarching data management working group.
- ○ Special issue on Big Data in diabetology in the medical journal “Der Diabetologe”.

● Target achieved ○ Ongoing project

JOINT INTERDISCIPLINARY RESEARCH

Close cooperation and intensive interdisciplinary exchange are the cornerstones of successful translation. *To be able to ensure this during the Corona pandemic, the DZD has successfully established new meeting structures for research, collaboration, and communication.*

Only an open, creative, and constructive dialog between basic researchers and clinicians opens the way to new research approaches. With its structures and measures, the DZD specifically promotes networking among DZD partners and cooperation with excellent external research groups.

Internal communication

Because of the Corona pandemic, the introduction of new meeting formats and structures for research, collaboration, and communication was necessary. In order to keep in touch and exchange scientific results, projects and ideas when a face-to-face meeting is not possible, the DZD conducts video conferences, for both virtual meetings for smaller groups and the newly introduced “Community Meetings” for larger groups. The DZD “Community Meetings” – a series of 90-minute web conferences – have been set up by the DZD in order to inform all DZD scientists about news, updates from research, and new results. On average, more than 140 scientists attended each community meeting. Community meetings were held in July, September, and November.

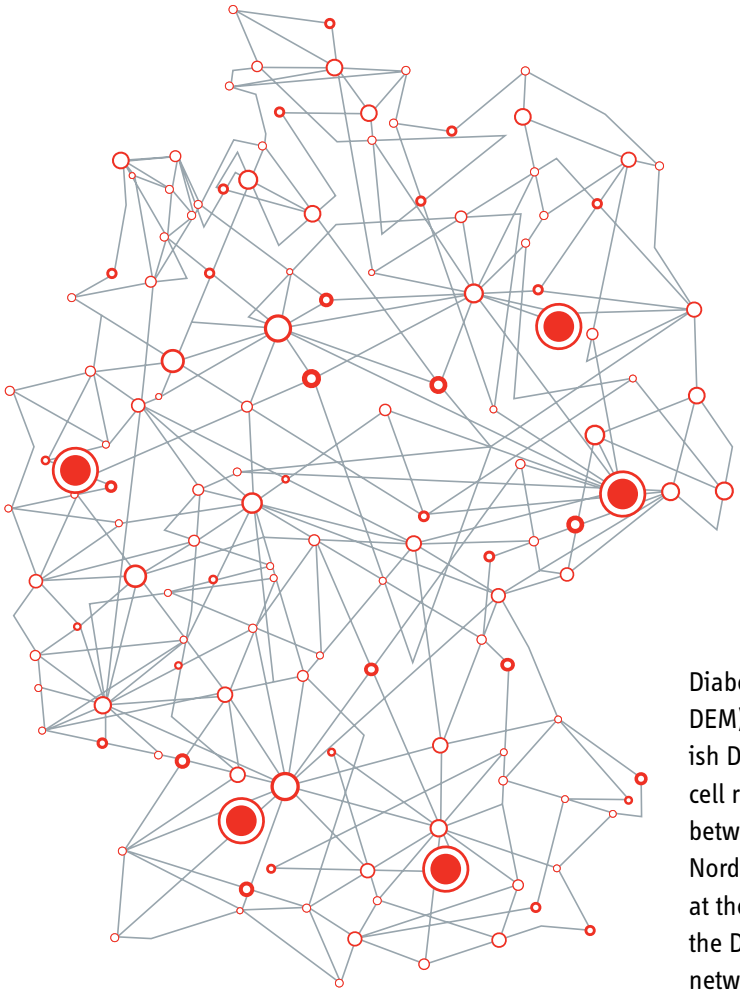
Face-to-face meetings, web conferences, and newsletters

For the implementation of the DZD research program and the further development of the Academies, in addition to the biweekly video conferences of the DZD speakers, there were two strategy meetings, a virtual meeting with the Research Coordination Board (RCB), and regular web conferences of the members of the individual Academies as well as the Clinical Study Board, the Biobanking Board, and the DZD Data Management Board.

In addition, all DZD members receive the monthly newsletter “DZD Info for Scientists” or the newsletter DZD NEXT for young talent.

Well networked

The DZD actively contributes to Germany-wide networking in medical research. It works closely with the other German Centers for Health Research (DZG) (see page 53). DZD researchers are also significantly involved in the diabetes-relevant area of the NAKO Health Study, the largest German population study investigating common diseases. In



addition, DZD researchers are collaborating on the National Diabetes Surveillance of the Robert Koch Institute (RKI).

The DZD is in close contact with the German Diabetes Society (DDG). DZD researchers are represented there in numerous working groups and committees. The DZD is active in the national education campaign of the German Federal Center for Health Education (BZgA) – the DZD, the Helmholtz Zentrum, and the German Diabetes Center (DDZ) are publishers of the national diabetes information portal **diabinfo.de** initiated by the BZgA. As a member of the Platform for Technology, Methods, and Infrastructure for Networked Medical Research (TMF), the DZD supports the continuous improvement of the organization and infrastructure of medical research in cooperative structures.

International cooperations

The DZD is a member of EURADIA, the Alliance for European Diabetes Research. It also collaborates with the French Institute for Health and Medical Research INSERM/AVIESAN, the Spanish Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), the Danish Diabetes Academy (DDA), and the Swedish Diabetes Center at Lund University. In translational stem cell research on type 1 diabetes, there is a strategic alliance between the Helmholtz Zentrum München and the Novo Nordisk Foundation Center for Stem Cell Biology (DanStem) at the University of Copenhagen. In addition, the DZD and the DZD partners are involved in numerous international networks and collaborations – such as the International Mouse Phenotyping Consortium (IMPC), the global platform for diabetes and obesity research (InterConnect), the global platform for the prevention of type 1 diabetes (GPPAD), and the network for pancreas organ donors with diabetes (nPOD).

Cooperations with the industry

The health care industry is an important cooperation partner of the DZD. For the further development of new drug candidates, the DZD collaborates with various pharmaceutical companies – such as Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Novartis, Novo Nordisk, and Sanofi Aventis. The DZD is an associated partner in the European network EIT Health. EIT Health includes members from academia, the public sector, and industry. It brings together organizations across the value chain in order to promote healthy living, support active aging, and improve health care. In 2020, the DZD was involved in a project funded by EIT Health: “Integrated Personalized Diabetes Management Goes Europe” (iPDM-GO) is led by Roche. DZD partners are members of the IMIDIA consortium, which brings together European academic institutions and large pharmaceutical and biotech companies in order to identify new ways to regenerate, maintain, and protect insulin-producing beta cells.

Promotion of young talent:

NETWORKING, LEARNING, PROGRESS

Young researchers need support. The DZD NEXT funding program helps talented young DZD scientists to continue their education, network, and take the next steps in their careers. In this way, the DZD also contributes to making Germany an attractive location for young scientists.

Continuing as before was not possible in 2020. Nowhere. The outbreak of the Corona pandemic also required a great deal of flexibility from the DZD NEXT grant program: "We had to completely reorient ourselves in order to be able to continue the various programs for promotion, international networking, and career development online," says Dr. Brigitte Fröhlich, head of DZD NEXT. "Events that had already been planned were canceled or moved to the virtual space. It then became necessary to develop innovative formats and test new communication platforms." Despite the restrictions brought about by the pandemic, the established programs – the International DZD Diabetes Research School, the DZD Awards, and the DZD Fellowships – were successfully continued, and virtual communication was strengthened.

One program, three goals

The DZD NEXT program is open to all young scientists – from master's students to junior research group leaders – who work in one of the DZD partner organizations. Prerequisite for participation and sponsorship is membership in DZD NEXT, for researchers up to 40 years of age. End of 2020, 150 scientists – including 121 doctoral students, post-docs, and 12 junior research group leaders – are taking advantage of the services offered. These are aimed at gaining experience in international research programs, building a national or international network, and improving career opportunities through special funding programs.

Successful through the pandemic

Because no face-to-face events were possible in 2020, the focus of DZD NEXT was on virtual offerings. In order to strengthen the exchange of young talent, a group was created in LinkedIn, an established social network for professional contacts. This "DZD NEXT Network" contains information on program offerings and events as well as job postings. Active and also former participants can use the network to stay connected as well as to present and discuss their research.

Since 2019, DZD NEXT has been informing its members regularly via email with the DZD NEXT News. In 2020, eight issues were published.

Cooperation in virtual space

Close cooperation with other scientific institutions was continued virtually in 2020. In February, DZD NEXT members participated in a workshop on science communication, which was held by the working group "Promotion of Young Talent and Career Paths" of the German Centers for Health Research (DZG). Here, the young researchers got ideas on how to prepare science topics for a broad audience and disseminate them in social media. At the fall meeting of the German Diabetes Society DDG, which was held online in 2020, scholarships were also awarded to DZD NEXT members. These scholarships include participation in special events organized by the "Young Talent" Working Group. The DZD and the Danish Diabetes Academy DDA opened access to seminars and events for members of each other's organizations so that collaborations between the DDA and the DZD would be able to continue. There is also a close cooperation with the graduate programs of the DZD partners such as Helmholtz Diabetes School and the graduate college Vivid, which is being carried out under the leadership of the DDZ.

Learning from the best

The international "DZD Diabetes Research School 2020" was conducted as a webinar on six afternoons between Septem-

ber 29 and October 15. The event was attended by 170 PhD students and post-docs interested in diabetes and metabolism research as well as young physicians, who were able to expand their personal networks. Some had the opportunity to present their work in short presentations and to discuss this with the participants. Six internationally renowned experts appeared as guest speakers: Philipp Scherer and Kathleen Page (USA), Marit Eika Jørgensen (Denmark), Colin Dayan (UK), Miriam Cnop (Belgium), and Bente K. Pedersen (Denmark). The spectrum of scientific presentations ranged from the importance of the largest endocrine organ (adipose tissue) and the effect of a high-fructose diet on the brain to insights into practical epidemiological research in Greenland and immunotherapies that open up new possibilities for the prevention of type 1 diabetes.

Springboard for young talent

In 2020, the "DZD NEXT Young Talent Program" was launched specifically for junior research group leaders. 18 researchers applied for the funding, which can be used to finance one post-doctoral position each for two years. Applications were evaluated in a two-stage evaluation process. In the end, four scientists were selected: Stephanie Kullmann, Institute of Diabetes Research and Metabolic Diseases (IDM) Tübingen, Max Kleinert and Rachel Lippert, German Institute of Human Nutrition (DIfE) Potsdam, Teresa Rodriguez-Calvo, Helmholtz Zentrum München.

Excellent research

National and international cooperation is the basic prerequisite for successful research. The DZD promotes networks and new collaborations by providing financial support for conference visits or courses. Because face-to-face events were not possible, there was an increase in scholarships for online training.

The ceremonial presentation of the DZD Awards 2020 had to be dispensed with. But as in previous years, nine young researchers received the award for scientifically outstanding presentations and posters. For the first time, achievements in science communication were honored with a separate award.

Excellent scientific support

The DZD NEXT Board in which the five partner institutes, the associated partners, and the DZD head office are represented, provided scientific support for the DZD NEXT Program 2020: Dr. Nadja Brehme (head office), Prof. Dr. Ünal Coskun (Dresden), Dr. Brigitte Fröhlich (head office), Prof. Dr. Christian Herder (Düsseldorf), Dr. Wenke Jonas (Potsdam), Prof. Dr. Henriette Kirchner (Lübeck), Prof. Dr. Cora Weigert (Tübingen), and Dr. Anja Zeigerer (Munich).

Next career steps
Support of young talent at all career stages – from master's students to junior research group leaders – with funding and programs for future scientific independence.

Professional network
Networking of young and renowned researchers at both the national and international level in order to establish a national or international network.

Expertise in translational research
Qualification to bridge the gap between research and medical application.

INTERVIEWS WITH YOUNG TALENTS

Prof. Henriette Kirchner

researches epigenetic influences on metabolism at the Center of Brain, Behavior and Metabolism (CBBM) and the Institute of Human Genetics at the University of Lübeck. Since 2020, the nutrition scientist has been a professor of epigenetic regulation of liver metabolism and a member of the DZD NEXT Board.

What influence did DZD NEXT have on your career? The DZD NEXT program was a lucky break for me. When I came to Lübeck in 2016 to set up a research group with an Emmy Noether fellowship from the DFG, I hardly knew anyone in Germany. I had done my PhD in the U.S. and had been a post-doc in Stockholm. Because the University of Lübeck is an associated partner of the DZD, I got the invitation to DZD NEXT there and immediately became a member. By taking part in various courses and workshops, I was able to quickly build up a network. At one of these events, I got to know my colleagues in Munich better. Since then, we have been conducting several joint research projects.

You became a member of the DZD NEXT Board in 2020. What appeals to you about this task? My goal was always to integrate into the DZD and take on responsibilities. I now represent the associated partners of the DZD on the Board. In the process, I've already learned a lot about the structure of the DZD, decision-making processes, and resources that I didn't know much about. It's absolutely fascinating for me to look behind the scenes there.

Your next objective? I have actually already achieved my greatest career goal: I was appointed professor before my 40th birthday. But there are still some things I would like to achieve scientifically: I would like to understand the epigenetic mechanisms that cause people to have an increased risk of diabetes – because of heredity or lifestyle. With this, I hope to contribute to new therapeutic approaches.

Dr. Sofiya Gancheva

works as a senior physician at the Clinic for Endocrinology and Diabetology at the University Hospital Düsseldorf and the German Diabetes Center. As a research physician, she studies the role of metabolic changes in the liver in type 2 diabetes. Another focus of her research is the effects of bariatric surgery on metabolism and insulin resistance.

Dr. Raffaele Gerlini

is a postdoc at the Institute for Experimental Genetics at Helmholtz Zentrum München. There he heads the Metabolism Division of the German Mouse Clinic.

To what extent is the DZD NEXT program interesting for young clinician scienctits? The funding creates freedom. Those who receive financial support for their research are free to choose their topics. The DZD NEXT funding programs, such as the DZD Grants, open up opportunities for young physicians to pursue new approaches.

To what extent have you personally benefited from the DZD NEXT program? For me, especially the workshops were a great experience: I met many young colleagues who are active in diabetes research. Cooperation projects often develop from these contacts.

In addition, these workshops offer young scientists a unique opportunity to meet the stars of diabetes research: At conferences, you usually can't even get close to these renowned professors. But at the workshops, they take their time, present their findings, and answer questions. I have even had the honor of meeting Prof. Sreekumaran Nair from the Mayo Clinic in Rochester, Minnesota at the International DZD Diabetes Research School and introducing his talk as a moderator. That's how we got talking and have stayed in touch to this day.

Are such contacts helpful for further career planning? This is simply about visibility. It is important that the results of young researchers are noticed. It is a great help to have a network in which you can exchange ideas and receive feedback and appreciation. Prizes also contribute to visibility. When I received the DZD NEXT Award in 2016, the interest in my work increased enormously. Something like this is quite important for young researchers.

At what point in your career was the DZD NEXT program helpful to you? DZD NEXT has given me a new perspective on the world of research: When I came from Naples to Munich to do my PhD at Helmholtz Zentrum München, the International DZD Research School was just taking place in Munich. I was allowed to attend and was very impressed by how researchers from all over the world came together, shared their results and exchanged ideas. It was my first encounter with this international community. And the first time I met leading experts who willingly answered all my questions. I have participated in the Research School several more times over the years, always learning a lot and making important contacts.

Were you also able to benefit from the DZD NEXT offerings in your research? The DZD NEXT program supports and promotes young scientists who want to contribute to diabetes research and therapy with new findings. This is unique and I think it's very good: it gives researchers the chance to take risks and increase their visibility. I myself have worked in a group that, thanks to the help of the DZD, was actually able to identify new genes that were not previously known to affect metabolic health.

You want to use this to develop new approaches to therapies? I'm now trying to translate findings from mouse research into the clinic. In a DZD NEXT webinar series I recently participated in, I learned more about translating pre-clinical research into clinical practice, how to develop and patent industrial products, the requirements for clinical development of therapeutics, and how to market products. These aspects, along with communicating science, are of great importance in moving research from "bench to bedside".

ACTIVELY INVOLVE PEOPLE WITH DIABETES

The aim of the DZD is to prevent diabetes and to treat people with diabetes precisely and prevent complications. In order to better take into account the needs and interests of people with diabetes, the DZD is increasingly involving patients.

Clinical studies are important for medical progress. In most cases, patients are only involved as study participants. The DZD has begun to involve study participants more closely and, for example, informs those in Tübingen about the study results in a newsletter. In addition, annual meetings are held with subjects to provide information about the study results and to allow people with diabetes to share their experiences and wishes.

Get to know the patient's perspective

In order to better take into account the patient's perspective in terms of patient-centered care and precision medicine, the DZD has assessed what information people with prediabetes and diabetes need and how much time they need for health-related activities. The KORA study identified four classes of individuals with different information needs. These differ primarily in age, years of education, diabetes type, diabetes duration, diabetes-related comorbidities, smoking behavior, and time preference. Information should therefore be prepared specifically for the different groups. Surveys in the KORA study also show that people with diabetes spend an average of 2.5 hours per week on self-management activities. DZD researchers have also investigated what information people with recently diagnosed diabetes (GDS participants) need. Here, interest is particularly high in diabetes research as well as diabetes therapy.

However, people with diabetes are also driving developments in diabetes research and therapy themselves – for example, in the further development and use of closed-loop systems that deliver insulin on demand in an automated manner. At the project "TeQfor1 – Effects of technical systems on the quality of life of people with type 1 diabetes" of the KIT, DZD researchers are collaborating.

Provide comprehensive and understandable information

An important concern of the DZD is to provide comprehensive information to people with diabetes. That's why the national diabetes information portal diabinfo.de was set up. Even before the portal was launched, patients were actively involved – for example, through round tables and surveys at World Diabetes Day. It was thus possible to build a portal tailored to the needs of the target group.

Citizen Science Project

The DIfE and the DZD developed the DIfE - DEUTSCHER DIABETES-RISIKO-TEST® (DRT) several years ago. But how do participants in the test perceive their risk? What is the most appropriate form of risk communication? These questions were investigated in the web-based Citizen Science project DIRIKO. Initial analyses suggest that the perceived risk of diabetes does not match the objective risk for a large proportion of users. Men, in particular, underestimate their risk. The results should help to improve the presentation of risk and thus the understanding of the test result.

Assess the patient's perspective

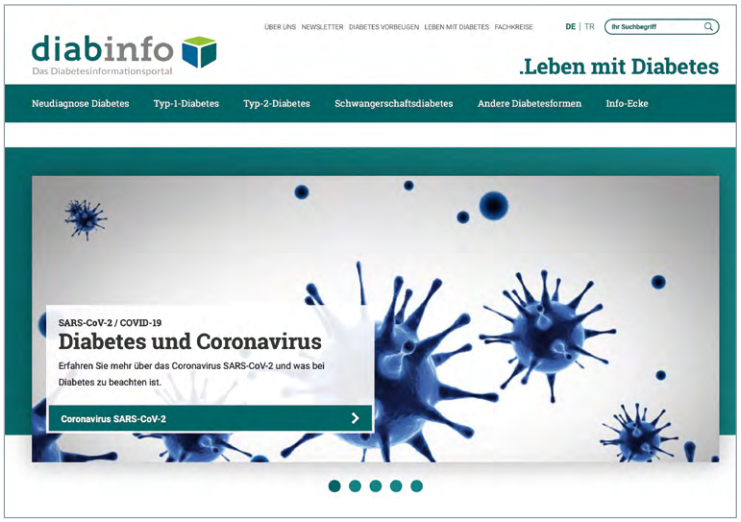
In the coming years, the DZD intends to intensify patient participation even further. The establishment of a patient and citizen advisory board is in preparation. In order to take greater account of the opinions, wishes, concerns, fears, and expectations of citizens in research and to better identify existing research gaps, the DZD partner German Diabetes Center founded a "Citizens' Advisory Council" in 2020.

The DZD is also working with the German Centers for Health Research in order to find new ways to better engage and empower patients in data-driven research.

ACTIVELY COMMUNICATE AND INFORM

A strong focus of the DZD is on communication *in order to inform people with diabetes, professionals, and interested parties about its scientific achievements, research activities, and translational work.*

The national diabetes information portal diabinfo.de has been providing information about the metabolic disease diabetes since the beginning of 2020.



The pandemic has presented new challenges for DZD communications. Planned events, trade fairs, and conferences were not possible, and media attention was mainly focused on the COVID-19 issue; other health research topics received little attention. In order to nevertheless inform the media about current results from translational diabetes research, the DZD has also increasingly relied on direct cooperation with specialist and special interest journals in the past year.

For example, the DZD has produced three focal points for the medical journal “Der Diabetologe” on the topics of “Prevention”, “Liver Diseases”, and “News from Diabetes Research”. In the “Diabetes Journal”, the most important print magazine for people with diabetes, the DZD also designed a 10-page thematic focus. Various articles and news items presented current DZD research results such as diabetes clusters, work on new therapies, and digitalization.

Information on "Diabetes and Corona"

At the same time, it was important to provide information on issues related to diabetes and COVID-19. Especially in times of a pandemic, it is essential that people with diabetes receive reliable and scientifically proven information. On the national diabetes information portal **diabinfo.de**, the section "Diabetes and Coronavirus" has been set up for this purpose. It includes up-to-date information and answers to frequently asked questions on the subject. With interviews, articles, and reports in the "diabetes zeitung" (medium of the German Diabetes Association), the DZD also informed diabetologists and physicians about current findings. We have also compiled the research activities of the DZD on diabetes and the coronavirus SARS-COV-2 on a special page on the DZD website.

Public and people with diabetes

A special concern of the DZD is to inform the general public and people with diabetes. The national diabetes information portal **diabinfo.de**, which was launched at the beginning of 2020, plays a key role in this regard. The portal is a joint service of the DZD, the Helmholtz Zentrum München, and the German Diabetes Center. It was initiated by the Federal Center for Health Education (BZgA). At diabinfo.de, interested parties will find reliable and scientifically proven information, some of which is prepared in multimedia form (podcasts + videos). The portal has been continuously expanded since its launch. For people with a migration background, large sections are also available in Turkish. The diabinfo podcast series started in July. In the approximately ten-minute audio clips, experts from the DZD provide information on all aspects of diabetes prevention. The portal also offers coaching videos. Since fall 2020, the subportal "Information for Professionals" has been online. This is aimed at diabetes advisors. In October 2020, the portal received HONCode certification.

Media and press

Even in times of the COVID-19 pandemic, it is important to provide comprehensive information about current results from diabetes research. The DZD has published press releases, announcements (52), newsletters (9), and scientific articles on current research highlights. The DZD is an important contact for media publishing about diabetes research. Researchers support the communication of the DZD and are available for interviews and questions from the media. The targeted media work has resulted in numerous print and online articles. In the past year, 22 articles (print and online) reported on the DZD every week.

Internet and social media

All DZD information and news are available on the DZD website **dzd-ev.de** in both German and English. In 2020, the DZD revised its research pages on dzd-ev.de. The redesigned pages present the seven DZD Academies, including multimedia content. Direct communication via various social media channels, is also important to us. The DZD has its own Twitter account (@DiabResearch). The channel is used mainly by journalists, research associations, multipliers, and scientists. Scientific news and press releases are published on the DZD LinkedIn account. The channel is in English.

Trade audience – national and international

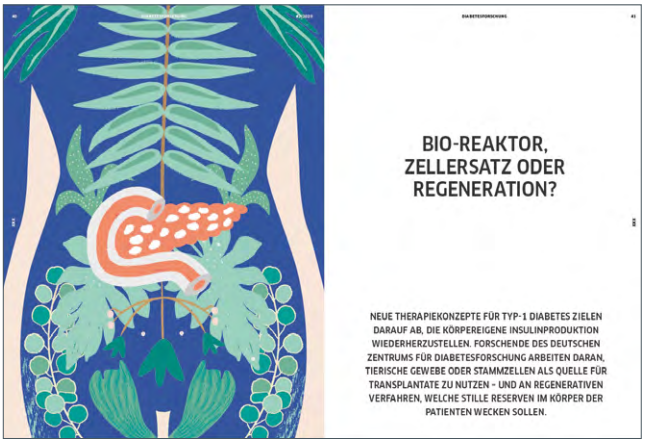
The DZD is an important scientific contact for trade media in the field of diabetes and metabolism. The DZD regularly publishes columns in various professional journals (including Info_Diabetologie, diabetes zeitung, Der Privatarzt, and Diabetes und Stoffwechsel).

Because of the Corona pandemic, the convention business shifted to online events. DZD scientists were nevertheless represented in large numbers. diabinfo.de also participated with content contributions as well as with a virtual booth at the DDG Fall Meeting. Numerous DZD experts gave scientific presentations at the virtual congress of the European Association for the Study of Diabetes (EASD) at the end of September 2020. There, DZD researcher Jens Brüning was also awarded the Diabetes Prize for Excellence.

Virtual World Diabetes Day

At the Internet-based World Diabetes Day, the DZD gave a presentation on type 1 diabetes and showed videos on the topics of diabetes and diabetes prevention (diabinfo.de). In addition, diabinfo.de supports the project "Fit in Gesundheitsfragen" (fit in health issues; joint project of the DZD partner Helmholtz Zentrum München and the German Cancer Research Center in Heidelberg), which provides teachers with practical knowledge in online seminars to strengthen the health literacy of students and supplies interactive teaching materials for schools.

The joint DZG magazine SYNERGIE focuses on translational research.



DZG Magazine SYNERGIE

The six German Centers for Health Research also communicate together. The most prominent product is the magazine SYNERGIE. Since 2019, two issues have been published each year. The magazine can be subscribed to free of charge at dzg-magazin.de. In 2020, the focus was on diagnosis and therapy. The topics of the magazine are also disseminated via the social media channels Instagram and Facebook.

OUTSTANDING RESEARCH IDEAS AS COOPERATION PROJECTS

In a competitive process, the DZD Grants *fund promising cross-site research projects with at least two DZD partners. The scientific advisory board reviews the applications. The interdisciplinary exchange within the DZD forms an ideal basis for innovative hypotheses.*

DZD Grants for the years 2020 and 2021 (all 2020/2021)

Title	Principal Investigator (PI)
Circadian regulation of skeletal muscle insulin sensitivity by TBC1D1 isoforms	Kenneth Allen Dyar, Helmholtz Zentrum München; Alexandra Chadt, DDZ
The role of glucocorticoid signaling in age-related adipose tissue dysfunction and metabolic disorders	Nina Henriette Uhlenhaut, Helmholtz Zentrum München; Tim Julius Schulz, DIfE
Cell free DNA as a biomarker of type 2 diabetes and diabetic complications	Bilgen Ekim Üstünel, UKH; Stefan Kopf, UKH; Dominik Lutter, DDZ
Defining glypicans as insulin binding proteins mediating tissue selective insulin action	Siegfried Ussar, Helmholtz Zentrum München; Ünal Coskun, PLID
Regulation of motivational drive by sensory food perception	Marc Tittgemeyer, MPI; Soyoung Park, DIfE
The potential of fasting regimens to improve beta-cell function, insulin sensitivity and energy metabolism in skeletal muscle and the heart of diabetes patients with increased risk of diabetes complications	Julia Szendrödi, until 2020, DDZ; from 2021, UKH; Alba Sulaj; UKH
Characterization of the cellular and molecular regulatory principles of insulin- and leptin signaling in the hypothalamus and olfactory bulb	Sophie Marie Steculorum, MPI; Paul Pfluger, Helmholtz Zentrum München
Single-cell RNA-seq-based identification of cell-type specific diabetes genes in pancreatic islets of obese mice	Mandy Stadion, DIfE; Heiko Lickert, Fabian Theis, both Helmholtz Zentrum München
Novel regulators for the etiology and reversal of hepatic steatosis in mice and men	Sonja Schriever, Helmholtz Zentrum München; Andreas Peter, IDM
Unraveling the role of oxytocin in glucose homeostasis: from basic insights to clinical interventions	Manfred Hallschmid, IDM; Cristina García Cáceres, Matthias Tschöp, both Helmholtz Zentrum München

DZD NEXT Grants for outstanding projects by young talents (all 2021/2022)

Title	PI
The crosstalk between the duodenum and the pancreas: Profiling the immune system to identify the role of the gut in the pathogenesis and prevention of type 1 diabetes	Maria Teresa Rodriguez-Calvo, Helmholtz Zentrum München
Impact of gestational diabetes mellitus treatments on brain development	Rachel Nicole Lippert, DIfE
Keeping of the momentum: enhancing brain health to prevent T2D and its complications	Stephanie Kullmann, IDM
CRISPR-mediated simultaneous activation of endogenous Gdf15 and Ucp1 in skeletal muscle to treat insulin resistance and obesity	Maximilian Kleinert, DIfE

GERMAN CENTERS FOR HEALTH RESEARCH

A key goal of the health research program of the federal government is to be able to combat widespread diseases more effectively. With the establishment of the German Centers for Health Research (DZG), the federal and state governments have created the prerequisites for this.

The German Centers for Health Research are long-term, equal partnerships of non-university research institutions such as Max Planck, Helmholtz, and Leibniz Institutes as well as universities with university hospitals. The DZD is one of six DZG established between 2009 and 2012 on the initiative of the German Federal Ministry of Education and Research. They pool existing expertise and thus make a significant contribution to closing knowledge gaps and improving the prevention, diagnosis, and treatment of common diseases. The centers are dedicated to the following diseases: cancer (DKTK), neurodegenerative diseases (German Center for Neurodegenerative Diseases; DZNE), infectious diseases (German Center for Infection Research; DZIF), diabetes (DZD), lung diseases (German Center for Lung Research; DZL), and cardiovascular diseases (German Center for Cardiovascular Research; DZHK). Two additional Centers for Child and Adolescent Health and Mental Health are being established.

The strategic collaboration of leading researchers in the DZG strengthens Germany's position as a center of science in international competition and significantly increases its attractiveness for young talents in Germany and abroad. The bundling of different disciplines and competencies has already led to a significantly increased international visibility of translational, clinical application-oriented research in Germany.

The six DZG have been working closely together from the outset in order to share experience and exploit synergies. The DZG forums (four times a year) focus on the strategic further development and cooperation of the DZG. At the end of 2020, a strategy paper for the future cooperation of the DZG and the use of funding was adopted. In recent years, cross-DZG collaboration has been further expanded, and working groups have been established for biobanking, IT and AI, the promotion of young talents, public relations, prevention, global health, stakeholder capacity, medical chemistry and communication, among others.

In 2020, the DZG jointly carried out various Corona projects – such as the establishment of a Europe-wide database to record COVID-19 sufferers – which provides an important basis for research projects. As part of the promotion of young talents, a course on science communication for young talents was offered jointly with the National Institute for Science Communication in the DZG.

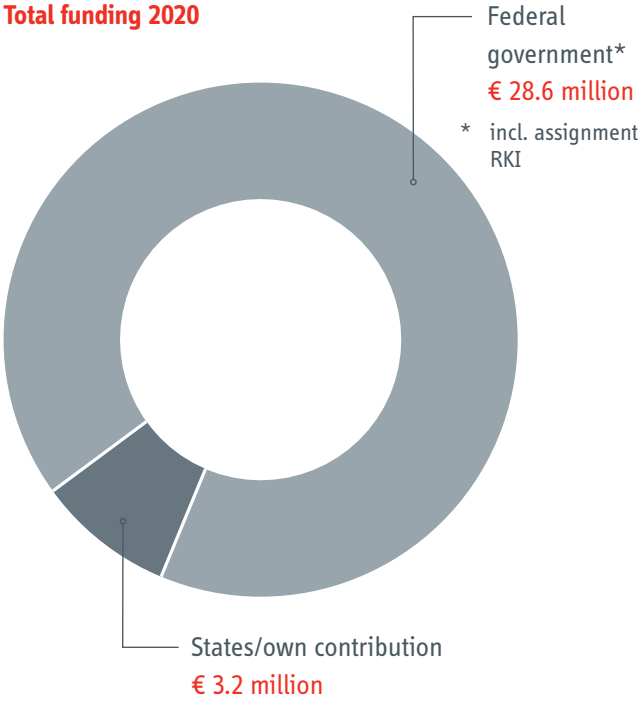
In order to inform the members of the Bundestag about the successful work of the DZG and to exchange ideas with the parliamentarians, a Parliamentary Evening was planned for 2020. Unfortunately, this had to be canceled at short notice because of the pandemic. A short image trailer presenting the DZG and its mission was also produced for this purpose. This trailer is now being used at online events as well as on the websites of the DZG. At the beginning of 2019, the jointly conceived health research magazine SYNERGIE appeared for the first time - as a high-quality print product as well as an online edition. Two more issues were published in 2020.

FINANCES AND PERSONNEL

Finances

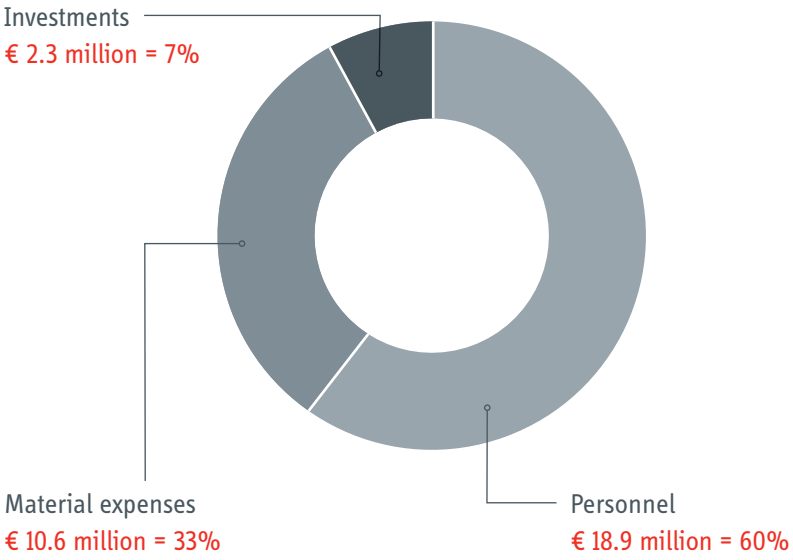
The German Center for Diabetes Research (DZD) had total expenditures of € 31.8 million in 2020. Of this, 28.6 million came from federal funds and 3.2 million from state funds or the partners' own contributions. The funding management at the Helmholtz Zentrum München forwarded the funds to the DZD partners within the framework of project funding. The Interim and where-used reports for 2020 prepared by the partners was reviewed.

Total funding 2020



DZD Financial Data 2020

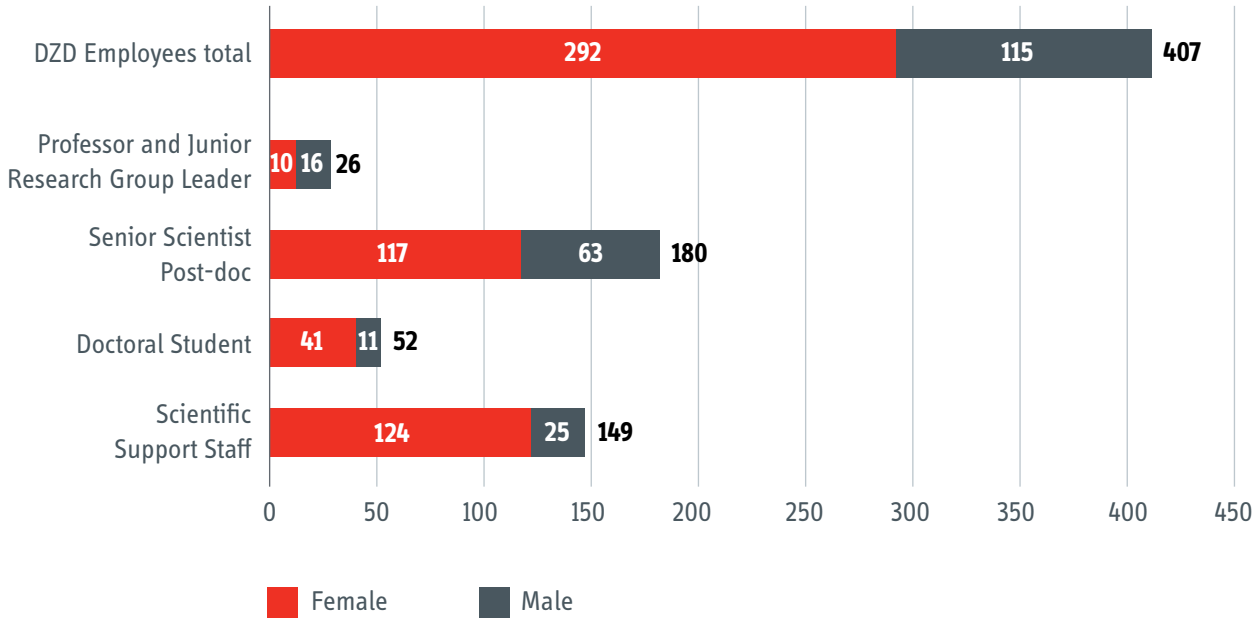
Actual expenditures in 2020 in € and %



DZD Association

The head office of the DZD is financed by membership fees. Last year, the DZD Association had € 1.33 million at its disposal; this included income from donations and funds carried forward. Expenditures amounted to € 1.04 million. They are distributed as follows: 62.5% personnel, 36% material expenses, and 1.5% investments. The annual financial statements were audited by the auditing firm Deloitte.

Employees DZD 2020



Personnel

In 2020, DZD funds were used to finance a total of 407 employees, including 258 scientists and 149 science support staff. The contribution of additional employees to the DZD projects was financed from the own funds of the DZD partners.

New professorships and working groups

In 2020, Michael Laxy from the Helmholtz Zentrum München received a W2 professorship from TUM. Ünal Coskun (PLID) has accepted a W2 professorship in Membrane Biochemistry and Lipid Research in Dresden. Anthony Gavalas (PLID) has been appointed Professor (W2) of Stem Cells in Pancreatic Development and Disease. A professorship in Molecular and Experimental Nutritional Medicine has been awarded to André Kleinridders (DIfE) at the University of Potsdam. Nutritionist Henriette Kichner (UKSH) has been appointed Professor of Epigenetic Regulation of Liver Metabolism. Dr. Dominik Pesta (DDZ) has accepted the W1 junior professorship in Translational Metabolism at the DLR, Cologne. The young scientist Dr. Rachel Lippert was won as head of the newly created junior research group "Neuronal Circuits" at the DIfE. Lippert and her team are using a mouse model to study basic processes for processing food stimuli in the brain.

Equal opportunities

The DZD and its partners are committed to equal opportunities for women and men as well as to a family-friendly human resources policy. In order to promote the compatibility of family and career, part-time employment, childcare facilities, dual-career measures, and equal-opportunity appointments to committees and review groups are offered. During the lock downs, employees were able to work more flexible hours.

The German Institute of Human Nutrition and the German Diabetes Center in Düsseldorf are certified by the "audit berufundfamilie", the Helmholtz Zentrum München by the "European Charter for Researchers" and the "Code of Conduct for the Recruitment of Researchers".

Women account for more than 70% of DZD-funded positions. The high proportion of women among senior scientists and post-docs (65%) and among doctoral students (79%) is particularly gratifying. The proportion of female professors and junior research group leaders is now 38%.

ORGANIZATION AND COMMITTEES

In 2009, the German Center for Diabetes Research (DZD) was founded in the legal form of an association. *Five scientific research institutions with equal rights (five partners) form the DZD. The organs of the DZD e.V. are the General Assembly, the Board of Directors, the Commission of the Public Grant Providers, and the Scientific Advisory Board.*

Scientific partners are the following non-university research institutes and universities:

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

German Institute of Human Nutrition Potsdam
Speaker: Prof. Dr. Annette Schürmann

Helmholtz Zentrum München
Speaker: Prof. Dr. Dr. h.c. mult. Martin Hrabě de Angelis

University Hospital Carl Gustav Carus Dresden
Speaker: Prof. Dr. Dr. Michele Solimena

Eberhard Karls University of Tübingen
Speaker: Prof. Dr. Andreas Birkenfeld

The associated partners expand the expertise in the DZD:

- Prof. Dr. Jens Brüning, University of Cologne and Max Planck Institute for Metabolism Research
- Prof. Dr. Sebastian Schmid, University Hospital Schleswig-Holstein – Lübeck Campus
- Prof. Dr. Dr. h.c. Peter Nawroth, from February 2021 Prof. Dr. Julia Szendrödi, University Hospital Heidelberg
- Prof. Dr. Michael Stumvoll, University Hospital Leipzig
- Prof. Dr. Eckhard Wolf, Ludwig Maximilian University of Munich

General Assembly

As the central decision-making body of the DZD, the General Assembly elects the Board of Directors, decides on the admission of new members, is responsible for the scientific strategy in the DZD, and decides on the orientation of the association. Members are the five partners of the DZD, the Helmholtz Association of German Research Centers, and the Leibniz Association.

Meeting: March 19, 2020

DZD Board of Directors

One representative each from the Helmholtz Association (Prof. Dr. Martin Hrabě de Angelis), the Leibniz Association (Prof. Dr. Michael Roden) and the universities (Prof. Dr. Dr. Michele Solimena) form the DZD Board of Directors. Strategic decisions are made by the extended Board of Directors, which is composed of the five spokespersons of the partner institutes.

Scientific Advisory Board (SAB)

In the strategic development of the DZD research program, the DZD is advised by a scientific advisory board. The advisory board is formed by six members from the international academic and industrial diabetes research community.

Members of the Advisory Board:

- Prof. Dr. Ulf Smith, University of Gothenburg, Sweden (Speaker of the Advisory Board)
- Prof. Dr. Domenico Accili, Columbia University, USA
- Prof. Dr. Fatima Bosch, Universitat Autònoma Barcelona (UAB), Spain
- Prof. Dr. Marit Jørgensen, Steno Diabetes Center, Copenhagen, Denmark. From April 2021, University of Greenland
- Prof. Dr. Edward Leiter, The Jackson Laboratory, USA
- Dr. Michael Mark, Boehringer Ingelheim, Germany

Advisory Board Meeting (Virtual): December 17/18, 2020

Commission of the Public Grant Providers

As a body of funders, the Commission of the Public Grant Providers assists the Association. The DZD is funded by the federal government as well as the federal states in which the DZD sites are located. The federal government and each federal state send representatives to the Commission of the Public Grant Providers. The meeting is chaired by the representative of the Federal Government. In 2020, because of the pandemic, the Commission was informed in writing of all funding activities in the spring, and a video conference was held in the fall. Resolutions were adopted by written circular. The DZD receives 90% of funding from the federal government and 10% from the respective federal states.

Representatives of the federal government:
MinR Dr. Jan Grapentin, André Wecker

Representatives of the federal states:
Dr. Annerose Beck, Saxony
Dr. Florian Leiner, Bavaria
Dr. Beate Müller, North Rhine-Westphalia
Dr. Karin Schwarzenbacher, Baden-Württemberg
Katrin Pörksen, Brandenburg
Meeting as a video conference: October 1, 2020

Head Office

Dr. Astrid Glaser is Managing Director of the DZD e. V. and heads the office based at the Helmholtz Zentrum München. The team of the head office is responsible for the organization and administration of the DZD Association on the instructions of the DZD Board of Directors. These include contractual and legal matters, scientific coordination, the establishment of relevant structures (e.g., biobanks, data management, clinical studies), the promotion of young talent, collaborations, and internal and external communication.

Grant management

The grant management of the DZD is anchored at the Helmholtz Zentrum München and is headed by Dr. Florian Mertes. The department manages the financial resources provided to the DZD by the federal government and is responsible for forwarding them to the DZD partners. In this context, the funding management department reviews the awarding of grants and the reallocations of funds as well as interim reports and proof of use.

Research Coordination Board

The Research Coordination Board (RCB) is made up of 40 scientists – the five DZD speakers, a further six representatives per DZD partner, and one representative per associated partner. The task of the RCB is to further develop the scientific DZD program. Prof. Dr. Julia Szendrödi and Prof. Dr. Hubert Preißl head the Research Coordination Board.

Session (virtual): November 27, 2020

Research Coordination Board

DDZ	DIfE	HMGU	IDM	PLID	Associates
H. Al-Hasani	T. Grune	S. Herzig	A. Birkenfeld	E. Bonifacio	J. Brüning
C. Herder	S. Park	M. Hrabě de Angelis	A. Fritsche	S. Bornstein	S. Schmid
A. Icks	A. Pfeiffer	H. Lickert	M. Heni	U. Coskun	J. Szendrödi
S. Kahl	A. Schürmann	A. Peters	A. Peter	A. Gavalas	M. Stumvoll
E. Lammert	T. Schulz	R. Schneider	H. Preißl	B. Ludwig	E. Wolf
M. Roden	M. Schulze	M. Tschöp	N. Stefan	M. Solimena	
S. Schlesinger	J. Spranger	A.-G. Ziegler	C. Weigert	S. Speier	

(as of May 2021)

DIfE Deutsches Institut für Ernährungsforschung Potsdam-Rehbrücke

DDZ Deutsches Diabetes-Zentrum

Universitätsklinikum Carl Gustav Carus

EBERHARD KARLS UNIVERSITÄT TÜBINGEN

HelmholtzZentrum münchen
Deutsches Forschungszentrum für Gesundheit und Umwelt

- DZD Partner | DZD Partners
- DZD Assoziierte Partner | DZD Associated Partners
- DZD Projektpartner | DZD Project Partners
- DZD Geschäftsstelle | DZD Head Office

PARTNER 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 integrates basic research, epidemiology, and clinical application. The five partners and founding members are:

German Diabetes Center (Düsseldorf)

Site speaker: Prof. Dr. Dr. h.c. mult. Michael Roden

Researching diabetes – helping people: The German Diabetes Center (DDZ) in Düsseldorf is an interdisciplinary research institution that closely integrates molecular and cell biological basic research with clinical and epidemiological research expertise.

The DDZ coordinates the multicenter German Diabetes Study (GDS). The GDS study cohort will be enrolled at all DZD partner sites. The DDZ is also an important partner in other DZD studies such as the Pregnancy Diabetes (PREG) study, EMLIFA, and COMBAT_T2_NASH.

The DDZ works on experimental genetics in cell and animal models. In humans, DDZ researchers gain insights using magnetic resonance imaging and spectroscopy. In addition, the experts at the DDZ conduct population-based studies on the descriptive epidemiology of the two types of diabetes and their complications as well as on improving prevention, early detection, and medical care for diabetes patients.

In 2020, a Citizens' Advisory Board was established at the Institute for Health Services Research and Health Economics (IVG) of the DDZ in order, to be able to take greater account of citizens' opinions, wishes, concerns, fears, and expectations in research and to support the expansion of participatory research.

In 2020, the DDZ was awarded the berufundfamilie audit certificate for the fourth time by berufundfamilie Service GmbH.

Last year, Dr. Dominik Pesta took up a W1 junior professorship in Translational Metabolism at the DLR Institute of Aerospace Medicine, Department of Muscle and Bone Metabolism in Cologne.

German Institute of Human Nutrition Potsdam-Rehbrücke

Site speaker: Prof. Dr. Annette Schürmann

As an internationally renowned research institution for nutrition-associated diseases, the German Institute of Human Nutrition Potsdam-Rehbrücke (DIfE) is one of the five founding partners of the DZD. In cooperation with other DZD partners, DIfE scientists are investigating, the pathogenesis of type 2 diabetes in order to develop new strategies for the prevention and therapy of this disease. To this end, they use a broad spectrum of scientific, epidemiological, and medical methods.

Together with the Helmholtz Zentrum München, the DIfE is pursuing a particularly innovative research approach with the German Diabetes Mouse Clinic. For example, researchers are using mouse models in order to identify genes associated with diabetes and to functionally characterize them. In this way, they can gain insight into the molecular mechanisms involved in the development of diabetes. A better understanding of these mechanisms helps to develop new approaches to drug therapies.

In addition, DIfE epidemiologists are using study data from the EPIC (European Prospective Investigation into Cancer and Nutrition) Potsdam study to investigate the relationships between lifestyle, biomarkers, and diabetes risk. This study is a prospective long-term observational study with more than 27,500 subjects. Based on the data from this cohort study, DIfE researchers have developed the DIfE – DEUTSCHER DIABETES-RISIKO-TEST®. As a precise screening tool, the test is available as an interactive online version as well as a paper questionnaire in several languages. The DIfE, with its expertise in clinical studies, is also involved in the human studies of the DZD.

In 2020, André Kleinridders took over the professorship of Molecular and Experimental Nutritional Medicine at the University of Potsdam. Junior scientist Dr. Rachel Lippert is the head of the newly created junior research group "Neuronal Circuits" at the DIfE. Lippert and her team are using a mouse model to study basic processes for processing food stimuli in the brain.

Helmholtz Zentrum München

Site speaker: Prof. Dr. Dr. h.c. mult. Martin Hrabě de Angelis

Diabetes research is one of the thematic priorities at the Helmholtz Zentrum München. In recent years, this area has been further strengthened by the establishment of the "Helmholtz Diabetes Center" and the appointment of internationally renowned experts as well as by the targeted expansion of the research environment for the study of metabolic diseases. In 2020, the center celebrated its 60th anniversary. The official celebrations were planned for 2021.

In close cooperation with the DZD partners, the researchers at the Helmholtz Zentrum München illuminate the multi-factorial disease diabetes in an integrative, systemic research approach from the perspective of various scientific disciplines such as genetics, epidemiology, immunology, stem cell research, and systems biology. Diabetes research at the Helmholtz Zentrum München is dedicated to the main types of this disease – type 1, type 2, and gestational diabetes as well as the causes such as metabolic and immunological disorders. Other focal points are the development and regeneration of insulin-producing beta cells in the pancreas. With the Metabolomics Platform, a Genome Analysis Center, the German Diabetes Mouse Clinic and the KORA Cohort, the Helmholtz Zentrum München contributes state-of-the-art technology platforms to the DZD research network. The researchers at the Helmholtz Zentrum München work closely with clinical partners from the two Munich elite universities – TUM and LMU – and DZD partners. With the DZD head office and the funding management located at the Helmholtz Zentrum München, the professional administration of the DZD is guaranteed.

Together with the DDZ and the DZD, the Helmholtz Zentrum München established and maintains the diabetes information portal diabinfo.de, which was launched in 2020. Last year, Michael Laxy was awarded a W2 professorship at TUM.

Paul Langerhans Institute Dresden of the Helmholtz Zentrum München at the University Hospital of the TU Dresden

Site speaker: Prof. Dr. Dr. Michele Solimena

In the course of founding the DZD, the Paul Langerhans Institute Dresden (PLID) was founded at the University Hospital Carl Gustav Carus of the TU Dresden in 2009. For over 10 years, diabetes research has been one of the pillars of the Medical Faculty in Dresden. In 2015, the PLID became a branch of the Helmholtz Zentrum München.

The central goal of the DZD projects at PLID is to prevent the destruction of beta cells and to treat insufficient insulin secretion. In addition, the role of the PLID as the only German transplant center for human pancreatic islet cells is outstanding.

Interdisciplinary collaboration with DZD partners is a top priority at the PLID. The close linking of experts from different disciplines such as genetics, immunology, cell, and developmental biology with the clinical departments of internal medicine and VTG surgery as well as with DZD colleagues from the German Diabetes Mouse Clinic and stem cell experts guarantees the translational orientation of the research. The excellent research infrastructure at the Dresden site provides the basis for future scientific excellence. For example, the establishment of a biobank with samples from human pancreatic islets facilitates diabetes research directly in humans and may lead to the development of new drugs.

Last year, Ünal Coskun received a W2 professorship in Membrane Biochemistry and Lipid Research. Anthony Gavalas has been appointed Professor (W2) of Stem Cells in Pancreatic Development and Disease.

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

Site speaker: Prof. Dr. Andreas Birkenfeld

How can the development of type 2 diabetes be successfully prevented? This is the focus of diabetes research at the DZD site in Tübingen.

As a strong clinical partner, the University of Tübingen was involved in the founding of the DZD. For closer integration of basic research and clinical practice, the University of Tübingen and the Helmholtz Zentrum München moved even closer together with the establishment of the Institute of Diabetes Research and Metabolic Diseases of the Helmholtz Zentrum München at the University of Tübingen (IDM). At the IDM, the improved assessment of individual diabetes risk and the development of personalized prevention strategies are the primary research goals.

Through the establishment of well-phenotyped cohort studies with more than 3,000 subjects with an increased risk of diabetes, Tübingen has considerable expertise in the prediction and prevention of type 2 diabetes and its complications. Building on this, a large multicenter clinical study was conducted at all DZD sites under the coordination of the IDM with the Prediabetes Lifestyle Intervention Study (PLIS). The IDM identified six subtypes of prediabetes.

A study on gestational diabetes (PREG) aims to identify female subjects at risk for this form of diabetes at an early stage and reduce their risk of developing type 2 diabetes later on. IDM is also significantly involved in the DAG study. In addition, IDM researchers are preparing the IFIS multicenter study, which will investigate the effect of Intermittent fasting in people with prediabetes or diabetes with an increased risk of complications.

One focus is the study of the effect of insulin resistance in the human brain on metabolism. To translate these findings into humans, the IDM has access to state-of-the-art technologies such as magnetoencephalography, fetal magnetoencephalography, and functional magnetic resonance imaging. These studies on the human brain open up completely new therapeutic approaches.

Associated partners

Five associated partners expand the competencies of the DZD and strengthen the network of the national research association.

Prof. Dr. Jens Brüning
University Hospital Cologne and Max Planck Institute for Metabolic Research Cologne
CNS control of metabolism

Prof. Dr. Dr. h.c. Peter Nawroth
(from February 2021, Prof. Dr. Julia Szendrödi)
University Hospital Heidelberg (UKH)
Diabetes and its complications

Prof. Dr. Sebastian Schmid
University Medical Center Schleswig Holstein (UKSH)
CNS control of energy balance

Prof. Dr. Michael Stumvoll
University Hospital Leipzig
Diabetes and obesity

Prof. Dr. Eckhard Wolf
Ludwig Maximilian University of Munich (LMU)
Large animal models for diabetes research

Project partners

In addition, the DZD cooperates with project partners:

Prof. Dr. Reinhard Holl
Ulm University

Prof. Dr. Johannes Kruse
University of Giessen

Prof. Dr. Bernd Kulzer
Diabetes Academy Bad Mergentheim

PD Dr. Andreas Lechner
Ludwig Maximilian University of Munich

Dr. Christa Scheidt-Nave
Robert Koch Institute, Berlin

Prof. Dr. Joachim Spranger
Charité Berlin

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DIfE (page 10), DIfE/Till Budde (page 45)
David Ausserhofer/DIfE (page 5 top)
Universität Tübingen (page 5 center)
wirdesign (page 51)
Helmholtz Zentrum München (page 3 right, 14, 24, 38 M. Balk, 60)
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www.dzd-ev.de/en

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www.diabinfo.de

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