German Center for Diabetes Research

Research for a Future without Diabetes
Health research opens up many new opportunities in medical care. It will help us to cope with the great challenges our society is facing. In Germany, demographic trends in particular have played a major role in making diabetes mellitus one of the most widespread diseases. We need suitable therapies for this and other common diseases.

We want to tap all of the enormous potential that our research landscape harbours. This is why we are pooling German expertise in the area of diabetes research in the German Center for Diabetes Research (DZD). This national centre is made up of equal partners from the Helmholtz Association, the Leibniz Association and universities. It brings together the country’s best scientists in the fields of basic research, health care research and translational research. We can thereby significantly boost efficiency and also strengthen our top position in the field of diabetes research internationally. In the first instance, however, the DZD is paving the way for urgently needed innovative approaches in prevention and therapy. After all, health research has only achieved its aim when it actually benefits the patient.
Diabetes mellitus is a serious chronic disease that affects more than 6 million people in Germany. We know that this number will increase without research into effective prevention and treatment strategies. To counteract this dramatic trend, the German Center for Diabetes Research (DZD) developed a unique integrative research approach that unites basic research and clinical applications. The DZD is well-equipped to transfer scientific insights quickly into medical practice and to improve the lives of people affected by diabetes. This is possible due to the wide range and high level of expertise, running network projects and the top level research infrastructures provided by the DZD partners.

This booklet should introduce the DZD concept and the main research areas of the DZD research groups. Following our mission “Research for a Future without Diabetes”, we face together the challenge of developing personalized prevention and treatment strategies.
German Center for Diabetes Research
Deutsches Zentrum für Diabetesforschung (DZD)

The German Center for Diabetes Research (DZD) is a national association of leading scientists in the field of diabetes research. The DZD was founded in 2009 to create excellent research conditions for developing individualized strategies for the prevention, diagnosis and treatment of the globally threatening disease diabetes. It is funded by the German Federal Ministry for Education and Research.

Diabetes
Diabetes is one of the most prevalent diseases in Germany. Due to changing lifestyle and diet the number of people with diabetes is still rapidly increasing. To counteract this dramatic trend and to develop innovative strategies for the prevention and treatment of type 1 and type 2 diabetes, the DZD sets up a unique research concept.

Interdisciplinary and Translational Diabetes Research
In course of the integrative research approach of the DZD, basic scientists work hand in glove with clinicians, epidemiologists and health care experts to accelerate the translation of promising basic research findings into clinical praxis. These collaborations not only facilitate translational research, but they also allow for scientific research on findings coming from the clinical routine.

Communication and Evaluation is Crucial for Success
Regular meetings of the management board and the project teams at the DZD workshops provide the basis for a continuous discussion and optimization of the scientific projects. Once a year the programs are evaluated by an international scientific advisory board.
DZD Mission
Research for a Future without Diabetes

The DZD is committed to creating individualized strategies for the early detection and prevention of the disease and its complications. Furthermore, personalized causal therapies are being developed which should halt its progression and improve patient care. To this end, detailed research on the underlying causes of diabetes is of critical importance.

DZD Members
Top-level scientific research organizations and excellent universities.

The central office of the DZD is located at the Helmholtz Zentrum München.
DZD Research Infrastructure
Shared Cutting-Edge Platforms and Technologies

Clinical Study Platform
Centralized study management and a shared DZD Clinical Study Platform is the important key for successfully conducting the DZD multicenter studies, in which more than 3000 patients will be involved.

Common Biobanks
The DZD biobank provides an organized collection of biosamples with an extensive set of data obtained by deep phenotyping and focused on a single indication – diabetes.

Cohorts
Data from existing prospective epidemiologic population-based studies are at the DZD partners’ disposal for epidemiological and health economic scientific questions.
- **KORA** Cooperative Health Research in the Augsburg Region (*Helmholtz Zentrum München in cooperation with the German Diabetes Center Düsseldorf*)
- **EPIC-Potsdam** European Prospective Investigation into Cancer and Nutrition (*German Institute of Human Nutrition Potsdam-Rehbrücke*)

Metabolomics Platform
The examination of individual profiles of metabolites opens a broad new field for identifying additional biomarkers that allow the definition of subgroups of diabetes and of new diagnostic parameters.

Jerzy Adamski, Philippe Schmitt-Kopplin
(*Helmholtz Zentrum München*)

German Diabetes Mouse Clinic
The German Diabetes Mouse Clinic is a unique institution that allows a standardized investigation of the molecular causes of diabetes in mouse models. Different organ systems and the influence of environmental challenges could be screened. Focus is on metabolic disorders, especially diabetes. Furthermore, new diabetic mouse models are developed in order to test new therapeutic approaches and to identify risk factors and biomarkers for the early detection of diabetes.

Martin Hrabě de Angelis (*Helmholtz Zentrum München*)
Hans-Georg Joost (*German Institute of Human Nutrition Potsdam-Rehbrücke*)

Islet Cell Transplant Program
An islet cell transplant program for the treatment of severe cases of type 1 diabetes was successfully established. The scientists seek to enhance the efficiency of the transplantation method by improving the preparation technologies for donor organs.

Stefan Bornstein, Barbara Ludwig
(*University Hospital C.G.C. Dresden*)

DZD PartnerNet
The DZD PartnerNet as a multifunctional IT platform facilitates a safe sharing and storing of information, data and documents combined with a sound software solution supporting the project management.
DZD Research Program
For Innovative Strategies in Diabetes Prevention and Therapy

The key point of the research program is the interdisciplinary collaboration between leading basic and clinical scientists running translational projects in four programs.

**Program A**
Clinical Trials / Applications
New prevention and treatment strategies for persons at risk and/or patients with diabetes are developed.

- A1 German Prediabetes Intervention Study
- A2 German Diabetes Study
- A3 Type 1 Diabetes Prevention Study
- A4 Functional Diabetes Phenotyping
- A5 Gestational Diabetes Study

**Program B**
Molecular Mechanisms
Deeper knowledge about the molecular mechanism of diabetes mellitus will lead to innovative therapy approaches.

- B1 German Diabetes Mouse Clinic
- B2 Susceptibility Genes

**Program C**
Epidemiology
Environmental, lifestyle and genetic effects on the development of diabetes are examined in large population-based studies. New biomarkers will improve the diagnosis of diabetes.

- C1 Predictive Markers
- C2 Type 2 Diabetes and Secondary Complications Risk Score
- C3 Diabetes Register

**Program D**
Biology of the Beta Cell
Maintaining or restoring the activity of the beta cells is crucial to prevent diabetes.

- D1 Biology of the Beta Cell
- D2 Stem Cell Biology
Education of the Next Generation of Diabetes Scientists

With its unique focus on all aspects of translational research, the German Center for Diabetes Research is dedicated to educating a new generation of internationally competitive scientists and clinicians in the diabetes field. The DZD Training and Education Program provides a high-level qualification in diabetes research and is a key to a successful career for young scientists. A close collaboration with the established graduate schools of the DZD partners completes the program with trainings in management, leadership, and communication.
Identification of genes involved in diabetes and adipositas

Genetic variations in the human metabolism as a basis for personalized medicine

Regeneration and keeping the function of beta cells

Insulin resistance of the brain

Improvement of islet function in a bioartificial pancreas

German Diabetes Mouse Clinic

Transgenic pigs: pathophysiology of diabetes – screening of compounds – xenotransplantation of islets

Identification of obesity genes points to new ways of preventing diabetes

BMI more closely associated with body fat distribution

German Diabetes Risk Score

Contribution of a common genetic variation of PEDF to adipose tissue related prediabetes

Impaired insulin secretion by distinct genetic polymorphism of PTBP 1

Low levels of vitamin D in the blood elevates risk for type 2 diabetes

Novel mechanism for insulin release opens new therapy strategies
Clinical Studies / Applications

Currently, there is a lack of detailed systemic and patient-specific understanding of the pathogenesis of diabetes. One major aim in the DZD is the implementation of concepts for the prevention and intervention in the frame of clinical studies with deeply phenotyped collectives in order to develop personalized prevention and treatment strategies. Furthermore, the cost-benefit calculations for these programs will be considered.

### DZD Clinical Studies

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* Leading study center
** The medical clinic of the University of Heidelberg (Peter Nawroth) is supporting the program A as associated member of the DZD.
Personalized Lifestyle Intervention for the Prevention of Type 2 Diabetes and Gestational Diabetes

Recent studies revealed that many people at high risk for type 2 diabetes do not benefit from preventative lifestyle intervention programs. Reasons might be found in individual genetic and phenotypic characteristics of different subgroups of prediabetic individuals.

Gestational diabetes is a risk factor for type 2 diabetes. However, the individual pathophysiological mechanisms for the progression of the disease are far less known.

The identification and detailed description of these groups as well as an improved prediction of diabetes risk and the development of individualized diabetes prevention measures are objectives of the Prediabetes Lifestyle Intervention Study (PLIS) and the Gestational Diabetes Study (PREG), which are conducted by all DZD partners.

Research aims:
- New non-invasive methods for assessing the individual risk of type 2 and gestational diabetes
- Early markers of impaired glucose metabolism by analyzing blood metabolites for potential diagnostic use
- Identification of the best diabetes prevention measures for the individual diabetes risk phenotypes

Hans-Ulrich Häring, Andreas Fritsche, Norbert Stefan, Anita Hennige
Institute of Diabetes Research and Metabolic Diseases of Helmholtz Zentrum München at the University of Tübingen

Diabetologia (2011) 54: 864
Diabetes (2010) 59: 747

Metabolic, Immunologic and Diet-related Effects on the Onset and Progression of Diabetes

The individual interplay of genetic and environmental conditions in type 2 diabetes is responsible for the very different progressions and development of secondary diseases.

The results of the German Diabetes Study (GDS), conducted at all DZD locations, will give a more detailed picture of the pathophysiological processes causing disease progression and secondary complications. Aims of the study are the development of improved personalized treatment and the prediction of the risk for secondary diseases.

The DDIET study analyses whether an increased intake of fiber, caffeine and reduced intake of red meat improves insulin sensitivity and secretion in recently diagnosed type 2 diabetes patients.

Research questions:
- What are the mechanisms in the progression of diabetes and in the development of its complications? What is the impact of metabolic, immunologic and diet-related factors?
- Are the disease course and the development of complications modifiable by interventions?

Besides regular clinical examinations, numerous specialized analysis methods are available at the institute, such as clamp studies, ivGTT, endothelial function (FMD) and intima media thickness (IMT), indirect calorimetry, spiroergometry, immunological characterization, biopsies and microdialysis of subcutaneous adipose tissue, MR imaging and spectroscopy for fat quantification, and investigation of the mitochondrial function using P-31 MR spectroscopy.

Michael Roden, Bettina Nowotny, Karsten Müssig
German Diabetes Center, Düsseldorf


Immune-monitoring and -modulation for the Prevention of Type 1 Diabetes

Type 1 diabetes (T1D) results from impaired immunological tolerance. The restoration of immune tolerance against islet autoantigens is a crucial step for successful prevention of T1D. Autoantigen vaccination for prevention is based on the induction of an antigen-specific regulatory immune response, providing substantial advantages over general immune suppressive treatment. Despite its attractiveness, autoantigen vaccination has had only limited success in T1D and specific biomarkers characterizing alterations in the immune response upon vaccination have mostly been missing.

At the institute a comprehensive immune-monitoring platform permits the detailed characterization of immune related biomarkers in order to assess altered immune responses upon autoantigen vaccination (clinical study resources: Pre-Point and INIT II). These research endeavor could provide a significant advance in the development of autoantigen-specific vaccination strategies for prevention of T1D.

Research aims:
- Identification of changes in T cell-specific biomarkers correlating with and indicating the active vaccination of individuals with autoantigen
- Characterization of metabolomic biomarkers (metabolomics in blood, volatile organic compounds in breath gas) documenting a specific change per se induced by autoantigen application
- Discrimination of individuals who respond favorably to autoantigen vaccination.
- Development of novel autoantigen-specific vaccination approaches for safe and specific prevention of T1D

Anette-Gabriele Ziegler, Peter Achenbach, Christiane Winkler, Sandra Hummel, Andreas Beyerlein, Carolin Daniel
Helmholtz Zentrum München

Prediction, Prevention and Subclassification of Type 2 Diabetes

Gestational diabetes (GDM) is a common reversible situation that exposes an underlying predisposition for type 2 diabetes. In the PPS-Diab Study, women after GDM and matched healthy controls are phenotyped by clinical/metabolic tests and MR imaging. Prospective follow-up investigations are performed to study transition from normoglycemic to hyperglycemic state to characterize pathogenetic mechanisms involved in the development of type 2 diabetes.

Research aims:
- Subclassification of type 2 diabetes and prediction of time to progression to type 2 diabetes by metabolic, genetic and MR imaging biomarker profiles
- Development of new intervention strategies for the prevention of type 2 diabetes in women with gestational diabetes

Jochen Seissler, Andreas Lechner
Clinical Cooperation Group of the Helmholtz Zentrum München at the Ludwig-Maximilians-Universität München

Effects of Nutrition-Dependent Factors on Metabolic Diseases

The composition of nutrition has individual effects on people based on genetic and environmental conditions. The effects of specific diets on the development of metabolic diseases are investigated at this institute.

Research focus:
- Nutrigenetic and epigenetic differences in metabolic responses to nutrients
- Intestinal and hepatic signaling pathways involved in the generation of fatty liver
- Regulation of inflammatory cytokines, chemokines and gut hormones by nutrients
- Effect of specific nutrients on insulin sensitivity and their mechanisms of action

Andreas Pfeiffer
German Institute of Human Nutrition Potsdam-Rehbrücke

Nutrigenomics and Type 2 Diabetes

The investigation of interrelations between diabetes risk genes, diet and metabolism will give rise to better understanding of the mechanisms that determine individual diabetes risk. The underlying molecular mechanisms within susceptibility loci are investigated. In particular, the identification of novel cis-regulatory variants will enable the analysis of genotype-specific effects on the development of obesity, diabetes, and the metabolic syndrome and the interaction with diet and single nutrients.

Selected research projects:
- Identification of novel, potentially causal cis-regulatory variants at T2D susceptibility loci
- Elucidation of upstream signaling (genotype DNA-binding proteins) and downstream signaling (genotype dependent gene regulation) at T2D loci
- Establishment and characterization (geno-/phenotyping) of a cohort of subjects with increased risk of T2D to search for potential new biomarkers, for a better understanding of in vivo functional consequences of genetic variants in humans and for proof of concept studies

Hans Hauner, Helmut Laumen
Clinical Cooperation Group of the Helmholtz Zentrum München and the Else Kröner-Fresenius-Centre at the Technische Universität München

Prevention of Type 2 Diabetes

In future one major challenge in diabetology is the implementation of programs for the prevention of type 2 diabetes. Genetic information can help us to identify disease risks and to understand pathology in more detail.

Aims focusing on the prevention of type 2 diabetes:
- Determining the prevalence of risk for the disease and risk factors
- Implementing a national early risk detection strategy based on a low-cost screening system
- Implementing an intervention program for the prevention of type 2 diabetes

Another focus is the identification of genetic variants predisposing for type 2 diabetes.
- Analyzing the heterogeneity of genetic variants in different populations in the world
- Testing the association of key variants with type 2 diabetes

Peter Schwarz
University Hospital C.G.C. Dresden and Paul Langerhans Institute Dresden

Diabetes (2009) 58: 984
Nat Rev Endocrinol (2012) 8: 363
Nat Genet (2012) 44: 991
Program B
**Molecular Mechanisms**

The pathogenesis of type 2 diabetes is a complex process which proceeds over years or even decades. It is driven by the interplay between genetic background and extrinsic factors such as lifestyle and environment. Furthermore, people suffering from type 2 diabetes cannot be considered a homogeneous group. Anyway, individual variations in the molecular physiological pathways and signaling cascades in these patients have resulted in diabetes. Thus, detailed knowledge of these systems and their variations is a prerequisite for an individualized prevention and therapy.

More than 40 genes have already been found to affect diabetes susceptibility in humans. However, these genes explain only partly the total risk; the major part of the inherited diabetes risk is still unknown. Experimental mouse genetics may show new avenues to elucidate the incompletely understood genetic basis of the disease. Moreover, mouse models play a pivotal role in the investigation of the pathogenesis of multifactorial diseases. The German Diabetes Mouse Clinic as well as transgenic pigs are indispensable for translational research in the DZD.

Intensive organ cross talk is involved in the pathogenesis of diabetes. Besides the classical key players, pancreas, liver, muscle, and fat tissue, recent DZD studies show an increasing important role for the brain. Its increasing importance in the context of the onset and progression of metabolic syndrome and diabetes makes the brain an interesting novel target for innovative therapies.

Due to the DZD network scientific hypothesis and findings can be analyzed and verified on the cellular, the tissue, and the organism level. System biological approaches are utilized to identify yet unknown pathogenic pathways that may result in the discovery of biomarkers or new drug targets. These are evaluated in cell-based and even in *in vivo* screening platforms facilitating a high-throughput scan of compounds.

**Molecular Mechanisms of Metabolic Diseases in Mouse Models**

Mouse models of metabolic disorders and concomitant complications present important tools that help facilitate a basic understanding of mechanisms underlying the etiology of diabetes and its complications. To better understand the function of genes and gene/environment/phenotype interactions in diabetes pathogenesis, the DZD Diabetes Mouse Clinic focuses on advancing and accelerating research by applying a large spectrum of standardized phenotyping techniques. Ongoing research projects explore the epigenetic inheritance of maternally acquired insulin resistance and obesity, the action of compounds and drugs in diabetes therapy and aim on identifying novel players maintaining beta cell integrity and affecting energy metabolism and insulin action. Employing *-omics technologies (transcriptomics, metabolomics), novel gene targets involved in the regulation of insulin action have been identified and are translated into mouse models by exploiting resources such as the Munich ENU Mutagenesis Project, FI-DNA archive, or EUCOMM. Novel insights from mouse studies promise to aid the early diagnosis, prevention and therapy of human diabetes.

**Selected research topics:**

- Identification of novel players in obesity and diabetes pathogenesis: neuronal growth regulator 1, osteopontin, epidermal growth factor receptor kinase substrate 8, cyclooxygenase-2, delta-notch pathway
- Systemic analysis of anti-diabetic drug action
- Lipid-mediated hepatic insulin resistance
- Epigenetics of obesity and insulin resistance
- *In silico* modeling of complex biological systems using Notch signaling cascade
- Mitochondrial dysfunction and oxidative stress in insulin resistance
- Role of fatty acids as modulators of peripheral insulin action

Martin Hrabě de Angelis, Jerzy Adamski, Johannes Beckers, Helmut Fuchs, Valerie Gallus-Durner, Susanna Hofmann, Susanne Neschen, Gerhard Przemeck, Jan Rozman, Sibylle Sabrautzki

Helmholtz Zentrum München

*PLoS Genet (2012) 8: e1002568
Diabetologia (2011) 54: 2132*
Causes and Biomarkers of Metabolically Malign Adiposity and Non-Response to Lifestyle Intervention

The aim is to improve early diagnostic markers and to develop preventive strategies for prediabetic individuals at particularly high risk for type 2 diabetes mellitus, i.e., individuals with metabolically malign adiposity and individuals with non-response to lifestyle intervention. The scientists make use of primary adipocytes and electro-stimulated myotubes derived from deeply phenotyped human donors and apply comprehensive analytical -omics technologies to gain a deep molecular insight into the pathomechanisms underlying the aforementioned high-risk prediabetic states and to identify novel biomarkers which can be used for an improved assessment of the individual risk for type 2 diabetes. Furthermore, new molecular target structures for innovative therapies to prevent type 2 diabetes will be defined.

Selected research topics in the context with the non-response to lifestyle intervention and the metabolic malign adiposity/adipogenesis:
- Identification of genetic, epigenetic, and biochemical determinants
- Assessment of the impact of candidate genes (e.g., PPARD) and hormonal mediators (e.g., irisin, FGF21) on (i) response to lifestyle intervention and (ii) preadipocyte fate/adipocyte metabolism
- Development of mouse models
- Establishment and validation of early biomarkers in large cross-sectional and prospective human cohorts
- Definition of novel therapeutic target structures

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Institute of Diabetes Research and Metabolic Diseases of Helmholtz Zentrum München at the University of Tübingen

Gut (2009) 58: 1281

Identification and Function of Susceptibility Genes for the Metabolic Syndrome

Despite considerable progress in the identification of type 2 diabetes risk genes the underlying molecular mechanisms resulting in defective insulin signaling and beta cell failure are still incompletely understood.

The aim is to investigate the genetic and pathophysiological basis of the metabolic syndrome and in particular of type 2 diabetes in animal models. Specifically, it is intended to identify and characterize susceptibility genes for insulin resistance and type 2 diabetes in mouse models, to investigate the mechanisms of lipid storage in adipose tissue, and to study the molecular basis of beta cell failure. Moreover, the scientists are interested in the regulation of energy balance with particular focus on gene-nutrient interactions.

Selected projects:
- Collaborative diabetes cross
- Lipoglucotoxicity in beta cells
- DNA-methylation and obesity susceptibility in inbred mouse strains

Hans-Georg Joost, Annette Schürmann
German Institute of Human Nutrition Potsdam-Rehbrücke


The Role of Cellular Energy Metabolism in Insulin Resistance and Diabetes

The identification and characterization of environmental and genetic triggers of mitochondrial abnormalities and their contribution to the development of insulin resistance could offer new options for the prevention and treatment of type 2 diabetes and its complications. Abnormal mitochondrial function in patients with diabetes or in those at risk is predicted by plasma free fatty acids, the degree of the insulin resistance and body mass.

Novel methods for extensive phenotyping including non-invasive, multi-nuclear magnetic resonance spectroscopy, which allows determination of intracellular metabolites and metabolic flux rates (ATP synthesis, glycogen synthesis, glucose transport/phosphorylation) in liver, muscle and the human brain, combined with stable isotope dilution and ex vivo high resolution respirometry make detailed tissue-specific analysis of metabolism possible.

Research topics include:
- Regulation of the function of mitochondria in muscle and liver of healthy humans as well as in people at increased risk or with overt diabetes
- Impact of nutritive factors on insulin signaling and energy metabolism
- Role of the liver and the non-alcoholic-fatty liver diseases (NAFLD) for insulin resistance and the metabolic syndrome
- Development of new methods for the non-invasive investigation of metabolism in humans and mouse models

Michael Roden, Julia Szendrődi, Jong-Hee Hwang
German Diabetes Center, Düsseldorf

Hepatology (2009) 50: 1079
Discovering Novel Targets and Therapeutics for Obesity and Diabetes

The newly founded Helmholtz Institute for Diabetes and Obesity (IDO) aims to discover novel signaling pathways, biomarkers and drug candidates that will enable individualized and improved prevention and therapies for diabetes, obesity and comorbidities such as cancer and cardiovascular disease. This goal will be reached using an interdisciplinary and translational approach based on the following nine research divisions within the institute: Functional Neuroanatomy, Neuroendocrinology, Biochemistry, Nutrition Biology, Metabolism & Cancer, Metabolic Physiology, Mitochondrial Biology, Molecular Pharmacology and Target Discovery.

The four overarching research themes are:
- Neuroendocrinology of obesity and diabetes
- Mitochondrial biology of obesity and diabetes
- Vesicular transport in obesity and diabetes
- Pharmacotherapy of obesity and diabetes

Selected projects:
- The role of insulin signaling in the brain in the regulation of appetite, exercise, insulin sensitivity, insulin secretion, and ectopic fat accumulation in tissue
- Saturated free fatty acids as a cause of insulin resistance and inflammation of the brain

Hans-Ulrich Häring, Anita Henning, Manfred Hallschmid, Andreas Fritsche, Hubert Preißl
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Diabetes (2012) 61: 1669
Diabetologia (2012) 55: 175

Molecular Basis of Obesity-induced Inflammation, Insulin Resistance, and Vascular Alterations

Obesity and adipose tissue inflammation are crucial for the development of metabolic diseases like diabetes. The underlying mechanisms will be elucidated by an integrative approach including the detailed investigation of various involved tissues and cell types like adipocytes, skeletal muscle cells, and elements of the vascular wall. The scientists are specifically interested in the role of adipokines and myokines in this complex system, and aim to dissect the bi-directional crosstalk between muscle and fat.

Selected projects:
- Adipose tissue secretion and inflammation
- Insulin resistance due to crosstalk between adipose tissue and muscle

Jürgen Eckel, Henrike Sell
German Diabetes Center, Düsseldorf


Impact of Interactions Between Genes, Cells and Organs on Obesity and Diabetes

Several research strategies will give deeper insights into the complex gene/gene and gene/environment interactions as well as into the crosstalk of different organs and cell types playing a pivotal role in the onset and progression of obesity, insulin resistance and type 2 diabetes. In a genetics approach (positional cloning) polygenic mouse models are used to identify novel susceptibility genes and relevant pathomechanisms. The molecular analysis of insulin action, with respect to glucose and lipid metabolism, gene/gene and gene/environment interactions, and associated metabolic impairments of insulin-target tissues in diabetes, is of main interest. Physiological studies focus on the contribution of secretory products of adipose tissue of obese humans to insulin resistance and diabetes-related heart disease.

High-throughput methods, such as mass spectrometry-based proteome mapping of the secretome of adipocytes and muscle cells, allow comprehensive investigation of complex regulatory networks and identification of novel predictive biomarkers for diabetes and secondary complications.

Hadi Al-Hasani, Margriet Ouwens, Stefan Lehr
German Diabetes Center, Düsseldorf

Nat Genet (2008) 40: 1354
Mol Cell Proteomics (2012) 11:M111.010504
Epidemiology

The development of type 2 diabetes is influenced by individual genetic background, lifestyle and further environmental factors. Population-based prospective epidemiological studies provide insight into these complex interactions. To this end, the Helmholtz Zentrum München and the German Institute of Human Nutrition conduct the KORA (Cooperative Health Research in the Augsburg Region) and EPIC-Potsdam (European Prospective Investigation into Cancer and Nutrition) studies, respectively. In this way, several diabetic risk markers related to lipid metabolism or to inflammatory processes were identified in recent years. These new biomarkers will improve the diagnosis of diabetes in the future. Moreover, innovative new approaches in the field of -omics, techniques established at the Helmholtz Zentrum München, have large potential for the discovery of further risk factors.

The German Diabetes Risk Score enables an early identification of persons at high risk for diabetes that is prerequisite for successful prevention of the onset of the disease. The test was developed at the German Institute of Human Nutrition based on data from the EPIC-Potsdam study. Parameters like waist-to-hip ratio, age, weight, and family history, as well as information about co-morbidities like hypertension determine the diabetes risk. The integration of values of the measurement of distinct biomarkers will improve the test in the future and should allow a prognosis for the risk for secondary complications of diabetes as micro- and macrovascular damages.

Epidemiologic diabetes registries allow for monitoring of the diabetes incidence in populations. Thus they are essential tools to set public health priorities in respect to prevention and treatment programs and to monitor the effectiveness of such initiatives. With DiMelli the DZD supports the first German diabetes register for children and young adults that collects blood samples.

Environmental, Lifestyle and Metabolic Risk Factors for Type 2 Diabetes

The identification of novel risk factors for type 2 diabetes, such as environmental and lifestyle factors as well as early biomarkers is essential for a better understanding of the pathogenetic mechanisms, for early disease prediction as well as for an effective prevention of type 2 diabetes. Therefore, based on the unique resources of the KORA cohort comprising biological samples and medical data of 18,000 population-based persons, we aim to address for type 2 diabetes and its complications the following major research topics:

- Environment: Short-term and long-term effects of ambient particulate matter and of weather and climate
- Lifestyle: Role of lifestyle risk factors such as diet and physical activity as risk factors
- Mental health: Role of depression, work stress and other mental health states as risk factors
- Novel biomarkers: Identification of novel biomarkers which predict incident

Annette Peters, Barbara Thorand, Karl-Heinz Ladwig, Christa Meisinger
Helmholtz Zentrum München

Diabetes Care (2011) 34: 2320
Environ Health Perspect (2011) 119: 778
Molecular Causes for Diabetes

The main objective is to decipher the molecular causes and mechanisms of complex diseases like type 2 diabetes. Methods and systems for genomics, epigenomics, transcriptomics, proteomics, metabolomics and functional analyses are utilized to map molecular disease mechanisms from early stages in disease development to manifest disease, as well as resulting complications. This enables the combination of different molecular -omics data and facilitates the functional characterization of new biomarkers for early diagnosis and prevention purposes.

Research aims:
- Identification of early candidate biomarkers of metabolic diseases
- Network and pathway analysis
- Integration of -omics data to understand the causality of type 2 diabetes

Harald Grallert, Rui Wang-Sattler
Helmholtz Zentrum München

Risk Assessment of Type 2 Diabetes

An early detection of an elevated risk for type 2 diabetes is indispensable for the successful prevention of the onset of the disease. As type 2 diabetes is the consequence of many different factors as genetic heritage, diet, lifestyle, and other environmental conditions, a better understanding of this complex interplay is prerequisite for the development of any risk assessment test. Investigating the data of cohort studies like EPIC-Potsdam (European Prospective Investigation into Cancer and Nutrition) with 27,500 participants facilitates the evaluation of the role of lifestyle factors and the identification of predictive phenotypic traits and biochemical or genetic biomarkers. Based on these results the German Diabetes Risk Score was developed for the prognosis of the risk for type 2 diabetes.

Current research interests:
- Interplay between nutritional exposures and metabolic status as well as gene-environment interaction and the incidence of type 2 diabetes
- Approaches to diabetes risk prediction

Matthias Schulze
German Institute of Human Nutrition Potsdam-Rehbrücke

Diabetes Care (2009) 32: 2116

Inflammation and Diabetes

The development and progression of type 2 diabetes is influenced by subclinical inflammation. Previous work of this group demonstrated the association between lifestyle factors, inflammation-related biomarkers and type 2 diabetes in large cohort studies. Increased concentrations of several acute-phase proteins, cytokines and chemokines as well as reduced levels of the adipokine adiponectin are associated with an elevated risk for type 2 diabetes and diabetic complications independently of anthropometric or metabolic risk factors.

In addition to serum and plasma proteins, mRNA transcripts in blood are promising biomarkers for the risk of complex diseases. Thus, the analysis of gene expression profiles in whole blood as predictors of type 2 diabetes and diabetic comorbidities represents the second research focus of this group.

Research aims:
- Investigation of the interplay between lifestyle and environmental factors, subclinical inflammation and incidence of type 2 diabetes
- Identification of diabetes-related genes and transcripts that can be used as biomarkers

Christian Herder
German Diabetes Center, Düsseldorf

Diabetes Care (2009) 32: 1921
Diabetes (2010) 59: 1222
Prevalence of Diabetes in Germany

Population-based studies gain insight into the current epidemiological situation of diabetes and consequent secondary diseases in Germany and will improve the early recognition and prevention in the future. Besides genetic, lifestyle, and environmental risk factors, the scientists investigate the impact of socio-economic factors like income and education on type 1 and type 2 diabetes incidences. Moreover, the aim is the prediction of future diabetes prevalence in Germany and the evaluation of methods (biomarkers, risk scores, novel diabetes genes) to identify target groups for diabetes prevention programs.

Guido Giani, Wolfgang Rathmann
German Diabetes Center, Düsseldorf

Eur J Epidemiol (2011) 26: 637

Health Economics and Health Care Management

The economic analysis of new strategies of prevention and health care in chronic diseases like diabetes becomes more and more important due to rising health care costs. The Institute of Health Economics and Health Care Management (IGM) focuses on the development of methods for the clinical and economical evaluation of health care interventions and the application of these methods within economic evaluation studies. As a contribution to the DZD activities, we work on several research topics, including the evaluation of disease management programs (DMPs) for patients with diabetes with respect to process and outcome indicators, and on determinants of health related quality of life in patients with type 2 diabetes. In cooperation with clinical partners from the DZD, we introduce economic aspects in ongoing clinical studies with different aims, such as the prevention of type 2 diabetes and individualized prediction of drug response.

Rolf Holle, Reiner Leidl
Helmholtz Zentrum München


Health Outcome Research and Health Economics Evaluation

The focus of our research group is health outcome research and health economics evaluation. Objectives are (1) in the field of health services research, the analysis of outcomes of health care, especially in diabetic late complications (St. Vincent targets) and comorbide depression, including modeling of the course of the disease, and the evaluation of evidence-based patient information, and (2) in the field of health economics, cost-of-illness studies for pre- and early-stage diabetic costs as well as cost-effectiveness analysis of interventions which aim at preventing diabetes and reducing late complications and depressive comorbidity. In addition, instruments for the ascertainment of effectiveness measures and cost data are developed and validated. The analysis of information needs, health care use and associated cost, self care and associated patient time cost, quality of life and patient’s preferences was implemented in cooperation with the Helmholtz Zentrum München in two clinical studies of the DZD (GDS study and PLIS).

Andrea Icks
German Diabetes Center, Düsseldorf

Diabetes Care (2012) 35: 1868
Program D
Beta Cell Research

Increasing clinical and genetic evidence points to the deficit of beta cell function and viability as the common denominator and the ultimate cause for the pathogenesis of all forms of diabetes. Hence, a strong emphasis on islet research is critical for the mission of the DZD. An important research field is the protection and production of pancreatic beta cells and pancreatic islets as a whole. Research in \textit{in vitro} systems as well as in animal models and human islet tissues provide a deep understanding of the molecular mechanism that regulates the viability of beta cells and the production and secretion of insulin. The aim is the identification of new drug targets and the development of functional drug compound screening platforms.

Islet or pancreas transplantation, two procedures that are carried out at the DZD site in Dresden, can cure or at least greatly improve the life quality of diabetic people. However, there is a lack of donors of transplantable cells. In the DZD, two initiatives have been set up to evade this problem: (1) \textit{in situ} stimulation of pancreatic regenerative mechanisms and (2) generation of beta cells for transplantation via the differentiation of precursor cells.

With the establishment of collaborations among partners in the DZD, many of the activities, such as research on stem/progenitor cells to beta cells, animal models of diabetes, and human subjects are being consolidated and rapidly expanding their scope.

Stem and Progenitor Cells in Pancreas Development, Regeneration and Drug Screening

The primary objective of the Institute of Diabetes and Regeneration Research (IDR) at the Helmholtz Zentrum München is to develop regenerative therapeutic approaches to treat diabetes – complementary and alternative to the classical immunological and metabolic therapy strategies.

\textit{In vitro} generation of beta cells from pluripotent stem cells for cell-replacement therapy or triggering endogenous mechanisms of beta cell repair have great potential in the field of regenerative medicine. Both approaches rely on a thorough understanding of beta cell development and homeostasis in pre-clinical models.

Therefore the aim is to improve current strategies for functional beta cell production \textit{in vitro} with the ultimate goal to provide alternative sources of beta cells for therapy. Additionally, we analyze and characterize the embryonic and adult pancreatic progenitor cells to understand beta cell development, homeostasis and function for \textit{in vivo} regeneration.

Research aims:
- Identification of novel signals and factors involved in pancreas development
- Progenitor cells and mechanisms involved in pancreas regeneration
- Embryonic stem cell differentiation into beta cells for cell-replacement therapy
- Identification of novel small molecules with therapeutic potential able to trigger beta cell repair or endocrine-lineage differentiation

Heiko Lickert
Helmholtz Zentrum München

Effect of Obesity Linked Factors on Beta Cell Function

During obesity, a variety of molecular changes induce beta cell dysfunction. An interaction of genetic predisposition with metabolic changes such as sustained hyperglycemia, saturated free fatty acids, cytokines and interleukins trigger beta cell failure. The molecular changes include accumulation of metabolites such as ceramide and NO, oxidative stress, mitochondrial dysfunction, ER stress and induction of pro-apoptotic transcription factors. A further, more detailed examination of this complex interplay might offer novel therapeutic targets.

Specific research projects:
- Effects of fatty acids in insulin secreting cells: molecular changes which conduct from stimulation to inhibition of beta cell function
- Role of PI3K pathway in the regulation of insulin secretion and beta cell survival
- Modulation of IRS-2 signalling in insulin secreting cells
- Effects of fetuin-A on beta cell

Role of Endothelial Cells and Beta Cells in Type 2 Diabetes

It is hypothesized that blood vascular changes support the development of type 2 diabetes. This hypothesis is consistent with the finding that many type 2 diabetes associated genes have a cardiovascular function. Moreover, mice with vascular defects in pancreatic islets are glucose intolerant and lack first phase insulin secretion. Therefore, the phenotype of these mice resembles the phenotype of early type 2 diabetic patients. To analyze blood vessels and vascular changes systematically, an imaging platform has been developed to qualitatively and quantitatively analyze blood vessels in tissues in vivo and in a 96-well screenable format in vitro.

Mitochondria of pancreatic beta cells in diabetic and pre-diabetic mice show several changes. The underlying hypothesis is that the beta cells, besides the cells of peripheral tissues, harbor mitochondrial defects during type 2 diabetes. The molecular pathomechanisms in mitochondria are analyzed during the development of type 2 diabetes and glucose intolerance in mice.

Research topics:
- Analysis and pharmacological manipulation of blood vessels in 96-well assays
- Analysis of blood vessels in mouse pancreatic islets
- Analysis of pancreatic islets with mitochondrial defects in type 2 diabetic or glucose intolerant mice

Immunomodulation

The research group investigates mechanisms of the innate and adaptive immune system which are involved in the pathogenesis of diabetes. The studies are driven by the fact that central components of the immune system are able to control inflammatory as well as metabolic processes. The major focus of research is on the elucidation of the immunomodulatory potential of molecular mediators, such as cytokines, chemokines, stress proteins and Toll-like receptors as well as cell populations with innate immune properties, such as macrophages and adipocytes. Consequently, the scientific work of the group comprises complementary in vitro and in vivo approaches from the fields of basic molecular and cellular research, the use of animal models as well as studies in healthy human subjects and patients with type 1 diabetes, type 2 diabetes and latent autoimmune diabetes of the adult (LADA).

Research aims:
- Elucidation of the role of the innate and adaptive immune mechanisms contributing to the pathogenesis of diabetes
- Identification of molecular or cellular targets to modulate innate or adaptive immune reactivity in order to develop strategies for the prevention of or therapy of diabetes

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Autoimmunity in Type 1 Diabetes

The pathogenesis of diabetes mellitus hinges on the loss of pancreatic islet beta cells which in type 1 diabetes is mediated by autoimmunity. The group is interested in how autoimmunity develops in children, the target beta cell antigens and epitopes, and the immune processes which get activated when beta cells are replaced such as in transplantation. Novel technology to identify single T and B lymphocyte clones based on the antigen receptors, and profiling of single cells is used to determine expansion, diversity and quality of responses in the course of disease as well as after intervention therapy which includes the primary vaccine study Pre-POINT undertaken by the group. Activation and expansion of autoimmunity and mechanisms of regulation of immune responses are related to genetic profiles in order to understand how genetic susceptibility may modulate disease risk. As a special investigative model, the group follows patients who receive new islet beta cells through transplantation, where novel mechanisms of autoimmune expansion that include homeostatic proliferation have been identified. The final objective is to translate findings into therapies that prevent autoimmune destruction of beta cells both before disease onset and when regenerating or replacing lost islet beta cells.

Future prospects and goals:
- Identify the mechanisms of autoreactive T effector and T regulatory expansion in man that can be harnessed to reinstate self immune tolerance
- Determine immune and metabolic states that increase the likelihood of developing and expanding autoimmunity against islet beta cells
- Implement therapies that prevent activation and expansion of islet autoimmunity

Ezio Bonifacio
Paul Langerhans Institute and Center for Regenerative Therapies at the Technische Universität Dresden

Regulation of Vascular Inflammation and the Connection to Metabolism

Recent studies indicate increasingly the crucial role of the inflammatory process for the development of diabetes mellitus, as well as in diabetic vascular complications. For instance, inflammation in the obese adipose tissue is a major player in the development of insulin resistance. On the other hand, inflammation in the pancreatic islet contributes to beta cell apoptosis and islet dysfunction. In addition, the enhanced inflammatory response of the diabetic vasculature is the common denominator of microvascular diabetic complications. In this context, our research group focuses on inflammatory cell interactions with the endothelium and pathways of innate immunity at the cross-talk between immunology and metabolism. Specifically, we are studying the cellular and molecular mechanisms underlying inflammatory cell recruitment and immune cell activation into the adipose tissue in the course of obesity and insulin resistance development, as well as endothelial inflammation in the diabetic pancreatic islet and in the context of diabetic vascular complications.

Research topics:
- Mechanisms governing the accumulation of inflammatory cells in the obese adipose tissue and their contribution to insulin resistance development
- Vascular inflammation and endothelial dysfunction in diabetic vascular complications, especially diabetic retinopathy
- The role of endothelial inflammation pathways in islet dysfunction

Triantafyllos Chavakis
University Hospital C.G.C. Dresden and Paul Langerhans Institute Dresden
Diabetologia (2012) 55: 2583

Secretory Pathway of Insulin in Beta Cells

Beta cells store the insulin hormone within organelles termed secretory granules, which release insulin in response to high levels of circulating blood glucose. Prolonged glucose stimulation depleted beta cells of insulin secretory granules, which must be quickly replenished.

The main question that the group is addressing is how beta cells regulate the turnover of insulin secretory granules, including their biogenesis, exocytosis and destruction. A mechanistic description of these processes may provide insight into the pathogenesis of diabetes and contribute to the development of novel approaches for its treatment.

Research key questions:
- How is a beta cell counting the size of its insulin secretory granule stores?
- Which are the molecular signatures associated with granule aging?
- What accounts for changes in granule mobility with time?
- Which RNA binding protein and posttranscriptional mechanisms allow glucose and GLP-1 to prompt the rapid biogenesis of insulin secretory granules? Are these mechanisms impaired in type 2 diabetes?
- Which retrograde signaling pathways couple the exocytosis of insulin secretory granules with regulation of beta cell gene expression and replication?

Michele Solimena
Paul Langerhans Institute Dresden


Human Islet Transplantation

Islet transplantation holds great promise for treating patients with type 1 diabetes by restoring endogenous insulin secretion. The Dresden Islet Center is currently the only active islet transplantation program in Germany. Within the DZD network the therapeutic option of islet transplantation will be extended to a larger group of patients by the establishment of a clinical transplantation network. Evaluation of patients as well as post transplantation follow-up is sought to be conducted in the associated centers under the coordination of the Dresden transplant center. The great expertise in clinical and experimental diabetes therapy clustered within the DZD will facilitate state-of-the-art patient care and inspirit novel research fields in metabolic, immunologic and psychological aspects of transplanted patients.

Stefan Bornstein, Barbara Ludwig
University Hospital C.G.C. Dresden
and Paul Langerhans Institute Dresden

PNAS (2012) 109: 5022

Islet Cell Regeneration

In order to elucidate the mechanisms leading to functional adaptation and regeneration of islet cells in mice and humans, the scientists put a special emphasis on the use of in situ and in vivo technical platforms to study these complex, interactive processes and to overcome the limitations of commonly used in vitro methods. In particular, they have developed sophisticated methods to visualize and to quantify various aspects of islet biology over time in animal models. The group is especially interested in how islets adapt to specific physiological and pathophysiological conditions and how neogenesis and/or proliferation contribute to beta cell mass expansion. Furthermore, they want to investigate the origin of pancreatic endocrine progenitor cells and assess the role of specific regulatory molecules in the signaling pathways, leading to replication of islet cells.

Future projects and goals:
- Assessing the contribution of neogenesis and proliferation to islet cell regeneration
- Evaluating the role of specific regulatory molecules of beta cell proliferation
- Development of novel techniques and tools for the study of islet cell regeneration

Stephan Speier
Paul Langerhans Institute Dresden

Current Diabetes Reports (2011) 11: 420

Islet Cell Physiology

The group focuses on regeneration and proliferation of beta and alpha cells in islets of Langerhans. Using several different animal models such as partial pancreatectomy, induction of pancreatitis, transplantation under the kidney capsule and into the liver, they evaluate the regenerative potential of the endocrine islet cells under various conditions, e.g. after pancreatic injury, under immunosuppression and after transplantation. In these models, using microdissection, gene and microRNA expression analysis, and in vitro in insulinoma cell lines, they try to clarify the mechanisms involved in the regeneration in islets of Langerhans. They thereby try to transfer our clinical experience from pancreatic resections, pancreas and islet transplantation back from the bedside to the bench to understand the underlying principles.

Stephan Kersting
Paul Langerhans Institute Dresden

J Vis Exp (2011) 53: 2962
Large Animal Models for Translational Diabetes Research

Animal models closely mimic human anatomy and physiology are urgently required, as findings in rodent models do not always reflect the clinical situation. In this respect, the pig is an excellent candidate sharing many anatomical and physiological characteristics with humans. According to this principle, genetically modified pig models for diabetes research are currently generated and analyzed. In addition, multi-transgenic pigs could serve as organ donors for xenotransplantation.

Eckhard Wolf (associate DZD member)
Ludwig-Maximilians-Universität München

Diabetes (2012) 61: 1527
Diabetes (2012) 61: 2166

Extracellular Signals and Transcription Factors in Beta Cell Biogenesis

The group investigates the molecular mechanisms underlying pancreas development and particularly the late events that determine lineage specification of endocrine progenitor cells. Additionally, they are exploring the function of potential stem / progenitor cells in the adult pancreas. The ultimate goals are to develop approaches for (a) the efficient conversion of human pluripotent stem cells into bona fide insulinogenic cells and (b) the stimulation of beta cell biogenesis from endogenous resident stem / progenitor cells.

Research key questions:
- Which are the genetic networks regulated by the key transcription factors guiding late endocrine specification?
- Which are the signal receptors implicated in these late stages and how do they modulate the key transcription factors?
- What are the properties and developmental potential of stem / progenitor cells that are mobilized in response to pancreas injury?
- How can we take advantage of basic pancreas developmental biology to efficiently convert human pluripotent stem cells into functional beta cells?

Anthony Gavalas
Paul Langerhans Institute Dresden

Stem Cells (2008) 26: 3
Mol Cell Biol (2011) 31: 5702

Membrane Biochemistry and Diabetes

The fusion of secretory granules with the plasma membrane of beta cells not only results in the secretion of insulin, but also in rapid and massive changes of the beta cell plasma membrane lipid composition. What are the consequences of these changes on the bioactivity of protein-lipid interactions and consequently on cell signaling? We study lipid-protein interaction-based phenomena at different scales, from the organ and cellular systems down to minimal synthetic systems. We challenge the mutual interdependence of lipid-protein interactions by an interdisciplinary approach, combining cell biology and synthetic biology as well as protein biochemistry, structure biology and biophysics. Overall our approach allows us to challenge the pathology of diabetes from the membrane biochemical point of view.

Research key questions:
- What is the quantitative lipid composition of plasma membrane before and after insulin secretion and of secretory granules?
- How are lipidome changes of the plasma membrane reflected in cell signaling?
- Do beta cells use lipid allostery as a feedback mechanism to choose between proliferation and insulin secretory granule (ISG) production?
- How can beta cells generate a graded response to insulin or even remain sensitive to it, being conceivably exposed to far greater concentrations of the hormone?

Ünal Coskun
Paul Langerhans Institute Dresden

Structure (2011) 19: 1543
PNAS (2011) 108, 9044