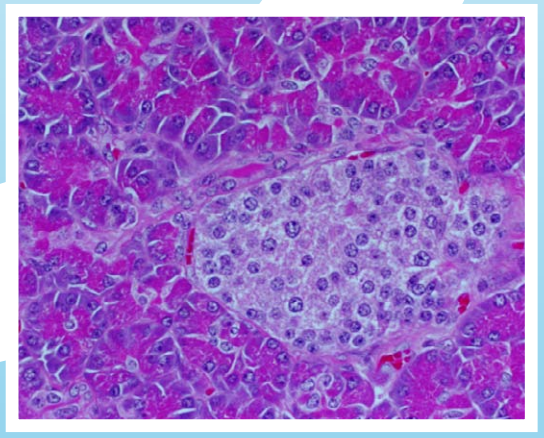
# Oslo Diabetes Research Centre



## ANNUAL REPORT 2009

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*Picture frontpage: Islet cell transplantation*

## How Islet Transplants are Done

*Procedure for islet cell transplantation, see Jenssen's group page 12*


## Board for Aker and Ullevål Diabetes Research Fund

- Knut Dahl-Jørgensen, Professor dr.med.
- Kristian F. Hanssen, Professor dr.med.
- Erik Schultz, MBA
- Per M. Thorsby, Consultant

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- Kristian F. Hanssen, Professor dr.med.
- Anne-Marie Aas, Clinical nutrionist Ph.D.

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- Margareta Wandel, professor
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- Wenche Nystad, Ph.D.

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***University of Northern Norway***
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- Prof Johnny Ludvigsson, Linköping University, Sweden
- Prof Mikael Knip, Helsinki University, Finland
- Prof Heikki Hyöty, University of Tampere, Finland
- Prof Ian W. Lipkin, Columbia University, NY, USA
- Prof John Todd, University of Cambridge, UK
- Flemming Poicot, Jim McGuire and Jørn Nerup, Steno Diabetes Centre, Copenhagen, Denmark
- Prof John Gerich, Rochester NY, USA
- Prof Michael Stumvoll, Tübingen, Germany
- Prof Ashimina Mitrakou, Athens, Greece
- Prof Timon van Haeften, Holland
- Prof Ole Schmitz, Aarhus, Denmark
- Prof Allan Flyvbjerg, Aarhus, Denmark
- Prof Steve Chadban, Sydney, Australia
- Prof Olle Korsgren, Uppsala, Sweden

# 2009 – an exciting year for the Research Centre

We have simplified the annual report as we have a new webside: *www.oslodiabetes.no*
2009 did turn out to be a fine year for Oslo Diabetes Research Centre. We had two dissertations from the Institute of Medical Genetics:

- Marit Bjørnvold "Candidate gene studies in type 1 diabetes and other immune-mediated diseases"
- Anne Blomhoff: "Genetic predisposition to autoimmune diseases"

These theses are very modern: They compare the genetic signature of the different autoimmune diseases. The different endocrine autoimmune diseases have a lot in common and a comparison can lead to new insights. We now know more than 40 genes that predispose to type 1 diabetes.
In general, genetics in diabetes are moving very fast these days and we are discovering new and surprising facts: Rare mutations contribute to common diseases!
The research centre has discovered that gestational diabetes is much more common in Oslo than previous thought. New data from the STORK STUDY and STORK Groruddalen (Henriksen and Jenum) have found that among pregnant women of Norwegian extraction about 10% have gestational diabetes according to the WHO criteria! These are really surprising numbers given that we thought that about 1-2% had gestational diabetes! The reason(s) for this increase is not obvious although body mass is part of the answer. The research groups are investigating this in detail and there are a lot of data to be analyzed. This will have large consequences for the care of pregnant women also in Norway given that small increases in blood glucose in pregnancy have been shown to be deleterious for the baby (HAPO study). This is truly translational research.
Vitamin D research is gearing up and a large randomized study in type 2 diabetes is underway at the research centre. Vitamin D in pregnancy is also covered.
Type 1 diabetes is still increasing also in Norway. In the Lancet the recent incidence 15-year incidence data collected by 20 population-based registries (our registry included) in 17 countries were used to estimate rates of increase in geographical regions in Europe. The prediction is that between 2005 and 2020, new cases of type 1 diabetes in European children younger than 5 years will double and that the prevalence of cases in those who are younger than 15 years will increase by 70%. We still do not know what factors initiate the autoimmune process, but our research centre has several new and important projects in this field (see the individual research groups).
The quality of care for young people with diabetes is an important question and The Norwegian Childhood Diabetes Registry affiliated with the research centre (see report) has established a superb system to implement quality improvements in the care.
The research in late complications especially in diabetic heart, kidney, retinal and neuropathy is going well (see reports).
There is a lot of research going on in the different research groups (see reports).

## Seminars and symposia

Our intern seminar, Solstua, had nutrition as a main topic. Nutrition is becoming more and more important in todays societies and critical important for type 2 diabetes. Ulf Riserus from Uppsala discussed "Metabolic syndrome and lipids – where are we today? And lipids in the diet and prevention of type 2 diabetes".
Furthermore, we had a debate between Fedon Lindberg and Anne-Marie Aas on what we need to know in the future about low carb diet. We all agreed that low carb is one but only one option in the treatment of diabetes.

We had two larger symposia i 2009: the one was "challenges in type 1 diabetes" where some of Europe's foremost researchers about type 1 diabetes in children and adolescence participated. Mikael Knip from Helsinki covered among other topics if virus is a pathogenic factor or an innocent bystander in the etiology of type 1 diabetes. New aspects of continuous blood glucose monitoring were discussed by Thomas Danne from Hannover. We all hope that this new technology will become more "mature" in the near future to help our patients. The motivational aspects of diabetes in children were covered by Ragnar Hanas from Uddevalla. The pediatricians have been excellent in writing international guidelines and more importantly, implementing them! This topic was covered by Peter Swift from Sheffield. The symposium celebrated Knut Dahl-Jørgensen's 60 year's birthday.
The second symposium covered Diabetic nephropathy, still a major problem in diabetes. Per-Henrik Groop from Helsinki discussed new markers and hypotheses on the pathogenesis of diabetic nephropathy. He is also on track to discover new genes of importance for diabetic nephropathy. Peter Rossing from Steno Diabetes Centre in Copenhagen gave an updated lecture on treatment in diabetic nephropathy and Trond Jenssen from our research centre discussed advanced diabetic kidney disease. Ulla Berg and Nina Perrin from Stockholm discussed morphological changes in the kidney in young persons with type 1 diabetes; a topic studied in depth by Hasse Bangstad previously. This symposium celebrated Hasse's 60 year's birthday.

## Organization of diabetes research and clinical work in the Oslo area

We are developing our organization by starting a strategic discussion on Oslo Diabetes Research Centre. Furthermore, we have applied the medical faculty to start a research school in diabetes and metabolism.


Some of the members of the Research Centre

The diabetes research in Oslo University Hospital is organized through Oslo Diabetes Research Centre which is a thematic organization. This is a robust and flexible organization. However, the clinical work in adult diabetes in Oslo University Hospital (OUH) is going through a difficult transitional phase. The regional health Authority, Helse Sør-Øst, has decided to move a large part of clinicial work to other hospitals and organization of adult diabetes care in the future has not been decided yet. This is a challenge and a robust plan for diabetes care localized in one teaching hospital with sufficient space is very much needed and must be a high priority for the top administration of this mammoth called OUH.

## Major funding

Regional Health Authority (Helse Sør-Øst), Oslo University Hospital, Medical Faculty University of Oslo (thematic area) Aker and Ullevål Diabetes Research Fund, Norwegian Research Council, EU grants, Juvenile Diabetes Foundation.

Kristian F. Hanssen
Chairman Professor dr.med.

| Leader | Work place | Research Area | Email |
|---|---|---|---|
| Kristian F. Hanssen (Chairman) | Dep of Endocrinology, Oslo University Hospital | Diabetic late complications | k.f.hanssen@medisin.uio.no |
| Knut Dahl-Jørgensen (vice-chairman) | Pediatric Department, Oslo University Hospital | Diabetes in children and adolescents Etiology of type 1 diabetes, complications | knut.dahl-jorgensen@medisin.uio.no |
| Geir Joner | Pediatric Department, Oslo University Hospital | Epidemiology and etiology of type 1 diabetes, complications, mortality | geir.joner@medisin.uio.no |
| Dag Undlien | Institute of medical genetics, Oslo University Hospital | Genetics and epigenetic of type 1 diabetes | d.a.undlien@medisin.uio.no |
| Benedicte Lie | Institute of Immunology, Oslo University Hospital | Genetics in type 1 diabetes | benedicte.lie@rr-research.no |
| Kåre I. Birkeland | Dep. Of Endocrinology, Oslo University Hospital | Prevention and treatment of type 2 diabetes | k.i.birkeland@medisin.uio.no |
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| Trond Jenssen | Oslo University Hospital, Department of Nephrology | Diabetic nephropathy | trond.jenssen@rikshospitalet.no |

# Group leader: Kristian F. Hanssen

Group name: Diabetic late complications

***Research focus:***
Epidemiology and mechanisms of late complications. The mechanism by which hyperglycaemia is so deleterious to large and small blood vessels is basically unknown. A leading hypothesis is that glycation (the chemical reaction between glucose or intracellular metabolites of glucose and proteins) and subsequent rearrangements (Advanced Glycation Endproducts AGE's) is a main culprit. We have developed unique assays for different AGE's (CML, hydroimidazolone and Glucosepane) in blood. We have previously shown that serum AGE is associated with and predicts coronary heart disease in type 2 diabetes. Furthermore, that serum AGE is associated with micro-vascular complications.

***Projects:***
***A. 30 years prospective study of late complications in type 1 diabetes (The Oslo Study)***

***1. Prospective study:***
We will investigate progression of vascular changes, especially coronary vascular changes as measured by intravascular ultrasound (IVUS) and coronary angiography in the prospective Oslo Study and identify predictive parameters for this progression, especially AGE parameters.

***2. Cross-sectional study:***
Assess both macro and micro vascular status of the patients in 2008-2009 and associate with skin (measured in Dr. Monnier's lab Cleveland, USA) and serum AGE. A number of parameters have been followed prospectively over 25 years, and will give valuable data for our cross-sectional study.

***Specific aims:***
- To study cardiac events; sub endpoints will be the vessel area stenosis, significant plaque (>0.5 mm) progression both on IVUS, and coronary artery stenosis on coronary angiography.
- Serum and skin AGE and oxidative markers in relationship to complication status.

There are few studies that have examined long term complications and intensive diabetes treatment with such a long duration of the disease, and it is a unique opportunity to study the relationship between complications and biochemical markers of complications.

***B. Glycation in the arterial wall.***
We are studying glycation modification in the arterial wall in atherosclerosis with and without diabetes by western analysis, immunohistochemistry and LC MS/MS (mass spectrometry). We have already discovered some modifications in the wall that might be involved in the increased propensity to atherosclerosis in diabetes.

***C. Advanced glycation of proteins and vascular complications in childhood diabetes*** (together with Dahl-Jørgensen`s group).
Prospective study of early markers of atherosclerosis in a large group of adolescents with type 1 diabetes and controls its relationship to glycation.

***D. Coronary and glomerular morphology in kidney transplants. Long term study in two contrasting groups. PI: Trond G. Jenssen***
Study the effect of long-term normoglycaemia vs. hyperglycaemia on changes in the coronary arteries and the renal function and structure in type 1 diabetes patients. Two groups of patients with type 1 diabetes are studied, one group transplanted with a single kidney (HbA1c 8-8.5%), the other who received combined kidney-pancreas grafts and has obtained perfect normoglyacaemia over the same period of time (HbA1c 4.5-5.5%).
- To investigate proteoglycans and glyco-saminoglycans which are important components of the filter network of the basement membrane
- To explore proteoglycans (syndecan-1) and macrophage transcription factors (Id-1) in blood samples as markers of early kidney changes
- Advanced Glycation Endproducts (AGE, CML, hydroimidazolone) by immunohistochemistry in the glomerulus and in serum sampes to test the hypothesis that glycation markers can predict the development and progression of late complication (specifically early diabetic nephropathy and coronary heart disease)

***E. A long term randomized, double blind controlled study of Benfotiamin (vitamin B1) in type 1 Diabetes***
A two year study with neurograhy as the primary endpoint.



***Group members:***
- Kari Anne Sveen, Ph.D. student
- Terje Lund, Ph.D.
- Bente K. Kilhovd, Consultant dr.med.
- Tore J. Berg, Consultant dr. med.
- Peter Torjesen, Ph.D.
- Martin Heier, Ph.D. student (together with Dahl-Jørgensens group)
- Miliam Pepaj, Ph.D.
- Dag Fosmark, Consultant dr. med.

# Group Leader: Knut Dahl-Jørgensen

Research Group: Childhood Diabetes

***Research focus:***
The group has four main research areas. The first is the ethiology and prevention of type 1 diabetes and autoimmune diseases, especially focusing the role of viruses and the interaction with the immune system in pancreatic tissue samples. We now start a GAD intervention trial with in debt mechanistic studies. The second area is diabetes late complications. We have long term clinical studies on micro vascular complications and the influence of glycemic control and advanced glycation. Recently the risk of early atherosclerosis in type 1 diabetes has been the focus in several of our studies, with measurement of vessel wall thickness (IVUS and IMT) and vessel elasticity, and biochemical markers, as well as clinical data and risk factors. In our large, nationwide clinical studies, now as part of the Childhood Diabetes Registry, we focus on important issues like intensified insulin treatment and pumps, diet, physical activity, quality of life and psychosocial problems.

***Projects:***
***Ethiology and prevention of type 1 diabetes and autoimmune diseases:***
***1.*** Diabetes Virus Detection Project
***2.*** Nordic Diabetes Prevention Trial
***3.*** Disease eliciting T cell epitopes in type 1 diabetes
***4.*** Genetic studies of the importance of copy-number polymorphism in the development of type 1 diabetes
***5.*** Viruses, genetics and autoimmunity in thyroiditis. A biopsy study

***Diabetes late complications:***
***6.*** Atherosclerosis in Childhood Diabetes
***7.*** Long term vascular changes in type 1 diabetes – Clinical aspects and biological markers – 27 years follow-up of the Oslo Study
***8.*** Advanced glycation of proteins and vascular complications in childhood diabetes

***Clinical diabetes:***
***9.*** Norwegian Childhood Diabetes and Quality project (NCDQ) - a nationwide prospective population-based study for research and quality improvement by means of benchmarking
***10.*** Dietary intake, meal pattern and physical activity in children and adolescents with type 1 diabetes
***11.*** Diabetes in body and mind. The theory of the specific psychological processes in type 1 diabetes
***12.*** Children and adolescents with diabetes - present state and future possibilities - A population-based study of factors affecting competences and treatment results in children and adolescents with type 1 diabetes
***13.*** Childhood diabetes and celiac disease – a population based study
***14.*** Serotonin receptor mutations, psychological state and metabolic control in childhood diabetes
***15.*** A systematic, nationwide study of diabetes team resources in paediatric departments

***Obesity and type 2 diabetes:***
***16.*** Pathways to social inequalities in childhood weight development and overweight in Norway. Sub-study of The Mother and Child National Cohort

***Group members:***
- Hans-Jacob Bangstad, Consultant physician dr.med.
  Project: Diabetic nephropathy in children and adolescents. Microalbuminuria, hypertension and putative risk factors in the Norwegian pediatric patients

*Ph.D. students:*

- Hanna Dis Margeirsdottir, M.D., pediatrician
  Projects: 6, 8, 9, 10, 13
- Jon Haug, Psychologist, Project 11
- Lars Krogvold, M.D., pediatrician
  Project 1, 2, 3
- Kari Anne Sveen, M.D., physician
  Project 7
- Dag Helge Frøisland, M.D., pediatrician
  Project 12, 14
- Martin Heier, M.D., pediatrician
  Project 8
- Sara Hammerstad, M.D., endocrinologist
  Project 5
- Unni Mette Køpp, M.D., pediatrician
  Project 16

*Master students:*

- Siv Janne Kummernes, R.N., diabetes specialist nurse. Project 15.
- Ingvild Ellingsrud, medical student
  Project 13
- Marie D. Tonga, medical student
  Project 13
- Stig Tollefsen, PhD.
  Project 1, 3
- Nina Øverby Ph.D., dietician
  Project 10

## Group leader: Geir Joner

Group name: Geir Joner's research group

***Research focus:***
Etiology, epidemiology and prevention of childhood onset diabetes and its complications

***1. Projects:***
***Prospective study of diabetes in children and adolescents in Norway.***
Study ongoing since 1989 collecting data on all newly-diagnosed cases of diabetes 0-17 years in Norway. Personal, clinical data and biological samples for studies on the etiology of diabetes, gene-environment interaction, clinical course, complications, mortality and QL. All data included in the nationwide Norwegian Childhood Diabetes Registry. PI: Prof. Geir Joner, Co-PI: Prof. Pål R. Njølstad (Bergen) and Prof. Dag E. Undlien (Oslo). Collaborators: Lars Chr. Stene and Torild Skrivarhaug (Oslo).

***2. Epidemiology of complications, mortality and causes of death in Norway 1956-2015.***
Clinical follow-up of different national cohorts of diabetes patients diagnoses 1956-66, 1973-1982 and 1989-2008. Studies trends in mortality, temporal changes in causes of death and risk factors for premature death. PI: Torild Skrivarhaug. Co-PI: Geir Joner. Collaborators in clinical endocrinology, pathology and forensic medicine.

***3. Environmental factors and t1d in children. A case-control study of early diet, genes, and development of type 1 diabetes (T1D).***
Merged with nuclear family triads for studies of novel genetic susceptibility loci in T1D and celiac disease and gene-gene interaction studies in T1D. Material from the Norwegian Childhood Diabetes Registry. PI: Lars Chr. Stene. Co-PI: Geir Joner. Collaborators: Kjersti Skjold Rønningen, Dag E. Undlien, Jens P. Berg and Per Thorsby (Oslo).

***4. Pregnancy outcome in families with type 1 diabetes.***
PhD-project. A study on pregnancy complications, malformations, prematurety and prenatal mortality in families where the mother or father has t1d. Record-linking between the Norwegian Childhood Diabetes Registry and the Medical Birth Registry of Norway. Ph-student Ingvild Eidem (MD). PI: Lars Chr. Stene. Collaborators. Prof. Tore Henriksen, Prof. Kristian F. Hanssen and Siri Vangen, MD, PhD.

***5. Clinical characteristics/detailed description of phenotype of newly diagnosed children with diabetes;***
1000 newly diagnoses cases from the Norwegian Childhood Diabetes Registry – study of classification based on HLA, auto antibodies and clinical data. PI: Geir Joner. Co-PI: Torild Skrivarhaug, MD, PhD. Collaborators: Prof. Dag Undlien, Lars Chr. Stene, Prof. Pål R. Njølstad, Marit Bjørnvold.

***6. Maternal virus infections and nutrition in pregnancy as risk factor for type 1 diabetes in children.***
PhD-project. Nested case control study on the effect of omega-3-fatty acids, with D and viral markers in pregnant women on the risk of t1d in the offspring. Linking the Norwegian Childhood Diabetes Registry with a biobank with sera from a cohort of 30 000 pregnant women. Ph-student Ingvild Menes Sørensen. PI: Geir Joner, Co-PI: Lars Chr. Stene. Collaborators: Prof. Anne Eskild and Prof. Pål Jenum, Prof. Heiiki Hyöty (Turku).



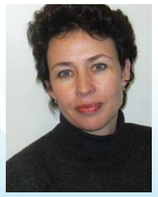
***7. The MIDIA-study.***
The MIDIA-study, a prospective cohort study initiated at the NIPH in 2001. Newborns have been screened for HLA genes conferring risk for type 1 diabetes and enrolled for follow-up if carrying the high-risk genotype. Follow-up with serial blood samples for islet autoantibody testing and identification of biomarkers, as well as with very frequent stool samples for molecular identification of infections. The aim is to identify internal viral infections as risk factors for t1d in children. Extended case-finding in the Norwegian Childhood Diabetes Registry. PI: Kjersti Skjold Rønningen, NIPH. Collaborators: Lars Chr. Stene, Geir Joner and others.

***8. The MO-BA-DIA-study.***
The Norwegian Mother and Child Cohort - Sub study on diabetes. The MoBa database is established with data and biological samples from mother and child in pregnancy and by time of delivery (approx. 1000 pregnancies). This unique database will be linked to the Norwegian Childhood Diabetes Registry to study environmental risk factors and gene-environment interactions related to t1d with nested case-control design. PI: Lars Christian Stene, Co-PI: Geir Joner. Collaborators: Prof. Per Magnus, NIPH and others.

***9. Health consequences and obesity in children and adolescents.***
Study on children and adolescents included in "The Oslo Adiposity Intervention Study" including markers of metabolic syndrome and insulin resistance and effect of intervention on BMI z-zcore and biochemical markers. Ph-student. Magnhild P. Kolsgaard, PI. Geir Joner. Collaborators: Prof. Dag Undlien, Lars Retterstøl, MD, PhD, Prof. Serena Tonstad, Prof. Lene Frost-Andersen

***Group members:***

- Lars Christian Stene, Ph.D.,
  epidemiologist, senior researcher
- Torild Skrivarhaug, M.D., Ph.D.,
  senior physician and Director of The Norwegian Childhood Diabetes Register
- Ingvild Menes Sørensen, M.D., Ph.D.-student
- Ingvild Eidem, M.D., Ph.D. student
- Magnhild Pollestad Kolsgaard, clinical nutritionist, Ph.D.-student



## Chairperson of the Registry: Torild Skrivarhaug

Group name: The Norwegian Childhood Diabetes Registry

***Research focus:***
The main research focus in this population-based, nation-wide childhood-onset diabetes registry:

- Epidemiology in childhood-onset diabetes
- Quality in childhood diabetes care including nation-wide benchmarking of all pediatric departments treating children with diabetes in Norway

***Projects:***
***Incidence and prevalence of childhood-onset type 1 diabetes in Norway.***
This is the first time The Norwegian Prescription Database at the National Institute of Public Health project are linked with the purpose to give information about incidence of childhood onset type 1 diabetes and completeness of The Norwegian Childhood Diabetes Registry.

***Classification of childhood-onset diabetes in Norway.***
The aim of this project is to study the epidemiology of different forms of diabetes and to classify incident cases on the basis of family history, clinical data, C-peptide, auto antibodies and HLA-genotypes.

***Co-morbidity in children and adolescents with type 1 diabetes.***
This is a sub study of The Norwegian Childhood Diabetes Registry assessing competencies and coping; factors affecting functional and dysfunctional behavior in children and adolescents with diabetes.

***A systematic nationwide study of diabetes team resources in paediatric departments.***
The aim of this project is to assess the multi-disciplinary resources allocated to different paediatric departments treating diabetes in Norway and the relation to key clinical outcome data.

***A national, population based study of the double diagnosis of celiac disease and type 1 diabetes.***
The aim is to investigate the relationship between type 1 diabetes and celiac disease and to explore the extent of symptoms, treatment and quality of life.

***Diabetes in children, a global comparative study.***
This study will be carried out in Norway, USA, Australia, Canada and India. The aim of this study is to assess 1) the difference in epidemiology of type 1 and type 2 diabetes, 2) the differences in treatment, treatment guidelines and key clinical outcome data in different paediatric departments in these countries.

***Ethnicity and diabetes in the Nordic countries.***
This project is collaboration between the Nordic Childhood Diabetes Registries (Sweden, Denmark, Iceland and Norway). The aim is to assess if ethnicity is an independent factor influencing metabolic control in children and adolescents with type 1 diabetes residing in Nordic countries.

***Group members:***
- Geir Joner, Professor dr.med.
- Knut Dahl-Jørgensen, Professor dr.med.
- Siv Janne Kummernes, Research nurse
- Ann Kristin Drivvoll, statistician

## Group leader: Dag Undlien

Group name:
Diabetes genetics group,
Department of medical genetics,
Oslo University Hospital

***Research focus:***
Genetics and epigenetics of type 1 diabetes and other immune-mediated diseases. Genetics of obesity.

***Projects:***
Epigenetics of immune mediated diseases
Genetics and epigenetics of asthma
Genetics of Addison's disease.

***Group members:***
- Beate Skinningsrud, Ph.D. student
- Kristina Gervin, Ph.D. student
- Gregor Gilfillan, Ph.D., postdoc
- Monica Cheng Munthe-Kaas, M.D., Ph.D., postdoc
- Hanne Akselsen, Research engineer
- Kristin Brandal
- Hanne Hjorthaug
- Teresia Wangensteen, Ph.D



## Group leader: Kåre Birkeland

Group name: Research group for type 2 diabetes

***Vision:***
To make a significant contribution to the understanding of type 2 diabetes, both to lessen the burden of disease for people with diabetes and to prevent more people from getting type 2 diabetes.

***Research focus:***
Epidemiology, etiology, pathogenesis, prevention and treatment of type 2 diabetes.

***Research facilities:***
The Diabetes Research Laboratory at the Department of Endocrinology at Oslo University Hospital is a clinical research laboratory with expertise and facilities for eu- and hyperglycemic clamp examinations, oral and intravenous glucose tolerance testing, meal challenges, indirect calorimetry and muscle and fat biopsies. We have close collaboration with the Analytical and Research divisions of the Hormone Laboratory that have a broad range of analytical methods e.g. immunoassay, HPLC, GC-MS, LC-MS and molecular biology.

***Projects:***
The main projects at present are
***1.*** The STORK-Groruddalen study, a study of 800 pregnant multiethnic women investigating the effect of ethnicity and a range of environmental determinants on the prevalence of gestational diabetes (GDM), intrauterine growth and development and birth weight and anthropometric measures in the children.
***2.*** The DIVINE – a prospective, randomized, controlled trial of high dose D-vitamin supplementation in subjects with type 2 diabetes evaluating the effect on insulin sensitivity and a range of related outcomes.
Other important projects include genetic and functional studies of the Liver-X-receptor and its interaction with other nuclear receptors, a follow-up study of women with previous GDM and a comparative study of younger adults with type 2 diabetes from Norway and Pakistan. We also participate in several multicenter pharmacological intervention studies in subjects with type 2 diabetes.

***Group members:***
- Anne Karen Jenum, post.doc.
- Karianne Solaas, post.doc.
- Per M. Thorsby, Consultant
- Anne-Marie Aas, Ph.D.
- Cecilie Wium, Ph.D student
- Kirsti Bjerkan, Ph.D. student
- Hanne L. Gulseth, Ph.D. student
- Erlend T. Aasheim, Ph.D. student
- Anh Thi Tran, Ph.D. student
- Line Sletner, Ph.D. student

## Group leader: Benedicte Lie

Group name:
Benedicte Lie group

***Research focus:***
Our main research focus is to identify and characterize genetic factors which are predisposed to type 1 diabetes and other autoimmune diseases.

***Projects:***
We have systematically assess the gene expression profile of several novel type 1 diabetes and autoimmune risk genes, identified by genome-wide association studies, in thymic tissue and correlated expression levels with risk genotypes. An association between risk variants and level of gene expression has so far been observed for CLEC16A and IRF5. We are currently expanding these studies to include evaluation of alternative transcripts, allele specific gene expression profiling and inclusion of more genes.
We have published several studies this year where we have further dissected the MHC-linked genetic predisposition to type 1 diabetes. We have found that at least four additional risk factors exist in the MHC, including HLA-B, near HLA-G, near HLA-DPB1, near AIF1 and in the extended class I region. Hence the genetic contribution to type 1 diabetes from this major genetic determinant, harboring numerous immune genes, is both multifactorial and complex.
Another ongoing project is to explore the genetic risk profile of patients having both type 1 diabetes and celiac disease, as these two diseases both share and have distinct predisposing genetic variants. Some shared susceptibility variants also have opposite or different risk alleles. Hence, it will be interesting to see whether the patients with both diagnoses have a more type 1 diabetes like or celiac disease like genetic risk profile.

***Group members:***
- Marte K. Viken, Post doc
- Gry B.N. Nordang, Ph.D. student
- Haleh Saeedi, Master student
- Siri Flåm, Medical laboratory scientist

## Group leaders: Tore Henriksen/ Jens Bollerslev

Group name: Diabetes and Pregnancy

***Research focus:***
Diabetes and Pregnancy, Nutrition and pregnancy.

***Projects:***
The STORK study aims at finding the reasons for the increase in large babies at birth in Norway. To be born too large can have detetrimal consequences for both mother and child. In addition to delivery complications, the health of the child may be affected in the long term. In a similar way as children who are born very small, children who are born large, develop more overweigh, diabetes and possibly some forms of cancer in adult life compared to those who are born with normal birth weight.

The STORK study has from 2002 to 2005 prospectively followed 553 women through pregnancy and birth. They were investigated with ultrasound three times and twice with glucose tolerance test.

The STORK study showed that lack of physical activity and overweight before pregnancy increased the risk of giving birth to large babies. Lack of physical activity before pregnancy may also be a contributing factor for serious laceration during delivery. Some overweight women had normal weight babies and others had large babies. In the overweight women who delivered large babies, the fasting blood glucose levels increased during

pregnancy in contrast to the overweight women who delivered normal weight babies. Male babies had an association with their father's birth weight. The mother's blood glucose levels during pregnancy had two times the influence on females birth weight compared to males. Girl`s birth weight were more influenced by mother's weight gain during pregnancy than boys.

We monitored beta-cell function and insulin sensitivity glycemic control in the STORK project. Insulin sensitivity (Matsuda index) and beta-cell function (ratio of AUC (insulin) to AUC (glucose), AUC (ins/glc)) were calculated from 520 complete tests, and subsequently beta-cell function was adjusted for insulin sensitivity, rendering an oral disposition index (DI (o).

2.1% had gestational diabetes mellitus (GDM1) at weeks 14-16, and 9.4% at weeks 30-32 (GDM2), which is higher than that previously reported in this region. In the subdivision of OGTT, more overweight (body mass index>25) was found in glucose-intolerant groups (glucose-tolerant women (normal glucose tolerance, NGT) 38 versus GDM2 women 58 and GDM1 women 82%, P<0.005). In early pregnancy, insulin sensitivity was lowest in GDM1, intermediate in GDM2, and highest in NGT. In late pregnancy, insulin sensitivity decreased in all groups, most in gestational diabetes. beta-cell function demonstrated minor shifts during pregnancy, but when adjusted for decreasing insulin sensitivity, DI(o) levels fell by 40% (P<0.001). DI (o) was significantly attenuated relative to glucose intolerance (GDM1 25% and GDM2 53%) during pregnancy. In overweight women, DI (o) levels were lower throughout pregnancy (P<0.001 versus normal weight women), this reduction was significant (P<0.01) in both NGT (21-25%) and GDM2 subjects (26-49%).

CONCLUSION: beta-cell function adjusted for insulin sensitivity (DI (o)) deteriorated during pregnancy in both glucose-tolerant and glucose-intolerant women. The failure to compensate the decrease in insulin sensitivity was accentuated in overweight women.

***Group members:***

- Nanna Voldner, Ph.D. 100%. Glucose intolerance, overweight and pregnancy
- Tove Lekva, Ph. Student 100%. Diabetes and pregnancy
- Camilla M. Hoff., Ph.D.Student 100%. Inflammation, overweight and pregnancy
- Elisabeth Qvigstad Postdoc. 100%. Diabetes and pregnancy
- Marie Cecilie Paasche Roland Ph.D. Student 100%. Foetal growth and pre-eclampsia
- Kathrine Frey Frøslie Ph.D. Student 100%. Diabetic and other factors influencing foetal growth, Path analysis

## Group leader: Trond Jenssen

Group name: Diabetic nephropathy

***Research focus:***
Post-transplant diabetes mellitus. Transplantation of insulin producing islets of Langerhans and of vascularizec pancreas grafts. Molecular mechanisms of diabetes nephropathy.

***Projects:***

1. 10-years follow-up of type 1 diabetes patients transplanted with either single kidney grafts or simultaneous pancreas-kidney grafts
2. Mechanisms of post-transplant diabetes mellitus
3. Long-term follow-up and cardiovascular complications of patients who have developed post-transplant diabetes mellitus
4. Molecular mechanisms of diabetes nephropathy in transplanted kidneys
5. Islet cell transplantation

***Group members:***

- Anders Hartmann, M.D., Ph.D., Consultant/ Professor of Medicine
- Karsten Midtvedt, M.D., Ph.D., Consultant
- Henrik Bergrem, M.D., Research Fellow
- Tone Valderhaug, M.D., Research Fellow
- Svein O Kolset, Ph.D., Professor of Medicine
- Line Grønning-Wang, Dr.scient
- Trine Marita Reina, Cand.scient



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Birkeland KI, Gulseth HL, Gjelstad IMF, Lovegrove JA, Blaak EE, Lopez-Miranda J, Defoort C, Dembinska-Kiec A, Karlström A, Roche HM, Drevon CA. Relationship between Vitamin D Status and Insulin Secretion and Action assessed by the Frequently Sampled Intravenous Glucose Tolerance Test in Subjects with the Metabolic Syndrome, poster ADA 2009, New Orleans 2009.

Birkeland KI, Gulseth HL, Drevon CA on behalf of the LIPGENE-consortium Relationship between Vitamin D Status and Insulin Secretion and Action assessed by the Frequently Sampled Intravenous Glucose Tolerance Test in Subjects with the Metabolic Syndrome. Vintermøtet Norsk Selskap for Endokrinologi, Solstrand, March 2009.
Birkeland KI. European Congress in Preventive Cardiology, Stockholm: How to wage war on physical inalctivity?

Birkeland KI. Nasjonalt diabetesforum, Oslo 23-24. april. Metabolsk syndrom hos barn og unge. Uoppdaget diabetes. Behandling av type 2 diabetes – nye retningslinjer.

Birkeland KI. Behandling av type 2 diabetes. Diabetesmøte for leger i sjukehus og allmennpraksis. Nordlandssykehuset, Bodø, April 2009.

Birkeland KI. Insulin Induced Weight Gain - Potential Mechanisms and Consequences? NOS-M Seminar: "Current Approaches to Metabolic and Nutritional Disorders: From Genes to Prevention" Soria Moria Conference Centre, Oslo, Norway, August 28.

Birkeland KI. Internasjonalt diabetesmøte, Wien, 11. juni 2009: "The new long-acting insulin analogue SIBA: Results from phase 1 and phase 2 studies." Novo Nordisk Pharma.

Birkeland KI. "Hot topics" meeting Gardermoen Nov 6, 2009: "Treat to target in diabetes". Abbot.

Frigstad SO, Haukeland JW, Søvik TT, Schou CF, Aasheim ET, Konopski Z. Liver failure after malabsorptive bariatric surgery. Annual Meeting of the Norwegian Society for Gastroenterology, Lillehammer 2009.

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Gjelstad IMF, Norheim F, Raastad T, DrevonCA. Altered mRNA expression levels of lipid droplet coat protein in human skeletal muscle during strength training, poster NUGO week 2009.

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Gulseth HL. Nasjonalt diabetesforum, Oslo 23-24. april. Nytt fra behandling av type 2 diabetes.

Hanssen KF. Diabetes og Graviditet. Møte i Harstad 21. september 2009.

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Johnson LK, Hofsø D, Oppedal B, Aasheim ET, Tanbo T, Holven KB, Hjelmesæth J. Circulating concentrations and dietary intake of vitamin D in Norwegian morbidly obese patients, Nordic Obesity Meeting, Oslo 2009.

Joner G. Is there a change in the incidence of diabetes types in Norway? Invited lecture and abstract presented at the 44th Annual Meeting of the Scandinavian Society for the Study of Diabetes, Bergen, April 24-26, 2009.

Kolsgaard MP, Joner G, Anderssen SA, Tonstad S, Andersen LF. The Oslo Adiposity Intervention Study. Improved BMI-z score, insulin sensitivity and physical fitness. Abstract presented at the 27th Annual Scientific Meeting of The Obesity Society, Washington DC, October 24-28, 2009. Obesity 2009; 17(Suppl 2):182.

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Skrivarhaug T. Free range living with diabetes. Diabetes in the young, The Royal Society of Medicine, February 24, 2009, London.

Skrivarhaug T. What is the prognosis for the present children with type 1 diabetes? SSSD, Scandinavian Society for the Study of Diabetes, 44th Annual Meeting, April 24-26, 2009, Bergen, Norway.

Skrivarhaug T. Childhood-onset diabetes and the Norwegian Childhood Diabetes Registry. The Friday meeting, Oslo University Hospital, Ullevål, May 8, 2009.

Skrivarhaug T. Increasing weight in children and youth with type 1 diabetes? National paediatric meeting, Novo Nordisk, Sundvollen Oct 16,.2009.

Skrivarhaug T. Childhood onset diabetes in Norway; Treatment, epidemiology, research. Norges Diabetesforbunds lokallag for barn og unge i Oslo, Quality Hotel & Resort Sarpsborg 25.10.2009.

Skrivarhaug T. The impact of overweight, physical activity and nutrition. Hypoglycaemia: The fear of hypoglycaemia. How dangerous is hypoglycaemia? Celiac disease: Clinic and Science. Childhood diabetes meeting 24.11.2009, Oslo.

Skrivarhaug T, Kummernes SJ, Drivvoll AK, Brunborg C, Margeirsdottir HD, Njølstad PR, Joner G, Dahl-Jørgensen. Nation-Wide Quality Work in Childhood-Onset Diabetes - National Childhood Diabetes Registry Increases Awareness among Paediatricians Treating Childhood-Onset Diabetes. Poster presentation and abstract at the 35th Annual Meeting of the International Society for Pediatric and Adolescent Diabetes (ISPAD), Ljubljana, Slovenia, September 2-5, 2009. Paediatric Diabetes 2009;10(Suppl 119):81

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Stene LC, Undlien DE, Rønningen KS, Joner G. Does the relative risk for type 1 diabetes conferred by HLA, INS and PTPN22 polymorphisms vary by perinatal factors? Abstract presented at the 10th International Congress of the Immunology of Diabetes Society, Malmö, May 17-20, 2009.

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Sørensen IM, Joner G, Jenum PA, Eskild A, Stene LC. Maternal fatty acid status during pregnancy and risk of type 1 diabetes in the offspring (Abstract). Diabetologia 2009;52 (suppl 1):S464. Poster presentation at the 45th European Association for the Stury of Diabetes (EASD). Annual Meeting in Vienna, Austria, September 29 – October 2, 2009.

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Aasheim ET, Frigstad SO, Søvik TT, Schou CF, Konopski Z, Haukeland JW. Hypoglycaemia after bariatric surgery: A case report. Annual Meeting of the Norwegian Society for Chemical Pathology, Oslo 2009.

Aasheim ET. Wernicke encephalopathy: A rare, but severe complication of bariatric surgery. Annual Meeting of the Norwegian Society for Clinical Nutrition, Oslo 2009.

### *Thesis:*

Anne Blomhoff: “Genetic predisposition to autoimmune diseases. Studies of polymorphisms in the HLA complex and the CTLA4 gene”, 2009.

Marit Bjørnvold: “Candidate gene studies in type 1 diabetes and other immune-mediated diseases”, 2009.

### *Book chapters:*

Jenum AK (2009). Etniske og kulturelle faktorers betydning for helse. In Mæland J.G, Elstad J.I, Næss Ø, og Westin S (Eds.), Sosial Epidemiologi (pp.170-192), Gyldendal Akademisk.

Östensom C-G, Henriksson J, Birkeland K. Diabetes mellitus – type 1. In Bahr, R (Eds) Aktivitetshåndboken. Fysisk aktivitet i forebygging og behandling (chapter 22) Helsedirektoratet 2009.

### *Populærvitenskap og annen formidling:*

Birkeland KI. Insulinbehandling ved type 2 diabetes. Indremedisineren 2009 nr 3.

Birkeland KI. Forskningsspalten, Diabetes (Tidsskrift for Norges Diabetesforbund, opplag ca 35 000). Fast spalte i hvert av 7 nummer som omhandler aktuelt fra diabetesforskning.

Birkeland KI. TV 2 God morgen Norge, 12. november, intervju i forbindelse med Verdens diabetesdag.

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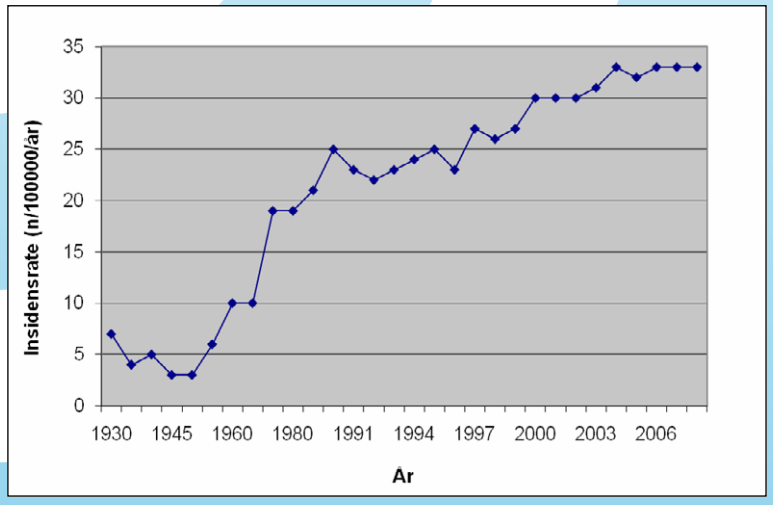


*Incidence for type 1 diabetes in Norway is increasing dramatically*

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