

# Oslo Diabetes Research Centre



## Big is not necessarily better (macrosomia)

- Fat shoulders
- Short neck
- Big cheeks
- Red skin
- Lots of hair

Induced by high levels of maternal  
postprandial glucose

See page 11-13 for comments on  
research into big babies

# CONTENT

|  |           |
|--|-----------|
| <b>1. Steering Committee for Oslo Diabetes Research Centre</b> .....         | <b>2</b>  |
| <b>Board for Aker and Ullevål Diabetes Research Fund</b> .....               | <b>2</b>  |
| <b>Collaborating partners</b> .....  | <b>2</b>  |
| <br>   |           |
| <b>2. Another satisfactory year!</b>   |           |
| <b>Kristian F. Hanssen</b> .....   | <b>4</b>  |
| <br>   |           |
| <b>3. Report from the research groups</b>                                    |           |
| <b>Kristian F. Hanssen</b> .....   | <b>6</b>  |
| <b>Knut Dahl-Jørgensen</b> .....   | <b>7</b>  |
| <b>Geir Joner</b> .....  | <b>8</b>  |
| <b>Torild Skriverhaug</b> .....  | <b>9</b>  |
| <b>Dag Undlien</b> .....   | <b>10</b> |
| <b>Benedicte Lie</b> .....   | <b>11</b> |
| <b>Kåre Birkeland</b> .....  | <b>11</b> |
| <b>Tore Henriksen/Jens Bollerslev</b> .....                                  | <b>12</b> |
| <b>Trond Jenssen</b> .....   | <b>13</b> |
| <b>Jens Petter Berg</b> .....  | <b>14</b> |
| <br>   |           |
| <b>4. Scientific production</b>  |           |
| <b>Publications</b> .....  | <b>14</b> |
| <b>Accepted Papers</b> .....   | <b>16</b> |
| <b>Some national and international presentations/abstracts/posters</b> ..... | <b>17</b> |
| <b>Thesis</b> .....  | <b>19</b> |
| <b>Book chapters</b> .....   | <b>19</b> |

Picture frontpage: Macrosomia

## Steering Committee for Oslo Diabetes Research Centre

- Kåre Birkeland, Professor dr.med.
- Knut Dahl-Jørgensen, Professor dr.med.
- Kristian F. Hanssen, Professor dr.med.
- Geir Joner, Professor dr.med.
- Benedicte Lie, Professor dr.med.
- Dag Undlien, Professor dr.med.
- Trond G. Jenssen, Professor dr.med.
- Tore Henriksen, Professor dr.med.
- Jens Bollerslev, Professor dr.med.
- Jens Petter Berg, Professor dr.med.
  
- Beth Tyrddal, Research secretary

## 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

## Collaborating partners

### **Oslo University Hospital**

- Harald Arnesen, Professor dr.med. (Em),  
Cardiology Department
- Ragnheidur Bragadottir, Consultant dr.med.,  
Ophtalmological Department
- Magne Brekke, Consultant,  
Dep of Interventional Radiology
- Cathrine Brunborg, Statistician,  
Centre for Clinical Research
- Helene Holm, Midwife/Diabetes nurse,  
Dep of Obstetrics and Gynecology
- Peter Kierulf, Professor dr.med. (Em),  
Dep of Clinical Biochemistry
- Leiv Sandvik, Ph.D., Centre for Clinical Research
- Ingebjørg Seljeflot, Professor Ph.D.,  
Centre for Clinical Research
- John Wilson, Consultant dr.med.,  
Dep of Neurophysiology
- Mario Gaarder, Dep of Radiology
- Ellen Jørum, Professor dr.med.,  
Dep of Neurophysiology
- Kristin Ørstavik, Ph.D., Dep of Neurophysiology
- Bassam Karime, Ph.D., Dep of Neurophysiology

- Kjetil Steine, Ass. Professor dr. med.,  
Dep of Cardiology, AHUS
- Tone Nerdrum, Consultant Ph.D.,  
Dep of Cardiology, AHUS
- Reidun Mosand, Diabetes nurse
- Anders Hartmann, Professor, Dep of Nephrology
- Ludvig Sollid, M.D. Professor,  
Institute of Immunology
- Erik Thorsby, Professor dr.med.,  
Institute of Immunology
- Siri Vangen, Consultant dr.med.,  
Centre for Women's health
- Haakon Stenseth, M.D., Dep Radiology
- Frode Lars Jahnsen, M.D. Ph.D.,  
Dep of Pathology
- Bjørn Edwin, M.D. Ph.D, Dep of Surgery,
- Arne Rosseland, M.D. Ph.D., Dep of Surgery

#### **Department of Nutrition University of Oslo**

- Lene Frost Andersen, Professor dr.philos.
- Christian A. Drevon, Professor dr.med.
- Per Ole Iversen, Professor dr.med.
- Svein Olav Kolset, Professor dr.philos.
- Hilde Nebb, Professor
- Margareta Wandel, Professor
- Lena Grønning-Wang, Ph.D.

#### **Asker and Bærum Hospital**

- Odd Erik Johansen, Dr.med.

#### **Norwegian Institute of public health**

- Sidsel Graff-Iversen, Researcher Ph.D.
- Kjersti Skjold Rønningen, Professor dr.med.
- Wenche Nystad, Ph.D.

#### **Institute for general practice and public health, University of Oslo**

- Gerd Holmboe-Ottesen, Professor dr.philos.
- Bernadette Kumar, Cand.med., Ph.D. student
- Bjørgulf Clausen, Professor dr.med.
- Akthar Hussain, Professor dr.philos.

#### **Norwegian School of Sports Science**

- Roald Bahr, Professor dr.med.
- Sigmund Andersen, Professor dr.philos

#### **Lillehammer University College**

- Finn Skårderud, Professor Ph.D.

#### **Helseundersøkelsen i Nord-Trøndelag (HUNT)**

- Kristian Midthjell, Professor dr.med.

#### **University of Bergen, Haukeland University Hospital**

- Rolv Terje Lie, Professor, Medical Birth Registry
- Pål Rasmus Njølstad, Professor dr.med.,  
Dep of Pediatrics
- Oddmund Søvik, Professor dr.med. (Em),  
Dep of Pediatrics
- Trond Markestad, Professor dr.med.,  
Dep of Pediatrics

#### **Bergen University College**

- Marit Graue, Ph.D., Assoc. Professor

#### **University of Northern Norway**

- Svein Ivar Mellgren, Professor dr. med.,  
Dep of Neurology

#### **Sunnås sykehus**

- Nils Hjeltnes, Consultant dr.med.

#### **Others**

- Jacob R. Larsen, M.D. Ph.D., Medical Director

#### **International Collaborators**

- Prof Vincent Monnier, CWRU, Cleveland,  
Ohio, USA
- Prof Timothy Lyons, Oklahoma University,  
Oklahoma, USA
- Prof Alicia Jenkins, University of Melbourne,  
Australia
- Prof Johnny Ludvigsson, Linköping University,  
Sweden
- Prof Mikael Knip, Helsinki University, Finland
- Prof Heikki Hyöty, University of Tampere, Finland
- 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

## Another satisfactory year!

2010 was a highly satisfactory year for Oslo Diabetes Research Centre.

We had five candidates majoring for Ph.D:

**Jon Haug, Clinical psychologist. Diabetes in body and mind - the theory of the specific psychological processes in type 1 diabetes.** He has developed an unique theory of the relationship between the somatic and psychological challenges living with type 1 diabetes. These principles may probably be implemented for other chronic diseases as well.

**Nanna Voldner, Cand. san. Modifiable determinants of newborn macrosomia and birth complications.** The study aimed to identify factors participating to large babies. Among overweight mothers giving birth to large babies, in the STORK study e.g., fasting blood glucose increased during pregnancy in contrast to those giving birth to normal weight babies.

**Erlend T. Aasheim, Cand.med. Vitamin concentrations in Scandinavian obese subjects undergoing surgical and non-surgical weight loss.** An increasing number of patients with extreme obesity is undergoing adipose surgery, but not without a lot of risks. This thesis focuses on vitamin deficiency following surgery.

**Hanne L. Gulseth, Cand. med. "Diet and the metabolic syndrome – The LIPGENE dietary intervention study"** has studied the relationship between dietary factors and metabolic syndrome in a large EU project. They performed a diet intervention study where changes in fat amount and composition were studied with regard to insulin secretion and insulin sensitivity.

**Henrik Andreas Bergrem, Cand.med. Hyperglycaemia before and after renal transplantation.** Blood glucose measurements are important before and after renal transplantation. Many patients develop diabetes after renal transplantation and this has a deleterious effect on prognosis.

We here highlight some few areas in our research. For a more comprehensive survey, see the individual reports from the research groups. We still do not know what initiates the autoimmune process in type 1 diabetes, but our research centre has several new and important projects in this field

(see the individual research groups).

**Pregnancy and type 1 diabetes.** We have coupled the birth registry and the Norwegian Childhood Diabetes registry and studied more than 1400 pregnancies and their outcome. This project is the Ph.D. project of Ingvild Eidem working at the National Institute of Public Health. She has identified as have others that there still is an increased burden in these babies with increased rate of malformation, sudden intrauterine deaths and pre-eclampsia. The hypothesis is that most of these unfortunate events are due to the fact that we are still not able to totally normalize the blood glucose levels in these pregnant mothers. In addition we have performed a large prospective study in pregnant type 1 diabetes together with groups in Australia and the US looking at pre-eclampsia which is far more common among type 1 diabetes patients (approx. 20 %) than in other pregnancies. We have identified several angiogenetic factors predicting pre-eclampsia and we are now pursuing other important factors especially lipids.

**Bariatric surgery** is becoming an important treatment option for patients with extreme obesity and many of them have type 2 diabetes which may wane after the operation. The question if their cardio-vascular risk profile changes after operation is an interesting one and is pursued by the type 2 research group.

Our internal seminar (Solstua seminar) this time dealt with low grade inflammation and was held at a large cottage in the woods, Kleivstua. We had speakers from different parts of Oslo University Hospital covering inflammation in genetics, atherosclerosis, obesity, metabolic syndrome and diabetes. We had a lively discussion and got new knowledge of how to interpret these new inflammatory markers.

### Organizational development

We have applied successfully to the regional Health board Helse Sør-Øst to be a Research Group Diabetes for the years 2011-2014 and received a relatively large grant for that period. The regional organization of specialized health care in Norway has come under attack recently. However, it is no doubt from the research point of view this organization has been a major "boost" for research.

We have performed the first Ph.D. course in Diabetes, Endocrinology and Metabolism for the Medical Faculty with 14 Ph.D. students for two days. This method based program was a success

and we will arrange this on a regular basis.

Institute of Nutrition, Institute of Basal Medicine has a strong background and is performing excellent basal and clinical research. We have developed several projects together and in the future we will utilize their strong molecular biology knowledge to create translational projects.

We need more mentors for our Ph.D. students and we are starting a program to support ambitious persons who have already fulfilled a Ph.D. to develop into “independent investigators”.

The joint efforts by the Medical Faculty and Oslo University Hospital to create a common strong research organization is most welcome and is well under way. There is a trend to create larger and larger research groups. This in principle is a great idea and will create a “critical mass” for research. However the need to pull the different research groups together to work towards a common goal is a challenge. In a small research environment, it is difficult to cover all basic questions within the field with such an organization.

The diabetes research in Oslo University Hospital is organized through Oslo Diabetes Research

Centre which is a flexible and robust organization. However, the clinical work in adult diabetes in Oslo University Hospital is going through a difficult transitional phase as the practical organization for patients has not been determined yet.

I mentioned last year in the annual report that Oslo University Hospital had some problems with the future organization. This year it is far worse. It is like a horse trying to cross a river with a heavy current. At the time of writing, the horse is stuck in the middle of the river, not moving anywhere. As you will understand, the horse will not be able to stand there for a undefined period. Somebody has to pull the horse up to the river bed very soon. At the present time, it is difficult to see whom that might be. Hopefully, there will be a comprehensive and future oriented solution soon!

### Major Funding

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



Kristian F. Hanssen  
Chairman Professor dr.med.

| Leader                                 | Work place   | Research Area  | Email   |
|--|--|--|---|
| Kristian F. Hanssen<br>(Chairman)      | Dep of Endocrinology,<br>Oslo University Hospital                    | Diabetic late complications  | k.f.hanssen@medisin.uio.no  |
| Knut Dahl-Jørgensen<br>(vice-chairman) | Pediatric Department,<br>Oslo University Hospital                    | Diabetes in children and adolescents<br>Etiology of type 1 diabetes, complications | knut.dahl-jorgensen@<br>medisin.uio.no                                |
| Geir Joner                             | Pediatric Department,<br>Oslo University Hospital                    | Epidemiology and etiology of type 1<br>diabetes, complications, mortality          | geir.joner@medisin.uio.no   |
| Dag Undlien                            | Institute of medical genetics, Oslo<br>University Hospital           | Genetics and epigenetic of<br>type 1 diabetes                                      | d.a.undlien@medisin.uio.no  |
| Benedicte Lie                          | Institute of Immunology,<br>Oslo University Hospital                 | Genetics in<br>type 1 diabetes   | benedicte.lie@rr-research.no  |
| Kåre I. Birkeland                      | Dep. Of Endocrinology,<br>Oslo University Hospital                   | Prevention and treatment of<br>type 2 diabetes                                     | k.i.birkeland@medisin.uio.no  |
| Jens Bollerslev/<br>Tore Henriksen     | Oslo University Hospital,<br>Dep. Of Endocrinology<br>And Obstetrics | Pregnancy and diabetes   | jens.bollerslev@rikshospitalet.no<br>tore.henriksen@rikshospitalet.no |
| Trond Jenssen                          | Oslo University Hospital,<br>Department of Nephrology                | Diabetic nephropathy   | trond.jenssen@rikshospitalet.no                                       |
| Jens Petter Berg                       | Department of Clinical Biochemistry<br>Oslo University Hospital      | Metabolomics of hyperglycemia  | j.p.berg@medisin.uio.no   |



## Group leader: Kristian F. Hanssen

Research Group: 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:**

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

**A. 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.

**B. 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.

**2. 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.

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

#### **4. 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 normoglycaemia over the same period of time (HbA1c 4.5-5.5%).

- To investigate proteoglycans and glycosaminoglycans 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 samples to test the hypothesis that glycation markers can predict the development and progression of late complication (specifically early diabetic nephropathy and coronary heart disease)

**5. A long term randomized, double blind controlled study of Benfotiamin (vitamin B1) in type 1 Diabetes.** A two year study with neurography as the primary end point.

## **6. A prospective study of pre-eclampsia in type 1 diabetes.**

### **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.



## **Group Leader: Knut Dahl-Jørgensen**

**Research Group: Childhood Diabetes**

### **Research focus:**

The group has four main research areas. The first is the etiology 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 microvascular 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 as intensified insulin treatment and pumps, diabetic nephropathy, diet, physical activity, quality of life and psychosocial problems.

### **Projects:**

#### **Etiology 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
9. Diabetic nephropathy: Hypertension and microalbuminuria in Norwegian children with type 1 diabetes

### **Clinical diabetes:**

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

### **Obesity and type 2 diabetes:**

17. Pathways to social inequalities in childhood weight development and overweight in Norway. Sub-study of The Mother and Child National Cohort

### **Group members:**

#### **Ph.D. students:**

1. Hanna Dis Margeirsdottir, M.D. Pediatrician. Projects: 6, 8, 9, 10, 13. email: h.d.margeirsdottir@medisin.uio.no
2. Jon Haug, psychologist. Project 11. email: psykologjonhaug@gmail.com
3. Lars Krogvold, M.D., Pediatrician. Project 1,2,3. email: lars.krogvold@medisin.uio
4. Kari Anne Sveen, M.D., physician. Project 7. email: k.a.sveen@medisin.uio.no
5. Dag Helge Frøisland, M.D. Pediatrician. Project 12,14. email: dag.froisland@hil.no
6. Martin Heier, M.D. Pediatrician. Project 8. email: martin.heier@ullevaal.no

7. Sara Hammerstad, M.D. Endocrinologist. Project 5. email: s.s.hammerstad@medisin.uio.no
8. Unni Mette Køpp, M.D. Pediatrician. Project 16. email: unni.mette.kopp@sshf.no

**Master students:**

9. Siv Janne Kummernes, R.N. Diabetes specialist nurse. Project 15. email: sivjanne.kummernes@ulleval.no
10. Ingvild Ellingsrud, Medical student. Project 13. email: ingvibel@studmed.uio.no
11. Marie D. Tonga, Medical student. Project 13. email: m.d.tonga@studmed.uio.no

**Postdoc:**

12. Stig Tollefsen, PhD. Project 1,3. email: Stig.Tollefsen@rr-research.no
13. Nina Øverby, Dietician. Project 10. email: nina.c.overby@uia.no

**Senior Independent Investigators:**

14. Hans Jacob Bangstad, MD. Ph.D, Professor. Project 9.



Group leader:  
Geir Joner

Group name: Geir Joner's  
research group

**Research focus:**

Epidemiology of diabetes, type 1 diabetes etiology and prevention. Nutritional factors and viral infections as risk factor for childhood onset type 1 diabetes.

Diabetes complications, epidemiology of complications, risk factors, mortality  
Health care research (quality measurements, quality indicators, inequalities in therapy and access to specialized health services)

**Projects:**

1. **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 Skriverhaug (Oslo).

2. **Epidemiology of complications, mortality and causes of death in Norway 1956-2005.** Clinical follow-up of different national cohorts of diabetes patients diagnosed 1956-1966, 1973-1982 and 1989-2008. Studies trends in mortality, temporal changes in causes of death and risk factors for premature death. PI: Torild Skriverhaug. Co-PI: Geir Joner. Collaborators in clinical endocrinology, pathology and forensic medicine.
3. **Pregnancy outcome in families with type 1 diabetes.** PhD-project. A study on pregnancy complications, malformations, prematurity and perinatal 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 Senior researcher Siri Vangen (MD, Ph.D).
4. **Clinical characteristics/detailed description of phenotype of newly diagnosed children with diabetes;** 1000 newly diagnosed cases from the Norwegian Childhood Diabetes Registry with HLA, autoantibodies and clinical data. PI: Geir Joner (MD, Ph.D) Collaborators: Torild Skriverhaug (MD, Ph.D), Prof. Dag Undlien, Lars Chr. Stene (MSc, Ph.D), Prof. Pål R. Njølstad.
5. **Maternal virus infections and nutrition in pregnancy as risk factor for type 1 diabetes in children.** Ph.D-project. Linking the Norwegian Childhood Diabetes Registry with plasma samples 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.
6. **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. These are followed 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 enteral viral infections as risk factors for t1d



in children. Extended case-finding in the Norwegian Childhood Diabetes Registry. PI: Per Magnus, NIPH. Collaborators: Kjersti Skjold Rønningen and Lars Chr. Stene.

7. **MO-BA-DIA:** The Norwegian Mother and Child Cohort is established with data and biological samples from mother and child in pregnancy and by time of delivery. The cohort is set up to study causes of disease in mother and their offspring. This unique database will be linked to the Norwegian Childhood Diabetes Registry to study environmental risk factors and gene-environment interactions related to t1d. PI: Lars Chr. Stene. Co-PI: Geir Joner. Collaborator: Prof. Per Magnus, NIPH.

**Group members:**

- Group leader: Geir Joner, MD, Ph.D. Senior consultant at Dept. of Pediatrics, Oslo University Hospital Ullevål. Professor, Institute of Health Management and Health Economy, University of Oslo. Project Manager. Supervisor for Ingvild Menes Sørensen and Magnhild P. Kolsgaard.
- Lars Chr. Stene, MSc, Ph.D. Researcher, Norwegian Institute of Public Health, Division of Epidemiology. Supervisor for Ingvild Eidem and Ingvild Menes Sørensen. Research area is etiology of type 1 diabetes and gene-environment interaction.
- Torild Skrivarhaug, MD, Ph.D. Director, The Norwegian Childhood Diabetes Registry. Research on diabetes complications and mortality.
- Ingvild Menes Sørensen, MD, Ph.D-student. Research projekt: "Maternal virus infections and nutritional status during pregnancy and risk of type 1 diabetes in children."
- Ingvild Eidem, MD, Ph.D-student. Research project: Pregnancy outcome in families with type 1 diabetes.
- Magnhild P. Kolsgaard, MSc (clinical nutritionist), Ph.D-student. Research project: Health consequences of obesity in children and adolescents (Subproject in "The Oslo Adiposity Intervention Study").
- Kjersti S. Rønningen, MD, Ph.D. Senior researcher. Research area is etiology of type 1 diabetes with focus on environmental factors.



## 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 nationwide benchmarking of all pediatric departments treating children with diabetes in Norway.

**Projects:**

1. **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 and The Norwegian Childhood Diabetes Registry are linked with the purpose to give information about incidence of childhood onset type 1 diabetes and completeness of The Norwegian Childhood Diabetes Registry.
2. **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, autoantibodies and HLA-genotypes.
3. **Co-morbidity in children and adolescents with type 1 diabetes.** This is a substudy of The Norwegian Childhood Diabetes Registry assessing competencies and coping; factors affecting functional and dysfunctional behaviour in children and adolescents with diabetes.
4. **A systematic nationwide study of diabetes team resources in paediatric departments.** The aim of this project is to assess the multidisciplinary resources allocated to different paediatric departments treating diabetes in Norway and the relation to key clinical outcome data.
5. **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.

6. **Diabetes in children, a global comparative study.** This study will be carried out in Norway, USA, Australia, Canada, Africa, Argentina 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.

7. **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.

8. **Co-morbid diabetes and eating disorders – an exploration of prevalence, psychological correlates and diabetic control.** This project is a collaboration between the Norwegian Childhood Diabetes Registry and the Regional Eating Disorder Service (RASP) at Oslo University Hospital, Ullevål. The aims of this study are to 1) explore the cognitive and behavioural correlates of comorbid type 1 diabetes and eating disorders. 2) assess the prevalence and co-morbid type 1 diabetes and eating disorders in Norway.

9. **Treatment in childhood type 1 diabetes and the transition from pediatric to adult diabetes care – a prospective, population based, nationwide study.** The aims are to 1) assess the extensiveness of treatment with insulin pump in children and adolescents in Norway and to find the predictors for successful insulin pump treatment 2) to describe and evaluate the practices of transition from pediatric to adult diabetes care.

#### **Group members:**

- Torild Skrivarhaug, Consultant dr.med., Director of The Norwegian Childhood Diabetes Registry
- Geir Joner, Consultant dr.med., Professor
- Knut Dahl-Jørgensen, Consultant dr.med., Professor
- Siv Janne Kummernes, R.N., Diabetes nurse, Masterstudent
- Ann Kristin Drivvoll, MSc
- Dag Helge Frøisland, M.D., PhD student
- Line Wisting, Master in psychology, Ph.D student



**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 autoimmune (immune mediated) diseases; genetics of obesity. In our diabetes research we are doing classical genetic association analysis to identify novel susceptibility genes. Further we have for a few years now been doing epigenetic studies in disease discordant twins and have focused on immune-mediated diseases. We are currently looking at psoriasis and asthma in particular, but plan to include also type 1 diabetes. Doing large scale analysis of DNA methylation and histone modifications we are trying to identify disease associated epigenetic variation.

In our genetics of obesity project we have been studying two different patient groups, one hospital based and one population based. The hospital based patient cohort consists of consecutively recruited severely obese adult (BMI>35) and pediatric patients. The population based case control material is from the HUNT study where we have a material of extremely discordant cases (BMI>35) and controls (BMI<25). With these materials we are trying to identify novel disease susceptibility genes by means of association analysis.

#### **Projects:**

1. Genetics of obesity. In this project we have been studying two different patient groups, one hospital based and one population based. The hospital based patient cohort consists of consecutively recruited severely obese adult (BMI>35) and pediatric patients. The population based case control material is from the HUNT study where we have a material of extremely discordant cases (BMI>35) and controls (BMI<25). With these materials we are trying to identify novel disease susceptibility genes by means of association analysis.
2. Genetics of Addison's disease
3. Genetics and epigenetics of asthma
4. The Divid project. Virus identification and functional genomics of the inflamed islets in newly diagnosed type 1 diabetes

### **Group members:**

- Teresia Wangensteen MD, Ph.D,
- Beate Skinningsrud, MSc, Ph.D student,
- Magnus Dehli Vigeland, Ph.D, postdoc,
- Monica Cheng Munthe-Kaas, MD, Ph.D, postdoc,
- Kristina Gervin, MSc, Ph.D student,
- Morten C. Eike, Ph.D, postdoc,
- Hanne Hjørhaug, MSc, research assistant,
- Alice Stormyhr, MSc, research assistant



### **Group leader: Benedicte Lie**

**Group name:**  
Benedicte Lie group

### **Research focus:**

Our main research focus is to identify and characterize genetic factors which predispose to type 1 diabetes and other autoimmune diseases. We also explore the functional relevance of risk variants regarding their influence of gene expression, as well as their clinical relevance on disease progression.

### **Projects:**

1. Correlation between genetic risk variants for type 1 diabetes and other autoimmune diseases and their gene expression in the immunologically important thymus
2. Identification of all risk factors in the major genetic determinant for type 1 diabetes, the HLA complex
3. Differences and similarities between genetic predisposition to type 1 diabetes and celiac diseases addressed in individuals with both diagnosis
4. Copy number variations and predisposition to autoimmune diseases
5. Influence of genetic risk variants on disease progression assessed in rheumatoid arthritis, a disease sharing many risk factors with type 1 diabetes

### **Group members:**

- Marte K. Viken, Post doc
- Gry BN Nordang, Ph.D student
- Marthe Mæhlen, Ph.D student
- Haleh Saeedi, Masterstudent
- Siri Flåm, Technician



### **Group leader: Kåre Birkeland**

**Group name:** Research group for type 2 diabetes

### **Research focus:**

To increase the knowledge about the factors that lead to type 2 diabetes and its complications in a way that on short and long term will make us able to prevent the development of the disease and its complications. Our research includes basic and clinical studies in diabetes pathophysiology, single- and multi-center randomized controlled trials (RCTs) and observational epidemiological studies.

### **Research facilities:**

We work in close collaboration with the Hormone Laboratory that is a core facility for endocrine research in Oslo University Hospital, with a broad repertoire of analytical methods including immunoassays, GC/MS, LC/MS, molecular biology etc. Together we run the Diabetes Research Laboratory situated within the outpatient diabetes clinic, with facilities for oral and intravenous glucose tolerance tests, meal tests, hyper- and euglycaemic clamp studies with tracer methodology, muscle and fat biopsies, indirect calorimetry and measurements of VO<sub>2</sub> max. Furthermore, we collaborate closely with basic medical research groups at Dep. of Nutrition at the Institute of Basic Medical Sciences, University of Oslo and Research Institute for Internal Medicine at Oslo University Hospital Rikshospitalet.

### **Our most important studies in 2010 were:**

1. The STORK-Groruddalen Research program is population-based, prospective cohort study of pregnant women in three multi-ethnic districts of Oslo. The cohort comprises 823 women and their offspring, and constitutes a large database for present and future research into the biochemical, clinical and psychosocial factors that determine gestational diabetes, offspring birth weight and future health for mother and child.
2. The ongoing DIVINE study, a single center, researcher-initiated RCT of high dose vitamin D (cholecalciferol) to subjects with type 2 diabetes and hypovitaminosis D, with main study endpoints being the effects on insulin sensitivity and insulin secretion.

3. Asker and Bærum Cardiovascular Diabetes Study (ABCD) was a RCT of intensive vs. conventional multifactorial intervention to reduce complications in patients with type 2 diabetes. We now collect long term follow-up data on the patients.
4. Follow-up of subjects after bariatric surgery – effects on BMI, nutritional factors and cardiovascular risk factors.
5. Several multicenter pharmacological studies in diabetes. The most important being the ORIGIN study, of which we have the national coordinating responsibility.

**Group members:**

- Kåre I. Birkeland, M.D., Ph.D, professor II, group leader
- Anne Karen Jenum, M.D., Ph.D, post. doc and professor II at University College of Oslo, Senior Researcher at Institute for General Practice,
- Anne Marie Aas, Ph.D Assistant professor II, Department of Nutrition,
- Hanne Løvdal Gulseth, M.D., Ph.D, post. doc
- Erlend Aasheim, M.D., Ph.D.
- John Willy Haukeland, M.D., Ph.D., Senior physician
- Per Medbøe Thorsby, M.D, Ph.D. student
- Cecilie Wium, M.D., Ph.D. student
- Kirsti Bjerkan, Ph.D. student
- Ingrid M Fange Gjelstad, Ph.D. student
- Line Sletner, MD Ph.D. student
- Kjersti Mørkrid, Ph.D. student
- Anne Pernille Ofstad, M.D., Ph.D. student
- Anh Trahn, M.D., Ph.D. student

**Study nurses:**

Åse Halsne and Gøril Vinje,  
Bioengineer Lise Marit Amlie.

**Medical students:**

Elin M. Karlsson, Tuva Wyller, Sara K. Fidjeland,  
Hildegunn Grødal, Thea Drivnes,



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 detrimental 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 overweight, 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 birthweight. 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 glucoseintolerant women. The failure to compensate for 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.D. 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:**

Cardiovascular risk factors and diabetes after organ transplantation. Pancreas and islet cell transplantation. Molecular and morphological changes in the diabetic kidney

#### **Projects:**

1. New onset diabetes after transplantation (NODAT). Occurrence, Pathogenesis, Risk factors, Follow-up and Treatment.  
10-15 % of alle patients undergoing organ transplantation develop NODAT within the first 3 months post tx, and a similar share of patients develops prediabetes (Impaired Glucose Tolerance or Impaired Fasting Glucose). One third of those with prediabetes develop NODAT within six years. Our results from a national database show that a substantial number of patients (10%) undergoes organ transplantation without having an existing pretransplant diabetes diagnosed. Furthermore, NODAT and postchallenge hyperglycemia are significant risk factors for cardiovascular disease and death post-transplant. This was recently published (in 2011).
2. Pancreas transplantation. Long-term development of diabetic and non-diabetic complications. Our results show that the microstructures of the transplanted kidney are better preserved when transplanted together with a pancreas graft. Observation time: 8-10 years. The results are to be presented at the EASD September 2011.
3. Islet cell transplantation. The islet cell transplantation program has improved over the last two years in that more patients become insulin dependent after treatment. The majority reaches insulin independence after two islet cell infusions. Our research is part of a large scientific program on islet cell transplantation developed by the National Institute of Health in the USA.
4. Metabolic risk factors for graft and patient survival in renal transplant patients.
5. Molecular changes in transplanted kidneys, with emphasis on diabetes, the basement membrane and proteoglycans.

### Group members:

- Professor Trond Jenssen OUS Rikshospitalet
- Jørn Petter Lindahl, MD OUS Rikshospitalet
- Professor Anders Hartmann OUS Rikshospitalet
- Karsten Midtvedt, MD Ph.D OUS Rikshospitalet
- Ivar Eide, MD OUS Rikshospitalet
- Professor Finn Reinholt OUS Rikshospitalet
- Professor Svein O Kolset University of Oslo
- Trine Reine, Ph.D University of Oslo
- Annicke Stranda, Ph.D University of Oslo



Group leader:  
**Jens P Berg**

Group name:

### Research focus:

Diabetes is a group of metabolic disorders characterized by hyperglycemia. Our research aims to increase our understanding of the mechanisms leading to and the metabolic consequences of increased blood glucose by studies of small molecule metabolite profiles. We have established methods of metabolomics and multivariate data analysis, which allows the detection and quantification of compounds in complex mixtures, such as the products of metabolism in biological fluids and tissues.

### Projects:

1. Studies of metabolic profiles in gestational diabetes; in collaboration with Dr. Anne Karen Jenum.
2. Metabolic changes during Norwegian and Pakistani meals and during euglycemic glucose clamp; in collaboration with Dr. Cecilie Wium.
3. Urine metabolite profiles and diabetic nephropathy, in collaboration with Dr. Hans-Jacob Bangstad.

### Group members:

- Professor Jens Petter Berg, University of Oslo
- Daniel Sachse, Ph.D student, University of Oslo
- Armin Piehler, MD Ph.D, OUS Ullevål
- Professor Frode Rise, University of Oslo

## Publications:

Amundsen SS, Rundberg J, Adamovic S, Gudjonsdottir AH, Ascher H, Ek J, Nilsson S, Lie BA, Nalwai AT, Sollid LM. Four novel coeliac disease regions replicated in an association study of a Swedish/Norwegian family cohort. *Genes Immun* 2010; 11: 79-86.

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Bangstad HJ. Den vanskelige pasient. Diabetes hos Barn. Sundvollenmøtet 2010.

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Haug J. Når tiden lager alle sår. Seminar. Trondheim. 3 samlinger: 26-28.03.10, 11-12.06.10, 16-17.10.10.

Haug J. Psykologi og diabetes. DIP – kurset, insulin in the prospective pioglitazone clinical trial Stockholm, 22.04.10.

Haug J. Å leve med kronisk sykdom - utfordring og mestring. Preventiv kardiologi, Ullevål sykehus. 26.04.10.

Haug J. Hva endres når man får diabetes? Hvordan kan helsepersonell hjelpe?? Primærmedisinsk Uke, Oslo 26.10.10.

Haug J. Diabetes slitenhet - eksisterer det?. Diabetesforum Oslo/ Akershus, Oslo 10.11.10

Haug J. Diabetes en ensom sykdom. Seminar Norsk Diabetikersenter, Oslo 18.11.10.

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## Thesis (ph.D.), University of Oslo:

Henrik Andreas Bergrem (Ph.D.) Hyperglycaemia before and after transplantation.

Gulseth HL Diet and the metabolic syndrome: the LIPGENE dietary intervention study.

Jon Haug. "Diabetes in body and mind. The theory about specific psychological processes in type 1 diabetes". (Diabetes i kropp og sinn. Teorien om de spesifikke psykologiske prosessene ved Type 1- diabetes).

Aasheim ET Vitamin concentrations in Scandinavian obese subjects undergoing surgical and non-surgical weight loss

Nanna Voldner, Modifiable determinants of newborn macrosomia and birth complications

## Book chapters:

Birkeland KI. Chapters "Diabetes mellitus", "Parenterale antidiabetika", "Perorale antidiabetika" and "Blodglukoseøkende midler" in *Norsk legemiddelhandbok for helsepersonell 2010*. Foreningen for utgivelse av norsk legemiddelhandbok, Oslo 2010. ISBN-978-82-90732-10-8.

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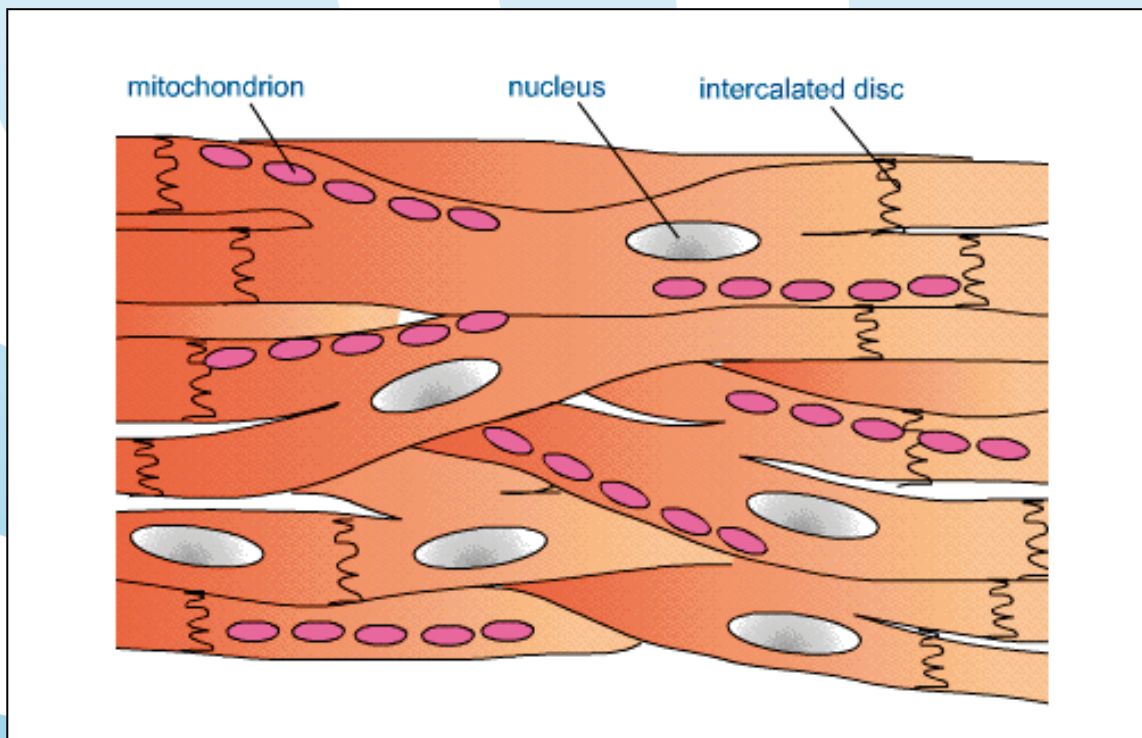
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Muscle cells (myocytes) are important for glucose turn over in the body. In a new research project, we will search for signal molecules from myocytes to other parts of the body in normal situations and in type 2 diabetes. The study is a joint project with Institute of Nutrition