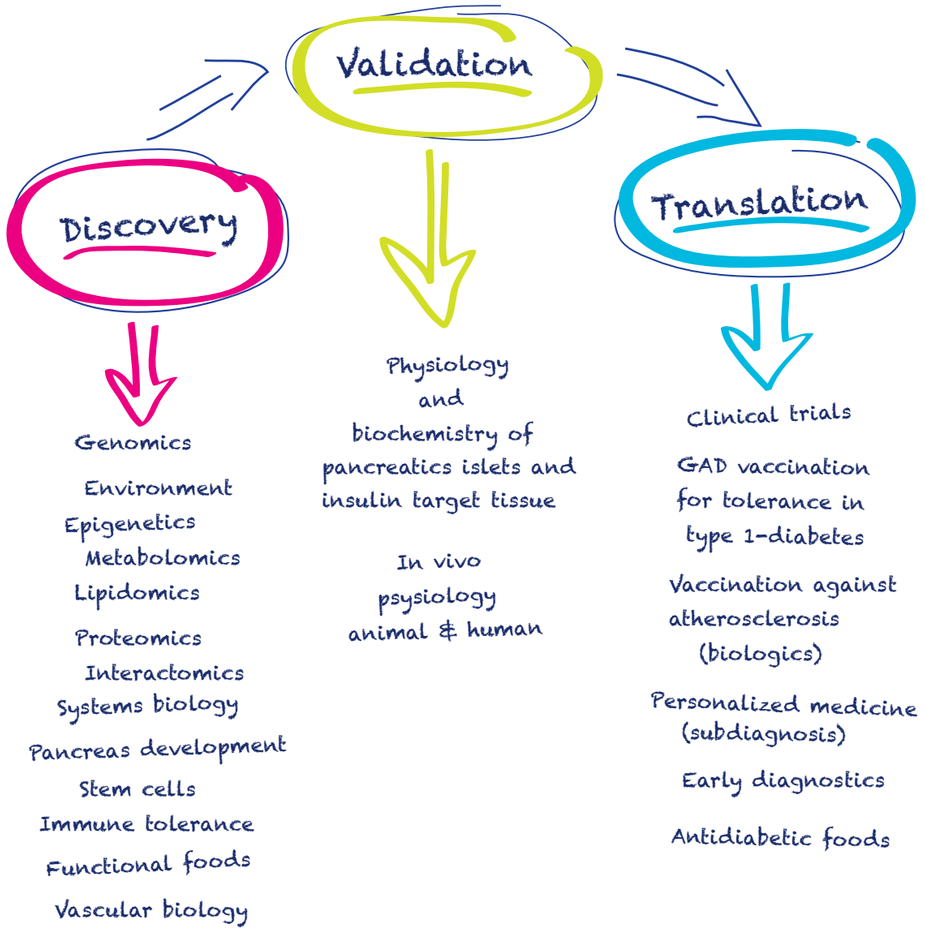
FOR PEOPLE BY PEOPLE


Validation
Discovery
Translation
Genomics
Environment
Epigenetics
Metabolomics
Lipidomics
Proteomics
Interactomics
Systems biology
Pancreas development
Stem cells
Immune tolerance
Functional foods
Vascular biology
Physiology and biochemistry of pancreatics islets and insulin target tissue
In vivo psysiology animal & human
Clinical trials
GAD vaccination for tolerance in type 1-diabetes
Vaccination against atherosclerosis (biologics)
Personalized medicine (subdiagnosis)
Early diagnostics
Antidiabetic foods

LUND UNIVERSITY DIABETES CENTRE (LUDC) was created in 2006 and is funded by a Linneus grant from the Swedish Research Council for a period of ten years. LUDC builds upon a strong tradition of diabetes research at LU and is today the centre for more than 250 persons actively involved in all aspects of diabetes research; the centre is located at CRC in Malmö and BMC in Lund.

Diabetes research at LUDC can be subdivided into three parts; discovery, validation and translation. The aim of the discovery is to identify genetic and non-genetic factors responsible for development of diabetes and its complications. And in the validation phase to describe how they interact with the environment and cause impairment of insulin secretion and action, characteristic of the disease. Ultimately, this knowledge will be translated into the clinic as improved personalized medicine and development of novel therapies.

The EXODIAB (Excellence of Diabetes Research in Sweden) consortium was created in 2009 as a Strategic Research Area at Lund and Uppsala Universitiets (70/30), funded by a strategic Research Grant from the Swedish Government. LUDC forms the bulk of the Lund University part of EXODIAB.

A central mission of EXODIAB is to create strong infrastructures which can serve all researchers and shorten the start up time for young researchers.
A prerequisite for this is access to some of the best and largest biobanks in diabetes research in the world.

A big hurdle in diabetes research has always been the difficulty of getting access to the key organ in the pathogenesis of the disease, the pancreatic islets.

The Human Tissue Lab has to a large extent solved this problem and provides from the Nordic Transplantation Program human pancreatic islets to researchers at LU and UU. ■

MAJOR PRIORITIES WITHIN LUDC/EXODIAB are to accelerate the rate of innovations developed from inventions and discoveries in the area, to ensure that the benefits reach the public and to reach the scientific goal of developing novel therapies for prevention and treatment of diabetes and its complications. Interaction between academia and the industry is a key component of this consortium.

In order to realize this goal, an Innovation Officer (IO) with extensive experience from the Life Science industry has been hired. Her task is to manage relationships with the industry and accelerate the rate of innovation coming from LUDC/EXODIAB.

Commercializing our research findings is part of our vision to make a difference in the world by providing the best research and innovation in diabetes. The vision is to develop LUDC/EXODIAB to become a major partner to the industry in supporting the development of novel treatment approaches, thus strengthening the consortium, resulting in attracting new and ambitious PhD students and funding collaboration projects. The IO will also help the LUDC/EXODIAB members with commercialization along the conventional, intellectual property based path.

HOW WILL WE INNOVATE

3 WAYS HAVE BEEN IDENTIFIED FOR ensuring that research results lead to better patient treatment:

I
Identifying areas for IP activities leading to start-up

II
Testing of ”leads” within existing models, in collaboration with external partners

III
Longer-term strategic collaborations, with life science industry, investigating biological systems ▶







A centralized approach to customer contacts is preferred where the one point of contact is the IO. A Commercial Advisory Board (Innovation Board) has been created to bring market needs and industry competence into the selection process. Project teams will be created for each collaboration.

At the interface between Academia and the business sector is the Innovation Board that oversees development of innovation projects funded by agencies such as VINNOVA, SSF or in collaboration with industrial partners.

Our aim is to develop the projects to a point where we can either start a commercial entity or license them out to an industry partner. ■

THE LUDC ACTION GROUPS ARE the scientific storm troops of the consortium. They are flexible teams that form around a focused scientific task.

The expertise required for solving the task is gathered within the LUDC, but Action groups also collaborate with external partners when necessary.

Action groups organize regular meetings that are advertised and open to all interested LUDC members.

All are welcome to learn more about current progress or to share their expertise. Most of the scientific interactions within the LUDC take place within the Action groups, which are also prioritized when distributing positions and grants.

An Action group is expected to meet the standards required for submitting a sound proposal for Collaborative Grants from the Swedish Research Council (Vetenskapsrådet). ■

TO GAIN FROM AN EXTERNAL VIEW ON its scientific actions, LUDC installed already in its first year a Scientific Advisory Board (SAB) of distinguished researchers in the field of diabetes research: Eric Lander (Broad Institute), Gerald Shulman (Yale Institute), Juleen Zierath (Karolinska Institute), Frances Ashcroft (Univ. of Oxford), Leena Peltonen (Helsinki University) and Claes Wollheim (Geneva University). Michael A. Brownlee (Albert Einstein College of Medicine, New York) and Ele Ferrannini (Univ. of Pisa) joined the SAB filling the footsteps of Leena Peltonen and Claes Wolheim. ■

LUDC HAS A STRONG FOCUS ON younger researchers and aims to promote their careers with Post-Doctoral Fellowships, by supporting the academic network of PhD students and Postdoctoral Fellows DPLU (Diabetes Programme at Lund University), and by widening their horizons through active involvement in research networks and the aforementioned Action Groups.

Since 2010, LUDC has appointed distinguished researchers as Mentors to the younger scientific staff: Claes Wolheim, former member of LUDC's Scientific Advisory Board and beta cell expert, David Nicholls, world leader in mitochondrial pathophysiology and in situ bioenergetics and, since 2012, also Sam Cushman, renowned for his work on adipocytes and glucose transporters. ■





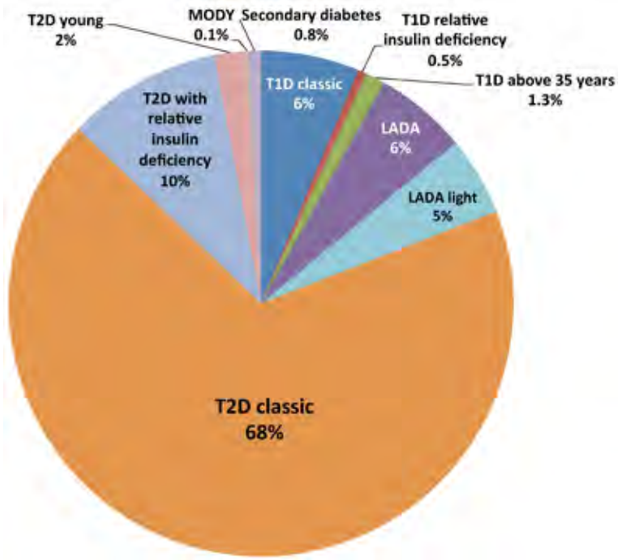

BIOBANKS

LUDC HAS PROBABLY THE LARGEST and best characterized biobanks in the diabetes field in the world

SOME EXAMPLES:

- ANDIS (All New Diabetics In Scania): registers since 2009 all newly diagnosed diabetes patients in the region (at the moment >7,200 patients).
- Botnia study: family- and population-based studies from the west coast of Finland (Botnia) (>12,000 individuals), includes also a prospective arm.
- MPP (Malmö Prevention Project): started in 1974, MPP screened over a period of 18 years > 33,000 persons in Malmö, in order to find high-risk individuals for preventive intervention.
- MDC (Malmö Diet and Cancer): a population-based prospective cohort of 30,000 individuals from Malmö, recruited 1991–1996. The study has a cardiovascular arm with patient evaluations for cardiovascular and metabolic risk factors.
- SDR (Scania Diabetes Registry): a databank and biobank of diabetic patients in Scania initiated in 1996 (>7,500 patients) to allow better prediction of development and progression of diabetic complications. ■

ANDIS diabetic subgroups Feb 2013 (N=7000)



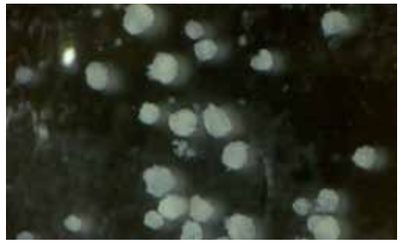
HUMAN TISSUE LAB

THE LUDC HUMAN TISSUE LABORATORY AT CRC IS a collaboration between LUDC and the Nordic Network for Clinical Islet Transplantation headed by Prof. Olle Korsgren at Uppsala University.

In Uppsala pancreases from human donors are collected, primarily for transplantation purposes, and are treated by enzyme digestion to isolate the islets of Langerhans.

A fraction of these islets can be used for research and are distributed to laboratories in Scandinavia, including the Human Tissue Laboratory at CRC. This is a unique material for both functional and genetic studies which enables the LUDC investigators to perform ground breaking research. We are now extending our facility to also include other important tissues in diabetes, such as liver, muscle, fat and intestine. Access to all these tissues from the same individual gives us an outstanding opportunity to map the molecular events taking place in each of the tissues involved in diabetes. This will increase our understanding of the development of both Type 1 and Type 2 diabetes.

Isolated human islets seen through a light microscope.



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Olsson AH, Yang BT, Hall E, Taneera J, Salehi A, Dekker Nitert M, Ling C. Decreased expression of genes involved in oxidative phosphorylation in human pancreatic islets from patients with type 2 diabetes. Eur J Endocrinol. 165(4):589-95, 2011.

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OMICS AND IMAGING

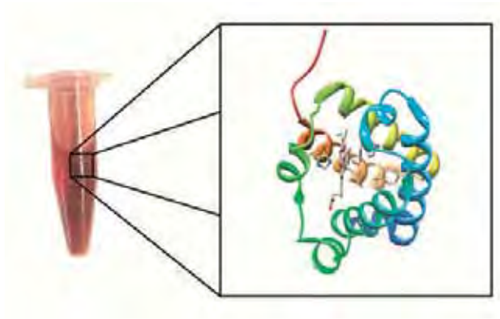
IN THIS AGE OF "OMICS" RESEARCH, WE HAVE the possibility to investigate anything from DNA regulation and gene-environment interactions to changes in metabolite levels, metabolic pathways and cellular structures in diabetes and beta cell dysfunctioning. Combining omics with clinical and phenotypic data of patients with different forms of diabetes opens possibilities of true systems biology of human disease.

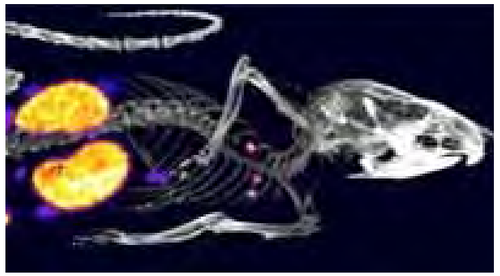
LUDC is well-equipped for **genomics** with state-of-the-art platforms for genotyping, GWAS, WGS, ChIP sequencing, expression profiling of human tissues including islets as well as studies of chromatin modifications including DNA methylation.

LUDC has **proteomics** platforms for human tissue global analyses and for protein interaction and function, and is expanding its possibilities to study subtle quantitative changes in the proteome at the (intra) cellular level. The Lund University protein production platform supports research groups with custom made proteins for specific questions.

Metabolomics – the possibility to obtain a comprehensive view of changes in metabolite levels – allows dissection of dysregulated pathways in metabolic diseases. GC/MS, LC/MS-MS and Flux analyzers at LUDC are available to study metabolic pathways and beta-cell function.

Cellular imaging is well provided for with confocal microscopes, Multi-photon imaging and Total Internal Reflection microscopy in both Lund and Malmö. The LUDC also has access to a clinical 3T MRI/MRS facility and the Lund University Bioimaging Center, which provides MRI and MRS, as well as Preclinical PET/CT, SPECT/CT and TEM for animal studies. ■





THE INFORMATICS UNIT

THE LUDC INFORMATICS UNIT PROVIDES LUDC WITH expertise in IT, databases, bioinformatics and statistics. We strive to provide researchers with the tools and support needed to analyze their data, to facilitate data intensive tasks and to stimulate collaborations and knowledge transfer within LUDC.

In recent years technological advances have provided medical researchers the opportunity to perform experiments that would have appeared to be science fiction just a few years back. Some of these novel technologies generate vast amounts of data, and specific knowledge and tools are needed to process the raw information. The LUDC Informatics Unit deals with the challenge of storing, combining and making use of large amount of data generated by research activities within the LUDC. We also integrate information from publicly available databases with our data. The unit is central to bioinformatic activities within LUDC and provides a common platform for knowledge transfer between PhD students, post-docs, researchers and Informatics Unit staff. Furthermore, the statisticians within the Unit provide biostatistical and analytical support to LUDC and participate in various internal and international collaborations.

A large part of the Informatics unit work is dedicated to providing the infrastructure needed to work with modern population genetics and data generated using modern sequencing or GWAS approaches. The storage and calculation capacities of our servers have increased tremendously over the past few years and today LUDC researchers have the capacity to work with very large datasets generated from different experiments and platforms such as modern sequencing, GWAS genotyping, mRNA expression, epigenetic data and ChIP-on-chip.

Central to our task is the maintenance and continuous development of databases that contain individual level information on participants from studies performed by LUDC researchers. The aim is to provide a means for researchers to easily obtain reliable information from our databases, while having the possibility to monitor who has access to data. Further, the Unit has experience from designing questionnaires and data entry procedures for several ongoing studies.

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VISION: PATIENTS WITH OBESITY AND TYPE 2 DIABETES HAVE a reduced sensitivity to insulin and other hormones in their target tissues; skeletal muscle, liver and adipose tissue. This so-called insulin resistance is associated with increased circulating levels of glucose and fatty acids, as well as altered levels of adipocyte-derived hormones and cytokines.

The exact cellular and molecular mechanisms causing systemic insulin resistance are not known. Still, insulin resistance is closely associated with the prevalence of obesity which suggests that primary or secondary defects in the adipose tissue constitutes an underlying problem. By dissecting signalling pathways regulating glucose- and lipid metabolism, particularly in adipose tissue, our aim is to identify new molecular targets of relevance for diabetes pathophysiology and drug development.

Our research groups focus on the interplay between insulin, cyclic AMP, AMP activated protein kinase (AMPK), a key cellular energy sensor, and AMPK-related kinases. By elucidating such signalling networks we will learn more about the regulation of cellular energy balance and insulin sensitivity.

Also, we aim to dissect the rate-limiting steps of insulin induced glucose transport at the subcellular level of adipose and muscle cells. This knowledge is fundamental in order to develop drugs targeted to lower blood glucose levels and thereby improve whole body energy homeostasis.

We are also engaged in functional investigation of new risk genes for diabetes, for example the GIP receptor and serotonin receptors that have emerged from genome wide association studies by other members of the LUDC.

Our vision is to identify new mechanisms and molecular targets of relevance for the treatment of human diabetes and to identify defects in signalling patterns that can predict development of the disease.

Crosstalk between insulin, cAMP and AMPK signalling networks.

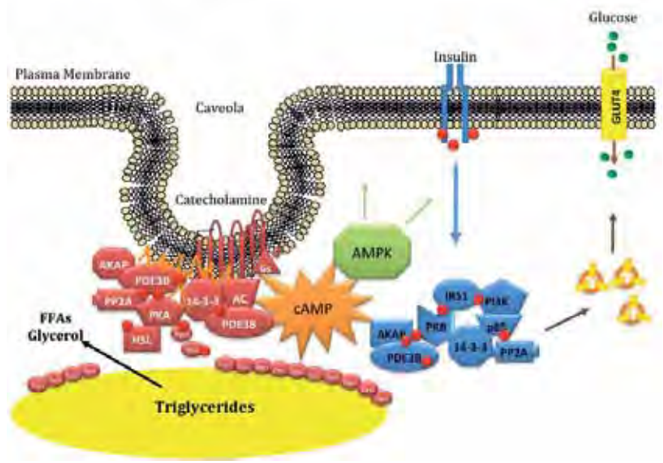

FIGURE: *Interplay between cAMP, insulin and AMPK signalling networks in the regulation of adipocyte functions. The figure illustrates the complex pattern of interactions between interconnected signalling networks in adipocytes. For example, insulin and catecholamines induce the formation of unique multiprotein complexes involving protein and lipid kinases, protein phosphatases, scaffolding proteins and effector molecules at different locations in the cell. These signalling events have important roles for the regulation of lipid and glucose metabolism.*

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RESEARCH AREA:
Genomics

VISION: TO USE GENETICS AND SYSTEMS BIOLOGY TO IDENTIFY THE CAUSES OF TYPE 2 DIABETES. T2D is the fastest growing disease worldwide, affecting more than 350 million people today and the number is predicted to double within the next 20 years. T2D is assumed to develop from the interaction between genetic predisposition and an affluent westernized environment but the underlying mechanisms are unknown.

Our strategy to unravel the mechanisms of diabetes is to identify the genetic and epigenetic variation involved in disease predisposition. Several different strategies and techniques are adopted to accomplish this task, including genome-wide association studies (GWAS), next-generation sequencing of DNA and RNA, ChIP sequencing to dissect chromatin modifications, and global DNA methylation analysis. These methods are combined with careful phenotypic *in vitro* and *in vivo* characterization of human tissues and patients to create a complete picture of how genetic variation is translated into protein modifications using systems biology.

A prerequisite for these studies is access to some of the largest and best characterized study populations in the diabetes field: the Botnia Study, the Malmö Preventive Project, ANDIS (All Diabetics in Scania), Diabetes Registry Scania etc. These studies allow translation of findings into personalized medicine and prediction of development of diabetes and disease progression.

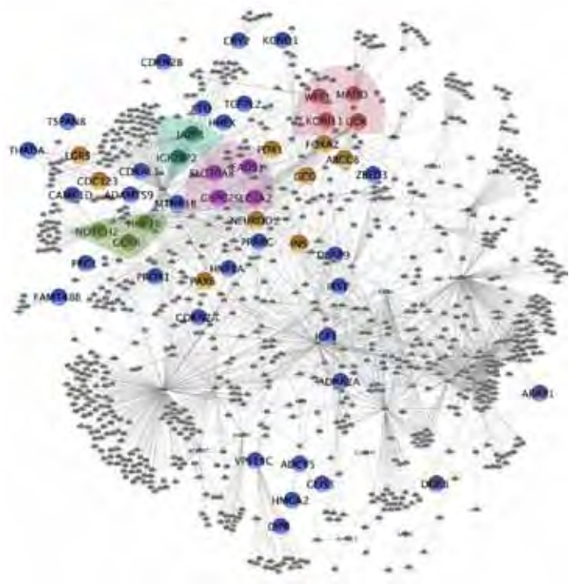

FIGURE: *A protein-protein interaction network for 248 genes whose mRNA expression in human pancreatic islets correlates with the expression of diabetes genes identified by GWAS (from Taneera et al., 2012).*

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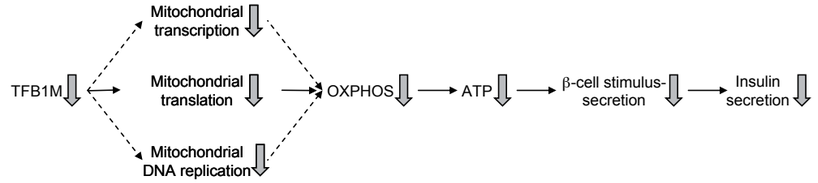
VISION: OUR VISION IS FOUNDED ON THE NOTION THAT mitochondrial metabolism in the pancreatic β-cell is responsible for proper insulin secretion. The metabolism of glucose and other fuels translates the rise in extracellular glucose, which is the main determinant of insulin secretion, to intracellular signals that trigger and amplify insulin secretion.

Moreover, mitochondrial metabolism in target tissues for insulin, i.e. skeletal muscle, adipose tissue and the liver, may also play an important role in glucose homeostasis. The pathophysiological significance of this notion is underscored by the fact that inherited, albeit rare, abnormalities of mitochondrial DNA lead to a Type 2 diabetes-like condition.

We believe that both common and rare abnormalities of genes that are involved in control of mitochondria play an important role in the development of Type 2 diabetes. Our assumption is that these genes can be identified by genetic approaches in humans and in animal models of inherited diabetes.

The pathogenetic processes can be unraveled by genetic studies and further characterized by functional studies. Learning more about the pathogenesis of Type 2 Diabetes will lead to development of novel treatments for the disease.



MODEL FOR A POSSIBLE ROLE OF TFB1M IN THE DEVELOPMENT OF TYPE 2 DIABETES (T2D). *Mining data from the Diabetes Genetics Initiative Genomewide Association Study revealed that Transcription factor B1 mitochondrial (TFB1M), a protein which controls translation in mitochondria, is associated with impaired mitochondrial metabolism, reduced insulin secretion and increased future risk of Type 2 Diabetes.*
The data suggest a model where the risk SNP confers lower TFB1M protein expression. Consequently, mitochondrially encoded proteins will be reduced, oxidative phosphorylation (OXPHOS) restrained, and stimulus-secretion coupling in the β-cell will be abrogated. All this will result in impaired insulin secretion.

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Olsson AH, Yang BT, Hall E, Taneera J, Salehi A, Nitert MD, Ling C. Decreased expression of genes involved in oxidative phosphorylation in human pancreatic islets from patients with type 2 diabetes. Eur J Endocrinol 165(4):589-95, 2011

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RESEARCH AREA:
Adipotoxicity – Glucolipotoxicity

VISION: THE STRONG ASSOCIATION BETWEEN OBESITY AND T2DM – "diabesity" – has emphasized the role of adipose tissue and lipids in the development of T2DM.

Circulating lipids, in the form of non-esterified fatty acids (NEFA) and triglycerides, are elevated and causally linked to the cardiovascular complications of the disease. Moreover, ectopic lipid deposition (i.e. outside adipose tissue) is believed to be a precipitating event in the development of both islet dysfunction and insulin resistance, the two hallmarks of T2DM. This has been termed "lipotoxicity" or "glucolipotoxicity".

Besides lipotoxicity, the inflammatory response of hypertrophic adipose tissue expansion contributes to development of insulin resistance through release of cytokines capable of impairing insulin signalling ("adipotoxicity").

In addition to elevation of circulating lipids T2DM is also associated with altered functionality of plasma high density lipoprotein (HDL). HDL and its major protein component, apoA-I, are central to the reverse cholesterol pathway (removal of excessive and harmful cholesterol), and as such directly important for cardiovascular health. Interestingly, recent studies show that HDL/apoA-I particles can influence insulin secretion of pancreatic beta-cells, and also stimulate glucose uptake in skeletal muscle of T2DM patients. Clearly, these findings add to the complexity of the disease but, importantly, also provide new potential targets in the search to reduce the incidence and complications of T2DM.

The overall objective of our research is to elucidate mechanisms underlying obesity-associated insulin resistance and islet dysfunction and to identify novel targets for the prevention and reversal of these hallmarks of T2DM.

More specifically we aim to identify novel factors involved in adipocyte differentiation, describe how lipids are stored and handled in pancreatic beta-cells under normal as well as diabetic conditions and unravel the molecular and cellular basis for the HDL/apoA-I triggered enhancement of skeletal muscle glucose metabolism. We also perform functional studies of potential risk genes for diabetes, such as adiponutrin, identified through genome wide association studies by other members of the LUDC.

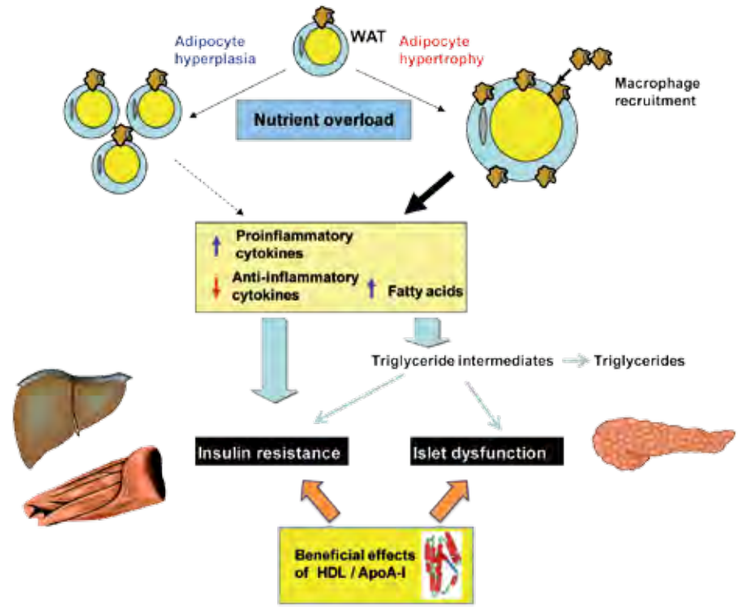

FIGURE: *Schematic representation of mechanisms underlying obesity-associ-ated insulin resistance and islet dysfunction, and the beneficial function of HDL/apoA-I in preventing/reversing their progression (for more details, see text).*

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”A creative office environment makes way for creative science”

RESEARCH AREA:
Epigenetics

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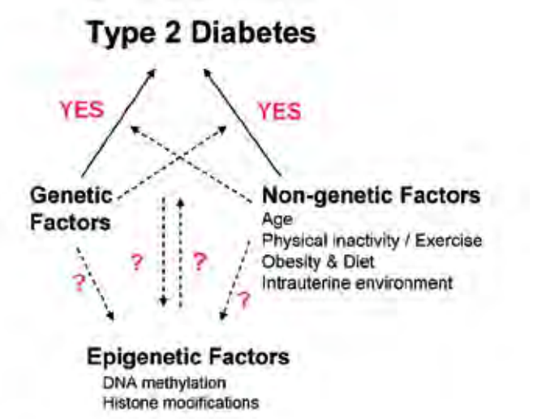
VISION: TO IDENTIFY EPIGENETIC MODIFICATIONS influencing the pathogenesis of diabetes and its complications in humans.

Although our knowledge of genetic variation predisposing to diabetes has increased dramatically over the past years, we still have a limited understanding of whether epigenetic factors affect the pathogenesis of diabetes and its complications.

Epigenetics has been defined as heritable changes in gene function that occur without a change in nucleotide sequence. Nevertheless, recent studies demonstrate that the human epigenome is dynamic and that it may change due to environmental exposures.
Environmental risk factors for diabetes may thereby change the epigenetic pattern in target tissues for diabetes and thereby affect the pathogenesis for the disease.

Studies from the LUDC have identified epigenetic modifications in pancreatic islets and skeletal muscle from patients with type 2 diabetes. Our studies have also shown that non-genetic factors, including exercise, diet and age, are associated with differential DNA methylation and gene expression in human skeletal muscle. Moreover, we have shown that genetic variation affects DNA methylation, which may affect the risk for diabetes. Our ongoing studies are further dissecting if genetic and non-genetic risk factors for type 2 diabetes influence the epigenetic pattern (DNA methylation, histone modifications and microRNA) and hence gene expression and metabolism in human skeletal muscle, adipose tissue and pancreatic islets.



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RESEARCH AREA:
GLP-1 Based Therapy

VISION: GLUCAGON-LIKE PEPTIDE-1 HAS BEEN DEVELOPED AS a novel therapy of type 2 diabetes, mainly because its dual hormonal action on islet function. Hence, GLP-1 elicits glucose-dependent stimulation of insulin secretion and inhibition of glucagon secretion. A challenge in the development of GLP-1 based therapy is that the active form of GLP-1 is rapidly inactivated through truncation of the peptide by removal of the N-terminal dipeptide end through the enzyme dipeptidyl peptidase-4 (DPP-4).

To overcome this problem, two strategies have been developed: the use of GLP-1 receptor agonists, which are largely resistant to the action of DPP-4, and the inhibition of DPP-4, which prevents the inactivation of GLP-1 and thereby enhances and prolongs the action of the endogenous incretin hormone. Our studies aim at elucidating the islet and extra-pancreatic effects of this treatment in animal models of diabetes as well as in subjects with Type 2 diabetes, and to identify and examine the positioning of this novel therapy within the management of the disease.

Our studies also aim at developing further the GLP-1-based therapy by exploring the activation of the G-protein coupled receptor 119 (GPR119), which is expressed in both insulin-producing cells and GLP-1-producing cells, and the activation of which stimulates release of both hormones. In addition, we search for novel islet and gut messengers e.g. regulatory peptides that modulate islet hormone release. Information about the roles of regulatory peptides in beta-cell function and in Type 2 diabetes is still meager and our studies will aim in the search for new strategies for prevention and treatment of Type 2 diabetes.

A main focus is the regulatory peptide cocaine and amphetamine-regulated transcript (CART). A body of evidence shows that CART has positive effects on glucose homeostasis, i.e. CART increases GLP-1 mediated insulin secretion, inhibits glucagon secretion, CART inhibits glucose-induced cell death, CART is overexpressed in islets of T2D subjects, and CART null mutant mice exhibit severely impaired islet function. These data suggest that CART is a highly interesting drug candidate, and the so far unknown CART-receptor a potential drug target, for treatment of T2D.

Another main focus is to understand the mechanisms that underlie the curative effect of gastric bypass surgery on Type 2 diabetes. This is a highly interesting model for identification of curative processes that can form the basis for future treatment of Type 2 diabetes.

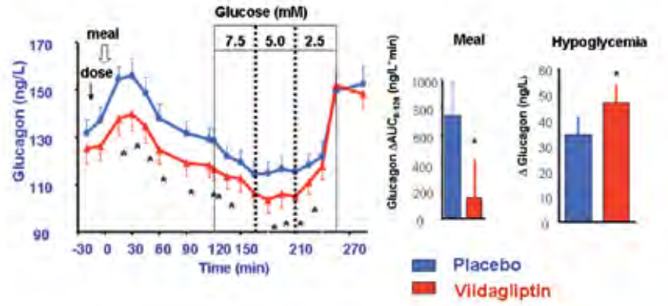

FIGURE: *Result for a study exploring whether DPP-4 inhibition compromises the glucagon response to hypoglycemia, in analogy with its inhibition of glucagon secretion after meal ingestion. Subjects with type 2 diabetes were treated with vildagliptin (a DPP-4 inhibitor) or a placebo for four weeks. Therafter a step-wise hypoglycemic clamp was undertaken (glucose clamped at 7.5, 5.0 and 2.5 mmol/l respectively) after a test meal ingestion, and the glucagon responses to meal versus hypoglycemia were determined. Results show the glucose-dependency of the action on glucagon by DPP-4 inhibition: the response is inhibited at hyperglycemia during meal ingestion but augmented during hypoglycemia. This provides rationale for the conclusion that hypoglycemia is a low risk during treatment with DPP-4 inhibition. (from Ahrén et al., J Clin Endocrinol Metab 94:1236, 2009).*

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RESEARCH AREA:
Islet Pathophysiology

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VISION: THE PROPER FUNCTION AND MAINTAINED MASS OF the pancreatic islets is vital for preventing development of Type 2 diabetes. This is to a large extent under genetic control.

The big challenge is to understand exactly how genetic variations affect cellular functions in the pancreatic islets, in order to identify suitable targets for causative treatment.

Functional gene networks (Rosengren). We develop models that take into account the contribution of several genes and their encoded proteins for the altered cellular functions that predispose for Type 2 diabetes. To do this we analyse gene regulatory co-expression networks in islet cells, followed by functional validation down to the molecular level.

Protein interactions (Renström). Protein function is determined by its interactions, which we address by discovery techniques (2-hybrid systems) and focused low-throughput methods (e.g., immunoprecipitation, affinity purification). This also includes real time discovery (fluctuation correlation spectroscopy).

Therapeutic targets (Salehi). G-protein coupled receptors attract interest as obvious targets for treatment of Type 2-diabetes and other diseases. Orphan GPCRs will be systematically investigated for their capacity to correct hormone secretion in Type 2-diabetes.

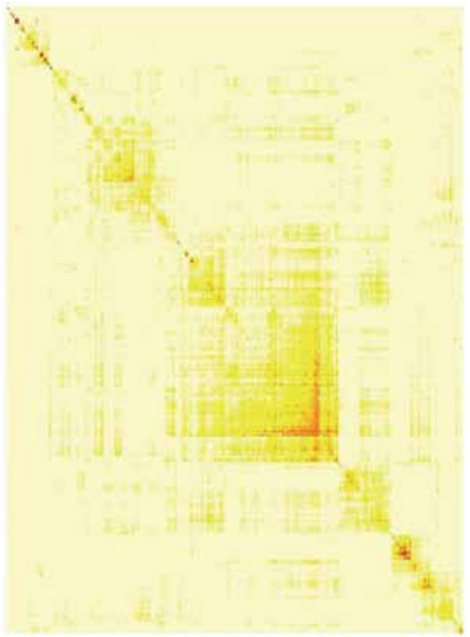

FIGURE: *Topological overlap presentation of clusters of co-expressed genes in donor human islets. Analysis was confined to the 5000 most highly expressed genes, which are presented along the x and y axes. Gene pairs exhibiting the highest connectivity (|correlation|10) are denoted in red, whereas pairs without connectivity are in white.*

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RESEARCH AREA:
Vascular Diabetic Complications

VISION: DIABETES IS ASSOCIATED WITH DEVASTATING macrovascular complications including coronary heart disease and stroke as well as microvascular disorders leading to damage of the small vessels of the kidney (nephropathy), eye (retinopathy) and peripheral nerves (neuropathy).

These impose a huge burden on the quality of life of the patients and account for more than 10% of health care costs in Europe. This unit at LUDC focuses on understanding the chain of events leading to vascular disease in diabetes, and on developing tools, which can make the development of novel drugs/therapies for prevention and/or treatment more feasible.

Important steps are the identification of novel biomarkers for disease prediction and monitoring, the development of new treatment approaches and imaging techniques for monitoring the atherosclerotic process and retinopathy and the creation of animal models that better reproduce human disease.

SOME EXAMPLES OF SPECIFIC ON-GOING STUDIES:

- On autoimmune responses against modified self-anti gens, such as oxidized-LDL, AGE-modified proteins and aldehydemodified proteins in the vascular wall as potential contributors to diabetic complications. Development of vaccines to modulate these responses.
- On the transcription factor NFAT (Nuclear Factor of Activated T Cells), recently described as a glucose sensor in macrovessels and microvessels *in vivo*, as a novel target for treatment of vascular complications.
- On the role of circulating anti-pericyte autoantibodies (APAA) in the blood of diabetic patients, as predictors for impending vascular disease.
- On the mechanisms underlying the beneficial outcome of laser coagulation therapy in retinopathy and on the role of the retinal pigment epithelium (RPE) and RPE-released factors in this context.

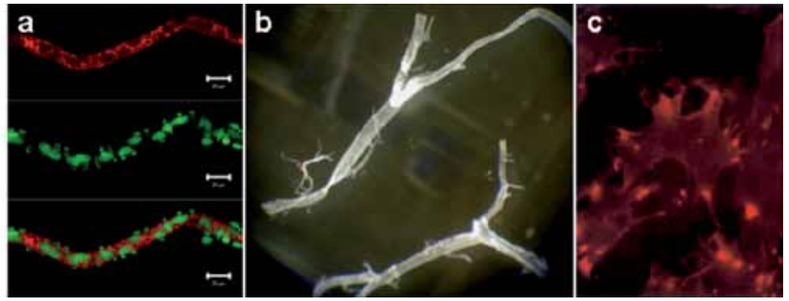

FIGURE:
a) Confocal image showing VCAM-1 expression (red) and cell nuclei (green) in mouse cerebral microvessels in response to hyperlipidemia;
b) Atherosclerotic plaque in the bifurcation of a mouse cerebral artery (white opaque area); c) Serum anti-pericyte autoantibody binding to bovine retinal pericytes (red).

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RESEARCH AREA:
Pancreas development and human embryonic stem cell differentiation

VISION: TYPE 1 DIABETES RESULTS FROM SPECIFIC autoimmune mediated destruction of beta cells. Considerable efforts are now focused on trying to develop functional insulin-producing cells from adult and embryonic stem cells as a consequence of encouraging results obtained in reversing Type 1 diabetes upon human islet transplantation.

Thus, a hope is that human embryonic stem cells (hESC) can be used in this endeavor due to their remarkable differentiation potential. In fact, recent studies report that insulin+ cells can be produced from embryonic stem cells. However, these cells differed significantly from mature pancreatic beta cells in lacking proper glucose responsiveness.

Ultimate success in developing therapeutically useful cells will depend on a fundamental understanding of the regulatory factors that are required for controlling the specialized genetic programs associated with the formation of functional beta cells. To work towards successful islet transplantation we are studying the mechanisms governing beta cell differentiation in the embryonic pancreas (specifically the role of transcription factors).

Knowledge obtained for these experiments is directly applied in our experiments to differentiate hESCs into transplantable insulin producing cells. Ultimately our results will be applied to develop novel protocols to generate unlimited amounts of beta cells (from hESCs). The goal of our program is to accelerate the production of a cell-based therapy for diabetic patients.

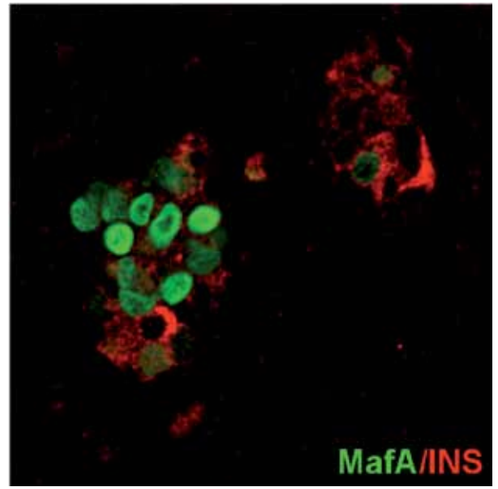

FIGURE. *Expression of MafA, Pdx1, and Ngn3 induces insulin production in the chick gut endoderm. This over-expression experiment illustrates the significance of these transcription factors to insulin production and beta cell differentiation.*

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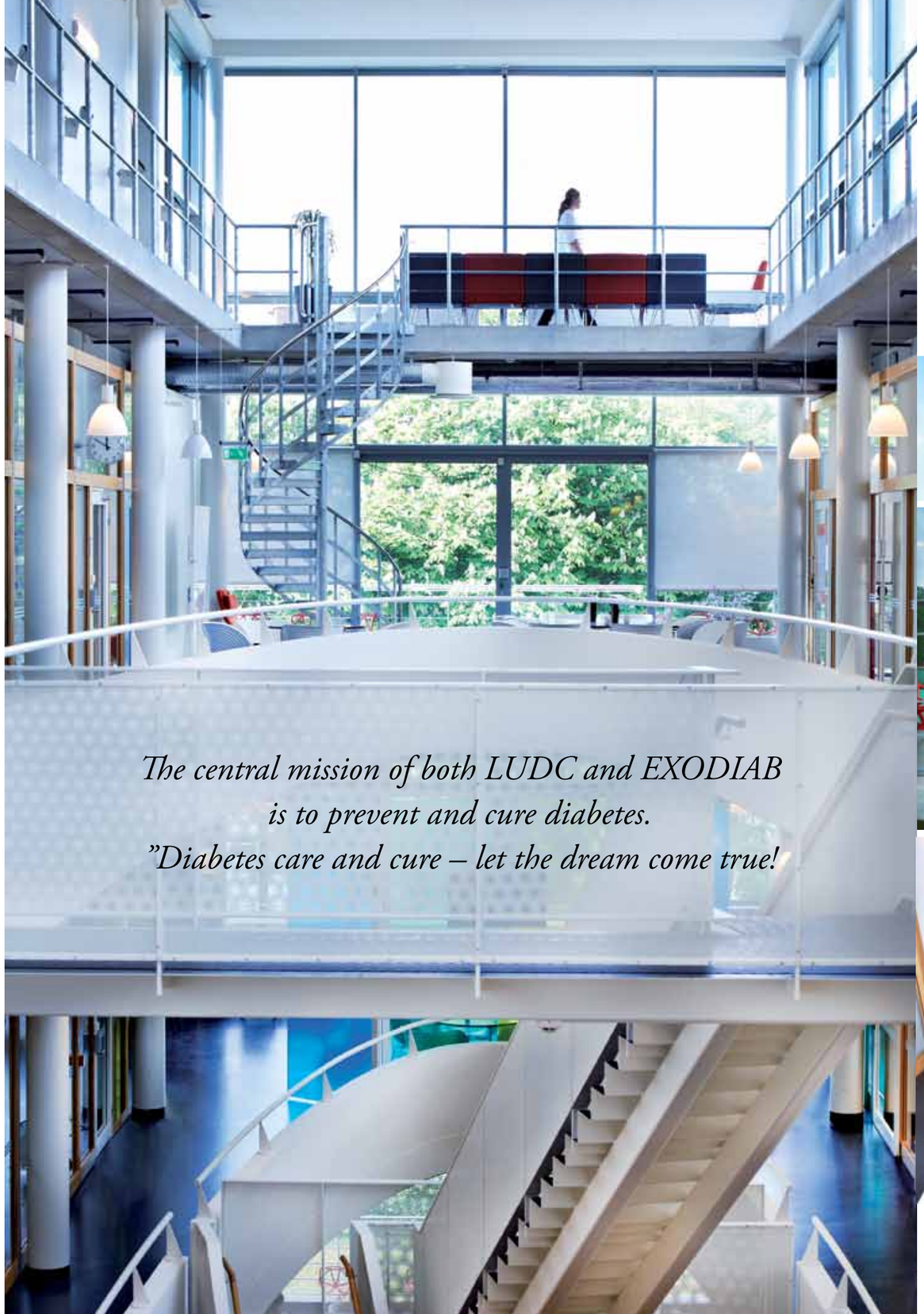
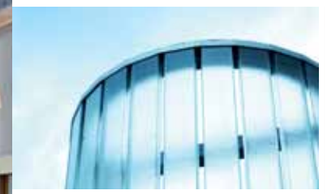


The central mission of both LUDC and EXODIAB
is to prevent and cure diabetes.
”Diabetes care and cure – let the dream come true!



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RESEARCH AREA:
Cellular regulation of islet hormone secretion

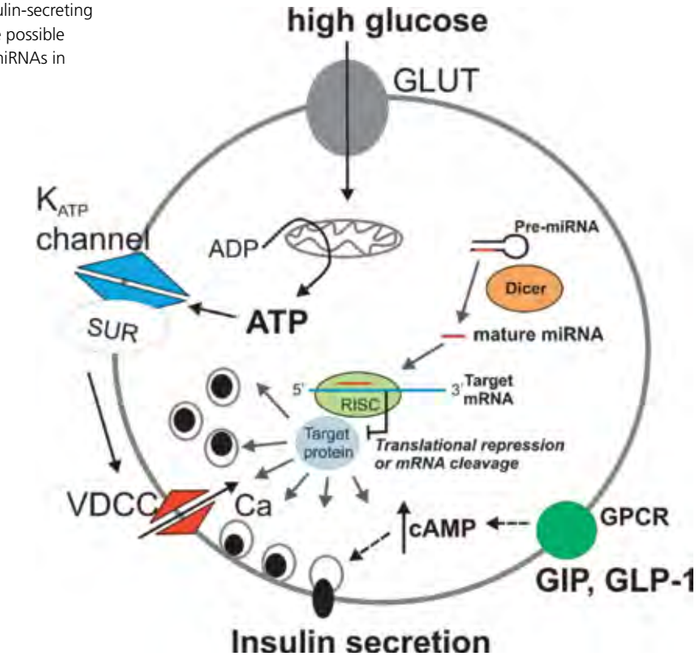
VISION: THE MAIN FOCUS OF OUR RESEARCH IS THE CELLULAR mechanism by which insulin and glucagon is secreted from the pancreatic beta-cells and alpha-cells, respectively. Secretion of both these hormones is known to be disturbed in Type 2 diabetes.

We have a specific interest in how microRNAs (miRNAs) are involved in this regulation. MicroRNAs are a class of non-coding regulatory RNA molecules that affect gene expression by binding to 3´-untranslated regions of messenger RNAs (mRNAs), preventing the translation of the mRNAs.

OUR VISION IS THAT WE WILL;

- Gain better knowledge regarding the cellular regulation of the stimulus-secretion coupling in the pancreatic hormone secreting cells and regarding how disturbances in these processes are involved in diabetes development.
- Achieve a better understanding of miRNAs and their role in insulin secretion and glucagon secretion and in diabetes development.
- Identify miRNAs that will work as biomarkers for diabetes and its complications.

Model describing the stimulus-secretion coupling in pancreatic insulin-secreting beta-cells. Notice possible involvement of miRNAs in this process.



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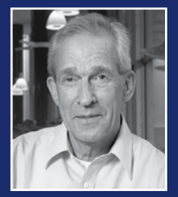

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RESEARCH AREA:
Autoimmune diabetes and celiac disease pathogenesis, prediction and immune intervention

VISION: THE RESEARCH FOCUS OF THE GROUP IS to uncover the etiology and pathogenesis of autoimmune diabetes (T1D) and celiac disease (CD). The long-term goal is to predict and to develop novel approaches that could prevent or revert the disease. The current research on the dissection of T1D genes in humans and in the spontaneously diabetic BB rat is directed to the identification of genetic factors within and outside the Human Leukocyte Antigen (HLA) complex that are critical to disease risk.

The focus is also to identify markers that predict either islet autoimmunity, T1D, or both as well as to monitor immunotherapeutic strategies to prevent and cure T1D. The same strategy is used for CD and as T1D is increasing the risk for CD, the two disorders are studied in parallel. With the help of a large longitudinal international NIH-funded study, the TEDDY study, we will be able in the near future to dissect the role of environmental factors impinging on the risk for T1D and to identify gene-environment interactions that may trigger either disease.

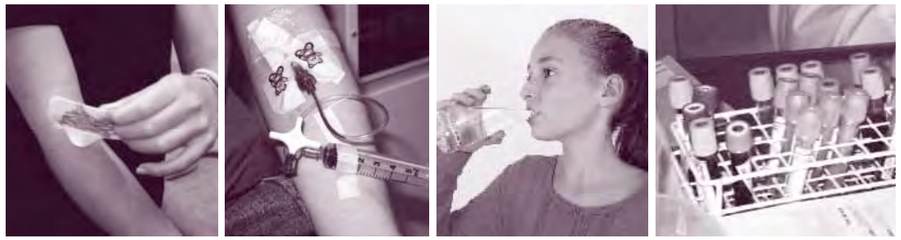
Extensive analysis of lymphocytes and their antigen-specific cellular responses and their control of autoantibody formation is on-going. The detailed analysis of circulating autoantibodies and their regulation by lymphocytes is currently used to monitor both prevention and intervention clinical trials. Our group is an affiliate to the NIH-funded TrialNet and we currently randomize participants to an oral insulin trial to prevent T1D in subjects with insulin autoantibodies. The study of components of the innate immunity, which represent the interface between infections and adaptive immune responses, will complement the extensive studies aimed at defining the environmental factors leading to either islet autoimmunity, T1D, or both. In parallel immunogenetic and environmental factors that trigger autoreactivity to tissue transglutaminase and lead to progression to CD are investigated.

Gestational infections are studied by molecular virology as they increase the risk for the offspring to develop either T1D or CD.
Finally, we will continue to study the interplay between immune cells and the pancreatic islet by studying the immunological responses in pancreatic lymph nodes and in T cells infiltrating the islets in organ donors with T1D, T2D or only autoantibody positive through the EXODIAB established collaboration with Olle Korsgren in Uppsala (Nordic Islet Transplantation Network).

The strong translational focus of our research is reflected by the development of both autoantibody and lymphocyte assays to predict and improve diabetes classification as well as ongoing immunomodulatory clinical trails (GAD65 vaccination in the DIAPREV-IT study) to halt beta cell autoimmunity and of tTG autoantibody positive children to halt CD with probiotics in the CIPP study.

IN SUMMARY, OUR RESEARCH CONTRIBUTES TO

- Genomics in autoimmune diabetes (T1D) and CD including HLA and non-HLA genes. Dissection of diabetes genes in the BB rat;
- Inflammatory markers analyses including multiplex serum cytokines and metabolomics analyses;
- Autoantigen identification including standardization of novel autoantibody assays to predict T1D and CD and
- Novel therapies in investigator-initiated prevention and interven tion therapies to induce immunological tolerance to autoanti gens to prevent T1D and CD.



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RESEARCH AREA:
"Meta-immunology": systemic and cellular inflammatory processes in diabetes

VISION: THERE ARE STRONG EVIDENCES INDICATING THAT systemic and cellular inflammatory processes are not only marking progression to type 1 diabetes (T1D) but they may play an important role in inducing insulin-resistance and in hampering beta cell function in type 2 diabetes (T2D) and obesity.

While immune system deregulation plays a central role in the pathogenesis of T1D, the contribution of inflammation in metabolic disorders, like T2D and obesity, is less clear.
During the past years, several lines of evidence have emerged demonstrating a close link between metabolism and immunity and therefore derangements at the intersection of metabolism and immunity have emerged as a key process linking several pathogenic aspects of diabetes.

T1D is an autoimmune disorder, where the β-cells are selectively destroyed by the body's own immune system. Major genetic predictors for T1D are specific HLA genotypes with autoantibodies against β-cell antigens as specific markers for disease. In T1D, pancreatic islet inflammation (insulitis) contributes to the progressive loss of insulin producing β-cells, which renders the patients insulin- dependent for life.

The latest advances in this field suggest that inflammatory mediators have a broader role in T2D and obesity than initially assumed; they contribute to the induction and amplification of β-cell dysfunction and at later stages the same inflammatory components might contribute to insulin resistance and overt diabetes.
These different roles of inflammation take place during different phases of the course of T1D, T2D and obesity and may be influenced by patients' genetic background, which contributes to disease heterogeneity. Inflammation is therefore a common denominator for T1D, T2D and obesity related metabolic disorders like insulin resistance.

The development of this LUDC area will provide a comprehensive immunological analysis of the crosstalk between inflammation, autoimmunity and metabolic disorders leading to diabetes.

Understanding these mechanisms will have important implications for the design of novel therapies based on the prevention of diabetes-associated chronic inflammation.

RESEARCH FOCUS:

- To study the role of cellular and systemic inflammatory responses in T1D, T2D and obesity.
- To study the close interplay between metabolism and autoimmune responses and dissect how systemic and cellular metabolic changes can induce or protect from inflammatory responses and diabetes
- To implement the discovery and standardization of immunological/ inflammatory markers of disease progression and as surrogate markers to monitor immunotherapy directed to the cure and prevention of diabetes.
- To study the gray zone between T1D, T2D and obesity using already established animal models and selected patients' cohorts: pre-T1D, T1D, pediatric obesity with and without T1D, LADA, adult T1D and obese adults.
- To directly study cellular and systemic inflammatory responses in human islets and lymph nodes from T1D, T2D and obese donors.
- To potentiate and implement immunotherapy in T1D using novel approaches.

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RESEARCH AREA:
Genetic Epidemiology & Translational Genomics

VISION: THE ELUCIDATION OF COMPLEX TRAIT GENETICS by characterizing the spectrum of disease risk associated with genetic variants, defining the functional basis to these associations, and outlining how genetic risk is modified by behavioral risk factors (e.g., diet, physical activity, obesity and smoking) that can be improved through medical intervention.

One important challenge is to explore whether genetics can be used to predict the occurrence of disease and response to preventive interventions better than existing non-genetic approaches and demonstrate that prognosis improves when genetic information is used to personalize medical interventions.

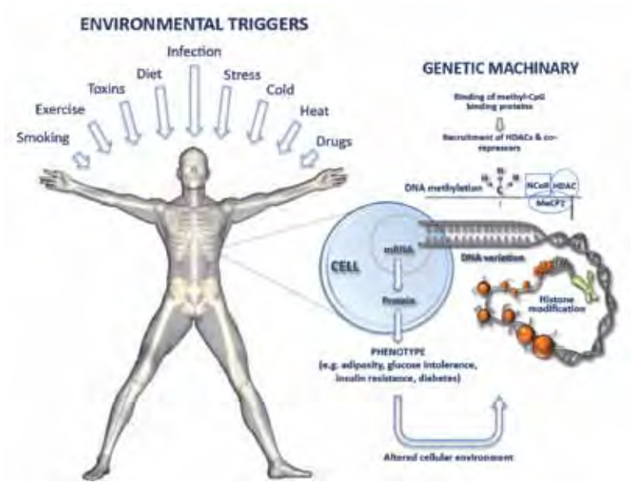

FIGURE 1: *Mechanisms through which the environment interacts with variations in the genome, epigenome, and transcriptome to influence disease phenotypes (From: Franks PW & Ling C. BMC Medicine).*

The process of defining this evidence-base has involved studies, which test whether an individual's genetic background modifies their response to diabetogenic lifestyle exposures or to medical interventions designed to mitigate disease risk (figure 1).

This has and will continue to involve large-scale studies that examine such interactions within well-characterized epidemiological cohorts.

In one recent study, we reported interactions between a variant at the FTO locus, lifestyle factors and mortality in 28,000 people from the Malmö Diet and Cancer study1.

These and other epidemiologic studies have helped define how specific genetic loci modify the relationships of lifestyle exposures with diabetes-related traits.

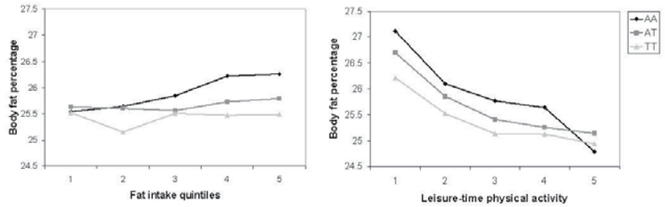

FIGURE: *The FTO genotype interacted with fat intake and physical activity level on body fat-% and fat mass with interaction p-values of p=0.01 and p=0.005, respectively1*

Whilst epidemiological studies will help unravel the complex interplay of genetic and lifestyle factors in diabetes etiology, one must also translate epidemiological observations into the clinical setting using randomized controlled trials (RCTs).

We participate in the Diabetes Prevention Program, a US-based randomized clinical trial of intensive lifestyle modification or metformin monotherapy for diabetes prevention, which showed that risk allele carriers at the FTO locus, although predisposed to gain abdominal adipose tissue when assigned to placebo intervention, lose more abdominal adipose tissue when assigned to metformin or lifestyle interventions than persons with the low risk FTO genotype2. Recent DPP studies have shown that lipid-associated gene variants modify the effects of lifestyle intervention on improvements in small-LDL particle concentrations3 (figure 3).

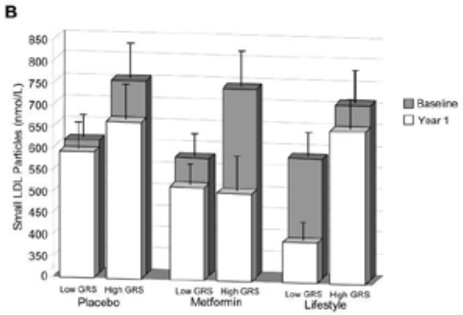

FIGURE 3: *Small LDL particle levels at baseline and 1 year stratified by treatment group and lipid genetic risk score (GRS). Each column shows ethnicity-adjusted geometric means (with upper 95 % confidence), stratified above and below the ethnic-specific median GRS value.*

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Diet, exercise and other lifestyle factors in prevention of diabetes and obesity An LUDC-wide field of research

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VISION: TO DEVELOP DIET AND EXERCISE PROGRAMS and food products with metabolic benefits for use in the prevention and treatment of diabetes and obesity.

What kind of diet is healthy in a given genetic background? Should extreme diets be used or avoided due to individual genetic makeup? Is it useful to exercise at low intensity or is high intensity exercise necessary to obtain beneficial effects, such as increased skeletal muscle oxidative capacity and glucose uptake?

To be able to answer these key questions it is of great importance to better understand how diet and exercise may affect physiological mechanisms involved in the development of diabetes and how heritable factors can influence these mechanisms. Although diabetes is known to result from interplay between genetic predisposition and unfavourable environment, very little is known about such interactions. Our recent epidemiological studies indicate that our genetic make-up modifies how environmental factors such as diet, smoking or physical activity affect our susceptibility to obesity and diabetes indicating that environment modifies our genetic susceptibility. We study interactions between genetic and environmental factors to understand interactions them between and to elucidate the underlying mechanism/s. Further, detailed metabolic measurements during different forms of exercise (e.g. type, intensity, frequency and volume) will be combined with information on genetic susceptibility, to define who will benefit most from which type of diet or exercise. Finally, we use clinical trials to follow-up on epidemiological observations to determine the causal nature of gene-lifestyle interactions.

Diet and exercise may also directly modify the genome through epigenetic mechanisms, including DNA methylation and histone modifications, and thereby affect the risk for diabetes. We have shown that an exercise intervention changes the genome-wide DNA methylation pattern in human skeletal muscle and that a high fat diet introduced epigenetic modifications in skeletal muscle of young men. Our further studies will dissect how exercise and diet affect the risk for diabetes and obesity through epigenetic modifications in target tissues for the disease.

We also screen food concepts for beneficial metabolic effects in rodent models of human obesity and prediabetes. Concepts of interest include, but are not limited to, prebiotics, probiotics and synbiotics acting through modulation of the gut microflora. Promising concepts are further evaluated with regard to mechanisms of action and bioactive components and uses human intervention studies.

Finally, we challenge the question of environmental triggers (diet, exercise, psycho-social factors) among children with increased genetic risk for type 1 diabetes and celiac disease.

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