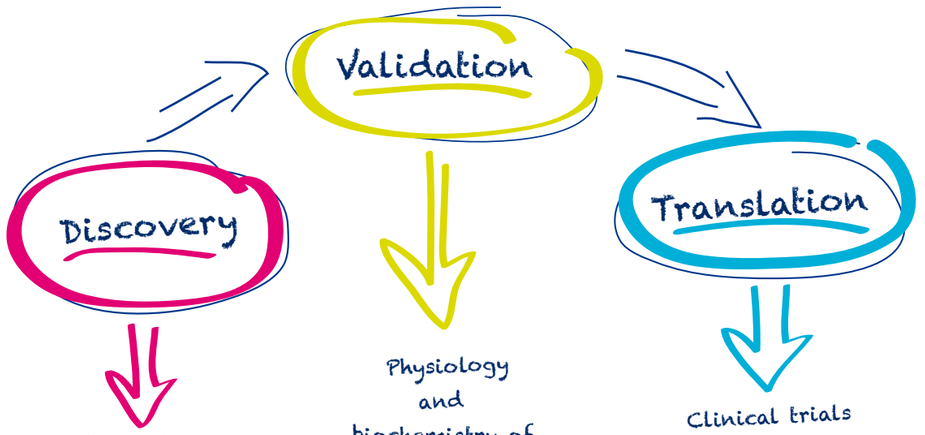
FOR PEOPLE BY PEOPLE


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 is today the center 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 (70 %) and Uppsala Universities funded by a strategic Research Grant from the Swedish Government. LUDC forms the bulk of the Lund University part of EXODIAB with the addition of the Antidiabetic Food Centre, which has the aim to explore novel food products in the prevention and treatment of diabetes.

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. ■

SEVERAL 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.

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
shorter-term collaborations, testing of "leads" within existing models

II
longer-term strategic collaborations, investigating biological systems

III
Identifying areas for IP activities leading to start-up







A centralized approach to customer contacts is preferred where the one point of contact is the IO. A Commercial Advisory Board (CAB) will be 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 an Innovation Advisory Board that oversees development of innovation projects funded by agencies such as VINNOVA, SSF or in collaboration with industrial partners.

When such projects have developed their commercial potential sufficiently for being launched on the commercial market they will be transferred to a partner or "project takers". ■

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). ■

MODERN POPULATION GENETICS AND system biology approaches use technology platforms that generate vast amounts of data. In the bioinformatics group we face the challenge of combining and making use of data generated from several different experiments and platforms. We also integrate information from publicly available databases into our data.

Central to our task is the creation and maintenance of a database that can store and query these different datasets in a unified manner. The aim is to provide a means for LUDC researchers to easily obtain valuable information from the database. ■

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. LUDC investigators will be able to perform ground breaking research which will increase our understanding of the human islet and the development of both Type 1 and Type 2 diabetes. ■

PI
Eva Degerman,
Insulin Signal Transduction Unit
Eva.Degerman@med.lu.se

CO-PI
Lena Stenson,
Insulin Signal Transduction Unit
Lena.Stenson@med.lu.se

CO-PI
Olga Göransson,
Protein Phosphorylation Unit
Olga.Goransson@med.lu.se

RESEARCH AREA:
Cellular signalling in diabetes

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

The insulin resistance and resulting dys-regulated metabolism is a cornerstone in the development of diabetes. The exact cellular and molecular mechanisms causing systemic insulin resistance is not known, but its strong link to obesity suggests that primary or secondary defects in adipose tissue is an underlying problem.
By dissecting signalling pathways regulating glucose metabolism 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.

We are also engaged in functional investigation of new risk genes for diabetes, for example TCF7L2 and the GIP receptor, 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.

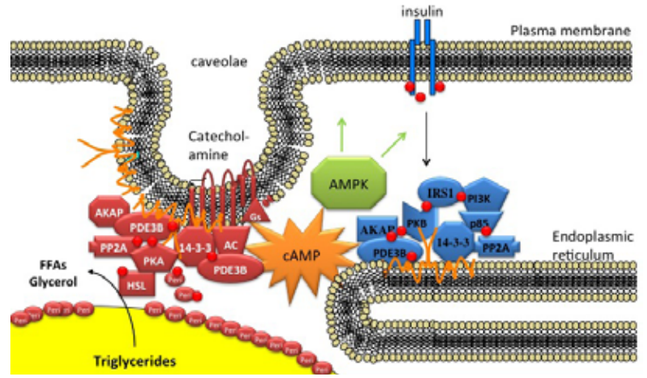


FIGURE: *Interplay between cAMP, insulin and AMPK signalling networks in the regulation of adipocyte functions. The figure illustrates the complex pattern of interactions between interconnected signalling networks in adipocytes. For example, insulin and catecholamines induce the formation of unique multiprotein 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

PI
Leif Groop,
Diabetes and
Endocrinology Unit
Leif.Groop@med.lu.se

CO-PI
Valeriya Lyssenko,
Diabetes and
Endocrinology Unit
Valeri.Lyssenko@med.lu.se

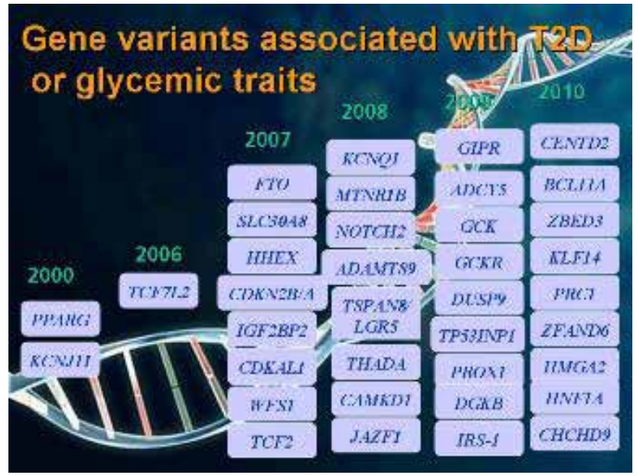
CO-PI
Ola Hansson,
Diabetes and
Endocrinology Unit
Ola.Hansson@med.lu.se

VISION: TO IDENTIFY THE GENETIC CAUSES OF TYPE 2 DIABETES.
Type 2 diabetes is the fastest growing disease affecting 250 million people worldwide and the number is predicted to double within the next 15 years. T2D is assumed to develop from the interaction between genetic predisposition and an affluent environment. Yet, the underlying genetic causes of the disease are unknown.

To accomplish this task different strategies are being adopted, including genome wide association studies (GWAS), next-generation sequencing, expression profiling of target tissues (human islets, muscle, fat and liver), as well as studies of epigenetic modifications (DNA and histone methylation, acetylation, etc).

A prerequisite for these studies is access to some of the largest and best characterized populations in the field, including the Botnia Study, the Malmö Diet and Cancer Study, etc. These studies allow exploration of gene-environment interactions as well as prediction of disease development and progression.

Gene variants associated with T2D or glycemic traits.



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PI
Hindrik Mulder, Molecular Metabolism Unit
Hindrik.Mulder@med.lu.se

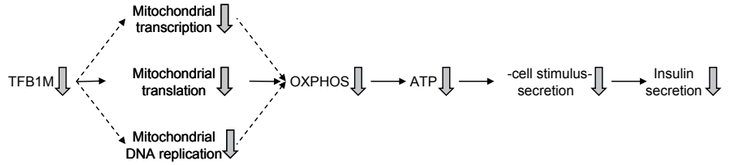
CO-PI
Holger Luthman, Medical Genetics Unit
Holger.Luthman@med.lu.se

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 T 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 Genome-wide 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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PI
Cecilia Holm,
Molecular
Endocrinology Unit
Cecilia.Holm@med.lu.se

CO-PI
Jens Lagerstedt,
Medical Protein
Science Unit
Jens.Lagerstedt@med.lu.se

CO-PI
Karin Berger,
Molecular
Endocrinology Unit
Karin.Berger@med.lu.se

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.

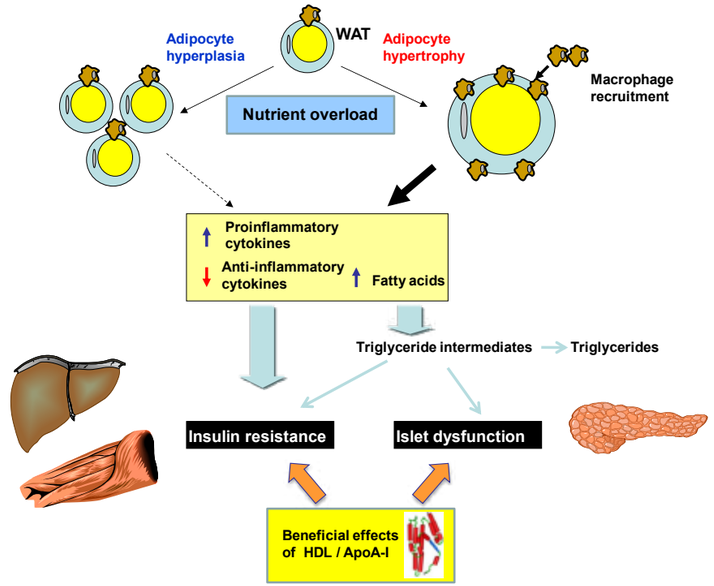

FIGURE. *Schematic representation of mechanisms underlying obesity-associated insulin resistance and islet dysfunction, and the beneficial function of HDL/apoA-I in preventing/reversing their progression (for more details, see text).*

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”A creative office environment makes way for creative science”

PI
Charlotte Ling,
Epigenetics and
Diabetes Unit
Charlotte.Ling@med.lu.se

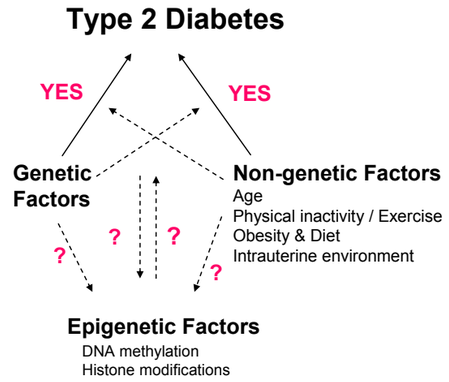
RESEARCH AREA:
Epigenetics

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 hence affect the pathogenesis for the disease.

Recent studies from the LUDC demonstrate that epigenetic modifications, including DNA methylation and histone modifications, of candidate genes for Type 2 diabetes are associated with both impaired insulin secretion and action. Our ongoing studies examine 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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PI
Bo Ahren,
Medicine Unit
bo.ahren@med.lu.se

CO-PI
Bilal Omar,
Neuroendocrine
Cell Biology Unit
Bilal.Omar@med.lu.se

CO-PI
Nils Wierup,
Neuroendocrine
Cell Biology Unit
Nils.Wierup@med.lu.se

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 aid 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.

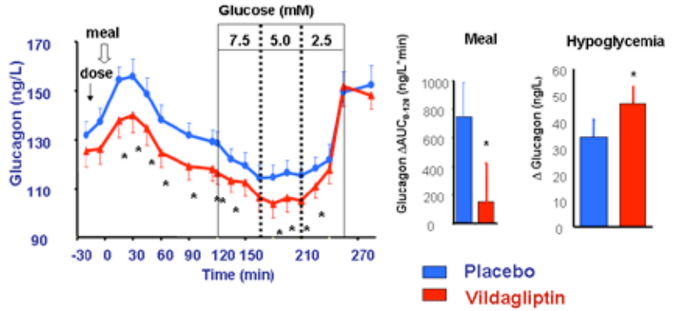

FIGURE. *Result for a study exploring whether DPP-4 inhibition compromises the glucagon response to hypoglycemia, in analogy with its inhibition of glucagon secretion after meal ingestion. Subjects with type 2 diabetes were treated with vildagliptin (a DPP-4 inhibitor) or a placebo for four weeks. Therafter 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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PI
Erik Renström,
Islet Patophysiology Unit
Erik.Renstrom@med.lu.se

CO-PI
Albert Salehi,
Islet Cell Physiology Unit
S_Albert.Salehi@med.lu.se

CO-PI
Anders Rosengren,
Islet Patophysiology Unit
Anders.Rosengren@med.lu.se

RESEARCH AREA:
Islet Patophysiology

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., immuno-precipitation, 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.

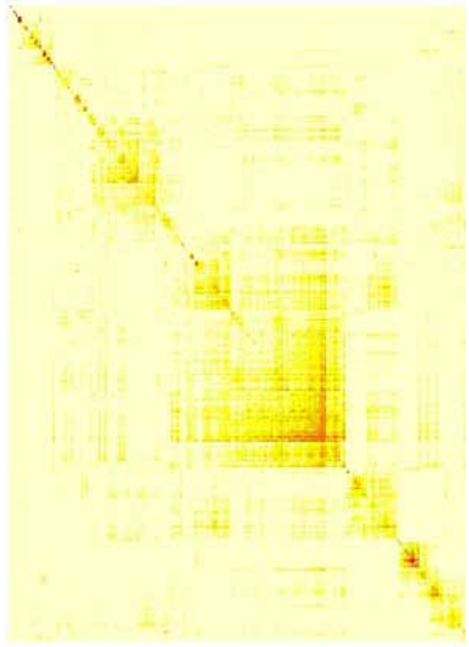

FIGURE. *Topological overlap presentation of clusters of co-expressed genes in donor human islets. Analysis was confined to the 5000 most highly expressed genes, which are presented along the x and y axes. Gene pairs exhibiting the highest connectivity (|correlation|10) are denoted in red, whereas pairs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

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RESEARCH AREA:
Vascular Diabetic Complications

PI
Carl-David Agardh, Vascular Diabetic Complications Unit
Carl-David.Agardh@med.lu.se

CO-PI
Jan Nilsson, Experimental Cardiovascular Research Unit
Jan.Nilsson@med.lu.se

CO-PI
Maria Gomez, Vascular ET-coupling Unit
Maria.Gomez@med.lu.se

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-antigens, such as oxidized-LDL, AGE-modified proteins and aldehyde-modified 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.

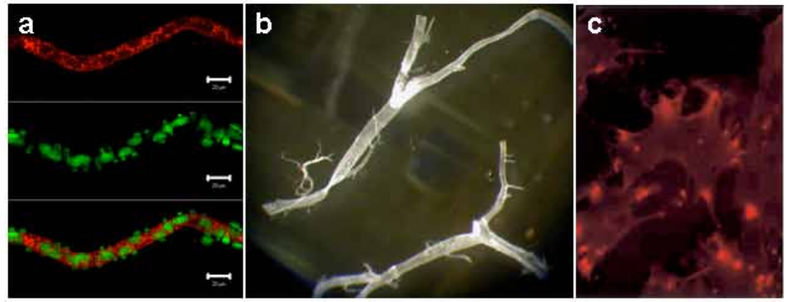

FIGURE LEGEND:
a) Confocal image showing VCAM-1 expression (red) and cell nuclei (green) in mouse cerebral microvessels in response to hyperlipidemia;
b) Atherosclerotic plaque in the bifurcation of a mouse cerebral artery (white opaque area); c) Serum anti-pericyte autoantibody binding to bovine retinal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

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PI
Henrik Semb,
Stem Cell Center
Henrik.Semb@med.lu.se

CO-PI
Isabella Artner,
Stem Cell Center
Isabella.Artner@med.lu.se

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.

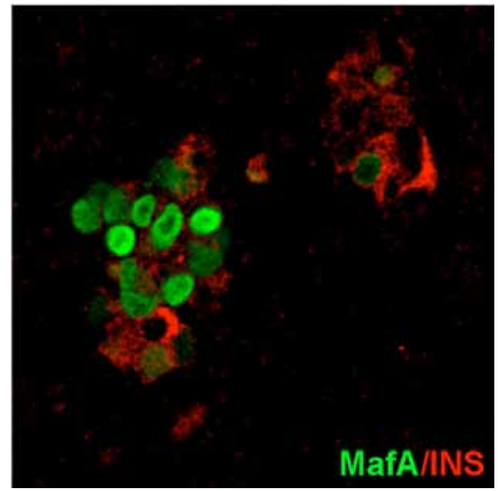

FIGURE. *Expression of MafA, Pdx1, and Ngn3 induces insulin production in the chick gut endoderm. This over-expression experiment illustrates the significance of these transcription factors to insulin production and beta cell differentiation.*

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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!

PI
Lena Eliasson,
Islet Cell
Exocytosis Unit
Lena.Eliasson@med.lu.se

CO-PI
Jonathan Esguerra,
Islet Cell
Exocytosis Unit
Jonathan.Esguerra@med.lu.se

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.

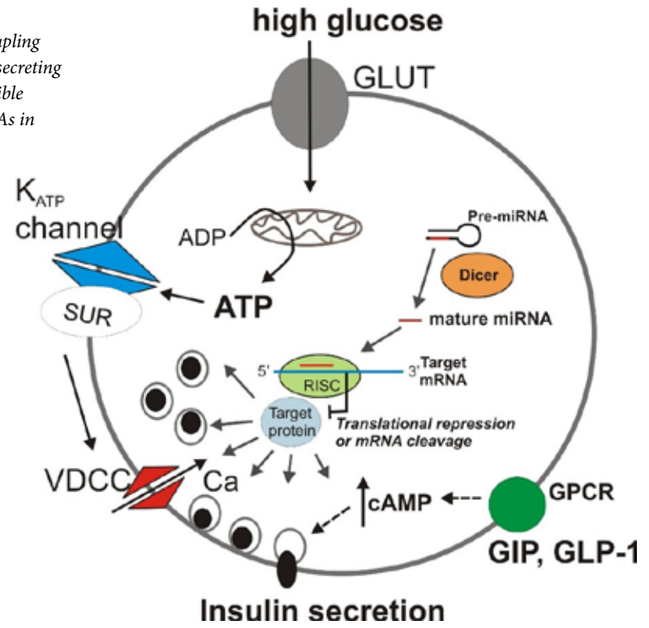
Our vision is that we will;

I) 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.

II) Achieve a better understanding of miRNAs and their role in insulin secretion and glucagon secretion and in diabetes development.

III) 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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PI
Inger Björck,
AFC
Inger.Bjorck@
appliednutrition.lth.se

CO-PI
Maria Johansson,
AFC
Maria.Johansson@
appliednutrition.lth.se

CO-PI
Juscelino Tovar,
AFC
Juscelino.Tovar@
appliednutrition.lth.se

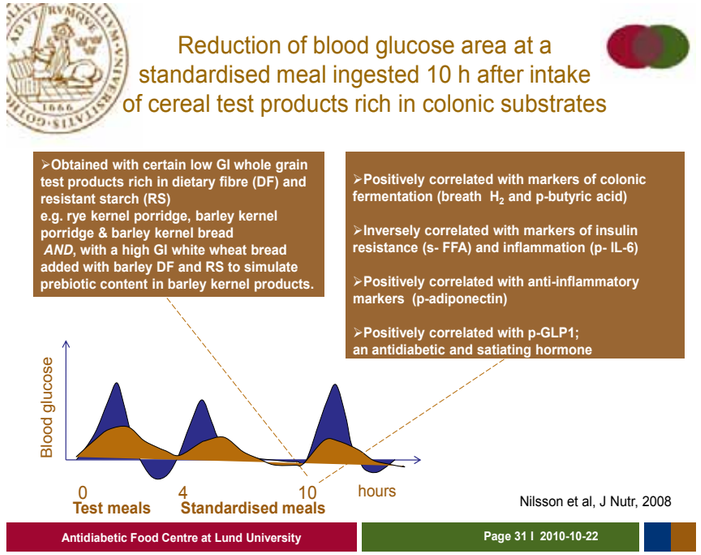
RESEARCH AREA:
Tailoring of foods for metabolic benefits/antidiabetic foods

VISION: ANTIDIABETIC FOOD CENTRE (AFC)
The vision of AFC is to constitute an environment that stimulates establishment of innovative and preventive food concepts thus providing community benefits and sustainable growth by preventing obesity, Type 2 diabetes and other manifestations of the insulin resistance syndrome (www.ffsc.lu.se/afc).

Collaboration within EXODIAB makes possible exploitation of synergistic competences regarding research techniques.

Additionally, EXODIAB collaboration provides substantial added value by allowing for studies of the therapeutic potential of prototype foods.

Research activities within AFC focus on studies of various food factors and/or properties of importance for metabolic risk factors. One recent finding concerns the link between colonic fermentation of indigestible carbohydrates, and systemic benefits probably mediated through stimulation of GLP-1.



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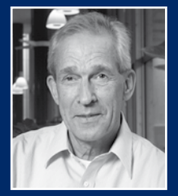
RESEARCH AREA:
Autoimmune diabetes and celiac disease pathogenesis, prediction and immune intervention



PI
Åke Lernmark, Diabetes and Celiac Disease Unit
Ake.Lernmark@med.lu.se

CO-PI
Helena E Larsson, Paediatric Endocrinology Research Group
Helena.Larsson@med.lu.se

CO-PI
Daniel Agardh, Diabetes and Celiac Disease Unit
Daniel.Agardh@med.lu.se

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 processes. The current research on the dissection of T1D genes in humans and in several animal models is directed to the identification of genetic factors within and outside the Major Histocompatibility Complex (MHC) 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. 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 a well established collaboration with Olle Korsgren in Uppsala (Nordic Islet Transplantation Network).

The strong translational focus of our research platform 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) to halt beta cell autoimmunity.

In summary, our research contributes to *1.* Genomics in autoimmune diabetes (T1D) and CD including HLA and non-HLA genes. Dissection of diabetes genes in the BB rat; *2.* Inflammatory markers analyses including multiplex serum cytokines and metabolomics analyses; *3.* Autoantigen identification and development as well as standardization of novel autoantibody assays to predict T1D and CD and *4.* Novel therapies in investigator-initiated prevention and intervention therapies to induce immunological tolerance to autoantigens.

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PI
Corrado M. Cilio, MD, PhD Cellular Autoimmunity Unit
corrado.cilio@med.lu.se

CO-PI
Annelie Carlsson, MD, PhD
Annelie.Carlsson@med.lu.se

CO-PI
Malin Fex, PhD
malin.fex@med.lu.se

VISION: THERE ARE STRONG EVIDENCES INDICATING THAT SYSTEMIC and cellular inflammatory processes are not only marking progression to autoimmune diabetes 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 the role of the immune system and its regulation play a central role in the pathogenesis of Type 1 diabetes (T1D), less clear is the contribution of inflammation in metabolic disorders like T2D and obesity.

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 predictor for T1D is 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 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:

a) To study the role of cellular and systemic inflammatory responses in T1D, T2D and obesity.
b) 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
c) 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.
d) To study the gray zone between T1D, T2D and obesity using already established animal model (NOD.ob) and selected patients' cohorts: pre-T1D, T1D, pediatric obesity with and without T1D, LADA, adult T1D and obese adults.
e) To directly study cellular and systemic inflammatory responses in human islets and lymph nodes from T1D, T2D and obese donors.
f) To potentiate and implement immunotherapy in T1D with the establishment of a pediatric immunotherapy unit combining tolerance induction for allergic and autoimmune/inflammatory diseases, like T1D

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PI
Paul Franks, Professor of Genetic Epidemiology
Paul.Franks@med.lu.se

CO-PI
Marju Orho-Melander, Professor of Genetic Epidemiology
marju.orho-melander@med.lu.se

CO-PI
Olle Melander, Professor of Internal Medicine, Consultant
Olle.Melander@med.lu.se

RESEARCH AREA:
Genetic Epidemiology & Translational Genomics

VISION: THE ELUCIDATION OF COMPLEX TRAIT GENETICS IS set to continue as ongoing next-generation sequencing efforts begin to reveal the identities of rare disease-predisposing variants. LUDC is uniquely situated to expand on these discoveries 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.

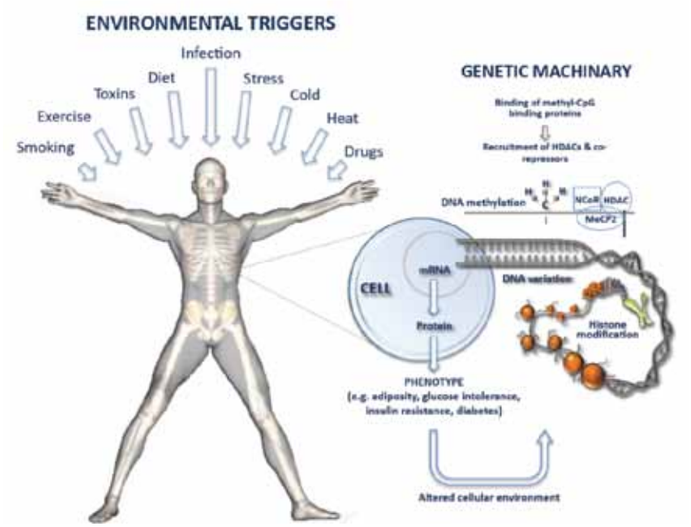

FIGURE 1: *Mechanisms through which the environment interacts with variations in the genome, epigenome, and transcriptome to influence disease phenotypes (From: Franks PW & Ling C. BMC Medicine).*

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

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

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).

Our work in this area has been based primarily on the Diabetes Prevention Program, a US-based randomized clinical trial of intensive lifestyle modification or metformin monotherapy for diabetes prevention (Knowler et al, NEJM, 2002). For example, in support of the epidemiological observations of gene x lifestyle interactions described above, we 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 genotype (Franks et al, Diabetologia, 2007).

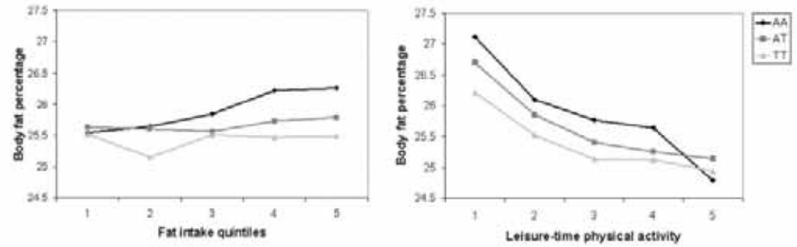

FIGURE 2: *The FTO genotype interacted with fat intake and physical activity level on body fat-% and fat mass in the Malmö Diet and Cancer study (N>28,000) with interaction p-values of p=0.01 and p=0.005, respectively. FTO was not a significant determinant of fatness among individuals in the three lowest quintiles of fat intake, neither among individuals in the highest quintile of leisure time physical activity (From: Sonestedt et al. Int J Obes, 2010)*

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CONTACT INFORMATION:

Sylvie Bove
Innovation Officer

Phone: +46 40 39 11 55
Mobile: +46 708 19 11 55
Fax: +46 40 39 12 22
sylvie.bove@med.lu.se

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LUND UNIVERSITY

VISITING ADDRESS:
CRC, entr 72, bldg 91, floor 11

POSTAL ADDRESS:
CRC, Ingång 72 UMAS,
SE-205 02 Malmö, Sweden
www.ludc.med.lu.se

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