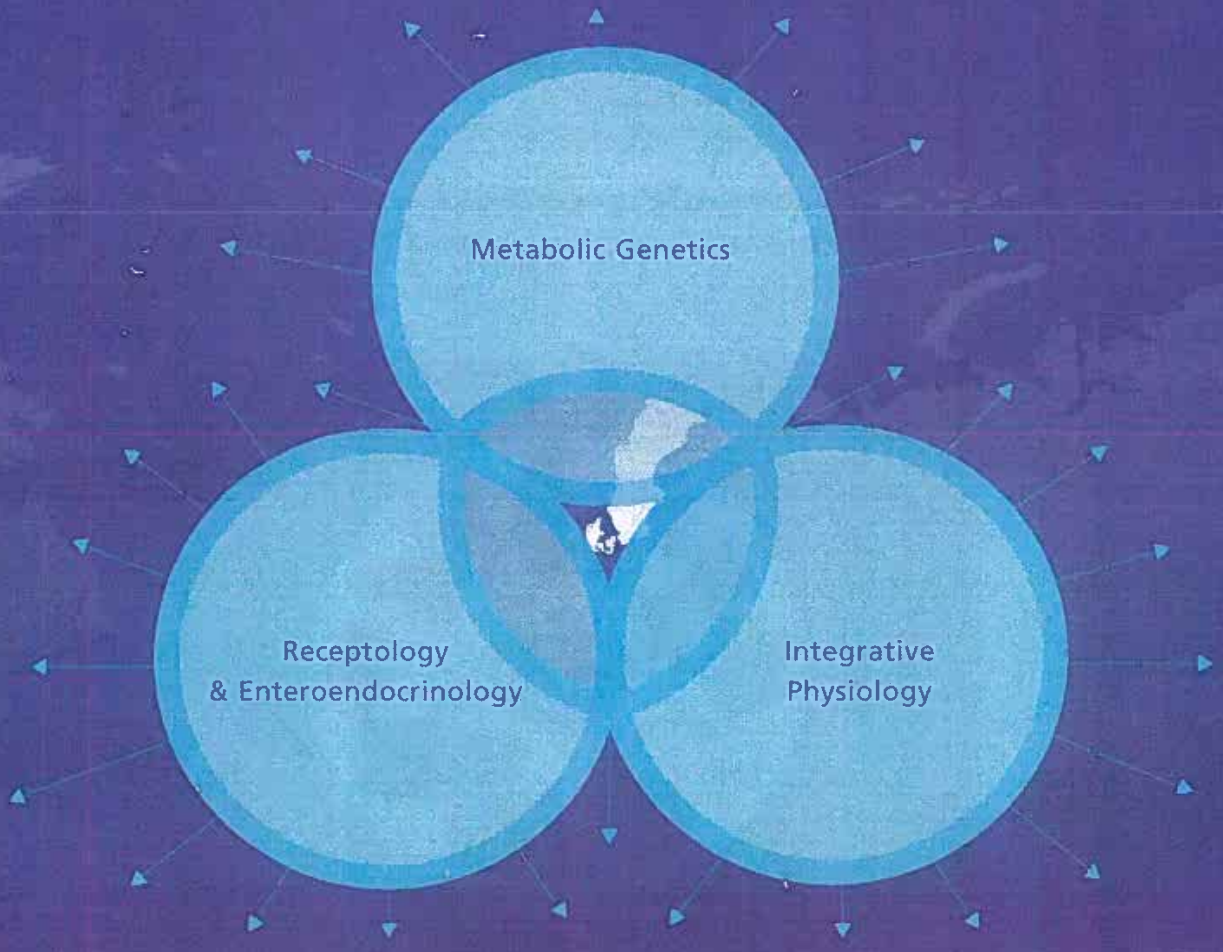
FACULTY OF HEALTH SCIENCES
UNIVERSITY OF COPENHAGEN

The Novo Nordisk Foundation Center for Basic Metabolic Research



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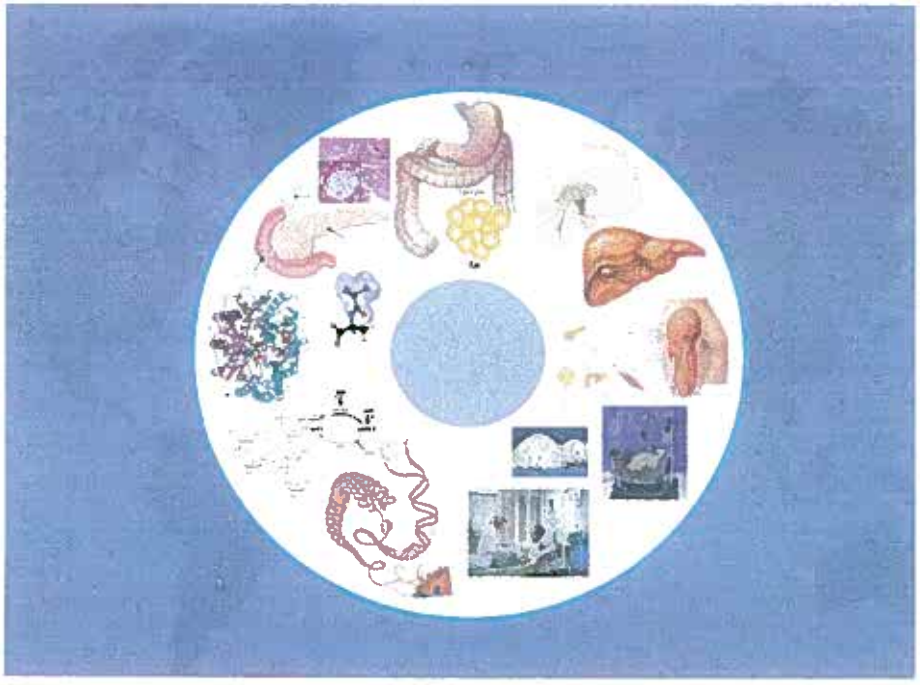


Executive Summary

The Challenge and Motivation

Modern living is associated with an upsurge in the incidence and prevalence of metabolic disturbances characterized by a core of excessive body fat and elevations of blood glucose to levels that increase the risk of premature ischemic cardiovascular morbidity and mortality. In fact, in many parts of the world, 30-40% of the adult population is overweight or obese and the total diagnosed and undiagnosed hyperglycemic cases amounts to about 30%. Needless to say, these common metabolic dysfunctions place an enormous burden on the affected individuals and society.

Although increased knowledge has been achieved during the last decades, the persistent growth of body adiposity and the increase in blood glucose (hyperglycemia) levels in the general population call for a much deeper understanding of the pathogenesis and the pathophysiological features of these abnormalities. Thus, concerted research efforts taking advantage of genetics, physiology and molecular biology, will allow powerful science-based strategies to combat metabolic disease. Moreover, new and experimentally validated public health initiatives targeting well-defined subsets of individuals at high risk of overt type 2 diabetes and morbid obesity, as well as major innovations in a series of intervention modalities for those who already have developed clinical metabolic disorders are required.

Historically, Scandinavian biomedical laboratories hold internationally recognized, leading positions within critically important aspects of basic metabolic research. However, these activities have often been driven without a coordinated focus and strategic research plan. The recent technology-driven, momentous breakthrough in fundamental genome research and the derived major progress in molecular and cellular biology, physiology and molecular pharmacology now call for the establishment of a Scandinavian epicenter for global basic metabolic research as the focal-point for translational, clinical research and technical innovation to attack and concur the overwhelming challenge of the epidemic of obesity and type 2 diabetes.

Vision

To establish a world-leading Center of Excellence for interdisciplinary basic metabolic research evolving from the thematic areas of Metabolic Genetics, Integrative Physiology, and Metabolic Receptology/Enteroendocrinology in order to generate cutting edge and profound knowledge about metabolic functions as the basis for the development of novel means of diagnosis, prevention and individualized treatment of common metabolic disorders.

It is the intention of the Center to advance research discoveries, education and innovation in metabolic diseases beyond the frontier. This will be achieved by systematic and integrated studies of human genetics and genomics, cellular biology, animal biology, human physiology, targeted molecular pharmacology, and environmental factors. The concerted and integrated actions will advance key knowledge leading to improved health and quality of life for the patients, which will translate into a positive benefit for society.

Focus of the Center

The Novo Nordisk Foundation (NNF) Center will focus its activities on basic metabolic research within Metabolic Genetics, Integrative Physiology, and Metabolic Receptology/

Enteroendocrinology. To ensure the necessary tool- and model developments, as well as technical performances within specific parts of the three thematic areas, a series of tight collaborations with satellite laboratories inside and outside of Scandinavia are going to be established. Effective systems for communication and data sharing between the NNF Center and its satellites will be developed. The NNF Center will concentrate its activities on basic metabolic research, but a series of alliances with clinical partners will facilitate the immediate testing of basic metabolic discoveries for their intervention and prevention potentials in statistically powered subsets of patients and of people at risk of common metabolic disorders.

The Region of Copenhagen and Øresund already features strong basic and clinical research and pharmaceutical industry within the field of metabolic diseases. The NNF Center will fuel these activities to become a world-leading epicenter of metabolic research through targeted internalization, innovation, dissemination, and public outreach in order to substantially contribute to future developments and profiling of the Region as an international "hot spot" for metabolic research for biotech and pharmaceutical industry and for dissemination of research results to the public.

Site of the Center: The Panum Tower, University of Copenhagen

To fulfill this mission, the NNF Center will be placed in a new 30.000 m^2 research building called The Panum Tower, which will be a part of the Faculty of Health Sciences, University of Copenhagen. The different sections of the Center will be physically located in an architectural context and infrastructure that deliberately will optimize for daily close interactions especially between scientists and students within and across the whole Center, but also with other researchers at the Faculty including the Novo Nordisk Foundation (NNF) Center for Protein Research (see Appendix 1 for further information).

Strategic Themes and Research Programs

Three main strategic research themes with defined goals will be pursued to meet the overall aims of the NNF Center. To realize these goals, five Scientific Directors have been identified to head the research and a number of international top senior scientists and junior principle investigators (PI's) will further be recruited to the Center.

Metabolic Genetics: (Scientific Director, Professor Oluf Borbye Pedersen)

Applying a variety of genomic technologies, bioinformatics, and computational statistics, the research program is focused on novel discoveries of variations in the human genome that associate with common metabolic dysfunctions in the general population and with increased risk of overt type 2 diabetes and obesity. The genome variations which are associated with common metabolic disturbances are characterized in a systematic series of epidemiological studies and delivered to the two other themes of the NNF Center for in-depth physiological and molecular explorations. The expected long-term outcomes of the genetics program are valid algorithms for assessment of individuals at high risk for progressing within defined time frames in hyperglycemia and adiposity. Such efficacious prediction scores will pave the way for a series of public health initiatives to prevent the epidemics of type 2 diabetes and obesity. Similarly, the genetics initiatives are likely to identify multiple naturally occurring gene variants that associate with common metabolic phenotypes, suggesting that the underlying biological pathways need careful examination for their potentials as novel targets for lifestyle- and drug interventions.

Integrative Physiology: (Scientific Director, Professor Juleen R. Zierath)
This program will be focused on defining the physiological role of novel and previously identified candidate genes/proteins linked to type 2 diabetes and obesity using functional genomics, epigenetics and miRNA approaches. Model organisms and animal models will be used to assess the functional role of these targets in the pathogenesis of type 2 diabetes and obesity. Detailed metabolic studies will be performed to determine genotype/phenotype interactions and to identify diabetes risk-factors. Inter- and intra-cellular signaling pathways controlling glucose and lipid homeostasis will be identified and integrated with the aim to validate diabetes prevention and treatment targets. The molecular and physiological mechanism by which diet, weight loss, and exercise improve insulin sensitivity to prevent and treat type 2 diabetes and its complications will also be identified and characterized.

Metabolic Receptology and Enteroendocrinology:
(Scientific Director, Professor Thue W. Schwartz)
This research program is based on the notion that the highly beneficial effects of bariatric surgery, the only known cure for type 2 diabetes and obesity to date, are conferred by altered signaling from the gastrointestinal tract (GI)-tract. Moreover, receptor proteins are key regulators of the enteroendocrine cells, of the central and peripheral elements of the brain-gut axis and of the end-target metabolic organs. The entire elusive enteroendocrine system, with respect to the repertoire of peptide hormones and regulatory chemo-sensors/receptors, will be mapped as a basis for the development of non-surgical strategies to mimic the curative effect of bariatric surgery. Based on the exhaustive identification of genetic variants performed in the "Metabolic Genetics" research theme, the role played by novel metabolic receptors in the pathogenesis of type 2 diabetes and obesity and their potential use as drug targets for the prevention and treatment of metabolic disorders will be characterized and validated. This theme will also function as a research-hub for satellite projects related to pancreatic islet biology and gut microbiota. An important contribution to the "Metabolic Genetics" theme and "Integrative Physiology" will be the structure/knowledge-based development of pharmaceutical tool compounds for target validation.

These three research themes are joined together by the translational, metabolic physiology research function which takes advantage of the uniquely broad expertise of Scientific Director, Professor Jens J. Holst who embraces basically all of the research areas of the Center. The research will here exploit elements from all three research themes and cover areas such as: the integrated secretion and function of GI-tract hormones; physiological dissection of the relative importance of paracrine versus endocrine and neuronal functions of the hormones; the autonomous nervous system with special focus on the brain-gut axis with characterization of afferent and efferent part of the axis including, for example control of hepatic metabolism; and the relative importance of endocrine, paracrine and neuronal regulation of the function of pancreatic islets and adipose tissue. This cross disciplinary research function is particularly suited for harvesting the synergies created across the Center and will be central in connecting the basis metabolic research performed at the Center with metabolic, endocrinological clinics nationally and globally to generate the panoramic view required to obtain the ambitious goals of the Center.

The International Scientific Director, Professor Gerald I. Shulman will like Professor Jens J. Holst serve an overarching, conjoining role as his research also reaches deep into all three research themes of the Center and has profound translational character connected to clinical inspiration and application. The international Scientific Director will in particular – together with the four other Scientific Directors - ensure that the Center develops into an internationally outstanding and renowned research and education Center and will advocate

for and "brand" the Center internationally. He will conduct high impact metabolic research closely integrated with the other groups at the Center and with his research group at Yale University.

National and International Outreach through Collaborative Research and Training Programs

The NNF Center will develop and foster collaboration and research education at the highest level with National and International Research Departments and Hospitals and further promote partnerships with the industry sector. The Marie Krogh Fellowship Program will be established by the Center to support postdoctoral fellows to pursue their studies both at the Center as well as at Satellite Centers.

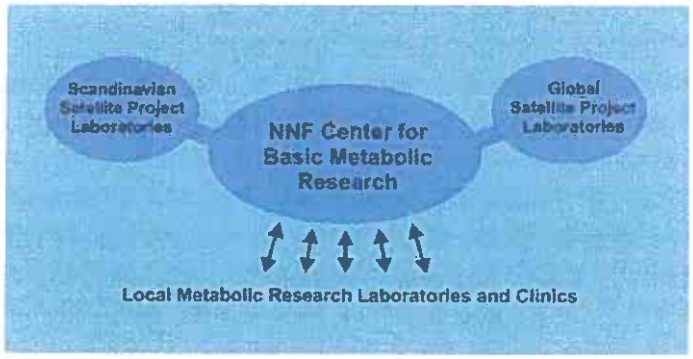


Figure 1: The NNF Center for Basic Metabolic Research – Schematic diagram depicts the integrated collaboration with leading complementary international – Scandinavian and Global – Laboratories where "satellite projects" are performed as joint ventures with the groups at the main Center. Also the close interactions with local metabolic research laboratories and clinics are indicated.

Satellite Project Laboratories

As a novel instrument to optimize knowledge interactions and synergy on an international scale, a number of "satellite projects" will be carried out in key Scandinavian and International laboratories in close collaboration with laboratories at the NNF Center. Research activities of the satellite projects performed abroad will be funded through the center. Exchange students and postdocs will be important parts of the satellite projects, which also will be supported through extensive, frequent use of state-of-the-art IT communication. Through these funded satellite projects a number of internationally leading laboratories with complementary skills corresponding to each of the focus areas will become integrated and committed research partners of the NNF Center.

Education and Research Training

It is the vision that the NNF Center should become a global focal point in basic metabolic research. Consequently, the NNF Center will function as a scientific magnet for top grade international students and postdoctoral fellows who will constitute a major fraction of the staff at the Center. A dedicated Educational Director will become an important integrated part of the management team of the Center. Post-graduate research training with exchange of PhD students, post-doctoral fellows, as well as senior scientists (on sabbatical etc.) will be an important element of the NNF Center. This international dimension of the Center's organization will enable strong, committed interaction and exchange between relevant laboratories world-wide.

The Research Program

Scale of the Problem

We are in the midst of a World-wide epidemic of type 2 diabetes. Globally, the increase in type 2 diabetes amounts to a growth from 246 million people in 2006 to over 380 million by 2025. In a small country like Denmark, one out of 20 people suffer from diabetes, thereby imposing a tremendous human burden and a cost to the Danish society in the range of 20 billions of Danish kroner per year. The epidemic increase in type 2 diabetes is partly driven by sedentary lifestyles, which lead to a greater propensity for obesity that in predisposed individuals results in pre-diabetes, and ultimately type 2 diabetes. Type 2 diabetes is manifested by insulin resistance in liver and skeletal muscle which leads to a progressive decline in insulin secretion from pancreatic beta-cells. Importantly, the strong heritability of type 2 diabetes makes it a most complex disease. Type 2 diabetes affects all organs of the body. The disease is associated with microangiopathy making it the leading cause of blindness in working adults, the leading cause of end stage renal disease and the leading cause of non traumatic loss of limb. In addition it is associated with a 2-6-fold increased risk of myocardial infarction, stroke, and peripheral artery disease, as well as premature mortality. Thus, on top of the individual sufferings, the socioeconomic impact of diabetes to society is enormous. Effective methods to prevent or cure type 2 diabetes are unavailable. Also current modalities have limited efficacy and have not been developed to target the individual patient. Therefore, future research at the genetic, molecular, and physiological levels is essential to dissect the complex causes and phenotypes associated with altered glucose metabolism and energy homeostasis in type 2 diabetes and obesity, as well as the accompanying severely increased risk of early-onset organ damage. Research along these lines is projected to provide new opportunities for individualized prevention and treatment of these two common metabolic disorders, encompassing both tailored pharmacology and lifestyle modifications that have increased efficacy and with fewer side effects.

Research Strategy Focused on Basic and Applied Metabolic Research

The Faculty of Health Sciences at the University of Copenhagen has a long-standing commitment to basic research in metabolic disease, particularly in the area of diabetes and the development of cutting edge technologies including genetics, proteomics and integrative physiology. This is evident by the development of the NNF Center for Protein Research and our large-scale core facility for animal research. Based on the expertise of the principle investigators collaborating on the present application (Figure 2), and the opportunities and infrastructure available at the Faculty and the collaborating satellites, the research of the Center will be focused on genetics, integrative physiology and hormone/receptor biology in type 2 diabetes and obesity.

Long-term Goals of the Novo Nordisk Foundation Center for Basic Metabolic Research

The long-term goals are to establish a basic and translational research and post-graduate educational program that is specifically focused at understanding the basic mechanisms of metabolic disease(s). To accomplish this, the Center will:

- Dissect the underlying genetic causes of type 2 diabetes, obesity and pre-disorder quantitative metabolic traits
- Delineate basic molecular and physiological mechanisms of glucose and energy homeostasis

- Identify and functionally characterize novel metabolic hormones and receptors and validate their pathogenic and therapeutic role in common metabolic diseases
- Develop rational algorithms that allow for efficacious intervention- and prevention strategies in well-defined subsets of type 2 diabetic or obese individuals and of individuals with increased risk for these common metabolic diseases
- Train the next generation of experimental researchers in basic metabolic research
- Develop and strengthen an international scientific network to achieve a strong integration and concerted actions.

To meet these aims, three strategic research themes have been identified: a) Metabolic Genetics, b) Integrative Physiology, and c) Receptology & Enteroendocrinology (Figure 2). The rationale, the aim, specific goal, and research areas for each strategic theme are identified below.

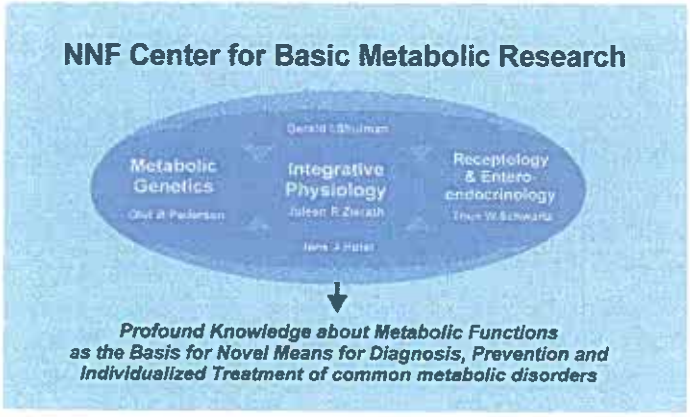


Figure 2: Research Themes and Scientific Directors at the NNF Center for Basic Metabolic Research. The relation of the Center with the satellite project laboratories is depicted in Figure 1 (see page 5).

Metabolic Genetics Research Theme

Scientific Director, Professor Oluf Borbye Pedersen

Rationale

Within the last three years we have experienced a breakthrough in our ability to discover the first set of molecular genetic determinants of common metabolic dysfunctions in the general population predisposing for overt disorders such as obesity and type 2 diabetes and the associated ischemic cardiovascular co-morbidities. This knowledge progress in metabolic genetics has emerged from genome-wide association studies based upon dense single nucleotide polymorphism (SNP) array genotyping. Yet, this approach does not target variations with a frequency below 5-10% and only covers about 80% of the human genome. The heritability of fasting plasma glucose is about 40% and the heritability of body mass index (BMI), is about 70%. Today less than 3% of the heritability of these quantitative metabolic traits in the general population is explained. Also less than 5% of the heritability of type 2 diabetes and obesity can be explained by reported common genetic variants. As a new frontier in advanced genomics, a Danish-Chinese initiative (www. lucamp.org) has initiated global sequencing of the accessible coding parts of the human genome (representing 18,600 genes) in 2,000 Danes followed by large-scale mapping of common and rare deleterious variants in thousands of Danes. Although this approach has the potential to identify novel functional variants that associate with common quantitative metabolic traits and disorders, much of the genomic variation which makes an individual sensitive to the diabetogenic and obesogenic influences of modern living is unexplored. Such genomic variation is hypothesized to be caused by variation in the regulatory parts of the genome including promoters, untranslated regions (UTRs), non-coding RNAs and intronic regulatory regions, as well as by major structural variation in DNA (copy number variations).

Goals

- To discover and annotate novel genome variation in Danish and Chinese cohorts
- To examine which genome variations ('genetic initiators') associate with quantitative metabolic traits in the general population such as insulin secretion, whole-body insulin sensitivity, body fat distribution and content, and serum lipids (baseline studies)
- To examine which genome variations ('genetic modifiers') are determinants for lifestyle-adjusted changes over 5 and 10 years, respectively, in quantitative metabolic traits in the general population such as insulin secretion, whole-body insulin sensitivity, body fat distribution and content, and serum lipids (prospective cohort studies)
- To examine how the interactions of genome variations with fetal health, as reflected by birth weight and length and adult health behavior as informed by questionnaires and interviews on diet and physical activity, impact on quantitative metabolic phenotypes at baseline and after 5 and 10 years, respectively, of follow-up in the general population
- To examine which genetic initiators and genetic modifiers alone and in combination with health behavior confer development of dichotomous metabolic traits such as defined subsets of obesity (central versus peripheral), type 2 diabetes, dyslipidemia, hypertension, defined ischemic cardiovascular outcomes (primarily acute coronary syndrome and stroke) and mortality
- To examine the physiological and pharmacological responses of selected genome variant carriers and non-carriers to standardized acute loads of specified nutrition, exercise or drugs/drug candidates
- To deliver metabolic disease-/ quantitative trait-associated genome variations to the other sections of the NNF Center for in-depth physiological and mechanistic characterization

- To identify novel targets for a variety of specific interventions including lifestyle modifications and drugs to prevent progression in subclinical metabolic dysfunctions at the population level and eventually to prevent type 2 diabetes, obesity and ischemic cardiovascular events
- To develop clinically useful algorithms for 5 years type 2 diabetes risk prediction and 5 years progression in body fat content and distribution by applying advanced integrative statistics. Such algorithms will be developed by integrating identified genome risk markers, quantified circulating protein- and metabolite risk markers and conventional risk factors (age, gender, family history, BMI and waist circumference). The risk scores are expected to facilitate novel pathogenesis-based diagnosis of subsets of type 2 diabetes and obesity, more individualized and efficacious treatment options with fewer side effects, as well as better prediction of those individuals in the general population who are at highest risk for developing overt type 2 diabetes or morbid obesity and associated vascular complications.

Research Area and Questions

The research area is focused on basic and applied molecular genetics of common metabolic quantitative traits and disorders with an emphasis on type 2 diabetes and obesity and is thereby called "Metabolic Genetics". In the context of the present application, the broad term 'metabolic genetics' covers activities of *'basic metabolic genetics', 'genetic epidemiology' and 'applied metabolic genetics'.*

Human genome research is proceeding at an amazing rate, with novel large-scale data being generated World-wide on a daily basis. Details of the proposed experimental protocols for metabolic genetics to be carried at the NNF Center are therefore expected to be subject to relatively rapid adaptation, depending on new, as yet unknown progress in basic genome insights, as well as developments in genome research technology, mathematical modeling and statistical genetics. Therefore, in order to be at the frontline of this very dynamic research field, flexibility is required to accommodate protocol *adjustments*. This will be crucial to achieve the outlined goals.

Nevertheless, the experimental protocols that will address the major goals presented in this proposal are founded on the unique and competitive competences and resources within the area of metabolic genetics in Denmark and on the complementary strengths of partners in satellites and alliances with the NNF Center. Thus, the "Metabolic Genetics" theme will integrate strong national competence within epidemiological genetics, physiological and pharmacological genetics, applied clinical genetics and statistical genetics and bioinformatics with a world-leading Chinese technical facility for basic genome discoveries, as well as with a front-runner US Center for mathematical genetics development.

The "Metabolic Genetics" research theme of the NNF Center will transfer its validated genome discoveries to achieve a comprehensive functional characterization of metabolic disease-associated encoded proteins in the "Metabolic Hormone and Receptor Biology" and the "Integrative Physiology" research themes at the NNF Center.

Approaches and Methods

The Metabolic Genetics research activities are structured following three complementary and interacting approaches:

Basic Metabolic Genetics

The genome variation discoveries are divided into four chronological steps, which are deter-

mined by the maturation and availability of current technology within the genetics field:

- Search for single nucleotide polymorphisms (SNPs) and copy number variations (primarily duplications, insertions and deletions) in the coding parts of the human genome (the exome)
- Search for genome-wide variation in promoters and un-translated regions (UTRs) ('regulatory genetics')
- Search for genome-wide variation in non-coding RNA genes and non-coding RNA binding sites (included in 'regulatory genetics')
- Whole genome sequencing to identify the cumulative load of rare and common variants including global structural variation ('whole genomics').

The variant discoveries outlined in the project dealing with the exome and 'regulatory genetics' are categorized and quality assured in the NNF Center, whereas the 'whole genome sequencing' project is a daunting task, which only can be approached through a massive and structured multinational concerted action involving multiple genome- and clinical centers.

Due to the extremely expensive and relatively short-living nature of genome dissection technologies (2-4 years), all technology-driven genome explorations are expected to be undertaken at the NNF Center satellite laboratory of the well-recognized Beijing Genomics Institute (BGI), Shenzhen, China.

The outcome of genome variant categorization and quality assurance will be delivered to the unit of Genetic Epidemiology.

Genetic Epidemiology

Through satellites and strategic alliances to be negotiated with a number of collaborating epidemiological groups and clinical centers in Denmark and China genomic DNA and a series of key metabolic phenotypes will be available.

Large prospective cohorts with 10 years follow-up of the general adult Danish population (about 62,000 middle-aged people) with online vital statistics (development of type 2 diabetes and progression in BMI and associated vascular morbidities and premature mortality) and in subgroups with detailed quantitative metabolic phenotype information are being prepared for studies of gene variant relationships with quantitative measures of glucose tolerance, insulin secretion, insulin sensitivity, serum lipids and body composition and amount of body fat.

Similarly, a population-based prospective cohort of 46,000 middle-aged Han Chinese has been prepared for the collaborative studies in the present NNF Center. All Chinese individuals have been examined at baseline in the same way as the Danish cohorts. The same quantitative metabolic traits have therefore been measured.

In prospective cohorts of about 6,000 middle-aged Danes followed for 10 years, information on birth weight and length is available. This will allow for studies of the interaction of fetal programming and genome variation on metabolic phenotype presentations.
Studies of the impact of the interaction of genome variation and adult health behavior (diet, exercise, and smoking) are undertaken in a cohort of 56,000 middle-aged Danes with 10 years of follow-up.

For case-control studies 5,000 type 2 diabetic cases, 5,000 obese cases and 8,000 age- and gender-matched non-diabetic control subjects will immediately be available. The number

of cases will be rapidly expanded through the intended collaboration with the nation-wide Danish Diabetes Study (DD2) of newly diagnosed type 2 diabetic patients. Replication of significant findings in Danish case-control studies are undertaken in statistically powered Nordic study samples (primarily from University of Lund).

In studies of carriers and non-carriers of disease-associated gene variants alone or in various combinations, the acute physiological responses to standardized loads of specified nutrition, exercise and drugs/drug candidates will be characterized. Variants conferring biological relevant alterations in physiological and/or pharmacological responses are further evaluated in mechanistic studies by the other partners of the NNF Center with the purpose of final validation of novel targets for drug/and or lifestyle interventions.

The large-scale gene variant mapping will be undertaken both at the NNF Center and BGI, dependent on the nature of the variant.

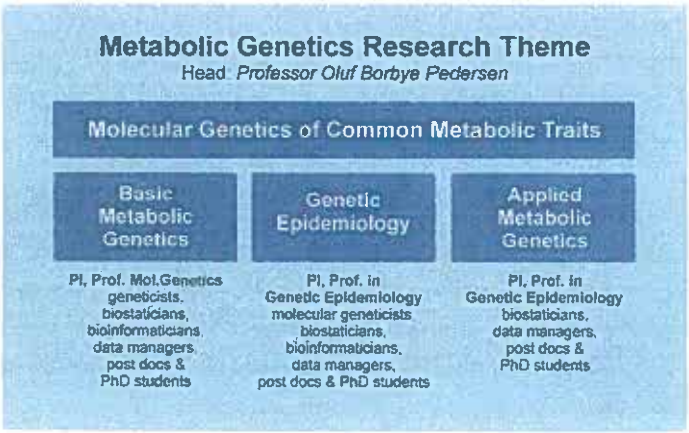
Development and validation of novel nonlinear computational statistics for analyses of the genome data sets are undertaken in the satellite at Department of Integrative Biology and Statistics at Berkeley University, CA, US.

Applied Metabolic Genetics

The development of algorithms for type 2 diabetes and obesity subset diagnosis, treatment and prevention is an ultimate goal for the "Metabolic Genetics" research theme. To accomplish this, several national and international research groups with advanced statistical knowledge and experience within the themes of system biology and individualized treatment and prevention will need to be involved. The NNF Center unit of Applied Metabolic Genetics will take the initiative and lead for these concerted activities integrating numerous signatures of prospective genetics, proteomics, metabolomics and anthropometrical phenotyping in the large Danish cohorts.

Research activities related to whole body physiology, including glucose and lipid homeostasis in genetically modified animal models, and cellular studies to validate novel targets arising from the genetic studies will be performed with the groups of Professor Juleen R. Zierath and the Integrative Physiology theme as well as the groups of Professors Jens J. Holst and Thue W. Schwartz.

Organization of the Metabolic Genetics Research Theme



Collaborations with Local Core Facilities

- Core laboratory for gene variant mapping
- Human test centre
- Data management group and data work stations
- The National Biobank at "Statens Serum Institut" (recent NNF initiative) with bioanalytical crew.

Satellite Project Laboratories

- For technical platforms needed for fundamental genome dissection: Beijing Genomics Institute (BGI), Shenzhen, China
- For mathematical modeling and statistical developments: Department of Integrative Biology and Statistics, Berkeley University, CA, USA
- For epidemiological developments: A) Research Center for Prevention and Health, Glostrup University Hospital and B) Institute of Preventive Medicine, Copenhagen University Hospital, Copenhagen.

Alliances

For Epidemiological Genetics:

- Research Center for Prevention and Health, Glostrup University Hospital (Inter99, Health 06, and MONICA 10. These cohorts equal a total of about 15,000 Danes with extensive phenotypic characterizations and follow-up examinations)
- Institute of Preventive Medicine, Copenhagen University Hospital, Copenhagen (The ORG and ADIGEN cohorts, a total of 1,400 individuals with long-term follow-up and including about 700 juvenile-onset obese individuals and the DNBC cohort (Danish National Birth Cohort) which is a nationwide study, where 100,419 pregnancies in 92,274 women were enrolled in 1996-2002. A 7-year follow-up is ongoing)
- China-Japan Friendship Hospital, Beijing. A prospective cohort of 46,000 Han Chinese with extensive metabolic phenotypes and ongoing 5 years follow-up
- Institute of General Medicine, University of Aarhus (Addition cohort with about 8,000 middle-aged individuals most of whom at time of recruitment suffer from the metabolic syndrome)
- A study sample of about 3,000 type 2 diabetes patients at Steno Diabetes Center, Gentofte
- Biobank of Vejle Hospital (2,000 patients with type 2 diabetes and 2,000 normoglycemic control subjects)
- The Danish Center for Strategic Research in type 2 diabetes (The DD2 Study). Head: Professor Henning Beck-Nielsen. The Center will on a nationwide basis recruit 10,000 newly diagnosed cases of type 2 diabetes during 2010-2013
- Nordic Biobank for Studies of Genomics of type 2 diabetes and Associated Quantitative Prediabetic Traits involving Sweden (Professor Leif Groop), Norway (Professor Pål Njølstad), Iceland (Professor Kari Stefansson) and Finland (Professor Markku Laakso) includes about 25,000 type 2 diabetic cases and a similar number of healthy controls
- `Ulsam Cohort` encompassing detailed euglycemic hyperinsulinemic and insulin secretion studies of 1,500 middle-aged men from Uppsala with long-term follow-up and vital statistics recordings (PI's are Professor Christian Berne and Professor Björn Zethelius)
- First large-scale whole genome sequencing consortium focused on type 2 diabetes initiated by Professor Mark Mc'Carthy, UK, Dr. David Altshuler, Broad Institute, Boston, Professor Francis Collins, NIH, USA, Professor Philippe Froguel, France and Professor Leif Groop, Sweden).

For Physiological and Pharmacological Genomics:

- Steno Diabetes Center with expertise in in vivo insulin action in liver, muscle and fat tissues and hormonal secretion (PI: Professor Allan Vaag)
- Endocrine Unit, Hvidovre Hospital with expertise in hormonal secretion (PI: Professor Sten Madsbad)
- Institute of Human Nutrition, LIFE with expertise in direct and indirect thermogenesis (PI: Professor Arne Astrup).

For Bioinformatics:

- NNF Center for Protein Research, the Faculty of Health Sciences, University of Copenhagen.

Integrative Physiology Research Theme with a Focus on Type 2 Diabetes and Obesity

Scientific Director, Professor Juleen R. Zierath

Rationale

The research in this theme is focused on delineating novel pathways and regulators of glucose and energy homeostasis to resolve the complex metabolic phenotypes that drive the development of insulin resistance and increased adipose mass in type 2 diabetes and obesity. Research efforts directed towards identifying the cause of type 2 diabetes have transcended into the post-genomic era. We have vast information about the human genome and candidate proteins that influence insulin action and adipogenesis, but a functional understanding of these proteins in the context of human physiology is warranted. Functional genomics in genetically modified rodent models and well-characterized clinical cohorts have uncovered the importance of gene/environment interactions. Recent technological advances in genetics, epigenetics, genomics and proteomics, present an important opportunity to fully characterize the relationship between disease pathways, genes, and gene variants with environmental factors including the fetal environment, diet, and exercise on the pathogenesis of type 2 diabetes. Thus, a major emphasis will be placed on elucidating the gene/environmental factors that contribute to the development of insulin resistance and expanded adipose mass in type 2 diabetes and obesity. We will also explore inter- and intra-cellular communication in diabetes and obesity since alterations in cellular and organ-to-organ signaling may contribute to disturbances in glucose and energy homeostasis in type 2 diabetes and obesity. Finally, we will focus on the identification and validation of factors that control energy intake and expenditure by placing a special emphasis on the role of diet and physical activity in the regulation of insulin sensitivity and fat mass.

Goals

Current therapeutic agents to treat type 2 diabetes are insufficient, and newer approaches are desperately needed. This research proposal is focused on the identification and biological validation of metabolic pathways and key regulatory genes that cause insulin resistance in type 2 diabetes. Special emphasis will be placed on understanding the mechanism by which lifestyle factors including nutrition and physical exercise influence whole body insulin sensitivity and energy homeostasis in type 2 diabetes and obesity.
Specific research areas include the following:

- Gene/environmental factors in type 2 diabetes pathogenesis
- Inter- and intra-cellular communication in diabetes and obesity
- Energy intake and expenditure.

Research Areas and Questions

Metabolic Receptology and Enteroendocrinology Research Theme

Scientific Director, Professor Thue W. Schwartz

Rationale

Gastric bypass operation surprisingly cures type 2 diabetes in few days, before any weight loss occurs. Moreover, gastric bypass surgery mediates long lasting, substantial weight reduction that approaches a near normal body weight, independent of malabsorption. The mechanism behind these highly beneficial effects of gastric bypass surgery is unclear, but may be related to an altered neuro-hormonal signaling from the GI-tract to the central nervous system (CNS) and to peripheral target organs. The key regulatory proteins of neuro-hormonal signaling are the G-protein coupled or 7 transmembrane (TM) membrane receptors, which also constitute the largest family of proteins in the human genome. They function as receptors for hormones, neurotransmitters and paracrine mediators, as well as sensors of nutrients and metabolites and thereby regulate the function of the hormone producing cells and the metabolic end-organs. Although a multitude of novel receptors are expressed and regulated in endocrine, neuronal and metabolic tissues, the function of the majority of these receptors is unclear. Likewise, in a given cell, studies of the molecular and cell physiological interplay of the many receptors in regulating its function are only in their infancy. Importantly, 7TM receptors are highly "drugable" proteins constituting the majority of current drug targets. Nevertheless, only a very small fraction of the ~400 different types of 7TM receptors are currently exploited as drug targets. Thus, there is a great potential for developing new receptor-based drugs against diabetes and obesity, as exemplified by the unexplored components of the gut-brain axis, as illustrated by gastric bypass surgery.

Major Goals

- *To fully map and characterize the entire elusive enteroendocrine system* in respect to cell - biology, peptide hormone usage, as well as genetic and especially receptological control as the basis for the development of a non-surgical therapeutic strategy that can mimic the curative effects of bariatric surgery on type 2 diabetes and obesity.

- *To identify and functionally characterize in vitro and in vivo novel metabolic receptor targets* in central (CNS) and peripheral sites, based on the exhaustive mapping of genetic variants associated with obesity and type 2 diabetes as performed in the Metabolic Genetics research theme.

- *To validate metabolic target molecules through generation of pharmacological tool compounds* using chemical biology and computational chemistry approaches based on cutting-edge research on the relationship between the molecular structure and the cellular function of receptors and ligands, combined with physiological studies in transgenic animal models and other innovative means.

Research Areas and Questions

Translational Metabolic Physiology

Scientific Director, Professor Jens J. Holst

This is not a separate "Research Theme" as such but, more importantly, an overarching or intersecting research function, which covers and joins the three main research themes of the Center (Figure 2). This takes advantage of the unique, broad expertise of Professor Jens J. Holst – the most productive and cited physiologist in Europe – who personally embraces basically all of the research areas at the Center. Although all the Scientific Directors have brilliant track records in exploiting the translational aspects of metabolic research, the Translational Metabolic Physiology research function and Professor Jens J. Holst will be particularly important in harvesting the synergies which will be created across the Center, and he and his research group will be central in connecting the basic metabolic research performed at the Center with metabolic, endocrinological clinics both nationally and internationally.

International Scientific Director

Gerald I. Shulman, M.D., PhD., F.A.C.P.

George R. Cowgill Professor of Physiological Chemistry, Professor of Internal Medicine and Cellular & Molecular Physiology, Investigator, Howard Hughes Medical Institute, Yale University School of Medicine.

Synergy Between the Strategic Research Themes

The NNF Center for Basic Metabolic Research will serve as a research platform for local, regional, national and international research in basic metabolic research.

In Copenhagen the NNF Center will harbor three leading research themes and five Scientific Directors that will work in a concerted manner to de-fragment infrastructure and research approaches to solve the complex genetic, environmental, and molecular problems associated with common metabolic diseases. Thus, one obvious place for collaboration will be at the interface between the genetic, physiology and molecular mechanisms behind common metabolic diseases.

An exhaustive characterization of all the variants in the humane genome responsible for the strong hereditability of type 2 diabetes, obesity and the associated vascular morbidities is currently underway and new candidates have been identified. Thus, the "Metabolic Genetics" theme at the Center will be at the forefront of this venture and will provide the other research themes "Integrative Physiology" and "Metabolic Receptology" with key information about biological target molecules involved in the pathogenesis of metabolic disease for in-depth physiological and molecular characterization. This work will feed back into the research efforts in the "Metabolic Genetics" research theme and will provide important physiological and molecular validation of new targets in the area of "Applied Metabolic Genetics" in relation to individualized treatment and prevention of metabolic disease.

The principle investigators in the "Integrative Physiology" research theme have utilized functional genomics in experimental studies, and well-characterized patients in clinical studies, to uncover novel pathways and regulators of whole body and tissue-specific glucose and energy homeostasis to resolve the complex metabolic phenotype in type 2 diabetes. Through collaborative efforts with the themes for "Metabolic Genetics" and "Metabolic Receptology", complex phenotypes can be better resolved to consider genetic and molecular mechanism in the context of whole body physiology. This will be particularly important when considering the gene/environmental interactions on whole body physiology. The "Integrative Physiology" research theme will provide tools and resources to the NNF Center in the way of whole body studies of glucose and energy homeostasis in genetically modified animal models of metabolic disease. The generation of new models can be based on the genetic and molecular discoveries within the NNF Center.

Another example of synergies between the different themes of the Center is the generation of pharmacological tool compounds in the "Metabolic Receptology" theme for both *in vitro* and *in vivo* use in target characterization and validation also in the "Integrative Physiology" theme. It should also be noted that within each of the three themes, a number of novel groups are brought together and key competences are recruited who will benefit highly from the close cross-disciplinary activities of the NNF Center.

Infrastructures as Strategic Research Resources

Building of Infrastructure and Method Platforms at the Faculty
The Faculty has established and support state-of-the-art technical platforms and core facilities that are crucial for the proposed project. These include an AALLAC accredited animal facilities (~60,000 mice) and an imaging- and microscopy core facility. In addition, the Faculty is currently establishing a 400 m^2 Core Facility for Integrated Microscopy.

Several biobanks/databases have been established in the Copenhagen area, including some with large collections of patient samples, which are available for the proposed basic and translational programs. The most recent biobank that has been established is the The National Biobank at "Statens Serum Institut" (recent NNF initiative) with a bioanalytical team of researchers (see appendix 2).

The Center will develop, refine and expand on the Rodent Metabolic Phenotyping Center for genetically modified animal models of metabolic disease and the Human Test Center /Lab at the Faculty.

The Rodent Metabolic Phenotyping Center is established in the Animal Facility at the Faculty of Health Sciences at Panum (please refer to the Copenhagen University home page at http://www.ivs.life.ku.dk/English/Sections/Biomedicine/Laboratory_Animal_Facility/Core%20facilities.aspx for additional information). This facility has state-of-the-art specialized cage systems for housing animals and monitoring on-line food intake (Embrose systems), energy expenditure and locomotor activity (TSE calometry cages), as well as behavior/cognition (IntelliCages) and body composition (Echo MRI, four-in-one scanner). A large number of standardized procedures have been established for physiological assays to measure glucose tolerance, insulin sensitivity, and gastric emptying on rodents. Procedures for the in vivo analysis of glucose homeostasis (euglycemic-hyperinsulinemic clamp techniques in conscious mice) are currently being established. In connection with the establishment of the NNF Center for Basic Metabolic Research, the capacity and capabilities of the Rodent Metabolic Phenotyping Center will be expanded through the establishment of a "rodent clinical biochemistry unit" where comprehensive clinical biochemical profiles can be generated for transgenic animal models using, for example the Luminex system. Moreover, the number of specialized metabolic test systems will be expanded, especially systems with specialized exercise systems (treadmill and voluntary wheel-running).

The Human Test Center/lab: The new NNF Center will support the further establishment and running costs of two complementary facilities for testing healthy people and patients with metabolic disorders. One facility is already located at the Rigshospitalet and it focuses on translational research moving from humans to molecule (Professor Bente Klarlund Pedersen). The other facility is located at Panum and also focuses on translational research moving from molecule to humans (Professor Flemming Dela) (See Budget p 43-44).

International Top Researchers as Scientific Directors (Brief CVs)

Gerald I. Shulman

Gerald I. Shulman, M.D., PhD, F.A.C.P. is the George R. Cowgill Professor of Physiological Chemistry at Yale University where he is also Professor of Internal Medicine and Cellular & Molecular Physiology and an Investigator of the Howard Hughes Medical Institute. Dr. Shulman's pioneering use of NMR spectroscopy has made it possible to directly examine intracellular metabolism in liver and muscle of humans for the first time. This approach has afforded a dynamic view of intracellular glucose and lipid metabolism not before possible in humans. Using NMR spectroscopy his group found that decreased insulin-stimulated muscle glycogen synthesis, due to defects in insulin stimulated glucose transport, is the major factor responsible for peripheral insulin resistance and that increased hepatic gluconeogenesis is responsible for fasting hyperglycemia in T2D. His group then went on to demonstrate that these defects could be attributed to increased intracellular lipid accumulation. His group went on to explore the mechanism by which fatty acids cause insulin resistance and in a seminal series of studies they found that fatty acids induced insulin resistance through a reduction in insulin stimulated muscle glycogen synthesis, which could be attributed to reduced glucose transport activity due a block in insulin signaling. These results led him to propose a unifying hypothesis for insulin resistance, which postulates that an increase in intracellular diacylglycerol, due to an imbalance between fatty acid delivery versus fatty acid oxidation/storage, causes insulin resistance by activation of a serine kinase cascade involving nPKCs leading to inhibition of insulin signaling at the level of IRS-1 tyrosine phosphorylation. His group has gone on to validate this hypothesis in studies performed in transgenic and knockout mice. His group has also found that a similar mechanism causes hepatic insulin resistance associated with non alcoholic fatty liver disease (NAFLD) and that NAFLD and hepatic insulin resistance can be reversed with modest weight reduction in T2D or with leptin replacement in lipodystrophy. Most recently his group has identified a common polymorphism in apolipoprotein C3, which predisposes individuals to NAFLD and insulin resistance. Dr. Shulman has been elected to the American Society for Clinical Investigation, the Association of American Physicians, the Institute of Medicine and the National Academy of Sciences.

Key Recent Discoveries

- Demonstrated a primary role for skeletal muscle insulin resistance in the pathogenesis of atherogenic dyslipidemia and NAFLD associated with the metabolic syndrome

  Petersen, KF, Dufour, S, Savage, D, Bilz, S, Solomon, G., Yonemitsu, S, Cline, G, Befroy, D, Zemany, L, Kahn, B, Papademetris, X, Rothman, D, Shulman, GI. The Role of Skeletal Muscle Insulin Resistance in the Pathogenesis of the Metabolic Syndrome. Proc Natl Acad Sci USA 2007:104;12587-12594.

- Identification of a novel gut-derived phospholipid that regulates food intake

  Gillum, M, Zhang, D, Zhang, X-M, Erion, D, Jamison, R, Choi, C, Dong, J, Shanabrough, M, Duenas, H, Frederick, D, Hsiao, J, Horvath, T, Lo, C, Tso, P, Cline, G, Shulman, GI. N-acylphosphatidylethanolamine, a Gut-Derived Circulating Factor Induced by Fat Ingestion, Inhibits Food Intake. Cell 2008:135;813-824.

- Identified common gene variants in Apo C3, which predispose individuals to NAFLD and hepatic insulin resistance and delineated the mechanism by which they do so

  Petersen, KF, Dufour, S, Hariri, A, Nelson-Williams, C, Foo, J, Zhang, XM, Dziura, J, Lifton, R, and Shulman, GI. Apolipoprotein C3 Gene Variants Promote Non-Alcoholic Fatty Liver Disease and Insulin Resistance. N Engl J Med (in press 2010).

Jens J. Holst

Jens J. Holst is MD and Dr Med Sci and is presently Professor of Medical Physiology at the Department of Biomedical Sciences at the Faculty of Health Sciences, University of Copenhagen, where he is vicechairman. Since 2006 he has also been Director of the Research Cluster for Diabetes and Obesity at the Faculty. He is a member of the Royal Society of Science and Letters, and has received a number of awards including the NovoNordisk Award, the Paul Langerhans Award of the German Diabetes Society, the Knud Lundbæk Award, the KFJ-award of the Faculty of Health Sciences, University of Copenhagen, the Bagger-Sørensen Award and the prestigious Claude Bernard Award of the European Association of the Study of Diabetes. His research group is partner of the DANORC Centre for obesity research and the UNIK-consortium "Food, Fitness & Pharma". Professor Holst is currently member of the editorial boards of Regulatory peptides, Endocrinology, Journal of Clinical Endocrinology and Metabolism, the American Journal of Physiology, and Diabetes. Key discoveries was the isolation and characterization of GLP-1, discovery of the metabolic actions of GLP-1; identification of the underlying endocrine disturbances of incretin function in diabetes and obesity; discovery of the potential of GLP-1 for treatment of diabetes and obesity; characterization of the metabolism of GLP-1 and of the particular importance of the dipeptidyl peptidase-4; demonstration of the efficacy of DPP-4 stabilized analogues of GLP-1; and demonstration of the potential of DPP-4 inhibitors for diabetes therapy. Jens J. Holst has authored ~ 1000 scientific papers (currently about 800 listed in PubMed) which have received > 30.000 citations and he has an h-index of 85 (Web-of Science).

Key Recent Discoveries

- Identification of the detailed mode of action of incretin hormones through a paracrine mechanism identified through the use of the isolated perfused porcine pancreas model

  de Heer J, Rasmussen C, Coy DH, Holst JJ. Glucagon-like peptide-1, but not glucose-dependent insulinotropic peptide, inhibits glucagon secretion via somatostatin (receptor subtype 2) in the perfused rat pancreas. Diabetologia 51: 2263-2270, 2008.

- Most compelling evidence that gut peptides play an essential role in the acute anti-diabetic effect of bariatric surgery

  Dirksen C, Hansen DL, Madsbad S, Hvolris LE, Naver L, Holst JJ, Worm D. Postprandial diabetic glucose tolerance is normalized by gastric bypass feeding as opposed to gastric feeding and is associated with exaggerated GLP-1 secretion: a case report. Diabetes Care 33: 375-7, 2010.

- Example of the execution of a highly complex clinical protocol which demonstrates the great importance of the glucagonostatic effect of GLP-1

  Hare KJ, Vilsbøll T, Asmar M, Deacon CF, Knop FJ, Holst JJ. The glucagonostatic and

insulinotropic effects of glucagon-like peptide-1 contribute equally to its glucose-lowering action. Diabetes (in press).

Oluf Borbye Pedersen

Oluf Borbye Pedersen is presently Chief Physician and Director of Research at Hagedorn Research Institute in Copenhagen (www.hagedorn.dk). Since 2007 he is also Director of The Lundbeck Foundation Center of Applied Medical Genomics in Personalized Disease Prediction, Prevention and Care (www.LuCAMP.org). He is Professor of Molecular Metabolism at the University of Copenhagen and adjunct professor of Molecular Diabetology at Aarhus University and Peking Union Medical College University. Currently, his research group is a partner in four EU-funded research consortia including EXGENESIS (www.dundee.ac.uk/lifesciences/exgenesis), HEPADIP (www.hepadip.org), INTERACT (www.inter-act.eu), and METAHIT (www.metahit.eu). Per 2009 the research group of Oluf Pedersen is also partner in four Danish research consortia: DANORC (www.danorc.dk), "Global fetal and maternal care in prevention of adult non-communicable disease", "Food, obesity and overt cardiovascular disease – the FOOD study group" and the UNIK-consortium entitled "Food, Fitness & Pharma, an interdisciplinary research program for lifestyle diseases". Oluf Pedersen has authored 490 scientific papers including 402 peer-reviewed original papers – with reports in high impact journals like New England Journal of Medicine, Nature, Nature Genetics, Lancet, Proceedings of National Academy of Science and Journal of Clinical Investigation. In addition, 90+ review papers, editorials and textbooks chapters. Web of Science Bibliometry: citations 13,663; h-index 58. For his contributions Oluf Pedersen has received recognition including the Knud Lundbaek Prize, the August Krogh Honour, the Codan Award, Kroc Awards and from European Association for the Study of Diabetes (EASD) the prestigious Claude Bernard Award.

Key Recent Discoveries

- The demonstration that a majority of novel type 2 diabetes gene variants associate with impaired glucose-stimulated insulin release

  Grarup N, Andersen G, Krarup NT, Albrechtsen A, Schmitz O, Jørgensen T, Borch-Johnsen K, Hansen T, Pedersen O: Association testing of novel type 2 diabetes risk-alleles in the JAZF1, CDC123/CAMK1D, TSPAN8, THADA, ADAMTS9, and NOTCH2 loci with insulin release, insulin sensitivity and obesity in a population-based sample of 4,516 glucose-tolerant middle-aged Danes. Diabetes 57: 2534-2540, 2008.

- The identification applying the genome-wide association study approach of a novel type 2 diabetes-gene variant that is linked to insulin resistance

  Rung J, Cauchi S, Albrechtsen A, Shen L, Rocheleau G, Cavalcanti-Proença C, Bacot F, Balkau B, Belisle A, Borch-Johnsen K, Charpentier G, Dina C, Durand E, Elliott P, Hadjadj S, Järvelin MR, Laitinen J, Lauritzen T, Marre M, Mazur A, Meyre D, Montpetit A, Pisinger C, Posner B, Poulsen P, Pouta A, Prentki M, Ribel-Madsen R, Ruokonen A, Sandbaek A, Serre D, Tichet J, Vaxillaire M, Wojtaszewski JF, Vaag A, Hansen T, Polychronakos C, Pedersen O, Froguel P, Sladek R. Nat Genet.;41:1110-5, 2009. (OP is Co-PI and corresponding author).

- The identification applying the genome-wide association study approach of a novel type 2 diabetes- gene variant that is linked to impaired insulin secretion

Bouatia-Naji N, Bonnefond A, Cavalcanti-Proenca C, Sparsø T, Holmkvist J, Marchand M, Delplanque J, Lobbens S, Rocheleau G, Durand E, De Graeve F, Chevre JC, Borch-Johnsen K, Hertikainen AL, Ruokonen A, Tichet J, Marre M, Weill J, Heude B, Tauber M, Lemaire K, Schuit F, Elliott P, Jørgensen T, Charpentier G, Hadjadj S, Cauchi S, Vaxillaire M, Saldek R, Visvikis-Siest S, Balkau B, Levy-Machal C, Pattou F, Meyre D, Blakemore AI, Jarvelin MR, Walley AJ, Hansen T, Dina C, Pedersen O, Froguel P: A variant near MTNR1B is associated with increased fasting plasma glucose levels and type 2 diabetes risk. Nat Genet 41: 89-94, 2009. (OP is Co-PI).

Juleen R. Zierath

Juleen R. Zierath is presently Professor of Integrative Physiology, Karolinska Institute. Her research focuses on cellular mechanisms underlying the development of insulin resistance in type 2 diabetes. She has published over 140 research papers and 50 review articles, with key discoveries published in Science, Cell, Nature Genetics, and Cell Metabolism and an h-index of 47. She was awarded the Fernström Prize (1999) and the Hagberg Prize (2001) from Karolinska Institute, the Minkowski Prize from the European Association for the Study of Diabetes (2001), a Strategic Research Grant from the Foundation for Strategic Research in Sweden (2005) and a European Research Council Advanced Grant Award in 2008 (78 grants in Life Sciences were awarded in 2008). She is the recipients of several diabetes-focused European Union grants in the 6th and 7th framework programs, including EUGENE2, EUGENEHEART, and EXGENESIS. She was appointed to the Nobel Assembly in 2006 and an Adjunct Member of the Nobel Committee since 2008 at Karolinska Institute. She is a member of the Swedish Research Council Board for Medicine, a member of the scientific advisory and executive board for Keystone Symposia, and a member of the Nordic Research Committee for Novo Nordisk. Professor Zierath holds editorial positions with several leading scientific journals in the area of endocrinology and metabolism and will serve as Editor-in-Chief of the EASD journal Diabetologia (2010-2016).

Key Recent Discoveries

- The identification of specificity in insulin signaling cascades

  Bouzakri KA, Zachrisson L, Al-Khalili BB, Zhang HA, Koistinen, Krook A, and Zierath JR. siRNA Based gene silencing reveals specialized roles of IRS-1/Akt2 and IRS-2/Akt1 in glucose and lipid metabolism in human skeletal muscle. Cell Metabolism 4:89-96, 2006.

- The identification of a novel pathway regulating glucose and energy homeostasis

  Chibalin AV, Leng Y, Vieira E, Krook A, Bjornholm M, Long YC, Kotova O, Zhong Z, Sakane F, Steiler T, Nylen C, Wang J, Laakso M, Topham MK, Gilbert M, Wallberg-Henriksson H, Zierath JR. Downregulation of diacylglycerol kinase delta contributes to hyperglycemia-induced insulin resistance. Cell 132:375-386, 2008.

- The identification that non-CpG methylation contributes to insulin resistance in diabetes

  Barrès R, Osler ME, Yan J, Rune A, Fritz T, Caidahl K, Krook A, and J.R. Zierath. Non-CpG methylation of the PGC-1_ promoter through DNMT3B controls mitochondrial density. Cell Metabolism 10:189-198, 2009.

Thue W. Schwartz

Thue W. Schwartz is presently Professor of Molecular Pharmacology at the University of Copenhagen and was in the early 90's VP of research in corporate research at Novo Nordisk. In 2000 TWS was the founder and chief scientific officer of the biotech company 7TM Pharma A/S devoted to discoveries of pharmaceuticals against metabolic diseases based on his insight into the molecular mechanisms of action of 7TM receptors and TWS was, for example the sole inventor of two drug candidates based on enteroendocrine hormones which have both been taken into clinical phase-II studies. TWS has been the recipient of European Union grants in the 6th and 7th framework programs devoted to for example 7TM receptor structure and function (GPCR) and to obesity (GIPIO – gastrointestinal peptides in the treatment of obesity) and is the head of the cross disciplinary "Food Fitness & Pharma" UNIK grant (~20 M EUR, 2009-13) directed against life style diseases from the Danish Ministry of Science and Innovation. TWS has authored approx. 250 scientific publications of which 9 are published Nature or Science (6 of which as first and/or corresponding author) and he has an h-index of 59 and an average number of citations per publication of 45 (ISI). TWS has received a number of prizes and honors including the Anders Jahre Prize, the Novo Nordisk Foundation Prize and the Lundbeck Foundation Price and was in 1994 elected as member of the Royal Danish Academy of Science and Letters.

Key Recent Discoveries

- Identification of the ghrelin receptor and its constitutive activity as being involved in regulation of food intake, for example

  B.Holst, N.Holliday, A.Bach, C.E.Elling, H.Cox & T.W.Schwartz: Common structural basis for constitutive activity in the ghrelin receptor family. J. Biol. Chem. (2004) 279:53806-53817. (cited more than 80 times).

- Identification of the molecular activation mechanism for 7TM receptors, the larges family of proteins in the human genome, reviewed in

  T.W.Schwartz, T.M.Frimurer, B.Holst, M.M.Rosenkilde & C.E.Elling: Molecular Mechanism of 7TM Receptor Activation – a Global Toggle Switch Model. Annu. Rev. Pharmacol. Toxicol. (2006) 46: 481-519 (cited more 80 times).

- Identification of the GPR39 receptor as an important regulator of pancreatic islet function, for example

  B.Holst, K.L.Egerod, C.Jin, P.S.Petersen, M.V.Østergaard, J.Hald, J.Størling, T.Mandrup-Poulsen, J.J.Holst, P.Thams, C.Ørskov. N.Wierup, F.Sundler, O.D.Madsen & T.W.Schwartz: GPR39 deficiency is associated with pancreatic islet cell dysfunction. Endocrinology (2009) 150: 2577-85.

International Satellite Project Laboratories and Collaborations

The development of excellent research is critically dependent upon tight international collaborations. As a novel instrument to optimize knowledge interactions and synergy on an international scale, a number of "satellite projects" will be performed in key Scandinavian and International laboratories in close collaboration with laboratories at the NNF Center. Research activities of the satellite projects,which are performed abroad will be funded through the Center. Exchange students and postdoctoral fellows will be important parts of the satellite projects, which also will be supported through extensive, frequent use of state-of-the-art IT communication systems to ensure tight exchange of information, ideas etc. In addition to common research programs, these collaborations also include joint PhD programs, common workshops, and guest professorships. Through these funded satellite projects a number of internationally leading laboratories with complementary skills corresponding to each of the focus areas will become integrated and committed research partners of the Center.

The Satellite Project Laboratories include key laboratories at:

- Beijing Genomics Institute (BGI), Shenzhen, China
- Department of Biostatistics and Bioinformatics, Berkeley University, CA, USA
- University of Massachusetts Medical School, Worcester, MA, USA
- Albert Einstein College of Medicine, Bronx, NY, USA
- Yale Medical School, New Haven CT, USA
- Joslin Diabetes Center, Harvard Medical School, Boston, USA
- Cambridge University, UK
- South Western Medical School, Dallas, USA
- Stanford University, CA, USA
- Marburg University, Germany
- Karolinska Institutet, Stockholm, Sweden
- Lund University, Sweden
- Göteborg University, Sweden
- Ruhr University at Bochum, Germany
- Diabeteszentrum, Bad Lauterberg, Germany
- Catholic University, Rome, Italy

We will also build strong collaborations and network activities with other laboratories in Sweden and Denmark.

Educational Activities in the Center

It is a mission for any University to teach and educate because education is an important investment in the future.

We are proud that at the Faculty of Health Sciences we feature 10 different educations including medicine, dental medicine, public health and human biology. Besides we share an education in molecular medicine with Faculty of Science and one in medico-engineering with The Danish Technical University. At the present we have approximately 4,500 undergraduate students and an annual undergraduate intake of 800 undergraduate students.

The Faculty of Health Sciences is also proud that we have developed Denmark's largest PhD school with 900 PhD students enrolled. In 2009 ~250 new PhD students have started and about 200 finished with their diploma.

The Educational Director

The new Center will contribute to the overall teaching and education portfolio of the Faculty and we see the Center as a very strong value for the Faculty. In particular the Center will develop PhD courses and supervise Master projects. To maintain focus, facilitate and coordinate these activities we will appoint an Educational Director. This person will get an increment in salary; "funktionstillæg" paid by the Center.

We suggest the Following Terms for the Researchers:

Full professors, associate and assistant professors that are currently employed at the Faculty will stay employed and paid by the Faculty and continue with their teaching obligations with reference to their Departmental Chair. We will accept up to 30% "frikøb" i.e. the Center can "buy" up to 1/3 of the person by paying 1/3 of the full salary to the relevant Department. This will reduce the teaching load by 1/3. Negotiations about teaching will generally take place between the researcher(s) in question, the Director of Education and the Scientific Director/ Director (Chief Center and Science Officer) of the Center.

New Researchers appointed at Center will also participate in the teaching activities at the Faculty for example by supervising bachelor/candidate projects and dissertations. They will also be part of the ongoing PhD education and provide 1-2 PhD courses. Besides undergraduate teaching is very much welcomed. In the new research building we will establish an "elite" laboratory that can be used for advanced experimental teaching activities.

Exchange and guest researcher programmes between the Center and the satellites will be arranged for undergraduate students and PhD students as well as for the senior researchers.

Science communication/ Public engagement with science

The NNF Center will develop a robust research-based communication platform to 1) create a strong collaborative culture within the Center, 2) strengthen its identity as a global focal point for metabolic science and related biotech and pharmaceutical industries, and 3) promote a broad public engagement with metabolic science.

Collaborative research communication culture
The NNF Center will develop a strong collaborative culture within the Center and with the Satellites. In addition to established means of communication, such as informal meeting events, seminars and teleconferences, the Center will implement best practices for using new online tools and social web media to facilitate critical discussions, knowledge exchange and sharing of data and methods throughout the Center and its Satellites. This will be consistent with the NNF Center motto "It is all about people".

Communication with the scientific community at large
Publication of scientific results in journals of the highest quality is of critical importance. As a matter of course, the NNF Center will publish its scientific results in top-ranked international journals. Major findings with translational implications will be communicated to a wider audience of health professionals, targeted stakeholders, including public health policy makers, and the citizenry. To strengthen open access, researchers will be encouraged to deposit their results in the PubMed Central digital archive of biomedical journal literature.

Communication with society at large and the general public (scientific citizenship)
The focus on metabolic life-style diseases and individualized medicine with the long-term goal to further individual and collective competences to prevent life-style diseases requires a sustained effort to promote scientific citizenship, including a deep public engagement with metabolic science. The NNF Center will therefore initiate a program in science communication studies with the aim of developing new research-based methods for encouraging communication between metabolic scientists and members of the public.

The program is based on the assumptions that science is an integrated part of our culture and common history, that public engagement with science is best promoted by dialogue and open access to the creative process ('science in the making'), and that the aesthetics of science is an important feature of science communication. To that end a number of experimental communication activities will be set up, including:

- establishing a public science-art-culture venue as a hot spot for metabolic science and its implications for health
- creating mobile exhibitions to a broad public audience, including schools and science centers
- creating temporary exhibitions about the cultural and historical significance of metabolic science in connection with scientific congresses
- inviting visiting artists to create metabolic sciart and wetart installations

- establishing a material and visual object acquisition venue focused on metabolic science
- holding an international conference on communicating metabolic science to the scientific community and general public
- organizing open seminars and other events that link metabolic science with art, culture and public participation
- developing social web media platforms for 1) the dissemination of news from the Center to the general public, 2) for promoting public engagement with metabolic science, and 3) for facilitating critical discussions, knowledge exchange and sharing of data and methods throughout the Center and its Satellites.

Special emphasis will be put on 1) methods for making sense of the material manifestations and the invisible features of laboratory and clinical practice in physical and online exhibitions, 2) the integration between physical exhibitions and the web ('museum 2.0'), and 3) the interaction between intrascientific communication and public engagement with science through social web media ('science communicaton 2.0').

The experimental communication activites will be supported by a number of research projects focusing on the material, visual and digital culture of metabolic science from a historical, biographical, aesthetic and philosophical point of view. Senior researchers, postdocs and PhD students in the programme will share their time between experimental communication activities and individual research projects that sustain these activities.

The Director of Medical Museion, Professor Thomas Söderqvist, will be principal investigator of the program in science communication studies. Thomas Söderqvist in an internationally recognized historian of 20th century life sciences (history of ecology, history of immunology) and a leading specialist in methods for writing the history of contemporary science and scientific biography. During the last ten years he has developed the medical history museum at the University of Copenhagen into an internationally acknowledged research museum for the study of the contemporary biomedical sciences in a cultural, historical and philosophical perspective and for the public communication of biomedicine through exhibitions and social web media.

Medical Museion

Within few years, Medical Museion has emerged as an internationally acknowledged research museum for the study of contemporary medicine in a cultural, historical and philosophical perspective, and for the public communication of medical science through exhibitions and on the web. This position is based on an unparalleled combination of world-class collections of historical medical science artefacts, a strong international research profile, and an innovative science communication practice, all brought together in a unique 18th century medical building.

- In 2008 and 2009, the International Advisory Board of Medical Museion has evaluated the academic and museological level as "impressive", and has especially "praised and expressed their respect for MM's internationally oriented research focus".

- Medical Museion has close cooperation with a number of leading European science, technology and medical museums; e.g., in 2010, Medical Museion is a partner in five applications to the EC 7FP together with institutions like Science Gallery (Dublin), Le Laboratoire (Paris, Harvard), Swiss National Museum (Zurich), Science Museum (London), etc.

- In 2010, Medical Museion organises the 15th Congress of the European Association for Museums of the History of Medical Sciences on the theme 'Contemporary medical science and technology as a challenge for museums'.

- In 2008, Medical Museion was awarded the annual prize of Medicoindustrien (the Danish medical device industry association) "as a recognition of the effort to collect, preserve and display the medical industrial heritage".

www.mhm.ku.dk

Innovation and Entrepreneurships

Denmark has a long history of both *state-of-the-art* academic research and pharmaceutical industry. In contrast, the Danish biotechnology sector was established just a decade ago and has only recently been acknowledged as an important sector for the translation of basic science into applied research. To bridge the early basic research results to applied science it is important to build and nurture an entrepreneurial culture for commercialization of research findings.

Research findings at the NNF Center of Basic Metabolic Research have the potential to shed light on a large number of new biological targets that will enable development by the pharmaceutical and biotech industries of novel and individualized treatments for obesity and type 2 diabetes. Moreover, results generated by the Center are expected to form the basis for developing new diagnostic tools. It is the Center's strategy that these discoveries be translated into a clinical benefit for patient in the most efficient way.

The intention is that an innovation scout will proactively search for and identify research results that can be exploited for commercialization. The innovation scout and the Tech-Transfer Unit at the University of Copenhagen will then manage the commercialization process (filing for patents; facilitating contact to consultants, venture capitalists, or established pharma/biotech; expectation management; etc.) with the least possible draw on scientist resources.

To secure optimal competences, the innovation scout must have a solid scientific background and a significant network (i.e. at least at a post doc level within the metabolic research field) preferably combined with entrepreneurial/biotech experience and knowledge of the venture capital area.

Other innovation and entrepreneurship initiatives might include (possibly in collaboration with other NNF Centers):

- Entrepreneurial courses offered to researchers at the NNF Center with topics including (but not limited to) "entrepreneurship", "strategies for building biotech", "raising capital", "finance", and "building network". The course form will be lecturing and real case studies from the biotech environment. Teachers must have the relevant operational experience (hands-on) and will be identified both locally and globally.
- Entrepreneurial grants will be available for researchers who wish to test the commercial potential of an idea/hypothesis. Applications for grants will be evaluated at the same level as pre-seed projects and by people with knowledge of commercialization, biotechnology and entrepreneurship. The entrepreneurial grant will enable the researchers to mature their discovery to either a pre-seed or seed investment stage.
- Building multi-branched networks. 1) Mini network meetings with specific themes will be held at the Centers. 2) The innovation scout will invite keynote speakers from the global biotech arena on a regular basis to give researchers the opportunity of interacting with biotech experts and exchange views/ideas. 3) The Center will host an annual large network meeting where the biotech community is invited. Selected researchers (i.e. researchers who have received an entrepreneurial grant) will present their work and international invited guest speakers will present their view and experience on entrepreneurship. 4) Researchers at the Center will be encouraged to participate in local networks such as BiotechBuilders and Dansk Biotek.

The innovation scout will work part-time as a consultant or alternatively be appointed full time and shared among the NNF Centers at the Faculty of Health Sciences. A dialogue will be initiated with Novo Seeds about advantages and drawbacks with the different models, as they have extensive experience and strong competences in this field. The scout will refer to the Managing Director.

Budget

Total budget for 10 years:

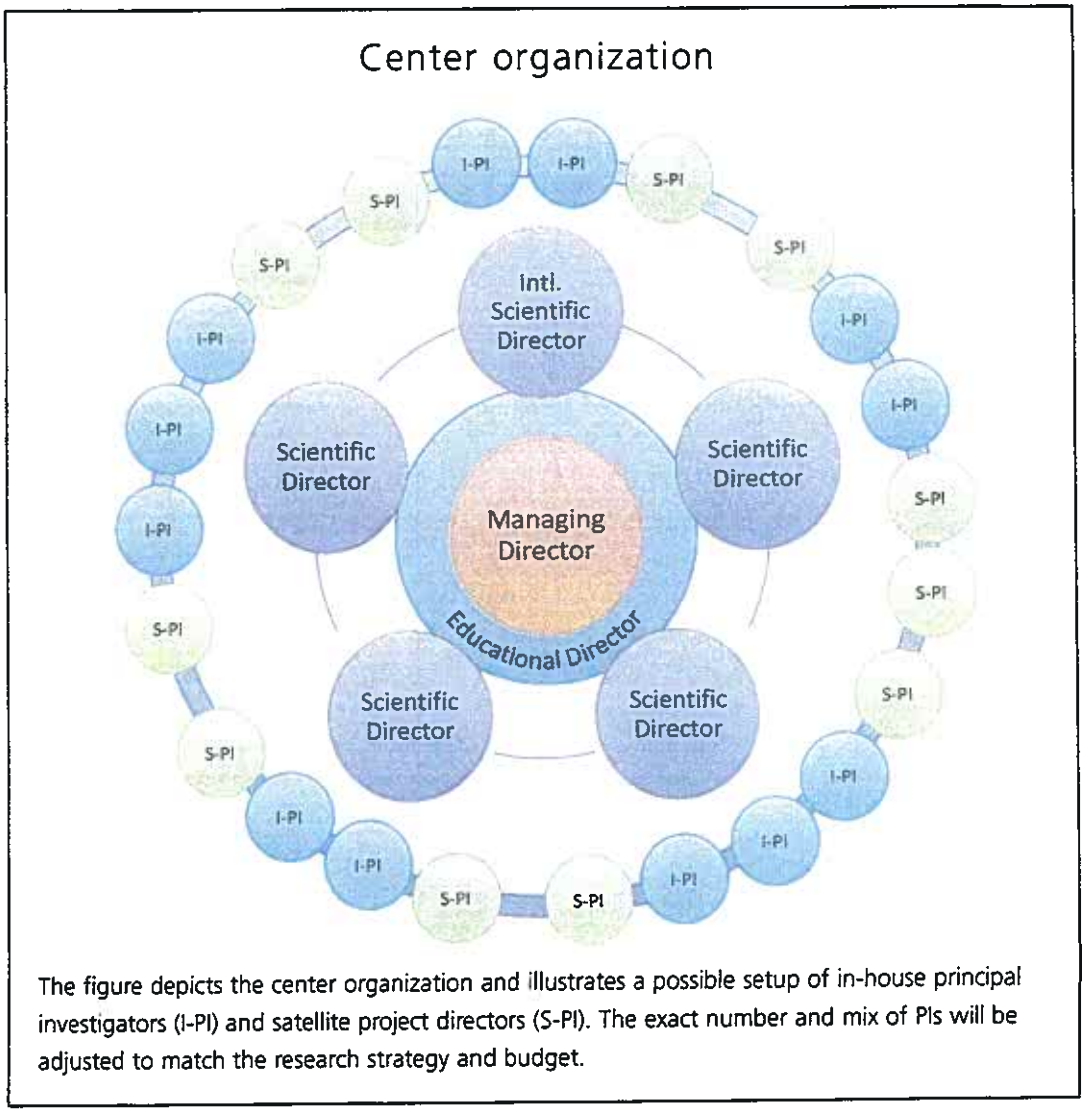
Research and Administration, 5 sections and satellites	840 mio DKK
Start-up, equipment[1]	45 mio DKK
Total	885 mio DKK

Organization and Governance

Summary
This governance model is designed to support the successful implementation of the NNF Center's vision and overall research strategy. The structures, processes, and fora are in place to ensure a strong governance to drive top-class research with optimal collaboration and synergy. Close collaboration will exist between the individual projects and satellites within a section, but also among projects across sections in the Center.

The Center has a Managing Director, who reports to the Dean of the Faculty of Health Sciences, and the Center is governed by a leadership team consisting of the Dean (chairman of the leadership team), the Managing Director, and five Scientific Directors, three of whom head a research theme each, and two who have a cross-sectional function to facilitate synergy. Furthermore, an Educational Director is responsible for exchange and education within the Center including its satellite projects. The leadership team has the overall scientific responsibility for the Center.

The Dean is responsible to the Director of the Novo Nordisk Foundation and these two form the executive committee of the Center. A scientific advisory board advises the executive committee and the leadership team on an annual basis.



The figure depicts the center organization and illustrates a possible setup of in-house principal investigators (I-PI) and satellite project directors (S-PI). The exact number and mix of PIs will be adjusted to match the research strategy and budget.

Introduction

The NNF Center for Basic Metabolic Research has ambitious goals for its impact on the research society and society as a whole. To increase and accelerate its impact, several initiatives will be implemented focused on optimizing knowledge interactions and synergy within the Center through education and exchange of ideas (satellites and education), on optimizing commercialization opportunities (innovation scouting), and on disseminating research findings to the general public (science communication).

The Center's core is formed by three research themes made up of a number of in-house research groups. As a novel instrument to optimize knowledge interactions on an international scale, a number of "satellite projects" will be carried out in key Scandinavian and international laboratories in close collaboration with laboratories at the NNF Center. The satellite project research activities will be funded through the Center. In this way, a number of internationally leading laboratories with complementary skills corresponding to each of the focus areas will become integrated and committed research partners of the NNF Center. The integration will be supported by extensive use of state-of-the-art communication technology, by the center language being English, and by encouraging the exchange of students, postdoctoral fellows, and senior scientists (on sabbatical leave). Research is unrestricted within the agreed projects for the Center.

The vision of the NNF Center is to become a global focal point in basic metabolic research and serve as a scientific magnet to attract top grade international students, postdoctoral fellows, and principal investigators, who should constitute a major proportion of the staff at the Center. To brand the NNF Center, all scientific communication from the Center, including scientific publications, will acknowledge affiliation with the NNF Center for Basic Metabolic Research, University of Copenhagen. In addition, the PhD-stipends and postdoctoral fellowships will be entitled "Marie Krogh stipends" or "Marie Krogh Fellows". The educational aspect is important to the success of the Center and therefore all participating researchers will engage in teaching activities. In addition, the Center will offer seminars, workshops, and supervision of master's degree projects.

The aim of this document is to present a governance model for the Center that takes into account these initiatives, and to describe the proposed processes and structures, roles and responsibilities, as well as governance fora of the Center in detail.

Vision and purpose of the governance model

The NNF Center governance model is designed to ensure effective governance and leadership of the Center and its international satellite network. It aims at achieving:

- Efficient processes for projects, progress reporting, and finance
- Accountability between sections and their satellites
- Dynamic ability to adjust research strategy with re-allocation of resources
- Ability to attract leading scientists and talents in the field.

In addition to governing the Center, the model may have other attractive consequences:

- Enable accelerated knowledge sharing and synergies
  - provide channels for rapid communication exchange between hotspots
  - give access to and exchange of new methods and technologies within the network
  - enable new collaborations within and outside the Center
  - facilitate visits, exchange, sharing of knowledge and data, collaboration and networking for both the growth layer (master's degree students, PhD students, post doctoral fellows) and senior scientists.
- Share tasks across the Center
  - promote the use of the best in-house/satellite core facilities when this is more efficient than outsourcing
  - enable the establishment of world-class core facilities

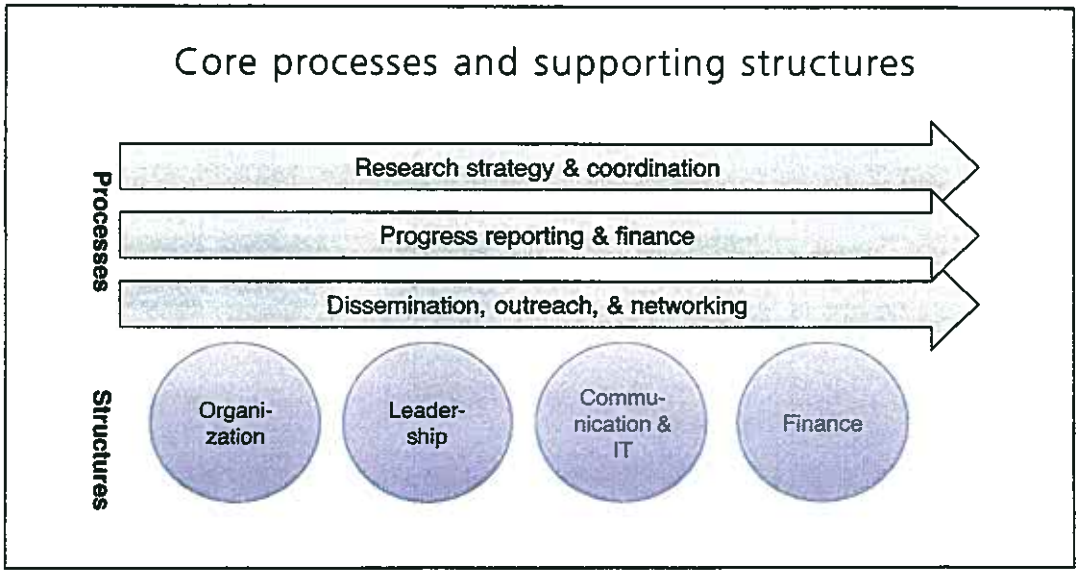
- Support branding of the national metabolic research strength by demonstrating leadership in this field
- Inspire others (academia, other NNF Centers, and university networks) with this pioneering Center governance model.

Processes and structures

The governance model is based on three core processes:

- Research strategy & coordination
- Progress reporting & finance
- Dissemination, outreach & networking

The administrative functions will be designed to support these processes.



Research strategy & coordination

This process gives direction to all research activities in the Center and forms the foundation for the progress reporting & finance process as well as the dissemination, outreach & networking process. The research strategy & coordination process encompasses:

- Developing the annual research plan according to the agreed strategy, as well as aligning across all three research themes and the five sections including satellites
- Coordinating efforts within a section and its satellites on a monthly basis
- Ensuring collaboration and synergy across the Center
- Evaluating and re-focusing the research strategy based on new knowledge becoming available, progress, or lack of progress. The leadership team has the obligation to terminate fruitless projects and re-allocate resources between sections, as needed, in order to achieve the best possible research progress for the Center as a whole
- Eliciting Center continuation at the 5-year and 9-year milestones based on a formal external evaluation (including site visit) of the Center's function, structure, and scientific output.

Progress reporting & finance

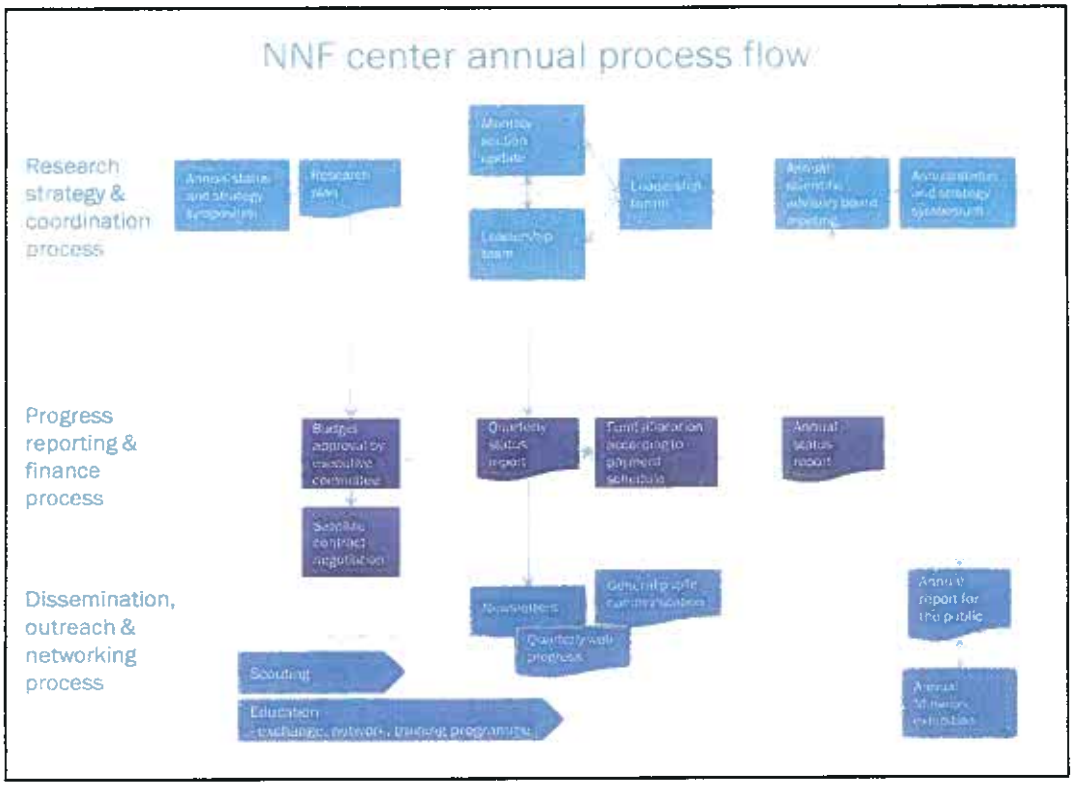
This process is built on contract management and encompasses:

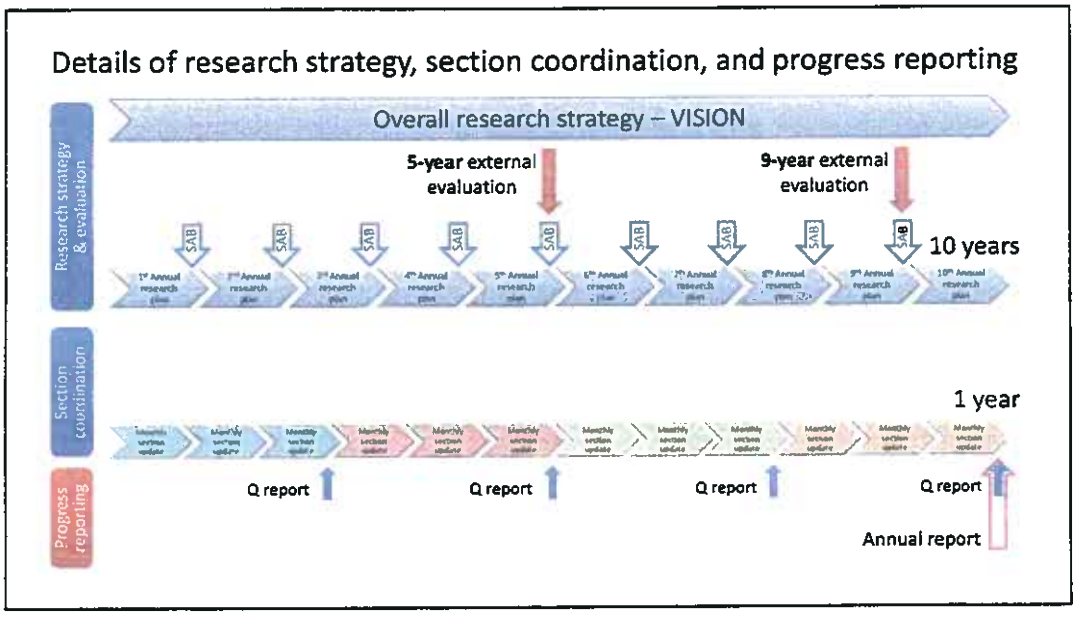
- Drawing up annual budgets by the leadership team based on the annual research plan (includes negotiation of contracts with the satellite project directors)
- Following up on research efforts by quarterly and annual progress reporting
- Allocating funds by the NNF on a quarterly basis based on a forecasted payment schedule.

Dissemination, outreach & networking

Dissemination of the Center's findings will take place in a structured fashion within the Center itself and to the outside world through, for example, annual exhibitions, the Center's website, magazines, etc. Dissemination activities will be targeted at both scientists and the general public. As part of the outreach process, additional activities will be innovation scouting and educational efforts, such as cultural and scientific exchange as well as formalized training in the form of undergraduate, postgraduate, and postdoctoral courses.

The annual process flow





Roles and responsibilities

Roles in the governance structure:

NNF	University of Copenhagen	Leadership forum (NNF Center faculty)	Center administration
• Director of NNF • NNF liaison • NNF finance manager	• Dean	• Scientific directors • Educational director • In-house research leaders • Satellite project directors	• Managing director • Innovation scout • Science communication expert • Fundraiser • Medical writer • Supporting roles such as: HR, IT, accounting

Managing Director

The Managing Director (Anne Stæhr Johansen) is in charge of the NNF Center and reports to the Dean of the Faculty of Health Sciences, who is responsible to the Novo Nordisk Foundation. The Managing Director is responsible for the overall operation and management of the Center, including management of the budget and preparation of the required reports to be submitted to the executive committee. She will also be responsible for creating a strong collaborative culture within the Center. All contracts related to the Center, including contracting for, and monitoring of, satellite projects and staff will be managed by the Managing Director. The Center's administrative staff, e.g. those responsible for budgeting, accounting, procurement, IT, HR, integrative activities, education, commercialization, and science communication, report to the Managing Director. The Managing Director will also be responsible for recruiting any additional staff needed in the Center administration, including, but not limited to, a full-time fundraiser with international experience and a part-time medical writer.

NNF liaison

A day-to-day contact person in the NNF whose role is to assist the Managing Director in sorting out urgent operational matters delegated from the executive committee.

Scientific Directors

The five Scientific Directors (Gerald Shulman, Jens J. Holst, Thue W. Schwartz, Oluf Borbye Pedersen, and Juleen R. Zierath) report to the Managing Director and head the Center's research sections. Each section will consist of up to three in-house research groups and a number of satellite project groups. The major roles of the Scientific Directors are:

- To ensure that the Center develops into an internationally outstanding and renowned research and education Center
- To be an advocate for the Center and "brand" it to the scientific community and society as a whole
- To be the driving force in promoting collaboration between Center participants and projects
- To facilitate synergy between the sections and their satellites
- To attract and orchestrate national and international grants to the Center
- To conduct high impact research.

The Scientific Directors are also responsible for recruiting researchers in consultation with the leadership team, including identification of satellites according to need and research strategy. Within each section, the Scientific Director is responsible for monthly section updates and quarterly progress reporting. Three of the Scientific Directors head the research themes of the Center (TWS, JZ, OBP), while two serve as cross-sectional bridge-builders (GS, JJH).

The Scientific Directors are professors at the Faculty of Health Sciences and may choose to dedicate themselves to the leadership role or may choose a dual role as PI for one of the section's research groups in addition to being its Scientific Director.

International Scientific Director

The International Scientific Director (GS) has a special mission to serve as a bridge-builder to pertinent international scientific collaborators and funding agencies, and to advise the Dean of the Faculty of Health Sciences. The International Scientific Director should be a respected scientist with the following qualifications/experience:

- Has a track record of high level research
- Has a record of successful leadership in an academic environment
- Has experience with evaluation of international top class research
- Has experience with facilitation of research collaboration and creating synergy across projects as well as scientific disciplines.

In-house research leaders and satellite project directors (principal investigators, PIs)

The group leaders (in-house research leaders and satellite project directors) are independent PIs, but coordinate with the Scientific Director of the section. Each PI is responsible for research progress according to plans and funding. This includes giving input to the quarterly progress reporting and budget status. Furthermore, the PI is responsible for providing monthly updates on their research to other section projects and the Scientific Director.

Educational Director

One of the Center professors will have the responsibility of Educational Director in addition to carrying out his/her own research. This job entails ensuring and facilitating network and exchange among all researchers in the Center. It is the educational director's responsibility to maintain focus, facilitate, and coordinate all educational activities associated with the Center. These include the development of PhD courses, seminars and workshops, supervision of master's degree projects, coordination of undergraduate teaching, establishment of a Metabolic Research Student Network, and supporting exchange of PhD students, postdoctoral fellows and senior scientists. The Educational Director should also offer career mentoring to junior scientists.

A dedicated Educational Director is an integral part of the leadership team and will receive an increment in salary ("funktionstillæg") funded by the Center.

Fundraiser

The support provided by the Novo Nordisk Foundation is to be considered "seed money". It will be necessary to attract additional major grants from international and national public as well as private grant bodies for the Center to be internationally competitive. A full-time fundraiser (at the post doc level and with international experience) is responsible for writing grant applications and facilitating lobbying for funding from both private and public sources.

Medical writer

The NNF Center will appoint a part-time medical writer to facilitate a high level of publication success in high impact journals. The medical writer should have experience at a high international level with writing and editing scientific papers as well as experience with publication strategies.

Innovation scout

The NNF Center will appoint a part-time external person as an "innovation scout" who will proactively search for and identify research results that can be exploited for commercialization. We expect the Center research to shed light on a large number of new biological targets that will enable the development of novel and individualized treatments for obesity and type 2 diabetes by the pharmaceutical and biotech industries. Moreover, results generated by the

Center are expected to form the basis for the generation of novel diagnostic tools. In collaboration with the Tech-Transfer Unit at the University of Copenhagen, it is the responsibility of the innovation scout to manage the process leading to a patent, etc., to minimize the burden imposed by this process on scientist resources. On behalf of the leadership team, the innovation scout plays a leading role in executing the strategy of letting individual patients benefit from the knowledge generated in the Center. The innovation scout will report to the managing director and coordinate with the leadership team.

Science communication expert

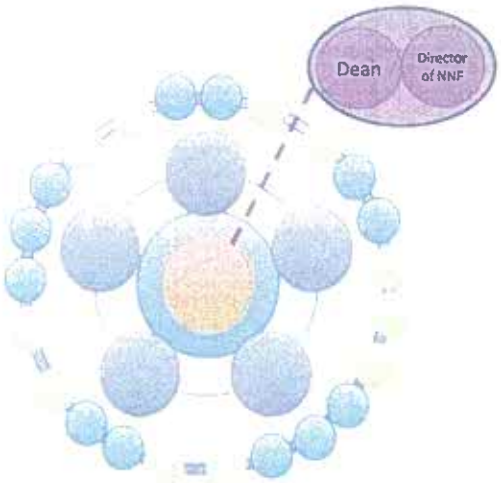
The NNF Center will appoint a "science communication expert" to head the research-based science communication program, which is designed to strengthen the Center's culture and identity as a global focal point for metabolic science and related biotech and pharmaceutical industries, and to promote a broad public engagement with metabolic science.

Governance fora

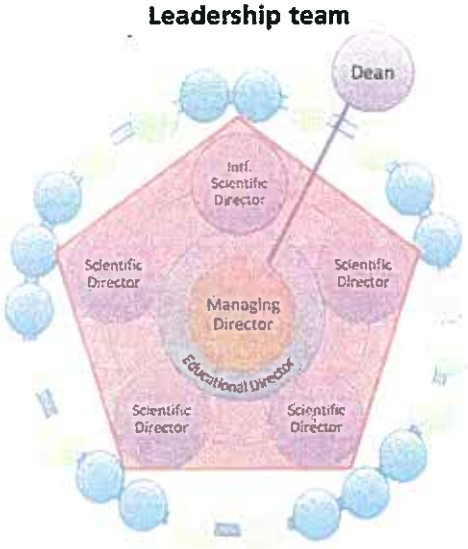
The governance processes are linked by a series of meetings, which may be physical or virtual depending on their nature and the participants involved. Participation in these meetings will be mandatory and considered an integralpart of the contractual commitment to the governance model.

Participants of each forum are indicated by the colored shade. The Scientific Advisory Board advises the executive committee and the leadership team, of which the dean is a member.

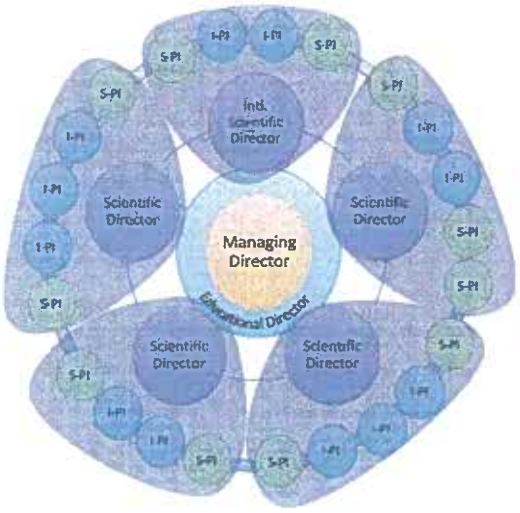
Executive committee



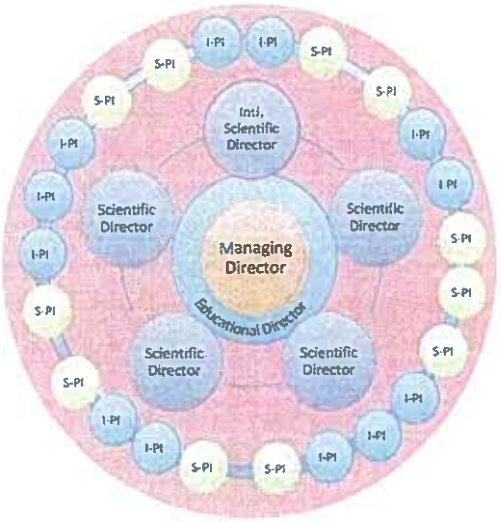
Leadership team



Monthly section update



Leadership forum & annual status and strategy sympsium



Research strategy and coordination fora

Annual status & strategy symposium (3S):

Purpose

a. To agree on the annual research plan and align the whole Center with the research strategy for the coming year
b. To provide a platform for networking and knowledge sharing across all parties in the Center
c. To collect knowledge from the sections and their satellites for dissemination to the general public.

Participants

All in-house research leaders and satellite project directors, the scientific directors, the managing director, and the science communication expert.

Executive committee:

Purpose

a. To approve the overall strategy, direction and progress of the Center
b. To approve budgets and proactive re-allocation of funds.

Participants

The dean and the director of NNF. The managing director participates as an observer. The scientific directors and the educational director may participate ad hoc.

Frequency

Quarterly, or more frequently, if required.

Dean meeting:

Purpose

a. To generate ideas, visions, and solutions to ensure the future execution of the Center strategy
b. To honor the dean's responsibility to the Novo Nordisk Foundation as the Center's institutional host.

Participants

The dean, the managing director, and other NNF Center directors as needed.

Frequency

Every two weeks.

Leadership Team (LT):

Purpose

a. To align research in the 5 sections
b. To update and re-focus the research strategy according to new knowledge and developments, and to propose a re-allocation of funds and resources to the executive committee
c. To create synergy within the Center and facilitate collaboration between sections.

The leadership team has the overall scientific responsibility for the NNF Center.

Participants

The dean (chairman), the managing director, and the five scientific directors. The educational director, the fundraiser, the innovation scout, and the science communication expert participate on an ad hoc basis.

Frequency & format
Every month, except in July. The LT meetings follow an agenda, and meeting minutes will be prepared for the dean. A Center progress report is prepared every quarter for the executive committee (see quarterly and annual progress reporting under "Progress reporting and finance fora").

Monthly section update:
Purpose
a. To share knowledge of developments and progress across groups and satellites
b. To provide the managing director with a forum to discuss financial issues.

Participants
The scientific director, the satellite project directors, the in-house research leaders, and the managing director (ad hoc). Participants might be divided into groups/meetings according to research interaction.

Frequency & format
These meetings may be held as webinars on a monthly basis, or more frequently, if needed. The meeting agenda must very specifically cover results, progress, resource sharing, and ways to help and accelerate research progress. These meetings constitute the monthly updates and form the basis for the quarterly progress reporting (see quarterly and annual progress reporting under "Progress reporting and finance fora").

Leadership forum:
Purpose
To facilitate network, knowledge sharing, sharing of resources, etc., to optimize progress.

Participants
All in-house leaders (the managing director, the scientific directors, the in-house research leaders, and the educational director). The satellite project directors, innovation scout, and science communication expert may participate ad hoc.

Frequency
Quarterly.

Scientific advisory board (SAB):
Purpose
To offer advice on the scientific developments and directions of the NNF Center.

Participants
SAB members, the director of NNF and NNF liaison, the dean, the managing director, the scientific directors, and some of the professors.

Frequency & format
This group will meet once a year for a 1-day meeting before the annual status and strategy symposium. SAB members will be a number of top researchers nominated by the scientific directors and appointed by the executive committee. They will mirror the scientific profile of the Center. If the scientific profile changes over the years, SAB members may be substituted to match it. The SAB will have a chair appointed by the executive committee. The chair will compile the advice from the SAB in a report to be submitted to the executive committee and the leadership team.

Progress reporting & finance fora

Annual budget:
Purpose
To link in-house research groups and satellite projects to the Center through annual budgets, including contracts with satellite projects and a quarterly funding scheme.

Participants
The managing director and the scientific directors.

Frequency
Annually.

Quarterly budget status:
Purpose
To ensure that the budget status is approved on a quarterly basis.

Participants
The managing director and the scientific directors.

Frequency
Quarterly.

Quarterly and annual progress reporting:
Purpose
To report on the Center's research progress to the executive committee.

Participants
Based on the monthly section updates, the scientific directors report on the progress of their section to the managing director, who is responsible for compiling the quarterly and annual reports.

Frequency
Quarterly.

Examples of fora in the dissemination, outreach & networking process

- Annual exhibition
  An outreach activity from the Center to outside researchers and the general public in an innovative format.
  The exhibition will be offered to display in participating universities.
- PR strategy
  To ensure broad public acceptance of the Center.
- Innovation scouting
- Metabolic Research Student Network
- Newsletters
- Annual conference in collaboration with NNF
- Open house event for other NNF Center researchers.

Prerequisites for success of the governance model

The following points are critical to ensure the efficient management of the Center. Hence it is important that these factors are negotiated and signed off by the involved parties (leaders, satellites, the University of Copenhagen) before entering the Center and drawing on resources.

- Commitment to the governance model.
  - Scientist commitment to the governance model, including progress reporting and mandatory knowledge sharing and meeting participation.
  - All leaders in the Center (including satellite project directors) must sign-off on the governance model to ensure commitment to the common processes in the Center, e.g. mandatory participation in knowledge sharing and progress reporting. This will be a precondition for funding.
- Close co-operation between the Novo Nordisk Foundation and the Faculty of Health Sciences through a contact person approved by NNF – at present the Dean, Ulla Wewer. If Ulla Wewer changes position NNF must approve her successor as contact person.
- Strong leadership across the Center's diverse research groups and satellites, especially of high profile scientists employed by other institutions and only working part time in this NNF Center.
- Acceptance of the Center language being English.
- This governance model must be able to comply with the University of Copenhagen governance as well as with the satellites' local institutional governance models.
- An IPR policy must be agreed with the University of Copenhagen and satellite project institutions.

Appendix 1

The New Research Building – the Panum Tower

A new Center of Basic Metabolic Research at the Faculty of Health Sciences will enjoy the best setting possible in the forthcoming new research building at Panum, the Panum Tower.

The Panum Tower will be a modern 17 floor building 90 m high and of 30.000 m^2 that costs approximately one billion Danish kroner. The Panum Tower will contain research laboratories built and appointed on new principles ensuring that they can be used for years to come. The tower will be attached to the "Old Panum", establishing a coherent platform with core facilities and other infrastructure where everything is close to hand and allowing for dynamic development.

The timetable for building the Panum Tower: A program for the design competition is being drawn up and will be issued in April 2010. Construction should be completed by 2014. A steering is responsible for the overall management of the construction program; there is close, formal cooperation with the Municipality of Copenhagen (on the planning process etc). Although planning and construction will be carried out with great logistical precision of course it will be some years until the Tower is ready for us to move in. The best solution is to start the new Center in the "Old Panum" as this will allow recruitment of key researchers as soon as possible, enabling them to make an active contribution as the new building is set up. For the interim period the new center can be located in newly renovated laboratories in the "Old Panum".

Over the next year and even more so when the Tower is complete, the unified Panum will offer Center researchers a wide range of attractive services and collaborations, including:

- Modern, flexible new research laboratories ready to "plug and play", including GMO I, II and III labs, isotope labs, and other specialist laboratories
- The NNF Center for Protein Research with its 4000 m^2 of renovated laboratories conducting frontline research into proteins and disease mechanisms
- The largest animal stabling in Scandinavia, newly-refurbished and containing a newly-established core facility for in vivo research into metabolism and diabesity (the Rodent Metabolic Test Center)
- A new core facility for integrated microscopy, covering almost 400 square meters and containing state-of-the-art apparatus and preparation rooms (currently under construction)
- Modern imaging facilities (PET-CT, with a 9.4 Tesla and MEG for in vivo animal research planned)
- A Faculty Club and Gym located in two glass domes on the roof of the Old Panum (funding of DKK 20 million has been granted and planning is underway)
- Proximity to the other faculties at the Universities of Copenhagen and Lund, Rigshospitalet, and important partners at pharmaceutical companies in Eastern Denmark and the Øresund Region.

Enclosed please find press release from The Ministry of Science, Technology and Innovation (in Danish) concerning funding of the Panum Tower.

01.02.2010

Sander underskriver milliardaftale med universiteterne

Videnskabsminister Helge Sander har underskrevet aftaler om fordelingen af 6 mia. kroner med bestyrelsesformændene for Københavns Universitet, Aarhus Universitet, Syddansk Universitet, Aalborg Universitet og Roskilde Universitet. Pengene skal forbedre universiteternes laboratorier.

> – Med aftalerne på plads kan vi nu for alvor begynde arbejdet med at bringe laboratorierne på Danmarks universiteter op til international standard. Det er nødvendigt for at vi kan tiltrække og fastholde de bedste forskere i verden, siger videnskabsminister Helge Sander.

Regeringen har afsat i alt 6 mia. kroner på finansloven for 2010 til at renovere universiteternes laboratorier. Videnskabsministeriet og Københavns Universitet, Aarhus Universitet, Syddansk Universitet, Aalborg Universitet og Roskilde Universitet har nu underskrevet aftaler for, hvordan pengene skal prioriteres. Fordelingen er foretaget på baggrund af den såkaldte UNIlab-undersøgelse fra 2009 og universiteternes egne investeringsplaner.

Universitets- og Bygningsstyrelsen, der er ansvarlig for at gennemføre laboratorierenoveringerne, påbegynder nu arbejdet med at beskrive de konkrete byggeprojekter i tæt dialog med universiteterne. Moderniseringerne vil strække sig over de næste 6-7 år.

> – Investeringerne har en klar grøn profil. Laboratorielokaler er blandt de helt store energislugere, men ved at give laboratorierne et teknologisk løft, hjælper vi universiteterne med at spare på energiforbruget og på elregningen. Det giver ekstra midler, som universiteterne kan bruge på forskning og uddannelse. Laboratorieinvesteringerne er altså en gevinst – både for miljøet og for forskningen, siger Helge Sander.

Udover de underskrevne aftaler, vil der på et senere tidspunkt blive indgået aftale med Danmarks Tekniske Universitet om renoveringer for ca. 0,6 mia. kroner. Handelshøjskolen i København og IT-Universitetet rummer ikke laboratorielokaler lejet hos Videnskabsministeriet og er derfor ikke omfattet af bevillingen.

Fakta om investeringsplanerne:

› Københavns Universitet
› Aarhus Universitet
› Syddansk Universitet
› Aalborg Universitet
› Roskilde Universitet

› Fotos fra underskrivelsen af aftalerne
› UNIlabrapporten hos Universitets- og Bygningsstyrelsen

Appendix 2

Collaboration with Other NNF Initiatives

The new Center for Basic Metabolic Research will collaborate with researchers in the local community including the two novel NNF initiatives ie the NNF Center for Protein Research and the NNF National BioBank.

The Novo Nordisk Foundation Center for Protein Research at the Faculty of Health Sciences, University of Copenhagen was established in 2007 through a donation of 600 million DKK and opened in June 2009.

The Center comprises a wide range of expertise and skills within its research departments, with activities in the areas of disease systems biology, proteomics, high throughput protein production and characterization, chemical biology, disease biology, and protein therapeutics. The Center will also contribute to the progress of translational research within medicine and provide fundamental insights which can be used to promote drug discovery and development.

The Core Facility for Biotechnology and Chemical Biology is lead by Director Michael Sundstrøm, Professor Matthias Mann heads the Proteomics Research and Professor Søren Brunak the research on Disease Systems Biology. Several group leaders have been recruited, including: Jesper Olsen, Michael Lund Nielsen, Chunaram Choudhary, Lars J. Jensen, Amilkar Flores Morales, Niels Mailand and Simon Bekker Jensen, and more on their way.

Collaborations between the researchers in the new Center for Metabolic Research and the Protein Center will undoubtedly be most productive.

The Novo Nordisk Foundation National Biobank at "Statens Serum Institut" was established through an 85 million DKK donation from the Novo Nordisk Foundation, together with a 36 million DKK from the Danish Government in cooperation with hospitals, universities and other public institutions that collect or make use of biological material. The Biobank is headed by:

The initiative aims to benefit research into the causes of diseases, their prevention and treatment. The objective of the initiative is to give Danish and foreign researchers a unique overview of and access to more than 15 million biological samples in existing and future collections. Researchers will be able to link biological material from an individual with the large quantity of additional data available in the national registers, for instance within the healthcare sector.

This Biobank will no doubt be of tremendous use for the researchers in the new Center for Metabolic Research.

Appendix 3

Co-financing by the Faculty of Health Sciences

The Faculty of Health Sciences, University of Copenhagen will co-finance the Center in the following way:

General

- Rent for laboratory and office space in the New Research Building (the Tower) approx 1-1275 DDK pr netto m^2/year i.e. with a brutto-netto factor 2.51 it is 3200 DKK per brutto m^2 = total 15.4 mio DKK per year for 4800 m^2 (3 floors each 1600 m^2 brutto)
- Running cost of the building (cleaning, waste disposal, electricity, heating, etc.) approx 1000 DKK pr. brutto m^2 /year = total 4.8 mio DKK per year
- Auditing (all accounts will be performed according and as part the general rules of the University of Copenhagen).

Research Facilities

- Access to core-facilities, such as the Copenhagen Animal Research Unit and the Core Facility for Integrated Microscopy. The core facilities charge user-fees but the Faculty generally heavily subsidises these facilities
- Access to Ph.D.-scholarships provided by the Faculty
- Free access to international literature databases
- Access to it-infrastructure and it-facilities
- Access to telepresence-facilities (planned)
- Free access to meeting and conference facilities.

Staff Facilities

- Faculty canteen
- Faculty Club
- Fitness Center.

Appendix 4

Managing Director for the Center for Basic Metabolic Research – Anne Stæhr Johansen, M.Phil, MA, PhD

Summary of Dr. Anne Stæhr Johansen's qualifications

- PhD, MA in economics and 15+ years of relevant leadership experience
- Extensive experience in international settings/organizations and/or academic settings
- Documented experience with managing large budgets, programs, and leading teams of experts and support staff
- Track record of establishing successful partnerships and collaboration within and across organizations
- Exceptional ability to work collaboratively and create synergies between different members of diverse teams
- Record of research and publications
- Experience with teaching using distance learning techniques and new IT technologies
- Fluency in English
- Excellent communication skills both verbally and in writing
- Excellent organizational skills and ability to work under pressure
- Ability to work in a multi-sectoral setting
- Track record of mentoring junior staff

Biography

Dr. Johansen has a Master's degree in economics, an M.Phil in public policy, and a PhD in Health Policy Analysis.

Anne S. Johansen is currently *Senior Health Specialist* in the Health, Nutrition, and Population Department of the Africa Region in the World Bank. In her 13 years at the World Bank, she has carried out policy dialogue on health systems development and reform with top level government officials in numerous low- and middle-income countries, in many cases leading to important policy changes that have contributed to improved health system outcomes. She has also carried out and/or contributed to analytical studies that have laid the foundation for subsequent World Bank project and/or national programs, including the establishment of a national diabetes program in the West Bank and Gaza. While at the World Bank, Dr. Johansen has been responsible for the design, preparation, supervision and evaluation of Bank-financed projects in a number of countries in the Middle East and North Africa (MENA) Region, as well as the [Sub-Saharan] Africa Region. She has extensive leadership experience and has managed large budgets as well as teams of experts and support staff.

Dr. Johansen has led a number of innovative programs and initiatives aimed at building individual and institutional capacity in health systems development, working closely with faculties in university centers and mid- to high-level government officials, leading to the establishment of several centers of excellence in Middle and Eastern Europe, Thailand, and China. She is also a founding member of the MENA Health Policy Forum and has served on its Board. During her five-year tenure in the World Bank Institute, Dr. Johansen pioneered a number of distance-learning courses using the latest available IT-technology, in

addition to being responsible for more than 50 training courses and senior policy seminars on health sector reform and sustainable finance throughout the developing world.

Dr. Johansen's pre-Bank experience includes working as a public health expert in the Policy Development Office of the Public Health Directorate of the European Commission, where she was responsible for the development and adoption of a Health Monitoring Program for the European Community. Dr. Johansen also has experience in the Prime Care Office of the Danish Ministry of Health, where she was a member of the secretariat to the Life Expectancy Committee and a contributing author to Committee's report, which resulted in a number of policy and program changes that have led to a more than 2-year increase in life expectancy among Danish women during the past two decades. Dr. Johansen was also a member of the team that revised all the Danish public health programs for children and adolescents.

Prior to working for the Danish Ministry of Health, Dr. Johansen was *Assistant Professor* in the (then) Department of Maternal and Child Health of the Johns Hopkins School of Hygiene and Public Health. In that role she taught and supervised graduate students, provided technical assistance to the regional Bureaus of Maternal and Child Health, and was co-principal investigator for a federally funded Center for Child and Adolescent Health Policy. She also published a number of articles, reports, and book chapters.

Curriculum Vitae for Anne Stæhr Johansen

Personal Data

- Danish national; US permanent resident
- Birth date: May 14, 1958
- Languages: Danish (native), English (fluent), French (Excellent), and German (proficient)
- Divorced, one child (aged 28 years)

Contact Information

Address: 3900 Tunlaw Road NW Apt. 305
Washington, DC 20007
USA
Telephone: (+1 202) 415-6462
Email: ajohansen@worldbank.org

Education

- Ph.D., 1990, Public Policy Analysis, The Frederick S. Pardee RAND Graduate School, Santa Monica, CA, USA
- M.Phil, 1986, Public Policy, The Frederick S. Pardee RAND Graduate School of Policy Studies, Santa Monica, CA, USA
- M.A., 1984, Economics, University of California, Los Angeles, CA, USA
- B.A., summa cum laude, 1983, Economics, University of California, Los Angeles, CA, USA

Specializations

- Health systems development/health sector reform
- Health economics and finance
- Institutional capacity building
- Monitoring and evaluation
- Quality of Care

Work Experience

1997-Present: World Bank

3/2009 - Sr. Health Specialist; Health, Nutrition, and Population Unit; Africa Region

- World Bank focal point for Harmonization for Health in Africa (HHA), responsible for coordination and harmonization efforts with external development clients
- Focal point for the Africa Region's Human Resources for Health Program
- Responsible for the organization and delivery of a conference on "The Regional Health Workforce in Africa: Human Resources for Health Results," Addis Ababa, Ethiopia, May 10-15, 2009
- Africa Region's counterpart to the World Bank IHP+ Core Team Member
- Responsible for the preparation of project evaluation reports
- Technical assistance on results framework, strategic plans, and monitoring and evaluation
- Responsible for the delivery and organization of IHP+ and HHA-related activities, including the organization and delivery of the "Second (IHP+) Annual Interagency Country Health Systems Teams' Meeting," Bamako, Mali, June 15-16, 2009, and the HHA conference on "Health Systems for Results: Strengthening Capacity in Africa" Bamako, Mali, June 17-28, 2009.
- Responsible for institutional capacity building efforts in health in the Africa region
- Responsible for the establishment, in collaboration with HHA partners, of a Health Systems Observatory

5/2008-3/2009 Coordinator for the 2008 Human Development Forum, Office of the Vice President, Human Development Network

- Responsible for the preparation and delivery of the 2008 HD Forum (conference with 1000 participants)
- Responsible for the development of the Forum agenda
- Managed the HD Forum support team
- Supervised administrative and logistical arrangements
- Managed the Forum (US$0.5 mill) budget
- Collaborated with and provided support to the HD Learning Week team
- Analyzed evaluation results and prepared an assessment report

2002-5/2008 Sr. Health Specialist; Human Development Group, Middle East and North Africa (MENA) Region (2 years stationed in the West Bank and Gaza (WBG) Country Office, West Bank, oPt)

- Responsible for policy dialogue and project preparation, supervision, and evaluation in Egypt, Yemen, and the West Bank and Gaza
- Responsible for supervision of US$100 million health sector reform project in Tunisia (US$50 million in loan; US$50 million in local financing)
- Responsible for, or contributing to, the preparation of all types of analytical and advisory activities (health sector strategies, public expenditure reviews, country assistance strategies)
- Provided technical assistance on diabetes, quality of care, and health sector reform, and strategic planning
- Provided leadership in donor coordination and harmonization efforts
- Managed health team staff and program budgets
- Mentored junior staff
- Founding member of MENA Health Policy Forum and member of the Forum Board; responsible for the organization of the first Regional Health Policy Conference

1998-2002 Sr. Health Specialist/Health Specialist, Human Development Group, World Bank Institute

- Manager of the Flagship Program on Health Sector Reform and Sustainable Financing; managed staff and budgets (US$ 1.2 million)
- Carried out Flagship capacity building and training courses at country, regional, and global levels, including Training-of-Trainer Courses, and Senior Policy Seminars (50 between 1998-2002)
- Established and developed the capacity of faculty at Regional Flagship Partner Institutes in China, East Asia and the Pacific (EAP), and Europe and Central Asia (ECA)
- Team member of the Flagship Program on Health Sector Reform and Sustainable Financing
- Focal point for regional Flagship activities for South Asia, ECA, EAP, and China

1997-1998 HD Coordinator, World Bank Institute

- Team member of the Flagship Program on Health Sector Reform and Sustainable Financing
- Contributed to the development and delivery of the first Global Flagship Course on Health Sector Reform
- Responsible for the first regional and country-specific Flagship courses

1995-1997 European Commission:
DG V/F/1, Public Health Expert, Luxembourg

- Responsible for the development and approval of an Action Program to Establish a Health Monitoring Program for the European Community
- Responsible for the preparation of annual EC Health Status Reports
- Contributed to the design of an EC-wide health survey

1993-1995 Ministry of Health:
Head of Section, Office of Primary Care, Copenhagen, Denmark

- Responsible for the evaluation and subsequent instutionalization of an experimental program to provide (limited) coverage for psychological counseling for trauma victims under the national health insurance scheme
- Contributed to a major reform of all public health programs for children and youth
- Member of the Secretariat for the "Life Expectancy" Committee and contributing author of the Report from the Life Expectancy Committee which led to a number of policy changes that have led to significant increases in the average life expectancy of the Danish population, particularly women.
- Responsible for overseeing negotiations between the national health insurance office and the Union of Medical Doctors
- Responsible for estimating the fiscal impact of primary health care reform

1990-1993 The Johns Hopkins Bloomberg School of Public Health:
Assistant Professor, Department of Maternal and Child Health

- Taught graduate courses in program, planning, and evaluation; women, work and families;
- Was Co-Principal Investigator of the Child and Adolescent Health Policy Center
- Provided TA to the Maternal and Child Health Bureau of the Public Health Services
- Curriculum Committee member
- Advised and supervised graduate students

1990-1997 RAND Corporation:
Consultant, Department of Human Capital, Santa Monica, CA

- Carried a large child care study for the US Department of Defense that led to significant changes in the military child care system

1987-1990 RAND Corporation:
Research Associate, Department of Human Capital, Santa Monica, CA

- Carried an analysis of the US military child care system for the US Department of Defense
- Carried out statistical analysis of the influence of the child care tax credit on parents' choice of child care
- Carried out statistical analysis of the impact of preferences for particular types of child care on parents' choice of care

1984-1987 The RAND/UCLA Center for Health Policy Study, the Pardee RAND Graduate School: Pew Health Policy Fellow, Santa Monica, CA

- Carried out statistical analysis of the impact of different types of child care on pre-school children's illness

1983-1984 University of California, Los Angeles: Teaching Assistant, Department of Economics, Los Angeles, CA

Selected Honors and Awards

- Outstanding Contributor Award, presented by the Chinese Ministry of Health for contribution to the China Network for Training and Research in Health Economics and Finance (2006)
- MNSHD Spot Award (2005, 2006, 2007)
- President's Award for Excellence to the West Bank and Gaza Country Team 2004
- WBI Spot Award (2001 and 2002)
- WBI Performance Award (2000)
- Pew Memorial Health Policy Fellowship (1984-1987)
- Proctor and Gamble Undergraduate Scholarship in Economics (1982-1983)
- Departmental Scholar in Economics, University of California, Los Angeles, CA (1982-1983)
- Phi Beta Kappa, University of California, Los Angeles, CA (1983)

Selected Professional and Community Activities

- Peer Reviewer for Health Affairs, Health Policy, and the American Public Health Association
- Interim Board member, and founding member, of the MENA Health Policy Forum
- Guest lecturer at the University of Aarhus; Department of Public Health, Southern University of Denmark; Birzeit University, Ramallah, Palestine

Publications, Reports, and Book Chapters

Implementation Completion and Results Report on a Grant in the Amount of US$25.0 Million to the Republic of Niger for a Multisectoral STI/HIV/AIDS Support Project, Health Nutrition and Population Group, Africa Region, World Bank; 12/2009.

Evaluation Report on the 2008 Human Development Forum, Office of the Vice President, Human Development Network, World Bank; 4/2009.

Republic of Tunisia: Health Sector Study, Human Development Group, Middle East and North Africa Region, World Bank (co-authored); 5/2006.

West Bank and Gaza: Framework for a Medium Term Human Development Strategy, Human Development Group, Middle East and North Africa Region, World Bank (co-authored); 5/2006.

Implementation Completion Report on a Trust Fund Credit in the Amount of US$7.9 to the West Bank and Gaza for a Health Systems Development; Human Development Group, Middle East and North Africa Region, World Bank (co-authored); 10/2005.

Implementation Completion Report on a Loan in the Amount of US$50 Million to the Government of Tunisia for a Health Sector Loan, Human Development Group, Middle East and North Africa Region, World Bank (co-authored); 6/2004.

Decentralization in Denmark: Lessons for Developing Countries. Case Study Prepared for the Flagship Program on Health Sector Reform and Sustainable Finance, World Bank Institute (with Jakob Kjellberg Christensen); 11/2000.

Report from the Commission on the State of Women's Health in the European Community, European Commission, DGV/F/1, Luxembourg (co-authored); 9/1997.

The Importance of Child Care Characteristics to Choice of Care, Journal of Marriage and the Family, Vol. 58 (with A. Leibowitz & LJ Waite); 7/1996.

The Effects of Accreditation on Care in Military Child Development Centers, in S. Bredekamp and B. Willer (Eds.): NAEYC Accreditation: A Decade of Learning and the Years Ahead, NAEYC (with GL Zellman); 5/1996.

Investment or Overkill: Should Military Child Development Centers Be Accredited? Armed Forces and Society, Vol. 23 (with GL Zellman); 4/1996.

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Military Child Care: Toward an Integrative Delivery System, Armed Forces and Society, Vol. 21 (with GL Zellman); 8/1995.

Examining the Effects of Accreditation on Military Child Development Center Operations and Outcomes, MR-524-OSD, RAND, Santa Monica, CA, USA (with GL Zellman and J Van Winkle); 10/1994.

Life Time in Denmark, Report from the Life Expectancy Committee, Ministry of Health, Denmark (co-authored); 3/1994.

Analysis of the Concept of Primary Care for Children and Adolescents, The Child and Adolescent Health Policy Center, Johns Hopkins University, School of Hygiene and Public Health, Baltimore, MD, USA (co-authored); 3/1994.

Report on Documents Produced or Supported by the Division of Children with Special Health Care Needs which Address Primary Care; Johns Hopkins University, School of Hygiene and Public Health. Prepared for the Bureau of Maternal and Child Health, Public Health Service, Rockville, MD, USA (with J. Harlow); 5/1993.

Improving the Delivery of Military Child Care: An Analysis of Current Operations and New Approaches. R-4145-FMP, RAND, Santa Monica, CA, USA (with GL Zellman and L Meredith); 10/1992.

Report on the Feasibility of Using the National Health Interview Survey Child Health Supplement for Title V Reporting; Johns Hopkins University, School of Hygiene and Public Health. Prepared for the National Center for Health Statistics, Hyattsville, MD, USA (with C. Alexander and B. Guyer; 06/1992.

Child Care: Preferences, Choice, and Consequences, N-3237-RGSD, RAND, Santa Monica, CA, USA; 1/1992

Child Care and Children's Illness, American Journal of Public Health, Vol. 78. Also published as N-2865-NICHD, RAND, Santa Monica, CA (with A Leibowitz and LJ Waite); 5/1988.

Controlling the Volume of Medicare Hospital Admissions under PPS: Volume Adjusters and Preadmission Review, WD-22767-1-HCFA, RAND, Santa Monica, CA, USA (with P. Ginsburg and M. Cvitanic); 09/1985.

References upon request.

Appendix 5

Advantages of part-time employment of Scientific Director – including an assessment of the part-time employment of Matthias Mann

Professor Matthias Mann (MM) was initially employed as a consultant and is now employed as a part-time Professor and Scientific Director (20%) at the Novo Nordisk Foundation Center for Protein Research, Faculty of Health Sciences, University of Copenhagen.

His employment as a consultant before the Center was operational at Panum allowed the Center to start up at the Max Planck Institute for Biochemistry in Munich (MM's host institution in Germany) two years before the official opening in Copenhagen. Three Group Leaders, several PhD students and others were trained and were then able to 'hit the ground running' when the Center opened its doors in June 2009. MM estimates that his proteomic section of the Protein Center saved up to a full year's work in this way – a very significant lead compared to starting from scratch in Copenhagen in the middle of 2009. This would have been the alternative if a full-time director had had to relocate to the Protein Center.

In starting up the Protein Center, it was essential for state-of-the-art equipment to be purchased. Proteomics is an expensive technology and only a few places in the world have the latest cutting edge technology. As a world leading scientist in the field of proteomics, MM has special knowledge and a special relationship with the company that makes the most advanced mass spectrometers. MM's section was therefore able to obtain the very latest technology (LTQ-Orbitrap Velos) immediately the Protein Center opened. The Center also obtained a very good deal with the company, the same as that obtained by MM's group because they are involved in the actual design of the new instrument and act as the global showcase for the technology. This alone has repaid all the investment in MM's employment at the Center and illustrates the power of knowledge-sharing that MM provided when the Protein Center was set up.

Most importantly, the part-time employment of MM allowed the Protein Center to recruit absolutely top rank junior proteomics researchers and these researchers brought with them the latest technology from Munich. This path of immediate technology and science transfer between the Protein Center and the Munich group, which is the world leader, makes the Protein Center extremely competitive internationally. If someone else had been engaged, there is a considerable possibility that the Protein Center would have started out and remained at a mediocre position in proteomics despite greater costs. MM's part-time position has allowed an otherwise inaccessible competitive advantage in terms of achieving the international standing of the Protein Center.

The 'branding' due to the collaboration of MM and Professor Søren Brunak (SB) who is also employed as a part-time Professor and Research Director, has like-wise helped the Protein Center tremendously. So the role of MM and SB has been crucial and the investment in them has already repaid itself many times over.

MM as the Chair and mentor of his Section.

The idea for the proteomics department is that Group Leaders should increasingly take on international leadership roles. They are relatively young but Jesper Olsen especially already has international standing and is frequently invited to meetings. He will be able to take on a greater role in leadership over the next few years. Chunaram Choudhary provides biological insights at the highest level and is poised to become a major player in signalling proteomics. Michael Lund Nielsen will focus on technological developments and on the important goal of disseminating use of the technology in this field. Although all three are now independent Group Leaders, they benefit from mentoring and assistance from MM as a senior mentor. This is because the field of proteomics is becoming ever more competitive and many places have invested huge sums in this technology. The Protein Center, with the combination of MM and the three Group Leaders, draws on the combined resources of the Max-Planck group in Munich and the Protein Center. Together, these teams represent one of the largest and certainly the technologically leading proteomics constellation in the world.

I believe that the alternative to part-time employment would have been that MM would not have been associated with the Protein Center, for personal reasons and because the resources and long-term perspectives at the Max-Planck are unmatched. It is unlikely that one of the very top world leaders in the field would have come to Copenhagen (there are very few and they all have top positions in their respective home countries). Starting out with only junior teams would have been uncertain because the field is too mature for junior teams to break in at this point.

MM is a top international scientist and having him as Research Director part-time achieves a number of other clear, very strong advantages such as publications in the leading international journals, big external grants (including EU grants) and international branding that the Center and our University would not otherwise obtain.

Maintaining MM's involvement in the development and success of the Protein Center is of fundamental importance not only because of his own obvious star class research but also because of the synergy from the Max-Planck Institute team.

In conclusion, the current construction with MM as a part-time Research Director at the Protein Center has worked extremely well and I can only recommend this model in our globalized, highly competitive world where there is such enormous mobility for researchers.

Professor Ulla Wewer
Dean, Faculty of Health Sciences
19.02.2010

Appendix 6

KØBENHAVNS UNIVERSITET

The Novo Nordisk Foundation
Brogaardsvej 70
2820 Gentofte

17. NOVEMBER 2009

We would like to express our strongest commitment to the establishment of the Novo Nordisk Foundation Marie Krogh Center for Basic Metabolic Research at the Faculty of Health Sciences, University of Copenhagen.

Thus we state that:

The Dean of the Faculty of Health Sciences, University of Copenhagen – presently professor Ulla Wewer – is responsible to the Novo Nordisk Foundation for the project as described in the application submitted November 23 2009.

The University of Copenhagen ensures that the Center can start in Q3 of 2010 at the Faculty of Health Sciences. The first 4 years, the Center will be located in the Panum Building in close proximity to the NNF Center for Protein Research. We are currently renovating laboratory space to accommodate existing and new research groups the best possible way. For example, we are in the midst of renovating laboratory space in Panum (18.6) for professor Thue Schwartz's research activities, and we plan to renovate laboratory space in Panum (6.6) for Juleen R. Zierath's Section. We propose that professor Oluf Borbye Pedersen's Section resides at the University and at Hagedorn Research Institute. As soon as the Panum Tower (end of 2014) is completed, the Center will be assembled in a 3 floor coherent area (approx 4800 m^2). Importantly, the Director and the Scientific Directors will participate in the planning process of the practical arrangements of the laboratories to ensure optimal functionality of the Center.

The University of Copenhagen will pay rent and running costs (electricity, heat etc) for the Center as well as the mandatory auditing according to the rules of University of Copenhagen.

REKTOR

NØRREGADE 10
POSTBOKS 2177
1017 KØBENHAVN K

DIR 35322612

WWW.KU.DK

The Center and the employees will be a fully integrated part of the Faculty of Health Sciences at the University of Copenhagen. All employees will be appointed at the Faculty (full-time or part-time) and shall confer to the general rules including the current IPR rules of the University of Copenhagen. All employees will have full access to all the facilities and offers of the Faculty, i.e. be treated as any other employee at the Faculty.

We will ensure competent administrative processes to aid in the formation of international collaborations, including exchange of master- and PhD students, postdoctoral fellows and other Faculty members.

The NNF will be acknowledged in all publications and presentations made by researchers at the Center.

The annual grant will be transferred from NNF to a given account at the University of Copenhagen. Any major changes in the research program or the budget over the years will be negotiated with the NNF. The Center submits an annual report through the Dean of the Faculty of Health Sciences. The Dean and the Director of the Center will have regular - at least quarterly - meetings with the Director of the NNF to discuss the progress of the activities and the budget.

We are most happy to continue our discussions and look forward to our continued collaboration.

Yours sincerely,

Ralf Hemmingsen
Rector

Ulla Wewer
Dean

FACULTY OF HEALTH SCIENCES
UNIVERSITY OF COPENHAGEN