Tuesday September 22, 2015
CHUV, César Roux Auditorium, Lausanne
Wednesday September 23, 2015
Olympic Museum, Lausanne

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Inauguration of the Obesity Center of the CHUV
Fourth LIMNA Symposium

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Organizing Committee: Prof. J. Auwerx, Prof. B. Desvergne, Prof. L. Fajas, Prof. F. Pralong, Prof. L. Tappy, Prof. B. Thorens, Prof. Kei Sakamoto and Dr. L. Descamps.

Speakers

Prof. David Arterburn
Health Research Institute and Department of Medicine at University of Washington, Seattle, USA

Prof. Barbara Cannon
Department of Molecular Biosciences, The Wenner-Gren Institute, Stockholm University, Sweden

Prof. Nouria Hernandez
Center for Integrative Genomics, University of Lausanne, Switzerland

Dr. Hutan Ashrafian
Faculty of Medecine, Department of Surgery and Cancer, Imperial College, London, UK

Prof. François Pattou
University Hospital, General and Endocrine Surgery, INSERM UMR 859 Biotherapies for Diabetes, Lille, France

Dr. Catherine Postic
Cochin Institute, Paris, France

Prof. David Mangelsdorf
University of Texas Southwestern Medical Center, Dallas, USA

Prof. Panda Sachidananda
Salk Institute for Biological Studies, La Jolla, USA

Prof. Philipp E. Scherer
Touchstone Diabetes Center, University of Texas Southwestern Medical Center, Dallas, USA

Prof. Bernard Thorens
Center for Integrative Genomics, University of Lausanne, Switzerland

Tuesday September 22

Inauguration of the Obesity Center of the CHUV, César Roux Auditorium, CHUV, 46 Rue du Bugnon, 1011 Lausanne

Welcome

17h00 Prof. François Pralong
Head of Endocrinology, Diabetes and Metabolism – CHUV

Opening

17h10 Prof. Pierre-François Leyvraz
Director of the CHUV

17h20 Prof. Manuel Pascual
Vice-Dean of strategic affairs, external relations and communication of the faculty of Biology and Medecine, Univerisity of Lausanne. Chief physician of organ transplant service, CHUV

Plenary Session

17h30 David Arterburn
«Investigating long-term bariatric surgery outcomes using large health care databases»

18h00 François Pattou
«Metabolic surgery: outcomes and mechanisms»

18h30 Questions

18h40 Aperitif

Wednesday September 23

Fourth LIMNA symposium – Olympic Museum, Quai d'Ouchy 1, 1006 Lausanne

8h30-9h00 Welcome and distribution of badges

Opening

9h00 *Welcome*
Johan Auwerx

Morning session

Chairman: Johan Auwerx

9h15 Barbara Cannon
«The metabolic capacities of brown adipose tissue»

9h50 Dr. Hutan Ashrafian
« Title to be communicated»

10h25 Coffee Break

Chairman: Lluis Fajas

10h55 Panda Sachidananda
« Eating pattern and metabolic diseases »

11h30 Bernard Thorens
« Brain glucose sensing in the control of glucose homeostasis and motivated feeding behavior »

12h05 -13h30 Lunch
13h30 - 14h30 Visit of Olympic Museum

Afternoon session

Chairman: Bernard Thorens

14h30 David Mangelsdorf
« Dissecting the Tissue Specific Actions of Endocrine FGF Signaling»

15h05 Nouria Hernandez
«Loss of the RNA polymerase III Repressor MAF1 confers obesity resistance and slightly smaller size»

15h40 Coffee Break

Chairman: Kei Sakamoto

16h10 Catherine Postic
«The transcription factor ChREBP: from glucose-sensing to liver pathophysiology»

16h45 Philipp E. Scherer
« Diabetes, Obesity and the Central Role of the Adipocyte in Maintaining Systemic Homeostasis »

17h20 Concluding remarks

ABSTRACTS

Prof. David Arterburn
Health Research Institute and Department of Medicine at University of Washington, Seattle, USA

Investigating long-term bariatric surgery outcomes using large health care databases

Electronic health care databases hold considerable promise for investigating the long-term outcomes of bariatric procedures for severe obesity. Nevertheless, these databases were designed primarily to support clinical care and the filing of insurance claims, so their use for research purposes requires considerable care. Dr. Arterburn will report on a decade of investigation into bariatric surgical outcomes using data from a variety of large health care databases in the US. Key areas of discussion will include the comparative effectiveness of bariatric procedures vs. routine clinical care, the impact of surgery on diabetes outcomes, and the economic impact of bariatric surgery.

Prof. Barbara Cannon
Department of Molecular Biosciences, The Wenner-Gren Institute, Stockholm University, Sweden

The metabolic capacities of brown adipose tissue

In rodents, brown adipose tissue is known to be a metabolically highly active organ. This concerns rates of blood flow, capacity for oxygen consumption and rates of uptake of lipid and carbohydrate substrates. The high rates of metabolism are dependent on stimulation of the tissue by norepinephrine, released from sympathetic neurons innervating the tissue. Following stimulation, thermogenesis occurs as a result of activation of the uncoupling protein UCP1 in the inner membrane of the numerous mitochondria. UCP1 is found only in brown adipocytes and in adipocytes with brown-like features, called brite (brown-like in white) or beige adipocytes, dispersed in several white adipose depots. Although the brite adipocytes appear attractive candidates to promote energy utilization and thus potentially weight loss, their natural abundance is markedly lower than that of classical brown adipocytes. The ability of brown adipose tissue to modulate body weight through UCP1-mediated thermogenesis, to dispose of whole body glucose and to clear triglycerides from the blood means that it has a capacity to improve many aspects of the metabolic syndrome. The confirmation of its activity in adult humans means that it is an interesting candidate for therapeutic development

Prof. Nouria Hernandez
Center for Integrative Genomics, University of Lausanne, Switzerland

Loss of the RNA polymerase III Repressor MAF1 confers obesity resistance and slightly smaller size

Nicolas Bonhoure1, Ashlee Byrnes2, Robyn Moir2, Wassim Hodroj1, Frédéric Preitner1, Viviane Praz1, Genevieve Marcelin3, Streamson C. Chua Jr.3, Nuria Martinez-Lopez3, Rajat Singh3, Norman Moullan4, Johan Auwerx4, Gilles Willemin1, Hardik Shah3, Kirsten Hartil3, Bhavapriya Vaitheesvaran3, Irwin Kurland3, Nouria Hernandez1, Ian Willis2

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RNA polymerase III is responsible for the synthesis of a collection of non-coding RNAs that exert a wide variety of cellular functions. For example, RNA polymerase III synthesizes 5S RNA, a component of the ribosome, as well as all the tRNAs, and its activity is thus essential for protein translation. RNA polymerase III transcription is regulated with cell growth and proliferation; in rapidly dividing cells or in growing cells, it is highly active to meet the demands in new ribosomes and tRNAs. Indeed, RNA polymerase III activity is up-regulated in malignant cells. In contrast, in resting cells, RNA polymerase III activity is low as it is only required for the maintenance of adequate levels of pol III RNA products, and most of these products have relatively long half-lives.

MAF1 is a protein originally identified in yeast, which is required for repression of RNA polymerase III transcription in response to various stresses. We have engineered a whole-body mouse knockout model lacking most of the Maf1 gene, and thus the protein MAF1. Surprisingly, these mice are leaner than their wild-type counterparts and resistant to high fat diet-induced obesity. They display increased synthesis and turnover of tRNAs and lipids, and increased energy expenditure. Consistent with previous work linking perturbations in the polyamine synthesis pathway with changes in adiposity, the levels of several polyamine pathway metabolites including ornithine, putrescine, and spermidine are increased in the liver of the Maf1-/- mice, and Nnmt RNA and protein levels are decreased. Reduced NNMT levels have been associated with increased NAD+ levels through nicotinamide salvage, and indeed NAD+ levels are increased in the muscle of these mice. In addition to being lean, the Maf1-/- mice are slightly smaller than wild-type mice. We will describe recent results relevant to this second phenotype.

Prof. Dr. Hutan Ashrafian
Faculty of Medecine, Department of Surgery and Cancer, Imperial College, London, UK

Prof. François Pattou
University Hospital, General and Endocrine Surgery, INSERM UMR 859 Biotherapies for Diabetes, Lille, France

Metabolic surgery: outcomes and mechanisms

Dr. Catherine Postic
Cochin Institute, Paris, France

The transcription factor ChREBP: from glucose-sensing to liver pathophysiology

Over the past years, important progress regarding the understanding of glucose signaling pathways in liver cells and in other key cells involved in energy homeostasis control has been obtained through the study of the transcription factor ChREBP (Carbohydrate Responsive Element Binding Protein) in cellular, animal and human studies. Understanding how carbohydrates affect negatively or positively cellular function through the regulation of the transcription factor ChREBP is of key importance for a better comprehension of human physiology and pathologies, such as metabolic syndrome, a major health concern, characterized by elevated blood glucose. Our laboratory focuses on the role of ChREBP in liver under both physiological and pathophysiological conditions, in particular in the context of NAFLD (Non Alcoholic Fatty Liver Diseases) and ALD (Alcoholic Liver Diseases). We studied the differential regulation of the glucose-sensitive transcription factor ChREBP in liver by nuclear receptors (LXR) and glucose (Denechaud et al. JCI 2008). We identified glucose 6-phosphate as the signal metabolite responsible for ChREBP nuclear translocation and activation in response to glucose in liver (Dentin et al. J Hepatol 2011). We also determined that various post-translational modifications (acetylation, O-glycosylation) govern ChREBP activity in response to glucose and ethanol (Bricambert et al. JCI 2010; Guinez et al. Diabetes 2011; Marmier et al. Hepatology) and how they relate to the pathophysiology of hepatic steatosis in mice. Recent results also reveal that ChREBP may interacts with key nuclear receptors involved in important metabolic pathways (Bile acid synthesis, detoxification) in liver. By identifying how ChREBP controls important cell-specific targets, future work will provide crucial information regarding the coordination, activities and assembly of key regulatory pathways in hepatocytes.

Prof. David Mangelsdorf
University of Texas Southwestern Medical Center, Dallas, USA

Dissecting the Tissue Specific Actions of Endocrine FGF Signaling

David J. Mangelsdorf and Steven A. Kliewer

Fibroblast growth factor 19 and 21 (FGF19 and FGF21) are endocrine factors that play important, but opposite, roles in governing the adaptive response to feeding and fasting, respectively. In contrast, in the setting of obesity and nutrient excess, FGF19 and FGF21 exhibit similar pharmacologic effects that include weight loss and improved insulin sensitivity. All of these effects of FGF19 and FGF21 require signaling through a common co-receptor, bKlotho. To gain mechanistic understanding of the various roles of FGF19 and FGF21, we have used tissue-selective deletions of bKlotho to reveal the similarities and differences in their modes of action.

Prof. Panda Sachidananda
Salk Institute for Biological Studies, La Jolla, USA

Eating pattern and metabolic diseases

Time-restricted feeding (TRF; 8-12 h food access in the active phase) without changing nutrient quantity improves daily oscillations in metabolic pathways and aligns them appropriately to the period of fasting or feeding. Subjecting rodents to TRF prevents excessive weight gain, adiposity, glucose intolerance, systemic inflammation, hepatosteatosis and hypercholesterolemia independent of diet type. Rodents on TRF also show increased endurance, motor coordination, and brown fat function. When high fat diet induced obese mice or mice with genetic predisposition to obesity are subjected to TRF, they also experience similar therapeutic benefits. TRF in Drosophila maintained body weight, improved sleep, and delayed age-dependent or high fat induced decline in cardiac performance. The beneficial TRF effect on cardiac function is dependent on a functional circadian clock and is partly mediated by ATP-dependent chaperone function. Unbiased assessment of the temporal changes in transcriptome, metabolome and gut microbiome revealed TRF exerts pleiotropic effect on metabolism in multiple tissue types in both rodents and insects. To test the translational potential of TRF in humans, we have begun to monitor daily eating pattern using a novel unbiased, evidence-based, and scalable method. Preliminary data shows erratic eating pattern with extended period of frequent caloric intake events that potentially maintains a post-prandial metabolic state in humans in widespread. Time-restricted feeding without overt attempt to alter nutrition quality or quantity might be a potential new lifestyle intervention to improve health in humans.

Prof. Philipp E. Scherer
Touchstone Diabetes Center, University of Texas Southwestern Medical Center, Dallas, USA

Diabetes, Obesity and the Central Role of the Adipocyte in Maintaining Systemic Homeostasis

During the progression from the lean to the obese state, adipose tissue undergoes **hyperplasia** as well as **hypertrophy** in an attempt to cope with the increased demand for triglyceride storage. This requires a high degree of plasticity at both the cellular and at the tissue level. The extracellular matrix of adipose tissue faces unique challenges with respect to adjusting to the need for remodeling and expansion. In parallel, the vasculature has to adapt to altered requirements for nutrient and oxygen exchange.

A decrease in the plasticity of these processes leads to metabolic dysfunction. Furthermore, to maintain a healthy, non-inflamed phenotype, complex regulatory mechanisms are in place to ensure adipocytes and stromal vascular cells efficiently crosstalk to allow adipose tissue to expand upon increased demand for storage of triglycerides. Therefore, we propose a model of stepwise adipose tissue dysfunction that is initiated by **rapid expansion of existing adipocytes** to accommodate triglycerides during excess caloric intake. This leads very quickly to an acute, and eventually chronic, state of **hypoxia** in adipose tissue.

Changes during the expansion process also affect adipocyte-derived secretory factors (**adipokines**), such as adiponectin. **Adiponectin** promotes insulin sensitivity, decreases inflammation and promotes cell survival. Its levels are frequently downregulated in the obese state. Avoiding the obesity-associated downregulation of adiponectin in fact allows the adipose tissue to further expand. This leads to a “healthy” expansion, with enlarged subcutaneous adipose tissue, improved vascularization and enhanced adipogenesis. As a result, we have improved systemic insulin sensitivity.

These phenotypes of healthy adipose tissue expansion have a positive effect on the systemic lipotoxic environment that prevails in the obese state. This may be particularly relevant for sphingolipids that tend to accumulate and prompt a high level of cytotoxicity under high fat diet conditions. Adiponectin potently stimulates a ceramidase activity associated with its two receptors, **adipoR1** and **adipoR2**, and enhances ceramide catabolism and formation of its anti-apoptotic metabolite – sphingosine-1-phosphate (S1P), independently of AMPK. These observations suggest a novel role of adipocyte-derived factors that have beneficial systemic effects, with **sphingolipid metabolism** as its core upstream component.

Prof. Bernard Thorens
Center for Integrative Genomics, University of Lausanne, Switzerland

Brain glucose-sensing in the control of glucose homeostasis and motivated feeding behavior

The brain utilizes glucose as principal source of metabolic energy. This has imposed the development of homeostatic mechanisms to maintain blood glucose at a minimal level of ~5 mM to ensure sufficient flux of glucose to the brain, and of hedonic mechanisms that attribute a high reward value to glucose-containing foods to increase the motivation to seek them. A large diversity of glucose-sensing cells involved in these glucoregulatory mechanisms are located in the brain. We have been interested for many years in the characterization of brain glucose-sensing cells with the goal of identifying their localization, their glucose sensitivity, the neuronal circuits as well as the physiological functions they control. Using the expression of the glucose transporter Glut2, a key element in glucose sensing by pancreatic beta-cells and insulin secretion, as a marker for glucose sensing cells, we have characterized different glucose-sensing neuronal populations. We have identified the role of Glut2 neurons from the nucleus tractus solitarius in hypoglycemia detection and the activation of the parasympathetic nerve to stimulate glucagon release. More recently we have identified a population of Glut2 neurons in the thalamus that controls motivated sucrose-seeking behavior through their connection to the nucleus accumbens, a key nucleus in reward system. These studies are based on the use of various mouse model for genetic marking of Glut2-expressing cells or for cell type-specific inactivation of the Glut2 genes, as well as various physiological, electrophysiological, optogenetic, and behavioral techniques. These studies provide a novel description at the molecular, cellular, and neuronal circuit levels of the regulation of complex physiological function by brain glucose-sensing cells.