Abstracts Diabetes Breakthrough projects

Johan Jocken - Maastricht University
Connecting autophagy and human adipose tissue lipid catabolism

Interestingly, over the years several studies have reported that pharmacological modulation of autophagy has favourable metabolic effects on both glucose control and lipid profiles, beyond their anti-inflammatory action, indicating its relevance in human health and diseases. Often an increased adipose tissue autophagy has been observed in obese humans. However, it is suggested that this increased adipose tissue autophagy is linked to the elevated number of immune cells infiltrated in the adipose tissue of obese insulin resistant individuals. Of interest, recent data showed existence of an autophagic flux defect, rather than elevated autophagy, in isolated adipocytes of obese patients. Nevertheless, this is not a universal finding in literature. Based on these observations and the pilot data dr. Jocken has recently generated, he hypothesizes that an impaired autophagy lysosomal mediated lipid breakdown contributes to adipose tissue mitochondrial dysfunction and the development of insulin resistance in human obesity. However, the first and most important question that needs to be addressed is whether and how the autophagy-lysosomal pathway is involved in lipid hydrolysis (RQ 1), and subsequent PPAR-mediated mitochondrial respiration in human adipocytes (RQ 2). To address this important question, dr. Jocken proposes a unique set of complex in vitro experiments.

Anton Jan van Zonneveld – Leiden University Medical Center
Estrogen driven post-transcriptional control of metabolism: the missing link in gestational diabetes mellitus

Gestational diabetes mellitus (GDM) affects 3-5% of pregnant women and is a severe metabolic disease which has long-term impact on the risk for type 2 diabetes and cardiovascular disease both for the mother and the child. In GDM, pregnancies are characterized by a progressive increase in metabolic dysregulation, insulin resistance and, in the later phase of the pregnancy, hyperglycaemia. Little is known about the molecular mechanisms underlying the progression to GDM except for that it may relate to the hyperestrogenemia that develops late in pregnancy and that has been associated with insulin resistance. This phenomenon also affects male-to-female transgenders that receive high doses of estrogen and develop insulin resistance after one year that can progress to type 2 diabetes on the long term. Their ‘out of the box’ approach to elucidate causal mechanisms in GDM is that they aim to explore the involvement of an estrogen regulated post-transcriptional mechanism that may drive insulin resistance that they identified in male-to-female transgenders. This post-transcriptional network, that they demonstrated to induce potent pro-diabetogenic metabolic shifts in mice, is regulated by estrogen controlled miRNAs and, when validated, may well provide a mechanistic explanation for GDM. With this project they will combine expertise on molecular genetics with the expertise on GDM to validate the involvement of their novel metabolic signalling network in GDM. Their unique access to clinical samples of three major GDM improvement trial will allow us to assess the relation between estrogen levels, metabolic parameters and miRNAs that drive metabolic signalling in plasma and visceral adipose tissue obtained from mothers with and without overt GDM. In addition they will explore foetal cord blood samples to explore whether circulating estrogen responsive miRNAs may serve as potential biomarkers for diabetic fetopathy. Dissection of this novel posttranscriptional network may provide the scientific breakthrough to identify novel therapeutic targets to counteract GDM and its long term complications in both mothers and children.
Jeanine Prompers – University Medical Center Utrecht
Development of a new, non-invasive imaging tool to map liver metabolism in type 2 diabetes

In type 2 diabetes, both carbohydrate and lipid metabolism in the liver are dysregulated, which is strongly related with hepatic insulin resistance. However, their knowledge of the exact disturbances in the metabolic pathways in the insulin resistant liver is limited due to the fact that sensitive, direct measurement methods are currently lacking. The aim of this project is to develop a completely novel and non-invasive method to measure hepatic carbohydrate and lipid metabolism directly inside the liver in humans. The method is based on deuterium metabolic imaging (DMI) combined with administration of 2H-labeled compounds. They hypothesize that DMI has sufficient sensitivity to dynamically probe metabolic pathways in the human liver in 3D imaging mode. The objectives of the project are: (1) Build and test a liver DMI setup for their clinical ultra-high field 7T MRI scanner; and demonstrate proof of concept to measure hepatic (2) glycogen synthesis and (3) de novo lipogenesis in healthy volunteers and people with type 2 diabetes.

Chun-Xia Yi – Amsterdam Medical Center University of Amsterdam
Reprogram microglial metabolism to curb insulin resistance

Dr. Yi has discovered that microglia in the mediobasal hypothalamus (MBH) become activated rapidly on an obesogenic diet. These reactive microglia are mostly nearby the key glucose sensing neurons in the same brain region. It is known that reactive microglia, just like activated macrophages in the periphery, become more glycolytic and take more glucose for ATP production. This will lead to local depletion of glucose supply to the neighbouring glucose-sensing neurons. In turn, the glucose-sensing neurons will make a misinterpretation of the “blood” glucose availability, and initiate a glucose-elevating response: increasing liver glucose production and reducing tissue glucose uptake by inducing insulin resistance. Dr. Yi therefore raises the hypothesis that obesogenic diet-induced microglial activation in the mediobasal hypothalamus disturbs the hypothalamic glucose sensing-regulation machinery, and induces insulin resistance, via depletion of glucose supply from the glucose-sensing neurons. To attest this hypothesis, dr. Yi will use rats in which insulin-resistance are induced by a high-fat high-sugar obesogenic diet. Dr. Yi will check whether insulin resistance can be improved by 1) increasing the local glucose level in the mediobasal hypothalamus; or 2) reprogramming the microglial metabolism, by specifically switching off microglial glucose utilization and enhancing lipids utilization, this will be achieved by using a nanoparticle-mediated microglia-targeted drugs delivery approach. Moreover, this nanoparticle approach is also a potential novel tool for pharmacotherapy of type 2 diabetes.
Janine Kruit – University Medical Center Groningen
Selective clearance of aged cells; a new cure for type 2 diabetes?

Visceral adipose tissue of people with type 2 diabetes shows increased senescence and excessive calorie intake is associated with senescent cell accumulation. Senescence associated secretory phenotype (SASP) factors could potentially contribute to low-grade chronic inflammation induced adipose dysfunction, ultimately increasing insulin resistance. Hyperglycaemia is known to induce premature senescence, suggesting a feedback loop between type 2 diabetes and senescence. Furthermore, polymorphisms in the CDKN2A locus encoding for tumour suppressor protein p16ink4a which is a key regulator in senescence, are associated with type 2 diabetes. However, whether ablation of the detrimental effect of senescent cells in type 2 diabetes prevents or declines the progression is not known, due to the lack of appropriate type 2 diabetes models in which senescence is an independent contributor to deranged glucose homeostasis. Basis for this proposal is my finding that selective “ageing” of β-cells is sufficient to drive cellular senescence and the development of type 2 diabetes independent of nutrient excess. Aging is attributed to the accumulation of stochastic damage of macromolecules. To determine whether spontaneous, endogenous DNA damage in β-cells is sufficient to drive loss of islet function and diabetes, they deleted Ercc1, a key DNA repair gene, specifically in pancreatic β-cells of mice (βErcc1KO mice). Loss of Ercc1 in β-cells of mice resulted in the development of an adult onset type 2 diabetes phenotype, due to loss of β-cell mass and β-cell function. Interestingly, although the primary insult in βErcc1KO mice lies within the β-cell, multiple peripheral tissues of in βErcc1KO mice showed increased cellular senescence and inflammation accompanied with insulin resistance independent of obesity or diet, indicating that β-cell dysfunction is sufficient to drive many hallmarks type 2 diabetes. Based on these experiments, dr. Kruit hypothesizes that islet dysfunction causes premature senescence which act through SASP factors to induce insulin resistance and further β-cell dysfunction, thereby contributing to the progression decline of health in the diabetic patient. Using the βErcc1KO mice dr. Kruit can test this hypothesis by selective ablation of senescent cells using senolytic drugs.

Eric Kalkhoven – University Medical Center Utrecht
Targeting the ‘undruggable’ pseudokinase TRIB3 to improve insulin sensitivity

Many people with type 2 diabetes are prescribed the same treatment, but individual differences in disease progression and risk of diabetic complications suggest that it should not be considered a single disease. New and more different treatments that are tailored and targeted to patients who benefit most are therefore required. For this they need to identify new cellular drug targets, and take for example genetic variation in patients into account in the early steps of drug development. The pseudokinase TRIB3 is an important cellular inhibitor of insulin signalling and therefore a potential anti-diabetic drug target, but this protein was so far considered to be ‘undruggable’ due to its lack of enzymatic activity. Recent insights from the cancer research field however suggest that pseudokinases like TRIB3 can be inhibited by small molecules that destabilize their structural state or by peptides that specifically block their binding to other proteins. They therefore hypothesize that targeting the ‘undruggable’ pseudokinase TRIB3 can improve insulin sensitivity. Before drug screening can be started, a proper read-out system needs to be developed. In these early steps they will immediately compare the common Q84 form and the R84 variant (which more strongly inhibits AKT) of TRIB3, as patients with the R84 variant may ultimately benefit most from treatment with TRIB3 inhibitors. They will develop a robust cell-based system that is needed to perform future drug screens, based on the TRIB3-AKT interaction. In addition, they will also identify the interactomes of TRIB3 Q84 and R84 in different cell types to be able to include additional relevant protein-protein interactions in future drug screens. Together these approaches will be the starting point of a new line of research towards the identification and validation of pseudokinase inhibitors as innovative anti-diabetic drugs.
Bruno Guigas – Leiden University Medical Center
Role of protein glycosylation in macrophage-adipocyte crosstalk during obesity

Obesity is associated with adipose tissue (AT) inflammation, which is one of the major contributors to insulin resistance and progression towards type 2 diabetes. The interaction and communication between immune cells, especially macrophages, and adipocytes within the AT are thought to play an important role in this process and is largely determined by complex carbohydrate structures, called glycans, located on their cell surface and/or secretory proteins. Protein glycosylation is the reaction in which a glycan is attached to protein, especially on asparagine residues (N-glycosylation), and is one of the most common cellular processes. Glycan composition and diversity is mainly determined by the activities of various components of the glycosylation machinery, especially by glycosyltransferases which are specific enzymes principally located in the Golgi apparatus. Changes in cell surface and/or secretory protein N-glycosylation affect intercellular communication through interaction with carbohydrate-binding receptors. Defects in glycosylation or alterations in protein glycan structure composition have been associated with various chronic diseases, such as cancer and inflammatory autoimmune diseases, but have not been yet extensively studied in the context of obesity and type 2 diabetes. Their working hypothesis is that changes in N-glycosylation of cell surface and/or secretory proteins resulting from cell-specific alterations of the glycosylation machinery during the course of obesity would affect macrophage-adipocyte crosstalk and contribute to AT insulin resistance. Their main objectives will be 1.) to study the effect of acute and chronic high-fat diet feeding on gene expression of key players of the glycosylation machinery and carbohydrate-binding receptors in AT macrophages (ATMs) and adipocytes from mice, and 2.) to characterize the cell surface and secretory protein N-glycome in both cell types.

Hilde Herrema – Amsterdam Medical Center
Bacteriophages as regulators of glucose metabolism

Modification of the gut microbiota by fecal microbiota transfer has the capacity to improve glucose handling and insulin sensitivity in people at risk to develop diabetes. This procedure might therefore hold merit to serve as preventive measure for development of diabetes or to lower the burden of those already suffering from the disease. However, the effect of fecal microbiota transplantation on insulin sensitivity differs significantly between recipients. This might in part be due to differences in donor bacterial engraftment and capacity of the donor transplant to increase bacterial diversity in the recipient. Mechanisms that drive donor bacterial engraftment and subsequent effects on glucose metabolism after fecal microbiota transplantation, however, remain largely unknown. Bacteriophages (phages) are viruses that exclusively infect and eliminate bacteria. There is substantial evidence for a role of phages in shaping microbial communities in many ecosystems. However, there is only limited insight in and attention for the role of phages in the human gut microbial community. The role of phages herein might be substantial but has thus far never been studied. To address this problem, they here propose a pilot study in which they will transfer faecal bacteriophages from lean, healthy subjects to the gut of obese, insulin resistant subjects and assess the effect on engraftment and glucose metabolism. They speculate that the virome composition of the lean donor and the subsequent interaction between phages and bacteria in the recipients are crucial determinants of stability and diversity of gut bacterial composition and glucose metabolism in humans after FMT. They hypothesize that lean donor phage transplantation will increase gut microbial diversity and improves glucose handling in insulin resistant recipients at risk to develop type 2 diabetes.
Andrea Evers – Leiden University
Conditioning of insulin responses: A high risk – high gain intervention for diabetes type-2

The present study will be the first to examine whether it is possible to classically condition endogenous insulin release in people with type 2 diabetes by pairing intranasal insulin administration with a distinctive odour. If this study successfully indicates that insulin is conditionable in people with type 2 diabetes, in a subsequent follow-up study they will test the possibilities to use conditioning as part of the regular treatment for people with type 2 diabetes. They furthermore aim to examine whether conditioning may also improve beta-cell functioning by including a glucose tolerance test at baseline and again after conditioning. They adopt a successful design used in healthy controls to elicit endogenous insulin release after intranasal insulin administration and now apply this design to people with diabetes for the first time. For this study, a conditioned group of people with type 2 diabetes will be compared to a control group of patients who are not conditioned. In line with previous findings, their key hypothesis is that after repeated pairing of a distinctive odour (CS) with intranasal insulin (US), participants in the conditioned group will demonstrate an increase in serum insulin in response to the odour (CS) alone in comparison to participants in the non-conditioned control group. Secondary, they will test the conditioning effects of insulin on lowering blood glucose levels. Additionally, they will explore the effects of conditioning with intranasal insulin on hunger and food intake.

Renée de Mutsert – Leiden University Medical Center
Timing of physical activity: breaking sitting time to reduce fatty liver and prevent type 2 diabetes

Excess hepatic triglyceride content is a strong risk factor for the development of type 2 diabetes. Reducing hepatic triglyceride content may therefore improve insulin sensitivity and subsequently prevent type 2 diabetes. An increasing number of studies have associated sedentary behaviour with detrimental health outcomes such as type 2 diabetes and cardiovascular disease. However, underlying mechanisms remain to be elucidated. Experimental studies in which the amount of sedentary time is replaced with standing and low intensity physical activity resulted in lower serum triglycerides and increased insulin sensitivity, but if reducing or interrupting sedentary behaviour may also result in lower hepatic triglyceride content remains unknown. Key hypothesis: Interrupting sitting time frequently will lead to reduced serum and hepatic triglycerides and thereby reduce the risk of type 2 diabetes.

1. Define patterns of daily activities, e.g. number of sedentary breaks, mean duration and intensity of one sedentary bout, and from this the timing and pattern in which total sedentary time is accumulated, using the accelerometer data collected in the NEO study.
2. Investigate relations of timing and frequency of sedentary breaks with circulating blood lipids (triglycerides, HDL- and LDL-cholesterol) and with directly assessed hepatic triglyceride content.
3. Investigate relations of timing and frequency of sedentary breaks with markers of diabetes risk (fasting and postprandial measures of glucose metabolism and insulin resistance).
Gert-Jan de Bruijn – University of Amsterdam

When the shopping gets tough, the tough train in virtual reality: a virtual reality approach to promote healthy grocery shopping

Innovative training methods employing new persuasion technologies are needed to make sure people engage in healthier grocery shopping. In the present proposal, they suggest that important properties of task-focused mindset training can be readily incorporated into mobile app-based virtual training to enhance healthier grocery shopping, even under high loads of external and internal temptations. Specifically, they will employ task-focused grocery shopping list training under both conditions of low and high blood glucose levels (internal temptations) and under conditions of low and high food cues and shopping distractions (external temptations) during a 5-day (study 1) and 10-day (study 2) training program.

Training will be done during lab sessions for consecutive days, and assessment of grocery shopping will be done the day after training completion. Training conditions will be experimentally manipulated in 2x2 between-subjects design. Specifically, they will manipulate food cues (low versus high distraction) and blood glucose levels (low versus high) in healthy controls (study 1), and they will manipulate the same external temptations in study 2 in healthy controls, pre-diabetic adults and diabetic adults, where diabetes status will function as a between-subject factor. After training completion, healthy and unhealthy grocery shopping will be assessed in a highly realistic virtual reality supermarket available at the host institutions laboratory (study 1 and study 2) and they will also assess real-life healthy and unhealthy grocery shopping during one month after training completion (study 2 only). It is hypothesized that those who are trained under high levels of internal and external temptations are better able to make healthier grocery shopping choices in both the virtual and real-life supermarket settings.

Joris Hoeks – Maastricht University

Targeting a novel, insulin-independent pathway to improve skeletal muscle glucose uptake in humans.

Dr. Hoeks has recently published that mild cold acclimatisation (15-16°C) for 10 consecutive days (6h/day) dramatically improved insulin sensitivity by ~43% in people with type 2 diabetes. Although the cold acclimatisation procedure was initially intended to activate brown adipose tissue (BAT), the effects of cold on insulin sensitivity were primarily mediated by a significant increase in skeletal muscle glucose uptake, through an increased translocation of glucose transporter 4 (GLUT4) proteins to muscle cell membranes. Interestingly, the mild cold-induced GLUT4 translocation did not appear to occur via the classical pathways, i.e. an improved insulin signalling or the activation of AMPK pathway, since key proteins of both pathways remained unaltered. As such, the precise underlying molecular mechanism of the profound mild cold induced improvement in skeletal muscle glucose uptake remains to be elucidated but their findings hint towards the existence of an alternative insulin/AMPK-independent pathway. Stimulation of β2-adrenergic receptors on L6 muscle cells significantly increased GLUT4-mediated glucose uptake through the activation of the mammalian target of rapamycin (mTOR) complex 2 (mTORC2). These effects were independent from the activation of the ‘classical’ glucose uptake regulating pathways, involving Akt (insulin), AS160 and AMPK. As cold exposure is well known for its capacity to activate the sympathetic nervous system, this mechanism hence provides a likely candidate to explain the effects of cold acclimatisation on skeletal muscle glucose disposal and presents an interesting new target to improve glucose homeostasis. The novel pathway appeared to also be functional in human skeletal muscle, since β-adrenoreceptor stimulation increased GLUT4 translocation in human primary skeletal muscle cells as well. Whether or not this pathway can be activated in humans in vivo to improve glucose disposal, is currently unknown. Here dr. Hoeks hypothesizes that activation of the novel mTORC2 pathway via selective β2-adrenergic receptor activation improves glucose uptake in human skeletal muscle in vivo.
Patrick Schrauwen – Maastricht University
It's time to deplete glycogen: novel strategy to improve insulin sensitivity

In our 24h society, food intake is no longer restricted to a limited time period during daytime. On the contrary, recent data suggest that we spread our food intake over ~15 hours per day. As a result, we are never in a true fasting, post-absorptive state. Under normal conditions, hepatic glycogen content is a major energy buffer to provide glucose and energy during the night, and glycogen stores will be low in the overnight fasted state. As a result, fat oxidation is increased during the night and carbohydrates from food intake in the morning will be rapidly taken up and used to replenish glycogen stores. Here the researchers hypothesize that in type 2 diabetes patients hepatic glycogen stores may not fully deplete overnight and that restricting food to a shorter period of time during the day, will lead to a larger reduction of hepatic glycogen stores, and thereby improve whole-body insulin sensitivity. Objective: to investigate if time restricted feeding leads to more reduced overnight fasted hepatic glycogen stores and improvement in insulin sensitivity in people with type 2 diabetes.

Mireille Serlie – Amsterdam Medical Center University of Amsterdam
Is the awakening brain a novel therapeutic target in the treatment of Diabetes Mellitus type 2?

The brain as master regulator of energy metabolism has long been ignored in clinical diabetes research. It has been shown that dopaminergic signalling is disturbed in obesity but whether this is also present in type 2 diabetes is unknown. Moreover, it has yet to be elucidated whether the findings in obese humans reflect disturbed dopamine release or reduced dopamine receptor expression. Studying the central regulation of glucose metabolism by brain dopaminergic systems in type 2 diabetes opens up new avenues and possibilities in the development of novel therapies. In addition, many metabolic and hormonal processes in the body follow daily rhythms, but this is often not taken into account when designing clinical trials and new treatment strategies. They here aim to follow the physiology of daily rhythmic dopamine release in reducing insulin resistance in type 2 diabetes. With this proof-of-concept study, they will address i. differences in dopamine release in people with type 2 diabetes versus historical lean controls, ii. whether timed restoring of dopamine signalling improves dopamine release and iii. whether this reinstatement of daily dopamine rhythms is associated with an improvement in insulin sensitivity. They will use state of the art techniques, i.e. hyperinsulinemic euglycemic clamps and SPECT imaging, to assess these study outcomes. Since animal studies indicate that decreased daily dopamine release may contribute to diet-induced insulin resistance and they recently showed that in humans, dopamine release enhances insulin sensitivity, it is timely and highly relevant to study whether dopamine release is impaired in patients with type 2 diabetes. Furthermore, a disturbed daily rhythm of dopamine signalling may underlie this decreased dopamine release and contribute to insulin resistance. Restoring this daily rhythm by simulating a peak in dopaminergic signalling in the morning, may form a novel treatment to improve insulin sensitivity and hyperglycaemia in people with type 2 diabetes.
Circulating small RNAs are mostly contained in extracellular vesicles or exosomes which originate from various tissues including tissues important in type 2 diabetes (fat, liver, pancreas, muscle). Whereas previously it was thought that small RNAs merely reflect degradation by-products it has now been shown that they exert important functions in cells and organisms. Such as for instance cell-to-cell communication, the regulation of gene expression, epigenetic and post-transcriptional gene silencing of retrotransposons and ribosomal RNA maturation. Circulating small RNAs thus provide an unique and novel tool to non-invasively study target tissue function in persons with type 2 diabetes and thus behold great promise as unique and novel biomarkers. For this study they will use retrospective samples from the Hoorn Diabetes Care System cohort study biobank (DCS). The DCS is a unique prospective study, started in 1998, in which patients visit the research center annually for highly standardized routine diabetes care. From these visits they collect in a large longitudinal database clinical data about their diabetes but also anthropometry, routine biochemistry, medication use and information about co-morbidities and mortality. In addition they have initiated since 2008 the collection of biospecimens (liquid biopsies) in a large biobank to facilitate for instance translational research (n=6000+). From this biobank they have selected 523 subjects with at least seven years follow-up data and liquid biopsy material collected within three years after diagnosis. The sample is enriched for persons who require insulin during follow-up. Using these existing liquid biopsies in combination with state of the art small RNA sequencing technology they are now for the first time able to perform a hypothesis free analysis of the whole small RNA transcriptome to facilitate risk stratification. Early identification of those with increased risk of rapid glycaemic progression may help to redirect their clinical resources to those who may benefit the most. Improving their quality of life and facilitating value based healthcare.

Femke Rutters – VU Medical Center Amsterdam
Pillow or Pills? The role of sleep in the progression of type 2 diabetes

Life-style factors such as diet and physical inactivity are well-known risk factors for type 2 diabetes progression. Sleep is a less-known lifestyle factor, which they previously showed to be associated with type 2 diabetes development. But is sleep also relevant for the progression of type 2 diabetes? Do people with type 2 diabetes with sleep-related problems have worse glycaemic control than those who do not? And if this is all true can we improve glycaemic control in people with type 2 diabetes by treating their sleep problems? These questions dr. Rutters will answer with my current proposal, which aims to decipher the role of sleep in the progression of type 2 diabetes. This out-of-the-box proposal combines the fields of epidemiology and experimental biology as well as combining the research areas diabetes and sleep. This research fills an important gap in the current research field, since 20-40% of all people with type 2 diabetes suffer from sleep problems. The importance of this research is further highlighted by their recent meta-analysis, which showed that for insomnia is up to 3 times more prevalent in people with type 2 diabetes, compared to the general population. In work package 1, they use observational data from 3000 people with type 2 diabetes, to study the role of insomnia in the progression of type 2 diabetes over 1 year. Insomnia is measured by the Dutch Insomnia Severity Index and defined as having trouble falling asleep, maintaining sleep, and/or suffering from early morning awakening. Type 2 diabetes progression is measured as changes in fasting glucose, HbA1c and diabetes medication use. In work package 2, 80 men and women with type 2 diabetes and insomnia are selected from the observational cohort, to compare the effect of care as usual (n=40) to treatment of sleep problems with cognitive behavioural therapy (n=40) on glycaemic control.
Marleen van Greevenbroek – Maastricht University  
Control of insulin secretion: Methylglyoxal (MGO)-modification of intracellular CD59 impairs insulin secretion by β-cells.

In this project dr. Van Greevenbroek will focus on a newly-identified molecule in the β-cell that has been classified as a novel player in the secretion of insulin from its secretory granules. The main goal of this project is to investigate how modifications of this protein, CD59, in prediabetes and (early) diabetes can impair the insulin secretion process. In this breakthrough project dr. Van Greevenbroek proposes a completely novel mechanism for the progression of β-cell dysfunction in individuals with prediabetes and early stages of type 2 diabetes. Dr. Greevenbroek hypothesize that increased concentrations of the glucose-derived α-dicarbonyl methylglyoxal (MGO) in the β-cell, as occur during (postprandial) episodes of hyperglycaemia, affect the function of intracellular CD59 via modification of its arginine residues by MGO. This impairs the bridge-function of CD59 in the release of insulin from its storage granules. This results in insufficient insulin secretion and, consequently, leads to development and progression of type 2 diabetes. Dr. Van Greevenbroek intends to address this hypothesis in 3 steps. Step 1: Proof on concept in vitro - Herein dr. Van Greevenbroek will investigate the formation of MGO adducts on CD59 in β-cells and evaluate how this affects insulin secretion. Step 2: Proof of concept in vivo – dr. Van Greevenbroek will evaluate the extent to which MGO-adducts are present in CD59 in the pancreas of rodents that were exposed to MGO. Step 3: Proof of concept in humans – dr. Van Greevenbroek will evaluate the relevance of this hypothesis for human (pre)diabetes. For this dr. Van Greevenbroek will study, in a prospective human cohort, how whole body MGO stress is related to (impaired) β-cell function.

Hiddo Lambers Heerspink – University Medical Center Groningen  
Imaging individual drug response: A breakthrough to personalized medicine in diabetes

The underlying factors explaining why patients respond so different to SGLT2 inhibitors (and other interventions) are poorly understood. This knowledge gap hampers the implementation of personalized medicine in clinical practice. They hypothesize that the underlying mechanisms of the varying responses between patients can be attributed to variability in the causal path between drug administration, drug (tissue) disposition to the site of action, and drug receptor interaction at the tissue level. To test this hypothesis they have synthesized an 18F-PET radiotracer of the SGLT2 inhibitor canagliflozin in order to image drug disposition and tissue-receptor interaction in people with type 2 diabetes. In a clinical study they will assess 18F-canagliflozin pharmacokinetic characteristics and determine specific receptor binding, receptor occupancy and optimal scanning-time in 9 people with type 2 diabetes and elevated albuminuria. To this end, PET CT scans will be performed to identify the region of interest (kidney, aorta and part of the liver). They will obtain two 90-minute dynamic PET scans; on the first study day after administration of an intravenous diagnostic 18F-canagliflozin tracer dose and on the second study day after combined oral canagliflozin and radiotracer administration. Using population approach pharmacokinetic-pharmacodynamic modelling, the pharmacokinetics of canagliflozin in plasma and in target tissues as well as receptor occupancy will be quantified and linked to pharmacodynamics responses.
iPAVE - imaging Pituitary ActiVation by Exendin

Glucagon-like peptide1 (GLP-1) regulates blood glucose levels via specific GLP-1 receptors (GLP-1Rs) on pancreatic beta cells (inducing insulin secretion), alpha cells (inhibiting glucagon release), and on gastric mucosa cells (slowing gastric emptying). GLP-1 analogues (GLP-1RA), such as exendin, have become potent antidiabetic drugs for treating type 2 diabetes. However, not all people with type 2 diabetes respond to treatment with GLP-1RA and some even respond with contradictory effects, but the underlying mechanism for this observation remains unclear. They have developed an exendin-based radiotracer for in vivo PET (positron emission tomography) imaging of GLP-1Rs for quantification of beta cell mass. They have proven the feasibility of this technology in humans and currently, they are conducting clinical studies in individuals with diabetes. They observe radiotracer uptake in the pancreas and the gastroduodenal area, corresponding to exendin effects on insulin secretion and gastric emptying. Interestingly, they also observe a marked radiotracer uptake in the area of the pituitary with high inter-individual variation. They believe that GLP-1RA binding to the pituitary stimulates the hypothalamic-pituitary-adrenal (HPA) axis leading to ACTH and subsequent cortisol secretion and that this effect shows individual variation. The high radiotracer uptake in the pituitary gland indicates a physiologically highly relevant mechanism. Individuals with severe obesity and type 2 diabetes have increased blood levels of glucocorticoids resulting from HPA activation. This may lead to insulin resistance, increase in fat tissue mass, reduced insulin secretion and enhanced stress response. Their preliminary data indicate a markedly higher uptake of the radiotracer into the pituitary in obese people with type 2 diabetes with insufficient response to medical treatment as compared to patients after bariatric surgery. They believe that the effects of GLP-1RA on the HPA axis have so far been underestimated and that the resulting chronically elevated glucocorticoid levels may significantly contribute to failure of GLP-1RA therapy. They therefore hypothesize that (a) stimulation of the HPA axis is mediated through GLP-1Rs in the pituitary gland, (b) high expression of GLP-1Rs increases the susceptibility for HPA activation by GLP-1RA and (c) pituitary exendin uptake is inversely associated with glucose levels and weight under GLP-1RA therapy.

Rinke Stienstra – Wageningen University
One Size does not fit all. Using energy metabolism in immune cells to predict metabolic heterogeneity of obesity

Dr. Stienstra hypothesizes that alterations in metabolic signatures of circulating innate immune cells can be used to predict the development of obesity-induced inflammation and subsequent insulin resistance and type 2 diabetes. Therefore, dr. Stienstra aim to analyse ex vivo metabolic signatures of circulating human innate immune cells isolated from obese individuals varying in the degree of insulin resistance. The metabolic response of the immune cells towards nutrient excess will be closely evaluated allowing me to couple energy metabolism of the immune cells to the level insulin resistance. Once the relevance of innate immune cell metabolism as an identifier of has been established, follow up studies would focus on individuals at an even earlier stage that would allow for the identification of those individuals at risk for the development of type 2 diabetes. Overall, results of this project will provide a stepping-stone to the development of personalized approaches aimed at identifying those obese individual at risk for the development of insulin resistance using alterations in innate immune cell metabolism as predictor.