International Research Training Group

DFG IRTG 2251:
Immunological and Cellular Strategies in Metabolic Disease




First Annual Update
04/2017 - 03/2018

transCampus
IRTG 2251: ICSMD
IMMUNOLOGICAL AND CELLULAR STRATEGIES IN METABOLIC DISEASE

DFG

TECHNISCHE UNIVERSITÄT DRESDEN

KING'S College LONDON

transCampus
IRTG 2251: ICSMD
IMMUNOLOGICAL AND CELLULAR STRATEGIES IN METABOLIC DISEASE

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PREFACE

> *"All the major problems of the world today are global in essence, and they cannot be solved unless through some kind of global cooperation.*
>
> — Yuval Noah Harari

The first twelve months of the International Research Training Group "Immunological and Cellular Strategies in Metabolic Disease" have been highly successful, exciting, and rewarding.

As of now, the Research Training Group already comprises 21 ambitious projects, each of which is being jointly supervised by renowned experts from King's College London and TU Dresden. The vast majority of our students participates in the Joint PhD programme.

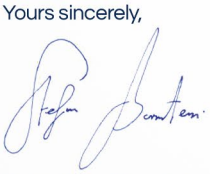
A selection of publications of the IRTG consortium from the last twelve months shows the combined impact of our work in the scientific community.

For us, the most remarkable moments were our student kick-offs in Dresden and London. There we got the chance to witness a group of highly ambitious, motivated, and self-confident IRTG students just about to start their PhD projects. In these moments we felt a satisfying emotional reward for two years of synchronized work and preparation.

We would like to express our warmest thanks to all colleagues involved, and our students, for making this success story happen. Naturally, we owe a great debt of gratitude to the German Research Foundation (DFG) for initiating and administering this amazing funding scheme.

This booklet provides a brief insight into what we have achieved so far. We kindly invite you to browse through the list of previous events and ongoing projects. We strongly encourage interested students and colleagues to get in touch with us, if you wish to support or join the IRTG.

Yours sincerely,



Prof. Stefan Bornstein

Prof. Mark Peakman

Spokesperson TU Dresden
International Research Training Group
"Immunological and Cellular Strategies
in Metabolic Disease"

Director of the Centre for Internal Medicine
and the Medical Clinic and Policlinic III
at the University Hospital Carl Gustav Carus

Vice Dean of International Affairs
and Development

transCampus Dean

Spokesperson King's College London
International Research Training Group
"Immunological and Cellular Strategies
in Metabolic Disease"

Head of Diabetes
Professor of Clinical Immunology
Honorary Consultant Immunologist
at King's College Hospital

NHS Foundation Trust

transCampus Professor

GOVERNANCE STRUCTURE

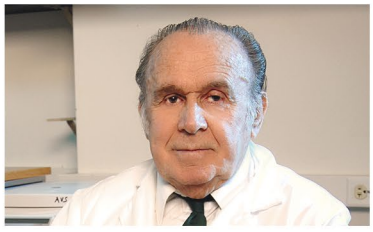
STEERING COMMITTEE

The Steering Committee (SC) is responsible for ensuring a quality-oriented management. The composition of the SC ensures that all involved career levels and institutions are being represented. The SC is in charge of all fundamental control tasks and development processes of the research training group.

Stefan Bornstein	Spokesperson, TU Dresden
Mark Peakman	Spokesperson, King's College London
Andreas Birkenfeld	Representative of Faculty of Medicine, TU Dresden | Curriculum Development Manager
Shanta Persaud	Representative of King's College London
Stephan Speier	Representative of Paul Langerhans Institute Dresden (PLID)
Anne Eugster	Representative of Center of Regenerative Therapies Dresden (CRTD) | Coordinator Gender Equality
Diana Willmes	PostDoc Representative
Rocio Sancho	Junior Faculty Representative King's College London
Margrit Kamel	Student Representative
Alice Santambrogio	Student Representative
Bassam Aljani	Student Representative

EXTERNAL ADVISORY BOARD

For external supervision and as a platform to give new stimuli to the network, an international External Advisory Board (EAB) of three renowned experts of higher education in the metabolic field has been established.



Professor Andrew V. Schally

Andrew V. Schally won the Nobel Prize for Medicine or Physiology in 1977, for his research on hypothalamic control of the pituitary gland. He developed a new realm of knowledge concerning the brain's endocrine control over the body's functions. He isolated and then synthesized the neurohormone GnRH/LHRH that controls FSH and LH secretion and reproduction. Dr. Schally worked at VA Hospital and Tulane University School of Medicine in New Orleans, LA, from 1962-2005. Subsequently, he was transferred to the Miami VA Hospital and the University of Miami School of Medicine. He is now working on the application of antagonists of growth hormone-releasing hormone in the therapy of cancer, dyslipidemia, Alzheimer's disease and on the effects of GHRH agonists in cardiology, diabetes and ophthalmology.

Professor Felix Beuschlein

Felix Beuschlein is Professor of Internal Medicine/ Endocrinology and Director of the Clinic for Endocrinology, Diabetology and Clinical Nutrition at the University Clinic Zurich in Switzerland. He serves on several boards including the Annual Meeting Committee of the Endocrine Society and has been the vice president of the German Endocrine Society and the chairman of the Adrenal, Hypertension and Steroid-Section. The scientific interests of Professor Beuschlein mainly relate to adrenal disorders and endocrine tumors. He has authored more than 250 publications in high ranking international journals and has received a number of awards including the European Journal of Endocrinology Prize.

Professor Jay S. Skyler

Jay S. Skyler, MD, MACP is a graduate of Jefferson Medical College. He did postgraduate training at Duke and NIH. He is Professor of Medicine, Pediatrics, and Psychology at the University of Miami, and Deputy Director at the Diabetes Research Institute. For 22 years (1993-2015), he was Study Chairman for the NIH Diabetes Prevention Trial for T1D (DPT-1) and its successor the T1D TrialNet. Professor Skyler was the President of ADA and the Vice-President of IDF. He was founding Editor-in-Chief of Diabetes Care and founding Scientific Editor of the International Diabetes Monitor, and is Senior Editor of Diabetes Technology & Therapeutics.

21 projects with jointly supervised MD and PhD students

High ranking publications

Cross-cultural: 21 students from 12 different countries

Joint PhD in place

Approved funding of € 4.5 m (04/2017 - 09/2021)

Strong academia-industry involvement (Eternygen, MetaCure, beta-O2, GWT)

High visibility and prestige

Student Kick-offs

September 2017 / December 2017
Dresden / London

Start of Funding

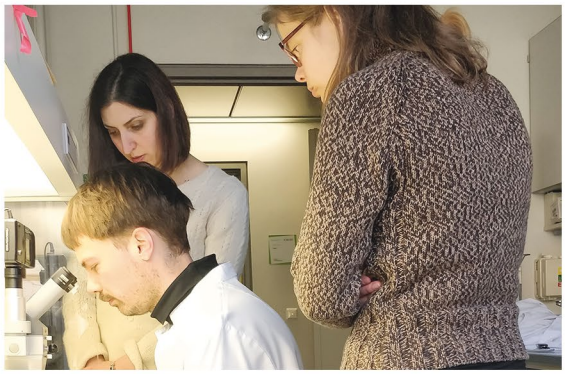
April 2017

May 2017
London

IRTG Kick-off Meeting

First Annual Retreat

February 2018
Dresden



Start of Lab Exchange

February 2018
Dresden / London

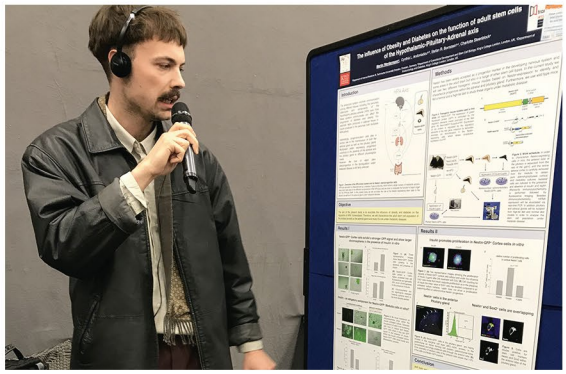
November 2017
Rome

Project Cluster Meeting

March 2018
Bonn

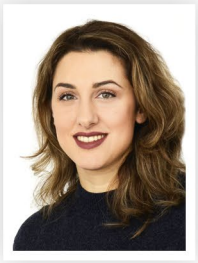
First Poster Presentations

61st German Congress of Endocrinology



Regulation vs activation of immune responses to autoantigens

Type 1 Diabetes (T1D) is characterized by the presence of autoreactive T cells at the site of beta cell destruction. These T cells can also be detected in the circulation. Changes in the number, and, in particular, the phenotype of these cells have become a paradigm for successful therapy to prevent the immune mediated destruction of insulin producing beta cells. We hypothesized that understanding the transcriptional profiles of autoantigen specific T cells at an early stage, before T1D clinical onset, will help to prevent or to halt autoimmunity. Here we apply novel gene and protein expression techniques on the single cell level to characterize T cell signatures and their stability in health and disease. We additionally aim to identify immunomodulators that will help to alter the profile of T cells with known antigen specificity. We test whether the profiles of antigen experienced cells can be selectively changed to finally achieve tolerance to islet antigens. This strategy may contribute to regain tolerance to pancreatic islet antigens in a therapeutic setting or the knowledge could be used to imprint tolerant profiles to islet-directed T cells to establish potent preventive therapies for T1D. 'Can we exploit immunomodulation to tip the balance towards immune tolerance in beta cell autoantigen responsive cells?' is the driving question of this project.



PhD student:
Antigoni Stavridou

Supervisor at TUD:
Ezio Bonifacio

Supervisor at KCL:
Timothy Tree

Start date:
06.07.2017

Presentation of insulin granule derived peptides on Major Histocompatibility Complex I (MHC I) in Entero-virus-infected beta cells and Type 1 Diabetes (T1D)

T1D results from the autoimmune destruction of the insulin producing pancreatic beta cells. Incidence has been rising at a fast rate and several environmental agents, specifically Coxsackievirus B (CVB), have been studied as possible factors for T1D onset and/or progression. Our lab has shown that CVB5 infection decreases the levels of mature secretory granule (SG) proteins such as insulin, ICA512/IA-2, PC1/3, PC2 and CgA, some of which have been identified as targets of autoimmunity in T1D. Our data suggests that mature SG proteins are undergoing intracellular protein degradation, which is the major pathway for the generation of antigen peptides presented on MHC I. We hypothesize that degradation of mature SG proteins during CVB5 infection enhances the presentation of peptides derived from SG components, hence skewing the response of activated autoreactive CD8+ T cells toward these antigens. To test this, we will define the peptide repertoire presented by the T1D MHC I susceptibility allele HLA A*0201 using mass spectrometry in uninfected and infected cells and characterize SG protein peptides for their CD8+ T cell autoreactivity.

PhD student:
Zuzana Marinicova

Supervisor at TUD:
Michele Solimena

Supervisor at KCL:
Mark Peakman

Start date:
04.09.2017

Human alpha cell physiology in the pathogenesis of Type 2 Diabetes

Type 2 Diabetes (T2D) is traditionally attributed to an absolute or relative lack of insulin. However, more than 40 years ago Unger and Orci proposed a role for glucagon in T2D related hyperglycemia. This so-called bihormonal-abnormality hypothesis indicates that both, hypoinsulinemia and aberrant glucagon secretion are involved in the development of diabetes mellitus. While insulin secreting beta cells have been widely investigated, glucagon releasing alpha cells have been neglected. Within this research project, we aim to investigate changes in alpha cell physiology in T2D pathogenesis. To address this matter, particularly in the human setting, in situ studies for the assessment of islet structure and function will be performed, using a novel tissue slicing technique previously established in our research group.

PhD student:
Denise Minerva Drotar

Supervisor at TUD:
Stephan Speier

Supervisor at KCL:
Axel Behrens

Start date:
14.08.2017

Signalling pathways in the conversion of human pluripotent stem (hPS) cells into functional beta cells

Pluripotent stem cells are cells that can develop into all three primary germ cell layers and therefore into all cells of an adult human body. The project will take advantage of novel signalling pathways in endocrine pancreas development identified in our lab to promote the efficient conversion of hPS cells into fully functional beta cells. Their maturation and function will be followed using reporter cell lines that are currently under development. Additionally, we will optimize the expansion of differentiation competent intermediate pancreas endoderm (PE) cells using appropriate signalling molecules. This will reduce the time and cost of the procedure, thus bringing it a step closer to the clinic. Finally, we will test the efficiency of the cells in insulin secretion and their ability to regulate glucose levels in vivo by transplanting them into mice and rats. Micro- and macroencapsulation will be used to protect them from immune attack while allowing the exchange of nutrients, oxygen and hormones with the blood.

PhD student:
Luka Jarc

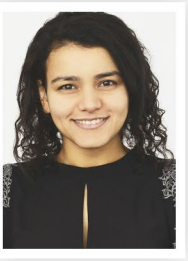
Supervisor at TUD:
Anthony Gavalas

Supervisor at KCL:
Aileen King

Start date:
01.09.2017

Targeting G-protein-coupled receptors to enhance beta cell function

In diabetes, glucose homeostasis can no longer be maintained without therapeutic intervention and lifestyle changes. Currently, most therapeutic strategies address the issue of glucose homeostasis by administering exogenous insulin or increasing the beta cells' capacity to secrete insulin. However, there is still a need for more effective therapies. G-protein coupled receptors (GPCRs) regulate hormone secretion in the pancreas, with more than 300 different receptors expressed in the human islet. However, only one GPCR has managed to reach the clinic. The overarching aim of this project is to identify potential GPCR drug targets for the treatment of diabetes. To that effect, we have already identified a promising candidate, the bile acid receptor TGR5, which significantly lowers glucose levels upon activation. We plan to use the zebrafish, a vertebrate model, to uncover the receptor's role in regulating glucose homeostasis.



PhD student:
Margrit Kamel

Supervisor at TUD:
Nikolay Ninov

Supervisor at KCL:
Shanta Persaud

Start date:
15.04.2017

Small RNA-Seq to reveal islet-miRNA modulation under stress- and transplantation conditions

Replacement of mature beta cells via islet transplantation is a treatment option for T1D, however, the treatment is offered only to selected patients with unstable T1D. Although we can temporarily restore metabolic control in most cases using current replacement strategies, islet loss remains a limiting issue. Unfortunately, so far there is no effective approach to monitor beta cell loss preceding islet graft rejection after human islet transplantation. Circulating biomarkers of early beta cell death, destruction or dysfunction, which are detected before hyperglycemia, may reflect early graft rejection. Such biomarkers would be highly valuable to follow beta cell transplantation success and would allow early intervention. MicroRNAs (miRNAs) belong to a class of small endogenous non-coding RNA molecules (~22 nucelotides). miRNAs play vital roles in regulating mRNA expression and fine-tuning protein levels post-transcriptionally. Substantial evidence has shown that miRNAs may serve as promising therapeutic targets for clinical cancer treatment in the near future. Meanwhile, the potential clinical applications of diagnostic- and prognostic biomarkers are also widely studied and strongly suggest the utility of measuring circulating miRNAs and miRNAs in biopsy tissue in the context of a variety of diseases. We therefore hypothesize that miRNAs could serve as biomarkers to monitor islet destruction after transplantation. Such markers would also provide information on molecular pathways involved in transplantation-induced stress.

PhD student:
Bassam Aljani

Supervisor at TUD:
Ezio Bonifacio, Anne Eugster

Supervisor at KCL:
Pratik Choudhary, Stephanie Amiel

Start date:
01.08.2017

Macroencapsulation of pancreatic islets

Islet transplantation provides a restoring treatment for patients with Type 1 Diabetes mellitus. Major drawbacks of this therapy are the requirement for lifelong immunosuppression and the critical shortage of donor organs, making this therapy only available for selected patients with severe symptoms. Encapsulation technology might provide beta cell replacement therapy to a broader cohort of patients by immunoprotection of the islet graft and the potential use of alternative cell sources. This would eliminate the need for immunosuppressive agents and enlarge the islet donor pool to animal tissue or novel insulin-producing cells. Recent advances in xenotransplantation and encapsulation technology have shown the success of this technology, but multiple issues concerning inflammatory response, nutrient supply, and acceptance of the grafted biomaterial still need to be addressed. Macroencapsulation of pancreatic islet cells grants adequate immunoisolation and has shown successful transplantation results in small and large animal models and a first human trial. The aim of this project is to further improve macroencapsulation technology and prolong optimal islet graft function.

PhD student:
Carolin Heller

Supervisor at TUD:
Barbara Ludwig

Supervisor at KCL:
Peter Jones

Start date:
01.09.2017

Signalling pathways in stem-like cells of the hypothalamic-pituitary-adrenal (HPA) axis during stress and metabolic changes

Response of the endocrine system to stress and metabolic changes is characterised by activation of the HPA axis. However, little is known about the adaptation of the organs of the HPA axis to long-term stress at the cellular level and the involvement of stem-like cells. Therefore, the aim of this project is to characterize stem-like cells of the HPA axis in relation to stress and metabolic changes and to establish the role of key signalling pathways during their differentiation. These processes will be analysed both in vivo and in primary cultures of stem-like cells of the murine HPA axis. Ultimately, revealing how stress and metabolic changes influence progenitor cell differentiation via signalling cascade activation will lead to a better understanding of the pathogenesis of metabolic diseases. Furthermore, our findings will introduce new concepts and therapeutic potential in the field of HPA research.

PhD student:
Ilona Berger

Supervisor at TUD:
Stefan Bornstein, Charlotte Steenblock

Supervisor at KCL:
Cynthia Andoniadou

Start date:
01.02.2018

Inflammation in metabolic organs

Inflammation in metabolic organs, including the liver and the adipose tissue is a major player in mediating obesity-related metabolic dysregulation leading to insulin resistance and associated diseases, such as Type 2 Diabetes or non-alcoholic fatty liver disease (NAFLD). However, the exact mechanisms how inflammation may regulate these processes in the adipose tissue and the liver are poorly understood. In this context, several immune cells have been shown to participate in adipose tissue and liver inflammation, including cells of the innate immunity, such as macrophages or Kupffer cells, as well as cells of the adaptive immunity, such as CD8 T cells and CD4 T cells, including regulatory T cells. These immune cells may also interact with parenchymal cells, such as adipocytes or hepatocytes, as well as other cells in the tissue, for instance, vascular endothelial cells or stellate cells. An important question addressed by the present project is how the interaction between cells of the adaptive and of the innate immunity, as well as between immune and non-immune cells is regulated in the process of metabolic inflammation. In this context, paracrine factors and/or molecules mediating direct intercellular interactions, such as costimulatory molecules or adhesion molecules may play an important role. Such intercellular interactions between immune and non-immune cells in the adipose tissue and/or the liver in the process of obesity-related metabolic inflammation are in the focus of the present project.

PhD student:
Iryna Pyrina

Supervisor at TUD:
Triantafyllos Chavakis

Supervisor at KCL:
Jane Howard

Start date:
01.09.2017

Diverse signalling forms of Shh ligands and their effect on the canonical and non-canonical signalling pathways

The Sonic Hedgehog Shh protein is produced as a precursor protein in the endoplasmic reticulum. It then undergoes a series of post-translational modifications in the secretory pathway generating the protein in two forms. One of them is sterol modified and lipoprotein associated when secreted and the other one is a sterol-free form (Palm et al., 2013) that can be further modified by palmitoylation (Pepinsky et al., 1998). Recently, we demonstrated the production of non-fatty acid N terminal modifications on the Shh ligand (Born et al., in preparation). Building upon these findings, my question is to understand the signalling capabilities of the specific N terminal modifications. To do so, we will use synthesised Shh peptides testing their specific effects throughout the canonical and non canonical shh signalling pathway. With the use of an in-vivo assay using dermal fibroblasts we will investigate the effect of specific N terminal ligand modifications on wound healing. As Shh pathway takes an important part in regulating metabolism.

PhD student:
Salma Ahmed

Supervisor at TUD:
Suzanne Eaton

Supervisor at KCL:
Fiona Watt

Start date:
01.10.2017

Inhibition of INDY (I'm Not Dead Yet) as a novel therapy for Diabetes and non-alcoholic fatty liver disease (NAFLD)

Reducing the expression of INDY gene in lower organisms extends the life span in a manner similar to caloric restriction. INDY is a plasma membrane citrate transporter that regulates several metabolic processes, in particular glucose and lipid metabolism, with highest expression in liver tissue. Hepatic mammalian INDY (mINDY) expression was found to be increased in obese humans and mice with NAFLD. Increased citrate uptake promotes lipogenesis and accumulation, accumulation of DAG with subsequent activation of PKC, causing impaired insulin signalling. Previous studies indicated that inducible and liver selective knock out of mINDY in mice protects from HFD-induced obesity, fatty liver and insulin resistance. Therefore, mINDY transporter has been proposed to be an ideal target for the treatment of metabolic diseases. Recently, small molecule inhibitors of mINDY transporter have been generated and have successfully enhanced insulin sensitivity and reduced both hepatic glucose and lipid production in HFD-induced obese mice. Taken together, studies from mammals and humans suggest that mINDY is an attractive therapeutic target for the treatment of Type 2 Diabetes and NAFLD.

PhD student:
Nermeen Elagroudy

Supervisor at TUD:
Andreas Birkenfeld

Supervisor at KCL:
Geltrude Mingrone

Start Date:
01.09.2017

Lipid-protein interactions as basis for Diabetes remission after bariatric surgery

Clinical remission of Type 2 Diabetes after bariatric surgery coincides with an acute increase in lipolysis and, consequently, in free fatty acids in the human blood serum. We aim at understanding the molecular consequences of acutely increased fatty acids on the remodeling of the cellular lipidome, and its implication in altering insulin receptor signalling. Within this project, we will perform shotgun lipidomics of patient plasma obtained before and after surgery. We will identify fatty acids and lipid species that are significantly altered, which will be then used in cellular models and in vitro membrane systems to study how membrane lipidome remodeling affects cellular signalling, focusing in particular on the lipid-dependent recruitment and activation of AKT, an essential signalling effector protein.

PhD student:
Fatma Betül Can Yakac

Supervisor at TUD:
Stefan Bornstein, Ünal Coskun

Supervisor at KCL:
Francesco Rubino

Start date:
15.10.2017

Discovering hybrid insulin peptide(s) and detecting reactivity by CD8+ T cells in Type 1 Diabetes

It is of vital importance to identify the autoantigens involved in triggering the destruction of insulin-producing beta islet cells by pathogenic T lymphocytes. New antigenic epitopes were established to be a product of preproinsulin peptide fusion that occurs in islet beta cells creating a highly immunogenic post-translational modification species called Hybrid Insulin Peptides (HIPs). Although post-translational modification is a well-known property of antigens in many autoimmune disorders, the identification and characterization of these modified peptides in Type 1 Diabetes is still at its infancy. The project aims to determine whether autoreactive CD8+ T cells that recognize HIPs are present in disease and could potentially be involved in breaking self-tolerance in patients. It seeks to discover and identify these HIPs presented by various high risk HLA Class I molecules and detect the autoreactive CD8+ T Cells in patients at various stages of the disease.

PhD student:
Norkhairin Yusuf

Supervisor at TUD:
Michele Solimena

Supervisor at KCL:
Mark Peakman, Timothy Tree

Start date:
03.10.2016

INDY (I'm Not Dead Yet) as a target for metabolic disease

INDY is a transporter for tri- and dicarboxylates with citrate as a preferential substrate. The electrogenic cotransporter is mainly expressed in the plasma membrane of liver and brain. Trials with INDY-/- mice have shown that loss of INDY leads to an increase of mitochondrial biogenesis, hepatic lipid oxidation and a decrease of de novo lipogenesis. Most importantly, INDY KO mice are protected against diet induced obesity and insulin resistance which goes along with reduced body weight and blood glucose levels. This project investigates whether these positive effects of a whole body knockout of INDY are still present in case of a tissue specific knockout. Therefore, tissue specific knockout mice using the Cre/loxP-System were generated. The research group is now studying the contribution of single tissues to the beneficial phenotype of the INDY KO model. The project is related to IRTG project 11 ("Peripheral mechanisms of diabetes remission after metabolic surgery"), which determines the therapeutic role of INDY inhibitors and bariatric surgery in metabolic disease.

PhD student:
Anica Kurzbach

Supervisor at TUD:
Andreas Birkenfeld

Supervisor at KCL:
Cynthia Andoniadou

Start date:
01.04.2015

The interaction between B cells and other immune cells in Type 1 Diabetes (T1D) pathogenesis

T1D is a chronic autoimmune disorder characterized by T cell mediated destruction of insulin producing beta cells of the pancreatic islets, through the induction of islet reactive CD8+ T cell cytotoxic responses. Interestingly, data have shown the importance of B cells in disease progression; with B cell depletion in mouse models and human studies correlating with disease improvement and increased beta cell function. Autoantibodies specific for islet autoantigens are a biomarker for disease risk and progression, however, no pathogenic function is directly attributed to them. This presents a paradigm that suggests B cells may have an alternative role in disease progression. This project therefore aims to use a multi-disciplinary approach to further investigate the hypothesis that the pathogenic role of B cells in T1D pathogenesis is through cognate interactions with other immune cells involved in the disorder´s pathophysiology.

PhD student:
Emily Hanton

Supervisor at TUD:
Ezio Bonifacio

Supervisor at KCL:
Mark Peakman, Fun Liu

Start date:
01.10.2017

How does low dose Interleukin 2 (IL-2) immunotherapy alter regulatory T cell frequency, phenotype and function?

There is currently great interest in using therapeutic strategies to boost the frequency or functional capacity of regulatory T cells (Tregs) for the treatment and prevention of a wide range of immune based pathologies including autoimmune and neuro-degenerative diseases. Administration of IL-2 is emerging as a potentially powerful therapeutic to achieve this aim but responses have been variable with some patients showing benefit whilst others suffer unwanted off target effects. It has emerged that Tregs are not a homogeneous group of cells but are in fact a complex mixture of functional and developmentally distinct subsets. Furthermore, we have recently shown that there is great inter-individual variation in the sensitivity of Tregs to IL-2 and that this influences Treg frequency and function. We therefore propose that a comprehensive analysis of the effect of IL-2 on its target cell population (Tregs) is required if we are to fully understand responses to therapy and eventually tailor doses or select individuals who may benefit most from this therapy. Analysis of placebo arms will also provide rich data on the natural history of Treg function in the peri-diagnostic period that is currently lacking in both Type 1 Diabetes and Amyotrophic Lateral Sclerosis.

PhD student:
Marius Mickunas

Supervisor at TUD:
Ezio Bonifacio

Supervisor at KCL:
Timothy Tree, Mark Peakman

Start date:
01.04.2017

Modelling Monogenic Diabetes using induced Pluripotent Stem Cells (iPSCs)

Diabetes is characterized by the body's inability to regulate blood glucose levels. Pancreatic beta cells regulate glucose through insulin release. Monogenic Diabetes is a rare type of diabetes caused by gene mutations that make beta cells dysfunctional. During my PhD project, I will be using iPSCs derived from patients with Monogenic Diabetes and healthy donors to understand how specific mutations affect pancreas development. The mechanism of action of the mutants will be investigated in vitro and in vivo. Through further understanding of the heterogeneity of Monogenic Diabetes phenotypes, this project aims to reveal more accurate detection targets and opportunities for personalised treatment.

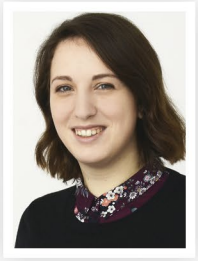
PhD student:
Ana-Maria Cujba

Supervisor at KCL:
Fiona Watt, Rocio Sancho

Start date:
01.10.2016

Stem cell regulation in endocrine glands

The Hypothalamic-Pituitary (HP) axis regulates major physiological processes including metabolism, the body's response to stress, growth and fertility. During physiological demand, feedback from target organs influences the HP axis, promoting adaptation. This project focuses on the impact of physiological stimuli, such as metabolic changes and chronic stress, on the stem cell populations in the HP axis and its target organs. We previously characterised the stem cell compartment of the pituitary gland and demonstrated that pituitary stem cells expressing Sox2 are a long-lived population contributing to cell turnover throughout life. Our preliminary data suggest the presence of uncommitted Sox2 expressing cells in target organs of the pituitary and similarities in their regulation. We are collectively investigating the impact of physiological stimuli on endocrine stem cell populations across the axes, as well as the signalling pathways that control cell fate decisions in response to physiological change.



PhD student:
Alice Santambrogio

Supervisor at TUD:
Stefan Bornstein, Charlotte Steenblock

Supervisor at KCL:
Cynthia Andoniadou

Start date:
01.09.2017

Investigating Insulin Promoter Factor 1 (Pdx1) stability for the generation of functional beta cells from adult progenitors and Induced Pluripotent Stem Cells (iPSCs)

Pdx1 is a major transcription factor required for the embryonic development and the adult neogenesis of beta cells. Pdx1 also plays a crucial role in adult beta cell function and has been linked to diabetes. Potent degradation pathways operate in order to regulate Pdx1 protein stability from embryogenesis until adulthood. Preliminary data from the Sancho lab demonstrate the strong regulation of proendocrine factors in progenitor cells, which makes the reprogramming process inefficient, resulting in dysfunctional beta cells. Understanding these regulatory mechanisms holds the key to explore new opportunities in regenerative medicine for diabetes. The main goal of this project is to delineate the molecular regulation of the proendocrine factor Pdx1 in stem cells, both adult and induced pluripotent. The project will provide insightful information on how to properly control Pdx1 levels, which will subsequently enable us to improve the efficiency of beta cell generation and achieve fully functional beta cells.

PhD student:
Theonie Demcollari

Supervisor at TUD:
Nikolay Ninov

Supervisor at KCL:
Rocio Sancho

Start date:
01.09.2017

The influence of obesity and diabetes on hypothalamic-pituitary-adrenal (HPA) function

This project seeks to study the influence of metabolic diseases on the regulation of hypothalamic, pituitary and adrenal homeostasis in vitro via the addition of leptin and insulin to cultures of adult stem cells. The central working hypothesis is that obesity and diabetes induce proliferation, differentiation and survival of these stem cells. Besides that, the role of adult stem cells under metabolic disease will be examined in vivo in a high-fat diet mouse model. Taken together, these analyses will provide important insight into the influence of obesity and diabetes on HPA function and reveal new strategies for tackling regulation of this axis during disease.

MD student:
Martin Werdermann

Supervisor at TUD:
Stefan Bornstein, Charlotte Steenblock

Supervisor at KCL:
Cynthia Andoniadou

Start date:
01.10.2017

Influence of bariatric surgery on cardiac beta-adrenergic signalling

Bariatric surgery can be a helpful assistance for very obese patients that suffer from the later comorbidities. These surgery techniques have been an effective method not only to induce weight loss but also to remediate Type 2 Diabetes, lipid metabolism, and in particular heart failure. However, the mechanisms leading to improvements in heart failure symptoms of bariatric surgery patients remain mostly unclear. Several recent studies have indicated effects on peripheral catecholamine and natriuretic peptide levels but did not examine direct effects of this signalling molecules on cardiac cells. Therefore, in our project we aim to investigate this possible link between bariatric surgery, the sympathetic nervous systems, and beta-adrenergic signalling in the heart.

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SELECTION OF PUBLICATIONS OF THE IRTG CONSORTIUM SINCE 01/2017

Immunology and Autoimmunity

Allele-specific methylation of type 1 diabetes susceptibility genes.
Kindt ASD, Fuerst RW, Knoop J, Laimighofer M, Telieps T, Hippich M, Woerheide MA, Wahl S, Wilson R, Sedlmeier EM, Hommel A, Todd JA, Krumsiek J, Ziegler AG, Bonifacio E.
Journal of Autoimmunity. 2018 May;89:63-74.

Genetic scores to stratify risk of developing multiple islet autoantibodies and type 1 diabetes: A prospective study in children.
Bonifacio E, Beyerlein A, Hippich M, Winkler C, Vehik K, Weedon MN, Laimighofer M, Hattersley AT, Krumsiek J, Frohnert BI, Steck AK, Hagopian WA, Krischer JP, Lernmark A, Rewers MJ, She J-X, Toppari J, Akolkar B, Oram RA, Rich SS, Ziegler A-G.
PLoS Medicine. 2018 Apr 3;15(4):e1002548.

Molecular Pathways for Immune Recognition of Preproinsulin Signal Peptide in Type 1 Diabetes.
Kronenberg-Versteeg D, Eichmann M, Russell MA, de Ru A, Hehn B, Yusuf N, van Veelen PA, Richardson SJ, Morgan NG, Lemberg MK, Peakman M.
Diabetes. 2018 Apr;67(4):687-696.

CD8+ T cells in beige adipogenesis and energy homeostasis.
Moysidou M, Karaliota S, Kodela E, Salagianni M, Koutmani Y, Katsouda A, Kodella K, Tsakanikas P, Ourailidou S, Andreakos E, Kostomitsopoulos N, Skokos D, Chatzigeorgiou A, Chung KJ, Bornstein S, Sleeman MW, Chavakis T, Karalis KP.
JCI Insight. 2018 Mar 8;3(5).

GM-CSF producing autoreactive CD4(+) T cells in type 1 diabetes.
Knoop J, Gavrisan A, Kuehn D, Reinhardt J, Heinrich M, Hippich M, Eugster A, Ockert C, Ziegler AG, Bonifacio E.
Clinical Immunology. 2018 Mar;188:23-30.

Peptide Immunotherapy for Type 1 Diabetes-Clinical Advances.
Smith EL, and Peakman M.
Frontiers in Immunology. 2018 Feb 28;9:392.

Islet-reactive CD8+ T cell frequencies in the pancreas, but not in blood, distinguish type 1 diabetic patients from healthy donors.
Culina S, Lalanne AI, Afonso G, Cerosaletti K, Pinto S, Sebastiani G, Kuranda K, Nigi L, Eugster A, Østerbye T, Maugein A, McLaren JE, Ladell K, Larger E, Beressi JP, Lissina A, Appay V, Davidson HW, Buus S, Price DA, Kuhn M, Bonifacio E, Battaglia M, Caillat-Zucman S, Dotta F, Scharfmann R, Kyewski B, Mallone R; ImMaDiab Study Group, Carel JC, Tubiana-Rufi N, Martinerie L, Poidvin A, JacqzAigrain E, Corvez L, Berruer V, Gautier JF, Baz B, Haddadi N, Andreelli F, Amouyal C, Jaqueminet S, Bourron O, Dasque E, Hartemann A, Lemoine-Yazigi A, Dubois-Laforgue D, Travert F, Feron M, Rolland P, Vignali V, Marre M, Chanson P, Briet C, Guillausseau PJ, Ait-Bachir L, Collet C, Beziaud F, Desforges-Bullet V, Petit-Aubert G, Christin-Maitre S, Fève B, Vatier C, Bourcigaux N, Lautridou C, Lahlou N, Bakouboula P, Elie C, Morel H, Treluyer JM, Gagnerault MC, Maillard C, Jones A.
Science Immunology. 2018 Feb 2;3(20).

Modulation of Myelopoiesis Progenitors Is an Integral Component of Trained Immunity.
Mitroulis I, Ruppova K, Wang B, Chen LS, Grzybek M, Grinenko T, Eugster A, Troullinaki M, Palladini A, Kourtzelis I, Chatzigeorgiou A, Schlitzer A, Beyer M, Joosten LAB, Isermann B, Lesche M, Petzold A, Simons K, Henry I, Dahl A, Schultze JL, Wielockx B, Zamboni N, Mirtschink P, Coskun Ü, Hajishengallis G, Netea MG, Chavakis T.
Cell. 2018 Jan 11;172(1-2):147-161.e12.

Mast cells acquire MHCII from dendritic cells during skin inflammation.
Dudeck J, Medyukhina A, Frobel J, Svensson CM, Kotrba J, Gerlach M, Gradtke AC, Schroder B, Speier S, Figge MT, Dudeck A.
Journal of Experimental Medicine. 2017 Dec 4;214:3791-3811.

T cell receptor β-chains display abnormal shortening and repertoire sharing in type 1 diabetes.
Gomez-Tourino I, Kamra Y, Baptista R, Lorenc A, Peakman M.
Nature Communications. 2017 Nov 27;8(1):1792.

New insights into non-conventional epitopes as T cell targets: The missing link for breaking immune tolerance in autoimmune disease?
Harbige J, Eichmann M, and Peakman M.
Journal of Autoimmunity. 2017 Nov;84(12-20).

An analysis of IL-36 signature genes and individuals with IL1RL2 knockout mutations validates IL-36 as a psoriasis therapeutic target.
Mahil SK, Catapano M, Di Meglio P, Dand N, Ahlfors H, Carr IM, Smith CH, Trembath RC, Peakman M, Wright J, Ciccarelli FD, Barker JN, Capon F.
Science Translational Medicine. 2017 Oct 11;9(411).

Regulatory T cell dysfunction in type 1 diabetes: what's broken and how can we fix it?
Hull CM, Peakman M, Tree TIM.
Diabetologia. 2017 Oct;60(10):1839-1850.

Persistence of Pancreatic Insulin mRNA Expression and Proinsulin Protein in Type 1 Diabetes Pancreata.
Wasserfall C, Nick HS, Campbell-Thompson M, Beachy D, Haataja L, Kusmartseva I, Posgai A, Beery M, Rhodes C, Bonifacio E, Arvan P, Atkinson M.
Cell Metabolism. 2017 Sep 5;26(3):568-575.e3.

Metabolic and immune effects of immunotherapy with proinsulin peptide in human new-onset type 1 diabetes.
Alhadj Ali M, Liu YF, Arif S, Tatovic D, Shariff H, Gibson VB, Yusuf N, Baptista R, Eichmann M, Petrov N, Heck S, Yang JHM, Tree TIM, Pujol-Autonell I, Yeo L, Baumard LR, Stenson R, Howell A, Clark A, Boult Z, Powrie J, Adams L, Wong FS, Luzio S, Dunseath G, Green K, O'Keefe A, Bayly G, Thorogood N, Andrews R, Leech N, Joseph F, Nair S, Seal S, Cheung H, Beam C, Hills R, Peakman M, Dayan CM.
Science Translational Medicine. 2017 Aug 9;9(402).

CD8(+) T cells specific for the islet autoantigen IGRP are restricted in their T cell receptor chain usage.
Fuchs YF, Eugster A, Dietz S, Sebelefsky C, Kühn D, Wilhelm C, Lindner A, Gavrisan A, Knoop J, Dahl A, Ziegler AG, Bonifacio E.
Scientific Reports. 2017 Mar 16;7:44661.

A divergent population of autoantigen-responsive CD4(+) T cells in infants prior to β cell autoimmunity.
Heninger AK, Eugster A, Kuehn D, Buettner F, Kuhn M, Lindner A, Dietz S, Jergens S, Wilhelm C, Beyerlein A, Ziegler AG, Bonifacio E.
Science Translational Medicine. 2017 Feb 22;9(378).

Islets and Islet Transplantation

The RNA-binding protein PTBP1 is necessary for B cell selection in germinal centers.
Monzón-Casanova E, Screen M, Díaz-Muñoz MD, Coulson RMR, Bell SE, Lamers G, Solimena M, Smith CWJ, Turner M.
Nature Immunology. 2018 Mar;19(3):267-278.

Systems biology of the IMIDIA biobank from organ donors and pancreatectomised patients defines a novel transcriptomic signature of islets from individuals with type 2 diabetes.
Solimena M, Schulte AM, Marselli L, Ehehalt F, Richter D, Kleeberg M, Mziaut H, Knoch KP, Parnis J, Bugliani M, Siddiq A, Jörns A, Burdet F, Liechti R, Suleiman M, Margerie D, Syed F, Distler M, Grützmann R, Petretto E, Moreno-Moral A, Wegbrod C, Sönmez A, Pfriem K, Friedrich A, Meinel J, Wollheim CB, Baretton GB, Scharfmann R, Nogoceke E, Bonifacio E, Sturm D, Meyer-Puttlitz B, Boggi U, Saeger HD, Filipponi F, Lesche M, Meda P, Dahl A, Wigger L, Xenarios I, Falchi M, Thorens B, Weitz J, Bokvist K, Lenzen S, Rutter GA, Froguel P, von Bülow M, Ibberson M, Marchetti P.
Diabetologia. 2018 Mar;61(3):641-657.

Mouse pancreatic islet macrophages use locally released ATP to monitor beta cell activity.
Weitz JR, Makhmutova M, Almaca J, Stertmann J, Aamodt K, Brissova M, Speier S, Rodriguez-Diaz R, Caicedo A.
Diabetologia. 2018 Jan;61:182-192.

Wnt/β-catenin signaling controls intrahepatic biliary network formation in zebrafish by regulating Notch activity
So J, Khaliq M, Evason K, Ninov N, Martin BL, Stainier DYR, Shin D.
Hepatology. 2017 Dec 21. [Epub ahead of print]

SELECTION OF PUBLICATIONS OF THE IRTG CONSORTIUM SINCE 01/2017

Dynamic Profiling of Insulin Secretion and ATP Generation in Isolated Human and Mouse Islets Reveals Differential Glucose Sensitivity.
Pingitore A, Ruz-Maldonado I, Liu B, Huang GC, Choudhary P, Persaud SJ.
Cellular Physiology and Biochemistry. 2017 Dec;44(4):1352-1359.

Mesenchymal stromal cells improve human islet function through released products and extracellular matrix.
Arzouni AA, Vargas-Seymour A, Rackham CL, Dhadda P, Huang GC, Choudhary P, Nardi N, King AJF, Jones PM.
Clinical Science (Lond). 2017 Nov 28;131(23):2835-2845.

Favorable outcome of experimental islet xenotransplantation without immunosuppression in a nonhuman primate model of diabetes.
Ludwig B, Ludwig S, Steffen A, Knauf Y, Zimerman B, Heinke S, Lehmann S, Schubert U, Schmid J, Bleyer M, Schönmann U, Colton CK, Bonifacio E, Solimena M, Reichel A, Schally AV, Rotem A, Barkai U, Grinberg-Rashi H, Kaup FJ, Avni Y, Jones P, Bornstein SR.
Proceedings of the National Academy of Sciences, USA. 2017 Oct 31;114(44):11745-11750.

Different developmental histories of beta-cells generate functional and proliferative heterogeneity during islet growth.
Singh SP, Janjuha S, Hartmann T, Kayisoglu Ö, Konantz J, Birke S, Murawala P, Alfar EA, Murata K, Eugster A, Tsuji N, Morrissey ER, Brand M, Ninov N.
Nature Communications. 2017 Sep 22;8(1):664.

A 4D view on insulin secretory granule turnover in the β-cell.
Müller A, Mziaut H, Neukam M, Knoch KP, Solimena M.
Diabetes, Obesity & Metabolism. 2017 Sep;19 Suppl 1:107-114.

Human beta cell mass and function in diabetes: Recent advances in knowledge and technologies to understand disease pathogenesis.
Chen C, Cohrs CM, Stertmann J, Bozsak R, Speier S.
Molecular Metabolism. 2017 Jul;6:943-957.

INS-eGFP transgenic pigs: a novel reporter system for studying maturation, growth and vascularisation of neonatal islet-like cell clusters.
Kemter E, Cohrs CM, Schafer M, Schuster M, Steinmeyer K, Wolf-van Buerck L, Wolf A, Wuensch A, Kurome M, Kessler B, Zakhartchenko V, Loehn M, Ivashchenko Y, Seissler J, Schulte AM, Speier S, Wolf E. Diabetologia. 2017 Jun;60:1152-1156.

Vessel Network Architecture of Adult Human Islets Promotes Distinct Cell-Cell Interactions In Situ and Is Altered After Transplantation.
Cohrs CM, Chen C, Jahn SR, Stertmann J, Chmelova H, Weitz J, Bähr A, Klymiuk N, Steffen A, Ludwig B, Kamvissi V, Wolf E, Bornstein SR, Solimena M, Speier S.
Endocrinology. 2017 May 1;158(5):1373-1385.

A comparative analysis of human and mouse islet G-protein coupled receptor expression.
Amisten S, Atanes P, Hawkes R, Ruz-Maldonado I, Liu B, Parandeh F, Zhao M, Huang GC, Salehi A, Persaud SJ.
Scientific Reports. 2017 Apr 19;7:46600.

Decreased STARD10 Expression Is Associated with Defective Insulin Secretion in Humans and Mice.
Carrat GR, Hu M, Nguyen-Tu MS, Chabosseau P, Gaulton KJ, van de Bunt M, Siddiq A, Falchi M, Thurner M, Canouil M, Pattou F, Leclerc I, Pullen TJ, Cane MC, Prabhala P, Greenwald W, Schulte A, Marchetti P, Ibberson M, MacDonald PE, Manning Fox JE, Gloyn AL, Froquel P, Solimena M, McCarthy MI, Rutter GA.
American Journal of Human Genetics. 2017 Feb 2;100(2):238-256.

A Global Approach for Quantitative Super Resolution and Electron Microscopy on Cryo and Epoxy Sections Using Self-labeling Protein Tags.
Müller A, Neukam M, Ivanova A, Sönmez A, Münster C, Kretschmar S, Kalaidzidis Y, Kurth T, Verbavatz JM, Solimena M.
Scientific Reports. 2017 Feb 2;7(1):23.

Diabetes in rats is cured by islet transplantation…but only during daytime.
King AJF, Austin ALF, Nandi M, Bowe JE.
Cell Transplant. 2017 Jan 24;26(1):171-172.

Metabolic Surgery and Lipidomics

Incidence of hypoglycemia after Gastric Bypass versus Sleeve Gastrectomy: a Randomized Trial.
Capristo E, Panunzi S, De Gaetano A, Spuntarelli V, Bellantone R, Giustacchini P, Birkenfeld AL, Amiel S, Bornstein SR, Raffaelli M, Mingrone G.
Journal of Clinical Endocrinology and Metabolism. 2018 Mar 23. [Epub ahead of print]

Metabolic surgery for the treatment of type 2 diabetes in obese individuals.
Cummings DE, Rubino F.
Diabetologia. 2018 Feb;61(2):257-264.

Metabolic Surgery: Weight Loss, Diabetes, and Beyond.
Pareek M, Schauer PR, Kaplan LK, Leiter LA, Rubino F, Bhatt DL.
Journal of the American College of Cardiology. 2018 Feb; 71, (6,):80–97.

Optimisation of follow-up after metabolic surgery.
Mingrone G, Bornstein SR, Le Roux CW.
Lancet Diabetes and Endocrinology. 2018 Jan 29. [Epub ahead of print]

Intensive lifestyle modifications with or without liraglutide 3mg vs sleeve gastrectomy: A three-arm non-randomised, controlled, pilot study.
Capristo E, Panunzi S, De Gaetano A, Raffaelli M, Guidone C, Iaconelli A, L'Abbate L, Birkenfeld AL, Bellantone R, Bornstein SR, Mingrone G.
Diabetes and Metabolism. 2017 Dec 29. [Epub ahead of print]

Roux-en-Y Gastric Bypass Surgery in the Management of Familial Partial Lipodystrophy Type 1.
Melvin A, Adams C, Flanagan C, Gaff L, Gratton B, Gribble F, Roberts G, Semple RK, O'Rahilly S, Rubino F, Stears A, Savage DB.
Journal of Clinical Endocrinology and Metabolism. 2017 Oct 1;102(10):3616-3620.

Spatiotemporal Control of Lipid Conversion, Actin-Based Mechanical Forces, and Curvature Sensors during Clathrin/AP-1-Coated Vesicle Biogenesis.
Anitei M, Stange C, Czupalla C, Niehage C, Schuhmann K, Sala P, Czogalla A, Pursche T, Coskun Ü, Shevchenko A, Hoflack B.
Cell Reports. 2017 Aug 29;20(9):2087-2099.

The human longevity gene homolog INDY and interleukin-6 interact in hepatic lipid metabolism.
von Loeffelholz C, Lieske S, Neuschäfer-Rube F, Willmes DM, Raschzok N, Sauer IM, König J, Fromm MF, Horn P, Chatzigeorgiou A, Pathe-Neuschäfer-Rube A, Jordan J, Pfeiffer AFH, Mingrone G, Bornstein SR, Stroehle P, Harms C, Wunderlich FT, Helfand SL, Bernier M, de Cabo R, Shulman GI, Chavakis T, Püschel GP, Birkenfeld AL.
Hepatology. 2017 Aug;66(2):616-630.

Surgery: Metabolic surgery: The cutting edge of diabetes care.
Rubino F, Panagiotopoulos.
Nature reviews. Gastroenterology & Hepatology. 2017 Jul;14(7):389-390.

Key steps in unconventional secretion of fibroblast growth factor 2 reconstituted with purified components.
Steringer JP, Lange S, Čujová S, Šachl R, Poojari C, Lolicato F, Beutel O, Müller HM, Unger S, Coskun Ü, Honigmann A, Vattulainen I, Hof M, Freund C, Nickel W.
eLife. 2017 Jul 19;6.

Urinary Lipidomics: evidence for multiple sources and sexual dimorphism in healthy individuals.
Graessler J, Mehnert CS, Schulte KM, Bergmann S, Strauss S, Bornstein TD, Licinio J, Wong ML, Birkenfeld AL, Bornstein SR.
The Pharmacogenomics Journal. 2017 Jun 13. [Epub ahead of print]

Calcium Directly Regulates Phosphatidylinositol 4,5-Bisphosphate Headgroup Conformation and Recognition.
Bilkova E, Pleskot R, Rissanen S, Sun S, Czogalla A, Cwiklik L, Róg T, Vattulainen I, Cremer PS, Jungwirth P, Coskun Ü.
Journal of the American Chemical Society. 2017 Mar 22;139(11):4019-4024.

The utility of weight loss medications after bariatric surgery for weight regain or inadequate weight loss: A multi-center study.
Stanford FC, Alfaris N, Gomez G, Ricks ET, Shukla AP, Corey KE, Pratt JS, Pomp A, Rubino F, Aronne LJ.
Surgery for Obesity and Related Diseases. 2017 Mar;13(3):491-500.

SELECTION OF PUBLICATIONS OF THE IRTG CONSORTIUM SINCE 01/2017

Diabetic Complications and Endocrinology

The Missed Notch to Bring Down Diabetes.
Mirtschink P, Chavakis T.
Trends in Endocrinology and Metabolism. 2018 Mar 29. [Epub ahead of print]

Basal Insulin Regimens for Adults with Type 1 Diabetes Mellitus: A Systematic Review and Network Meta-Analysis.
Dawoud D, O'Mahony R, Wonderling D, Cobb J, Higgins B, Amiel SA.
Value in Health. 2018 Feb;21(2):176-184.

Visualization of ligand-induced transmembrane signaling in the full-length human insulin receptor.
Gutmann T, Kim KH, Grzybek M, Walz T, Coskun Ü.
The Journal of Cell Biology. 2018 Feb 16. [Epub ahead of print]

A proteolytic fragment of histone deacetylase 4 protects the heart from failure by regulating the hexosamine biosynthetic pathway.
Lehmann LH, Jebessa ZH, Kreusser MM, Horsch A, He T, Kronlage M, Dewenter M, Sramek V, Oehl U, Krebs-Haupenthal J, von der Lieth AH, Schmidt A, Sun Q, Ritterhoff J, Finke D, Völkers M, Jungmann A, Sauer SW, Thiel C, Nickel A, Kohlhaas M, Schäfer M, Sticht C, Maack C, Gretz N, Wagner M, El-Armouche A, Maier LS, Londoño JEC, Meder B, Freichel M, Gröne HJ, Most P, Müller OJ, Herzig S, Furlong EEM, Katus HA, Backs J.
Nature Medicine. 2018 Jan;24(1):62-72.

Countering posttraumatic LHPA activation in refugee mothers and their infants.
Ullmann E, Bornstein SR, Lanzman RS, Kirschbaum C, Sierau S, Doehnert M, Zimmermann P, Kindler H, Schauer M, Ruf-Leuschner M, Fegert JM, von Klitzing K, Ziegenhain U.
Molecular Psychiatry. 2018 Jan;23(1):2-5.

International Consensus on Use of Continuous Glucose Monitoring.
Danne T, Nimri R, Battelino T, Bergenstal RM, Close KL, DeVries JH, Garg S, Heinemann L, Hirsch I, Amiel SA, Beck R, Bosi E, Buckingham B, Cobelli C, Dassau E, Doyle FJ 3rd, Heller S, Hovorka R, Jia W, Jones T, Kordonouri O, Kovatchev B, Kowalski A, Laffel L, Maahs D, Murphy HR, Nørgaard K, Parkin CG, Renard E, Saboo B, Scharf M, Tamborlane WV, Weinzimer SA, Phillip M.
Diabetes Care. 2017 Dec;40(12):1631-1640.

Stem cell senescence drives age-attenuated induction of pituitary tumours in mouse models of paediatric craniopharyngioma.
Mario Gonzalez-Meljem J, Haston S, Carreno G, Apps JR, Pozzi S, Stache C1, Kaushal G, Virasami A, Panousopoulos L, Neda Mousavy-Gharavy S, Guerrero A, Rashid M, Jani N, Goding CR, Jacques TS, Adams DJ, Gil J, Andoniadou CL, Martinez-Barbera JP.
Nature Communications. 2017 Nov 28;8(1):1819.

Downregulation of Insulin Sensitivity After Oral Glucose Administration: Evidence for the Anti-Incretin Effect.
Salinari S, Mingrone G, Bertuzzi A, Previti E, Capristo E, Rubino F.
Diabetes. 2017 Nov;66(11):2756-2763.

Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): A multicentre international randomised controlled trial.
Feig DS, Donovan LE, Corcoy R, Murphy KE, Amiel SA, Hunt KF, Asztalos E, Barrett JFR, Sanchez JJ, de Leiva A, Hod M, Jovanovic L, Keely E, McManus R, Hutton EK, Meek CL, Stewart ZA, Wysocki T, O'Brien R, Ruedy K, Kollman C, Tomlinson G, Murphy HR; CONCEPTT Collaborative Group.
Lancet. 2017 Nov 25;390(10110):2347-2359.

Two missense mutations in KCNQ1 cause pituitary hormone deficiency and maternally inherited gingival fibromatosis.
Tommiska J, Känsäkoski J, Skibsbye L, Vaaralahti K, Liu X, Lodge EJ, Tang C, Yuan L, Fagerholm R, Kanters JK, Lahermo P, Kaunisto M, Keski-Filppula R, Vuoristo S, Pulli K, Ebeling T, Valanne L, Sankila EM, Kivirikko S, Lääperi M, Casoni F, Giacobini P, Phan-Hug F, Buki T, Tena-Sempere M, Pitteloud N, Veijola R, Lipsanen-Nyman M, Kaunisto K, Mollard P, Andoniadou CL, Hirsch JA, Varjosalo M, Jespersen T, Raivio T.
Nature communications. 2017 Nov 3;8(1):1289.

Proportion of daily capillary blood glucose readings required in the target range for target glycaemic control: shift of focus from target range to proportion in range.
Sivasubramaniyam S, Amiel SA, Choudhary P.
Diabetic Medicine. 2017 Oct;34(10):1456-1460.

DHEA inhibits acute microglia-mediated inflammation through activation of the TrkA-Akt1/2-CREB-Jmjd3 pathway.
Alexaki VI, Fodelianaki G, Neuwirth A, Mund C, Kourgiantaki A, Ieronimaki E, Lyroni K, Troullinaki M, Fujii C, Kanczkowski W, Ziogas A, Peitzsch M, Grossklaus S, Sönnichsen B, Gravanis A, Bornstein SR, Charalampopoulos I, Tsatsanis C, Chavakis T.
Molecular Psychiatry. 2017 Sep 12. [Epub ahead of print]

Retinol saturase coordinates liver metabolism by regulating ChREBP activity.
Heidenreich S, Witte N, Weber P, Goehring I, Tolkachov A, von Loeffelholz C, Döcke S, Bauer M, Stockmann M, Pfeiffer AFH, Birkenfeld AL, Pietzke M, Kempa S, Muenzner M, Schupp M.
Nature Communications. 2017 Aug 30;8(1):384.

Regulation of body weight and energy homeostasis by neuronal cell adhesion molecule 1.
Rathjen T, Yan X, Kononenko NL, Ku MC, Song K, Ferrarese L, Tarallo V, Puchkov D, Kochlamazashvili G, Brachs S, Varela L, Szigeti-Buck K, Yi CX, Schriever SC, Tattikota SG, Carlo AS, Moroni M, Siemens J, Heuser A, van der Weyden L, Birkenfeld AL, Niendorf T, Poulet JFA, Horvath TL, Tschöp MH, Heinig M, Trajkovski M, Haucke V, Poy MN1.
Nature Neuroscience. 2017 Aug;20(8):1096-1103.

Pancreas lineage allocation and specification are regulated by sphingosine-1-phosphate signalling.
Serafimidis I, Rodriguez-Aznar E, Lesche M, Yoshioka K, Takuwa Y, Dahl A, Pan D, Gavalas A.
PLoS Biol. 2017 Mar 1;15(3):e2000949.

Stress-Activated Kinase Mitogen-Activated Kinase Kinase-7 Governs Epigenetics of Cardiac Repolarization for Arrhythmia Prevention.
Chowdhury SK, Liu W, Zi M, Li Y, Wang S, Tsui H, Prehar S, Castro S, Zhang H, Ji Y, Zhang X, Xiao R, Zhang R, Lei M, Cyganek L, Guan K, Millar CB, Liao X, Jain MK, Boyett MR, Cartwright EJ, Shiels HA, Wang X.
Circulation. 2017 Feb; 135:683-699.

A-FABP mediates adaptive thermogenesis by promoting intracellular activation of thyroid hormones in brown adipocytes.
Shu L, Hoo RL, Wu X, Pan Y, Lee IP, Cheong LY, Bornstein SR, Rong X, Guo J, Xu A.
Nature Communication. 2017 Jan 27;8:14147.

Rebranding asymptomatic type 1 diabetes: the case for autoimmune beta cell disorder as a pathological and diagnostic entity.
Bonifacio E, Mathieu C, Nepom GT, Ziegler AG, Anhalt H, Haller MJ, Harrison LC, Hebrok M, Kushner JA, Norris JM, Peakman M, Powers AC, Todd JA, Atkinson MA.
Diabetologia. 2017 Jan;60(1):35-38.

Glucose Concentrations of Less Than 3.0 mmol/L (54 mg/dL) Should Be Reported in Clinical Trials: A Joint Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes.
Amiel SA, Aschner P, Childs B, Cryer PE, de Galan BE, Heller SR, Frier BM, Gonder-Frederick L, Jones T, Khunti K, Leiter LA, McCrimmon RJ, Luo Y, People's Hospital, Beijing, China, Seaquist ER, Vigersky R, Zoungas S (International Hypoglycaemia Study Group.)
Diabetes Care. 2017 Jan; 40(1): 155-157 and Diabetologia. 2017; 60:3–6.

SELECTION OF PUBLICATIONS OF THE IRTG CONSORTIUM SINCE 01/2017

Stem Cells and Cell Differentiation

The deubiquitinase USP9X regulates FBW7 stability and suppresses colorectal cancer.
Khan OM, Carvalho J, Spencer-Dene B, Mitter R, Frith D, Snijders AP, Wood SA, Behrens A.
Journal of Clinical Investigation. 2018 Apr 2;128(4):1326-1337.

Expression of progenitor markers is associated with the functionality of a bioartificial adrenal cortex.
Balyura M, Gelfgat E, Steenblock C, Androutsellis-Theotokis A, Ruiz-Babot G, Guasti L, Werdermann M, Ludwig B, Bornstein T, Schally AV, Brennand A, Bornstein SR.
PLoS One. 2018 Mar 29;13(3):e0194643.

Hypertensive crisis in pregnancy due to a metamorphosing pheochromocytoma with postdelivery Cushing's syndrome.
Langton K, Gruber M, Masjkur J, Steenblock C, Peitzsch M, Meinel J, Lenders J, Bornstein S, Eisenhofer G.
Gynecological Endocrinoly. 2018 Jan;34(1):20-24.

Epidermal Wnt signalling regulates transcriptome heterogeneity and proliferative fate in neighbouring cells.
Ghahramani A, Donati G, Luscombe NM, Watt FM.
Genome Biology. 2018 Jan 15;19(1):3.

Fibroblast heterogeneity: implications for human disease.
Lynch MD, Watt FM.
The Journal of Clinical Investigation. 2018 Jan 2;128(1):26-35.

Modeling Congenital Adrenal Hyperplasia and Testing Interventions for Adrenal Insufficiency Using Donor-Specific Reprogrammed Cells.
Ruiz-Babot G, Balyura M, Hadjidemetriou I, Ajodha SJ, Taylor DR, Ghataore L, Taylor NF, Schubert U, Ziegler CG, Storr HL, Druce MR, Gevers EF, Drake WM, Srirangalingam U, Conway GS, King PJ, Metherell LA, Bornstein SR, Guasti L.
Cell Reports. 2018 Jan 30;22(5):1236-1249.

Phenotypic plasticity in the pancreas: new triggers, new players: Cell Differentiation and DevelopmentCell Differentiation and Development.
Demcollari TI, Cujba AM, Sancho R.
Current Opinion in Cell Biology. 2017 Dec;49:38-46.

Apoptosis in mesenchymal stromal cells induces in vivo recipient-mediated immunomodulation.
Galleu A, Riffo-Vasquez Y, Trento C, Lomas C, Dolcetti L, Cheung TS, von Bonin M, Barbieri L, Halai K, Ward S, Weng L, Chakraverty R, Lombardi G, Watt FM, Orchard K, Marks DI, Apperley J, Bornhauser M, Walczak H, Bennett C, Dazzi F.
Science Translational Medicine. 2017 Nov 15;9(416).

Spatial constraints govern competition of mutant clones in human epidermis.
Lynch MD, Lynch CNS, Craythorne E, Liakath-Ali K, Mallipeddi R, Barker JN, Watt FM.
Nature Communications. 2017 Oct 24;8(1):1119.

Duct and acinar-derived pancreatic ductal adenocarcinomas in mice show distinct tumor progression and marker expression
Ferreira RMM, Sancho R, Messal HA, Nye E, Spencer-Dene B, Stone RK, Stamp G, Rosewell I, Quaglia A, Behrens A.
Cell Reports. 2017 Oct 24, 21(4):966-978.

A protein phosphatase network controls the temporal and spatial dynamics of differentiation commitment in human epidermis.
Mishra A, Oulès B, Pisco AO, Ly T, Liakath-Ali K, Walko G, Viswanathan P, Tihy M, Nijjher J, Dunn SJ, Lamond AI, Watt FM.
eLife. 2017 Oct 18;6.

Common genetic variation drives molecular heterogeneity in human iPSCs.
Kilpinen H, Goncalves A, Leha A, Afzal V, Alasoo K, Ashford S, Bala S, Bensaddek D, Casale FP, Culley OJ, Danecek P, Faulconbridge A, Harrison PW, Kathuria A, McCarthy D, McCarthy SA, Meleckyte R, Memari Y, Moens N, Soares F, Mann A, Streeter I, Agu CA, Alderton A, Nelson R, Harper S, Patel M, White A, Patel SR, Clarke L, Halai R, Kirton CM, Kolb-Kokocinski A, Beales P, Birney E, Danovi D, Lamond AI, Ouwehand WH, Vallier L, Watt FM, Durbin R, Stegle O, Gaffney DJ.
Nature. 2017 Jun 15;546(7658):370-375.

Wounding induces dedifferentiation of epidermal Gata6+ cells and acquisition of stem cell properties.
Donati G, Rognoni E, Hiratsuka T, Liakath-Ali K, Hoste E, Kar G, Kayikci M, Russell R, Kretzschmar K, Mulder KW, Teichmann SA, Watt FM.
Nature Cell Biology. 2017 Jun;19(6):603-613.

G reprogramming of liver cells to a pancreas progenitor state by the transcriptional regulator Tgif2.
Cerdá-Esteban N, Naumann H Ruzittu S, Mah N, Pongrac IM, Cozzitorto C, Hommel A, Andrade-Navarro MA, Bonifacio E, Spagnoli FM.
Nature Communications. 2017 Feb 13;8:14127.

Adrenal cortical and chromaffin stem cells: Is there a common progeny related to stress adaptation?
Steenblock C, Rubin de Celis MF, Androutsellis-Theotokis A, Sue M, Delgadillo Silva LF, Eisenhofer G, Andoniadou CL, Bornstein SR.
Molecular and Cellular Endocrinology. 2017 Feb 5;441:156-163.

Global Approach for Quantitative Super Resolution and Electron Microscopy on Cryo and Epoxy Sections Using Self-labeling Protein Tags.
Müller A, Neukam M, Ivanova A, Sönmez A, Münster C, Kretschmar S, Kalaidzidis Y, Kurth T, Verbavatz JM, Solimena MA.
Scientific Reports. 2017 Feb 2;7(1):23.

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