IRTG 2251: ICSMD Kick-off Meeting

King's College London
4th of May, 2017

Summary of Talks

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

TECHNISCHE UNIVERSITÄT DRESDEN

KING'S College LONDON

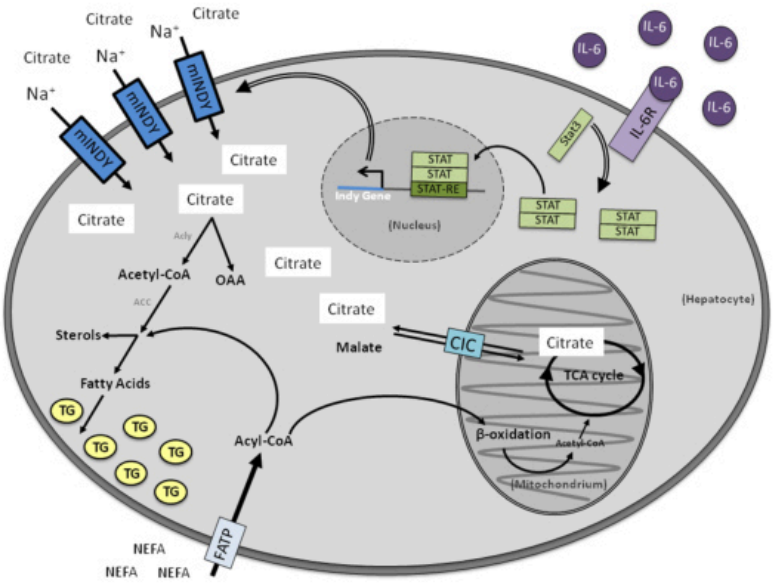
Following the official announcement of the German Research Foundation (DFG), the newly established **trans**Campus International Research Training Group 2251 "Immunological and Cellular Strategies in Metabolic Disease" (ICSMD) has started with its first kick-off meeting in London on 4th May 2017. After a warm welcome by the new interim Vice-Dean International at the Faculty of Lice Sciences and Medicine at King's College London, Dr. Richard Siow, the speakers and PIs of the IRTG presented their projects to the auditorium, followed by very productive discussions. While the first few students already had the chance to participate in this event, the official inauguration of the IRTG students will take place in September with the start of the Dresden International PhD Programme (DIPP).

Andreas Birkenfeld

Inhibition of INDY as a novel therapy for diabetes and nafld

The regulation of metabolic processes by the INDY (I'm Not Dead Yet) (SLC13A5/NaCT) gene was revealed through studies in Drosophila melanogaster and Caenorhabditis elegans. Reducing the expression of Indy in lower organisms extended life span by a mechanism resembling caloric restriction, without reducing food intake. In D. melanogaster, mutating the Indy gene reduced body fat content, insulin-like proteins and reactive oxygen species production. Subsequent studies indicated that Indy encodes a citrate transporter located on the cell plasma membrane, with high expression levels in the mammalian liver. We have generated the first mammalian knock out model deleting the mammalian homolog mINDY (SLC13A5). The mINDY-KO mice were protected from HFD induced obesity, fatty liver and insulin resistance.

Moreover, we have recently shown that inducible and liver selective knock down of mIndy protects against the development of fatty liver and insulin resistance and that obese humans with type 2 diabetes and non-alcoholic fatty liver disease have increased levels of mIndy. Therefore, the transporter mINDY has been proposed to be an 'ideal target for the treatment of metabolic and cardiovascular disease'. A small molecule inhibitor of the mINDY transporter has been generated, normalizing glucose levels and reducing fatty liver in a model of diet induced obese mice. Taken together, studies from lower organisms, mammals and humans suggest that mINDY (NaCT/SLC13A5) is an attractive target for the treatment of type 2 diabetes and non-alcoholic fatty liver disease.

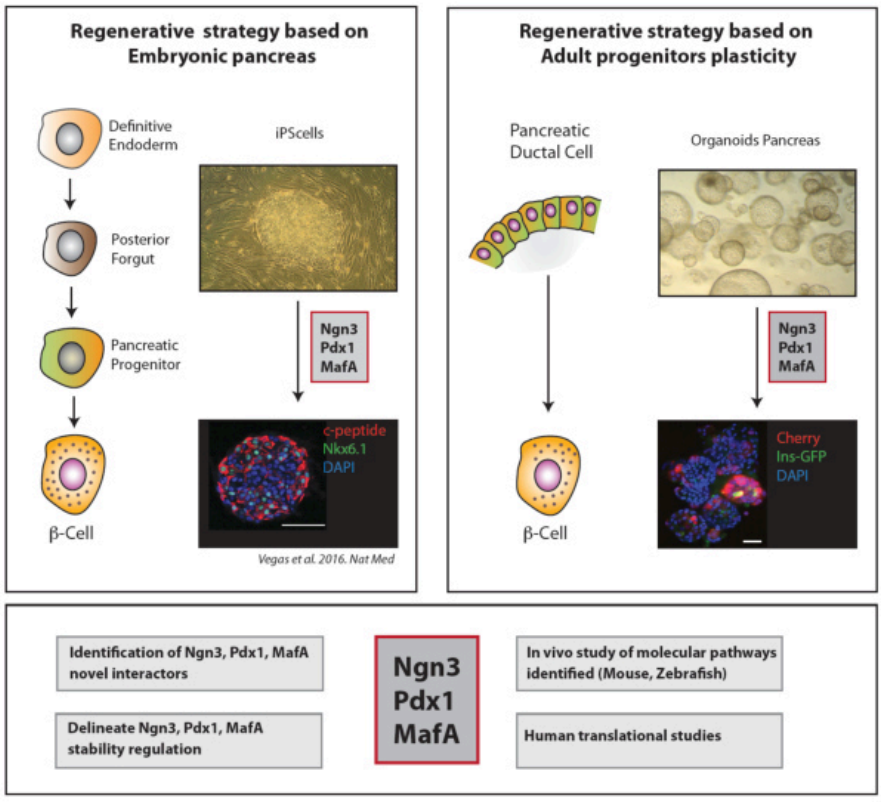


Dr. Rocio Sancho

Regulation of pro-endocrine factors and cell plasticity: new opportunities for regenerative medicine in Diabetes.

Diabetes is caused by the irreversible loss of insulin-producing beta-cells in the pancreas. While the incidence of diabetes is rising, therapy for this conditions remains burdensome and the risk of complications high. Current treatments include antidiabetic drugs or insulin injections, but the degree of glycemic control with these approaches does not compare to having functional pancreatic beta-cells. Exploiting cell plasticity for regenerative beta-cell treatments in diabetic patients could allow for the long-term restoration of normal glycemic control and represents a potentially curative therapy. Knowledge of the precise molecular regulation of embryonic beta-cell development and regeneration of adult pancreatic beta-cells has provided crucial information for diabetes regenerative medicine.

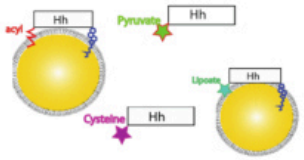
Recent research has revealed that the adult pancreas is capable of surprising cellular plasticity, opening new possibilities to reprogram adult stem/progenitor cells and iPScells into insulin-producing cells (Bayens et al. 2014, Sancho et al. 2014; Ben-Othman et al. 2017). Three key transcription factors are crucial to initiate a beta cell fate in adult stem/progenitor cells and iPScells: Ngn3, Pdx1 and MafA. However, the tight regulation of these factors makes the process inefficient, and the beta cells generated are often not fully functional. Deciphering the regulatory mechanisms for proendocrine factors, which is the main theme of the PhD-IRTG studentship project based at my lab, holds the key to explore new opportunities in regenerative medicine for diabetes.



Suzanne Eaton

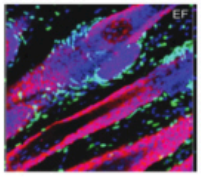
Different signalling outputs of Sonic Hedgehog isoforms (Sonic Hedgehog signalling in diabetic wound healing)

Wound healing in the skin involves communication between epidermal cells, dermal fibroblasts, and endothelial cells as they proliferate, migrate and differentiate to reconstitute the epidermal and dermal layers. Defective wound healing is a major complication of diabetes. Work from the Watt group has shown that Hedgehog signaling is required for this process, but the sources and regulation of Hedgehog ligands during wound healing are unclear, as are its cellular targets. Furthermore, we do not yet understand how the metabolic changes in diabetes alter the normal signaling events that underlie wound healing. Work from the Eaton lab has shown that Hedgehog can be secreted as a lipid modified protein that associates with lipoprotein particles. Alternatively, it can be modified by a variety of cellular metabolites, including pyruvate and cysteine. We want to understand how the state of cell metabolism and the availability of these metabolites influences the activity of the Sonic Hedgehog ligand. Furthermore, we want to understand how the metabolic changes associated with diabetes might alter the activity of Sonic Hedgehog during wound healing.



Sonic Hedgehog is post-translationally modified by different metabolites and secreted on different vehicles.

How does cell metabolism influence production of these different forms, and how do their signaling activities differ?



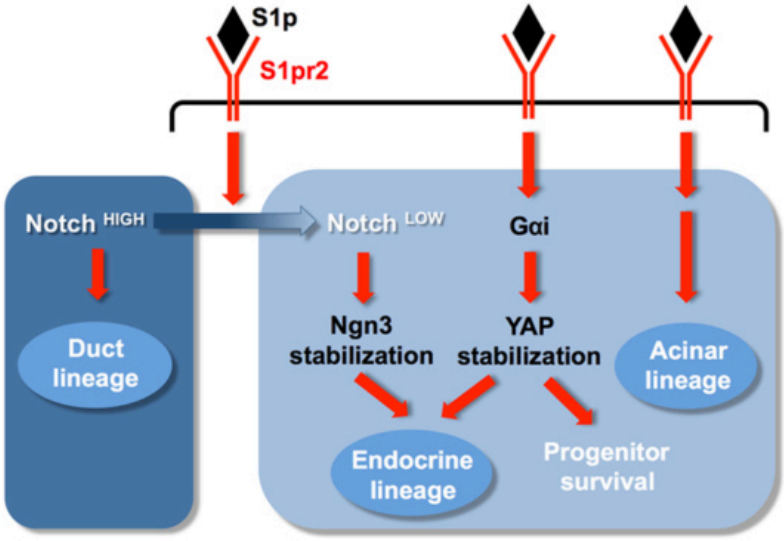
Sonic Hedgehog produced by epidermal cells in the stem cell compartment signals to the underlying dermis - causing proliferation of fibroblasts and ECM remodeling

How do the metabolic changes in diabetes influence Shh secretion forms? What are the consequences for wound healing?

Anthony Gavalas

Novel insights in pancreasdevelopment fort he differentiation of human pluripotent stem cells into beta cells (Microencapsulation of human PS cell derived beta cells)

The pancreas develops from a field of progenitor cells in a restricted region of the embryonic endoderm. These progenitors expand and eventually differentiate to generate the three distinct lineages comprising the endocrine, acinar and ductal cells. The molecular pathways implicated in the early generation of pancreas progenitors and their expansions are well understood. It is also known that the Notch signalling pathway is implicated in sequential binary cell fate decisions that generate the three lineages but other signals that may regulate this process remain unknown. Here we show that a phospholipid, sphingosine-1-phosphate (S1p), generated from the progenitors themselves, is necessary to define the acinar and endocrine lineage. In the absence of S1p signalling only duct cells are generated and the survival of pancreas progenitors is compromised. The function of this signalling pathway in the generation of the endocrine cells, which include the insulin producing β cells, is twofold. Firstly, it stabilizes YAP, a transcriptional gene co-activator that we show is necessary for the activation of the endocrine program. Secondly, it attenuates Notch signalling, thus allowing the generation of the endocrine and acinar cells. Notch attenuation is necessary for the stabilization of the transcription factor Ngn3 that is required for the generation of endocrine cells. Both YAP stabilization and Notch attenuation are necessary for the generation of endocrine cells. Finally, it was illustrated how such findings are being used in the differentiation of human pluripotent stem cells to beta cells.



Nikolay Ninov

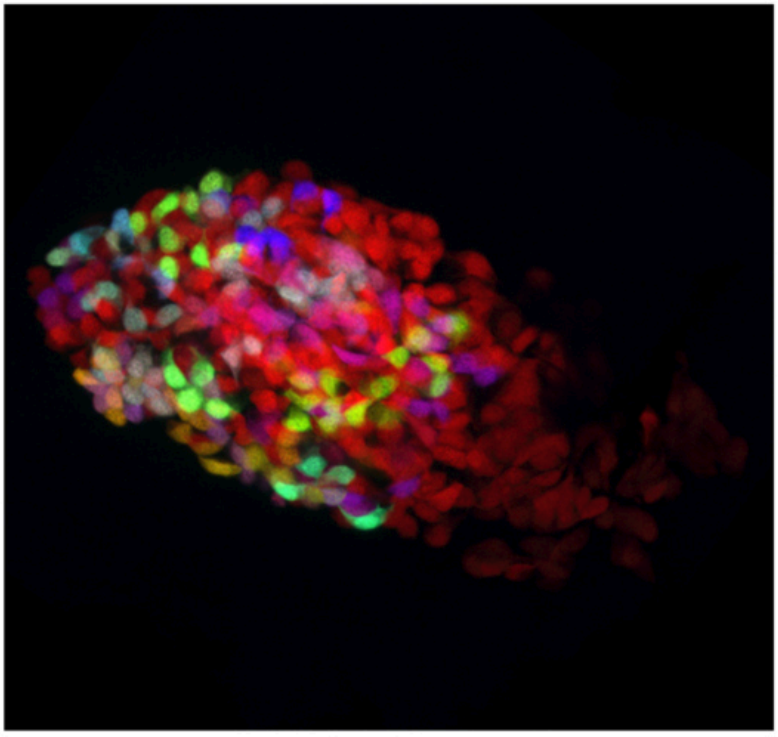
Single-cell insights on beta-cell development and function in vivo (G-protein-coupled receptors in beta-cell regeneration)

I presented our ongoing work on beta-cell function and proliferation in zebrafish. For this work, we developed cutting-edge technology allowing studying the glucose-responsiveness and development of maturation in beta-cells. To identify molecular mechanisms, I presented our single-cell and bulk-transcriptomics of beta-cells, which uncovered conserved regulators of beta-cell function and proliferation. I outlined specific future directions that will be explored in the IRTG 2251 project in collaboration with Shanta Persaud. In particular, we will use our novel tools to identify conserved GPCRs that promote beta-cell function, maturation and regeneration. The most promising candidates will then be tested in human islets and mouse models of diabetes.

References:

Ahmed Alfar et al., Distinct Levels of Reactive Oxygen Species Coordinate Metabolic Activity with Beta-cell Mass Plasticity (in press)

Pal-Singh et al. "Unequal developmental histories of beta-cells generate functional and proliferative heterogeneity during islet growth" (in revision).



Geltrude Mingrone

A randomized controlled trial comparing gastric bypass with Liraglutide to treat NASH and fibrosisin type 2 diabetes patients

Background: Conversion of Roux-en-Y Gastric-Bypass (RYGB) to sleeve-gastrectomy (SG) is currently used as an alternative to pancreatectomy to treat severe reactive-hypoglycemia, but prospective, randomized-trials are lacking.

Objective: To compare the incidence of reactive-hypoglycemia (<3.1 mmol/l) after RYGB versus SG.

Secondary aims: hypoglycemia under everyday-life conditions, insulin-sensitivity and insulin-secretion, lipid profile.

Design: Single-center, two-arm, parallel, randomized, open-label trial.

Setting: Outpatient obesity clinic in a university-hospital in Rome, Italy.

Patients: 120 obese, non-diabetic subjects (BMI 35-40 with complications or >40 kg/m^2, age 25-65 years).

Interventions: Roux-en-Y-Gastric-Bypass or Sleeve-Gastrectomy.

Measurements: Incidence of reactive hypoglycemia (<3.1 mmol/l after 75g-oral-glucose-load) up to 1year after surgery (intention-to-treat-analysis, carried-forward for missing data).

Results: Of 175 eligible patients, 120 were randomized 1:1to RYGB or SG; 117 (93%) completed the 12-months follow-up. Hypoglycemia (<3.1 mmol/l) was detected in 14% and 29% of SG and RYGB patients (P=0.079). Daily hypoglycemic episodes (≤3.1 mmol/l) during continuous-glucose-monitoring did not differ between groups (P=0.75). Four out 59 RYGB-subjects (6.8%) had 1-3 hospitalizations for symptomatic hypoglycemia. The static β-cell glucose-sensitivity-index increased after both treatments (from 50.99+-33.68·10^{9}min^{-1} to 120.43+-98.90·10^{9}min^{-1}, P<0.001), but the dynamic β-cell glucose-sensitivity-index increased significantly in SG (from 323.93+-480.87·10^9 to 933.32+-1063.86·10^9 min1, P=0.008) and decreased in RYGB (from 645.69+-733.21·10^9 to 414.90+-469.87·10^9 min^{-1}; P=0.004 for time x treatment interaction). Whole-body insulin-sensitivity increased about 10-times in both groups.

Limitations: Relatively short duration of follow-up and single-center, open-label nature of the study.

Conclusions: We show that SG is not a safer option than RYGB in leading reactive hypoglycemia 1 year after surgery. However, RYGB induced a higher number of severe hypoglycemic episodes likely due to the lack of improvement of β-cell sensitivity to changes in circulating glucose after RYGB, which determines an inappropriately high insulin-secretion in the face of a dramatically improved peripheral insulin-sensitivity. Clinicaltrials.gov Registration number NCT01581801.