



55th EASD Annual Meeting of the European Association for the Study of Diabetes

Barcelona, Spain, 16 – 20 September 2019

Abstracts

Index of Oral Presentations

- OP 01 SGLT2 inhibitors: glucose and beyond
- OP 02 Looking ahead towards better treatments for type 1 diabetes
- OP 03 Addressing limitations of insulin therapy
- OP 04 Mechanisms of adaptation of insulin secretion
- OP 05 Monitoring risk and prognosis of peripheral diabetic neuropathy
- OP 06 Novel biomarkers of CVD in type 2 diabetes
- OP 07 Benefits of technologies in type 1 diabetes
- OP 08 Inflammation: new and old kids on the block
- OP 09 Semaglutide: ingested or injected
- OP 10 Looking into the future: predicting renal outcomes
- OP 11 Lost islets in type 2 diabetes
- OP 12 Prediction of vascular complications in type 1 diabetes
- OP 13 Nephropathy: mechanisms of renal injury and nephroprotection
- OP 14 New insights on early onset type 2 diabetes
- OP 15 Clinical aspects of hypoglycaemia
- OP 16 The many faces of metabolic surgery
- OP 17 Are we making progress in diabetic neuropathy?
- OP 18 The still mysterious alpha cells
- OP 19 Treating diabetes with peptides from the gut
- OP 20 Youth-onset type 1 diabetes: Are we making progress?
- OP 21 Cardiovascular disease in diabetes: causes and consequences
- OP 22 Determinants of exercise response
- OP 23 The diabetic brain: culprit or victim?
- OP 24 More and better beta cells for therapy
- OP 25 New horizons in incretin-based therapies
- OP 26 Gestational diabetes: novel biomarkers and consequences
- OP 27 Modulations of insulin secretion
- OP 28 What you eat is what you are
- OP 29 Spotlights on prediction and prevention of type 2 diabetes
- OP 30 NAFLD and diabetes: new horizons
- OP 31 Innovative insulin therapy
- OP 32 Novel biomarkers in diabetes, towards precision medicine
- OP 33 Heart failure: a novel complication of diabetes?
Human and animal studies
- OP 34 New light into the signalling pathway
- OP 35 Novel concepts paving the way for future treatments
- OP 36 Genetics of diabetes: the final countdown?
- OP 37 New modes of organ crosstalk
- OP 38 Continuous measurement of glucose: standard of care?
- OP 39 Insights on retinopathy from observational studies
- OP 40 Novel treatments in obesity: lean on me
- OP 41 Cardiovascular hotspots in diabetes
- OP 42 The inner life of the beta cell
- OP 43 Disease progression in type 2 diabetes
- OP 44 Exploring novel mechanisms of action of SGLT2 inhibitors
- OP 45 Integrating psychology into diabetes care
- OP 46 Holistic view on ageing
- OP 47 Type 2 diabetes across ethnicities
- OP 48 Not all beta cells are alike

Index of Poster Sessions

- PS 001 Twisting the helix
- PS 002 The attack from within: autoimmunity in diabetes
- PS 003 Monogenic diabetes: from MODY and beyond
- PS 004 Additional spotlights on cardiovascular disease
- PS 005 Diagnostic discussions in diabetes
- PS 006 Trends, prevalence and incidence
- PS 007 Biomarkers and diabetes: new and old
- PS 008 Genetics of diabetes: more to know?
- PS 009 Diabetes: new lessons from animals
- PS 010 Treatments for type 2 diabetes
- PS 011 Control, incidence and risk factors in type 1 diabetes
- PS 012 You are what you do: environment, lifestyle and diabetes
- PS 013 Infections and pancreatitis in diabetes
- PS 014 Islets in the stream: transplantation for a better journey
- PS 015 You ain't seen nothin' yet with stem cells,
the best is yet to come
- PS 016 Reaching to the stars for future type 1 diabetes treatment
- PS 017 Beta cells: be yourself and grow
- PS 018 The ins and outs of ions in islets
- PS 019 GLPR and other GPCRs: juggling with acronyms
- PS 020 Rise and fall of the beta cell
- PS 021 Tales of the injured beta cell
- PS 022 Inflamed islets in type 1 diabetes
- PS 023 The downfall of beta cells
- PS 024 The endocrine role of the gut: incretins and other hormones
- PS 025 Changing insulin sensitivity: a stairway to heaven?
- PS 026 Causes and consequences of insulin resistance
- PS 027 Insulin secretion and beta cell function
- PS 028 Incretins regulating incretins
- PS 029 Modulation of islet hormones
- PS 030 How to optimise exercise
- PS 031 Sugar on the run
- PS 032 A mixed bag of metabolism
- PS 033 The many roles of other hormones
- PS 034 Surgery: What we need to learn
- PS 035 The obesity battle
- PS 036 Diabetic complications of the mind
- PS 037 Diet, bugs and drugs
- PS 038 Hungry like the wolf: What's in it for the brain?
- PS 039 Metabolic adaptations and outcomes
- PS 040 Diabetic staging
- PS 041 From mice to men?
- PS 042 The many ways of improving metabolism
- PS 043 Adipose tissue: what, where and how?
- PS 044 Inflammation and beyond
- PS 045 Not all fats are the same...
- PS 046 Burning down the fat
- PS 047 SGLT2 inhibitors and the cardiorenal axis
- PS 048 Combating diabetes with diet
- PS 049 Food, food, food... nutritional interventions
- PS 050 All the roads leading from SGLT2 inhibitors

lactated women. Both the Disposition index and Matsuda index was improved in previously lactated women, suggesting improved β cell function in lactated women. In mice, after 3 weeks after delivery, lactating mice had improved glucose tolerance and increased β cell mass compared to non-lactating mice. Lactating mice maintained high serum prolactin levels for milk production, which induced serotonin production in β cell via PRLR-STAT5-TPH1 cascade. Similar to pregnancy, increased β cell serotonin facilitated β cell proliferation and enhanced β cell function. Amelioration of glucose tolerance and β cell function were maintained for several months after the cessation of lactation. However, these beneficial effects were diminished in β cell-specific *Tph1* knockout mice. In addition, we demonstrated a novel mechanism of 5-HT derivatives acting as a direct anti-oxidant to enhance β cell survival upon oxidative stress.

Conclusion: Serotonin contributes to the beneficial metabolic effects of lactation by enhancing β cell mass and function.

Supported by: National Research Foundation of Korea, Health Fellowship Foundation

Disclosure: J. Moon: None.

142

In vitro and fully mature in vivo function of human induced pluripotent stem cell-derived beta cells

F. Fantuzzi^{1,2}, H. Chae³, Y. Cai², M. Igoillo-Esteve², C. Demarez², N. Pachera², S. Toivonen², B. Rajaei², L. Marselli⁴, P. Marchetti⁴, D.L. Eizirik², P. Gilon³, M. Cnop²;

¹Department of Medicine and Surgery, University of Parma, Parma, Italy,

²ULB Center for Diabetes Research, Université Libre de Bruxelles, Brussels, Belgium, ³Institute of Experimental and Clinical Research, Université Catholique de Louvain, Brussels, Belgium, ⁴Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy.

Background and aims: Pancreatic β -cell failure is central in the pathogenesis of diabetes. *In vitro* differentiation of human induced pluripotent stem cells (iPSCs) into β -cells represents a novel cell source for diabetes research. Here we differentiated iPSC- β -cells and tested their function *in vitro* and *in vivo* in humanized mice.

Materials and methods: iPSCs were differentiated into β -cells using a 7-step protocol. Markers of β -cell development were assessed by qPCR and immunocytochemistry and compared to organ donor human islets. *In vitro* iPSC- β -cell function was assessed by static glucose- and forskolin (Fk, 10 μ M)-stimulated insulin secretion. NOD-SCID mice were transplanted with iPSC- β -cells under the kidney capsule and underwent intraperitoneal glucose tolerance tests at 7, 14 and 20 weeks post-transplantation (n=8-13). At 21 weeks mice were injected with streptozotocin (STZ, 200 mg/kg) to selectively ablate the mouse β -cells, and glycemia was followed for 1 week before nephrectomy or *in situ* kidney perfusion (single-pass circuit through renal artery and vein, n=3), in order to evaluate *in vivo* function of the graft.

Results: iPSC- β -cells followed a proper developmental pathway as determined by gene expression. The yield of insulin-positive β -cells was comparable to that of human islets (44±3% versus 49±1%) as assessed by immunocytochemistry. iPSC- β -cells at stage 7 did not augment insulin release in response to glucose *in vitro* (16.7 mM versus 1.7 mM), but high glucose plus Fk increased insulin secretion by 4-fold (p<0.001). In transplanted mice, human C-peptide secretion was detectable at 7 weeks and grafts became glucose-responsive by 14-20 weeks. After STZ, transplanted mice maintained normoglycemia until graft removal by nephrectomy, when they became diabetic. *In situ* kidney perfusion showed marked human insulin secretion in response to glucose (20 mM) *in vivo*, and this was amplified by Fk (1 μ M). Diazoxide (a K_{ATP} channel opener, 250 μ M) fully inhibited insulin release, whereas gliclazide (K_{ATP} channel blocker, 25 μ M) or high K^+ (30 mM) strongly stimulated insulin secretion.

Conclusion: *In vitro* differentiation generates iPSC- β -cells with mature β -cell characteristics but still lacking fully mature β -cell function.

Transplantation and the *in vivo* environment boost their maturation to such an extent that they acquire the functional characteristics of adult human islets. This technology provides us with an unlimited supply of human β -cells that will be instrumental to study β -cell dysfunction and demise in diabetes.

Supported by: H2020 T2DSysTems, Innoviris, FNRS

Disclosure: F. Fantuzzi: None.

143

Diabetic condition upregulates insulin secreting capacity of human iPSC-derived pancreatic endocrine progenitor cells after implantation in mice

T. Mochida^{1,2}, H. Ueno^{1,2}, N. Yamazoe^{1,2}, H. Hiyoshi^{1,2}, R. Ito^{1,2}, H. Matsumoto^{1,2}, T. Toyoda^{3,2};

¹Takeda Pharmaceutical Company Limited, Kanagawa, ²Takeda-CiRA Joint Program (T-CiRA), Kanagawa, ³Center for iPS Cell Research and Application (CiRA), Kyoto, Japan.

Background and aims: Islet transplantation is a promising therapeutic option for patients with brittle type 1 diabetes, but does not meet clinical demand due to donor shortage. Stem cell-derived pancreatic cells have attracted interest as an alternative cell source. Given the difficulty in generating fully mature islets *in vitro* so far, host environment is an important factor to drive differentiation, cell-cycle and maintenance of implanted stem cell-derived pancreatic cells. The purpose of this study is to investigate whether host diabetic environment impacts the fate of pancreatic endocrine progenitor cells (EPCs) implanted in immunodeficient mice.

Materials and methods: EPCs were differentiated from human induced pluripotent stem cells (iPSCs) by reported differentiation protocols with some modifications, and then implanted into the kidney sub-capsular space of diabetic and non-diabetic NOD.CB17-Prkdcscid/J (NOD/SCID) mice. Status of cells was assessed by measuring plasma human C-peptide (hC-peptide) levels and by analyzing the explanted grafts.

Results: EPCs were comprised of >50% chromogranin A⁺ (CHGA⁺) cells and the majority of the cells expressed NKX6.1, indicating the potential to become β cells; few cells expressed insulin or glucagon. After implantation, plasma hC-peptide levels were higher in streptozotocin (STZ)-induced diabetic mice than in non-diabetic mice for 13 weeks, while the levels did not differ thereafter. The elevation of plasma hC-peptide levels was reproduced when EPCs were derived from another iPSC line or were implanted in genetically-induced diabetic Akita-NOD/SCID mice. These results suggest that the insulin secreting capacity of grafts is upregulated in a host diabetic environment. To clarify how the insulin secreting capacity of implanted cells is increased in host diabetic environment, cell mass and composition of explanted EPC grafts were analyzed. Appearance and weight of whole grafts were not different between diabetic and non-diabetic mice despite different plasma hC-peptide levels. In contrast, whole graft contents of insulin and glucagon were higher in the grafts from diabetic mice compared with those from non-diabetic mice by 3.1- and 4.1-fold, respectively. In addition, grafts from diabetic mice contained 3.0-fold more CHGA- and 3.7-fold more insulin-immunoreactivity areas. These results suggest that the host diabetic environment increases endocrine cells including insulin producing cells without affecting graft mass via facilitated hormone expression and endocrine cell commitment.

Conclusion: In this study, we demonstrated that diabetic condition upregulates the insulin secreting capacity of human iPSC-derived EPCs implanted in immune-deficient mice. These findings would provide important insights into postoperative diabetes care for cell therapy using stem cell-derived pancreatic cells in the future.

Disclosure: T. Mochida: None.