A PRIVATE PUBLIC PARTNERSHIP
AGAINST TYPE 1 DIABETES

21-25 September 2020

EASD2020

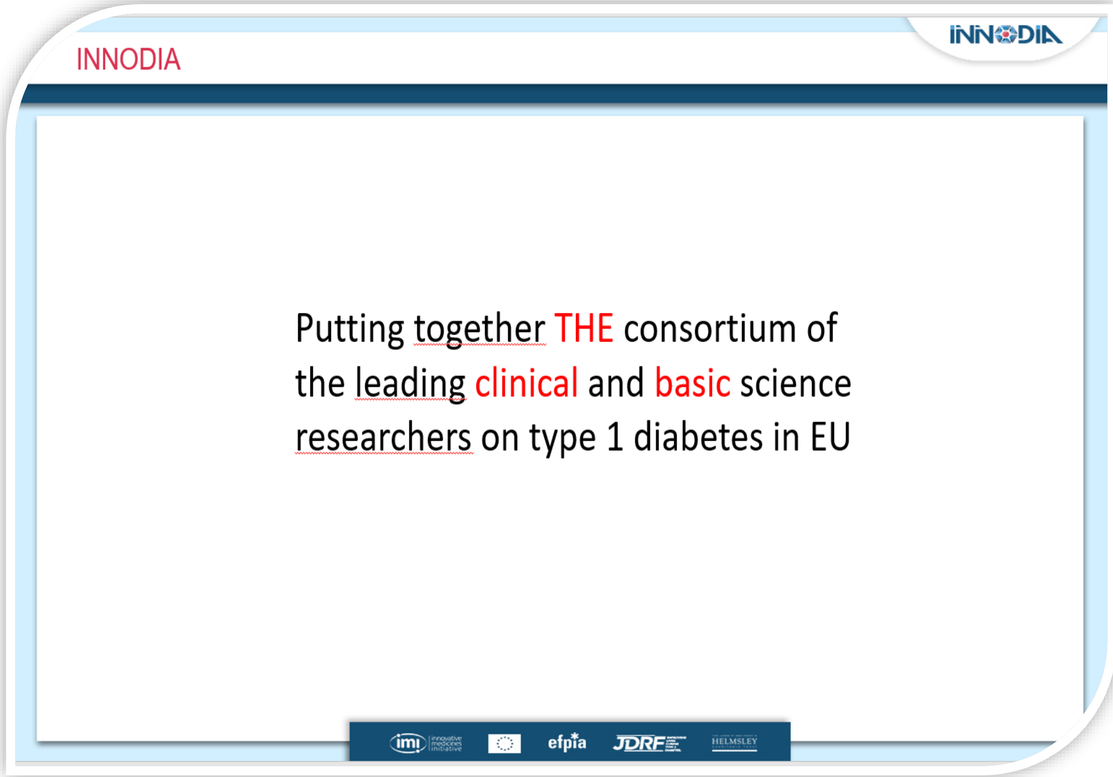
virtual

INNODIA-related oral presentations

Innovative medicines initiative (IMI): the power of public private partnerships in diabetes research: INNODIA

Prof. C. Mathieu

Chantal Mathieu, Professor of Medicine at the Katholieke Universiteit Leuven, Belgium & Chair of Endocrinology at the University Hospital Gasthuisberg Leuven.
Coordinator of the INNODIA project on prevention and intervention in type 1 diabetes in Europe, vice-president of EASD and Chair of Postgraduate Education at EASD.



INNODIA-related oral presentations

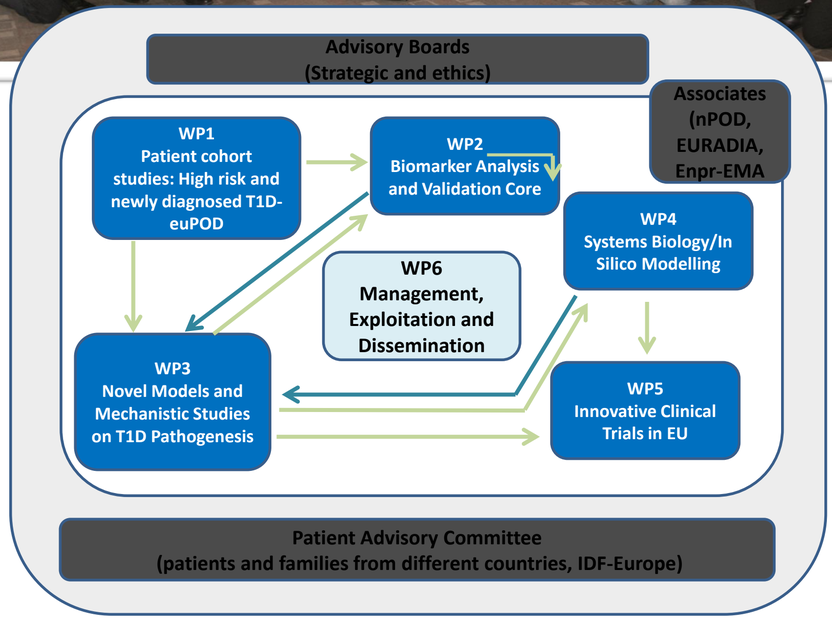
I. To develop an **EU infrastructure** for the recruitment, detailed clinical phenotyping and bio-sampling of a large cohort of newly diagnosed subjects with T1D and at risk family members, generating an **unrivalled bioresource of T1D discovery science**.

II. To establish a tight **collaborative network of basic and clinical researchers** working in a coordinated and focused way to address key knowledge gaps in relation to b-cell autoimmunity, leading to a better understanding of the pathogenesis of T1D and a cure for this disease. Research will focus on the question why the immune system loses tolerance towards the b-cell, the dialogue between b-cells and the immune system and which b-cell pathways contribute to its dysfunction and death in T1D.

III. To advance the **development and application of novel methodologies** by exploiting our major strengths in bioresource and 'omics' technologies.

IV. To establish a **unique integrated database** assimilating historical data, with data from clinical and experimental sources. This will permit bioinformatics-assisted visualization and modelling of interactions between phenotype, genetic, immune and metabolic pathways to explore subtypes, potentially redefining ontogeny of T1D in the context of prevention and intervention strategies.

V. To conceive **innovative clinical trial designs** that exploit novel validated biomarkers allowing better subject stratification and functioning as surrogate endpoints, thus yielding shorter and more focused intervention studies of single or combined therapies.



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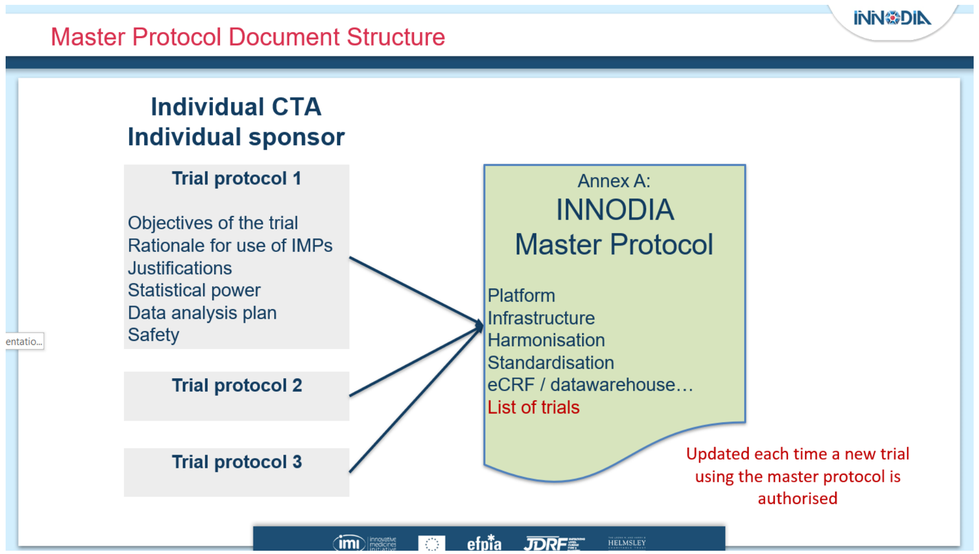
oral	244. Regulatory role of tyrosine kinase 2 (TYK2) in human pancreatic endocrine differentiation	V. Chandra, H. Ibrahim, J. Kvist, D. Balboa, R.B. Prasad, O.P. Dwivedi, L. Groop, **D. Eizirik, T. Otonkoski**, Finland, Spain, Sweden, Belgium
oral	49. Innodia master protocol for the evaluation of investigational medicinal products in children, adolescents and adults with newly diagnosed type 1 diabetes	**D.B. Dunger, S.F. Bruggraber, A.P. Mander, T. Tree, P. Jaroslaw Chmura, M.J. Knip, A.M. Schulte, C. Mathieu**, UK, Denmark, Finland, Germany, Belgium
oral	43. ^{111}In-exendin spect imaging suggests presence of residual beta cells in patients with longstanding type 1 diabetes	M. Boss, I. Kusmartseva, W. Woliner-van der Weg, L. Joosten, M. Brom, M. Béhe, C.J. Tack, O.C. Boerman, M.J. Janssen, M. Atkinson, **M. Gotthardt**, Netherlands, USA, Switzerland
oral	221. Presentation of insulin granule derived peptides on MHC I in Enterovirus-infected beta cells and type 1 diabetes	Z. Marinicova, M. Ghosh, K.-P. Knoch, A. Petzold, C. Wegbrod, A. Sönmez, **R. Scharfmann**, S. Stevanović, **M. Solimena**, Germany, France
oral	212. Integration of single-cell datasets reveals novel transcriptomic signatures of beta cells in human type 2 diabetes	**E. Bosi**, L. Marselli, C. De Luca, M. Suleiman, M. Tesi, M. **Cnop, D. Eizirik**, M. Ibberson, **P. Marchetti**, Italy, Belgium, Switzerland
oral	152. Identification and mechanistic studies of a novel form of neonatal diabetes caused by YIPF5 mutations leading to pancreatic beta cell endoplasmic reticulum stress	F. Fantuzzi, C. Demarez, E. De Franco, H. Ibrahim, Y. Cai, T. Sawatani, H. Shakeri, N. Pachera, M. Lytrivi, K. Patel, M. Yildiz, D.L. **Eizirik, T. Otonkoski**, A.T. Hattersley, M. Cnop, Belgium, Italy, UK, Finland, Turkey

poster	353. Integrated analysis of clinical and multi-dimension omics data from 100 newly diagnosed type 1 diabetes subjects from the INNODIA study	**C. Brorsson, P. Chmura, G. Mazzoni, D.D. Dunger, S.F. Bruggraber, M. Knip, T. Tree, M. Peakman, A.M. Schulte, R. Lahesmaa, T.R. Suvitaival, F. Dotta, G. Sebastiani, C. Mathieu, S. Brunak**, Denmark, UK, Finland, USA, Germany, Italy, Belgium
poster	361. The assessment of intrahepatic islet transplantation using exendin PET imaging	T.J. Jansen, M. Buitinga, M. Boss, E.J. De Koning, M.A. Engelse, M.F. Nijhoff, I. Velikyan, O. Korsgren, O. Eriksson, M. Brom, **M. Gotthardt**, Netherlands, Belgium, Sweden
poster	393. Validation of exendin for beta cell imaging: ex vivo autoradiography of human pancreas demonstrates specific accumulation of radiolabeled exendin in islets of Langerhans	**M. Gotthardt**, T.J. Jansen, M. Buitinga, C. Frielink, M.W. Stommel, M.B. Van der Kolk, H. Van Goor, B.E. De Galan, M. Boss, M. Brom, Netherlands, Belgium
poster	320. High-throughput sequencing of circulating plasma microRNAs in newly diagnosed type 1 diabetes identifies four different patient clusters	G. Sebastiani, G.E. Grieco, D. Fignani, P.J. Chmura, C.A. Brorsson, S. Bruggraber, A. Pugliese, C. Evans-Molina, **M. Knip, M. Peakman, A.M. Schulte, S. Brunak, D.B. Dunger, C. Mathieu, F. Dotta**, Italy, Denmark, UK, USA, Finland, Germany, Belgium
poster	360. Factors affecting function of human pancreatic islets after isolation	C. De Luca, M. Suleiman, **A.M. Schulte, D.L. Eizirik**, M. Tesi, W. Baronti, **E. Bosi, M. Solimena, M. Cnop, P. Marchetti**, L. Marselli, Italy, Germany, Belgium
poster	373. Phasor-flim analysis of beta cell metabolic trajectory upon glucose stimulation	G. Ferri, M. Tesi, F. Massarelli, L. Marselli, **P. Marchetti,** F. Cardarelli, Italy
poster	396. Glucose-lowering therapy and ex-vivo beta cell function in type 2 diabetes	M. Suleiman, C. De Luca, **A.M. Schulte, D.L. Eizirik**, M. Tesi, E. Gianetti, **M. Solimena, E. Bosi, M. Cnop, P. Marchetti**, L. Marselli, Italy, Germany, Belgium

49. Innodia master protocol for the evaluation of investigational medicinal products in children, adolescents and adults with newly diagnosed type 1 diabetes.

Authors: ***D.B. Dunger, S.F. Bruggraber, A.P. Mander, T. Tree, P. Jaroslaw Chmura, M.J. Knip, A.M. Schulte, C. Mathieu****, UK, Denmark, Finland, Germany, Belgium*



320. High-throughput sequencing of circulating plasma microRNAs in newly diagnosed type 1 diabetes identifies four different patient clusters.

Authors: ***G. Sebastiani, G.E. Grieco, D. Fignani, P.J. Chmura, C.A. Brorsson, S. Bruggraber, A. Pugliese, C. Evans-Molina, M. Knip, M. Peakman, A.M. Schulte, S. Brunak, D.B. Dunger, C. Mathieu, F. Dotta, Italy, Denmark, UK, USA, Finland, Germany, Belgium***

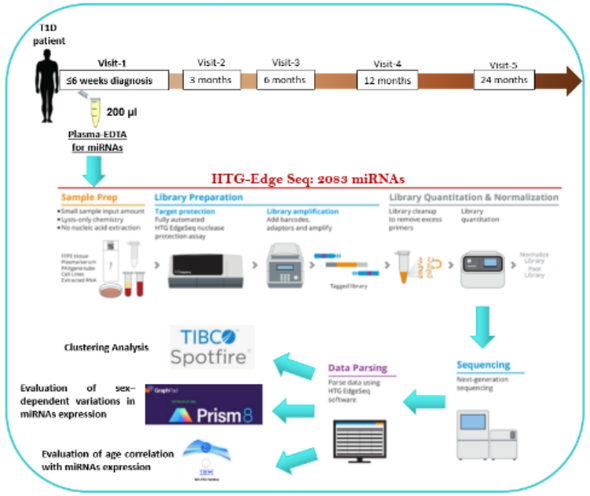
Experimental Design

INNODIA

116 T1D subjects characteristics

	Number of Patients (n)	Age at Onset (years)	Diabetes Duration (weeks)	Gender (F/M)
Pediatric Patients	100 (age<18y)	9,82±3,8y	4,5±1,5w	50/50
Adult Patients	16 (age≥18y)	28,0±7,1y	4,6±1,4w	9/7
ALL	116	12,4±7,7y	4,5±1,5w	59/57

Experimental Workflow

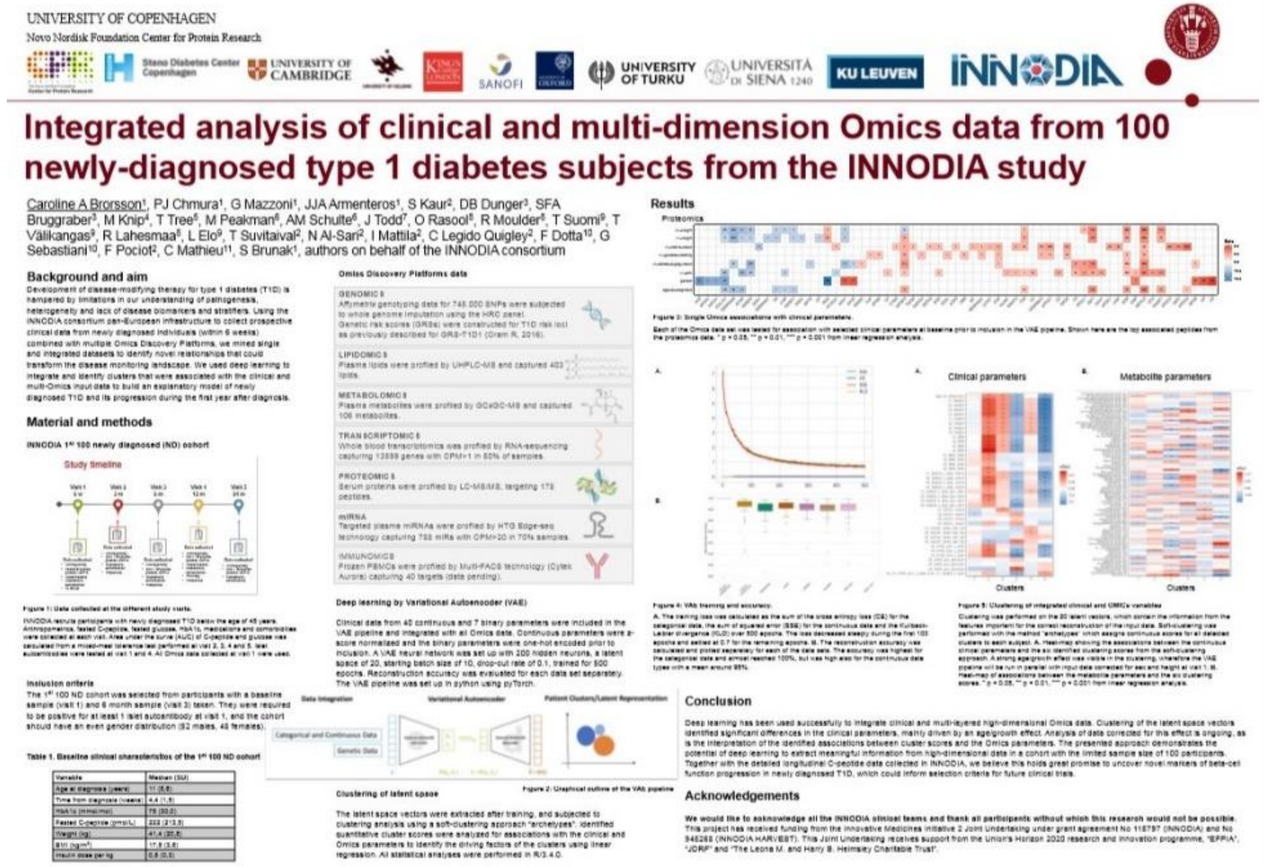


The team analyzed microRNA in plasma samples collected from 116 subjects with T1D recruited within INNODIA. Using a novel sequencing technology we measured the levels of 2083 microRNAs and found 803 clearly detected in these samples. The expression levels of microRNAs allows the identification of 4 clear distinct groups of T1D subjects, thus confirming the heterogeneity nature of T1D and also the possibility to stratify newly diagnosed T1D subjects at the very beginning if the desease using microRNAs, thus opening to new therapeutic opportunities for personalized medicine. In the next weeks/months we will get insight into specific differences among these 4 T1D subject groups and how they related in respect to the progression of the disease.

353. Integrated analysis of clinical and multi-dimension omics data from 100 newly diagnosed type 1 diabetes subjects from the INNODIA study

Authors: ***C. Brorsson, P. Chmura, G. Mazzoni, D.D. Dunger, S.F. Bruggraber, M. Knip, T. Tree, M. Peakman, A.M. Schulte, R. Lahesmaa, T.R. Suvitaival, F. Dotta, G. Sebastiani, C. Mathieu, S. Brunak***, *Denmark, UK, Finland, USA, Germany, Italy, Belgium*

Caroline Brorsson highlighted the wealth of data collected, both longitudinal clinical data and the large panel of ‘omics data. I also showcased the integrative analysis we are undertaking using deep learning, and highlighted some of the first preliminary results. We are firstly analysing the association with each single omics data type with baseline clinical characteristics , to understand the the data and its covariates. Then I showed a clustering approach where we did find different clinical patterns in the integrated data, and also patterns in the ‘omics data which can be explored to develop an explanatory model of T1D and its progression the first year after onset.



INNODIA-related oral presentations

152. Identification and mechanistic studies of a novel form of neonatal diabetes caused by YIPF5 mutations leading to pancreatic beta cell, endoplasmic reticulum stress.

Authors: ***F. Fantuzzi, C. Demarez, E. De Franco, H. Ibrahim, Y. Cai, T. Sawatani, H. Shakeri, N. Pachera, M. Lytrivi, K. Patel, M. Yildiz, D.L. Eizirik, T. Otonkoski, A.T. Hattersley, M. Cnop, Belgium, Italy, UK, Finland, Turkey***

ULB CENTER FOR DIABETES RESEARCH

INDIANA BIOSCIENCES RESEARCH INSTITUTE

CONCLUSIONS

- RNA sequencing of human islets exposed to proinflammatory cytokines (IL-1β + IFNγ or IFNα) identified thousands of cytokine-induced spliced variants; some of them are involved in antiviral responses.

- Some of these cytokine-induced isoforms can be recognized by autoreactive T cells and are potential neoantigens in T1D.

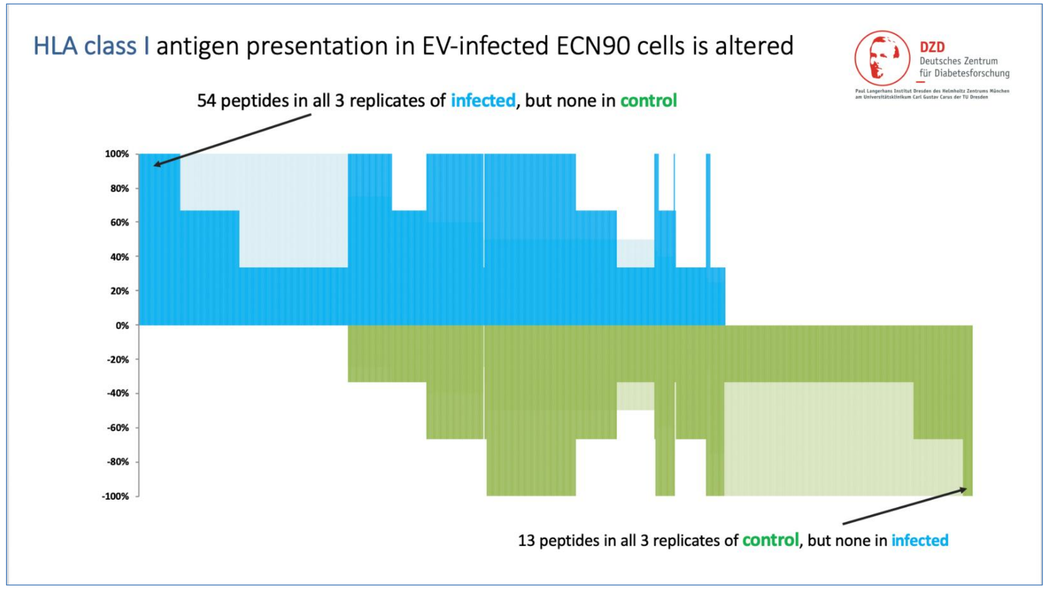
- SRp55, a splicing regulator downstream of the diabetes candidate gene GLIS3, is a master splicing factor in human beta cells, regulating splicing of genes involved in beta cell survival, JNK signalling and insulin secretion.

- The integration between RNA-seq and iCLIP-seq identified the sRp55 binding map in human beta cells.

- SRp55 regulates, directly or indirectly, the splicing of several diabetes candidate genes, suggesting the presence of an alternative splicing-regulated network of candidate genes for diabetes. This hypothesis remains to be further investigated.

221. Presentation of insulin granule derived peptides on MHC I in Enterovirus-infected beta cells and type 1 diabetes

Authors: ***Z. Marinicova, M. Ghosh, K.-P. Knoch, A. Petzold, C. Wegbrod, A. Sönmez, R. Scharfmann, S. Stevanović, M. Solimena, Germany, France***



393. Validation of exendin for beta cell imaging: *ex vivo* autoradiography of human pancreas demonstrates specific accumulation of radiolabeled exendin in islets of Langerhans

Authors: ***M. Gotthardt, T.J. Jansen, M. Buitinga, C. Frielink, M.W. Stommel, M.B. Van der Kolk, H. Van Goor, B.E. De Galan, M. Boss, M. Brom, Netherlands, Belgium***

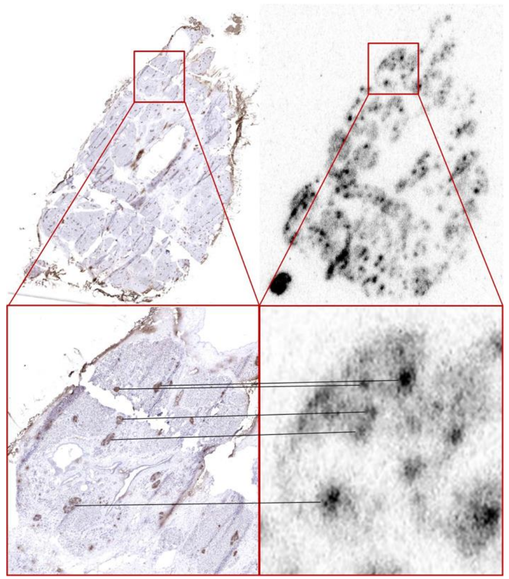


Figure 1: Human pancreatic tissue samples without tumour obtained after surgical resection. Tissue samples were immunohistochemically stained for insulin (left image) and used for autoradiography (right image). The islets of Langerhans can be distinguished on the insulin-stained section and colocalize with high tracer uptake at the position of the islets on the autoradiographic image (colocalized regions connected by lines). Exocrine uptake of the tracer is clearly lower than the uptake in the endocrine tissue (right image).

361. The assessment of intrahepatic islet transplantation using exendin PET imaging

Authors: ***T.J. Jansen, M. Buitinga, M. Boss, E.J. De Koning, M.A. Engelse, M.F. Nijhoff, I. Velikyan, O. Korsgren, O. Eriksson, M. Brom, M. Gotthardt, Netherlands, Belgium, Sweden***

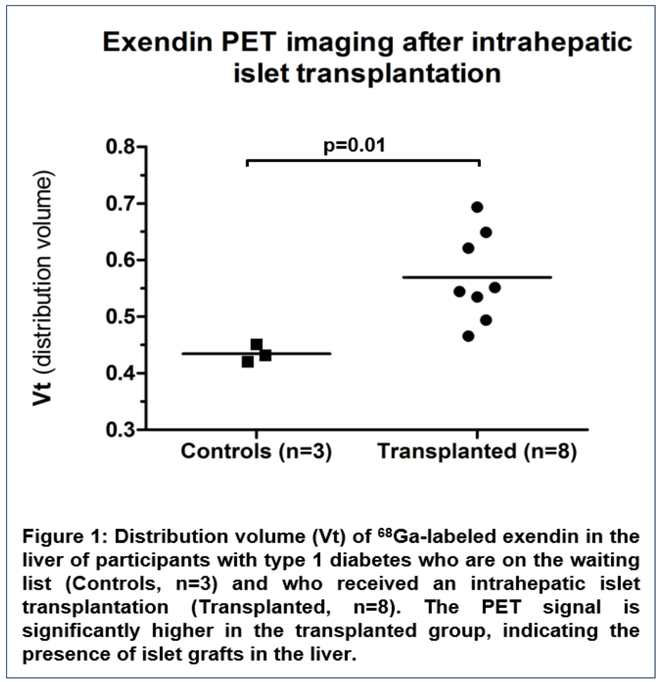


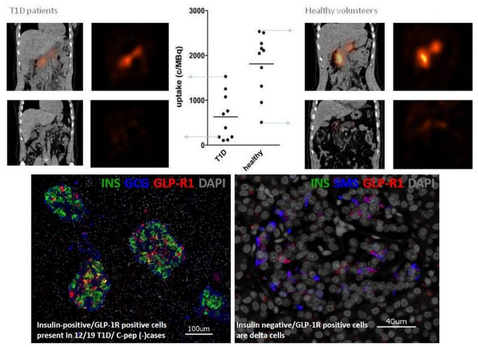
Figure 1: Distribution volume (Vt) of ^{68}Ga-labeled exendin in the liver of participants with type 1 diabetes who are on the waiting list (Controls, n=3) and who received an intrahepatic islet transplantation (Transplanted, n=8). The PET signal is significantly higher in the transplanted group, indicating the presence of islet grafts in the liver.

INNODIA-related oral presentations

43. ^{111}In-exendin spect imaging suggests presence of residual beta cells in patients with longstanding type 1 diabetes

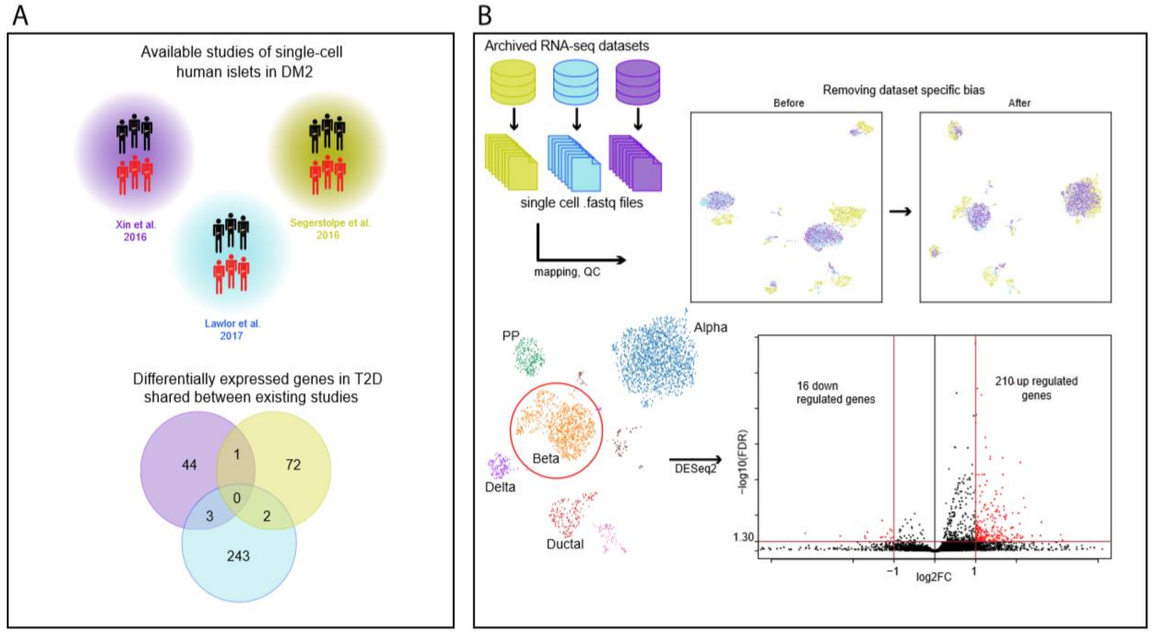
Authors: ***M. Boss, I. Kusmartseva, W. Woliner-van der Weg, L. Joosten, M. Brom, M. Béhe, C.J. Tack, O.C. Boerman, M.J. Janssen, M. Atkinson, M. Gotthardt, Netherlands, USA, Switzerland***

This is hampered by the lack of methods to quantify beta cell mass in vivo in humans. In this study, SPECT/CT imaging using radiolabeled exendin shows significant tracer uptake in the pancreas of 6/10 individuals with type 1 diabetes. Immunohistochemical analysis of pancreatic samples of C-peptide negative T1D patients corroborates these results showing remaining insulin/GLP-1R positive cells in 12/19 cases. Background tracer uptake in all patients seems to be te result of GLP-1R expression on delta cells.



212. Integration of single-cell datasets reveals novel transcriptomic signatures of beta cells in human type 2 diabetes

Authors: ***E. Bosi, L. Marselli, C. De Luca, M. Suleiman, M. Tesi, M. Cnop, D. Eizirik, M. Ibberson, P. Marchetti, Italy, Belgium, Switzerland***



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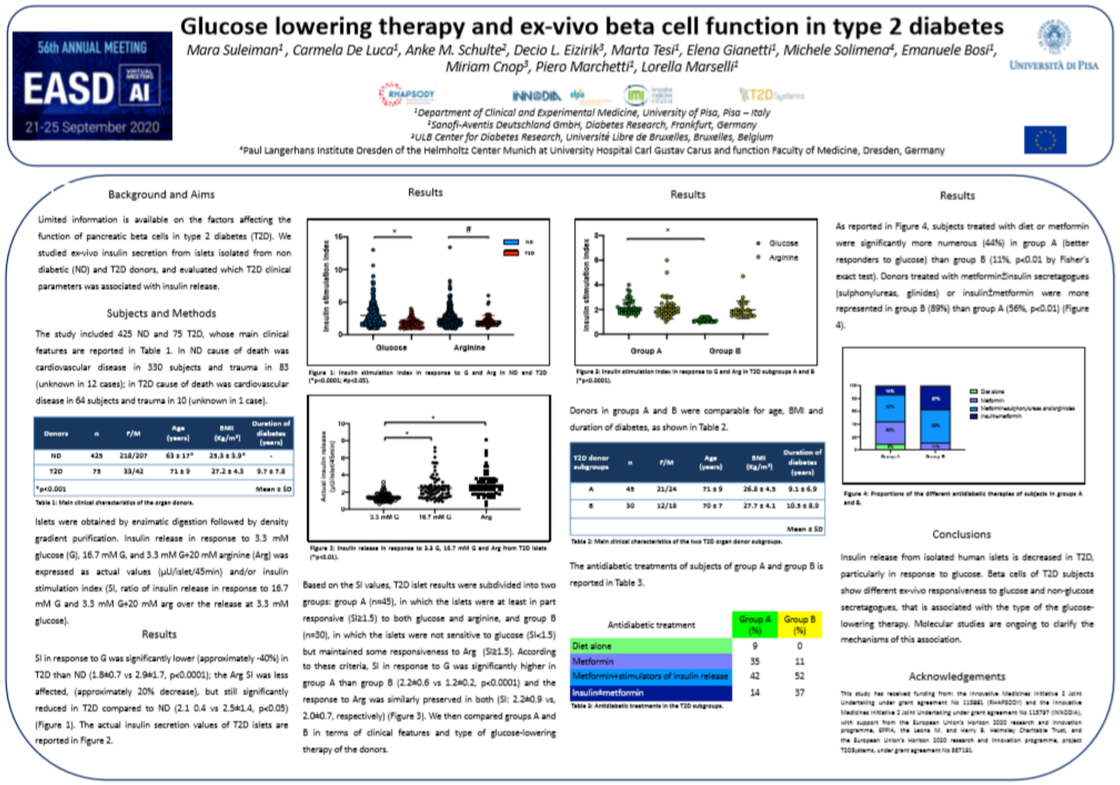
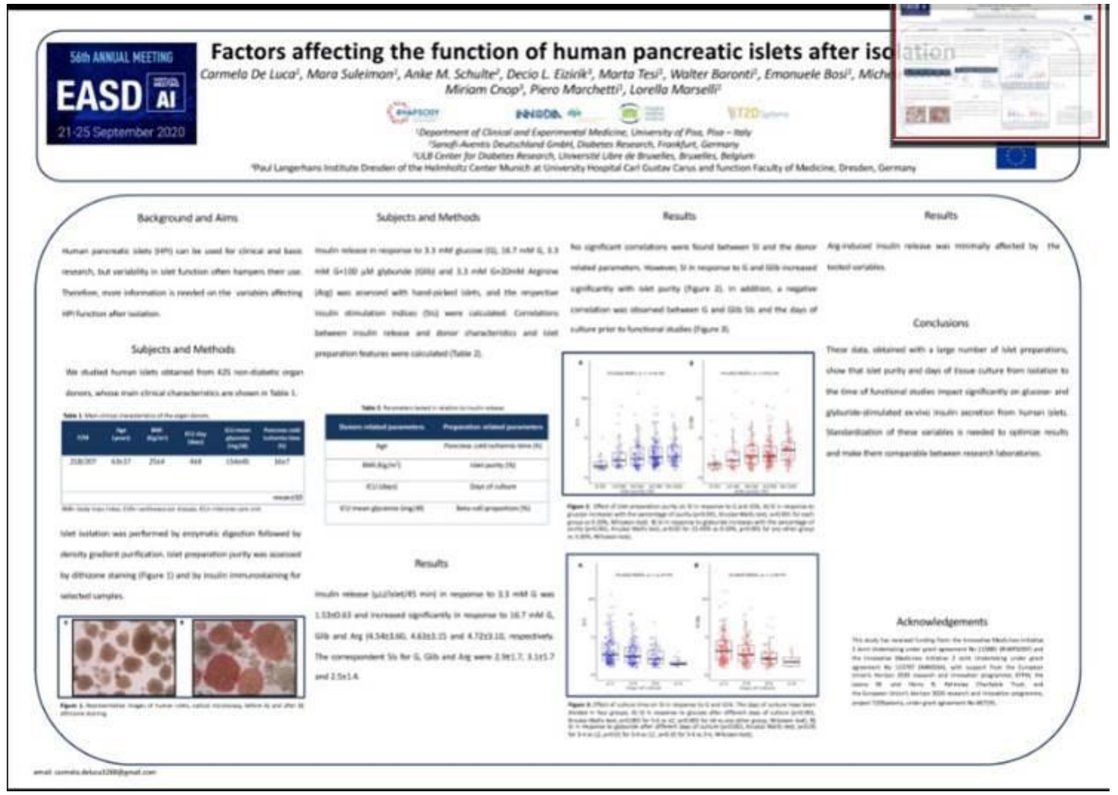
396. Glucose-lowering therapy and ex-vivo beta cell function in type 2 diabetes

Authors: ***M. Suleiman, C. De Luca, A.M. Schulte, D.L. Eizirik, M. Tesi, E. Gianetti, M. Solimena, E. Bosi, M. Cnop, P. Marchetti, L. Marselli, Italy, Germany, Belgium***



360. Factors affecting function of human pancreatic islets after isolation

Authors: ***C. De Luca, M. Suleiman, A.M. Schulte, D.L. Eizirik, M. Tesi, W. Baronti, E. Bosi, M. Solimena, M. Cnop, P. Marchetti, L. Marselli, Italy, Germany, Belgium***



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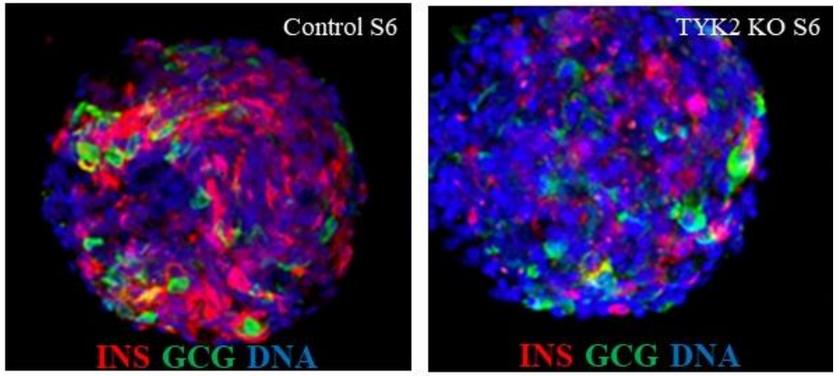
244. Regulatory role of tyrosine kinase 2 (TYK2) in human pancreatic endocrine differentiation

Authors: V. Chandra, H. Ibrahim, J. Kvist, D. Balboa, R.B. Prasad, O.P. Dwivedi, L. Groop, D. Eizirik, T. Otonkoski, Finland, Spain, Sweden, Belgium

Role of TYK2 in human pancreatic development and early innate immune response

- ✓ Tyrosine kinase 2 (TYK2) is a member of the Janus kinase (JAK) family of tyrosine kinases, plays critical role in the intracellular signalling of several cytokines (IL6, IL12, IL23 etc.) and type I interferons through activation of STATs signalling pathway
- ✓TYK2 has been associated with several autoimmune disease such as rheumatoid arthritis and type 1 diabetes
- ✓TYK2 complete knockout iPS model has been generated and validated for the modelling of pancreatic islet development and biology of type-I interferon
- ✓ TYK2 KO in iPS cells does not interfere with pluripotency properties and definitive endoderm differentiation
- ✓ TYK2 KO cells show impaired early pancreatic endocrine differentiation
- ✓ TYK2 KO completely abolishes STAT1 and STAT2 phosphorylation after treatment with IFN type I (but not type II)
- ✓Deep RNAseq and Single-cell RNAseq analysis shows marked KRAS upregulation in TYK2 KO cells at all differentiation stages
- ✓Inverse relationship of TYK2 and KRAS expression verified in human fetal pancreas and adult islets

Vikash Chandra, Decio Eizirik, Timo Otonkoski …
University of Helsinki, Finland



373. Phasor-film analysis of beta cell metabolic trajectory upon glucose stimulation

Authors: **G. Ferri, M. Tesi, F. Massarelli, L. Marselli, P. Marchetti, F. Cardarelli, Italy**