Defining Outcomes for β-Cell Replacement Therapy in the Treatment of Diabetes
THE INTERNATIONAL PANCREAS AND ISLET TRANSPLANT ASSOCIATION AND
THE EUROPEAN PANCREAS AND TRANSPLANT ASSOCIATION
WOULD LIKE TO THANK THE FOLLOWING ORGANIZATIONS FOR THEIR GENEROUS SUPPORT
WITHOUT WHOM THIS IMPORTANT MEETING WOULD NOT HAVE BEEN POSSIBLE.

VENUE INFORMATION

VENUE: The workshop will take place in the Panorama room of the Congresspark Igls.
Eugenpromenade 2, A-6080 Igls
p.a. Postfach 533
6020 Innsbruck, Austria
BREAKFAST: At your leisure at your hotel

07:30 REGISTRATION DESK OPENS

08:30 WELCOME BY MEETING ORGANIZERS AND REVIEW OF MEETING OBJECTIVES
Eelco de Koning, Lorenzo Piemonti, Hans Pratschke, Peter Stock and Michael Rickels

Workshop objectives:
• Develop consensus for an IPITA/EPITA Statement on the definition of complete function, partial function, and failure of current and future forms of β-cell replacement therapies
• Review the metabolic and immunologic outcome measures used to select patients for and assess the efficacy of β-cell replacement therapies in the treatment of diabetes
• Ensure consistency of definitions for glycemic control metrics with the field of artificial insulin delivery/artificial pancreas development
• Build network of collaborators to foster scientific synergy in the clinical investigation of various β-cell replacement and artificial insulin delivery approaches to diabetes

08:45 REPORT FROM THE JDRF T1D OUTCOMES PROGRAM
Marjana Marinac, USA

09:00 SESSION I: INDICATIONS FOR AND APPROACHES TO β-CELL REPLACEMENT THERAPY
Session Chairs: Hans Pratschke and Raja Kandaswamy

Objective:
Patient candidates and available forms of β-cell replacement vary. The goal of this session is to define those patient characteristics that directly influence the availability of β-cell grafts and measures of glycemic control and graft function, and so lay the framework for how definitions of successful outcomes may be tailored by indication.

09:05 1.1 | β-CELL REPLACEMENT FOR PATIENTS (TYPE 1 AND TYPE 2 DIABETES) REQUIRING RENAL REPLACEMENT THERAPY
Yogish Kudva, USA

09:20 1.2 | β-CELL REPLACEMENT THERAPY FOR PATIENTS EXPERIENCING PROBLEMATIC HYPOGLYCEMIA
James Shaw, United Kingdom

09:35 1.3 | WHAT NON-UREMIC, NON-TYPE 1 DIABETES PATIENTS SHOULD BE CONSIDERED FOR β-CELL REPLACEMENT?
Eelco de Koning, The Netherlands

09:50 1.4 | DISCUSSION
Moderators: Helmut Arbogast and Rodolfo Alejandro

10:10 COFFEE BREAK
10:30 SESSION 2: OUTCOME MEASURES OF GLUCOSE HOMEOSTASIS
Session Chairs: Eelco de Koning and Barbara Ludwig

Objective:
Regulation of glucose homeostasis involves the maintenance and return of glucose excursions to a non-diabetic range of glycemia. Various measures of glycemic control capture average glycemia, glycemic variability, and exposure to hyper- and hypoglycemia, as well as hypoglycemia awareness and severity. The goal of this session is to define successful outcomes for glycemic control, and align definitions with those used in the field of artificial insulin delivery/artificial pancreas development.

10:35 2.1 | MEASURES OF AVERAGE GLYCEMIC CONTROL AND GLYCEMIC VARIABILITY
Marie-Christine Vantyghem, France

10:50 2.2 | MEASURES OF HYPOGLYCEMIA EXPOSURE, AWARENESS AND SEVERITY
Pratik Choudhary, United Kingdom

11:05 2.3 | WHAT ARE THE MINIMUM CRITERIA FOR ASSESSING GLYCEMIC CONTROL AFFORDED BY β-CELL REPLACEMENT?
Roger Lehmann, Switzerland

11:20 2.4 | WHAT FURTHER CRITERIA SHOULD BE CONSIDERED FOR COMPARISON TO ARTIFICIAL PANCREAS SYSTEMS?
Melena Bellin, USA

11:35 2.5 | DISCUSSION
Moderators: Yogish Kudva and Esther Latres

12:00 LUNCH

13:00 SESSION 3: OUTCOMES MEASURES OF β-CELL GRAFT FUNCTION AND DEMAND
Session Chairs: Michael Rickels and Robert Langer

Objective:
Measures of β-cell graft function may vary by the stimulus for secretion, differences in metabolic clearance, demands for secretion imposed by differences in insulin sensitivity or the use of insulin, as well as any possible residual native β-cell function. The goal of this session is to define a meaningful reduction in insulin requirements attributable to β-cell graft function, necessary confirmatory testing, relationship to standardized measures of glucose tolerance, and differences between type 1 and type 2 diabetic recipients.

13:05 3.1 | MEASURES OF β-CELL GRAFT FUNCTION AND DEMAND DERIVED FROM FASTING BLOOD SAMPLING AND INSULIN REQUIREMENTS
Francois Pattou, France

13:20 3.2 | MEASURES OF β-CELL GRAFT FUNCTION DERIVED FROM ORAL GLUCOSE OR MIXED-NUTRIENT MEAL TOLERANCE TESTS
Peter Senior, Canada
13:35 3.3 | WHAT ARE THE MINIMUM CRITERIA FOR ASSESSING β-CELL GRAFT FUNCTION?
Raja Kandaswamy, USA

13:50 3.4 | WHAT FURTHER CRITERIA SHOULD BE CONSIDERED TO MOST ACCURATELY CHARACTERIZE β-CELL MASS?
Bart Keymeulen, Belgium

14:05 3.5 | DISCUSSION
Moderators: Melena Bellin and Barbara Ludwig

14:30 BREAK

15:00 SESSION 4: OUTCOME MEASURES OF IMMUNOLOGIC MECHANISMS
Session Chairs: Peter Stock and Jon Odorico

Objective:
Differentiating immunologic from metabolic mechanisms for β-cell graft dysfunction and/or failure is paramount to understanding the outcomes and implications of functional β-cell graft monitoring. The goal of this session is to define useful assays of allo- and autoimmune reactivity and when they should be employed to compliment the metabolic evaluation of β-cell replacement therapies.

15:05 4.1 | IDENTIFICATION AND INTERVENTION OF β-CELL GRAFT ALLOIMMUNITY IN THE CONTEXT OF GRAFT DYSFUNCTION
Thierry Berney, Switzerland

15:20 4.2 | IS THERE A ROLE FOR ASSESSMENT OF β-CELL GRAFT AUTOIMMUNITY IN THE CONTEXT OF GRAFT DYSFUNCTION?
Tom Kay, Australia

15:35 4.3 | PROPOSED ALGORITHM FOR THE ASSESSMENT OF DECLINING β-CELL GRAFT FUNCTION
Peter Stock, USA

15:50 4.4 | DISCUSSION
Moderators: Steve White and Lorenzo Piemonti

16:15 ADJOURN DAY 1

19:30 INVITED SPEAKER WORKSHOP DINNER (by invitation only)

Agidhof Restaurant
Bilgeristraße 1
Igls, Tirol
### BREAKFAST: At your leisure at your hotel

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<td>08:30</td>
<td>SATURDAY SESSION RECAP AND REVIEW OF OBJECTIVES FOR THE FINAL SESSION</td>
<td>Eelco de Koning, Lorenzo Piemonti, Hans Pratschke, Peter Stock and Michael Rickels</td>
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<td>08:45</td>
<td>SESSION 5: DEFINING SUCCESSFUL OUTCOMES</td>
<td>Session Chairs: Lorenzo Piemonti and Thierry Berney</td>
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<td>08:50</td>
<td>5.1</td>
<td>DEFINITION OF COMPLETE FUNCTION, PARTIAL FUNCTION, AND FAILURE OF CURRENT AND FUTURE FORMS OF β-CELL REPLACEMENT THERAPIES</td>
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<td>DEFINITION OF PATIENT SPECIFIC AND APPROACH SPECIFIC INCLUSION OF CRITERIA TAILORED TO EACH FORM OF β-CELL REPLACEMENT THERAPY</td>
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<td>09:25</td>
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<td>DEFINED METRICS THAT ARE COMPARABLE WITH THE FIELD OF ARTIFICIAL INSULIN DELIVERY/ARTIFICIAL PANCREAS DEVELOPMENT, AND WHICH MAY BE USED FOR FUTURE COMPARATIVE EFFICACY CLINICAL TRIALS</td>
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<td>10:30</td>
<td>MEETING WRAP-UP AND PLAN FORWARD</td>
<td>Eelco de Koning, Lorenzo Piemonti, Hans Pratschke, Peter Stock, Mike Rickels</td>
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DEFINITIONS

• Full function of a β-cell graft requires independence from exogenous insulin, and non-diabetic measures of glycemic control and tolerance (HbA1c ≤ 6.5%, fasting glucose < 126 mg/dl, 2-hour glucose < 200 mg/dl during an OGTT, and/or 90-minute glucose < 180 mg/dl during a MMTT).

Corollary: Insulin independence requires the maintenance of non-diabetic measures of glycemic control and tolerance. Diabetes in the presence of a β-cell graft should be treated with insulin to target non-diabetic ranges of glycemic exposure.

• Partial function of a β-cell graft requires a reduction from pre-transplant daily insulin requirements, and an increase from pre-transplant levels of C-peptide. The goal of supporting partial β-cell graft function is to maintain on-target glycemic control (HbA1c < 7.0%) in the absence of severe hypoglycemia. In the absence of on-target glycemic control by HbA1c, on-going support of partial β-cell graft function may be justified by documented reduction in exposure to serious hypoglycemia (glucose < 55 mg/dl) together with improved hypoglycemia awareness and avoidance of severe hypoglycemia.

• Failure of a β-cell graft is defined by a return to near pre-transplant daily insulin requirements, when absent prior to transplantation, loss of physiologically relevant levels of stimulated C-peptide, and is further supported by a return to the degree of hyper- or hypoglycemia present that indicated transplant therapy.

INDICATIONS

• A diabetic patient awaiting deceased donor kidney transplantation should be considered for simultaneous deceased donor pancreas (or where available islet) transplantation provided:
  - They are an appropriate procedural candidate by age and BMI;
  - Their daily insulin requirements are not excessive (< 1 unit/kg).

• A type 1 diabetic patient already immunosuppressed for a stable, functioning kidney graft should be considered for any β-cell replacement therapy provided:
  - They are an appropriate procedural candidate;
  - Their daily insulin requirements are not excessive (< 1 unit/kg);
  - Hyperglycemia (HbA1c > 7.5%) is present that threatens the longevity of their kidney graft;
  - There is problematic hypoglycemia.

• A type 1 diabetic patient with normal kidney function may be considered for any β-cell replacement therapy requiring immunosuppressive drug treatment provided:
  - They are an appropriate procedural and immunosuppressive drug candidate;
  - Their daily insulin requirements are not excessive (< 1 unit/kg);
  - There is problematic hypoglycemia.
METRICS

GLYCEMIC CONTROL FOR COMPARISON OF β-CELL REPLACEMENT AND ARTIFICIAL PANCREAS THERAPIES:

• Average glycemic control should be assessed by:
  - HbA1c;
  - Mean glucose by CGM;
  - Percent time in glucose range 70 – 140 or 70 – 180 mg/dl by CGM.

• Glycemic variability should be assessed by:
  - Glycemic lability index;
  - Glucose SD or CV by CGM.

• Hypoglycemia awareness should be assessed by:
  - Gold score;
  - Clarke score.

• Hypoglycemia severity should be assessed by:
  - HYPO score;
  - Percent time in glucose range < 70, 60, 55, or 50 mg/dl by CGM;
  - Incidence of severe hypoglycemia events.
For post-event information related to this meeting:

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