Highlights from IMI diabetes portfolio – paving the way for precision medicine and disease modifying therapies

Chantal Mathieu, MD PhD
Endocrinology, KULeuven, Leuven, Belgium

*IMI Impact on Diabetes*
CM serves or has served on the advisory panel for Novo Nordisk, Sanofi, Merck Sharp and Dohme Ltd., Eli Lilly and Company, Novartis, AstraZeneca, Boehringer Ingelheim, Roche, Medtronic, ActoBio Therapeutics, Pfizer, Insulet and Zealand Pharma. Financial compensation for these activities has been received by KU Leuven; KU Leuven has received research support for CM from Medtronic, Novo Nordisk, Sanofi and ActoBio Therapeutics; CM serves or has served on the speakers bureau for Novo Nordisk, Sanofi, Eli Lilly and Company, Boehringer Ingelheim, Astra Zeneca and Novartis. Financial compensation for these activities has been received by KU Leuven.
We have come a long way........in 100 years....
Intensive vs. conventional treatment in T1D
DCCT/EDIC follow-up data – intensive treatment yields long-term benefits

Glycaemic control and microvascular complications\textsuperscript{1,2}

<table>
<thead>
<tr>
<th>Complication</th>
<th>Conventional</th>
<th>Intensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinopathy</td>
<td>*66%</td>
<td>***76%</td>
</tr>
<tr>
<td>Neuropathy at EDIC year 1 positive examination</td>
<td>###62%</td>
<td>**53%</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td></td>
<td>***86%</td>
</tr>
</tbody>
</table>

Intensive glycemic control and macrovascular complications\textsuperscript{3}

Intensive treatment reduced CV risk by 42% ($p=0.02$)
10% decrease in HbA\textsubscript{1c} = 20% reduction in CV events ($p=0.01$)

CV, cardiovascular; DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications; T1D, type 1 diabetes

Achieving glycemic control

- Insulin
- Exercise
- Stress
- Food
- Stress
In detail, the Hypo-RESOLVE consortium will address the following challenges:

- Establish a dialogue with regulators and other stakeholders about hypoglycaemia in general and more specifically the limitations from the Hypo-RESOLVE project in order to develop a consensus on definitions and data collection methods for the anonymization of clinical investigations with regard to hypoglycaemia.

- Undertake health economic analyses which extend beyond severe hypoglycaemia and will measure the economic impact of hypoglycaemic episodes.

- Determine the psychological impact of hypoglycaemia in people with diabetes and family members, and develop patient reported outcome measures to assess the psychological impact of hypoglycaemia and can be included as standard outcome measures in future clinical trials, both commercial and academic.

- Conducting integrated non-clinical and translational studies to identify, understand molecular mechanisms, consequences and biomarkers of impaired awareness of hypoglycaemia (IAI) and recurrent hypoglycaemia.

- Combining large datasets obtained from various pharmaceutical technology companies using different methods of data capture.

- Conducting extensive statistical analyses in large data sets to confirm existing predictors and consequences of hypoglycaemia and identify new associations.

- Establishing how the best potential of continuous glucose monitoring (CGM) systems as clinical and research tools, can be used in clinical practice and incorporated successfully in future clinical trials.
Can you make it go away?
INNODIA and INNODIA HARVEST: Public Private Partnerships for T1D in Europe
Objectives of INNODIA

1. 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**.

2. 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.

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

4. 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.

5. 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.
1. **WE HAVE developed** 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. **WE HAVE generated** an **unrivalled bioresource of T1D discovery science**.

2. **We HAVE established** 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.

3. **We ARE advancing** the **development and application of novel methodologies** by exploiting our major strengths in bioresource and ‘omics’ technologies.

4. **We HAVE established** a **unique integrated database** assimilating historical data, with data from clinical and experimental sources. This **permits** 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**.

5. **We HAVE conceived** **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.
Organisation of INNODIA

Clinical EU Centers-Patient cohorts
- Newly Diagnosed
- Unaffected Family Members

WP1
- Centralized Sample storage

WP2
- Biomarker analysis, Validation core analytical Tools

WP3
- Basic Research
  - Animal models
  - Mechanistic studies

WP4
- Big Data systems biology, in silico modelling

WP5
- Innovative Clinical Protocols
  - Master Protocol
  - Standardisation
- Clinical trials
  - Acceleration
"OF THE PEOPLE, living with T1D
BY THE PEOPLE, living with T1D
FOR THE PEOPLE, living with T1D
INNODIA PAC Members

Anders

Johan

Nathalie

Jaivir

Olivier

Finn

Markku

Veerle

Kyle

Jente and Dries
Recruitment update
*Status on 7th June 2021*

4979 Participants recruited:
- 646 Newly Diagnosed **Target 750**
- 4333 First degree relatives screened **Target 4000**
- 324 UFM with AA+ (260 in follow-up so far)

Approval UK Ethics Nov 2016
All sites ready Oct 2017
Biomarker discovery

BIOMARKER MODULES

1. β-CELL
   1.1 Imaging
   1.2 Death assays

2. IMMUNOME
   2.1 Innate cells, T cells, B cells
   2.2 AAbs, isotypes
   2.3 Function & Regulation

3. GENOME
   3.1 Genotype
   3.2 Immune cell
   3.3 Single cell

4. PROTEOME
   4.1 Serum proteome
   4.2 Proteome in T cell subsets

5. METAB- /LIPID-OME
   5.1 Serum metabolome
   5.2 Metabolome in T cell subsets and primary islets

TEST SET PHASE I

- New-onset T1D
- High risk AAb+/genes
- Age-matched controls

NEW COLLECTIONS FROM WP1

VALIDATION SET PHASE II

- Biological sample collection
- ND: <= 6 weeks
  - 2 years collection
  - 3, 6 & 12 monthly
  - UFM AAB+
  - 4 years collection
  - 6 monthly

EXISTING COLLECTIONS FROM WP1

SYSTEMS BIOLOGY WP4

TRIAL DESIGN WP5

EUnPOD

Molecules/genes/pathways

PATHOGENESIS WP3

Validation Surrogates
Single/Combinatorial Trans-modular Integration
Sample transport and dispatching
Central database

Overview
Our Type 1 diabetes (T1D) is a life-threatening, autoimmune chronic disease present at any age. Typically presents in early life with a peak around puberty. It affects around 17 million people in Europe and there is no way to prevent it, and at present, no cure. Every hour, 24h a day, 365 days a year we, the members of the Patient Advisory Committee, live with this disease, with hypo and hyperglycaemia fear. Just like you.

Overall objective
The overall objective of INNODIA therefore is to advance in a decisive way how we predict, evaluate and prevent the onset and progression of type 1 diabetes (T1D), by creating novel tools, such as biomarkers, disease models and clinical trial paradigms. These tools will allow to distinguish and understand at the cellular and molecular level distinctive paths of ontogeny and progression in this heterogeneous disease, thus impacting on the future management of T1D patients and at risk individuals. For this goal, INNODIA will establish a comprehensive and interdisciplinary network of clinical and basic scientists, who are leading experts in the field of T1D research in Europe, with complementary expertise from the areas of immunology, beta-cell biology and biomarker research. The consortium will interact in a coordinated fashion with all major stakeholders in the process, in particular regulatory bodies and patients with T1D and their families.
Whole blood flow data is shown below the graph for PBMC yield.
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5. 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.
INNODIA and INNODIA HARVEST publications (as of end May 2021)

INNODIA (and INNODIA HARVEST) publications as of end May 2021

No. of publications | 1 | 2 | 3 | 4 | > 4
--- | --- | --- | --- | --- | ---
2017 | 15 | 8 | 21 | 3 | 2
2018 | 41 | 23 | 5 | 2 | 3
2019 | 36 | 22 | 7 | 3 | 1
2020 | 20 | 10 | 6 | 1 | 3
2021 | 13 | 7 | 8 | 1 | 6

No of PIs
- 2017
- 2018
- 2019
- 2020
- 2021

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Coordination of Clinical Trials in INNODIA and INNODIA HARVEST

Clinical Coordination Centre (CCC)
- Structure for overall trial coordination

Clinical Coordination Team (CCT)
- Day-to-day managing of the trial network
### Status clinical trials (June 7th 2021)

<table>
<thead>
<tr>
<th></th>
<th>MELD ATG</th>
<th>Ver-A-T1D</th>
<th>Impact</th>
<th>CFZ533</th>
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</thead>
<tbody>
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<td><strong>Open</strong></td>
<td>Belgium, Germany</td>
<td>Austria, Germany, Belgium, UK</td>
<td>Belgium, UK, Italy, Slovenia, Sweden</td>
<td>Belgium*, Slovenia, Italy*, UK (and Spain*)</td>
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<tr>
<td>screened</td>
<td>11</td>
<td>5</td>
<td>49</td>
<td>1</td>
</tr>
<tr>
<td>randomised</td>
<td>9</td>
<td>3</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>approved in</td>
<td>UK, Finland and Slovenia Other countries submitted or preparing submission</td>
<td>UK and Sweden Other countries submitted or preparing submission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start of study</td>
<td>Dec 2020</td>
<td>Feb 2021</td>
<td>Nov 2020</td>
<td>Nov 2020</td>
</tr>
</tbody>
</table>

*Spain and some sites in Belgium and Italy are non-INNODIA country/site, number for INNODIA sites only*
Conclusion

Stronger than ever
Open for business

Thank you to all!

INNODIA

LinkedIn
@innodiagroup

www.INNODIA.eu
INNODIA is a unique and interdisciplinary network of 40 partners, including preeminent academic institutions from Europe, industrial partners, charitable foundations and small sized enterprises and a dedicated group of advising patients, bringing together their knowledge and experience to achieve one common goal: "To fight type 1 diabetes". Launched in January 2016, this European-based public private partnership (PPP) receives funding from the Innovative Medicines Initiative 2 Joint Undertaking (Grant Agreement Number: 115797) and is supported by the European Union's Horizon 2020 Research and Innovation program, European Federation of Pharmaceutical Industries and Associations (EFPIA), The Leona M. and Harry B. Helmsley Charitable Trust and JDRF. INNODIA HARVEST (Grant Agreement Number: 945268) an extension of INNODIA, enables to run more clinical trials on the backbone of the INNODIA clinical network.