

### Summary of the context and overall objectives of the project

The overall objective of INNODIA is to advance in a decisive way how we predict, stage, evaluate and prevent the onset and progression of type 1 diabetes (T1D). We are achieving this by creating novel tools, such as biomarkers, disease models and clinical trial paradigms. These tools allow us 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. We have established an interdisciplinary network of clinical and basic scientists, who are leading experts in the field of T1D in Europe, with complementary expertise from the areas of immunology,  $\beta$ -cell biology, biomarker research and T1D therapy, joining forces in a coordinated fashion with our industry partners and two foundations, as well as with patients with T1D and their families.

### Work performed from the beginning of the project to the end of the period covered by the report and main results achieved so far

After our major efforts at the start of INNODIA focusing on standardization of sampling protocols and ethical approvals, all clinical partners (WP 1) are now recruiting at full speed, resulting in an exponential increase of recruitment to a total of 3000 participants (350 newly diagnosed T1D and 2650 first degree family members). Our clinical network is expanding, with new partners joining INNODIA (ULUND, UniSR and OPBG) and satellites of established INNODIA partners now present in 6 countries. All clinical centers are accredited (or in the process of accreditation) and have been trained for use of the INNODIA eCRF. Collaborations with the Patient Advisory Committee (PAC) have led to the production of materials for promoting and explaining the study to a range of audiences (see WP6). Normal and T1D whole pancreases were collected as part of EUnPOD. Those tissues, together with the Exeter Archival Diabetes Biobank are available for distribution to partners.

We have fully conceived the modular interrogation platforms for analysis of cellular and molecular features of T1D for beta-cell and immune cells, proteomes, lipidomes and metabolomes (WP2). Six Immune Hubs or Sub-Hubs (KCL, LUMC, INSERM, TUD, UNISI and UH) are installed and active. Sample type, collection process, storage etc. has been specified, and where necessary has been the subject of training, including Wet Workshops for the Immune Hubs. We are now in the final stages of performing an integrated multi-omics natural history study on samples of newly diagnosed (ND) participants in INNODIA ('the first 100' cohort; the first 100 ND individuals in INNODIA). For this purpose, we have identified longitudinal samples (up to 12 months follow up) from the defined 'first 100'. Within the multi-omics approach following data have been generated during or are in the process to be generated (delivery date Q1 2020): Plasma samples: Metabolomics, Lipidomics and micro/smallRNA; Genomics; Whole blood sample: RNAseq; Serum samples: Proteomics; Fresh & frozen PBMC: Immunomics. This has been made possible through an exceptional period of coordinated activity between WP1, 2 and 4, with blinded samples (accompanied by appropriate QC samples) being shipped to the laboratories.

WP3 aims to gain better insight in the way beta-cells are destroyed in T1D. Development of novel biomarkers in particular is being pursued. Our collaborative research, focusing on the interplay between beta-cell and immune system has progressed in period 4, with many exchanges, collaborations and face to face meetings, leading to presentations in national and international fora, publications in peer-reviewed scientific journals (43 manuscripts by different WP3 partners), and, as important, publications and presentation in lay fora. Of importance, novel biomarkers (in lipidomics, metabolomics, proteomics, siRNA-omics) issuing from WP3 work have now been incorporated in the multi-omics analysis performed on the 'first ND 100' described under WP2.

WP4 is devoted to the establishment of an integrative systems biology platform and in silico modelling for T1D. An eCRF data capture system has been developed for electronic capturing of patient data. The system is essential in enabling continuous, centralized monitoring of processed data and makes it possible to quickly detect and verify compliance of sites with Standard Operating Procedures developed by WP2. A crucial role for WP4 in period 4 has been the work in the biomarker identification effort on 'the first 100', preparing INNODIA for the first integrative analysis effort of clinical with multi-omics data. Finally, WP4 has been instrumental in expanding the eCRF system to comply with regulatory requirements to be used in intervention clinical trials e.g. the imminent MELD-ATG (Minimal effective low dose Thymoglobulin) trial.

As INNODIA moves to the next level (clinical trial initiation), the role of WP5 grows. In INNODIA we had foreseen the initiation of one clinical trial, but we have progressed more rapidly than foreseen and are already now at the stage of clinical trial initiation. To streamline our efforts, we have taken several steps:

1) Accreditation of clinical centers. All centers of the INNODIA clinical trial network have been accredited in 2017 and 2018 and are being followed up for quality in recruitment (see WP4). New centers will be accredited in Q1 2020, and re-accreditation of existing centers is planned; 2) Establishment of a Masterprotocol on which clinical trials in INNODIA will run and that allows adaptive and novel trial design. This has been finalized and presented for Scientific Advice (at SAWP EMA) in 2019; 3) Establishment of a Clinical Trial Prioritisation Committee (ICTPC, headed by HKA). In 2019, the ICTPC has received 3 new proposals, two of which were accepted. 4) Preparation and running of the first INNODIA trial: MELD-ATG (UCAM sponsor, KULeuven legal representation in EU, Sanofi providing study drug), scheduled to start in Q2 2020.

Finally, WP6 groups all the work of managing and running INNODIA. As INNODIA grows in partners, in recruitment and in scientific output, we are stepping up the management of INNODIA. Next to overall project management (scientific and financial reporting, financial follow up of partners, follow up of activities of partners, promoting collaborations and interactions, organizing meetings, interacting with IMI), specific attention has been dedicated in 2019 to communication and visibility (an extra communication person has been hired and the PAC has been more active than ever), expansion (in budget, partners and projects), long term sustainability and dealing with the issue of Brexit considering the number of British partners.

#### **Progress beyond the state of the art, expected results until the end of the project and potential impacts**

All activities have progressed well, with all deliverables and milestones achieved according to plan. All partners are working with full enthusiasm and energy, in the individual work packages (WP), linked together through the efforts of the Management and the Coordination team. We are now ready for important next steps: the 'first 100' integrated systems biology analysis of the clinical, metabolic and multi-omic data gathered in our natural history study and present in our central INNODIA data warehouse; the initiation of our first clinical trial (MELD-ATG) on the backbone of our innovative Masterprotocol and the realization of our view for the future, including expansion of the network with new partners and more basic research and clinical trials, all in close harmony with the guidance of our PAC, representing people living with T1D and their families.

