

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). This will be achieved by creating novel tools, such as biomarkers, disease models and clinical trial paradigms. These tools will 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, β -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

Whereas during the first INNODIA year, major efforts were focusing on standardization of sampling protocols and ethical approvals, all clinical partners (in work package 1) are now recruiting at full speed, resulting in an exponential increase of recruitment to a total of 1620 participants (160 newly diagnosed T1D and 1460 persons at increasing risk). Regional networks are being established by several partners. Collaborations with the Patient Advisory Committee have led to the production of materials for promoting and explaining the study to a range of audiences. In addition, normal and T1D whole pancreases were collected as part of EUnPOD. Those tissues, together with the Exeter Archival Diabetes Biobank (now included in the INNODIA collection) are available for distribution to partners.

Each clinical recruitment site is linked with one of the 6 Immune Hubs. Assays have been prepared to full readiness for use on fresh immune cell analysis in these Hubs. In addition, a suite of 'Omics' platforms were established (immunomics, genetics/genomics, transcriptomics, proteomics, lipidomics, metabolomics) for sample analysis. Also, we added proof-of-concept to the measurement of microRNAs from preclinical studies; initiated novel in vivo imaging studies in man, obtained extensive immunomic data in the setting of two longitudinal natural history studies and an immune intervention; developed and validated a pipeline for single cell RNA seq on T and B cells; and field tested on relevant samples our lipidomic and proteomic platforms. These achievements place WP2 in a state of advanced planning to conduct a longitudinal study across several selected platforms to identify biomarkers of progression of C-peptide loss. Considering the number of subjects now recruited, WP2 is gearing up to the first transectional cut of data.

WP3 aims to gain better insight in the way β -cells are destroyed in T1D and how the β -cell itself plays a role in its own destruction. Development of novel biomarkers in particular is being pursued. Important achievements of WP3 by the end of the third year include 1) discovery of new neo-autoantigenic epitopes, generated by post-translational modification; including several insulin granule proteins, mRNA splice products, fusion peptides and citrullinated epitopes; 2) generation of new human β -cell lines and patient-derived iPS cells; 3) discovery that miRNAs regulate the expression of pro-apoptotic BH3-only proteins DP5 and PUMA in human beta cells; 4) discovery of a new set of circulating microRNAs, as biomarker for progression of disease in NOD mice; 5) Identification of IFN- α as a key regulator of early markers of β -cell dysfunction/death, and validation of 3 new blockers of IFN- α signaling in human islets; 6) discovery that enteroviruses induce β -cell de-differentiation, 7) discovery that circulating CD8+ T cells are found at similar frequencies in T1D and healthy donors, suggesting a universal state of 'benign' β -cell autoimmunity; 8) development of a robust method for large-scale production of 3-D islet-like aggregates from human pluripotent stem cells; 9) a new biomarker for human β -cell imaging (DPP6) and validation for in vivo imaging; and 10) pre-clinical in vivo validation of a peptide for beta-cell imaging. All these new findings have led to the joint publication of 21 new manuscripts (7 in 2017, 14 in 2018) by different partners of WP3.

A full workpackage is devoted to the establishment of an integrative systems biology platform and in silico modelling for T1D. In this WP4, an eCRF data capture system has been developed for electronic capturing of patient data, which has been adjusted to operational differences of clinical sites recruiting



participants. This system has now received glucose and C-peptide results from Dried Blood Spot cards as well as Mixed Meal and Oral Glucose Tolerance Tests, and additional components have been created to visualize the results. The functionality serves not only as an overview to the researchers and site managers (e.g. for tracking compliance and monitoring quality of incoming data) but it has also been positively reviewed by the clinicians/recruiters as a tool that could be used to engage with the participants and their families.

The system aggregates and visualizes information in real time and allows for an easy comparison between sites with customizable filters (e.g. age of participants or specific visits). 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.

In WP5, a clinical trial coordination center and an accreditation database were established. All centers of the INNODIA clinical trial network have been visited and evaluated by representatives of WP1 and 5 in 2017 and 2018 and have been accredited as eligible clinical research centers for INNODIA.

An INNODIA Clinical Trial Prioritisation Committee (ICTPC) has been established in year 3 and a process to prioritize clinical trials has been introduced. An important deliverable was the design of a master protocol to run trials in INNODIA which was achieved in Q4 2018. According to this master protocol, trials will run on the backbone of INNODIA sample collection (as in WP1), but can collect over and beyond these samples. All data will go into the central INNODIA database (WP4). The ICTPC has already reviewed 3 proposals for clinical trials, of which 2 were accepted. The first clinical trial is expected to start 2019.

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. An important realisation was the establishment of the Patient Advisory Committee (PAC), a central feature of INNODIA. This PAC has been involved in the establishment of the EU INNODIA sampling network, in the writing of sampling protocols and information materials. All clinical trial centers have been accredited, an INNODIA Clinical Trial Prioritisation Committee has been established and 2 clinical trials have been accepted to start in 2019. Dissemination has been on the foreground, with the INNODIA website (www.INNODIA.eu) and an active twitter account (@innodiagroup) reaching a broad general public.

