

PERIODIC REPORT OF THE ACTION P1

Summary

The activities of the first year of INNODIA, an EU consortium with the ambitious aim to advance in a decisive way how we predict, stage, evaluate and prevent the onset and progression of type 1 diabetes (T1D), have progressed according to schedule, with deliverables and milestones achieved according to plan. After a successful launch meeting in Frankfurt in January 2016, all partners have started working in the individual work packages (WP), linked together through the efforts of the Management and the Coordination team. Intense contacts were made, with frequent teleconferences, face to face meetings and physical exchanges between research groups and EFPIA partners. 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. Dissemination has been on the foreground, with the establishment of an INNODIA website (www.INNODIA.eu), where information for the general public is gathered, with special attention to patients and their families. Testimonials, information and interactive tools can be found here. In preparation are cartoons, flyers, toys etc. to inform children and their families on why it is important for them to participate in research within INNODIA and what this research looks like. In addition, the INNODIA website also contains a secure member area in which protocols are shared, documents are available for downloading and internal communication is organised. Press releases informing the general public on the progression of INNODIA as well as a Twitter account, with releases, have been organised e.g. on the occasion of the first family screened within the sampling network. All dissemination is organised by the Management Team (Sanofi, KU Leuven) organised in WP6.

All individual WPs have initiated their work under guidance of the WP-leaders and work has nicely progressed. In WP1 the WP leaders (Dunger (UCAM), Youd (Sanofi) and Knip (UH)) have worked with all WP1 participants to develop the European Clinical Research Network and a coordinator was recruited to run the network in its day to day activities. The sampling protocol in newly diagnosed individuals and in first degree family members was approved by all partners in WP1 and subsequently reviewed by the PAC (Chair Arnaud) and the INNODIA Ethics Committee (Chair Bingley) who also reviewed/revised the patient information sheets, informed consent/assent forms. Pilot studies of home c-peptide studies were completed (Dunger) and standardised procedures for other biological sample collections were developed in collaboration with WP2 (Peakman (KCL)) and eCRF/data tracking systems designed in collaboration with WP4 (Brunak (UCPH) and Pociot (HH-RH)). Ethics and associated approvals for the overall clinical strategy was obtained from the UK in November 2016 and the first family was recruited for the unaffected family member auto-antibody screening later that month thus establishing the year 1 objectives of WP1. In the next weeks translations of the informed consents and information leaflets in 10 additional EU languages are made and roll out of sampling throughout the INNODIA network will happen in the next months. Another important topic in WP1 was the establishment of the INNODIA EUnPOD, a collection of pancreatic specimens and, if available, other tissues from people with T1D.

UNISI (Dotta) has commenced the collection using the same SOPs as the US-based nPOD and has also reached out to additional partners throughout INNODIA to create pancreas collection networks within INNODIA.

Partners in WP2 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. These have been back-tracked to the sample requirements, and a full set of standard operating procedures has been developed together with WP1 in order to commence clinical sample collection. For this purpose WP2 has identified 3 Immune Hubs (KCL, HMGU/TUD and LUMC) as well as 3 subhubs (INSERM, UH, USI) where samples can be frozen and prepared for shipment and analysis. Sample type, collection process, storage etc. has been clarified and specified, and where necessary has been the subject of training, including a Wet Workshop for the Immune Hubs. Additional training sessions for the subhub partners are planned. In addition, assays (eg immunomics) have been prepared to full readiness for use on fresh samples in the Immune Hubs, again with assay training in a Wet Workshop.

WP3 aims to gain better insight in the way beta-cells are destroyed in T1D and how the beta-cell itself plays a role in its own destruction. Development of novel biomarkers in particular is being pursued. This WP has had a very quick start-off, because many of the partners already knew each other, and different collaborations were already ongoing before the start of INNODIA. Important achievements of WP3 during the first year include 1) the discovery of a new neo-autoantigenic epitope, generated by post-translational modification in T1D patients; 2) The generation of new human beta-cell lines; 3) the discovery that miRNAs regulate the expression of pro-apoptotic BH3-only proteins DP5 and PUMA in human pancreatic beta cells; 4) Identification of Interferon-alpha as a key regulator of early markers of beta-cell dysfunction/death in human diabetes, suggesting this inflammatory cytokine could be a target for novel clinical interventions to prevent diabetes; and 5) the development of a robust method for large-scale production of 3-dimensional islet-like aggregates from human pluripotent stem cells.

A full workpackage is devoted to the establishment of an integrative systems biology platform and in silico modelling for T1D. In this WP4, a Secure Analysis Cloud infrastructure has been deployed. Deployment of the analysis infrastructure was completed in September, 2016, ahead of the initially planned completion date. Once the Analysis Cloud has active users and data have been imported and generated, a backup scheme will be implemented. Also, an eCRF data capture system has been developed for electronic capturing of patient data. Deployment of the eCRF capture system was completed in September, 2016, again ahead of the initially planned completion date (October 31st, 2016). The solution consists of a secure database established for entry of project data; 2) a database has a user-friendly interface for data entry; 3) integration of results of biological sample tests; 4) tracking of patients' clinical data as well as samples and 5) Tracking of sample shipments. Intense interactions between WP4 and other WPs have led to the refinement and enhancement of the user-friendliness of the tools that are now fully operational.

The ultimate goal of INNODIA is to establish a Clinical Trial Network, allowing to perform smart clinical trials using adaptive clinical trial designs. For this, a network of well characterised and accredited clinical centres throughout INNODIA is being established. A clinical trial coordination center and an accreditation data base were established. A self-assessment questionnaire was a first step for identification of the clinical trial performing capacity of the INNODIA members in a standardized way. Through this, a clinical profile of centers was made concerning clinical capacity (size of clinics, number of patients, adult and/or pediatric, clinical network capacity, access to an electronic patient record, meeting international standards of diabetes care ...). It became apparent that although all clinical centers of partners in INNODIA are well established and have excellent clinical reputations, level of trial experience in T1D studies varies. Currently a visitation handbook is prepared

and potential training to harmonize trial performance capabilities between the different centers will be developed. Roll out of accreditation will happen in the next months.

At the end of year one, all deliverables and milestones have been achieved, with all partners being active and research progressing to plan. Involvement of patients is crucial and dissemination activities will be intensified even further in the next months, in order to boost recruitment within the sample collection network and bring INNODIA to the attention of the general public.