

PERIODIC REPORT OF THE ACTION P2

Summary

The activities of the second 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 all deliverables and milestones achieved according to plan. After a successful launch meeting in Frankfurt in January 2016, and similar successful annual meeting in Leuven (Oct 2016) and Cambridge (Oct 2017) 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. 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), which is updated on a regular basis, where information for the general public is gathered, with special attention to patients and their families. Testimonials, 9 videos and interactive tools on how to take part as a patient or family member can be found here, but also information on the scientific progress made by INNODIA basic researchers is available on the website. A twitter account is in place and a Facebook-account was created. These tools are used by PAC members to disseminate INNODIA results and activities in layman terms. Cartoons, flyers, an animation video and a booklet for children has been made by the PAC 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. These tools are aimed at promoting participation into the program, but even more importantly are aimed at guaranteeing retention into the program. An important addition to the website in 2017 was the PAC-designed interactive 'map of Europe', featuring an interactive map, allowing potential candidates to find clinical centers of INNODIA in their neighbourhood. These tools has been elaborated in close contact with the INNODIA ethics committee and allows better recruitment (end of 2017 +300 participants) throughout the network. 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, 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, JDRF) organised in WP6.

During the first INNODIA year all individual WPs have initiated their work under guidance of the WP-leaders. During the second year, all partners are at full speed, and new collaborations have been initiated. 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 second year, all the informed consents and information leaflets have been translated in 10 additional EU languages with the help of the EFPIA partners, enabling a timely approval by ethical commission in all participating countries. All sites were visited by the clinical network coordinator (Bruggraber (UCAM)) in collaboration with WP5 (Aschemeier and Hiller (HKA)) and recruitment has started in all clinical centers by the end of year 2, thereby reaching a second important milestone. A webmap developed by the PAC (Arnaud, JDRF) listing recruitment sites is available on the INNODIA website.

Each collection site has been linked with one of the WP2 hubs (KCL, LUMC, TUD, INSERM, UNISI, UH) for the purpose of immune cell analysis and the eCRF/data tracking system has been further enhanced in collaboration with WP4 (Brunak (UCPH), Pociot (HH-RH)). 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 started 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, now including the Exeter collection (Noel Morgan) through subcontracting. A total of four normal and T1D whole pancreases were collected as part of EUnPOD and are available for distribution to partners.

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) 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. 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

and the first samples have been successfully analysed in the Hubs. In Year 2 the platform was further extended by inclusion (training, validation, opening) of 3 Immune Sub-Hubs (INSERM, UNISI, UH), which aim to extend sample collection/biobanking opportunities for fresh blood samples across all clinical sites. In addition, a suite of 'Omics' platforms were established (immunomics, genetics/genomics, transcriptomics, proteomics, lipidomics, metabolomics) for analysis of INNODIA samples, as reported in successful completion of an important milestone.

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 by the end of the second 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) the discovery of a new microRNA, as a biomarker in the circulation of NOD mice and T1D patients; 5) Identification of Interferon-alpha as a key regulator of early markers of beta-cell dysfunction/death in human diabetes, and the validation of 3 new blockers of interferon-alpha signaling, preventing ER stress and apoptosis in human islets, suggesting this inflammatory cytokine could be a target for novel clinical interventions to prevent diabetes; 6) the discovery that enteroviruses induce beta-cell de-differentiation, 7) the discovery that circulating CD8+ T cells are found at similar frequencies in T1D and healthy donors, suggesting a universal state of 'benign' beta-cell autoimmunity; 8) the development of a robust method for large-scale production of 3-dimensional islet-like aggregates from human pluripotent stem cells; and 9) a new biomarker for human beta cell imaging (DPP6) has been identified and validated for in vivo imaging. All these new findings have led to the joint publication of 10 new manuscripts 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, 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, and a backup scheme has been 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. 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. More recently the focus for the eCRF system has been put on implementing changes to the system to adjust it to operational differences of clinical sites recruiting participants. Very good collaboration with WP1 UCAM has been instrumental in translating local requirements, gathered during site enablement sessions, and transforming them into actionable development tasks and improvements to the system. WP4 is actively engaged with KCL and UH in establishing a common system for upload and quality control processing of analysis results. Finally, WP4 has teamed up with WP1 and 5 to establish an

INNODIA eCRF for clinical interventions that will serve for the first intervention trial starting in 2018 in the INNODIA network.

The work on biomarker identification tools is ongoing and is expected to continue over 2018 as data is being generated by analysing samples from newly recruited participants. We anticipate the volume of data to steadily increase over 2018 and peak in Q2 2019 leading to exciting opportunities in integrative analyses. It is foreseen that the INNODIA Data Warehouse will become an important element in T1D research on EU level not only by high quality of data gathered in the trial, but also by including datasets from other cohorts.

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 has been established. A clinical trial coordination center and an accreditation database 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. During the last 12 months the main aim was to prepare and execute audits of participating centers on site based following a structured review process outlined in the specific handbook. These visits are conducted in close association with WP1 and finally performed at the same time when the centers are trained and initiated for the planned sample collection within WP1. This should make it possible to examine, immediately before the start of the study, the specific local conditions (structure and function of the service / infrastructure, clinical research (general), clinical research (outcomes / indicators), coordination of clinical trials / patient pathways) regarding the suitability of the center to carry out the planned observational study. Importantly all visited centers could be accredited as eligible clinical research center for the INNODIA – trial initiated from WP1.

At the end of the second year, all deliverables and milestones have been achieved, with all partners being active and research progressing to or ahead of plan. Involvement of patients is crucial and dissemination activities are very intensive. This has boosted recruitment within the sample collection network and is bringing INNODIA to the attention of the general public. The first 'omics' analyses are about to start on the collected samples and the first clinical trial is planned for Q2 2018.