SUMMARY FOR PUBLICATION
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RHAPSODY
for precision therapy and prevention of diabetes

1 SUMMARY OF THE CONTEXT AND OVERALL OBJECTIVES OF THE ACTION

Diabetes is currently subdivided into two main forms, Type 1 Diabetes (T1D) and Type 2 Diabetes mellitus (T2D). Of them, T1D is more uniform and accounts for about 10% of all patients, whereas T2D, which accounts for about 80-90% of all patients, is much more heterogeneous, but the extent of this diversity is not known. Therefore, RHAPSODY will explore whether diverse sub-forms of T2D are characterized by different rates of progression from pre-diabetes to T2D and by differences in disease progression, e.g. development of complications. Establishing a better patient stratification already at diagnosis of diabetes will support the design of novel strategies for precision therapy and prevention of diabetes and of more efficient clinical trials.

2 WORK PERFORMED FROM THE BEGINNING OF THE ACTION TO THE END OF THE PERIOD COVERED BY THE REPORT AND MAIN RESULTS ACHIEVED SO FAR

Biomarker task force

Until now diabetes has mainly been diagnosed by measuring only one biomarker in blood, glucose. We think that increasing the number of biomarkers can grossly help to dissect the diversity of the disease. We have therefore established a cross-consortium "Biomarker task force" to generate a common definition of "biomarkers", of the procedures to identify them, and to define their expected use in disease stratification and in clinical management of diabetes. A list of biomarker candidates and a plan to identify new biomarkers, all of which can be measured quantitatively in the RHAPSODY's analytic platforms, have been established.

Data federation and systems biology

A key step has been to develop a secure central database, which all partners can access from their own locations. To progress towards establishing such a federated database, the following actions have been taken:

- We have completed the harmonization and formatting of six primary cohorts to a suitable and standardised data format.
- We have set up the computational infrastructure for a federated database with several clinical cohort nodes located across Europe.
- We have set out a data management plan describing how data will be stored and accessed.
- We have set up a secure RHAPSODY project database, which is accessible to all partners via individual username and password.
- We have provided a computational framework for prioritizing biomarker candidates.

Predictive biomarkers of glycaemic deterioration

The identification of prospective cohorts of people with and without T2D has started. We prioritized the RHAPSODY cohorts based upon availability of biomarkers and repeated-measures follow-up data, suitable for the detection/discovery of biomarkers predicting increase in glucose concentrations, before and after the onset of T2D. Two analysis subgroups are now focusing on modelling available variables that will be used in the downstream biomarker analyses.

Multi-omics biomarker discovery and assay development

Biomarker analyses will deliver a large amount of integrated data reflecting contributions of different tissues to the development or deterioration of the disease, also referred to as "multi-omic maps" integrating large data sets of genetic and epigenetic information, gene and protein expression in different tissues and a view of gut bacteria (microbiome). Towards this aim, quality control (QC) assessment of the chemical properties of biosamples available from the selected cohorts has been carried out. We created a central hub for the receipt and transmission of samples to four analytical platforms. These platforms will measure polar metabolites, lipids, peptides/proteins, and micro RNAs. Data analysis and, after unblinding, reporting of the QC results have been performed. We can confirm that four diabetes and three pre-diabetes cohorts meet the QC criteria for all platforms.

Predictive biomarkers of beta cell dysfunction

Diabetes usually develops when individuals no longer can increase their insulin secretion to meet increased demands imposed by obesity or insulin resistance. In order to generate a solid backbone for discovery and functional validation of biomarkers candidates of beta-cell dysfunction (impaired insulin secretion), we have installed procedures for procurement and analysis of human pancreatic islets and beta-cells. In particular we have:

- Established a robust infrastructure that includes documentation of available samples, sharing of protocols and samples, and mechanisms for effective decision-making and implementation.
- Initiated genomic and epigenetic investigation of human islets from non-diabetic, pre-diabetic and diabetic subjects. Paired blood samples from a subset of these islet samples have been made available for more sophisticated 'omic' analyses.
- Initiated studies of morphological (histological) changes, which take place during the development of T2D in humans.
- Established subgroups to i) characterize the cellular and genomic responses of human islets to specific physiological factors that may affect their function; ii) study how differences in the chromatin envelope covering our genome affects gene expression in islets recovered from organ donors.

Predictive biomarkers of insulin target tissue dysfunction

Following the IMI project IMIDIA's report of sphingolipids, in particular dihydroceramides, as biomarker candidates for increased risk of T2D, we have set out to identify which tissue(s) could be involved in their biosynthesis. A list of 26 genes involved in ceramide biosynthesis and degradation has been compiled to search for genetic variants in Genome-wide association study (GWAS) databases and whether they influence expression of genes in insulin target tissues (liver, fat, muscle) of different pre-diabetes and T2D cohorts. Separately, we are starting in vitro experiments to assess the effect of selected sphingolipids on the function of fat and liver cells.

RHAPSODY – Assessing risk and progression of pre-diabetes and type 2 diabetes to enable disease modification.

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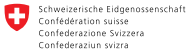

Mice have been studied to identify changes in genes, gene expression and epigenetic marks in insulin target tissues in both, normal and insulin resistant states. Islet function is also assessed in those mice so that changes in gene expression in insulin target tissues can be correlated with changes in insulin secretion.

Regulatory consensus for diabetes disease modification

RHAPSODY has established a regulatory framework within which it will operate. This involved drafting a briefing book in preparation for a meeting with the European Medicines Agency (EMA). The meeting allowed the RHAPSODY investigators to gain advice on the qualification of biomarkers for subsequent clinical trial evaluation. The meeting was followed-up by two calls with the chair of the EMA committee, as well as with internal RHAPSODY meetings to discuss the EMA recommendations and align these with ongoing activities within the consortium.

Modelling economic and public health impact of disease modification

We performed a systematic review of pre-diabetes economic models. The findings were presented at the Mt Hood Challenge, St Gallen, Switzerland in September 2016. The Mt Hood Challenges are undertaken collectively by an international group of researchers engaged in the development of diabetes simulation models for health economic evaluation. We found that the existing pre-diabetes models were of limited use to inform on the potential impact of biomarkers from RHAPSODY given the lack of glycaemic deterioration simulation (speed and extent of increase in glucose concentrations). Our findings reinforce the need for developing an adequate pre-diabetes model. The systematic review protocol was registered with the PROSPERO international prospective register of systematic reviews and accepted for publication in BMJ Open (May 2017).

The integration of pre-diabetes and T2D economic models is being informed by the systematic review findings. We developed a work plan for the validation of the T2D economic models available to RHAPSODY, and four cohorts were identified to undertake the work.

Management, communications, sustainability and ethics

RHAPSODY management has put procedures in place that ensure an efficient operational running of the project. We launched the RHAPSODY website and published a leaflet and a press release, introducing the project. The ethics committee is in place, supervising the RHAPSODY ethics management and ensuring ethical compliance.

3. PROGRESS BEYOND THE STATE OF THE ART AND EXPECTED POTENTIAL IMPACT

The major advances during the first year, and which clearly go beyond state of the art are as follows:

- The almost completion, in due time, of the harmonization of the cohorts' data annotation and their transfer in node specific database and beyond firewalls.
- The establishment of a RHAPSODY database with analysis and visualization tools to allow cross cohort data interrogation at an EU level; establishment of all regulatory/administrative requirements for data sharing. This will represent a research database for T2D with a tremendous potential impact on science.
- The quality control analysis of biosamples from all identified cohorts in order to prepare for network-wide analysis of candidate biomarkers using four different "omics" platforms; the establishment of platforms (polar metabolites, lipidomics) allowing quantitative measurements of plasma metabolites. This represents an important improvement as most previous studies of metabolites have measured relative rather than absolute values.
- The quality control of islet-derived human data and the possibility to co-analyse data generated at different sites provide unprecedented tools - for research in health and in T2D. Availability of a first series of paired plasmas and islets tissue from control and diabetic patients to facilitate identification of plasma biomarkers of beta-cell dysfunction.
- The identification of novel candidate biomarkers of deregulated insulin target tissue functions that may lead to increase sphingolipid biomarker production.