1. Executive summary Reporting Period 5

1.1. Project rationale and overall objectives of the project

Diabetes mellitus is a lifelong, incapacitating disease affecting multiple organs, which at present cannot be cured but only symptomatically treated or, at best, partially prevented in the case of type 2 diabetes (T2D). The disease is associated with devastating chronic complications including coronary heart disease, stroke and peripheral vascular disease (macrovascular disease) as well as micro-vascular disorders leading to damage of kidneys (nephropathy or DN), eyes (retinopathy or DR) and feet (Lower Extremity Arterial Disease or LEAD). These complications impose an immense burden on the quality of life of the patients and account for more than 10% of health care costs in Europe. Novel means to prevent and/or treat these devastating diabetic complications are urgently needed.

1.2. Overall deliverables of the project

SUMMIT develops innovative approaches to make clinical trial testing of novel medications in diabetic vascular complications faster and more efficient. To do so SUMMIT aims to develop novel **genetic markers** and **soluble biomarkers**, which can be used i) to identify patients at high risk (antecedent biomarkers), ii) differentiate between fast-progressors and slow-progressors and iii) monitor progression, reduction or prevention of diabetic vascular complications. In addition, SUMMIT aspires to develop novel and improve existing **imaging techniques** for monitoring progression in atherosclerosis and retinopathy, novel **animal models** for micro- and macrovascular complications to better replicate disease as seen in men and novel ***in silico* methods** for modelling and predicting diabetic complications. The ultimate goal is to make these markers and tools accepted by regulatory authorities and to disseminate the findings not only to the scientific community but also to lay people and patient organizations.

1.3. Summary of progress versus plan since last period

SUMMIT successfully applied for **additional funding** to increase the value of the work done in WP4 on animal models in the form of an IMI **ENSO (Explore New Scientific Opportunities) grant**, as well as **JDRF funding** to join forces in data analysis from GWAS and exome sequencing in diabetic nephropathy. With the expansion of the work came a 12-month extension of the whole project until Oct 31 2015, which was welcomed by all SUMMIT participants. In parallel the consortium received a budget-neutral extension during the same period of time in order to complete the clinical imaging studies of WP3.

The ***in silico* replications in DN and CVD are now complete** and have been combined with the discovery GWA sets. We have **replicated several signals at genome-wide significance** and identified others that are borderline genome-wide significant. The JDRF grant with the DNCRI will allow us to follow up putative signals from the exome data for DN. Analytical

approaches from WP5 have been employed to identify signals for replication from the GWAS data for LEAD and for pathways that may be involved in DN from the GWAS and exome data. *In silico* replication for DR and LEAD continues and involves the use of external cohorts and participants outside SUMMIT, to maximize output from SUMMIT results. Cross-WP integration (WP1, 2, 5) has highlighted **biomarkers and variants that are associated with DN or CVD**.

Year 5 SUMMIT has also focused on the completion of the outstanding analyses of the biomarker data from the discovery phase of SUMMIT and we have now **completed analysis of the DN data**. We have initiated the validation of key biomarkers of interest from the discovery phase in samples from the CARDS study (for CVD and DN validation), Go-DARTS (for DN validation), FINRISK (for CVD validation) and the Swedish Diabetes Registry (SDR, for DN validation). The collaborative work with WP1 and WP5 to undertake joint analyses of genetic and circulating biomarker data continues.

The novel ultrasound-based technique for analysis of atherosclerotic plaque structure has passed through the **final validation** with good results. The whole body MR angiography of systemic atherosclerotic burden has been completed. The 3-year follow-up investigations for the study to discriminate CVD in T2D as well as the multi-centre OCT study for DR risk prediction started late 2013 and are running according to plan. Analysis of the baseline OCT results has revealed **novel associations** between regional differences in macula thickness and retinopathy. WP1-2-3 completed joint biomarker and GWAS analyses of the baseline samples.

The **ENSO drug intervention studies** for the validation of 4 very promising SUMMIT models were initiated. A **PCT application** for the SUMMIT rat model has now been submitted to EPO. New models based on the latest GWAS findings, as well as additional two new mouse strains for type 2 diabetes are being characterized. Exciting new findings open up for new pathways and markers, involved in CVD and DN.

The WP5-developed software was used in multivariate ranking and selection of DN SNPs associated with diabetes complications. The strongest patterns of **relation between selected DN genetic and phenotypic markers** were identified with Bootstrapped Bayesian Networks, for the integration of WP1 and WP2 results. WP5 integrated SNPs and biomarkers data including by defining a **knowledge-based gene/protein network** and a computational method was developed to support identification of potential targets for diabetes complications through a network-based approach.

1.4. Significant achievements since last report

The complication-centered view as initiated in the previous reporting period instead of the technology-based focus, was continued and inspiring. Multi-disciplinary workshops were held for CVD, DN and DR. SUMMIT successfully applied for additional funding and project extension in the form of an ENSO project and a JDRF-DNCRI collaboration.

Cardiovascular complications

The previously identified GWAS signal remained genome wide significant for CVD in T2D after replication. Combination of metabolite and genetic data indicated metabolites that were independently associated with CVD, and a specific genetic risk score was associated with these metabolites. WP1-2 joint analysis has identified a genetic region that is associated both with CVD risk and biomarker levels suggesting a novel pathway for CVD in type 2 diabetes. In addition, evidence was collected for a causal role of a CVD biomarker by means of Mendelian randomization.

Ability of carotid ultrasound GSM, RF algorithms, Endo-Pat and PWV to discriminate DM subjects with prevalent cardiovascular events from DM without cardiovascular events was evaluated.

Associations between biomarkers, CVD and vascular changes in T2D were identified, as well as metabolic markers as possible links between renal dysfunction and CVD in T2D.

A PCT application for the diabetic CVD rat model has been submitted. Advanced scanning methods were successfully used in animal models to study cardiac distensibility.

Diabetic nephropathy

We have identified signals for DN at genome wide significance for CKD-DN (T1D+T2D) and two others at very near genome wide significance for macroalbuminuria (T1D and T2D). We have characterized panels of biomarkers that are predictive for DN progression.

A consistent up-regulation of markers in diabetic glomeruli in the Akita mouse model was reported.

The Dynamic Bayesian Networks model of T1D complications was completed. SUMMIT participants have started to use the developed tools and models for identification of novel targets and drug candidates for the treatment of T1D/T2D complications.

Diabetic retinopathy

Baseline analysis for the OCT study is completed and re-investigation is well on its way. Interesting findings so far include retinal thickness variations with retinopathy status.

The standardisation of different OCT devices has been assessed with the use of a retinal phantom and biological standard; a proposed method for combining the data was developed and validated.

We found new indications for disease pathways in microvascular complications in an animal model.

LEAD

A genome wide significant signal was identified for LEAD in T1D+T2D, with replication studies ongoing.