Interception of Immune Trajectory in Diabetes.

Type 2 diabetes occurs when insulin secretion from pancreatic beta cells cannot sufficiently be increased to compensate for insulin resistance. Causes of inadequate insulin secretion and the loss of insulin sensitivity are heterogeneous, as are individual trajectories of hyperglycemia and subsequent manifestation of diabetic complications. The development of type 2 diabetes is a slow process and its manifestation is preceded by a phase a prediabetes that often remains undiagnosed and difficult to prevent at the medical levels. By contrast, early diabetic complications including cardiac and kidney diseases, which represent a transition in type 2 diabetes evolutions, might require preventive actions. Dysimmunity has been proposed to be involved in the losses of insulin secretion and insulin sensitivity as well as in diabetic complications such as heart and kidney diseases. By establishing that a diabetic dysimminity is the cause of the early development of diabetics complications will allow the healthcare professional to diagnose the citizens at high risk of diabetic complications and propose a tailored treatment to prevent disease transition including a novel anti-inflammatory treatment. Importantly, our project will strongly improve the quality of life of diabetic's citizen.

The main challenges of INTERCEPT project are 1) to establish the subtype of type 2 diabetes characterised with a dysimmunity aetiology and 2) to prove its causal association with T2D transition towards complications, 3) to understand the biology of this diabetic dysimmunity and 4) to pharmacologically intercept this inflammatory transition to prevent diabetic complications (phase 2 clinical trial).

Human cohorts of citizens that cover diabetes transition and evolutions towards diabetes complications will be used to establish the immune trajectory of diabetic patients from diagnosis to complications (more than 10 years follow-up from diabetes diagnosis).

The extreme diversity of the human immune is the substrate upon which immune-associated diseases develop as diabetic complications. Among the drivers of diabetic immune variations, unequivocal experimental and clinical evidence support that NOD-like receptor pyrin-3 (NLRP3) inflammasome activity is associated with diabetes transition and evolution towards diabetes complications. **In the INTERCEPT-T2D proposal, we will combine genetic, biological and clinical approaches to prove the causal link between inflammasome mediated-diabetic dysimmunity and a specific trajectory towards diabetes transition towards complications.**

An important aspect of our proposal is to understand the biology underlying this aberrant activity of the inflammasome at the cellular and organ levels. **Deciphering the regulatory processes of NRLP3 inflammasomme at transcriptional and protein levels is of importance to better understand NRLP3-inflammasome aetiology of diabetes.** The NRLP3-Inflammasome may act as a potent immune regulator of islet inflammation and inadequate insulin secretion in diabetes transition. Despite that the concept of islet inflammation has been well characterised in cellular and rodent models, the nature of this islet inflammatory response has not been fully characterised and understood in human**. Using a unique biological resource of human pancreata (from living donors) covering the diabetes spectrum, we will establish the immune regulatory cascades and the dialog between immune and endocrine cells governing the deregulation insulin secretion.**

Interceptive medicine of NLRP3-inflammasome diabetes trajectory is a novel advance therapeutic intervention to prevent diabetes transition to complications. This innovative therapeutic action will provide to professional healthcare the opportunity to propose a tailored to citizens to limit diseases and improve the quality of life of citizens. **Intercept project will conduct a phase 2 clinical trial to intercept the NRLP3-inflammasopme trajectory and prevent its dependent diabetes complications.** Type 2 diabetic citizens suffering form

diabetes with early markers of heart and kidney dysfunctions will be treated with a specific NLRP3 inhibitor available within the consortium (Industrial partner). Clinical outcomes of the treatment in kidney and heart functions will be quantified and its efficiency (evolution versus resolution) will be associated to the inflammasome-dependent immune trajectory of type 2 diabetes.