Ultra-Low Dose Interleukin-2 to fight Type-1 Diabetes

DIABIL-2 is a 4-year European research network (Collaborative Project) supported by the European Commission under the Health Cooperation Work Programme of the 7th Framework Programme, under the Grant Agreement n° 305380.
Type 1 diabetes (T1D) is caused by the autoimmune mediated destruction of the pancreatic islet β-cells, leading eventually to absolute deficiency in insulin.

About Type 1 Diabetes (T1D)

T1D is one of the most common severe chronic autoimmune diseases worldwide. In Europe its incidence is rapidly rising in children, with a predicted 70% increase in cases over the next 15 years. The age at T1D diagnosis is decreasing, with a predicted doubling of cases in children under the age of 5 years in the same period. The cause of T1D is the autoimmune-mediated progressive destruction of insulin-producing pancreatic β-cells leading to insulin deficiency and hyperglycaemia.

The development of autoimmunity precedes the clinical diagnosis of diabetes and is due in large part to the inability of regulatory T cells (Tregs) to control the pathogenic autoreactive T cells from destroying the insulin-producing pancreatic islet β-cells. In clinical trials, less than 30% of patients T1D achieve glycaemic targets while in standard clinical practice rates are usually less than 16%. Importantly, at the time of diagnosis of T1D, there are residual β cells capable of producing insulin. Remission of the autoimmunity at this stage could have significant therapeutic benefit. Preservation of β-cell function has the potential to improve metabolic control more effectively, at lower cost and with higher patient acceptability than current standard insulin replacement therapy. The DIABIL-2 project aims to stimulate Tregs by ultra-low dose interleukin-2 (IL-2) at diagnosis of T1D to prevent further autoimmune-mediated destruction of β-cells. This will prevent or delay T1D disease progression and could improve clinical outcome for patients.

A Model for the Pathogenesis of Type 1 Diabetes Based on Genetic Etiological Studies in Humans
(From J. A. Todd, Etiology of Type 1 diabetes, Immunity, 2010)

The IL-2 pathway is central to the development of T1D. Tregs are dependent on IL-2. Treatment with IL-2 should improve Treg function and prevent effector CD4 and CD8 T cells killing of β cells and resulting destructive inflammation.

About Treg cells and Interleukin-2

Regulatory T cells (Tregs) form a subpopulation of T lymphocytes that regulate the immune system to maintain tolerance to self-antigens and prevent autoimmune diseases. As T1D is caused by the failure of Tregs to block autoimmune destruction of pancreatic β-cells, Treg stimulation has the potential to stop the process, preserve β cells’ insulin secretion, and likewise prevent or delay disease progression and improve clinical outcome for patients. The central role of Tregs in the control of the immune response has led to intensive research of Treg-based therapy to treat various immune dysfunctions.

We and others have shown recently that IL-2 can directly and specifically activate/expand Tregs. IL-2 is a soluble signaling molecule that regulates the activities of white blood cells (leukocytes, often lymphocytes). IL-2 mediates its effects by binding to IL-2 receptors, which are expressed by lymphocytes, notably at the highest levels on Tregs. IL-2 given at low dose stimulates Tregs without stimulating other lymphocytes and thus could be an ultimate Treg stimulator for fighting autoimmune diseases.
We recently demonstrated that ultra-low-dose IL-2 stimulates Tregs without stimulating effector T cells and that in a diabetic mouse model (NOD mice), IL-2 can prevent and cure diabetes. In humans, (I) we showed that low dose IL-2 is safe, induces Tregs and is associated with clinical improvement in hepatitis C autoimmune vasculitis; and (II) we defined an ultra-low dose IL-2 that is well tolerated, increases Treg number and functionality in a dose-finding study in T1D.

With this strong background:
- a well-defined mechanism of action,
- a proof of concept in NOD mice,
- a proof of concept clinical trial with another autoimmune disease,
- safety and activity/efficacy data in T1D,

the DIABIL-2 project proposes a phase-IIb clinical trial evaluating the efficacy and safety of ultra-low dose IL-2 for preserving β-cells in patients with newly-diagnosed T1D.

It will be a double-blind, randomised, placebo-controlled, stratified on age (7-12, 13-17, 18-35 years), parallel-group, multicentre European phase-IIb clinical trial.

This study will inform us if our approach can preserve remaining endogenous insulin secretion in patients with newly-diagnosed T1D.

In addition, the DIABIL-2 project will allow us:
- To further investigate response to ultra-low dose by molecular phenotyping using genetics, genomics, transcriptomics and cutting-edge immunological methods for stratification of individualized patient care.
- To strengthen basic and clinical European Scientific Excellence by the dissemination of landmark results and the foundation of a European network of excellence operating in the T1D field.

If successful, the DIABIL-2 trial will have profound impacts for the management of patients with newly diagnosed T1D, their families and EU economy.

**Impact on T1D management**
Ultra-low dose as a safe treatment aimed at halting autoimmune β-cell destruction could enable patients to achieve optimal glycaemic control without recurrent hypoglycaemia. Moreover, the efficacy of IL-2 at halting autoimmune β-cell destruction in newly diagnosed T1D could lead to further studies investigating its potential in prevention of T1D.

**Impact on child health**
This disease has a major impact on children and adolescents since it interferes with all aspects of life and is often disrupting for the whole family and social structure around the child. We firmly believe that by building on a strong model of T1D pathogenesis, supported by world-class research, we are proposing a rational approach towards intervening in T1D. We bring the hope of intervention in this disease.

**Impact on global health - issues-emerging epidemics**
More than 20 million people in Europe suffer from T1D. The costs of treating and managing this disease and its complications are approximately 2 billion € annually.

**Progress in autoimmune and inflammatory diseases management**
Noteworthy, any clinical success ultra-low dose in T1D could lead to its clinical development in other autoimmune diseases, including Multiple Sclerosis or Rheumatoid Arthritis, that have a significant public health burden. A confirmation of the global anti-inflammatory effect of IL-2 already observed in HCV-related vasculitis patients will pave the way for studying IL-2 in other inflammatory diseases.

**Economic impact**
The use of IL-2 in T1D and other autoimmune diseases has been patented by the DIABIL-2 coordinating public institution AP-HP, and the patent is currently licensed to ILTOO-biotech, a small company also a partner in this project. Demonstration of efficacy in this T1D trial should be a milestone in developing novel indications for IL-2. Europe will have a chance to become a leader in this field, which targets a very large market, and likewise this project should contribute to increasing employment in the pharmaceutical sector in the EU.
DIABIL-2 will be a double-blind randomised placebo-controlled age-stratified (7-35 year) multicentre European trial assessing efficacy and safety of uld-IL2 in 200 recently diagnosed T1D patients. Our methodology strictly follows the Immunology of Diabetes Society consensus recommendations and European regulatory guidelines.

The primary end-point is the change from baseline of AUC C-peptide during a mixed meal test at 1 year. The trial is precisely and conservatively powered to detect an effect size of d=0.5.

To achieve in 4 years the completion of this trial, the work programme has been structured in 5 complementary workpackages (WP):

**WP1** will ensure effective and efficient coordination and management throughout the duration of the project.

**WP2** - Clinical trials are governed by Regulatory and Good Practice rules (manufacturing of the product, clinical, laboratory). Compliance to these rules will be ensured during the first year as a mandatory prerequisite prior to undertaking our planned trial.

**WP3** - We will carry out the DIABIL-2 trial from year 2 to year 3 in compliance with GCPs/GCLPs rules, and analyse the data during the fourth year of the project in order to verify the efficacy and safety of ultra-low-dose IL-2 in patients with recently diagnosed Type-1 Diabetes (T1D).

**WP4** - We will gain insights into the molecular and cellular impact of ultra low-dose IL-2 treatment (versus a placebo control) in newly diagnosed T1D patients. Based on our previous studies and those of others, we expect a reduction in the autoimmune response associated with T1D in patients receiving IL-2 as compared to those receiving placebo. We also hypothesise that patients retaining more C-peptide will have a greater reduction in the assessed proinflammatory markers and antigen-specific responses.

**WP5** will organize a well targeted dissemination effort and early liaison with key stakeholders, including patients’ organisations and the pharmaceutical industry, in order to release the full exploitation potential of our approach.
Partners

DIABIL-2 is a 4-year European project (Collaborative Research Project) started in October 2012 coordinated by the Assistance Publique-Hôpitaux de Paris (AP-HP, Prof. David Klatzmann) from France. Our consortium brings together 6 complementary partners: 1 small and medium enterprise called ILTOO, dedicated to the development of ultra-low dose IL-2 in novel indications including T1D, as well as Inserm Transfert, a technology transfer / management company and 4 academic laboratories, from 3 European Member States (UK, France, Germany) and Switzerland. The project is supported by the European Commission under the Health Priority of the 7th Framework Programme.

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<th>No.</th>
<th>Participant organisation</th>
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