PRESS RELEASE

European BIOSID Project:
5.5 million Euro from the European Commission for the clinical validation of the MAILPAN® bioartificial pancreas

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Summary

European BIOSID Project:

5.5 million Euro from the European Commission for the clinical validation of the MAILPAN® bioartificial pancreas

The Centre européen d'étude du Diabète (CeeD) and its partners have just received nearly 5.5 million Euros for the co-funding of a European research project. It should lead to a first clinical validation of the bioartificial pancreas MAILPAN®, which prototype has been developed through two previous European projects, led by CeeD. Over a period of 36 months and called BIOSID, this project coordinated by the CeeD unites 7 partners from 3 different countries.

This new project co-funded under the 7th framework programme (7th FPRD) of the European Commission, aims to:

- understand the needs of insulin-secreting cells in the bioartificial pancreas
- meet these needs in order to improve their life expectancy in the bioartificial pancreas
- validate the bioartificial pancreas, associated with insulin-secreting cells, in large animals and then in humans

The ultimate goal of this project is to provide a solution to the main obstacles of human pancreatic transplants (islets of Langerhans or entire pancreas), which are immune rejection and the lack of matching donors.

To ensure all the chances of success of this project, the CeeD and its spin-off Defymed, two French SME[1]s based in Strasbourg, built a strong consortium uniting 5 other partners from complementary fields of expertise. In this case:

- AvantiCell (ACS), a Scottish SME,
- the Department of Endocrinology, Diabetes and Nutrition from the Montpellier UHC,
- the Nuffield department of Surgical Sciences of the Oxford University (NDS),
- Endocells, a French SME based in Paris,
- and the laboratory of Experimental Surgery of the Catholic University of Louvain (UCL).

The full consortium brings together **4 SMEs and 3 public research organizations**, from three different countries (France, Belgium and United Kingdom), which will each have a role in the validation of the various stages of the project. The consortium's expertise includes encapsulation techniques, cellular, transplantation and formulation engineering as well as a clinical expertise.

The intervention of the firm Efficient Innovation/HLP development, specialized in the administrative set-up of similar European collaborative projects, allowed the CeeD to maximize its chance in obtaining funding by the European Commission. Thanks to an "Aid for Technological Partnerships" from Oséo, CeeD

[1] SME : Small and Medium Entreprises

has been able to access the services of Efficient Innovation/HLP development. Alsace Innovation has also provided assistance to the CeeD during the setup of the project (connections with national contact points of the European Commission and reviewing the project).

BIOSID is based on the foundation of 16 years of research, which after the development and implementation of the first two European programs also controlled by the CeeD, and co-funded by the European Commission (BARP project conducted from 1996 to 2000 and BARP+ project conducted from 2004 to 2007), resulted in 2011 in the creation of the Defymed Start-Up.

The BIOSID project aims to bring the developed bioartificial pancreas MAILPAN® to the clinical stages of type 1 diabetic patients, a key step before it's placement on the market.

The principle of the bioartificial pancreas

From a clinical perspective, this device is a bioartificial pancreas that restores the physiological secretion of insulin necessary for the regulation of blood glucose. **With the bioartificial pancreas, instead of being grafted as such, the transplanted insulin-producing cells are surrounded by an immunoprotective envelope.** This module of macroencapsulation operates on the principle of a selective diffusion chamber. Nutrients, oxygen and insulin can cross it freely. However, antibodies and immune cells cannot cross its wall and destroy pancreatic islets.

A project that carries hope for patients

The MAILPAN® device is intended for type 1 diabetes patients, an estimated global population of 25 million people in 2012, including more than 300,000 in France. It will replace the destroyed pancreatic islets in these patients and therefore produce insulin which they lack to regulate their blood glucose levels.
Today, only a very small number of these patients (0.01%) could benefit from human pancreatic islet transplantation, mainly because of the very limited number of available pancreases but also because of the strong immunosuppressive therapies that are associated with it. For the majority of patients which are undergoing insulin therapy by injection or insulin pump, blood glucose levels remain unstable and the patient remains dependent on the contribution of insulin several times a day.

The BIOSID project aims to improve the lives of type 1 diabetes patients by providing them with physiological treatment. **In comparison with the current treatments of type 1 diabetes, the bioartificial pancreas should provide many benefits and impacts significantly improving the quality of life for many diabetic patients.**

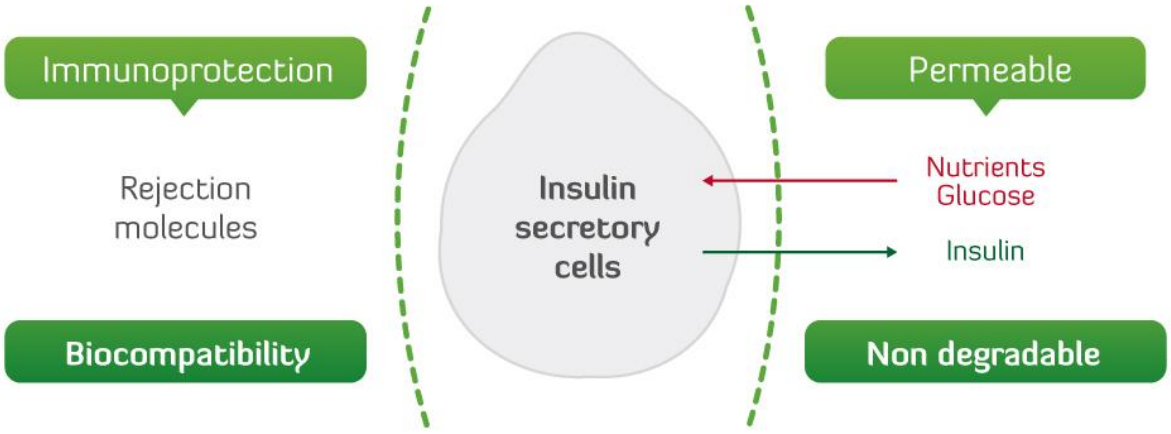
Principle

The development of a bioartificial pancreas is based on **an effective immuno-isolation of insulin-secreting cells** based primarily on their encapsulation using artificial membranes impermeable to molecules involved in the rejection but permeable to glucose, insulin, oxygen and nutrients.

Therefore, **no immunosuppressive therapy is required**. **This physiological solution allows the cellular therapy to become a widely deployed reality.**

Three functions are essential for the bioartificial pancreas:

- **Protect the transplanted cells from the recipient's immune system**
- **Protect the recipient from the transplanted cells**
- **Maximize the function of the transplanted cells**



Description

The bioartificial pancreas MAILPAN® fully meets these requirements.

This is a macro-encapsulation system of implantable insulin-secreting cells based on the following characteristics:

- a modular system enabling the required diffusion properties,
- a specific surface treatment increasing the biocompatibility of the system.

The insulin-secreting cells necessary for the functionality of the system may be of a variety of sources: islets isolated from human or porcine donors, or even genetically modified cells.

The industrial property MAILPAN® is based on three patents:

- the first, dating from 2002, protects the use of encapsulation membranes and their surface treatment to make them biocompatible and thus improve their diffusion properties,
- the second filed in 2010, covers the surface functionalization of the system allowing the optimization of its implantation,
- the third also filed in 2010, is dedicated to the design of MAILPAN®.

Innovation

The MAILPAN® prototype owes its innovative character to the following aspects:

- use of semi-permeable membranes, allowing the passage of glucose and insulin, but preventing the entry of the components of the immune system. Thus, no immunosuppressive therapy will be necessary,
- surface functionalization which considerably reduces the post-operative inflammation and accelerates vascularization around the system. This ensures optimal exchange at the system's surface,
- possibility of filling and emptying the system, as needed,
- discretion of the system by choosing the implantation site,
- patient autonomy through physiological treatment.

Project history

The Centre européen d'étude du Diabète (CeeD) of Strasbourg initiated this project in 1996 based on an innovative concept of a bioartificial pancreas, called MAILPAN® (macro-encapsulation of pancreatic islets) to design an implantable device for the macro-encapsulation of insulin-secreting cells in humans. This work was conducted in partnership with STATICE (Besancon) and with the Centre de Transfert de Technologie du Mans (CTTM).

This project involved the validation and integration of multiple technological steps, of which the first two were funded by the European Commission, via:

- The BARP project (Bioartificial Pancreas) developed within the 4th PCRD framework (1996-2000) which resulted in the **validation of the concept of islet immunoprotection** by encapsulation using semi-permeable artificial membranes.

- The BARP+ project developed within the 6th OCRD framework (2004-2007) which **defined the system materials** and **validated, in the small (rat) and/or large animal (pig),** the expected **features**: filling capacity, biocompatibility, implantation and function.

At this stage, it was then necessary **to change the system for a qualified medical device** for its placement on the market. **To do this, the DEFYMED Start-Up was born in march 2011, with the support of SEMIA, the incubator for innovative businesses in Alsace** accredited by the Ministry of National Education, Research and Technology.

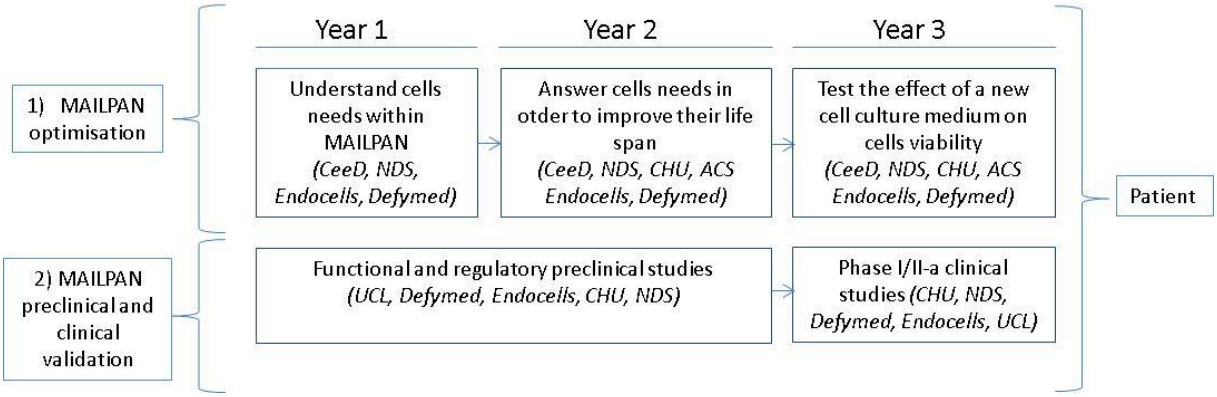
Since its foundation, DEFYMED was rewarded several times, receiving in particular:

- The national competition award for the creation of innovative technology companies in the "Emergence" category and the Innovation Award for the Alsace Region (2010)
- The national competition award for the creation of innovative technology companies in the "Creation-Development" category of the Ministry of Higher Education and Research (2011)
- The 1st national award in the "Life Sciences" category of the Senate Tremplin competition and winner of the Universal Biotech competition (2011)
- The "Talent d'Avenir" award from the Action Alsace Fund (2011)
- The Innovative Company Label of Alsace Biovalley (2012).

The framework programme for research and development (FPRD) is the main financing tool for research in the European Union. Currently underway, the 7th FPRD covers the period 2007-2013 for a total budget of over 50 billion Euro, including nearly 6 billion allocated to health.

Methodology and overall program strategy: optimization and clinical validation of MAILPAN®

Diagrams representing the main tasks of BIOSID inherent to each partner



The strategy of the BIOSID program consists of two main components:

- First, **optimize**, from year 1, the internal environment of MAILPAN® to ensure the best conditions for the survival and function of encapsulated cells. Therefore, a study of the environment of the cells in the MAILPAN® will be conducted in years 1 and 2. The ultimate goal is to formulate an innovative culture medium for cells, incorporating beneficial molecules for their survival and function in the MAILPAN®. The effect of this new culture medium will be tested for the survival and function of the encapsulated cells, in year 3. These various tasks will be carried out primarily by CEED, NDS and ACS, in close collaboration with Defymed, UHC and Endocells.

- Secondly, testing in parallel, from year 1, the existing MAILPAN® prototype (developed in the 6th FPRD), in the **preclinical phase**, in large animals, using different sources of insulin-secreting cells in order to enter into the human **clinical phases**. Among the encapsulated cells in the MAILPAN® are human or porcine pancreatic islets or even genetically modified cells. Thus, the MAILPAN®'s capacity, combined with the cells, to restore normal and stable blood sugar levels will be investigated. Finally, in order to obtain permission to enter human clinical phases, the MAILPAN®'s biocompatibility and safety should be validated in preclinical phases, in large animals. The various tasks of this component will be conducted primarily by the UCL, UHC, NDS, Defymed and Endocells.

Presentation

The Centre européen d'étude du Diabète (CeeD) was created in 1991 by Professor Michel Pinget, current leader of the NUDE center and Department of Endocrinology, Diabetes and Metabolic Diseases at the University Hospital of Strasbourg (UHS).

Structure of translational research, the CeeD combines physicians and researchers to respond via laboratory research to questions from health care teams and to patient's expectations.

Its main objectives are to:

- develop new therapies and improve the daily life of patients;
- initiate and drive innovative projects alongside the best European research teams, in permanent interaction with the hospital teams;
- inform and massively educate on this serious public health problem;
- promote and develop scientific exchanges at all levels of medicine and research.

Role in the project

BIOSID project **coordinator**, CeeD has extensive coordination experience through the 2 BARP European projects (4th FPRD) and BARP+ (6th FPRD) which gave rise to the current MAILPAN® bioartificial pancreas prototype. The BARP+ project was recognized as a "Success Story" by the European Commission. During these two projects, 3 patents protecting the MAILPAN® were filed and numerous scientific publications in international journals.

The CeeD has all the assets required to complete this project. In addition to coordinating the project, through Dr. Séverine Sigrist, the CeeD will work on understanding the needs of the islets in terms of viability and function. Thus, the CeeD will mobilize research teams in order to study the behavior of islets in the MAILPAN®, and this on animal models developed internally.

Presentation

AvantiCell (ACS), a biotechnology SME, based in Scotland (UK), is specialized in cell culture technologies and in the formulation of culture environments depending on the type and needs of the cells, carrying out large scale analyzes. More specifically, the ACS' expertise is based on the production of stem or primary cells of human origin, using proprietary technologies to mimic their physiological functions. In addition, ACS is specialized in the high-throughput screening of drug candidates on cells, for various therapeutic applications.

Role in the project

In BIOSID, ACS will work on making a culture medium meeting the needs of insulin-secreting cells in the bioartificial pancreas.
Indeed, ACS will test different formulations of culture environments in order to choose that which will best optimize the survival and function of cells in the MAILPAN®. This work will be done in close collaboration with the project partners. ACS also has a facility, through its extensive network of experts, of producing large-scale culture environments and under GMP conditions (Good Manufacturing Practices).
ACS participates in numerous European programs uniting many partners and this is a major asset for BIOSID.

Presentation

Coordinated by Professor Eric Renard, the Department of Endocrinology, Diabetes and Nutrition of the University Hospital Center (UHC) of Montpelier has over 20 years experience in optimizing therapy for type 1 diabetes. More specifically, this department contributes to a platform, called EVADIMM dedicated to the clinical trials of innovative medical devices for the treatment of diabetes (implantable and external pumps and the artificial pancreas). The UHC of Montpellier is also experienced in the isolation of human pancreatic islets and in the study of mechanisms involved in the survival of islets, before and after transplantation in humans. The UHC of Montpellier has participated from 2003 in the GRAGIL network (Rhine-Rhone-Alps Geneva Group for the transplantation of islets of Langerhans). The UHC has been involved in several European programs (7th FPRD and others) and its experience in the conduct of such projects is a great advantage for BIOSID.

Role in the project

Its role in BIOSID will mainly focus on the following tasks:

- the conduct of a large part of the clinical studies of bioartificial pancreas in diabetic patients, with focus on the study of the function, safety and tolerance of MAILPAN®,
- the isolation of human pancreatic islets from donors,
- the understanding the needs of insulin-secreting cells in the bioartificial pancreas, in partnersh with the Institute of Functional Genomics (UMR CNRS 5203/INSERM U661/Universities Montpellier 1&2), in order to improve the survival and function of these islets in the MAILPAN®.

Presentation

The Nuffield Department of Surgical Sciences at the University of Oxford, including the team led by Professor Paul Johnson, is a pioneering center in the isolation and clinical transplantation of human pancreatic islets. The research is divided into 11 themes among which transplantation is one of the most developed. Their work on the isolation of pancreatic islets began in the 80s, for applications in research, while clinical application began in the 90s. This department has access to unique facilities for the isolation of human pancreatic islets under GMP conditions, with transplantation success that exceeds 70% of transplant patients.

Role in the project

NDS will work closely with the CeeD to understand the needs of insulin-secreting cells in the bioartificial pancreas and provide the answers necessary for their survival in it. In addition, this public department will intervene in the supply of MAILPAN® with human pancreatic islets for clinical trials and perform a part of these tests, at Oxford.

Presentation

Spin-off of the CeeD, Defymed is a French SME specialized in the design and development of innovative bioartificial medical devices. Defymed is, first, focused on an application for the treatment of type 1 diabetes. The first product designed by Defymed is a bioartificial pancreas intended to be implanted in diabetic patients in order to restore normal and stable blood sugar levels in the latter. This device named MAILPAN (macro-encapsulation of pancreatic islets) is in the form of a pocket having functions of a bioartificial pancreas, which once implanted will be filled with insulin-secreting cells. Defymed's strength is based on its network of national and international partners, including historical partners such as the CTTM (Centre de Transfert de Technologie du Mans) and STATICE. Defymed has a unique technology which enables it to shape these medical devices to respond to other therapeutic applications.

Role in the project

As owner of the bioartificial pancreas MAILPAN®, on which the BIOSID project is based, **Defymed is responsible for manage the exploitation and dissemination of the BIOSID project.** The team from the start-up will also investigate the biocompatibility and function of the MAILPAN device in preclinical phases in large animals and in clinical phases in humans, with a particular focus on the regulatory aspects related to these studies. Finally, Defymed will be responsible for the design and manufacture of MAILPAN® adapted to the model used (small or large animals and humans) for the BIOSID partners.

Presentation

Endocells, a French biotechnology SME, is specialized in the development of technologies with the view of providing an unlimited source of human origin cells with endocrine properties possible. The first focus of Endocells concerns insulin-secreting cells in order to treat type 1 diabetes. These cells show a normal insulin secretion as measured by regulation of glucose level. Thanks to their unlimited availability, they are considered as good candidates for diabetes cell therapy. Directed by Prof. Paul Czernichow, Endocells counts among its team five engineers and scientists and works closely with the research teams from INSERM and CNRS.

Role in the project

In BIOSID, the Endocells team will work on the culture conditions of a human Beta cell line to understand its needs and improve its viability and function inside the MAILPAN® device. On one hand, Endocells will study the behavior and mortality of its cells in the preclinical phase and on the other hand, the effectiveness and safety of cells will be studied in animal models developed by the BIOSID partners

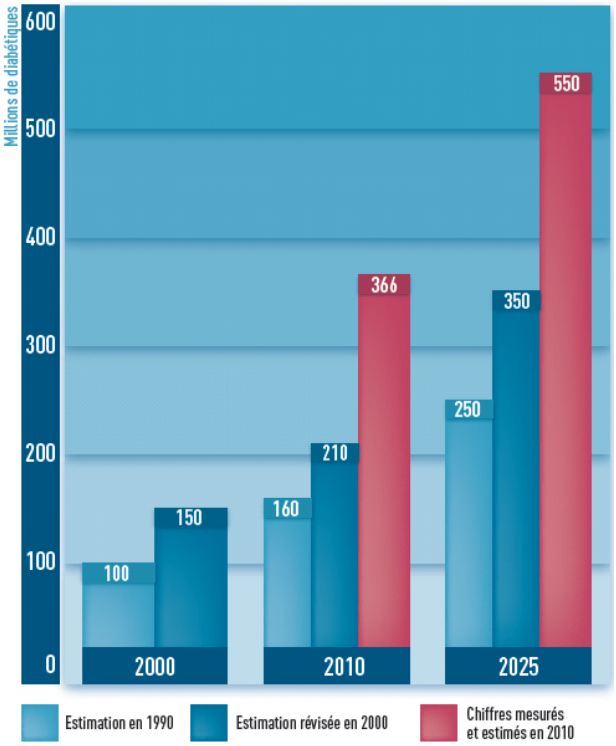
Présentation

The laboratory of experimental surgery of the UCL (Université Catholique de Louvain) in Brussels capitalizes on over 20 years experience in the field of transplantation (single cells and whole organs) and immunology in large animals. Directed by **Professor Pierre Gianello**, this laboratory is specialized in the encapsulation of insulin-secreting cells and in studying of this treatment in large animals. With an animal housing within a laboratory of an area over 600m2, it provides the best conditions and equipment for experimental surgery and monitoring of animal metabolism, as well as facilities for biological analysis and immunological monitoring.

Rôle dans le projet

The UCL team will intervene in the preclinical validation of the MAILPAN® device on large animals as well as the isolation of insulin-secreting cells of animal and human origin. The preclinical validation will include study of the function of MAILPAN® associated with different cells, its integration, immune responses within and around the device, in order to obtain permission to enter clinical trials, via the European regulatory authorities. UCL has developed its own large diabetic animal models which will be used for the implementation of the MAILPAN®.

Diabetes in figures



According to the latest figures published, the prevalence of diabetes **in France would be 6% or about 3.5 million people affected, including 500,000 to 800,000 diabetics who are unaware about their illness.**

This chronic disease is a **worldwide epidemic**, according to the World Health Organization (WHO). The latest data on diabetes, presented in mid-September in Lisbon at the EASD (European Association for the Study of Diabetes), have reported **366 million diabetics worldwide, of which the cost of care would rise in 2010 to 340 billion Euro**. Remember that this threshold of 350 million diabetics should be achieved by 2025 as originally forecast by the WHO, who consequently had to significantly increase its estimates.

In 2011, a diabetic dies every seven seconds in the world (a total of 4.6 million deaths in a single year).

The main causes of this increase are the aging of the population, extra weight and obesity, and a sedentary lifestyle.

Diabetes: a serious and expensive illness

Diabetes is characterized by a disorder of the assimilation, use and storage of sugars provided by food that is caused, either by a deficiency of insulin secretion by the beta cells of the pancreas islets of Langerhans (Type 1 diabetes, insulin-dependent), or by a disrupted action of insulin (type 2 diabetes, non-insulin-dependent).

It constitutes between 5 and 10% of health budgets in developed countries.
In January 2010, the Institute of Health published in its WER (Weekly Epidemiological Record) a cost analysis of diabetes in France, which reported a total repayment by Health insurance of 12.5 billion Euro per year to which 5 billion Euro of ”indirect” costs are added. **Diabetes is THE Public Health priority with a total economic impact of 17 billion Euros.**

Diabetes and medications:

Treatment for patients with type 1 diabetes is based on the administration of insulin (by insulin pen or by insulin pump). In the case of type 2 diabetes, the treatment consists in a first step of anti-diabetic drugs that improve the activity of insulin by the patient's pancreas, or which increase the production of insulin if this is too low. In fact, nearly half of the cases of type 2 diabetes evolve into a form requiring insulin administration.

Treatments offered to diabetic patients have evolved considerably in recent years, particularly in terms of efficiency and comfort.
What has been acquired in recent years is indisputably the control of insulin therapy with an efficiency that today means that if we take care of a diabetic early in the patient's life the development of complications will be limited.

However, this result is obtained at the cost of a heavy medical constraint with several insulin injections and glucose levels' monitoring per day.
For example, a patient who has had diabetes for 20 years will be pricked on average more than 45,000 times (with 3 injections and 3 blood sugar tests per day).
Getting rid of all these constraints is clearly one of the major challenges of current research.
The second challenge, but that goes in hand, is the patient's skill.

The only treatments that meet these needs in a completely **physiological** way are whole **pancreas transplantation** or pancreatic **islet transplantation** (pancreatic cells that secrete insulin among other hormones).

The pancreas transplant retains, at this time, an important place in the treatment of diabetic complications associated with renal failure and requiring a kidney transplant. At present, more than 9,000 vascularized pancreas transplants have been performed with a **success rate measured by an insulin independence of 75%.**

The transplantation of pancreatic islets is part of the therapeutic arsenal in the management of type 1 diabetes. The selective transplantation of pancreatic islets enables the transplantation of only endocrine tissue, representing about 1% of pancreatic tissue. It is performed during **minimal surgical intervention**, and therefore appears to be a particularly attractive alternative for diabetic patients.

Despite the hopes raised by these two treatments, the risks and constraints associated with long-term immunosuppressive therapy are significantly higher than those associated with disease progression in the majority of diabetic patients. In addition, these alternatives are reserved for a limited number of patients due to the low number of available and suitable donors.

In summary, an autonomous bioartificial pancreas able to replace multiple insulin injections and without immunosuppression will largely fulfill the diabetic patient's expectation.

Socio-Economic Impact

The lack of continuous monitoring of diabetes generally leads to the occurrence of complications in the medium and long term, which is a heavy burden for the patient and those around him. Currently, there is no treatment capable of continuously and stably normalizing sugar levels, with the exception of transplantation of insulin-producing cells.

The BIOSID project aims to improve the lives of patients with type 1 diabetes by providing a completely physiological treatment. **In comparison with current treatments for type 1 diabetes, the pancreas bioartificial hope to bring many benefits and impacts significantly improving the quality of life for many patients with diabetes,** allowing:

- The control of diabetes in a physiological way, without requiring an external supply of insulin and without the continuous monitoring of blood sugar,
- The transplantation of pancreatic islets without immunosuppressive treatment. Thus, this therapy could be extended to a larger number of patients,
- A simple routine visit to a diabetology unit every 3 to 6 months is required to replace the transplanted cells, in the case those are exhausted. Thus, the old cells are replaced by new ones by a simple drainage/ filling action through entry/ exit ports,
- The reduction of long-term complications of diabetes through a normalization of blood sugar,
- The disappearance of multiple daily insulin injections done by the patient, as well as the obligation of taking their meals at fixed times,
- Access to other sources of cells, of animal or genetically modified origin, available in infinite amounts. Thus, this solution will allow to treat a larger number of diabetic patients and alleviate the organ shortage.