PROJECT FINAL REPORT

Grant Agreement number: 305746

Project acronym: BIOSID

Project title:

A bioartificial pancreas to treat type1 diabetes: optimisation of cell survival and function in preclinical and clinical phases.

Funding Scheme: Small and medium-scale focused research project

Period covered: from 01/01/2013 to 31/12/2016

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[1] Usually the contact person of the coordinator as specified in Art. 8.1. of the Grant Agreement.

[2] The home page of the website should contain the generic European flag and the FP7 logo which are available in electronic format at the Europa website (logo of the European flag: http://europa.eu/abc/symbols/emblem/index_en.htm logo of the 7th FP: http://ec.europa.eu/research/fp7/index_en.cfm?pg=logos). The area of activity of the project should also be mentioned.

4.1 Final publishable summary report

Executive summary

MAILPAN® (MAcroencapsulation of PANcreatic Islets) is a prototype of bioartificial pancreas usable in the human designed to treat type 1 diabetic patients. The prototype was developed along different stages since 1996 and led to the creation of the SME called Defymed in 2011. The BIOSID project aimed to bring the prototype to the pre-clinical and clinical phases necessary to the ensuing commercialization of MAILPAN® whose ultimate goal is to improve the life of at least 20 million persons in the world while providing positive effects on healthcare management and expenses, the environment and the competitiveness of the biomaterials industry. In order to reach this goal, CeeD and Defymed gathered a consortium made of seven partners from academia, clinical/public health research sector and industry/SMEs from three different European countries –Belgium, France and UK. The consortium's expertise includes encapsulation techniques, islet isolation, cell engineering, islet transplantation, islet preconditioning, surgical implantation, and medium formulation; items that are complementary and essential for the implementation of the present project.

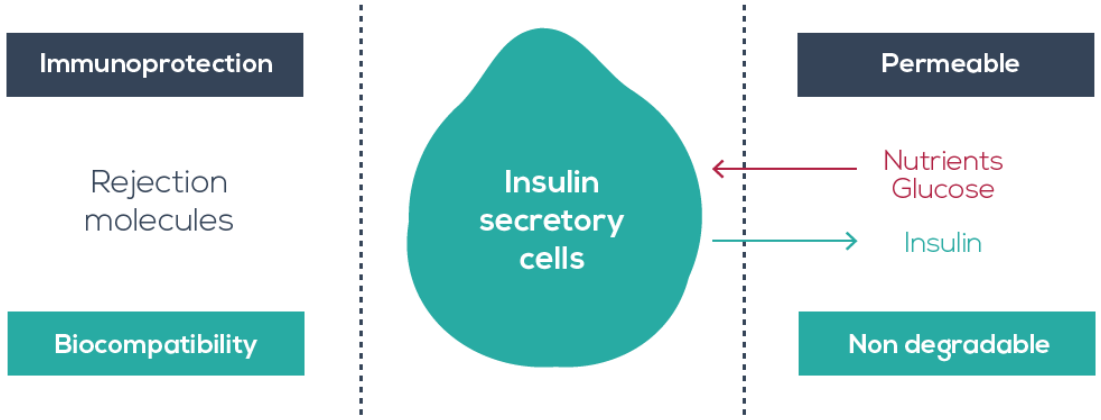
The project of a 48-month duration intended to bring the most modern and up to date improvements that the bioartificial pancreas still needs and can receive such as to enhance islet/cell survival and function inside the device. All along the scientific programme, the results have led to the clear **understanding of the physic-chemical conditions** present in the MAILPAN®, **the final formulation of a new adapted cell culture medium** characterized by an improved beneficial effect on islet/cell survival and function, the further **validation of the device in small and large animal models** by studying the function and safety/biocompatibility of the device in respect to the applied regulatory directives, and **to secure its further use in humans**.

As regarding dissemination activities, BIOSID project was valorized in several international meetings and media. We have noted more than **28 press releases/interviews** and participation in more than **20 congresses (40 presentations)**, where BIOSID partners have presented the BIOSID objectives and results. 11 abstracts (6) or full-articles (5) on project results have been published in peer-reviewed scientific journals. Furthermore, the project results will allow obtaining a short- or mid-term exploitation to the SME partners of the project.

Therefore, taken all together, the BIOSID project was considered by all project partners as a real success, that will allow to the cell therapy field to become, one day, a largely deployed reality to patients, such as Type 1 diabetic patients.

A summary description of project context and objectives

MAILPAN® (MAcroencapsulation of PANcreatic Islets) is a prototype of bioartificial pancreas usable in human designed to treat type 1 diabetic patients. The prototype was developed along different stages since 1996. Next step is now to bring the prototype to the pre-clinical and clinical phases necessary to the ensuing commercialization of MAILPAN® whose ultimate goal is to improve the life of at least 20 million persons in the world while providing positive effects on healthcare management and expenses, the environment and the competitiveness of the biomaterials industry in Europe. The development of a bioartificial pancreas is based on **an effective immune-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 anymore required**. **This physiological solution allows the cellular therapy to become a widely deployed reality.**



Principle of the bioartificial pancreas

Three functions are a pre-requisite 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

To answer these challenges, **BIOSID** project, of **48-month** duration, including **5 technical Work Packages (WPs 1→5), one dissemination Work Package (WP6) and one managerial Work Package (WP7**), has been launched since January 2013. This project intends to bring the most modern and up to date improvements that the MAILPAN® bioartificial pancreas still needs and can receive such as:

- to **understand the needs of insulin-secreting cells** in the bioartificial pancreas,
- to **meet these needs**, by formulating a **novel cell culture medium**, in order to improve their life expectancy in the bioartificial pancreas,
- to **validate the MAILPAN®,** associated with insulin-secreting cells of different types/origins, **in small and large animals**
- **to answer essential regulatory requirements in order to secure the entry of the MAILPAN® into clinical trials in human.**

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 SMEs based in Strasbourg (France), have built a strong consortium uniting 5 other partners from complementary fields of expertise. In this case:

- **AvantiCell** (ACS), a Scottish SME- UK,
- the Department of Endocrinology, Diabetes and Nutrition from the **University Hospital Center of Montpellier** (CHU)- France,
- the Nuffield department of Surgical Sciences from the **Oxford University** (NDS)- UK,
- **Univercell-biosolutions (formerly named Endocells)**, a French SME based in Toulouse-France,
- And the laboratory of Experimental Surgery of the **Catholic University of Louvain** (UCL) - Belgium.

Description of the main S&T results/foregrounds

The combination of in vivo, ex-vivo and in vitro experiments employed throughout the BIOSID project resulted in four principal outcomes:

1. A clear understanding of the physico-chemical conditions present in the MAILPAN® and the cell-biological mitigations required to sustain islet survival and function

Systematic investigation demonstrated that **islet confinement** and **resultant hypoxia** are major determinants of secretory function in any bio-artificial pancreases, and identified a number of mitigating conditions which could alleviate their adverse effects on primary or engineered ß-cells. The impact of cell confinement was addressed by determining an optimal density for cell loading into the MAILPAN® which improved cell/islet survival and function.

The project also identified intracellular mechanisms targetable by biochemical intervention with prospective protection against the most acute effect of hypoxia seen immediately after MAILPAN® loading. This was achieved in part through use of **a medium-throughput screening platform** (a suite of cell-based analytical tests) designed specifically for this purpose, and incorporating human pancreatic islets or the EndoC-ßH1 engineered pancreatic cell line. Using these platforms, we first selected a panel of interesting bioactive molecules which could potentially counteract the attritional effects of MAILPAN® hypoxia but also have identified methods to culture islets/cells in the MAILPAN®. The medium-throughput screening platform was then employed to evaluate these candidates in a wide variety of combinations, employing statistically-robust experimental designs to identify best-performing combinations. With this approach, BIOSID **identified a short-list of promising candidates for further evaluation through inclusion in a novel, customized medium formulation.** The formulation of that medium was performed with the dual objectives of maintaining glucose-sensitive insulin secretion whilst protecting pancreatic islet cells against the adverse effects of confinement within the MAILPAN® device.

2. The final formulation of new culture media designed to improve survival and function

Development of a novel culture medium able to protect human primary pancreatic islets against MAILPAN® confinement was built upon the systematic identification of “most promising” active

biomolecules performed across partner laboratories, and the subsequent combinatorial testing of those candidates using the purpose-designed medium-throughput screening platform. Medium development adopted the strategy of adding beneficial components to a standard (non-proprietary) base medium, with the base medium being used as a benchmark of improved secretory function or hypoxia-protection by novel formulations. Several distinct phases of medium enhancement occurred, as new candidate components were identified and new insights into islet performance emerged from other BIOSID activities. Ultimately, this development programme led to the final **formulation of two cell culture media characterized by an improved beneficial effect on cell/islet survival and function** (under hypoxia) with two distinct applications in human islet culture:

- for **cell-based analysis** that incorporate primary islets from humans;
- for use in **preclinical handling of islets**, and for islet equilibration prior to use in the MAILPAN®.

These novel medium formulations have been compared with commercially-available culture media designed for use with human pancreatic islets. This comparison confirmed the commercial potential of the BIOSID-developed products, and is resulted in the commissioning and **manufacture of GLP-grade batches** of the media by processes which are suitable for commercial exploitation on an industrial scale.

3. Reinforced preclinical validation of the MAILPAN® in small and large animal models

In parallel, preclinical studies performed in small and large animal models allowed us to overcome a number of important issues, including the following:

- **Validation of the surgical/operation protocol** (primates and pigs, with human size device),
- Excellent **bio integration** of the MAILPAN® into its implantation site: no tissue adhesion and easy retrieval**,**
- **Safety and biocompatibility** of the device demonstrated and **great vascularization** close to the MAILPAN® observed in rodents and primates**,**
- Very **encouraging functionality results**: rapid exchanges through the MAILPAN®. Moreover, Insulin-secreting cells encapsulated in the MAILPAN® are viable and **glucose responsive** in rats for a satisfying period.

4. A clearly defined regulatory route and production of a first batch of MAILPAN® in order to secure the entry into clinical trials

During this project, the aim was also to prepare properly the entry into clinical trials. In order to answer the essential regulatory requirements of the medical devices directive 93/42/CEE, the non-clinical and the clinical development plan were presented to the Competent Authorities. These discussions allowed to **confirm the regulatory route governing the MAILPAN® development** and helped us to work on a **first clinical protocol synopsis**. This first advice and synopsis will serve as a strong basis for the development of the clinical plan to seek for the authorization to enter into clinical trials. We are now close to a first phase of clinical trials which will aim to demonstrate the safety of the MAILPAN® in human.

Potential impact and main dissemination activities and exploitation results

Dissemination activities and exploitation of results

As regarding dissemination activities, BIOSID project was valorized in several international meetings and media. We have noted more than **28 press releases/interviews** and participation in more than **20 congresses (40 presentations)**, where BIOSID partners have presented the BIOSID objectives and results. **11 scientific publications** (abstracts (6) or full-articles (5)) on project results are published and minimum 2 others are under writing and should be published in the next few months. Finally, the BIOSID website has been launched in 2013 and will be maintained few months after the project ended (www.biosid-eu.org) and then transferred to the coordinator's website (www.ceed-diabete.org).

BIOSID's project results will allow obtaining a short or mid-term exploitation to the SME partners of the programme. The resulting products will be exploited through direct sale and/or out-licensing agreements.

Potential impact for type 1 diabetic patients

The ultimate aim would be to improve the lives of patients with type 1 diabetes by providing a complete physiological treatment. **In comparison with current treatments for type 1 diabetes, the bioartificial pancreas intends to bring several benefits and impacts significantly improving the quality of life for many patients with diabetes,** allowing thus:

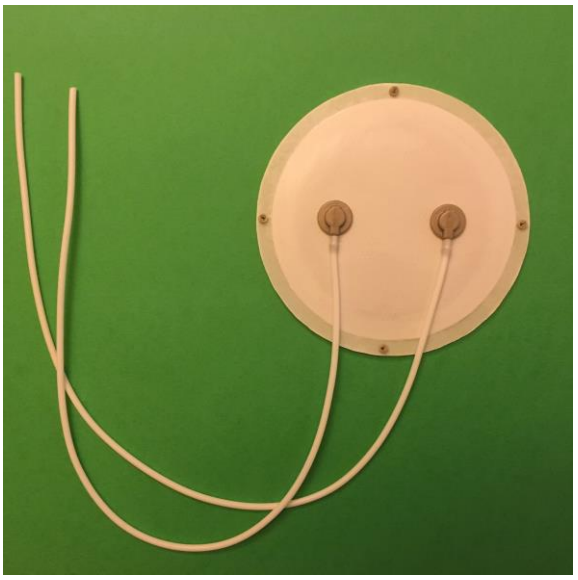
- The control of diabetes in a physiological way, without requiring an external supply of insulin and without the continuous monitoring of blood sugar,
- The transplantation of pancreatic islets without immunosuppressive treatment. Thus, this therapy could be extended to a larger number of patients,
- 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,
- Access to other sources of cells, of animal or stem-cell origin, available in infinite amounts. Thus, this solution will allow treating a larger number of diabetic patients and alleviating the organ shortage

If successful, the MAILPAN® could be adapted to other cell-therapy applications. Indeed, the financial outcome from this first application shall serve for the development of other bioartificial medical devices for other therapeutic applications, such as liver and/or kidney diseases, in a second step.

Therefore, taken all together, the BIOSID project was considered by all project partners as a real success, that will allow to the cell therapy field to become, one day, a largely deployed reality to patients, such as Type 1 diabetic patients.

Address of the project public website

The project public website will be maintained few months after the project ended at the following URL: http://www.biosid-eu.org and then transferred to the coordinator's permanent website at the following URL: http://www.ceed-diabete.org/fr/



MAILPAN® device

Logo of the BIOSID project