BETACELLTHERAPY Report Summary

Project ID: 241883  
Funded under: FP7-HEALTH  
Country: Belgium

Final Report Summary - BETACELLTHERAPY (Beta Cell Therapy in Diabetes)

Executive Summary:
Type 1 diabetes is a serious chronic disease with major health risks and heavy burden on patients and society. It is caused by a massive immune-mediated loss of insulin-producing beta cells in the pancreas, occurring preclinically and proceeding following clinical onset, often to depletion. Insulin treatment can meet metabolic demands but cannot mimic the physiologically regulated hormone response of a normal beta cell population. Consequently it cannot prevent episodes of hypo- or hyperglycaemia, and hence the risk for acute and chronic complications. Restoration of a functional beta cell mass is expected to correct glycemic control and thus to arrest deleterious clinical manifestations during progressing disease. Proof of principle is provided by intraportal islet cell implants that are prepared from human donor organs. However, the effect fades out in subsequent years, in part related to the limitations of this form of beta cell replacement, such as shortage and quality of organs and beta cell grafts, inability to analyze and optimize the implant site, need for continued immunosuppression.

The overall objective of the Beta Cell Therapy Consortium is to develop strategies for a durable restoration of a functional beta cell mass, with the perspective of interventions at different stages of the disease and of applications at a therapeutic scale. The consortium is composed of teams with expertise in beta cell and stem cell biology, clinical biology and cell banking, biomaterials and bioindustry, immunology, preclinical models and clinical trials. Its FP7 program assessed the following specific objectives as basis for therapeutic tracks:

1. Large-scale production of human beta (progenitor) cells that generate a functional beta cell mass when implanted in a confined site of preclinical models, and that can be translated to clinical testing;
2. Activation of beta progenitor cells endogenous to the pancreas, leading to identification of targets and compounds that can induce beta cell regeneration in the human pancreas;
3. Establishment of generic tolerance-inducing protocols relevant to both autotimmunity and transplantation and thus to therapeutic strategies in different stages of type 1 diabetes.

For each track several approaches were undertaken, based on prior work. Options were identified with methods and products that are ready for clinical studies or that are guided in their further translational development. Others were found to require revision or additional investigations before qualifying as potential component in a therapeutic track.

In the first track, four approaches were evaluated. Human embryonic stem cell-derived cells were advanced from the research phase over preclinical models to clinical development as combination product in a delivery device. In addition, methods were developed for reprogramming adult human cells to induced-pluripotent cells that differentiate to beta cell progenitors, a future source for preclinical testing. A human beta cell line was reprogrammed to serve as in vitro and in vivo model for studying regulation of human beta cell proliferation. Pathways for transdifferentiating human acinar cells to beta cells were recognized at the molecular level but were so far ineffective as driver to beta cell production. In order to test the therapeutic potential of novel cell sources, preclinical models for implants in confined sites were established using clinical-grade donor human beta cell grafts as reference. The biology of implants was investigated with in vivo and ex vivo markers that can also be implemented in patient studies. Advantages of micro-and macro-encapsulation were demonstrated in rodent models. Clinical pilot studies
were undertaken to prepare implants in a confined site and collect data for human beta cell grafts as used in intraportal transplantation.

The second track did not lead to the identification of beta progenitor cells in the human pancreas and methods for their activation. The mouse studies on beta cell regeneration in the pancreas reoriented the approach. Transient administration of cytokines was found to reprogram acinar cells to beta cells through progenitor-like intermediate cells. This conversion was capable of reversing a drug-induced diabetes but has not been tested in preclinical models; a path to clinical translation is still unclear.

In the third track, antibody-based protocols were shown to achieve tolerance to transplanted tissue through reconstitution of Treg cells and induction of a privileged microenvironment, a target for further therapeutic improvement.

Project Context and Objectives:

Objectives

Type 1 diabetes is caused by a major loss in insulin-producing beta cells, which proceeds after diagnosis, often to complete depletion. The objective of our consortium is to develop and implement interventions for restoring the beta cell mass. Methods can differ with the stage of the disease but will require the same insights and address similar targets. In this FP7 program we investigated three tracks that can lead to beta cell replacement in patients. The first aims large-scale production of human beta (progenitor) cells that can generate metabolically adequate beta cell implants. The second searches for cells and/or compounds that activate beta cell progenitors and/or beta cell proliferation with the purpose of inducing beta cell regeneration in the pancreas. The third track seeks to design antibody-based therapies that induce immune tolerance to regenerated beta cells or to a beta cell implant. Our five-year plan addressed the following specific objectives:

1. Generate human beta (progenitor) cells through programming of human embryonic stem cells or through reprogramming of human differentiated cells, and assess their therapeutic potential in preclinical models.
2. Activate beta cell formation in the pancreas and assess their therapeutic potential in preclinical models.
3. Develop generic tolerance-inducing protocols in animal models of autoimmunity and transplantation.
5. Translate findings to novel clinical protocols to restore functional beta cell mass in type 1 diabetes patients.

Work undertaken towards these objectives has provided tools and insights that should guide novel clinic trials in beta cell transplantation, in beta cell preservation and regeneration, as well as direct further laboratory research to overcome identified obstacles. These trials are aiming for a considerably better outcome and wider application than with current interventions, as have been undertaken
- shortly after clinical onset of the disease, consisting of transient suppression of autoimmune activity
- at a late stage of clinical disease, consisting of intraportal transplantation of human beta cell preparations isolated from donor organs

Consortium structure

The consortium addresses its overall objective through collaborative activities at and between three levels, i.e. an R&D platform, preclinical models and clinical trials. Its central unit manages and coordinates the program according to the roadmap, its milestones and its funding. For this FP7-supported program the tasks at the three levels are listed in Fig (see attachment) with indication of the associated WP-numbers.

Workplan
The WP activities were organised within three project areas, each addressing a set of milestones that had been defined as steps on the roadmap to novel cell therapy trials. Each WP was led by a principal investigator-PI belonging to a partner institution at a university or university hospital, a research institution, or a cell therapy SME.

The network has three core facilities, ie the MicroArray Center at Univ. Copenhagen (PI F.Nielsen), the Recombinant Virus Production Core at Centre National de la Recherche Scientifique (PI P.Ravassard) and the Beta Cell Bank at University Hospital Brussels (PI Z.Ling).

Project Area I. Laboratory generation of human beta cells and their progenitors
A major limitation of current transplant protocols is the shortage of beta cells that can be isolated from human donor pancreases. This part of the program aimed development of laboratory sources for human insulin-producing implants that allow mass production and clinical implementation. Four potential sources were investigated:

1) Human embryonic stem cells (PI E.Kroon, ViaCyte-Inc, San Diego-US). The team has pioneered the generation of insulin-producing implants from human embryonic stem cells. Methods were available to produce hESC-derived pancreatic precursor cells that differentiate into endocrine cells following transplantation in rodents. Implants were shown to reproducibly achieve glucose-regulated insulin release that corrects diabetes. This was to be tested in macro-encapsulating devices, which were manufactured as prototype for clinical trials (EncaptraR). Efficacy data on dose-response, long-term function and stability were to be collected, product composition to be defined and GLP-safety studies to be completed, assessing tolerability and efficacy of the device. Equivalency with primary human beta cells was to be studied in Project Area III. Strategies for phase I/II trials within the consortium to be discussed.

2) Human induced pluripotent cells (PI A. Smith, Cambridge-UK). The team is leader in the field of stem cell biology and differentiation. It planned to reprogram adult human keratinocytes to transgene-free human induced pluripotent cells and to develop robust protocols for their differentiation to endodermal cells and subsequently to pancreatic endocrine progenitors that can be amplified and further differentiated to beta cells. The goal is to implement the methods to cells isolated from type 1 diabetes patients so that these can be studied in preclinical models.

3) Human beta cell lines (PI R. Scharffmann, P. Ravassard in collaboration with Endocells-Sarl, Paris-F). The team has been the first to generate human beta cell lines that express markers and properties of primary human beta cells following SV40LT excision. These cells allow investigating the cell cycle of human beta cells in order to control their expansion. In the perspective of their implementation in cell therapy, conditions are to be identified for induced SV40 deletion and killing escaping cells, and for generating cell lines without passage in mice. The latter involves capture of proliferating pancreatic progenitor cells in the initial preparation and their in vitro differentiation, studies undertaken in collaboration with the teams in Cambridge and Brussels.

4) Human acinar cells (PI L. Bouwens in collaboration with H. Heimberg, Brussels-B). The team was the first to demonstrate transdifferentiation of rodent acinar cells to beta cells. This cell type is abundantly available as a discarded fraction at the BetaCellBank (Brussels), which prepares endocrine cell enriched fractions from human donor pancreases for transplantation in patients. Transdifferentiation of human acinar cells could thus become a large-scale source for human beta cell grafts and therefore became the goal for this WP. Genetic and non-genetic lineage tracing methods were needed to monitor this process for human acinar cells. Compounds acting on putative mechanisms were tested for their ability to induce a reprogrammed state in human acinar cells and subsequent formation of insulin-containing cells. This work became closely associated with activities in Area II aiming expansion of pancreatic epithelial cells before inducing their differentiation to beta cells.

Project Area II. Regeneration of beta cells in the pancreas.
Beta cell regeneration in the pancreas represents a second strategy towards beta cell replacement in diabetes. In this perspective, WP were undertaken to induce this process through activation of beta cell progenitors and defining conditions for their formation of functional beta cells. Initial studies were planned in rodents with the goal of translation to preclinical models.
and to human cells.

1) Activation of beta cell progenitors in the pancreas (PI H. Heimberg, Brussels-B). The team has identified and characterized beta cell progenitors in the adult mouse pancreas. This formed the basis for aiming, in the present project, the isolation of these cells, or their precursors, first from the rodent and then from the human pancreas. A culture model can then be established for seeking compounds that regulate expansion and differentiation. In vivo studies in mice are continued to identify conditions that induce neogenesis of beta cells.

2) Regulation of beta cell proliferation (PI Y. Dor, Jerusalem-Isr). The team has provided novel insights in the postnatal development and organisation of the rodent beta cell population. As partner to this program it planned to examine the role of the vascular niche, using transgenic mice for expansion or ablation of islet vasculature. During the second year the plan changed into (1) Studying the role of DNA demethylation in the endocrine fate of differentiating mouse progenitor cells. (2) Use of compounds that stimulate beta cell proliferation in mice.

3) Intrapancreatic injection of thymic epithelial cells reprogrammed to become a source for beta cell neogenesis (PI Y. Barrandon, Lausanne,Sw). The team has demonstrated the ability to reprogram thymic epithelial cells. In this project, it was examined whether endodermal cells can be derived from TECs and then driven to beta cells in laboratory models.

Project Area III. Translation to clinical trials

Track I. Cell transplantation

There is a need for cell transplant protocols that achieve metabolically adequate beta cell implants in a confined site, and that can be conducted with grafts produced from large-scale sources. These sites should be outside a vital organ, thus not the liver as in current trials, and allowing implant retrieval, be it for analysis or for safety. They will first be assessed with human beta cell grafts with and without encapsulation. Studies in preclinical models will guide translation to clinical trials; clinical biology markers will monitor both stages. This track consists of the following components:

1) Preclinical development (PI’s D. Pipeleers, Brussels, B- G. Skjaek-Brak/ Berit Strand, Trondheim, N -in collaboration with Beta-Cell nv, Brussels, B and ViaCyte-San Diego, US). This WP combines expertise in the field of beta cell biology and transplantation, in the production of novel cell therapy products and in encapsulation. It examined the biology of implants and assessed influences of graft source and composition, of encapsulation and of the implant site on the formation and preservation of a metabolically adequate beta cell implant. Rodent models were to be established for implantation of clinically relevant grafts, such as those currently used in trials and those in development as a large-scale source; a confined implant site was needed, allowing free as well as encapsulated grafts, and accessible to local monitoring, modulation and retrieval. Outcome of free, micro- and macroencapsulated grafts were compared for different implant sites and different source materials. Retrieved implants were quantitatively and qualitatively analysed as potential guide for interpreting in vivo data and for selecting targets and conditions to be further improved. The in vitro, in vivo and ex vivo data collected for clinical-grade human beta cell grafts are used as reference for assessing outcome of grafts from large-scale sources as produced by WP 2-4.

2) Clinical biology markers (PI’s F. Gorus, Brussels, B - B. Roep, Leiden, Neth). The team has state-of-the art markers for metabolic and immune follow-up of graft recipients during preclinical development and trials. Functional beta cell mass is assessed through assays for C-peptide and proinsulin. Episodes of beta cell destruction are searched through plasma detection of GAD and other beta cell proteins. The Diab-Q kit detects circulating autoreactive CD8+ T cells specific for different islet cell-associated epitopes. Antibody and cytokine profiles in plasma are comparatively analysed in light of the outcome of implants.

3) Clinical pilot studies and trials (PI’s B. Keymeulen, Brussels- F. Pattou, Lille, F- L. Piemonte, Milan, I). This multicenter team combines three clinical centers with long and profound expertise in the field of clinical islet cell transplantation. In this project
it undertook clinical pilot studies that prepare for novel cell therapy protocols. The first part examined whether the function of intraportal beta cell implants can be improved by complementing the standard ATG-MMF-TAC immune suppressive protocol with compounds administered at the time of implantation to suppress inflammatory and innate reactivity. The second part explored the possibility of implanting cells in an extrahepatic site, outside a vital organ, and preferentially in a confined area.

Track II. Beta cell regeneration in the pancreas

Compounds and cells are examined for their potential to induce regeneration in a pancreas with reduced or depleted beta cell mass. Such action could be beneficial at different stages of the disease, ie before or around the time of clinical onset when there is still a functional beta cell mass, or in a late stage when virtually no beta cells are left.

1) Preclinical models (D.Pipeleers, Brussels, B; C.Mathieu, Leuven, B). A method was developed that quantifies the number and distribution of beta cells in the rodent pancreas; it allows recognition of conditions that induce beta cell regeneration with therapeutic outcome. So far, no interventions have been identified that increase beta cell number in the pancreas.

2) Clinical biology markers (P1’s F. Gorus, Brussels, B; B. Roep, Leiden, Neth). State-of-the art immune, genetic and hormonal markers allow biology-based selection of individuals for participation in intervention trials and provide tools for assessment of the effects and their possible relationship with any of the entry characteristics.

3) Clinical trials (P1’s B.Keymeulen, Brussels, B; C.Mathieu, Leuven, B)

Our study in recent-onset type1 patients (12-39 years) has shown that antiCD3 treatment can transiently arrest the disease process. The effect is expected more pronounced in younger patients and in the preclinical phase. It is likely to benefit from an association with a compound that acts on residual beta cells, preserving their survival and ability to expand according to physiologic needs. Findings in the preclinical models will be translated to the design of further protocols with antiCD3 antibodies in patients.

Track III. Antibody-based therapy for inducing immune tolerance to beta cells in implant and pancreas

(P1 H. Waldmann-Oxford, A. Cooke-Cambridge, UK). The team is a pioneer in exploring the biologic basis of immune tolerance and in developing strategies for its induction. Its contribution to this project involves studies in laboratory models using methods that are applicable in patients. The goal was to design protocols that favour induction of Treg following T-cell depletion, that activate tissue-resident mechanisms preventing rejection and that increase the efficacy of anti-CD3 antibodies in suppressing autoimmune diabetes.

Project Results:

PROJECT AREA I.
LABORATORY GENERATION OF HUMAN BETA CELLS AND THEIR PROGENITORS

A major limitation of current transplant protocols is the shortage of beta cells that can be isolated from human donor pancreases. This part of the program aims development of laboratory sources for insulin-producing implants that allow mass production and clinical implementation. Four potential sources are investigated:

WP 1. Derivation from embryonic stem cells
WP-leader: E. Kroon (ViaCyte-Inc, San Diego-US, P14)

Significant progress was made in advancing stem cell-derived cells and a delivery device as combination product from the research phase to clinical development, including initiation of a Phase 1/2 clinical trial.

• In cell product development, the achievements included manufacture of Master and Working Cell Banks of the specific hESC starting material under Good Manufacturing Practices (GMP), development of a robust, reliable, scalable manufacturing process for differentiation of hESC into pancreatic progenitor cells (PEC-01™ cells), and development of cryopreservation and
thawing and recovery methods for preparation of PEC-01 cells prior to loading into macro-encapsulation (Encaptra®) devices.

- In device development, achievements included assessing and establishing materials and methods, and formalizing procedures for manufacturing Encaptra devices. Devices and their materials were thoroughly tested for biocompatibility and safety under ISO 10993 regulations. Custom manufacturing and testing methods and protocols were established.
- In parallel with cell and device development, the team established custom materials and methods for combining these two main components into the product candidate (VC-01™ product). This included aseptic processes for loading cells into devices, sealing the devices, and placing them into custom packaging for delivery to the clinic.
- Extensive Quality Control and Quality Assurance (QC/QA) systems were designed and implemented to assure standardized, reliable, safe and efficacious VC-01 product would be produced for clinical research. As biologicals (the cells) and devices fall under different regulations, the team needed to develop a custom hybrid quality management system that addressed both sets of regulations.
- Pre-clinical studies were performed in preparation for clinical testing, including three safety and efficacy studies of the VC-01 combination product under Good Laboratory Practices (GLP).
- A Phase 1/2 first-in-human clinical trial was designed to provide critical insights into safety and the potential efficacy of the product concept. A device master file (MAF) and investigational new drug application (IND) were submitted to the FDA and received no objections to proceed clinical testing of the product in patients with type 1 diabetes.

Key publications

WP 2. Derivation from Induced Pluripotent Stem Cells
WP-Leader: A. Smith (University of Cambridge, UK-P2a)

The overall objective was to develop human induced pluripotent stem (iPS) cells as a source of transplantable beta cells. Specific aims were to generate transgene-free iPS cells, to establish protocols for differentiation into beta cell progenitors, and to evaluate iPS cell-derived beta cell maturation and function. An original aim to derive iPS cells from Type I patients was not completed due to limited potential for immediate application and replaced by investigation into the more pressing issue of establishing expandable pancreatic progenitor cells.

The safe use of induced pluripotent stem (iPS) cells to generate autologous donor beta cells for replacement therapy requires an efficient methodology for generating iPS cells from adults without permanent genetic modification. We therefore investigated Sendai virus based vectors. Sendai is an RNA virus that is not reverse transcribed and exists only as an episomal element. We demonstrated reliable generation of transgene-free human iPS cells using Sendai virus vectors and also with
EBNA episomal vectors. We found that both reprogramming methods reliably produced transgene-free pluripotent stem cells from adult skin cells, although a proportion of iPS cell clones generated using the EBNA method contain integrated transgenes. Conventional human ES and iPS cells show variable differentiation behavior, which may be related to lineage priming. We developed a method for generating and maintaining naïve human pluripotent stem cells. An important future question is whether naïve cells may exhibit more consistent pancreatic differentiation behaviour than conventional pluripotent stem cells.

Several protocols have been reported for generating pancreatic progenitors by in vitro differentiation of human pluripotent stem cells. We assessed one of these protocols on a panel of ES and iPS cell lines for capacity to engender glucose sensitive insulin producing cells after engraftment in immunocompromised mice. We observed variable outcomes, with only one cell line showing a low level of glucose response. We therefore undertook a systematic comparison of different methods for inducing definitive endoderm and subsequently pancreatic differentiation. Of several protocols tested, we identified a combined approach that robustly generated PDX1-expressing progenitors in vitro from both ES and iPS cells. These findings suggest that, although there are intrinsic differences in lineage specification propensity between pluripotent stem cell lines, optimal differentiation procedures may consistently direct a substantial fraction of both hES and hiPS cells into pancreatic specification. Cells at the progenitor stage could be further differentiated to monohormonal insulin- or glucagon-positive cells using a recently published protocol, albeit with a low frequency. Further optimization is therefore required to develop a generally applicable method for robust and scaleable production of beta cells from progenitors.

The logistics and efficiency of run-through differentiation of pluripotent stem cells into mature phenotypes such as beta cells are challenging, even more so when considering the variability in behaviour between cell lines. These difficulties could be alleviated by capture and expansion of cells at a lineage-restricted progenitor stage. We therefore investigated the possibility of expanding PDX1 positive presumptive pancreatic progenitor cells. We developed conditions that enable reproducible isolation and long-term expansion of PDX1 expressing cells from either ES or iPS cells. These cells express additional pancreatic progenitor markers, FOXA2 and SOX9. They retain a normal karyotype and do not express pluripotency factors. The capacity of these progenitors to differentiate efficiently into hormone producing cells is under investigation.

Finally, to provide a comparative reference for in vitro progenitor cells and additionally obtain insight into their regulatory requirements we obtained ethical approval to source early human embryonic pancreata from elective terminations. We analysed marker protein expression and generated whole transcriptome profiles from this precious material. These data represent a valuable resource for future studies in the field.

Key Publications
3. Morrison, G. and Smith A. Convergence of cMyc and b-catenin on Tcf7l1 enables endoderm specification. EMBO J in press

WP 3. Derivation from pancreatic beta cell lines
WP-Leader: R. Scharffmann (INSERM, Paris-F, P5) in collaboration with Sarl Endocells (Paris-F, P16)

Cell therapy of Type 1 diabetes is a rapidly progressing field. However, a number of key questions remain to be solved and preclinical models are necessary for this purpose. At the start of this program, we were developing human beta cell lines to be used as a model for cell therapy of diabetes. During this FP7 program we
• Further characterized our first, available, human beta cell lines: We characterized in great details such human beta cell lines and demonstrated their functionality both in vitro and in vivo following transplantation in immuno-incompetent mice
• Progressed in the development of new lines that meet safety criteria to be considered as beta cell replacement therapy. We
next developed second-generation human beta cell lines where the immortalizing transgenes can be deleted. Again, such lines were phenotyped in detail and we demonstrated their functionality. While the process of transgene deletion was efficient, it was time-consuming and its efficiency was not perfect. We thus developed additional tools to fill such gaps. Finally, the process used to generate human beta cell lines requires a complex in vivo step and we progressed in the definition of new strategies that could replace such a step.

- Used the lines for investigating the biology of human beta cells and their cell cycle in order to control expansion. We demonstrated that Human beta cell lines can be used as a model better understand the role of human beta cell specific factors in physiological and pathological conditions. Towards progressing in the biology of human beta cells, we demonstrated that the developed human beta cell lines can be used as a model to study β cell (de)differentiation. Finally, we progressed in the description of human beta cell cycle and modified the human beta cell lines we had developed as a new tool to study in great details human beta cell proliferation and screen for signals that regulate this process.

Our achievements within the time frame of the program are centred on the development of a robust technology platform dedicated to production of human beta cell lines. Such technology is based on cell genetic engineering in order to (i) immortalize human beta cells and derive cell lines; (ii) delete immortalizing genes after cell amplification to get closer to cell therapy safety requirements; (iii) generate new reporter lines for easy cell proliferation read outs; (iv) perform loss of function studies of key beta cell regulators and unravel unknown beta cell functions.

Key publications

WP 4. Derivation from pancreatic acinar cells
WP-Leader: L. Bouwens (Brussels Free University-VUB, Brussels-B, P1c)

Transplantation of pancreatic beta cells can potentially cure type-1 diabetes but is hampered by the shortage of organ donors. Our project fits in the general aim of the program to find additional sources of transplantable beta cells for cell therapy. Our objective was to generate more beta cells from the available donor organs by inducing the non-endocrine fraction, more especially the exocrine acinar cells which form the majority of pancreatic cells, to transdifferentiate into endocrine beta cells. This is based on our previous results which showed that rodent acinar cells transdifferentiated to functional beta cells when treated with molecules like epidermal growth factor (EGF) in combination with leukemia inhibitory factor (LIF) or the related ciliary neurotrophic factor (CNTF). These molecules activated intracellular signaling pathways, namely JAK2/STAT3 and MAPK, leading to expression of the embryonic pro-endocrine transcription factor neurogenin-3 (Ngn3) prior to differentiation into insulin-producing beta cells. Our aim was to translate these findings to human cells in order to contribute to the generation of a much larger amount of transplantable beta cells. Such cells might be safer for transplantation into patients than cells derived from pluripotent stem cells, since they exhibit very limited proliferative activity and are less likely to become tumorigenic. However, applying the same procedure (EGF and LIF) to cultured human exocrine cells did not lead to the endocrine differentiation results previously obtained with rat cell cultures. To assess whether human exocrine cells may possibly have
less cytodifferentiation plasticity than their rodent counterparts, we studied the differentiation behavior of the human exocrine cells in various culture conditions. To evaluate their transdifferentiation potential we established new methods to label the cells in a specific way in order to follow their fate even when they change their original phenotype during culture. Two different cell tracing methods were developed, one that relies on the genetic labeling of cells after viral transduction of an acinar cell-specific and undelible reporter gene, and another that is based on the acinar-specific binding of a fluorochrome-coupled lectin that is incorporated in the cell cytoplasm. The optimal way to deliver transgenes into human acinar cells was determined.

Examination of cellular phenotype of pre-labelled human acinar cells revealed that the acinar cells spontaneously transdifferentiated to cells with a phenotype that was undistinguishable from duct cells, another type of pancreatic cells. These epithelial cells later further changed their phenotype into that of mesenchymal cells. This was the first direct demonstration of acinoductal and epithelial-to-mesenchymal transdifferentiation of these cells from human origin, phenomena that may also take place in certain pancreatic pathologies. It emphasizes that human acinar cells share similar differentiation plasticity with their rodent counterparts.

Since in rodents, activation of STAT3 and MAPK biochemical pathways in acinar cells lead to transient expression of Ngn3 prior to endocrine transdifferentiation, we assessed whether genetic activation of these pathways resulted in the same expression within the human acinar cells. Indeed, forced expression of activated STAT3 and MAPK induced expression of Ngn3 protein in transduced human cells. In appropriate culture conditions within a 3D Matrigel extracellular matrix or after transplantation into mice, the transduced Ngn3+ human acinar cells could further differentiate into functional, insulin-producing, beta-like cells. This further demonstrated that human acinar cells have the potential to transdifferentiate into beta cells when the appropriate intracellular signalling systems are activated.

Key Publications

PROJECT AREA II: REGENERATION OF BETA CELLS IN THE PANCREAS
Beta cell regeneration in the pancreas represents a second strategy towards beta cell replacement in diabetes. In this perspective the following studies have been undertaken:

WP 5. Beta cell progenitor activation
WP-Leader: H. Heimberg (Brussels Free University-VUB, Brussels-B, P1b)

Our objective was to activate stem- or (facultative) progenitor cells endogenous to the pancreas or recruited from other niches like bone marrow. To this end we addressed the following specific aims: (1) Identification, isolation, characterization and differentiation of self-renewable beta cell progenitors, (2) Investigation of the existence of beta cell progenitors in the human
pancreas, (3) Identification of cells and signals that activate beta cell progenitors to normalize hyperglycemia.

From adult mouse pancreas we dissected exocrine duct fragments that were cultured under conditions similar to the ones developed to expand intestinal stem cells and drive their spontaneous differentiation. Budding cyst-like structures (organoids) expanded 10-fold weekly for >40 weeks. Single isolated duct cells can also be cultured into pancreatic organoids that can be clonally expanded. Clonal pancreas organoids can be induced to differentiate into duct as well as endocrine-like cells, thus proving their bi-potentiality. Epidermal growth factor was found to contribute to the switch from expansion to differentiation. Similar results have been obtained with exocrine duct cells from adult human pancreas. The efficiency of the endocrine differentiation has been increased by introduction of transcription factors and signal transducing molecules. As this involved virus-mediated gene transfer we are now optimizing expression systems without viruses.

We demonstrated the existence of multipotent, endogenous islet cell progenitors in the adult mouse pancreas when activated by severe injury following partial duct ligation. Isolated pancreatic cells expressing the master switch transcription factor Neurogenin 3 (Ngn3) had similar ultrastructure and gene expression profile as bona fide embryonic beta cell progenitors. The Ngn3+ cells did not proliferate and differentiated to new beta cells with high cell cycle activity. Ngn3+ cells also play a crucial in beta cell regeneration in the pancreas of mice that were made diabetic by injection of the beta cell toxin alloxan and 35 days later treated with the cytokine combination epidermal growth factor and ciliary neurotrophic factor (EGF+CNTF). Cell type-specific lineage tracing showed that terminally differentiated acinar cells were reprogrammed to functional beta cells. The regenerative process was directed via an intermediate, progenitor-like cell with activated Ngn3 expression. Indeed, transient administration of EGF+CNTF to adult mice with chronic hyperglycemia efficiently stimulates the conversion of terminally differentiated acinar cells to beta-like cells. Newly generated beta-like cells are epigenetically reprogrammed, functional and glucose responsive, and they reinstate normal glycemic control long term. The regenerative process depends on Stat3 signaling and requires a threshold number of Ngn3-expressing acinar cells. In contrast to previous work demonstrating in vivo conversion of acinar cells to beta-like cells by viral delivery of exogenous transcription factors, our approach achieves acinar-to-beta-cell reprogramming through transient cytokine exposure rather than genetic modification and therefore will be more suitable for extrapolation to pre-clinical models.

This project has been scaled down after year 3.

Key Publications


WP 6. Vascular Niche for Beta Cell Proliferation
WP-Leader Y. Dor (Hebrew University of Jerusalem, Israel, P7)
The role of the vascular niche was studied using transgenic mice for expansion or ablation of islet vasculature. Quantification of islet vascular density showed a major decrease after conditional overexpression of sFlt1 in beta cells and an increase when VEGF was conditionally overexpressed.

Our plan was then changed to

• Studying the role of DNA demethylation in the endocrine fate of differentiating mouse progenitor cells. This line was supported by the observation of a demethylation state in endocrine pancreatic cells and a methylation state in non-endocrine pancreatic cells. This line was however discontinued in year 3
• The use of compounds that stimulate beta cell proliferation in mice. A glucokinase activator was shown to exhibit this effect but appeared associated with DNA damage and beta cell death. Further work was undertaken to understand the mechanism of G2/M beta cell death.

This project has been scaled down after year 3.

Key Publications

WP 7. Adult Stem Cell Potency for Beta Cell Regeneration
WP-Leader: Y. Barrandon (Ecole Polytechnique Fédérale de Lausanne,P8)

Aim
• to identify the conditions that allow reprogramming of thymic epithelial cells (TEC) to beta cells
• Intrapancreatic injection of thymic epithelial cells reprogrammed to become a source for beta cell neogenesis

The team has isolated rat TECs from GFP-mice and characterized their phenotype, expression profile and karyotype; a subpopulation was identified with endodermal marker expression. Microinjection in embryonic pancreas explants, or injured adult pancreas (PDL model) did not lead to beta cell neogenesis. Clonogenic human TEC have also been isolated and cultured, but no evidence was found that TECs could be reprogrammed into insulin expressing cells.

This project has been scaled down after year 3.

PROJECT AREA III: TRANSLATION TO CLINICAL TRIALS

Track I. Cell transplantation:

1) Preclinical models (WP8)

The objective is to design and assess cell transplant protocols that (1) achieve implants with metabolically adequate functional beta cell mass in an extrahepatic site, from where they can be retrieved for analysis, (2) can be extrapolated to patients, (3) are applicable to large-scale graft sources. The studies adopt cell biologic criteria and markers for quality control of grafts and implants, and for their adjustment. They have resulted in

1. Preclinical support for clinical pilots on free and encapsulated human beta cell implants in extrahepatic sites

Studies in immune-deficient rodents (Brussels) compared outcome of free and encapsulated human beta cell implants in peritoneal cavity, omentum, subcutis, and liver. Grafts and implants were analysed by in vitro (pretransplant), in vivo, in situ and ex vivo (after retrieval) markers. This combination provided a cell biologic interpretation of in vivo outcome. It validated plasma GAD levels as marker for detecting acute phases of beta cell destruction (see WP10). Data distinguished differences in the degree and timing of beta cell loss with the site of implantation, the endocrine purity and the existence of a capsule. Alginate-microencapsulated beta cells survived better than non-encapsulated cells whereas they did not survive in a macro-encapsulating device. Outcome resulted in pilot clinical studies on alginate-encapsulated implants in peritoneal cavity and subcutis, and free implants in omentum. (Pre) clinical observations with alginate-encapsulated cells defined aims for improving the biomaterial formula and its testing in laboratory models of biocompatibility. Studies in mini-pigs (Lille) investigated the intramuscular site for optimization of implant conditions and for their local analysis. It runs in parallel to pilot studies in patients (see WP11).

2. Comparative data on cellular composition and functions of clinical-grade human beta cell grafts and human ES-generated beta cell implants

Methods, markers and data from Aim 1 serve as reference to assess outcome of human beta cell implants generated from programmed human embryonic stem cells (WP1) or reprogrammed human adult differentiated cells (WP2 and 4). So far, only cells from WP1 were tested, since the other WP did not reach the stage for preclinical testing. A preclinical pilot study was undertaken with beta cell line-derived cells (WP3) showing its usefulness to measure the effects of further improvements that are needed for this source to become clinically applicable.

Human ES-derived pancreatic progenitor cells generated implants with higher beta cell purity when implanted in a TheraCyte device than non-encapsulated, both in subcutis, whereas a high alpha cell purity was observed in alginate-microencapsulated implants. Implants in a device were quantitatively retrieved at different time points and analysed for composition and function. At PT week 20, beta cells exhibited physiologic characteristics together with properties of cells that have not yet reached the mature stage.

Key publications

2) Clinical biology markers
WP-10 Leaders: F. Gorus (Univ Hospital Brussels-VUB, B, P1e) and B. Roep (Leiden Univ, Neth, P4)

The overall aim was to provide a platform with state-of-the-art biological markers that guide and monitor beta cell replacement therapies, both in animal models and in clinical trials. Current and newly developed markers were validated and implemented to measure, follow and/or predict immune reactivity, beta cell function and its metabolic impact. The significance of novel combinations of established markers and of newly developed assays was evaluated in different experimental and clinical settings, including various types of beta cell replacement therapies and protocols, various stages of type 1 diabetes, and various types of immune interventions. This led to novel biologic criteria for inclusion of participants, identification of responders, therapeutic monitoring and read-outs in beta cell therapy trials. These criteria were based on tests evaluating the following in vivo processes:

(1) Beta cell function:
- hyperglycemic clamp tests were used
  - to define minimal therapeutic targets in terms of reconstituted functional beta cell mass (FBM) in order to induce a metabolically beneficial reduction in glycemic variability;
  - to determine a threshold for FBM below which rapid progression to clinical onset of type 1 diabetes is very likely to occur in multiple autoantibody positive individuals;
  - identify simple but equally effective markers for identifying rapid progressors;

(2) Beta cell damage:
- plasma GAD65 level was validated as marker for beta cell loss following islet cell transplantation in patients;
- other beta cell proteins were found that could qualify as additional markers, and thus lead to a multiplex immunoassay with higher sensitivity which could open the perspective of detecting beta cell loss during more chronic low-level cell destruction processes.

(3) Immune status and reactivity:
- presence of insulin autoantibodies at clinical onset appeared associated with rapid loss of beta cell function and, consequently better responsiveness to anti-CD3 therapy
- significant increase in islet autoantibodies within 6 weeks after intraportal islet cell implantation was associated with poor metabolic outcome
- the Diab-Q-kit nanotechnology for determining absolute frequencies of islet autoreactive CD8 T-cells in blood revealed that a major cause for failing islet cell transplants can be attributed to failure of current immune suppressive agents to target islet autoreactive effector memory T-cells;
- human pancreatic beta cell lines from Endocells were assessed in vitro for their susceptibility to innate and adaptive immune challenges; data showed the ability of evaluating immune intervention strategies in preclinical models and searching for protecting strategies;

Key Publications

3) Clinical trials
WP-Leader: B. Keymeulen (Univ Hospital Brussels-VUB, B, P1d) in collaboration with F. Pattou (Univ.Lille, F, P6), L. Piemonti (Univ.Milan, I, P10)

This WP undertook pilot studies in preparation of novel cell replacement therapies.

The first part consisted in examining whether outcome of intraportal islet cell transplants in type 1 diabetic patients can be improved by compounds administered at the time of engraftment. All patient were on immunesuppressive treatment that consisted of ATG, tacrolimus and mycophenolate mofetil. The Milan team found a positive effect of reparixin, a CXCR1/2 inhibitor. The Brussels team tested the addition of rituximab, and of basiliximab, but none was able to improve outcome. The Lille team administered antitrombin but noticed an unfavourable efficacy /safety ratio.

In the second part phase 1 studies were undertaken to explore ways for implanting islet cell grafts in another site than the liver. This would open the perspective of using encapsulated cells, first from human donor organs and then from large-scale sources such as human stem cells and porcine pancreases. The Lille team showed the potential of the forearm by demonstrating function with an islet autotransplants in a pancreatectomized patient. At this moment there is no experimental plan to transplant type 1 diabetic patients. The Milan team found beta cell survival after implants in the bone marrow of pancreatectomized and type 1 patients. The Brussels team examined whether alginate-encapsulated human beta cells survive in the intraperitoneal cavity and under the skin; survival with ex vivo function was documented up to 3 months posttransplantation but only for a small fraction of the injected cells; possible reasons for beta cell loss were suggested and led to further development in preclinical models.

Key publications

Track II: Beta cell regeneration in the pancreas

Preclinical models (WP8)
WP-8 leader: D. Pipeleers (Brussels Free University-VUB, B, P1a) in collaboration with C.Mathieu (Kath.Univ.Leuven-KUL, B, P9)

The objective is to assess and compare the therapeutic potential of cells and/or compounds to induce beta cell regeneration in the pancreas.

AntiCD3 antibodies have been shown to preserve beta cell mass in type 1 diabetes patients. Their effect is mainly achieved at young age, where immune destruction might be most prominent. It did however not restore a normal beta cell mass, suggesting absence of regeneration towards a normal beta cell mass. Animal studies are therefore undertaken in search of interventions that induce beta cell regeneration in a diabetic pancreas, and could thus qualify to be combined with an antibody treatment of the immune system. They are conducted on mice with alloxan-induced diabetes or with an immune form (diabetic NOD mice) in which the beta cell population is quantified and further analysed in terms of organisation and phenotype using a newly developed procedure. The goal is to identify compounds or cells that, upon administration, increase the number of pancreatic beta cells. Cultured rodent beta cells are used as model to detect, or confirm, a direct effect on number, either through influencing their survival and/or replication; this allowed us to define the influences of glucose on both variables, and their dependency on age.

In diabetic NOD mice, the size of the beta cell mass at onset was 16% of that in normal controls. Administration of anti-CD3 antibodies prevented further loss in one third of the animals but did not lead to an increase in beta cell mass. Addition of GLP1 mimetics increased the fraction in which the beta cell mass at onset was preserved for at least five weeks, but did neither lead to a higher residual beta cell mass. This was also the case after combination with MK626, a DPP-4 inhibitor.

The initial plan also foresaw combination with cells/compounds that WP5-7 would identify as activators of beta cell progenitors in the mouse pancreas. This part of the study was not conducted as no such conditions were found as qualifying for preclinical testing. Pancreatic duct ligation-PDL had been previously reported to activate beta progenitor cells in the adult mouse pancreas and increase its beta cell mass. Using our quantification method we did not find that PDL increased total beta cell number; it did however stimulate neoformation of small beta cell clusters with more cells in proliferative activity, however not sufficient in numbers to increase totals in the entire tail part.

Translation to clinical trials
The observations with GLP1 mimetics support clinical testing of a GLP1-agonist in combination with aCD3. This will be considered after reviewing the outcome of a new aCD3 trial that is currently running in Brussels, in collaboration with GSK. It is undertaken in recent-onset type 1 diabetes patients with the goal of defining a dose with optimal efficacy/safety ratio.

Key publications


Track III: Antibody-based therapy for inducing immune tolerance to beta cells in implant and pancreas
WP 9-Leader: H. Waldmann (Univ.Oxford, UK, P3) in collaboration with A. Cooke (Univ.Cambridge, UK,P2b)

This part of the program aimed
- To establish generic tolerance-inducing protocols which promote regulation relevant to both autoimmunity and transplantation, with application for beta cell replacement in diabetes.
- To establish the extent to which immunomodulatory agents can synergise for promoting regulation and depend on recruitment of pre-existing natural regulatory T-cells.
- To investigate which of these protocols enable long-term acceptance of laboratory generated insulin-producing tissues derived from NOD mouse-derived ES cells in diabetic NOD mice.
- To determine the functional phenotype of infiltrating white cells in tissues protected as above.
- To determine tissue and blood markers for the immune tolerant state in recipients of a beta cell graft.
- To determine in beta cell implants the presence and role of tissue defence mechanisms interacting with infiltrating regulatory T-cells.

It has demonstrated that
- aglycosylated anti-CD3 antibodies can re-establish tolerance in murine models of diabetes, contributing to a preclinical model where a similar antibody to human CD3 can do the same.
- regulatory T-cells are potentially unstable, and that therapy should take into account the need to epigenetically stabilise them.
- tolerance to transplanted tissues can be achieved after lymphocyte depletion, by combination therapy designed to promote short-term competitive reconstitution by Treg, so minimising the impact of homeostatic expansion of effector lymphocytes.
- grafts accepted through our tolerising protocols appear different to the native tissue by their content of white blood cells which coordinate to create immunosuppressive milieu-in other words exhibit immunological privilege. This indicates that attention needs to be paid to how such privileged microenvironments can be enhanced therapeutically.
- imaging can be used to monitor the effects of therapeutic interventions.
- tolerated tissues may not provide tolerance-specific biomarkers, but instead lack of inflammation as evidence of harmony with the graft.
- CTLA4, IL-9, TGFβ, IDO, and GMCSF are all somehow involved in the creation of privileged microenvironments within tolerated tissues.
- short-term antibody-based protocols enable acceptance of lineages derived from human ES in outbred mice.

Key publications
COORDINATION

WP 12-13 Management and Dissemination
WP Leader K.Hellemans (Center Beta Cell Therapy, Brussels, B, P18) with associated core facilities: Beta Cell Bank (Univ Hospital Brussels-VUB, B P1d), Viral Core Facility (P.Ravassard, CNRS, Paris, P13), Microarray Facility (Univ Copenhagen, D, P12)

The coordination unit managed the consortium and its internal and external interactions with the objective of
(1) optimizing collaboration, use of resources and efforts for achieving the goals of the program
(2) disseminating information and implementations internally and externally

Its activities consisted in
- managing the program according to work plan and EC contract
- coordinating interactions between consortium components and partners,
- assessing and supporting progress along the road map
- facilitating translation to clinical and bio-industrial applications
- supervising use and justification of budgets, ethical and legal guidelines
- seeking additional expertise and financial support according to progress and needs
- disseminating information, in collaboration with EuroStemCell
- organizing meetings and training

Potential Impact:
1) Impact on health and related social-economics

Diabetes is a frequent chronic disease that reduces quality of life and increases the risk for life threatening complications despite current treatment. It causes a daily burden for all patients, related to care and knowledge of a life-long disease with risks for acute and chronic complications. With time, an increasing number will experience a higher morbidity and medical deterioration. Average lifespan is considerably shorter. Its economic burden is estimated at 15% of health care expenses, to be added to direct and indirect costs covered by the patients.

The disease can appear at all ages. When diagnosed under age 40, it mostly presents as the type 1 form. Compared to type 2 diabetes, this form is more severe since patients have lost their endogenous insulin control on metabolism, which makes them also dependent on insulin administration. The disease will also be a disturbing life companion for many more years, for some since childhood, thus increasing their exposure to metabolic derangements; risk for hypoglycemic coma is a serious concern for all, in particular children. This higher severity is also reflected in markedly higher costs for the health budget.

Type 1 diabetes is caused by a major loss in insulin-producing beta cells. It is generally accepted that restoring a functional beta cell mass can cure the disease and stop the progression of deleterious clinical manifestations. It makes exogenous insulin no longer necessary and eliminates risks for complications. The objective of the present program has thus a major relevance for patients and for the public health budget. Strategies aim restoration and preservation of the beta cell mass at different stages of the disease. Our findings show that we not only make scientific progress but also reach the level where patients experience a benefit, although transiently. The latter is however important as proof of principle and as support for claiming an impact of our work.

At an early phase of the type 1 disease, the beta cell population is under immune and inflammatory attack but still contains a residual mass of functional cells, in most patients with a metabolic role. At clinical onset, we previously showed that an antibody-treatment can preserve this residual mass, be it only transiently in a subpopulation; findings in this program form the
basis for novel antibody-based protocols in a biologically defined subgroup, by preference at young age and in a preclinical stage of the disease. Clinical markers are available for selection of individuals and monitoring the effects, in particular on beta cell mass. The ultimate goal is to prevent clinical onset of the disease, or to reduce its impact on the beta cell mass.

At a late phase, when the beta cell mass is depleted, recurrent hypoglycemia and signs of chronic diabetes lesions become prevalent. Intraportal beta cell transplantation restores a functional beta cell mass, which results in a stop of insulin injections in 40 percent of patients. However, its size is 40 to 80 percent smaller than that in non-diabetic individuals, and will decrease with time. Nevertheless, virtually all patients experience a disappearance of hypoglycemic events, often up to five years; in several of them chronic lesions stop progressing, and hospitalization days are significantly reduced. These observations demonstrate the impact of our cell transplant program. They also support the view that implants with a larger beta cell mass - as can be expected from large-scale sources - will be accompanied with a higher and longer metabolic benefit. Bringing stem-cell derived cells to the preparation of clinical protocols removes the current obstacle of shortage in human donor organs and in biologically adequate beta cell grafts, and opens a track towards translational development of a more potent cell therapy product that can be more intensively studied in clinical trials and, when successful, more widely implemented for the cure of diabetes, type 1 in the first place, but possible also severe cases of type 2, which are also characterized by a severe reduction in beta cell mass.

The knowledge and methods for driving human stem cells to pancreatic progenitors and beta cell implants has raised the possibility of generating grafts from patients and examining their outcome when implanted as autografts. This approach would eliminate the need for anti-rejection therapy and thus avoid the side effects of this treatment. It will have to consider possible recurrence of autoimmunity and means to handle this reactivity, such as in our immune-tolerance track. Our program has set this iP5-driven application on our agenda to be evaluated as a possible future project that assesses the feasibility of this form of personalized treatment, biologically, technically, and financially. If successful such approach could become applicable at earlier stages.

2) Impact of consortium on translational research and applications
The structure, organization and experience of our consortium represent a key asset for translational research and applications in the field of cell therapy in diabetes. The achievements have shown its efficacy in focusing a program to its objectives, in translating R&D findings into clinical and industrial applications. Preclinical models have been developed for assessing and comparing the therapeutic potential of cells and compounds. A novel set of markers allows a biologic evaluation of implants, their environment and their metabolic significance, an analysis that is also applicable to clinical implants. Preclinical observations and methods guide testing in clinical pilot studies and trials. A clinical biology reference center provides and extends state-of-the-art diagnostic and prognostic markers, ie blood and tissue markers for assessing functional beta cell mass and the metabolic and immune state of the patients. The trial team has a long experience in Phase I and Phase II studies and in valorizing protocols and therapeutics. A central unit with long track record in international programs coordinates the activities. This FP7 program has further consolidated the impact that the consortium can have on development of novel cell therapies.

3) Impact of WP potential on future projects and developments
WP1 has brought human embryonic stem-cell derived cells to clinical assessment of their potential to generate a functional beta cell mass in patients. A Phase 1 study protocol has been submitted and approved by FDA. A clinical research protocol will be submitted to the Belgian Regulatory authority in January 2016; it will be carried out with the preclinical and clinical partners of the present consortium. Data and translational path provide key information for other teams in the field.

WP2 has developed methods for generating and maintaining naive human pluripotent stem cells that were consistently differentiated in pancreatic progenitor cells with expansion potential and normal karyotype.

WP3 has a robust technology platform for production of human beta cell lines that can be reprogrammed to non-proliferating
beta cells that can be made available for academic and pharmaceutical studies.

WP4 and 5 have knowledge and tools to screen compounds for their ability to induce in vitro (human) and in vivo (mouse) transdifferentiation of acinar cells to beta cells, and to activate beta progenitor cells in the mouse pancreas.

WP8 has preclinical models and markers for assessing the functional beta cell mass in implants and in pancreas; the therapeutic potential of clinically-applicable cells and compounds can be tested and compared; methods are in place to investigate the effect of micro- or macro-encapsulation on cell engraftment and its survival and function as implant; knowledge in encapsulating biomaterials;

WP 9 has knowledge and expertise in immune-tolerance mechanisms and protocols, and use of antibody-protocols in clinical transplantation.

WP10 provides a clinical biology platform for state-of-the art monitoring of disease progression and immunotherapy through detection of immunological and metabolic biomarkers; synergizes with clinical teams in defining new inclusion criteria, intervention protocols and biological readouts for intervention trials; with associated Beta Cell Bank for provision of human pancreatic and beta cell preparations, free or encapsulated with associated Diabetes BioBank for provision of biologic samples and data from type 1 diabetes patients and first degree relatives at high-intermediate-low risk for the disease.

WP11 has a clinical trial team with expertise in multicenter studies in the field of prevention and treatment of type 1 diabetes, with specialists in implant techniques, anti-inflammatory and immune therapy, medical and biologic follow-up.

4) Main dissemination activities
4.1. Internal
- Kick-off meeting
- Project steering meetings for Principal Investigators-PI (every 6 months)
- Annual BetaCellTherapy meeting attended by scientific advisory board for PI and up to 3 collaborators
with annual reports by PI and poster presentations by collaborators and PI assembly
- Board meetings (every 6 months)
- Trainings/summer school (theory and practice) related to a research field in the program, open to junior researchers within the consortium.

4.2. External
- Public launch of program for broad audience of stakeholders;
- Website www.betacelltherapy.org with information on FP7 program and partners
- Member of EuroStemCell and its FP7-H2020 network, providing information and educational resources on stem cells and their impact on society; participation to EuroStemCell meetings
- Training course for PhD students
- Presentation of program at international conferences, research foundations, stakeholder meetings
- Interviews to press, participation at meetings at European parliament on stem cell research, letter to Nature on ban on stem cells

4.3. Publications:
An overview of achievements (publications, patents, methods, models, protocols) is provided in each internal WP report. Over
200 articles with FP7 support have been published in international peer reviewed journals since start of the program.

5) Exploitation of results
- valorization committee was active during two years and then replaced by collection, every 6 months, of reports on valorization, milestones and deliverables
- patent pending on screening assay for agents acting on beta cell proliferation (P1)

List of Websites:
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Last updated on 2016-02-09
Retrieved on 2018-11-15

Permalink: https://cordis.europa.eu/result/rcn/176334_en.html
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