PROJECT PERIODIC REPORT

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Table of Content:

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3	Servier	SERVIER
4	AstraZeneca	AZ
5	Boehringer Ingelheim	BI
6	Centre National de la Recherche Scientifique	CNRS
7	Commissariat à l'Energie Atomique	CEA
8	Endocells Sàrl	ENDOCELLS
9	Imperial College London	ICL
10	Institut Suisse de Bioinformatique	SIB
11	Institut National de la Santé et de la Recherche Médicale	INSERM
12	Eli Lilly	LILLY
13	Medizinische Hochschule Hannover	MHH
14	Novartis	NOVARTIS
15	Novo Nordisk	NOVO
16	Roche	ROCHE
18	Technische Universität Dresden	TUD
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20	Université Paris Diderot-Paris 7	UP7
21	Université de Genève	UNIGE
22	Vrije Universiteit Brussel	VUB

1 Publishable summary

A summary description of project context and objectives,

A complete or relative decrease in insulin secretion by pancreatic beta-cells underlies the development of type 1 and type 2 diabetes, respectively. These diseases impose huge burden to welfare systems, both in Europe and in other developed and developing countries. There are so far limited therapeutic options to treat both types of diabetes and none to cure or prevent the disease. This is due, in large part, to our limited knowledge of beta-cell biology in health and disease. Although a large body of knowledge has been gained on the function of beta-cells from animal models, knowledge on human beta-cell function, survival, and of the pathopyhsiological mechanisms that lead to their demise is still scarce.
The IMIDIA consortium, which consists of 14 leading European academic experts in the biology, physiology, and genetics of islet cells and in bioinformatics applied to systems biology, together with 8 major pharmaceutical industries and 1 SME, is developing an ambitious project to generate novel tools, biomarkers, and fundamental knowledge on islet-cell organization to accelerate the path to improved diabetes management.
The scientific program aims at delivering:

1- Novel tools for the study of human beta-cell development, function and survival; their modulation by potential therapeutic compounds; and for in vivo beta-cell imaging.
2- Biomarkers for the diagnosis and prognosis of beta-cell failure and for monitoring diabetes progression and treatment.
3- Knowledge on novel pathways and sites that control beta-cell proliferation, differentiation and apoptosis, and on the role of known nutrient regulated pathways and sites in controlling beta-cell mass and function.

To organize this work in a highly integrative and synergistic approach, IMIDIA has divided the project into five scientific work packages:

WP1 Beta-cell precursor and mature beta-cell lines and their use as discovery tools
WP2.A Identification of novel drug targets and biomarkers: study of mouse physiological response to a metabolic stress induced by high fat diet and modular analysis of beta cell organization
WP2.B Network for human islet procurement for experimental validation of drug targets and for genetic-genomic analysis
WP3 Beta-cell life and death: identification of novel pathways and sites controlling glucose competence, proliferation and apoptosis
WP4 Non-invasive imaging for in vivo diagnosing beta-cell mass and function in diabetes and following drug treatment
WP5 Data repository and knowledge management

Work performed during Year 1, main results achieved, expected final results and potential impact and use.

WP1- Beta-cell precursor and mature beta-cell lines and their use as discovery tools. In this WP, the first ever human beta-cell lines have been generated and their differentiation state has been characterized by testing the expression of beta-cell functional markers of differentiation and function, which have all shown to be present. Most importantly, is the demonstration of the preserved insulin storage and glucose-dependent secretion capacity. One of the cell lines has been used to initiate preparation of monoclonal antibodies to cell surface antigens.

The best cell line will be used to evaluate these cells' response to drugs targeting beta-cell function. Second generation of such cells is being prepared for conditional growth arrest and still improved insulin production and secretion response.

These cells will be used as a tool for further drug screening and the monoclonal antibodies to cell surface antigen will be used for imaging purposes.

WP2.A- Identification of novel drug targets and biomarkers: study of mouse physiological response to high fat diet and modular analysis of beta cell organization. This work package started a large program to investigate the genetic basis for differential response to metabolic stress of pancreatic islets and for identification of biomarkers that can predict the resistance or failure of beta-cells to high energy containing diets. During Year 1, all the conditions for mouse housing in a central facility, for high fat diet feeding, islet isolation and processing for RNA extraction, for plasma sampling for metabolomic analysis, as well as for automatic islet morphometric analysis have been established, through impressive cooperation of the different academic and EFPIA-pharma partners involved in this subproject. Furthermore, standardization of labeling of all data collected for each mouse has been established as well as the mechanisms to deposit these data in a central database, which will contain all phenotypic and genomic information.

This overall study will lead to identification of novel molecular pathways controlling beta-cell function and dysfunctions in response to metabolic stress and is expected to generate prognostic or diagnostic biomarkers for beta-cell failure.

WP2.B- Network for human islet procurement for experimental validation of drug targets and genetic-genomic analysis. The overall goal of this workpackage is to provide a link between the studies performed in mice and the dysfunctions of human beta-cells in diabetes. Plasma from the diabetic patients will help validate biomarkers that could be discovered in mouse studies and genetic-genomic analysis of human islets will also help interpret and mouse islet data and lead to additional lines of investigation in animal models.

A large highly concerted effort by all involved partners has led to establishment of standardized procedures for human islet isolation from autoptic pancreas, from surgical biopsies, as well as for islet isolation by laser capture microdissection. Standard procedures have also been established for histochemical, immunohistochemical, secretion, RNA and DNA extraction, procedures. The data structure has been defined as well as the mechanism of deposition of patient and islet data in the central database. Data have already been deposited and collection of islets from healthy or diabetic pancreas is well underway and meets the first year's goal. Associated with this work, all ethical issues for human islets procurement and use have been solved by all partners.

WP3- Beta-cell life and death: identification of novel pathways and sites controlling glucose competence, proliferation and apoptosis. This work package progresses along several lines to investigate important and novel intracellular pathways controlling beta-cell life and death. In the first aim, ER stress role in beta-cell apoptosis is being investigated and a progressive shift of attention towards understanding the importance of autophagy in these processes is being pursued. In a second aim, knockout mice are being generated to suppress expression of nutrient regulated kinase (AMP-kinase, LKB1) in beta-cells and alpha cells. In the third aim, mice with genetic inactivation of the Zinc transporter 8 (ZnT8) have been characterized. In the fourth aim, novel mechanisms mediating the effect of GLP-1 on beta-cell proliferation, glucose competence and apoptosis have been identified and are further investigated using gene knockout mice. In the fifth aim, mice have been generated that allows to follow the dynamics of insulin granule production, secretion and turnover. In the sixth aim, mice are being generated that will facilitate targeting of recombinant, pseudo-typed lentiviruses into beta-cells of living mice. Vector constructs have been generated and initial mouse recombination is underway.

This work package will generate novel knowledge on beta-cell signaling pathways controlling death, proliferation and glucose competence. It also provides all the necessary scientific and technical infrastructure for the study of other gene and gene pathways that may be discovered in WP1 and WP2. It will also provide an important tool for targeting gene expression in the beta-cells of living mice.

WP4- Non-invasive imaging for in vivo diagnosing beta-cell mass and function in diabetes and following drug treatment. In aim 1 production of new probes for the non-invasive imaging of pancreatic beta cells was initiated that target selectively the vesicular monoamine transporter 2, and molecules sensing the zinc released with insulin exocytosis. New glibenclamide derivatives are also being produced and the usefulness of antibodies to the polysialylated form of N-CAM is being evaluated as well as modified GLP-1 receptor ligands. In aim 2, new probes for optical methods have been tested on insulin cell lines; Optical Projection Tomography is also being tested for islet quantification. In aim 3, novel probes for the functional in vivo imaging of rodent cells is being evaluated and PET and 18F-DTBZ have been used to monitor the pancreas of minipigs

The overall goal of this work package is to provide non-invasive imaging methods to assess endocrine pancreas mass and function in diabetic patients and the response of beta-cells to anti-diabetic treatments.

WP5- Data repository and knowledge management. A database as well as a web user interface was designed and implemented to allow storage and tracking of experimental and annotation data for all work packages. An eRoom was developed for sharing of documents between all IMIDIA users. Domain specific databases for gene expression and genetics data are also being installed.

This central database will collect all data generated from all work packages. This will be necessary for the subsequent analysis of the data by the IMIDIA bioinformatic group to exploit data and generate novel knowledge on beta-cell function and on biomarkers.

The address of the project public website: www.imidia.org