ANNUAL REPORT 2015

ciberdem

Centro de Investigación Biomédica en Red
Diabetes y Enfermedades Metabólicas Asociadas

ciber

Centro de Investigación Biomédica en Red

Index

Scientific Director's Presentation

2015 brought some significant changes in CIBERDEM's organisational structure. A new Scientific Director was appointed, the membership of the Steering Committee was renewed, an area for Communication and Dissemination to Society was created and the scientific programmes were restructured. We also incorporated a new research group from the Instituto de Investigación Germans Trias i Pujol in Badalona, to which I would like to give a warm welcome to CIBERDEM. With the preparation in 2016 of a Strategic Plan for coming years the basic part of this structural renovation process of CIBERDEM will be completed. The death of Dr Anna María Gómez Foix, Principal Investigator of CIBERDEM, a research colleague for so many years, was very sad news for the CIBERDEM group of researchers.

In the area of scientific work, the achievements of CIBERDEM's research groups can be seen in the following pages. As Scientific Director it has meant great satisfaction for me to see that CIBERDEM got under way the second stage in the epidemiological study Di@bet.es in 2015. This study, which was carried out in 2008-2010, enabled establishing the prevalence of diabetes in Spain and now, with the Di@bet.es II study, we will establish its incidence.

Cooperation between research groups of CIBERDEM and with groups from other CIBERs is an essential feature of our research work. As regards our projects in cooperation we should stress the start of the Excellence Integrated Project INFLAMES, coordinated by Dr Zorzano, Principal Investigator of CIBERDEM, with the aim of identifying the mechanisms of chronic inflammatory processes in prevalent diseases such as type 2 diabetes and obesity and designing new therapeutic strategies for its treatment. CIBERDEM, CIBEROBN, CIBEREHD and CIBERESP research groups took part in the project.

CIBERDEM's international presence has continued to be highly significant, with its participation in European projects and the publication of a large percentage of articles in cooperation with foreign groups. Through Dr Ángel Nadal, CIBERDEM has taken part in the second Scientific Declaration of the Endocrine Society on endocrine-disrupting chemicals, an area of great current interest.

In its training activities CIBERDEM has taken an active part in organising courses and symposia. We should stress the participation in the organisation of the International Symposium "Diabetes, Oral Health and Nutrition", with the Joslin Diabetes Center of the University of Harvard and the Fundación Sunstar.

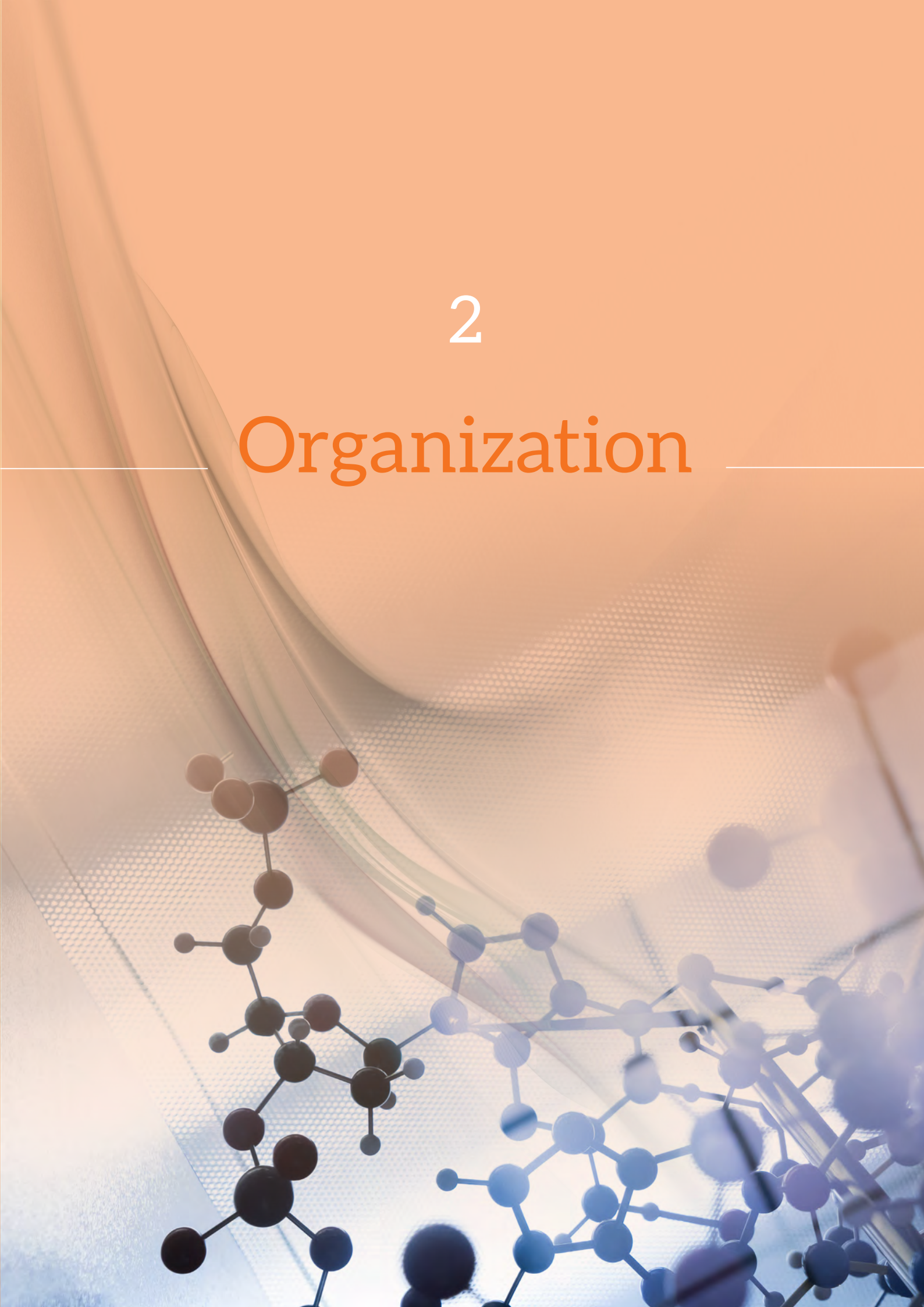
CIBERDEM has made a great effort to comunicate its activity in society, an effort which is going to continue in coming years. I would like to stress the agreement that we have reached with the Federación de Diabéticos Españoles to disseminate the research and innovation work done by CIBERDEM in each issue of its journal Diabetes FEDE. The journal thus contains the CIBERDEM SPACE from now on.

The Report now being presented gives more detailed knowledge about the work done and achievements of CIBERDEM, and provides an idea of the impact and quality of the research that we are carrying out.

Eduard Montanya
Scientific Director

2

Organization



Organisational structure

The CIBERDEM is one of the eight thematic areas forming the Centro de Investigación Biomédica en Red (CIBER), a Spanish research consortium in the field of biomedical research with great scientific potential, under the Instituto de Salud Carlos III (ISCIII) – Ministry of the Economy and Competitiveness.

The Diabetes and associated Metabolic Diseases area is made up of 29 research groups, keeping its independence as regards scientific management. Its organisational structure is based on the research groups belonging to this and its activity revolves around the Research Programmes and Transversal Programmes, with a coordinator for each Programme belonging to the Steering Committee. Scientific decisions are made by the Scientific Director, advised by said Steering Committee and the External Scientific Committee.

The Steering Committee is presided over by the Scientific Director and made up of the coordinators of the programmes and Managing Director of the CIBER.

The External Scientific Committee is a body for scientific support and advice, made up of relevant personalities in the field of health sciences standing out for their professional or scientific careers in line with the objectives of the of the thematic area.

The senior administrative bodies of the CIBERDEM are the Governing Body and the Permanent Commission, common for all the CIBER research areas.

The Governing Body is made up of three representatives of the ISCIII and by an institutional representative of each of the centres in the consortium. It is presided over by the Director of the ISCIII and meets every six months.

The Permanent Commission is an executive committee made up of the ISCIII and 8 members of the Governing Body, who can be renewed on an annual basis.

Both the operation and the purposes of the governing, support and advisory bodies are established in the statutes of the CIBER.

Members of the Steering Advisory Committee of CIBERDEM

NAME	POST HELD
Eduard Montanya	Scientific Director
Ángela Martínez	Programme 1 Coordinator
Franz Martín	Programme 2 Coordinator
Antonio Zorzano	Programme 3 Coordinator
Ángel Nadal	Training Coordinator
Anna Novials	Outreach Coordinator
Manuel Sánchez	Managing Director

Scientific Director Assistant: Isabel Ramis

External Advisory Scientific Committee

Made up of relevant personalities in the field of health sciences standing out for their professional or scientific careers in line with the objectives of the Consortium. This is a scientific assessment body which carries out the annual appraisal of the work done by CIBERDEM and its research groups.

José M. Ordovás	President. Tufts University, Boston (USA)
Francesc Xavier Pi-Sunyer	Member. Columbia University, New York (USA)
Décio L. Eizirik	Member. Université libre de Bruxelles (Belgium)
Antonio Vidal-Puig	Member. University of Cambridge (United Kingdom)
Eleuterio Ferrannini	Member. Università di Pisa (Italy)

Technical Unit

See list of personnel: http://www.ciber-bbn.es/en/about-us/structure/head-office

Directory of groups and institutions

Group leader	Institution	Centre	Centre Prov.
Álvarez Escola, Carmen	Universidad Complutense de Madrid	Facultad de Farmacia	Madrid
Ascaso Gimilio, Juan Francisco	Fundación para la Investigación del Hospital Clínico de la Comunidad Valenciana (Fundación INCLIVA)	Instituto de Investigación sanitaria INCLIVA	Valencia
Balsinde Rodríguez, Jesús	Agencia Estatal Consejo Superior de Investigaciones Científicas	Instituto de Biología y Genética Molecular	Valladolid
Benito de las Heras, Manuel Román	Universidad Complutense de Madrid	Facultad de Farmacia	Madrid
Blanco Vaca, Francisco	Instituto de Investigación del Hospital de la Santa Creu i Sant Pau	Instituto de investigación del Hospital de la Santa Creu i Sant Pau	Barcelona
Blázquez Fernández, Enrique	Universidad Complutense de Madrid	Facultad de Medicina	Madrid
Bosch Tubert, Fátima	Universitat Autònoma de Barcelona	Centro de biotecnología animal y terapia genética	Barcelona
Burks, Deborah	Fundación Centro de Investigación Príncipe Felipe	Centro de investigación Príncipe Felipe	Valencia
Castaño González, Luis	Asociación Instituto de Investigación Sanitaria de Biocruces	Hospital Universitario Cruces	Vizcaya
Correig Blanchart, Francesc Xavier	Fundación Institut d'Investigació Sanitària Pere Virgili	Universitat Rovira i Virgili	Tarragona
Egido de los Ríos, Jesús	Fundación Instituto de Investigación Sanitaria Fundación Jiménez Díaz	Instituto de investigación sanitaria - Fund. Jiménez Díaz	Madrid
Escobar Morreale, Héctor Francisco	Servicio Madrileño de Salud	Hospital Ramón y Cajal	Madrid
Ferrer Marrades, Jorge	Institut d'Investigacions Biomèdiques August Pi i Sunyer	Centro Esther Koplowitz	Barcelona
Gomis de Barbará, Ramon	Institut d'Investigacions Biomèdiques August Pi i Sunyer	Centro Esther Koplowitz	Barcelona
Guinovart Cirera, Joan Josep	Fundació Privada Institut de Recerca Biomèdica (IRB)	Fundació Privada Institut de Recerca Biomèdica IRB	Barcelona
Ibáñez Toda, Lourdes	Fundación para la Investigación y Docencia Sant Joan de Deu	Hospital Sant Joan de Deu	Barcelona
Martín Bermudo, Francisco	Universidad Pablo de Olavide	Centro andaluz de Biología Molecular y Medicina Regenerativa	Sevilla
Martínez Valverde, Ángela María	Agencia Estatal Consejo Superior de Investigaciones Científicas	Instituto de Investigaciones Biomédicas Alberto Sols	Madrid
Masana Marín, Luis	Fundación Institut d'Investigació Sanitària Pere Virgili	Universitat Rovira i Virgili	Tarragona

Group leader	Institution	Centre	Centre Prov.
Montanya Mías, Eduard	Fundación IDIBELL	Hospital universitario de Bellvitge	Barcelona
Nadal Navajas, Ángel	Universidad Miguel Hernández	Instituto de Bioingeniería	Alicante
Novials Sardá, Anna María	Institut d'Investigacions Biomèdiques August Pi i Sunyer	Centro Esther Koplowitz	Barcelona
Rojo Martínez, Gemma	Fundación Pública Andaluza para la Investigación de Málaga en Biomedicina y Salud (FIMABIS)	Hospital Universitario Carlos Haya	Malaga
Serrano Rios, Manuel	Servicio Madrileño de Salud	Hospital Clínico San Carlos	Madrid
Simó Canonge, Rafael	Fundación Hospital Universitario Vall d'Hebron - Institut de Recerca (VHIR)	Hospital Universitario Vall d'Hebron	Barcelona
Vallejo Fernández de la Reguera, Mario	Agencia Estatal Consejo Superior de Investigaciones Científicas	Universidad Autónoma de Madrid	Madrid
Vázquez Carrera, Manuel	Universitat de Barcelona	Facultad de Farmacia. Universitat de Barcelona	Barcelona
Vendrell Ortega, Joan Josep	Fundación Institut d'Investigació Sanitària Pere Virgili	Hospital Universitario Juan XXIII	Tarragona
Zorzano Olarte, Antonio	Fundació Privada Institut de Recerca Biomèdica IRB	Fundació Privada Institut de Recerca Biomèdica IRB	Barcelona

Budget

INCOME	4.402.990,42
NOMINAL ISCIII GRANT	2.796.280,00
INCOME FROM NEW GROUPS	60.000,00
AGREEMENTS AND CONTRACTS	370.802,73
OWN FUNDS	1.175.907,69

OUTGOINGS	3.121.660,03
GROUP	2.333.943,55
TRAINING	886,95
TECHNICAL OFFICE	146.500,00
SCIENTIFIC DIRECTION AND STEERING COMMITTEE	64.950,75
PLATFORMS	87.117,17
ROYALTY FRAMEWORK CONVENTION	43.694,09
INTRAMURAL P.	1.829,48
COMPETITIVE P.	442.738,04

Personnel

Personnel taken on during the year as of 31st December, separated by categories:

Category	Permanent	Temporary	Works & service	Post-doctoral	Main Total
Diploma holder	3		1		4
Doctor	30	1	2	3	36
Graduate	16	1	9		26
Technical	13		2		15
Total	**62**	**2**	**14**	**3**	**81**

Significant activities

Projects

These were the projects active in 2015:

NATIONAL PROJECTS

Financing Agency: Instituto de Salud Carlos III

- Miguel Servet Contract - Characterization of the Lipin family in human adipocytes.
- Effects of fatty acids in the diet on the expression and epigenetic changes in the VEGF-b-mediated fatty acid transport system in rats.
- Río Hortega Contract.
- Identification of novel modulators of chronic inflammation in prevalent diseases: unveiling divergent mechanisms of disease.

Financing Agency: Ministry of the Economy and Competitiveness:

- The regulation of progenitor cells by the signals of insulin /IRS2: implications in metabolic diseases.
- Identification of metabolic routes in the neurodegeneration of the retina induced by hyperglycaemia and ischaemia through a metabolomics and proteomics approach.
- Grant from the Sub-programme for Training of Research Staff - Miriam Navarro.
- Ramón y Cajal Contract.
- Aid for pre-doctoral mobility for going on short stays at R +D centres.
- Signalling of insulin located in the liver
- Reformulating the metabolism by identifying new metabolites and biochemical reactions using a new metabolomics tool.

We should stress the CIBERDEM's participation in the three CIBER interdisciplinary excellence projects financed by the AES. One of these three projects, coordinated by Antonio Zorzano, has the aim of identifying the mechanisms of inflammatory processes detected on one hand in persons with obesity or type 2 diabetes, and on the other in patients with Crohn's disease. Along with the CIBERDEM, groups from the CIBER of Obesity y Nutrition (CIBEROBN), of Hepatic and Digestive Diseases (CIBEREHD) and Epidemiology and Public Health (CIBERESP) are taking part in this.

INTERNATIONAL (EUROPEAN) PROJECTS

- DIAbetes Transnational Research Advancement for Investigators (DIATRAIN).
- Genetic and environmental factors of insulin resistance syndrome and its long-term complications in immigrant Mediterranean populations (MEDIGENE).

Technology transfer

One of the CIBER's main aims is the transfer of research results into clinical practice, and one of the best tools existing for this purpose is technology transfer. The Unit managing this at the CIBER sets out to act as a bridge between our researchers and other agents in the Science and Technology System (companies, business associations, other research organisations, etc.) to make cooperation with these bodies more effective. This means that research results will be efficiently developed and can succeed in being applied. Work is done in several lines to this end:

- **Training in innovation management and continuous contact with our researchers to monitor their results.**

  In this respect, last year the first general event of the CIBER in training on technology transfer and innovation was held, on 26th February 2015 and where national experts took part sharing their knowledge in matters such as industrial property, business creation or publication in open access, etc.

- **Protection of their research results and management of cooperation with other agents, as vouched for by applications for patents and signing licensing contracts, amongst other agreements.**

  Hence, over 20 new patent applications were made and seven licensing agreements were signed at the CIBER in 2015.

- **The presentation of research results and technological capacities of our groups.**

  Among many other measures and only as an example, in 2015, several projects were presented at the II Foro de Innovación en Diagnóstico in Vitro – FENIN in Barcelona (December 2015).

- **Support for technology-based business creation stemming from CIBER groups.**

  The CIBER has since 2014 taken part in Epidisease (http://www.epidisease.com/es/) which it continued to support in 2015.

- **Other activities connected with innovation, public-private cooperation and industrial and intellectual property.**

  For example, the registration of the "community trademark" of the CIBER has been processed, or steps have been taken for registering intellectual property rights for audio-visual projects, amongst many others.

Dissemination activities

In 2015 the CIBER's Communication Department carried out different measures for dissemination and disclosure in order to improve the Centre's visibility, as well as to make known the research work done by the groups in its eight thematic areas. We will now detail the 2015 Communication Activities of the CIBERDEM:

THE CIBERDEM IN THE MEDIA:

In the 2015 period 50 CIBER press notes were released, two of these from the CIBERDEM and four in cooperation between several CIBER areas.

Date	Thematic area	Title
January	SEVERAL CIBER	El CIBER pone en marcha tres proyectos de excelencia interdisciplinares financiados con casi 2 millones de euros por la AES
February	SEVERAL CIBER	Investigadores del CIBER identifican diversos factores de riesgo de sufrir cáncer
November	SEVERAL CIBER	El CIBER acerca su investigación al público de la mano de la improvisación teatral en #ImproCiencia
December	SEVERAL CIBER	El CIBER incorpora 11 nuevos grupos en diversas áreas de investigación
April	CIBERDEM	Los flavanoles del cacao podrían ayudar a retrasar la progresión de la diabetes tipo 2
April	CIBERDEM	Eduard Montanya, nuevo Director Científico del CIBER de Diabetes y Enfermedades Metabólicas Asociadas

407 appearances in the media were registered over this period:

CIBERDEM	NEWS	AUDIENCE
Internet	338	35.195.300
Press	69	9.398.000
Total	**407**	**44.593.300**

NEW WEB PAGE OF THE CIBERDEM:

In November 2015 the new web page of the CIBERDEM was launched in order to have a common structure, image and contents manager for all the CIBER areas.

http://www.ciberdem.org/en

CIBER NEWSLETTER

Over this period five CIBER newsletters were issued, including relevant contents on both the CIBERDEM and the other thematic areas. The digital newsletters were sent to around 4000 subscribers.

http://www.ciberisciii.es/comunicacion/boletines

SOCIAL NETWORKS

Main indicators of CIBERDEM's presence on Twitter:

UPDATES		FOLLOWERS		FOLLOWING		KLOUT (influence, values between 1 and 100)	
JANUARY	DECEMBER	JANUARY	DECEMBER	JANUARY	DECEMBER	JANUARY	DECEMBER
883	1040	796	1078	139	173	44	44

CIBERDEM ANNUAL REPORT

The Communication area of the CIBER in cooperation with the CIBERDEM coordinated the content of the CIBERDEM report 2014 in Spanish/English, drawing up and disseminating 2 reports in interactive format (Flipbook) and PDF. These were distributed over the web page and Twitter account: http://www.ciberisciii.es/en/press/annual-report

CIBER #IMPROCIENCIA SCIENCE WEEK

The #ImproCiencia dissemination event, arranged by the CIBER in the framework of the Madrid Science Week 2015, took place on 3rd November at the Nave 73 rooms in Madrid. The event combined science and theatre improvisation to give a light-hearted explanation of the biomedical research done by the CIBER in its eight thematic areas.

Games and improvisations were alternated with live connections with CIBER researchers during the event.

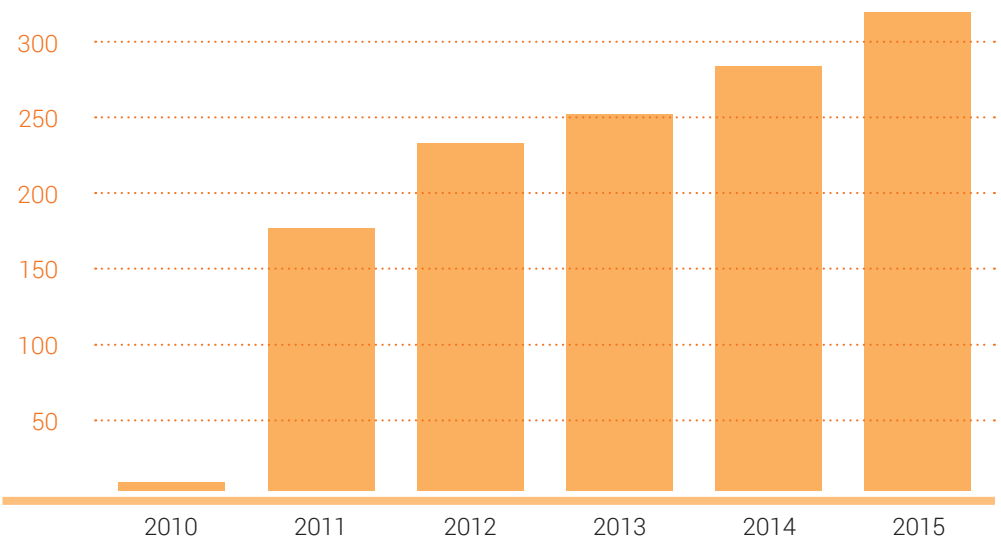
Scientific production

The evolution of CIBERDEM publications can be appreciated in the following graphics in which the data is analysed from 2010 to 2015.

Publications:

Nº of affiliated publications 2015	
Total publications	**316**
First quartile	177
First decile	69

EVOLUTION OF CIBERDEM PUBLICATIONS 2010-2015



MOST RELEVANT PUBLICATIONS OF THE CIBERDEM IN 2015 BY IMPACT FACTOR

Publication	Impact factor
GAULTON K.J., FERREIRA T., LEE Y., RAIMONDO A., MAGI R., RESCHEN M.E. ET AL. Genetic fine mapping and genomic annotation defines causal mechanisms at type 2 diabetes susceptibility loci. Nature Genetics. 2015;47(12):1415-1425.	29,352
MARQUARD J., OTTER S., WELTERS A., STIRBAN A., FISCHER A., EGLINGER J. ET AL. Characterization of pancreatic NMDA receptors as possible drug targets for diabetes treatment. Nature Medicine. 2015;21(4):363-376.	28,223
GORE A.C., CHAPPELL V.A., FENTON S.E., FLAWS J.A., NADAL A., PRINS G.S. ET AL. EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals.Endocrine Reviews. 2015;36(6):E1-E150.	21,059
CEBOLA I., RODRIGUEZ-SEGUI S.A., CHO C.H.-H., BESSA J., ROVIRA M., LUENGO M. ET AL. TEAD and YAP regulate the enhancer network of human embryonic pancreatic progenitors. Nature Cell Biology. 2015;17(5):615-626.	19,670
DURAN J., GUINOVART J.J. Brain glycogen in health and disease. Molecular Aspects of Medicine. 2015; 46:70-77.	10,238
SALVADÓ L., PALOMER X., BARROSO E., VÁZQUEZ-CARRERA M. Targeting endoplasmic reticulum stress in insulin resistance. Trends in Endocrinology and Metabolism. 2015;26(8):438-448.	9,392
ZORZANO A., HERNÁNDEZ-ÁLVAREZ M.I., SEBASTIÁN D., MUÑOZ J.P. Mitofusin 2 as a Driver That Controls Energy Metabolism and Insulin Signaling. Antioxidants and Redox Signaling. 2015;22(12):1020-1031.	7,400
MONTANYA E., FONSECA V., COLAGIURI S., BLONDE L., DONSMARK M., NAUCK M.A. HbA1c improvement evaluated by baseline BMI: a meta-analysis of the liraglutide phase 3 clinical trial programme. Diabetes, Obesity & Metabolism. 2015; DOI: 10.1111/dom.12617.	6,360
LLAURADÓ G., SEVASTIANOVA K., SADEVIRTA S., HAKKARAINEN A., LUNDBOM N., ORHO-MELANDER M. ET AL. Liver fat content and hepatic insulin sensitivity in overweight patients with type 1 diabetes. Journal of Clinical Endocrinology and Metabolism. 2015;100(2):607-616.	6,209
DE HOLLANDA A., CASALS G., DELGADO S., JIMÉNEZ A., VIAPLANA J., LACY A.M. ET AL. Gastrointestinal hormones and weight loss maintenance following roux-en-Y gastric bypass. Journal of Clinical Endocrinology and Metabolism. 2015;100(12):4677-4684.	6,209

COOPERATION:

No. of intraCIBER publications 2015: **48**

No. of interCIBER publications 2015: **82**

3

Scientific Programmes

In 2015, the groups forming the programmes were provided with financing from the ISCIII, from the Ministry of the Economy and Competitiveness, as well as from private institutions (European Foundation for the Study of Diabetes, Marató on TV3, CaixaImpulse, FIV Recoletos, etc.). The most relevant scientific milestones reached by the Programmes during 2015 are listed below, arranged on the basis of the main objectives of each Programme:

PROGRAMME 1. Epidemiology, genetics and epigenetics of diabetes mellitus. Chronic complications and comorbidities.

1. Epidemiology of diabetes mellitus, its chronic complications and comorbidities

In 2015 the field work for the di@bet.es study was organised and got under way and will determine the incidence of diabetes and associated metabolic diseases in Spain. As regards the Segovia study, a prospective investigation was carried out in which a total mortality of 7.4 % was determined, the main causes being cancer (49%) and cardiovascular events (21.6%), and the ictus being the most commonly registered cardiovascular event (24.83%). An epidemiology study has also been carried out which has revealed that the Adenine-Adenine (AA) genotype of the SNP-rs4730153 of the visfatin gene protects against cardiovascular disease in subjects with/without obesity.

2. Genetics, epigenetics and environmental factors involved in the development of diabetes and its complications

With regard to disorders in lipid metabolism, an NMR method has been developed to evaluate the lipoprotein profile in diabetic patients. Evidence has furthermore been given that the circulating levels of proteins FABP4 and FABP5 are not genetically determined and are associated with atherogenic dyslipidemia (Ibarretxe D, Nutr Metab Cardiovasc Dis. 2015). It has also been identified that circulating PCSK9 is increased and associated with atherogenic dyslipidemia in diabetic patients. The administration of mimetic peptides of the major protein of HDLs (apolipoprotein A-I) has been observed to significantly delay tumour growth in a murine model of inherited breast cancer.

3. Molecular mechanisms associated with the appearance and progression of chronic complications of diabetes: therapeutic strategies.

A new score for cardiovascular risk in the diabetic population has been defined. In connection with the study of vascular complications of diabetes, optimised peptides are being used to enter cells to inhibit two key pathways, the nuclear factor Kappa B (NF-KB) and that of the JAK/ STAT pathway. These peptides, in both in vitro and in vivo studies, have shown to be potent anti-inflammatory and anti-fibrotic agents. The studies carried out with a mimetic peptide of SOCS (Suppressors of Cytokine Signalling) are protected by a patent in the area of retinopathy, nephropathy and vascular affectation of diabetes (Recio C, Basic Res Cardiol. 2015).

Diabetes is a risk factor in Alzheimer Disease (AD). The usefulness of studying the neurodegeneration of the retina for predicting the risk of developing AD has been assessed. In preclinical studies of diabetic retinopathy (Simó and Hernández, Prog Retin Eye Res 2015) an animal model has been characterised (db/db mouse) which recapitulates the development of diabetic retinopathy in humans. This is a useful model for further studing the mechanisms leading to the diabetes-induced neurodegeneration of the retina and for testing neuroprotective drugs, with the effectiveness of GLP-1 administered in collyrium for preventing neurodegeneration and the first microvascular lesions being noteworthy (Hernández C, Diabetes 2015). The inhibition of phosphatase 1B proteins in photoreceptors and in retina explants has been shown to give protection against the action of proinflammatory cytokines in such a way as to keep the IGF-IR-mediated survival signalling active, reducing reactive gliosis. This work identifies a new therapeutic target against neuroinflammation which occurs in early phases of diabetic retinopathy (Arroba and Valverde, Invest Opthalmol Vis Sci 2015).

PROGRAMA 2. Molecular and cellular determinants of the function, damage and protection of pancreatic islets. Regenerative medicine and advanced therapies.

1. Function and regulation of pancreatic islets: molecular and cellular bases and therapeutic targets.

A new mechanism for autochrine action of pancreatic peptide IAPP on the proliferative capacity of the beta cell (Visa et al., FASEB J. 2015) and the role of enzyme BACE2, on the insulin secretory function, as well as its potential use as a therapeutic target (Alcarraz-Vizán et al., FASEB J. 2015). Furthermore a set of mirRNAs correlating with prediabetes and fatty liver in humans and animals has been identified (Parrizas et al., J Clin Endocrinol Metab 2015). It has also been shown that these mirRNAs become modify with the implementation of a programme of physical exercise.

A molecular mechanism by means of which the expression of the glucagon gene is repressed as a response to increases in the levels of blood glucose, thus helping to maintain glucose homeostasis, has been discovered and characterised. (Mirasierra and Vallejo, Diabetologia 2015).

It has been established that human islets have greater functional capacity and survive better in a culture medium supplemented with human serum against human albumin which enables improving the prognosis when these islets are transplanted later (Nacher et al., Cell Transplant. 2015).

It has been set up a protocol for differentiating human embryonic stem cells which improves the final stages of differentiation and maturation of endocrine progenitors, enabling a large number of completely functional insulin-producing cells to be obtained (Pezzolla et al., PloS One 2015).

2. Mechanisms damaging and regenerating pancreatic islets.

A map of "enhancers" active in human embryonic progenitors has been created and validated, enabling extending the list of active "enhancers" known in the embryonic pancreas (Cebola et al., Nat Cell Biol. 2015).

Defective processing of the α-MSH is a fundamental mediator of increased in gluconeogenesis which is observed in the setting of stress of the hypothalamic endoplasmic reticulum. The α-MSH deficit in POMC neurons can also contribute to the pathophysiology of diabetes mellitus type 2 (Schneeberger et al., Cell Rep. 2015).

3. Preventive and therapeutic strategies in regenerative medicine, cell therapy and gene therapy.

A moderately hypercaloric diet, after a situation of early nutritional restriction does not induce obesity but worsens insulin-resistance, dyslipidaemia and the proportion of ectopic lipids (Lizárraga-Mo- lline-do et al., J Biol Chem. 2015). Furthermore, a cocoa flavanol –rich diet prevents oxidative stress and the cell death appearing in pancreatic and hepatic insulin resistance, improving glucidic metabolism and preventing the loss of the function and mass of beta cells (Cordero-Herrera et al., J Nutr Biochem. 2015).

At the outset of obesity, caused by a fat-rich diet, there is a functional and structural adaptation of the pancreatic alpha cell which leads to a hypoglucagonaemia, which could have a positive influence on the adaptation of the pancreas to obesity, to maintain the homeostasis of glucose and prevent/delay the potential appearance of diabetes (Merino et al., Sci Rep. 2015). We have also shown that exposure to endocrine disruptors during pregnancy increases the mother's predisposition to undergoing obesity and diabetes throughout her life (Alonso-Magdalena et al., Endocrinology 2015).

PROGRAMA 3. Cellular and molecular mechanisms involved in the development and progression of type 2 diabetes and identification of new therapeutic targets

1. Determinants of resistance to insulin: molecular mechanisms involved.

We have shown that Osteoprotegerin is associated with bone markers and with bone mineral density in the lumbar spine after bariatric surgery. This can enable explaining the development of metabolic bone disease after bariatric surgery (Balsa et al., J Bone Miner Metab. 2015).

We have reported that the hepatic levels of phosphatase protein PPP2R5C are increased in type 2 diabetic patients and this is correlated with the degree of obesity and resistance to insulin in these patients. The PPP2R5C protein represents a relevant factor in the modulation of hepatic energy metabolism (Cheng et al., PLoS Genet. 2015).

2. Inflammation as a pathogenic process in diabetes mellitus: The role of adipose tissue and interaction with other tissues or organs.

An alteration in the glycogen metabolism in the adipose tissue represents a potential characteristic of metabolic stress related with inflammation in human obesity (Ceperuelo-Mallafré et al, Mol. Metab. 2015).

3. Identification of molecular mechanisms and new therapeutic targets for development of personalised early interventions in diabetes mellitus.

We have proved that the accumulation of hepatic glycogen causes a reduction in intake which promotes protection against the harmful effect in a fat-rich diet. Hepatic glycogen content can thus be considered as being a potential target for pharmacological manipulation in diabetes and obesity (López-Soldado et al., Diabetes 2015).

4. Identification of risk progression biomarkers in diabetes.

We have identified alterations in the levels of circulating miRNAs in maternal obesity and our results suggest a possible role of these miRNAs as markers for prenatal and postnatal growth (Carreras-Badosa et al., J.Clin.Endocrinol.Metab. 2015).

We have described an early increase in the circulating levels of FGF19 and FGF21 during infancy, which must play a relevant metabolic role during this condition (Sánchez-Infantes et al., Int.J. Obes. 2015).

The "Liposcale" test has been developed as a reproducible and effective method of detecting the lipoprotein profile based on the use of NMR spectroscopy (Mallol et al., J. Lipid Res. 2015).

The serum levels of sulfoxide of methionine are an indicator of the degree of oxidation of the residue of methionine 148 of apolipoproteín A1 in girls with hyperinsulinaemia through androgen excess (Samino et al., Sci Rep 2015). The oxidation of this methionine residue of apo-A1 leads to an altered maturing of HDL lipoproteins.

4

Transversal Programmes

Outreach activities

CIBERDEM has promoted and taken part in different measures for spreading information in society such as:

- "Els Juliols" of the Universitat de Barcelona (6-10 July 2015), arranged by CIBERDEM, IDIBAPS, Hospital Clinic, UB, Catedra AstraZeneca, with the aim of disseminating innovations in treatment of diabetes.
- First Diabetes and Sport Forum addressing 50 sportspersons with DM1 given by Anna Novials, Serafin Murillo and Laura Brugnara. October 2015.
- Diabetes and sport session for people undergoing treatment with insulin. Asociación de Diabéticos de Madrid. "Diabetes and sport. What do we do with the treatment?" October 2015.
- Participation in World Diabetes Day (14th November 2015), with cooperation of CIBERDEM in organising acts and participation of different researchers in informative interviews and other activities.
- Creation of ESPACIO CIBERDEM in the publication entitled DiabetesFEDE to publicise the research and innovation activities in diabetes promoted by CIBERDEM.
- Interviews for publicising work for the FEDE (Federación española de pacientes con diabetes) journal, given by:

  - Jesús Balsinde. "Lipids will give us the answer to diabetes". May 2015.

  - cHéctor Escobar "The polycystic ovary is a risk factor for diabetes". November 2015.

Training

Some of the training work given this year deserving mention are the following courses:

- Course-workshop "Innovating in nutrition: from the market garden to the molecule or vice versa, organised by CIBERDEM, IDIBAPS, Cátedra AZ y Fundación Alicia, Món Sant Benet (Barcelona) 23-24 October 2015.
- International Symposium on "Diabetes, Oral Health and Nutrition", arranged by the Joslin Diabetes Center of Harvard University and the Fundación Sunstar with the cooperation of CIBERDEM, Barcelona, 6th November 2015.
- Symposium "La diabetes a debate 2015: la diabetes en la frontera del conocimiento", organised by MSD and CIBERDEM, Madrid 21st November 2015.

5

Platforms

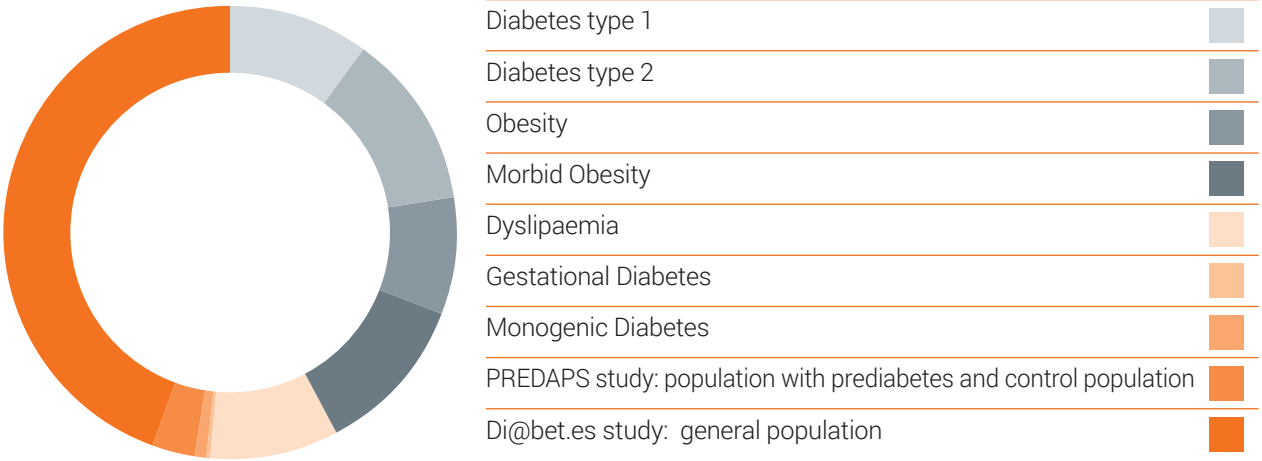
Biorepository of Diabetes and Metabolic Diseases CIBERDEM-IDIBAPS

This is a mixed CIBER-IDIBAPS platform forming part of the IDIBAPS Biobank with the aim of providing the scientific community with properly-characterised and standardised samples of the main metabolic diseases. The CIBERDEM groups providing samples to the Biorepository are:

- Hospital Clinic Barcelona
- Hospital Joan XXIII de Tarragona
- Hospital San Joan de Reus
- Hospital de Cruces de Barakaldo
- Hospital Clínico de Madrid
- Hospital Clínico de Valencia
- Hospital Carlos Haya de Málaga
- Hospital Santa Creu y San Pau de Barcelona

The Biorepository currently has a total number of 12399 samples of whole blood, plasma, serum, DNA and lymphocytes of people with the following characteristics:

SOURCES OF THE SAMPLES



The samples are deposited at the IDIBAPS Biobank. The Diabetes study has several copies of samples. One of these is deposited at the Hospital de Cruces and at the Hospital Carlos Haya (50% at each of these) as a backup copy.

In 2015 samples of donors belonging to the PREDAPS and follow-up donations were received.

In 2015 a total number of 10646 different aliquots were given, mainly for projects in the Di@bet.es study. The projects involved are as follows:

- Circulating exosomal miRNAs as potential biomarkers and mediators of tissue cross-talk in diabetes.
- Association of Fibroblast Growth Factor 21 with the ambient temperature in the general population of Spain. Di@bet.es study (proyecto Di@bet.es).
- Genetic and environmental factors of insulin resistance syndrome and its long-term complications in immigrant Mediterranean populations (proyecto Di@bet.es).
- Understanding the pathophysiological significance of succinate/SUCNR1 axis in obesity and type 2 diabetes: a translational approach (proyecto Di@bet.es).
- Profile of membrane fatty acids and glucose regulation profile: Di@bet.es cohort (Di@bet.es project).

In the framework of the European MEDIGENE project, the Biorepository also contains 75 samples of amplified DNA obtained from the molars found in the ancient Roman city of Tarraco.

Metabolomics Platform

http://www.metabolomicsplatform.com/

The Metabolomics Platform is a mixed CIBERDEM - Universitat Rovira i Virgili (URV) platform for giving technological services. The main aim of the Metabolomics Platform is to work as an integrated laboratory for CIBERDEM groups, defining objectives, dimensions and characteristics of both the set of samples and of experimental designs. The experimental data is processed by our staff team, facilitating the interpretation of results and providing solid, relevant clinical conclusions useful for the different research groups.

The equipment currently available in the NMR and LC/GC-MS field enables large-scale analysis of body fluids (serum or urine, for example) as well as tissues from biopsies of patients and/or animal models.

The use of advanced statistics, chemometrics and multivariate algorithms allows to transform a large set of data into metabolic profiles, and ultimately into clinical information. Our aim is to introduce metabolomics as a complementary research tool for both clinical diagnoses and to elucidate the unknown mechanisms associated with a specific disease.

The Metabolomics Platform specifically addresses the needs of the Research Groups of the CIBERDEM and the URV; its services, as well as potential scientific cooperation schemes, are nevertheless available for other CIBER groups.

In 2015 ten cooperation activities were carried out with CIBERDEM groups and four with groups from other CIBERs.

The platform's scientific work in 2015 can be summed up as:

- Publications in indexed journals: 13
- Average impact factor: 4,23
- Posters at international conferences: 9
- Projects started in 2015: 2 national projects (BFU2014-57466-P and EUIN2015-62503) and 2 European projects (EU660034-MSCA-IF-ES-FT and 645758-TROPSENSE)
- Agreements and contracts with companies: 1 (BIOS- FER TESLAB SL.)

Lines of research active during 2015

- Characterisation of lipoproteins by NMR for studying dyslipidaemias.
- Serum profiling procedure for studying resistance to insulin and diabetes in population studies.
- Development and study of statistical, chemometric multivariate and artificial intelligence algorithms enabling the analysis of large sets of data.
- Non-radioactive isotopomers for studying metabolic profiles and their flow in culture cells and animal models.
- Study of diabetic retinopathy.
- Study of molecular images of tissues and body fluid profiling by means of nanostructured surfaces.
- Metabolomics study on exposure to "thirdhand smoke" (THS).

6

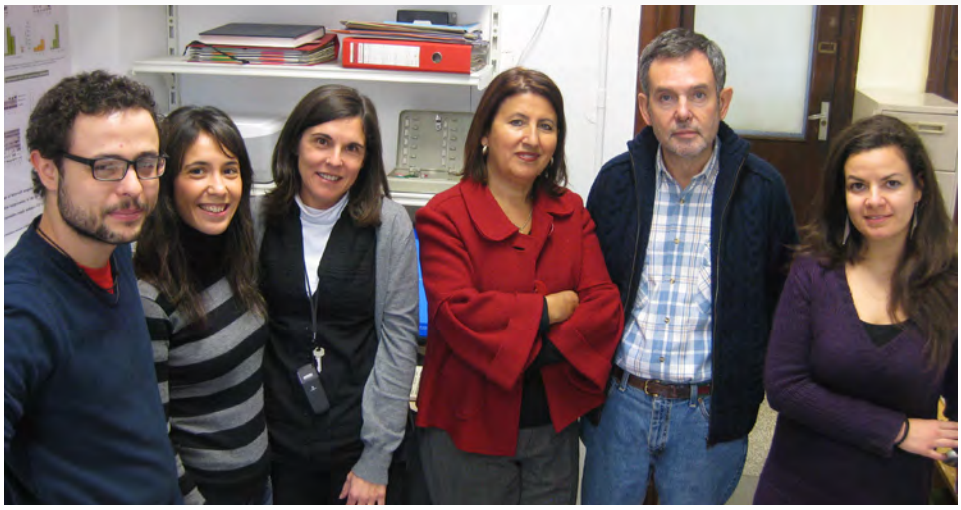
Research Groups

Endocrinology and metabolism

Programme: **P2**

Lead Researcher: **Álvarez Escola, Carmen**

Group members



STAFF MEMBERS: Fernández Millán, Elisa.

ASSOCIATED MEMBERS: Escrivá Pons, Fernando | Lizarraga Mollinedo, Esther | Martín Arribas, Mª Ángela.

Main lines of research

The identification of the cellular and molecular mechanisms that link poor perinatal growth with the increased risk of obesity and type 2 diabetes in the adulthood through the use of animal models of nutritional manipulation. To this end we have focused on:

- The search of new growth factors and mechanisms that regulate the development, growth and death of pancreatic islet cells.
- The study of the effect of nutrients on glucagon and insulin production and release from pancreatic alpha and beta cells, respectively.
- The potential role of incretins (GLP-1 and GIP) in the relationship between intrauterine growth restriction and the development of obesity and type 2 diabetes in the adulthood.
- The impact of early undernutrition on hypothalamic sensitivity to insulin and leptin as well as on the expression of orexigenic and anorexigenic factors (NPY, POMC).
- The study of gut microbiota composition as a new environmental factor involved in the development of metabolic syndrome in perinatal growth restricted individuals: possible alteration of entero-adipo-insular axis.
- The identification of natural compounds from food with favorable effects against diseases associated with oxidative stress and inflammation such as type 2 diabetes and the characterization of the specific mechanisms of action involved in their health benefits.

Most relevant scientific articles

GONZÁLEZ-RODRÍGUEZ A., SANTAMARIA B., MAS-GUTIÉRREZ J.A., RADA P., FERNÁNDEZ-MILLAN E., PARDO V. ET AL. Resveratrol treatment restores peripheral insulin sensitivity in diabetic mice in a sirt1-independent manner. Molecular Nutrition and Food Research. 2015;59(8):1431-1442.

FERNÁNDEZ-MILLÁN E, CORDERO-HERRERA I, RAMOS S, ESCRIVÁ F, ÁLVAREZ C, GOYA L ET AL. Cocoa-rich diet attenuates beta cell mass loss and function in young Zucker diabetic fatty rats by preventing oxidative stress and beta cell apoptosis.Molecular nutrition & food research. 2015;.

CORDERO-HERRERA I, MARTÍN MA, GOYA L, RAMOS S. Cocoa flavonoids protect hepatic cells against high-glucose-induced oxidative stress: Relevance of MAPKs.Molecular nutrition & food research. 2015;.

LIZARRAGA-MOLLINEDO E., FERNÁNDEZ-MILLAN E., FRUTOS M.G.-S., DE TORO-MARTÍN J., FERNÁNDEZ-AGULLO T., ROS M. ET AL. Early and long-term undernutrition in female rats exacerbates the metabolic risk associated with nutritional rehabilitation. Journal of Biological Chemistry. 2015;290(31):19353-19366.

CORDERO-HERRERA I., MARTÍN M., ESCRIVA F., ALVAREZ C., GOYA L., RAMOS S.. Cocoa-rich diet ameliorates hepatic insulin resistance by modulating insulin signaling and glucose homeostasis in Zucker diabetic fatty rats. Journal of Nutritional Biochemistry. 2015;26(7):704-712.

Highlights

Undernourished rats transferred to high-lipid diets did not develop obesity but showed increased metabolic risks including worsening of insulin resistance, dyslipidemia and ectopic lipids.

Our findings provide the first in vivo evidence that a cocoa flavonoid-rich diet may delay the progression of type 2 diabetes by preventing, both in pancreas and liver, oxidative stress and cell apoptosis which improves glucose metabolism and avoids the loss of functional beta-cell mass.

FUNDING:

Molecular and cellular mechanisms involved in T2DM and obesity pathogenesis in rats submitted to maternal undernutrition and refed a high fat diet after weaning. MINECO. BFU 2011-25420. PI: Carmen Álvarez (2012-2015).

Study of the mechanisms of insulin resistance: implication in obesity, diabetes and metabolic syndrome (MOIR). CAM P2010/BMD-2423 I+D Programs of Biomedicine/2010. Coordinator: Manuel Ros (URJC). Enmeper Group-PI: Fernando Escrivá (2012-2015).

CONGRESSES:

Fernández-Millán et al. El retraso en el crecimiento intrauterino compromete la movilización hepática del glucógeno tras el nacimiento asociada a un defecto del flujo autofágico en ratas Wistar. XXVI SED Congress. (Spain), 2015. Oral presentation.

De Toro-Martín et al. Maternal undernutrition induces defective autophagy and glycogen accumulation in the liver of newborn Wistar rats. 75th ADA Congress. (USA), 2015. Póster

LizárragaMollinedo et al. Alteraciones del tejido adiposo inducidas por la realimentación con dieta hiperlipídica en ratas con un antecedente previo de restricción calórica severa. XXXVIII SEBBM Congress. (Spain), 2015. Oral presentation.

Díaz-Castroverde et al. Gene therapy with insulin receptor isoform A as an approach for the treatment of type 2 diabetes. XXXVIII SEBBM Congress. (Spain) 7-10 Septiembre, 2015. Oral presentation.

Cordero-Herrera et al. Cocoa-rich diet improves hepatic lipid metabolism in Zucker diabetic fatty rats. 2nd ISCHOM Congress. (Spain), 2015. Oral presentation.

AWARDS:

Margarita Lorenzo Scientific Award (Lilly Fundation) (Congreso SEBBM 2015).

Juan Abelló Scientific Award (RANF 2015).

Institution: Universidad Complutense de Madrid · **Contact:** Facultad de Farmacia.
Ciudad Universitaria, S/N. 28040 Madrid · Tel.: (+34) 91 394 18 57 · E.mail: calvarez@ucm.es
Web: http://www.ucm.es/biomol2/endocrinologia-y-metabolismo-perinatal

Diabetes, Dyslipidaemia, Inflammation and Endothelial Dysfunction

Programme: **P1**

Lead Researcher: **Ascaso Gimilio, Juan Francisco**

Group members

STAFF MEMBERS: Benito Casado, Esther | García García, Ana Bárbara | Peiró Signes, Marta.

ASSOCIATED MEMBERS: Blesa Luján, Sebastián | Carmena Rodríguez, Rafael | Català Bauset, Miguel | Chaves Martínez, Felipe Javier | Martínez Hervás, Sergio | Real Collado, José Tomás.

Main lines of research

- Genetic diagnosis of primary hyperlipidemias and cardiovascular risk.
- Combination of primary huperlipemias with insulin resisteance and diabetes mellitus.
- Postprandial lipidemia and atherosclerosis in states of insulin resistence
- Insulin resistance, inflammation and oxidative stress.
- Diagnosis, prevention and treatment of diabetic foot.
- Genetic factors involved in the regulation of Body Mass Index and abdominal obesity.
- Sarcopenia and frailty in metabolic desease and diabetes

Most relevant scientific articles

MASANA L., CABRE A., HERAS M., AMIGO N., CORREIG X., MARTÍNEZ-HERVAS S. ET AL. Remarkable quantitative and qualitative differences in HDL after niacin or fenofibrate therapy in type 2 diabetic patients. Atherosclerosis. 2015;238(2):213-219.

MARTÍNEZ-BARQUERO V., DE MARCO G., MARTÍNEZ-HERVAS S., RENTERO P., GALAN-CHILET I., BLESA S. ET AL. Polymorphisms in endothelin system genes, arsenic levels and obesity risk. PLoS ONE. 2015;10(3).

GALAN-CHILET I, GUALLAR E, MARTIN-ESCUDERO JC, DE MARCO G, DOMÍNGUEZ-LUCAS A, GONZÁLEZ-MANZANO I ET AL. Do Genes Modify the Association of Selenium and Lipid Levels?. Antioxidants & redox signaling. 2015.

MORA M., ADAM V., PALOMERA E., BLESA S., DÍAZ G., BUQUET X. ET AL. Ghrelin gene variants influence on metabolic syndrome components in aged Spanish population. PLoS ONE. 2015;10(9).

MANSEGO M.L., DE MARCO G., IVORRA C., LÓPEZ-IZQUIERDO R., MORCILLO S., ROJO-MARTÍNEZ G. ET AL. The nutrigenetic influence of the interaction between dietary vitamin E and TXN and COMT gene polymorphisms on waist circumference: A case control study. Journal of Translational Medicine. 2015;13(1).

Highlights

The scientific research activity of the group during 2015 included the launch of two competitive and multidisciplinary research projects. On the one hand, the Project "Immunopharmacological modulation of the systemic inflammation associated to metabolic disorders. Search for new therapeutic targets and synthesis of novel drugs". This project deals with the study of the role of CCL11 / CCR3 axis in systemic inflammation associated with familial hypercholesterolemia and immunomodulation oral fat overload, and the study of the role of CXCL16 axis / CXCR6 on endothelial dysfunction induced by Ang-II and subjects with metabolic síndrome. On the other hand, the Project "MicroRNAs in insulin-resistant obese children. Diagnostic, prognostic and therapeutic implications on early vascular damage". The main objetives for this study is to determine the pattern of microRNAs in obese children with and without insulin resistance (IR), analyzing the relationship between the miroRNA patterns and vascular, inflammatory and oxidative stress alterations, as well as their variations after nutritional intervention.

Institution: Fund. para la Investigación del Hospital Clínico de la Comunidad Valenciana (Fundación INCLIVA)
Contact: Instituto de Investigación Sanitaria Incliva · Av Blasco Ibáñez, 17. 46010 Valencia
Tel.: 96 197 35 36 · E.mail: ascaso@uv.es

The Eicosanoid Research Division

Programme: **P3**

Lead Researcher: **Balsinde Rodríguez, Jesús**

Group members

STAFF MEMBERS: Meana González, Clara | Rubio Aranda, Julio Miguel

ASSOCIATED MEMBERS: Astudillo del Valle, Alma | Balboa, María Ángeles | de Pablo Herranz, Nagore | Duque de Cela, Montserrat | Gil de Gómez Sesma, Luis | Guijas Mate, Carlos | Lebrero Fernández, Patricia | Lorden Losada, Gema | Montero Domínguez, Olimpio | Sanjuán García, Miren Itziar

Main lines of research

Lipids are key to signaling events in cells. Hence, they are the ultimate controllers and regulators of our bodily processes. Further, imbalances in lipids are the hallmark of a large number of illnesses. If we are going to cure these diseases, we must know what the lipids are and what they do. Within this context our current research lines can be defined as follows:

- Cellular regulation of phospholipase A2s and lipins as key regulators of the production of arachidonate-derived eicosanoids, substances which can have pro- or and anti-inflammatory activity. There are multiple phospholipase A2s and lipins in the cells and our goal is to delineate the role that each of these forms plays in the production of eicosanoids in obesity, diabetes and cardiovascular disease.
- Biosynthesis and degradation of lipid droplets during cellular activation. Lipid droplets are the cytoplasmic organelles where monocytes/macrophages store fat, yet they also serve many other interesting roles, e.g. they may function as docking platforms for a number of enzymes involved in lipid signaling or as an intracellular site for the synthesis of lipid mediators.
- Application of mass spectrometry-based lipidomic strategies for the identification and quantification of cellular lipidomes. A major goal in this regard is to determine the origin and identity of the individual phospholipid molecular species that are produced under different conditions, as a key step to address their biological roles in cells.
- Role of omega-3 fatty acid derivatives as deactivators of monocyte/macrophage activation via their antagonistic effects on inflammasome activation or other mechanisms of pathophysiological relevance.

Most relevant scientific articles

RUBIO J.M., RODRÍGUEZ J.P., GIL-DE-GÓMEZ L., GUIJAS C., BALBOA M.A., BALSINDE J.. Group V secreted phospholipase A2 is upregulated by IL-4 in human macrophages and mediates phagocytosis via hydrolysis of ethanolamine phospholipids. Journal of Immunology. 2015;194(7):3327-3339.

PARDO V., GONZÁLEZ-RODRÍGUEZ A., GUIJAS C., BALSINDE J., VALVERDE A.M.. Opposite cross-talk by oleate and palmitate on insulin signaling in hepatocytes through macrophage activation. Journal of Biological Chemistry. 2015;290(18):11663-11677.

Highlights

GRANTS ACTIVE IN 2015

- "Role of lipin-2 in regulating autoinflammatory diseases". Autonomous Government of Casdtile and Leon, Heath Department (BIO/VA22/15).
- "Lipid Pathways Regulating the Inflammasome: Role of Omega-3 Fatty Acids and Lipin-2". Ministry of Economy and Competitiveness (SAF2013-48201-R).

RESEARCH CONTRACTS WITH PRIVATE COMPANIES

- FIV Recoletos, "Study of the role of the eicosanoids in implantation and in gestational diabetes".

MOST RELEVANT RESULTS

- Discovery of new lipids synthesized by inflammatory cells with possible roles in regulating fat storage in the form of lipid droplets.
- Demonstration that macrophages utilize different lipid signaling pathways depending on their state of polarized activation (M1 vs M2).
- Identification of a critical role for cytosolic group IVA phospholipase A2 in early adipocyte differentiation and diet-induced obesity.

TRAINING

- MSc thesis: "Regulation of lipid droplet formation in human cells", Rafael Sánchez Martínez, University of Valladolid.
- MSc thesis: "Activation of monocytes by oxidized derivatives of arachidonic acid". Miguel Angel Bermúdez Arias, University of Valladolid.
- Grade in Chemistry Thesis: "Identification of positional isomers of palmitoleic acid in biological samples", Ramón Francia Yanguas, University of Valladolid.

OTHER ACTIVITIES

- The group PI, Prof. J. Balsinde, was a keynote speaker in the 6th International Conference on Phospholipase A2: from Bench to Translational Medicine, held in Tokyo, Japan (Feb. 2015). He was appointed as Co-director of Research Programs by the Argentine National Research Council (CONICET). Finally, he continues to serve in the Editorial Boards of Journal of Lipid Research and Biochimica et Biophysica Acta - Molecular and Cell Biology of Lipids.

Institution: Agencia Estatal Consejo Superior de Investigaciones Científicas
Contact: Instituto de Biologia y Genética Molecular. C/ Sanz y Fores S/N. 47003 Valladolid
Tel.: 98 342 30 62 · E.mail: jbalsinde@ibgm.uva.es · Website: http://www.balsinde.org

Diabetes and cardiovascular

Programme: **P3**

Lead Researcher: **Benito de las Heras, Manuel Román**

Group members

STAFF MEMBERS: Fernández López, Silvia | García Gómez, Gema | González Trujillos, Elena.

ASSOCIATED MEMBERS: Bartolomé Herráinz, Alberto | Díaz-Castroverde Vicario, Sabela | Escribano Illanes, Óscar | Gómez Hernández, Almudena | Guillén Viejo, Carlos | Pedromo Loaiza, Liliana | Viana Huete, Vanesa.

Main lines of research

Compensatory mechanisms to hepatic insulin resistance: Progression to type 2 diabetes and the crossroad of autophagy and apoptosis in the pancreatic beta cells.

- The role of the liver-pancreas endocrine axis in triggering beta-cell hyperplasia. The insulin receptor and its isoforms as gene therapy of the diabetic hyperglycemia.
- The role of autophagy, mitophagy and ER stress in the regulation of beta-cell pancreatic mass and beta-cell failure.
- The role of human amylin as a link between the pancreatic beta cell failure and neurodegeneration.

Adipose organ inflammatory disease and the cardiovascular damage:

- BATIRKO/apoE -/- DKO mice: The role of the compensatory mechanisms of insulin resistance in the aggravation/attenuation of inflammation, oxidative stress and vascular lesion in the aorta.

Brown fat function/dysfunction and adipose organ inflammatory disease.

- New mouse models to study energy imbalance and body weight regulation: Brown adipose tissue-specific knockout of IGFIR and IGFIR/IR DKO.
- New mouse models of browning: Brown adipose tissue-specific knockout of p85 alpha/PI 3 kinase.
- Role of IR and IGFIR in the mitochondrial dynamics in vitro and in vivo.

Most relevant scientific articles

ESCRIBANO O., GÓMEZ-HERNÁNDEZ A., DÍAZ-CASTROVERDE S., NEVADO C., GARCÍA G., OTERO Y.F. ET AL. Insulin receptor isoform A confers a higher proliferative capability to pancreatic beta cells enabling glucose availability and IGF-I signaling. Molecular and Cellular Endocrinology. 2015;409:82-91.

PERDOMO L., BENEIT N., OTERO Y.F., ESCRIBANO O., DÍAZ-CASTROVERDE S., GÓMEZ-HERNÁNDEZ A. ET AL. Protective role of oleic acid against cardiovascular insulin resistance and in the early and late cellular atherosclerotic process. Cardiovascular Diabetology. 2015.

FUENTES-ANTRAS J., PICATOSTE B., GÓMEZ-HERNÁNDEZ A., EGIDO J., TUNON J., LORENZO O.. Updating experimental models of diabetic cardiomyopathy. Journal of Diabetes Research. 2015;2015.

Highlights

We developed iLIRKO as mouse model of diabetic progression. Thus, we have demonstrated that the reconstitution in hepatic-specific manner of iLIRKO mice, with adenosassociated viruses bearing IRA or IRB, showed a differential effect. Thus, IRA reverted the diabetic phenotype as revealed by glucose intolerance, circulating hyperinsulinemia, increased pancreatic beta cell mass and fasting hyperglycemia. Those effects upon infection with RIB weremostly limited. In vitro, in hepatic cell lines,IRA, but not IRB, positively regulated the glycogen synthesis and ultimately the glycogen content. Regarding the endocrine pancreas and its elastoplasticity, we previously demonstrated that autophagy was a protection mechanism against ER stress in pancreatic beta cells. More importantl,human amylin, but not rat amylin, inhibited the basal autophagy in insulinoma cells. Thus, pancreatic beta cells submitted to the ER stressor thapsigargin induced apoptosis in the presence of human amylin, but not in the presence of rat amylin.MEFs cells lacking TSC2 upregulated the mTORC1 signaling pathway and inhibited the autophagy and mitophagy. Those cells induced apoptosis in response to the ER stressor thapsigargin or in response to oxidative stressor CCCP.

ApoE mice induced hypercholesterolemia and vascular lesion. The double KO BATIRKO/ApoE aggravated the vascular damage owing to the failure of insulin secretion in response to the insulin resistance induced by HFD western diet.

Finally, we have characterized the phenotype of the IGFIR brown adipose tissue-specific KO (BATIGFIRKO). KO mice showed a normal brown adipose tissue development likely due to the enhanced circulating levels of IGFI, but not BMP-7. However, those mice showed a significant impairment to cold acclimatation at 12 h. owing to the loss of UCP-1 at the canonical brown adipose tissue and at the beige cell within the inguinal white adipose tissue. At 12 months, they developed a significant insulin resistance owing to a sever insulin resistance in the liver. However, the insulin sensitivity in the brown adipose tissue and in several compartments of white adipose tissue remained mostly unchanged.

Institution: Universidad Complutense de Madrid · **Contact:** Facultad de Farmacia
Ciudad Universitaria, S/N. 28040 Madrid · Tel.: 91 394 17 77 · E.mail: mbenito@ucm.es
Website: http://www.ciberdem.org

Metabolic disease and cardiovascular risk

Programme: **P1**

Lead Researcher: **Blanco Vaca, Francisco**

Group members

STAFF MEMBERS: Cedo Gine, Lidia | Santos Palacios, David

ASSOCIATED MEMBERS: Escolá Gil, Juan Carlos | Julve Gil, Josep | Laura Errico, Teresa | Martín, Jesús | Pérez Pérez, Antonio | Quesada Vázquez, Helena | Roig Martínez, Rosa | Rotllan Vila, Noemí.

Main lines of research

- Hypertriglyceridemia and low HDL (Atherogenic dyslipidemia): modulation by diet and drugs and role in diabetes mellitus and atherothrombotic cardiovascular disease development.
- Genetics of dyslipidaemia, type 2 diabetes and hyperhomocysteinaemia.
- Development of experimental-biochemistry and molecular biology techniques and their application to clinical laboratory practice (innovation).

Most relevant scientific articles

KAREINEN I., CEDO L., SILVENNOINEN R., LAURILA P.-P., JAUHIAINEN M., JULVE J. ET AL. Enhanced vascular permeability facilitates entry of plasma HDL and promotes macrophage-reverse cholesterol transport from skin in mice. Journal of Lipid Research. 2015;56(2):241-253.

CEDO L., METSO J., SANTOS D., SÁNCHEZ-QUESADA J.L., JULVE J., GARCÍA-LEON A. ET AL. Consumption of polyunsaturated fat improves the saturated fatty acid-mediated impairment of HDL antioxidant potential. Molecular Nutrition and Food Research. 2015;59(10):1987-1996.

MASANA L., CABRE A., HERAS M., AMIGO N., CORREIG X., MARTÍNEZ-HERVAS S. ET AL. Remarkable quantitative and qualitative differences in HDL after niacin or fenofibrate therapy in type 2 diabetic patients. Atherosclerosis. 2015;238(2):213-219.

REVUELTA-LÓPEZ E., CAL R., JULVE J., RULL A., MARTÍNEZ-BUJIDOS M., PEREZ-CUELLAR M. ET AL. Hypoxia worsens the impact of intracellular triglyceride accumulation promoted by electronegative low-density lipoprotein in cardiomyocytes by impairing perilipin 5 upregulation. International Journal of Biochemistry and Cell Biology. 2015;65:257-267.

MINAMBRES I., SÁNCHEZ-QUESADA J.L., VINAGRE I., SÁNCHEZ-HERNÁNDEZ J., URGELL E., DE LEIVA A. ET AL. Hypovitaminosis D in type 2 diabetes: Relation with features of the metabolic syndrome and glycemic control. Endocrine Research. 2015;40(3):160-165.

Highlights

During 2015 our group has secured new competitive funding through a coordinated project with other CIBERDEM group (P.I. Dr,. L. Masana) after a TV3 Marató public and competitive call on projects tackling heart disease.

On the other hand, there have significant advances in other group projects such as those analyzing the mechanisms of action of phytosterols, the effects on insulinsensitivity of LRP1 heart-condicional knockout, and the effects on breast tumour growth of HDL protein transgenesis, as to think that these studies will be published in 2016.

Institution: Instituto de Investigación del Hospital de la Santa Creu i Sant Pau
Contact: S Antoni Mª Claret 167 08025 Barcelona · Tel.: 93 553 73 58 · E.mail: fblancova@santpau.cat
Web: http://www.iibsantpau.cat; www.ciberdem.org

Brain glucose sensor, satiety control, insulin resistance and type 2 diabetes

Programme: **P1 / P3**

Lead Researcher: **Blázquez Fernández, Enrique**

Group members

STAFF MEMBERS: Gutiérrez Nogues, Ángel | Hurtado Carneiro, Verónica.

ASSOCIATED MEMBERS: Álvarez García, Elvira | Navas Hernández, María de los Ángeles | Roncero Rincón, Isabel | Ruiz Albusac, Juan Miguel | Sanz Miguel, Carmen | Velázquez Sánchez, Esther.

Main lines of research

- Modifications of cerebral glucose metabolism in pathophysiological states related to feeding behaviour.
- The effects of GLP-1 and GLP-2 on the expression and activity of hypothalamic metabolic sensors and characterization of the neuroprotective role of these peptides.
- The effect of GLP-2 on the proliferation and apoptosis of cultured rat astrocytes.
- Signalling and the biological effects of GLP-1 on mesenchymal stem cells of human bone marrow and mouse embryonic stem cells - its effect on cell differentiation.
- Molecular diagnosis of monogenic diabetes (MODY) and the functional characterization of MODY mutations.

Most relevant scientific articles

ORIOLA J, MORENO F, GUTIÉRREZ-NOGUÉS A, LEÓN S, GARCÍA-HERRERO CM, VINCENT O ET AL. Lack of glibenclamide response in a case of permanent neonatal diabetes caused by incomplete inactivation of glucokinase.JIMD reports. 2015;20:21-6.

Highlights

GRANTS AND COLLABORATIONS

- Grant from Fundación Mutua Madrileña, awarded to Dr. Enrique Blázquez Fernández in 2013.
- Collaboration with Dr.Isidre Ferrer (Neuropathology group, Instituto de Investigación Biomédica de Bellvitge (IDIBELL), Barcelona, Spain) and Dr. Alberto Rábano (Histological diagnostic responsible, Banco de Tejidos para Investigaciones Neurológicas de Madrid, Madrid, Spain) in the analysis of central nervous system insulin response.
- Collaboration and knowledge transfer contract with Sylentis S.A. under LOU 83th article, to analyze TRPV1 and ADRB2 expression through fine tunning western blot and performing it.
- Collaboration with Oriola J. (Servicio de Bioquímica y Genética Molecular. Hospital Clínic. Departamento de Ciencias Fisiológicas I. Facultad de Medicina., Universidad de Barcelona, Barcelona, Spain.) in the analysis of mutations in the GK gene identified in a children with permanent neonatal diabetes and his glibenclamide treatment.
- Collaboration with Prof. Roland H. Wenger (Institute of Physiology, University of Zürich- Irchel) in the study of PASK deficient animals. And establishment the roll of nutrient sensor PASK in enzyme regullation, hepatic metabolism and oxidative stress
- XII Course for Postgraduates. Fundamentos Moleculares de la Medicina, organized by Dr. Enrique Blázquez Fernández, at RANM (May 2015).

Institution: Universidad Complutense de Madrid · **Contact:** Facultad de Medicina · Pza. Ramón y Cajal, s/n. Ciudad Universitaria. 28040 Madrid · Tel.: 91 394 14 43 · E.mail: eblazquez@med.ucm.es

Transgenic animal models and gene therapy approaches for diabetes

Programme: P2

Lead Researcher: Bosch Tubert, Fátima

Group members

STAFF MEMBERS: Casellas Comallonga, Alba.

ASSOCIATED MEMBERS: Barrero Victorio, Jennifer | Carretero Romay, Ana | Elias Puigdoménech, Ivet | Ferré Masferrer, Mª del Tura | Franckhauser, Sylvie | García Martínez, Miguel | Haurigot, Virginia | Jiménez Cenzano, Veronica | León Madrenas, Xavier | Maggioni, Luca | Mallol Domínguez, Cristina | Melgarejo Bermúdez, Verònica | Molas Laplana, María | Morró Larrubia, Meritxell | Moya Martínez, Marta | Muñoz Forero, Sergio Antonio | Nacher García, Victor | Navarro Beltrán, Marcos | Otaegui Goya, Pedro José | Pujol Altarriba, Anna | Ribera Sánchez, Albert | Roca Lecha, Carles | Ruberte Paris, Jesús | Vilà Prats, Laia | Zaguirre Sánchez, Mireia.

Main lines of research

Study of causes and pathophysiological mechanisms of diabetes and obesity.

- Study of the role of pancreatic ß cell alterations in the development of diabetes.
- Identification of novel genes in adipose tissue involved in the development of diabetes and obesity.
- Identification of novel mechanisms involved in browning of white adipose tissue.

Development of new gene therapy approaches for diabetes

- Gene therapy approaches for the treatment of type 1 diabetes centered on genetic engineering of skeletal muscle to produce insulin and/or increase glucose uptake.
- Gene therapy approaches for type 2 diabetes and obesity centered on genetic engineering of skeletal muscle and/or the liver.
- Study of in vivo pancreas regeneration in diabetic animals:

  -Regeneration of endocrine pancreas by IGF-1

  -Betasel: in vivo selection of genes to improve beta cell mass
- Development of new approaches for type 2 diabetes and obesity centered on genetic engineering of adipose tissue.

Most relevant scientific articles

CASELLAS A., MALLOL C., SALAVERT A., JIMÉNEZ V., GARCÍA M., AGUDO J. ET AL. Insulin-like growth factor 2 overexpression induces β-Cell dysfunction and increases beta-cell susceptibility to damage. Journal of Biological Chemistry. 2015;290(27):16772-16785.

ARCE-CEREZO A., GARCÍA M., RODRÍGUEZ-NUEVO A., CROSA-BONELL M., ENGUIX N., PERO A. ET AL. HMGA1 overexpression in adipose tissue impairs adipogenesis and prevents diet-induced obesity and insulin resistance. Scientific Reports. 2015;5.

TEICHENNE J, MORRÓ M, CASELLAS A, JIMÉNEZ V, TELLEZ N, LEGER A ET AL. Identification of miRNAs Involved in Reprogramming Acinar Cells into Insulin Producing Cells.PloS one. 2015;10(12):e0145116.

GERST F., KAISER G., PANSE M., SARTORIUS T., PUJOL A., HENNIGE A.M. ET AL. Protein kinase Cδ regulates nuclear export of FOXO1 through phosphorylation of the chaperone 14-3-3ζ. Diabetologia. 2015;58(12):2819-2831.

VILLACAMPA P., HAURIGOT V., BOSCH F.. Proliferative retinopathies: Animal models and therapeutic opportunities. Current Neurovascular Research. 2015;12(2):189-198.

Highlights

In 2015, we have initiated a project financed by the Ministerio de Educación y Competitividad (SAF2014-54866-R), "Nuevas aproximaciones de terapia génica para la diabetes tipo 2 y la obesidad basadas en la activación del tejido adiposo marrón y browning del tejido adiposo blanco". This project is based on results obtained from a previous project ended in 2015 and financed by the "European Foundation for the Study of Diabetes": "Unravelling of novel factors capable of inducing browning of WAT in vivo". In addition, we have initiated the second part of a project financed by the Juvenile Diabetes Research Foundation (JDRF): "BetaSel2 – Therapeutic efficacy of novel cytokines and growth factors selected in vivo to improve beta cell mass", focused on searching new candidates to counteract type 1 diabetes. Our group is also involved in several international initiatives aiming at phenotyping, archiving and distributing mouse models for the biomedical research community. Namely, we are participating in the EU projects, "European infrastructure for phenotyping and archiving of model mammalian genomes (Infrafrontier-I3) (2013-2016)" and "Research Infrastructure for Phenotyping, Archiving and Distribution of Mouse Disease Models (IPAD-MD)", as well as in the International Consortium "International Mouse Phenotyping Consortium (IMPC)". We also are partners in the EU COST action "Development of a European network for preclinical testing of interventions in mouse models of age and age-related diseases (MouseAGE)", to study aging in mice. On the other hand, the public/private partnership between UAB and Esteve for the clinical development of gene therapy approaches for rare inherited metabolic disorders (Mucopolysaccharidosis) has been renewed (July 2015-June2017). In this field, we are also participating in the project "AAV-mediated gene therapy for the treatment of MPSIIID (Sanfilippo D)" financed by the Association Française contre les Myopathies (2014-2016).

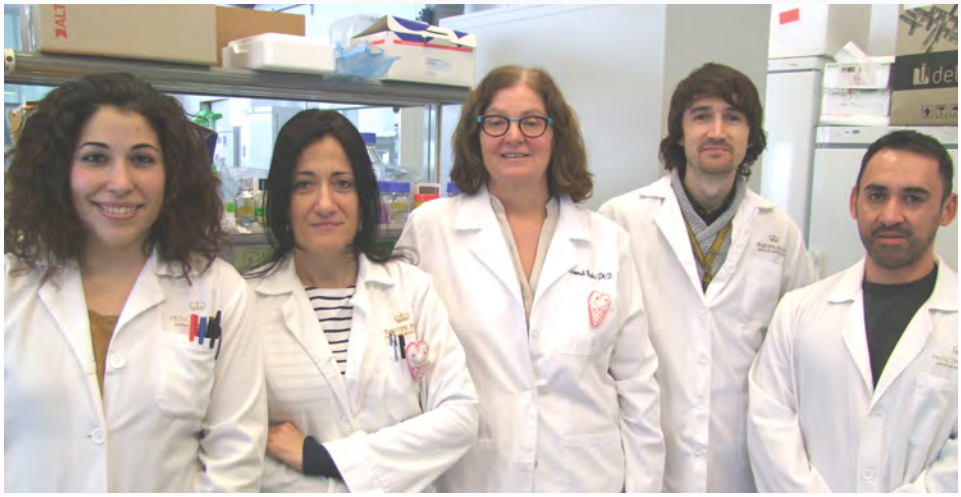
Institution: Universitat Autònoma de Barcelona · **Contact:** Centro de Biotecnología Animal y Terapia Genética Edificio H-Campus UAB. 08193 Bellaterra · Tel.: 93 581 41 82 · E.mail: fatima.bosch@uab.cat
Website: http://www.uab.cat

Laboratory of molecular endocrinology

Programme: **P2**

Lead Researcher: **Burks, Deborah**

Group members



STAFF MEMBERS: Acosta Umanzor, Carlos René | Manzano Núñez, Fátima | Noon, Luke.

ASSOCIATED MEMBERS: González Navarro, Herminia | Leal Tassias, Aranzazu | Moreno Gimeno, Inmaculada | Sánchez Pérez, Ana María | Sanz González, Silvia María.

Main lines of research

Our research focuses on insulin receptor substrate (IRS) proteins which are the major intracellular targets of the activated insulin receptor. Loss of Irs2 in both mice and humans is associated with a reduced mass of pancreatic beta cells and peripheral insulin resistance, hallmarks of diabetes.

Our core research consists of 4 major lines: 1) Regulation of beta cell compensation and pancreas regeneration. Given that proliferation of existing beta cells represents the fundamental mechanism for beta cell compensation, it is important to precisely define the signals which govern cell-cycle machinery in the endocrine pancreas. Recently, we have observed that IRS2 signals are essential for the regulation of the cyclin kinase CDK4 in beta cells. 2) The role of IRS2 signals in obesity-induced inflammation. Female Irs2-deficient mice display a dysregulation of appetite due to the role of IRS2 signals in the hypothalamus and thus, develop moderate obesity. We are currently characterizing the inflammation components that are regulated directly by the insulin resistance resulting from loss of Irs2. Also, Irs2-deficient mice have more adipose progenitors but these fail to differentiate to mature adipocytes. 3) Hepatic insulin resistance, liver regeneration, and mechanisms of NAFLD. Throughout the lifetime of an individual, adult stem cells represent a mechanism for the maintenance and regeneration of tissues. One of our objectives is to identify the molecular mechanisms by which insulin signaling modulates proliferation and differentiation of progenitor cells in insulin-sensitive tissues. These results may provide tools for maintaining stem cell function in the presence of aging-related and pathologic changes in metabolism. 4) Mechanisms of insulin resistance in the CNS. Aged Irs2-deficient mice present various manifestations of neurodegeneration including neuronal loss and deposits of hyperphosphorylated tau. Through the use of genomics and proteomics, we hope to identify new markers of neurodegeneration that are regulated by insulin signaling. Given that we seek to identify the molecular basis of obesity and insulin resistance, our research

may provide the rational basis for the development of new and innovative strategies for the detection, treatment and prevention of metabolic disorders including lifestyle changes or drugs that promote IRS2 expression or function.

Most relevant scientific articles

VINUE ÁNGELA, ANDRES-BLASCO I., HERRERO-CERVERA A., PIQUERAS L., ANDRES V., BURKS D.J. ET AL. Ink4/Arf locus restores glucose tolerance and insulin sensitivity by reducing hepatic steatosis and inflammation in mice with impaired IRS2-dependent signalling. Biochimica et Biophysica Acta - Molecular Basis of Disease. 2015;1852(9):1729-1742.

ANDRES-BLASCO I., HERRERO-CERVERA A., VINUE A., MARTÍNEZ-HERVAS S., PIQUERAS L., SANZ M.J. ET AL. Hepatic lipase deficiency produces glucose intolerance, inflammation and hepatic steatosis. Journal of Endocrinology. 2015;227(3):179-191.

TOLOSA L., CARON J., HANNOUN Z., ANTONI M., LÓPEZ S., BURKS D. ET AL. Transplantation of hESC-derived hepatocytes protects mice from liver injury. Stem Cell Research and Therapy. 2015.

Highlights

PROJECTS FUNDED/ACTIVATED IN 2015:

- BFU2014-58686-P (Luke Noon): "SIL-iver", Local insulin signaling in liver. 145.200,00€ administered by CIBERDEM.
- Proyecto Paula (Herminia Gonzalez). 50.000€. This grassroots funding effort seeks to strengthen diabetes research by providing laboratory personnel.
- PI13/00834, ISCIII (Herminia Gonzalez). 89.200€. "Study of Molecular Mechanisms of Diabetes and their role in the Development of Atherosclerosis".
- Private Contract with biotech Fibrostatin (Deborah Burks). 100.000€. Test potential anti-diabetic compound in mouse models.

STUDENTS TRAINED IN 2015:

- Proyecto TFG: María José Arámbul Anthony (NIF: 53788752D) – Universidad Politecnica de Valencia (600 hours) – Result 10/10 (Cum Laude), Defended 17/07/15
- Proyecto TFM: Luis Ferriol Huedo (NIF: 48596149R) – Universidad de Valencia (800 hours) – Result 9,5/10Defended 23/09/15
- FCT: Marta Galvez Viedma – Centre Integrat Públic de Formació Professional Mislata (380 hours)
- Prácticas: Irene Garcés Lázaro, NIF 73412297T – Universitat de Lleida (120 hours)

COLLABORATIONS: We have established a series of important collaborations with a diverse group of international researches, including:

- Professor Scott Friedman (MSSM, New York, USA)
- Professor Alexander Levitzki (Hebrew University of Jerusalem, Israel)
- Dr Anne Corlu (Inserm UMR991, Rennes, France)
- Dr Ann-Sophie Armand (Inserm UMR 1124, Paris, France)
- Professor Jerónimo Forteza (CIPF, Valencia, Spain)
- María J. Vicent (CIPF, Valencia, Spain)

We have also established collaborations with several small biotech companies:

- Oncovision (CIPF, Valencia, Spain)
- Cellgenix (Ursula Schultz, Freiburg, Germany)
- Fibrostatin (Valencia, Spain)

DISSEMINATION: Our work has been presented seminars as well as at a series of international congresses:

- 10/03/15: Inserm U522 "Local insulin signalling: A role in hepatogenesis and liver cancer?" Rennes, France.
- 17/07/15: CIPF internal seminar, "The Role of Insulin Substrate Receptor 2 (IRS2) in Hepatocellular Carcinoma (HCC): a local insulin signalling (LIS) view", Valencia.
- 12/02/15: CIPF internal seminar, "Patterning of local insulin/IGF1 signalling by insulin receptor substrate (IRS) gene expression in vitro and in vivo".
- 13-17/11/15: 66th Annual Meeting of the American-Association-for-the-Study-of-Liver-Diseases (AASLD). San Francisco, (USA).
- 14-18/09/15: 51st Annual Meeting of the European-Association-for-the-Study-of-Diabetes (EASD), Stockholm, (Sweden).

Institution: Fundación Centro de Investigación Príncipe Felipe · **Contact:** C/ Eduardo Primo Yúfera 3. 46013 Valencia · Tel.: 96 328 96 80 · E.mail: dburks@cipf.es · Web: http://www.cipf.es

Hospital Universitario Cruces Endocrinology and Diabetes Research Group

Programme: **P1**

Lead Researcher: **Castaño González, Luis**

Group members

STAFF MEMBERS: Martínez Salazar, Rosa María | Urrutia Echebarría, Inés María.

ASSOCIATED MEMBERS: Aguayo Calcena, Anibal | Bilbao Catala, José Ramon | Castellanos Rubio, Ainara | Cortázar Galarza, Alicia | Gaztambide Saenz, Sonia | González Frutos, Teba María Dolores | Pérez de Nanclares, Gustavo | Rica Etxebarria, Itxaso | Rivero, Sorkunde | Santamaría Sandi, Francisco Javier | Vázquez San Miguel, Federico | Vela, Amaia | Velayos Gainza, Teresa.

Main lines of research

- The identification of additional genetic susceptibility markers for type 1 diabetes and related autoimmune disorders in the extended MHC (6p21) and other regions using high throughput genotyping.
- The study of enviromental factors and immune mediators of disease development, characterization of novel autoantigens/antibodies and cell populations in patients: Th1, Th2 and Th17 responses.
- The identification of new genes responsible for monogenic diabetes by genome wide analysis (array-CGH approach), whole exome sequencing and next generation sequencing panels of candidate genes.
- The molecular and clinical characterization of monogenic diabetes and new therapeutic strategies for KATP channel alterations.
- The prediction and prevention of type 1 diabetes.
- The control of diabetes complications.
- The epidemiology of diabetes.

Most relevant scientific articles

ALONSO-MORAN E., ORUETA J.F., ESTEBAN J.I.F., AXPE J.M.A., GONZÁLEZ M.L.M., POLANCO N.T. ET AL. Multimorbidity in people with type 2 diabetes in the Basque Country (Spain): Prevalence, comorbidity clusters and comparison with other chronic patients. European Journal of Internal Medicine. 2015;26(3):197-202.

AMOR A.J., MASANA L., SORIGUER F., GODAY A., CALLE-PASCUAL A., GAZTAMBIDE S. ET AL. Estimating cardiovascular risk in spain by the European guidelines on cardiovascular disease prevention in clinical practice. Revista Espanola de Cardiologia. 2015;68(5):417-425.

NEU A., LANGE K., BARRETT T., CAMERON F., DORCHY H., HOEY H. ET AL. Classifying insulin regimens - difficulties and proposal for comprehensive new definitions. Pediatric Diabetes. 2015;16(6):402-406.

RAMIREZ-DOMÍNGUEZ M., CASTANO L.. Filtration is a time-efficient option to Histopaque, providing good-quality islets in mouse islet isolation. Cytotechnology. 2015;67(2):199-206.

FALORNI A., BINI V., BETTERLE C., BROZZETTI A., CASTANO L., FICHNA M. ET AL. Determination of 21-hydroxylase autoantibodies: Inter-laboratory concordance in the Euradrenal International Serum Exchange Program. Clinical Chemistry and Laboratory Medicine. 2015;53(11):1761-1770.

Highlights

- Endocrinology, Diabetes, Nutrition and Renal Alterations. Basque Government (IT 795-13). 2013-2018. Luis Castaño.
- Researchers: Incidence of diabetes and prevalence of monogenic-diabetes in the Di@bet.es study. ISCI-II–PI14/01104. Luis Castaño.
- Determinants of Diet and Physical Activity. DEDIPAC-KH (JPI) "Healthy Diet for Healthy Life" 2012-active. Luis Castaño.
- European Nutrition Phenotype Assessment and Data Sharing Initiative. ENPADASI. "Healthy Diet for Healthy Life". 2014-active. Luis Castaño.
- Prospective study: Incidence of diabetes and cardiovascular risk factors in Basque Country. Basque Government (2015111020) 2015-2017. Sonia Gaztambide.
- Functional characterization of the IDIN antiviral pathway: role in pancreatic ß-cell destruction and T1D progress. Basque Government (2015111068). 2015-2018. Izortze-Santin.
- Functional characterization of the genomic regions associated with celiac disease risk in cell populations of gut mucosa. ISCIII-MICINN (PI13/01201). 2014-2016. JR Bilbao.
- Functional study of candidate genes to celiac disease. Use as a diagnostic tool. Basque Government (2011111034). 2013-2015. JR Bilbao.
- Role of the cell cycle regulators E2F1 and E2F2 in the pathogenesis and prognosis of the hepatic disease. State Research Program(SAF2015-64352-R) 2015-2017. Sonia Gaztambide.
- Genetic and environmental factors of insulin-resistance syndrome. Long-term complications in immigrant Mediterranean populations. MEDIGENE (FP7-279171-1). 2011-active, Luis Castaño.
- Centre Differences study in children aged under 11 years. Hvidore Study Group on childhood Diabetes. 2009-2015. Luis Castaño.
- TRIGR project: Trial to reduce IDDM in children at genetic risk. National Institute of Health. 2007-2016. Luis Castaño.
- GESDIA2: Comprehensive management of T2D patients. Prospective and observational study. 2014-2015. Sonia Gaztambide.
- Randomized controlled study to evaluate the impact of a novel technique to detect glucose on hypoglycemia in T1D (ADC-CI-APO-13019). 2015, Sonia Gaztambide.
- Albiglutide+insulin-glargine vs. insulin lispro+insulin-glargine in the treatment of subjects with T2D. SWITCH (200977-EudraCTnumber: 2014-001821-34). 2015, Sonia Gaztambide.
- Phase III multicentric, randomized, double-blinded, placebo-controlled study to evaluate the impact of Diamyd® in the progression of diabetes in newly diagnosed T1D patients. (D/P3/07/4Nº EUDRACT: 2007-002728-13). 2015. Rica.

Institution: Asoc. Instituto de Investigación Sanitaria de Biocruces · **Contact:** Hospital Universitario Cruces. Pza. De Cruces, S/N. 48903 Cruces (Barakaldo) · Tel. 946006473 · E.mail: lcastano@osakidetza.net

Metabolomics Platform

Programme: **P3**

Lead Researcher: **Correig Blanchart, Francesc Xavier**

Group members

STAFF MEMBERS: Navarro Sanz, Miriam | Samino Gené, Sara | Yanes Torrado, Óscar

ASSOCIATED MEMBERS: Amigó Grau, Nuria | Brezmes Llecha, Jesús Jorge | Domingo Almenara, Xavier | Gómez Álvarez, Josep | Radu Ionescu, Radu | Vilalta Montlleo, Didac | Vinaixa Crevillent, Maria.

Main lines of research

- NMR lipoprotein characterization for the study of dyslipidaemias.
- A serum profiling method for the study of insulin resistance and diabetes in population studies.
- The development and study of advanced statistical, chemometric, multivariate and artificial intelligence algorithms which will allow large measurement datasets.
- Non-radioactive isotopomers for the study of metabolic profiling and its flux in cultured cells and animal models.
- The study of diabetic retinopathy.
- The study of tissue imaging and body fluid profiling with laser desorption ionization mass spectrometry (LDI-MS).
- Thirdhand smoke (THS) exposition assesment with metabolomics and their effects on metabolic diseases.

Most relevant scientific articles

SAMINO S., VINAIXA M., DÍAZ M., BELTRAN A., RODRÍGUEZ M.A., MALLOL R. ET AL. Metabolomics reveals impaired maturation of HDL particles in adolescents with hyperinsulinaemic androgen excess. Scientific Reports. 2015;5.

DOMINGO-ALMENARA X., PERERA A., RAMIREZ N., CANELLAS N., CORREIG X., BREZMES J.. Compound identification in gas chromatography/mass spectrometry-based metabolomics by blind source separation. Journal of Chromatography A. 2015;1409:226-233.

MALLOL R, AMIGÓ N, RODRÍGUEZ MA, HERAS M, VINAIXA M, PLANA N ET AL. Liposcale: a novel advanced lipoprotein test based on 2D diffusion-ordered 1H NMR spectroscopy.Journal of lipid research. 2015;56(3):737-46.

MASANA L., CABRE A., HERAS M., AMIGO N., CORREIG X., MARTÍNEZ-HERVAS S. ET AL. Remarkable quantitative and qualitative differences in HDL after niacin or fenofibrate therapy in type 2 diabetic patients. Atherosclerosis. 2015;238(2):213-219.

BRUGNARA L., MALLOL R., RIBALTA J., VINAIXA M., MURILLO S., CASSERRAS T. ET AL. Improving assessment of lipoprotein profile in type 1 diabetes by 1H NMR spectroscopy. PLoS ONE. 2015;10(8).

Highlights

COLLABORATIONS :

Ten collaborations with groups from Ciberdem: Dr. Egido; Dra. Rojo, Dr. Guinovart, Dr. Simó, Dr. Masana, Dra. Novials, Dr. Mauricio, Dr. Vendrell, Dra. Burks, Dra. Martínez Valverde; and 4 with other CIBER's: Dr. Azpiroz (CIBEREHD), Dr. Salas Salvadó (CIBEROBN), Dr. Vila Bover (CIBERNED), Dr. de la Torre (CIBEROBN). Other collaborations with national and international groups: Dr. Gomis (IRB), Dr. Stracker (IRB), Dr. González (IRB Barcelona), Dr. Quintela (CNIO), Dr. Salek (EBI-EMBL), Dr. Neumann (Leibniz Institute of Plant Biochemistry), Dra. Schymanski (Swiss Federal Institute of Aquatic Science and Technology), Dr. Jourdan (INRA), Dr. Shabaz Mohammed (University of Oxford), Dr. Thomas (IDIBELL, Barcelona), Dr. Buschbeck (IMPPC), Dr. Beato (CRG), Dr. Cantó (Nestlé Institute of Health Sciences), Dr. Jimenez Chillaron (Hospital Sant Joan de Deu), Dr. Guimerà (URV-ICREA), Dra. Colomina (URV, Tarragona), Dr. Méndez (IRB), Dr. Fajas (Universidad de Laussane), Dr. Heck (Utrecht University), Dr. Kessler (University of Oxford), Dr. Harris (University of Oxford), Dr. Loda (Dana-Farber Cancer Institute), Dra. Martins-Green (University of California), Dra. Mora (Brigham and Women's Hospital), Dra. Potrykus, (University of Aberdeen), Dr. Davidson (University of Ulster), Dr. Alexandrov (EMBL).

RELEVANT PROJECTS:

BFU2014-57466-P.Rethinking cellular metabolism through identification of unpredicted metabolites and biochemical transformations using a novel metabolomic approach.

SAF2011-30578: Identification of metabolic pathways in neurodegeneration of retina induced by hyperglycemia and ischemia through an approximation of metabolomics and proteomics.

TEC2012-31074: Development of nanostructured surfaces and metabolic image processing algorithms for NIMS: application to the study of pancreatic islets in diabetic rats.

RELEVANT RESULTS ACHIEVED:

- Clinical validation of an advanced method of lipoproteins.
- Identification of biomarkers of subclinical atherosclerosis in PCOS patients.
- Development of algorithms for fluxomics experiments based on LC-MS and NMR.
- Creation and validation of a new algorithm for the identification of unknown metabolites by GC-MS.
- Obtaining metabolic images of mass spectrometry by metal nanoparticles (NP-LDI-MSI).

Institution: Fundación Institut d'Investigació Sanitària Pere Virgili · **Contact:** Universitat Rovira i Virgili
C/ Sant Llorenç, 21 Planta baja del edificio 4 de la Facultat de Medicina i Ciències de la Salut. 43201 Reus
Tel.: 977 559 623 · E.mail: metabolomicsplatform@urv.cat · Web: http://www.metabolomicsplatform.com

Division of Nephrology and Hypertension

Programme: **P1**

Lead Researcher: **Egido de los Ríos, Jesús**

Group members

STAFF MEMBERS: Civantos Martin, Esther.

ASSOCIATED MEMBERS: Gómez Guerrero, Carmen | González Gómez, Nieves | Martín Crespo, Estrella | Mas Fontao, Sebastián | Oguiza Bilbao, Ainhoa | Recio Cruz, Carlota.

Main lines of research

- Vascular complications of diabetes (nephropathy and atherosclerosis).
- Inflammation and intracellular signals.
- New therapeutic approaches to diabetic kidney disease.
- Biomarkers.
- Renal lipotoxicity in the diabetic patient.

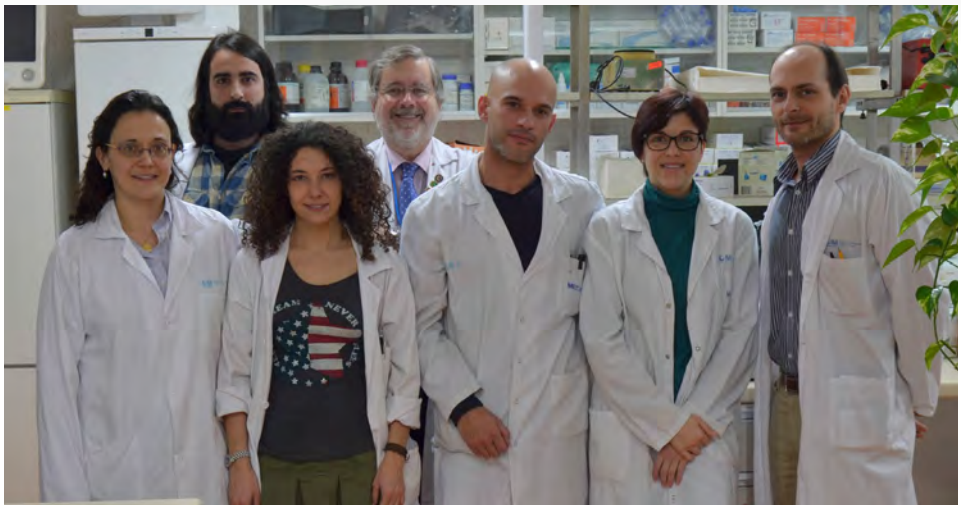
Institution: Fundación Instituto de Investigación Sanitaria Fundación Jiménez Díaz
Contact: Instituto de Investigación Sanitaria - Fundación Jiménez Díaz · Avda. Reyes Católicos, 2
28040 Madrid · Tel.: 91 550 48 00 (Ext. 3362/2294) · E.mail: jegido@fjd.es · Web: http://www.fjd.es

Diabetes, obesity and human reproduction

Programme: **P3**

Lead Researcher: **Escobar Morreale, Héctor Francisco**

Group members



STAFF MEMBERS: Fernández Durán, Elena | Insenser Nieto, María Rosa | Martínez García, Mª Ángeles.

ASSOCIATED MEMBERS: Álvarez Blasco, Francisco | Luque Ramírez, Manuel | Roldán Martín, María Belén | San Millán López, José Luis | Sanchón Rodríguez, Raúl.

Main lines of research

Influence of sex hormones on the development of abdominal adiposity and visceral adipose tissue dysfunction in humans as pathogenetic factors of insulin resistance and diabetes, including:

- an integrated approach to the influence of sex hormones on the amount and dysfunction of visceral and subcutaneous fat as studied by clinical research, molecular genetics, molecular biology, transcriptomics, proteomics and metabolomics.
- the identification of pathogenetic markers of diabetes in severe obesity and predictors of diabetes remission after bariatric surgery.
- the role of disordered iron metabolism on the metabolic associations of polycystic ovary syndrome.
- the effects of sex hormones on the metabolic and inflammatory responses to the oral administration of different macronutrients.
- influence of treatment of gonadal dysfunction (polycystic ovary syndrome or functional hypogonadotrophic hypogonadism) on visceral adiposity and intermediate metabolism.

Most relevant scientific articles

LUQUE-RAMIREZ M., ESCOBAR-MORREALE H.F.. Targets to treat androgen excess in polycystic ovary syndrome. Expert Opinion on Therapeutic Targets. 2015;19(11):1545-1560.

ALPANES M., LUQUE-RAMIREZ M., MARTÍNEZ-GARCÍA M.A., FERNÁNDEZ-DURAN E., ÁLVAREZ-BLASCO F., ESCOBAR-MORREALE H.F.. Influence of adrenal hyperandrogenism on the clinical and metabolic phenotype of women with polycystic ovary syndrome. Fertility and Sterility. 2015;103(3):795-801.e2.

ESCOBAR-MORREALE HF, BOTELLA-CARRETERO JI, MORREALE DE ESCOBAR G. Treatment of hypothyroidism with levothyroxine or a combination of levothyroxine plus L-triiodothyronine.Best practice & research. Clinical endocrinology & metabolism. 2015;29(1):57-75.

LUQUE-RAMÍREZ M, ALPAÑÉS M, SANCHÓN R, FERNÁNDEZ-DURÁN E, ORTIZ-FLORES AE, ESCOBAR-MORREALE HF. Referral bias in female functional hyperandrogenism and polycystic ovary syndrome.European journal of endocrinology / European Federation of Endocrine Societies. 2015;173(5):603-10.

ZAZO SECO C., SERRAO DE CASTRO L., VAN NIEROP J.W., MORIN M., JHANGIANI S., VERVER E.J.J. ET AL. Allelic mutations of KITLG, encoding KIT ligand, cause asymmetric and unilateral hearing loss and Waardenburg syndrome type 2. American Journal of Human Genetics. 2015;97(5):647-660.

Highlights

During 2015 Dr. Luque Ramirez has started as PI the research proyect FIS PI 1400649 Effects on cardiovascular risk factors of decreasing iron tissue deposits in women with polycystic ovary syndrome: a proof-of-concept study. We have to acknowledge the help that Dr. Luque Ramirez has received from IRYCIS in the form of a grant that permitted him to devote more time to research during this period.

Also in 2015 the group has received a new grant FIS PI1501686 Infuence of sex and sex hormones on adipose tissue dysfunction and chrnic metabolic disorders of complex etiology (SEXMETAB) . This grant will permit us to lead the aplication of sex/gender medicine to the field of metabolic dysfunction associated with diabetes and obesity.

Regarding scientific publications, 2015 has been a year of transition between proyects in which we have started the writting and submission process of the data derived from our previous Intrasalud grant FIS PI1100357 Hormonal, metabolic, inflammatory and oxidative stress response to dietary macronutrients: influence of sex steroids. These manuscripts will hopefully available during 2016 and 2017.

In the international arena, Dr. Escobar Morreale continues his role as member of the Board of Directors of the AE-PCOS Society and is a member of the PCOS Special Interest Group of the European Society of Endocrinology.

Institution: Servicio Madrileño de Salud · **Contact:** Hospital Ramón y Cajal · Carretera de Colmenar, Km 9.1 28034 Madrid · Tel.: 91 336 90 29 · E.mail: elena.fenandezd@salud.madrid.org

Genomic programming of beta cells

Programme: **P2**

Lead Researcher: **Ferrer, Jorge**

Group members

STAFF MEMBERS: García Hurtado, Javier | Grau Martínez, Vanessa | Maestro Garriga, Miguel Ángel | Sanahuja, Carme.

ASSOCIATED MEMBERS: Akerman, Ildem | Armengol, Mar | Miguel Escalada, Irene | Rovira Clusellas, Meritxell.

Main lines of research

- Dissection of the genetic mechanisms underlying the pathogenesis of human diabetes.
- Understanding the epigenome of pancreatic beta cells and its implications for the development, plasticity and growth of beta cells
- Mouse genetic analysis of beta-cell gene regulation.
- The regeneration of pancreatic beta cells.

Most relevant scientific articles

ROVIRA M., FERRER J.. Weaning Gives β Cells License to Regenerate. Developmental Cell. 2015;32(5):531-532.

CEBOLA I., RODRÍGUEZ-SEGUI S.A., CHO C.H.-H., BESSA J., ROVIRA M., LUENGO M. ET AL. TEAD and YAP regulate the enhancer network of human embryonic pancreatic progenitors. Nature Cell Biology. 2015;17(5):615-626.

MIGUEL-ESCALADA I., PASQUALI L., FERRER J.. Transcriptional enhancers: Functional insights and role in human disease. Current Opinion in Genetics and Development. 2015;33:71-76.

KIM Y.H., LARSEN H.L., RUE P., LEMAIRE L.A., FERRER J., GRAPIN-BOTTON A.. Cell Cycle–Dependent Differentiation Dynamics Balances Growth and Endocrine Differentiation in the Pancreas. PLoS Biology. 2015;13(3).

Highlights

This year the IDIBAPS group Genomic Programming of Beta Cells participated in new international projects (ZENCODE, University of Copenhagen International Alliance), and published a study that revealed novel regulatory programs of human embryonic pancreas (Cebola et al, Nat Cell Biol , 2015) as well as a review of the role of defects in regulatory programs in human disease (Miguel - Escalada et al, Curr Opinion Genet Dev, 2015).

Institution: Institut d'Investigacions Biomèdiques August Pi i Sunyer · **Contact:** Centro Esther Koplowitz
C/Rosselló, 149. 08036 Barcelona · Tel.: 93 227 54 00 xt 4542 · E.mail: jferrer@clinic.ub.es

Diabetes and obesity: biopathology and cellular plasticity

Programme: **P2**

Lead Researcher: **Gomis de Barbará, Ramon**

Group members

STAFF MEMBERS: Blanco Carrasco, Jesús | Esteban Romero, María Yaiza | Fernández Ruiz, Rebeca | García Alaman, Ainhoa | González Ruano, Elena | Katte, Kimberly | Viaplana Masclans, Judith

ASSOCIATED MEMBERS: Canivell Fusté, Silvia | Casamitjana Abella, Roser | Cervantes Roldán, Sara | Claret Carles, Marc | Conget Donlo, Ignacio | Esmatjes Mompo, Enrique | Flores Meneses, Lilliam | Gasa Arnaldich, Rosa María | Giménez Álvarez, Margarita | Hanzu, Felicia Alexandra | Martins de Sousa Maia Malpique, Rita María | Mora Porta, Mireia | Nadal Martín, Belén | Nicod, Nathalie | Papageorgiou, Aikaterini | Pradas Juni, Marta | Schneeberger Pane, Marc | Vidal Cortada, Josep.

Main lines of research

- The effects of pancreatic-mesenteric adipose tissue on beta-cell plasticity.
- Crosstalk between adipose tissue and endothelium in metabolic diseases: the role of adipocytokines in the aetiology and development of the atherothrombotic complications in both diseases.
- The molecular determinants involved in pancreatic beta-cell apoptosis and regeneration: clinical applications.
- Transcriptional networks which control beta-cell population and function.
- Pancreatic islet transplantation: role of PTP1B.
- The role of the hypothalamus in energy homeostasis control in obesity.
- Genetic determinants involved in the risk of type 2 diabetes.
- Intrinsic and extrinsic signals regulating beta cell mass.

Most relevant scientific articles

CANIVELL S., REBUFFAT S., G. RUANO E., KOSTOV B., SISO-ALMIRALL A., NOVIALS A. ET AL. Circulating SFRP5 levels are elevated in drug-naïve recently diagnosed type 2 diabetic patients as compared with prediabetic subjects and controls. Diabetes/Metabolism Research and Reviews. 2015;31(2):212-219.

SCHNEEBERGER M., GÓMEZ-VALADES A.G., ALTIRRIBA J., SEBASTIÁN D., RAMIREZ S., GARCÍA A. ET AL. Reduced α-MSH Underlies Hypothalamic ER-Stress-Induced Hepatic Gluconeogenesis. Cell Reports. 2015;12(3):361-370.

DE HOLLANDA A., CASALS G., DELGADO S., JIMÉNEZ A., VIAPLANA J., LACY A.M. ET AL. Gastrointestinal hormones and weight loss maintenance following roux-en-Y gastric bypass. Journal of Clinical Endocrinology and Metabolism. 2015;100(12):4677-4684.

JIMÉNEZ A., CERIELLO A., CASAMITJANA R., FLORES L., VIAPLANA-MASCLANS J., VIDAL J.. Remission of type 2 diabetes after roux-en-y gastric bypass or sleeve gastrectomy is associated with a distinct glycemic profile. Annals of Surgery. 2015;261(2):316-322.

BERNSTEIN D.L., LE LAY J.E., RUANO E.G., KAESTNER K.H.. TALE-mediated epigenetic suppression of CDKN2A increases replication in human fibroblasts. Journal of Clinical Investigation. 2015;125(5):1998-2006.

Highlights

During 2015, our group obtained funding from the European Commission for the LUCA project as well as a patent for the use of sodium tungstate as an anti-platelet agent. Meetings for the ongoing MEDIGENE project were organized, highlighting those held in Barcelona and Zagreb. In addition, group members participated in the organization of several scientific activities, including the following courses: Translational Research in Diabetes (INSERM, Montpellier), Diabetes under Debate (CIBERDEM, Madrid), Clinical Excellence (Hospital Clinic, Barcelona), and Innovation in the Treatment of Diabetes (Universitat de Barcelona). Invited lectures also stand out, such as those presented at the XXVI Congress of the SED (closing speech), Universidad Juan Carlos I (Madrid), the Latin American Forum Master (Boston), and the opening speech of the Medical Degree academic program (Universitat de Barcelona). Also worth mentioning are efforts devoted to social outreach activities such as an urban sketching event focused on diabetes, talks given with the framework of World Diabetes Day, and participation in the 2015 La Marató de TV3 telethon, centered on diabetes and metabolic diseases research. Some group members are responsible for the Master's Degree in Principles of Care and Education for Diabetes Surfferers, started in 2015 at the Universitat de Barcelona, and the initiation of a new laser methodology in thyroid nodules treatment. Finally, the participation of various group members in the publication of the textbook, *Molecular Nutrition and Diabetes* (Elsevier) is also featured.

Institution: Institut d'Investigacions Biomèdiques August Pi i Sunyer · **Contact:** Centro Esther Koplowitz
C/Rosselló, 149. 08036 Barcelona · Tel.: 93 312 94 11 · E.mail: ramon.gomis@idibaps.org
Website: http://www.diabetes-obesity-research.org

Metabolic engineering and diabetes therapy

Programme: **P3**

Lead Researcher: **Guinovart Cirera, Joan Josep**

Group members

STAFF MEMBERS: Duran Castells, Jordi | Veza Estévez, Emma.

ASSOCIATED MEMBERS: Adrover Palau, Anna | García Rocha, María del Mar | López Soldado Fernández, Iliana | Slebe Concha, Juan Felipe | Testoni, Giorgia | Zapata, Claire Alix.

Main lines of research

- The control mechanisms of glucose storage in the liver and their alterations in diabetes mellitus. Characterization of novel compounds with anti-diabetic action.
- The role of glycogen metabolism in the glucose-sensing function of pancreatic beta-cell and liver.
- The consequences of altered glycogen deposition in various tissues in diabetes mellitus and in several neurodegenerative diseases.

Most relevant scientific articles

LÓPEZ-SOLDADO I, NIISUKE K, VEIGA C, ADROVER A, MANZANO A, MARTÍNEZ-REDONDO V ET AL. Neuregulin improves response to glucose tolerance test in control and diabetic rats.American journal of physiology. Endocrinology and metabolism. 2015;:ajpendo.00226.2015.

DROPPELMANN C.A., SAEZ D.E., ASENJO J.L., YANEZ A.J., GARCÍA-ROCHA M., CONCHA I.I. ET AL. A new level of regulation in gluconeogenesis: Metabolic state modulates the intracellular localization of aldolase B and its interaction with liver fructose-1,6-bisphosphatase. Biochemical Journal. 2015;472(2):225-237.

DÍAZ-LOBO M., GARCÍA-AMOROS J., FITA I., VELASCO D., GUINOVART J.J., FERRER J.C.. Selective photoregulation of the activity of glycogen synthase and glycogen phosphorylase, two key enzymes in glycogen metabolism. Organic and Biomolecular Chemistry. 2015;13(26):7282-7288.

LÓPEZ-RAMOS J.C., DURAN J., GRUART A., GUINOVART J.J., DELGADO-GARCÍA J.M.. Role of brain glycogen in the response to hypoxia and in susceptibility to epilepsy. Frontiers in Cellular Neuroscience. 2015;9(OCTOBER):-.

DURAN J., GUINOVART J.J.. Brain glycogen in health and disease. Molecular Aspects of Medicine. 2015;46:70-77.

Highlights

The group is devoted to carbohydrate metabolism and its alterations in diabetes and other diseases related to glucose metabolism.

We have demonstrated that hepatic glycogen regulates appetite and decreases obesity and is therefore is a new target for the treatment of diabetes.

We have also furthered knowledge of gluconeogenesis, a key metabolic pathway for hyperglycaemia, by showing the interaction between two of key enzymes in this pathway, namely aldolase A and fructose-1,6-bisphosphatase.

The modification of the activity of glycogen synthase and glycogen phosphorylase opens up new avenues for the treatment of diabetes. We have studied new compounds capable of altering the activity of these crucial enzymes via a novel photoregulatory mechanism that will provide the basis for the design and development of new drugs for this disease and for some glycogenoses.

Furthermore, we have demonstrated that brain glycogen plays a key role in adaptation to hypoxia and susceptibility to epilepsy. In this field, we have published a review article on our recent work on the role of brain glycogen in physiological and pathological conditions. Our aim is to address whether diabetes has an impact on the accumulation of this polysaccharide in neurons, a process that we have shown induces neurodegeneration.

Regarding collaborations within CIBERDEM, we have worked with Dr. Ramón Gomis (IDIBAPS) on the role of glycogen metabolism in beta cells. Using genetically modified animals with an altered capacity to accumulate glycogen, we are able to rule out a role of beta cell glycogen in the regulation of glucose homeostasis. In addition, we have worked with Dr. Rafael Simó (VHIR) on the role of glycogen on diabetic retinopathy.

Institution: Fundació Privada Institut de Recerca Biomèdica (IRB-Barcelona)
Contact: C/ Baldiri Reixac 10-12. 08028 Barcelona · Tel.: 93 403 71 63 · E.mail: guinovart@irbbarcelona.org
Web: http://www.irbbarcelona.org/index.php/cat/research/programmes/molecular-medicine/metabolic-engineering-and-diabetes-therapy

Consequences of prenatal and perinatal disorders on postnatal development. Disorders of fetal origin

Programme: **P3**

Lead Researcher: **Ibáñez Toda, Lourdes**

Group members

STAFF MEMBERS: Díaz Silva, Marta | Quílez Moya, Jovita.

ASSOCIATED MEMBERS: Casano Sancho, Paula | García García, Francesc Josep | Marcos Salas, María Victoria | Sebastiani, Giorgia.

Main lines of research

- Childhood diabetes.
- Physiological and pathological states in newborns and their effects on evolution.
- Congenital malformations and their surgical management.
- Foetal medicine: foetal well-being markers.
- Intrauterine growth retardation and related disorders.

Most relevant scientific articles

SÁNCHEZ-INFANTES D, GALLEGO-ESCUREDO JM, DÍAZ M, ARAGONÉS G, SEBASTÁNI G, LÓPEZ-BERMEJO A ET AL. Circulating FGF19 and FGF21 surge in early infancy from infra- to supra-adult concentrations.International journal of obesity (2005). 2015.

DE ZEGHER F., DÍAZ M., IBANEZ L.. Association between long telomere length and insulin sensitization in adolescent girls with hyperinsulinemic androgen excess. JAMA Pediatrics. 2015;169(8):787-788.

DÍAZ M., BASSOLS J., SEBASTÁNI G., LÓPEZ-BERMEJO A., IBANEZ L., DE ZEGHER F.. Circulating GLP-1 in infants born small-for-gestational-age: Breast-feeding versus formula-feeding. International Journal of Obesity. 2015;39(10):1501-1503.

SEBASTÁNI G., DÍAZ M., BASSOLS J., ARAGONES G., LÓPEZ-BERMEJO A., DE ZEGHER F. ET AL. The sequence of prenatal growth restraint and post-natal catch-up growth leads to a thicker intima-media and more pre-peritoneal and hepatic fat by age 3-6 years. Pediatric Obesity. 2015.

SAMINO S., VINAIXA M., DÍAZ M., BELTRAN A., RODRÍGUEZ M.A., MALLOL R. ET AL. Metabolomics reveals impaired maturation of HDL particles in adolescents with hyperinsulinaemic androgen excess. Scientific Reports. 2015;5.

Highlights

RESEARCH GROUP:

Over 2015, the group has further developed the two main research lines:

1) ovarian androgen excess: start of a clinical trial with novel therapies (PI15/01078);
2) low birth weight and postnatal endocrine-metabolic abnormalities: we are finishing a project related to methylation and gene expression in newbors of low birthweigth (PI11/02403).

These are among the priority research lines of the Hospital Sant Joan de Déu, being part of a broader line entitled: Adult Diseases of Fetal Origin, coordinated by Dr. Lourdes Ibáñez since 2008 (UB; www.hsjdbcn.org).

The results of the recent progress have been presented in invited lectures at national and international forums, including those at the Endocrine Society (San Diego), ECE (Dublin), SLEP (Puerto Varas, Chile), 3rd ICED (Ryad), and 16th World Congress on Human Reproduction (Berlin), as well as ten update courses, eleven abstracts in international meetings and ten in national meetings.

COLLABORATIONS:

Since 1998, the research group has developed joint research projects (and derived manuscripts) with the University of Leuven, Belgium (Prof. F. de Zegher), the University of Cambridge, UK (Prof. D.B. Dunger, Dr. K. Ong) and the University of Girona (Dr. A. López-Bermejo).

AWARDS:

- Award of Clinical Researh, Spanish Society for Paediatrc Endocrinology (SEEP)
- Award in the Area of Pediatrics, XIX Convocatòria de la Fundació Agrupació Mútua
- Award Fundació Mar

OTHER (Dr. Lourdes Ibáñez):

- PhD thesis: direction (Míriam Pérez Cruz, 24/03/15), chair of the jury (Inés Osiniri, 15/07/15) and member of the academic committee (UB).
- Chair of Research Group recognised and funded by the Agència de Gestió d'Ajuts Universitaris i de Recerca en Catalunya (2014SGR512)
- Research time (2015) funded by ISCIII-Departament de Salut, Generalitat de Catalunya (INT14/00157).
- Coordination & Direction of the Master in Paediatric & Adolescent Endocrinology and Diabetes (UB).
- Chair: Pediatric & Adolescent Gynecology Working Group, ESPE (www.eurospe.org) & SGA Working Group, SEEP (www.seep.es/privado/ct-publi6.asp).
- National Chair: CADET European project (Children and Adolescent Diabetes and Endocrine Trials Network).

Institution: Fund. para la Investigación y Docencia Sant Joan de Déu · **Contact:** Hospital Sant Joan de Déu
C/ Santa Rosa, 39-57. 08950 Esplugues de Llobregat · Tel.: 93 280 40 00 (ext.4424, 70205)
E.mail: libanez@hsjdbcn.org · Website: http://www.fsjd.org

Islet cell and stem cell physiology

Programme: **P2**

Lead Researcher: **Martín Bermudo, Francisco**

Group members

STAFF MEMBERS: Araujo Legido, Raquel | Cárdenas García, Antonio Manuel | Díaz Contreras, Irene | Hitos Prados, Ana Belén.

ASSOCIATED MEMBERS: Bedoya Bergua, Francisco Javier | Berna Amorós, Genoveva | Cahuana Macedo, Gladys Margot | Carrasco Fernández, Manuel | Ortega de la Torre, María de los Ángeles | Rojas González, Ana Isabel | Soria Escoms, Bernat | Tejedo Huaman, Juan Rigoberto.

Main lines of research

- Role of GATA4 and GATA6 transcription factors to beta cell function and to acinar cell regeneration in cerulein-induced pancreatitis.
- Differentiation towards definitive endoderm (DE) and generation of beta cell-like from embryonic stem cells.
- Use of adult stem cells for pancreatic regeneration.
- Pancreatic acinar differentiation from embryonic stem cells.
- Survival of pancreatic beta cells and the role of nitric oxide.
- Role of nutrients in pathophysiology of Diabetes Mellitus.
- Uses of stem cells in cell therapy treatment of Diabetes Mellitus vascular complications.

Most relevant scientific articles

PEZZOLLA D., LÓPEZ-BEAS J., LACHAUD C.C., DOMÍNGUEZ-RODRÍGUEZ A., SMANI T., HMADCHA A. ET AL. Resveratrol ameliorates the maturation process of β-cell-like cells obtained from an optimized differentiation protocol of human embryonic stem cells. PLoS ONE. 2015;10(3).

SORIA B., GAUTHIER B.R., MARTÍN F., TEJEDO J.R., BEDOYA F.J., ROJAS A. ET AL. Using stem cells to produce insulin. Expert Opinion on Biological Therapy. 2015;15(10):1469-1489.

LORENZO P.I., FUENTE-MARTÍN E., BRUN T., COBO-VUILLEUMIER N., JIMÉNEZ-MORENO C.M., G. HERRERA GÓMEZ I. ET AL. PAX4 defines an expandable β-cell subpopulation in the adult pancreatic islet. Scientific Reports. 2015;5.

ESCOBEDO-COUSIN M., JACKSON N., LAZA-BRIVIESCA R., ARIZA-MCNAUGHTON L., LUEVANO M., DERNIAME S. ET AL. Natural killer cells improve hematopoietic stem cell engraftment by increasing stem cell clonogenicity in vitro and in a humanized mouse model. PLoS ONE. 2015;10(10).

VEGARA-MESEGUER JM, PÉREZ-SÁNCHEZ H, ARAUJO R, MARTÍN F, SORIA B. L-Type Ca2+ Channels and SK Channels in Mouse Embryonic Stem Cells and Their Contribution to Cell Proliferation.The Journal of membrane biology. 2015.

Highlights

PROJECTS:

"Mechanisms of protective action against Metabolic Syndrome and type 2 diabetes of hyperlipidic diets based on extra virgin olive oil". Franz Martín (Ref: AGL2014-54585-R.)

PATENTS:

Inventors: B. Soria, A. Hmadcha, MC Salguero-Aranda, F. Bedoya, JR Tejedo, F. Martín, and R. Tapia. Title: "Method for obtaining pancreatic beta-cell surrogates by increasing pancreatic and duodenal homeobox 1 (PDX1) expression". PCT extension (PCT/EP2015/07051).

Inventors: A. Rojas, D. Cano, I. Delgado, B. Soria and F. Martín. Title: "Methodology to obtain data useful for differential diagnostic of hepatic fibrosis". Extension to UE extension number EP14791963.3. USA extensión number 14/888,197. UAE extensión number 1477/2015. Saudi Arabia extensión number 515370084. Exploitation Vidia Health S.A.

Inventors: B. Soria, A. Hmadcha, JR Tejedo, F. Bedoya. Title: Improved cell culture médium for human progenitor cells. Registration number: EP15382417.2. Registration date: 05-08-2015. Countries: Spain.

AWARDS:

Juan Tejedo was appointed Visiting Professor at the Universidad Nacional Mayor de San Marco and at the Universidad Nacional Toribio Rodríguez de Mendoza de Amazonas, both of them from Peru.

Bernat Soria was appointed "Doctor Honoris Causa" at the Universidad Nacional Mayor de San Marco (Peru). Moreover, he was appointed Fellow of the Royal College of Physicians (London, UK).

RESULTS:

The best outcome of the refined protocols became apparent in the first clinical trial announced by ViaCyte (ViaCyte's VC-01 investigational stem cell-derived islet replacement therapy successfully implanted into first patient). This achievement has been made based on the tremendous progress in generating insulin-producing cells from pluripotent stem cells that include the work of our group (Pezzolla D et al. PloS One 2015) among with those pioneers in the field (Pagliuca FW et al. Cell 2014; and Rezania A et al. Nat. Biotecnol 2014).

Institution: Universidad Pablo de Olavide
Contact: Centro Andaluz de Biología Molecular y Medicina Regenerativa. Avda. Américo Vespucio S/N. 41092 Sevilla · Tel.: 95 597 79 44 · E.mail: fmarber@upo.es · Website: http://www.cabimer.es

Molecular mechanisms of insulin resistance, insulin sensitivity, islet development and diabetic complications

Programme: **P1**

Lead Researcher: **Martínez Valverde, Ángela María**

Group members

STAFF MEMBERS: García Ruiz, Inmaculada | Murillo Gómez, Cayetana | Pardo Marques, Virginia.

ASSOCIATED MEMBERS: Ahmed, Maysha | De Pablo Dávila, Flora | Hernández Sánchez, Catalina | Santamaría Pérez, Beatriz | Villar Lorenzo, Andrea.

Main lines of research

- Molecular mechanisms associated to the progression of non-alcoholic fatty liver disease (NAFLD):

  - Dual role of the protein tyrosine phosphatase 1B (PTP1B) in NAFLD: from intestinal inflammation to hepatic fibrosis.

  - Cross-talk between different liver cells (hepatocytes, Kuffer cells, stellate cells) in the context of NAFLD progression: molecular mechanisms involved.

  - Differential effects of single and dual agonists of glucagon-like peptide-1 receptor (GLP-1R) and glucagon receptor (GCGR) in the treatment of NAFLD at stages of steatohepatitis (NASH).

- Differential therapeutic effects of single and dual agonists of glucagon-like peptide-1 receptor (GLP-1R) and glucagon receptor (GCGR) in the treatment of insulin resistance associated to obesity: effects of these drugs in the brown adipose tissue.

- Effect of low grade chronic inflammation on insulin and catecholamine sensitivity in brown adipocytes: molecular mechanisms involved.

- Role of insulin receptor substrate 2 (IRS2) in the epithelial-mesenchymal transition (EMT) during pre-fibrotic stages in kidney and liver.

- Role of protein tyrosyne phosphatase 1B (PTP1B) in IGF-I and proinsulin-mediated signalling in the retina: possible benefits of PTP1B inhibition in the impairment of survival of photoreceptor cells.

- Study of the polarization of microglia (M1/M2) in diabetic retinopathy (DR): targeting microglia polarization as a therapeutic approach at the early stages of DR.

- Physiological role of proinsulin and the consequences of inappropriately high levels during cardiogenesis.

- Role of atypical catecholaminergic cells in developing mouse pancreas.
- Involvement of Tyrosine Hydroxilase in the metabolic adaptations to diet and temperature stressors.

Most relevant scientific articles

PILAR VALDECANTOS M., PRIETO-HONTORIA P.L., PARDO V., MODOL T., SANTAMARIA B., WEBER M. ET AL. Essential role of Nrf2 in the protective effect of lipoic acid against lipoapoptosis in hepatocytes. Free Radical Biology and Medicine. 2015;84:263-278.

PARDO V., GONZÁLEZ-RODRÍGUEZ A., GUIJAS C., BALSINDE J., VALVERDE A.M.. Opposite cross-talk by oleate and palmitate on insulin signaling in hepatocytes through macrophage activation. Journal of Biological Chemistry. 2015;290(18):11663-11677.

SANTAMARIA B., MARQUEZ E., LAY A., CAREW R.M., GONZÁLEZ-RODRÍGUEZ A., WELSH G.I. ET AL. IRS2 and PTEN are key molecules in controlling insulin sensitivity in podocytes. Biochimica et Biophysica Acta - Molecular Cell Research. 2015;1853(12):3224-3234.

ARROBA A.I., VALVERDE A.M.. Inhibition of protein tyrosine phosphatase 1B improves IGF-I receptor signaling and protects against inflammation-induced gliosis in the retina. Investigative Ophthalmology and Visual Science. 2015;56(13):8031-8044.

GONZÁLEZ-RODRÍGUEZ A., SANTAMARIA B., MAS-GUTIÉRREZ J.A., RADA P., FERNÁNDEZ-MILLAN E., PARDO V. ET AL. Resveratrol treatment restores peripheral insulin sensitivity in diabetic mice in a sirt1-independent manner. Molecular Nutrition and Food Research. 2015;59(8):1431-1442.

Highlights

RESEARCH PROJECTS:

- Inhibition of protein tyrosine phosphatase in the treatment of type 2 diabetes: effects in diabetic complications and cell proliferation (SAF2012-33283, MINECO, Spain).
- Neuroprotection in retinitis pigmentosa based on the modulation of cell death and inflammation (SAF2013-41059R, MINECO, Spain).
- Study of the mechanisms of insulin resistance: implications in obesity, diabetes and metabolic syndrom. S2010/BMD-2423. Consortium MOIR-CM (Comunidad de Madrid, Spain).
- Neurodegeneration as an early event in the Pathogenesis of Diabetic Retinopathy: A multicentric, prospective, phase II-III, double blind randomized controlled trial to assess the efficacy of neuroprotective drugs administered topically to prevent or arrest Diabetic Retinopathy (EUROCONDOR) FP7-HEALTH-2011-two-stage HEALTH.2011.2.4.3.1 (2012-2016).
- Identification of novel modulators of chronic inflammation in prevalent diseases: unveiling divergent mechanisms of disease. INFLAMES. PIE14/00045, Proyecto Integrado de Excelencia, Convocatoria 2014 de la Acción Estratégica en Salud 2013-16, ISCIII.

Institution: Agencia Estatal Consejo Superior de Investigaciones Científicas
Contact: Instituto de Investigaciones Biomédicas Alberto Sols. C/ Arturo Duperier 4. 28029 Madrid
Tel.: 91 585 44 97 · E.mail: avalverde@iib.uam.es · Website: http://www.iib.uam.es; www.cib.csic.es

Lipids and Arteriosclerosis Research Unit

Programme: **P1**

Lead Researcher: **Masana Marín, Luis**

Group members

STAFF MEMBERS: Merino Ribas, Jordi | Rodríguez Calvo, Ricardo | Rosales Ribas, Roser.

ASSOCIATED MEMBERS: Bosquet Agudo, Alba | Fernández Castillejo, Sandra | Ferré Vallès, Raimon | Girona Tell, Josefa | Guaita Esteruelas, Sandra | Guardiola Guionnet, Montserrat | Heras Ibáñez, Mercedes | Ibarretxe Guerediaga, Daiana | Plana Gil, Núria | Ribalta Vives, Josep | Saavedra García, Paula | Solà Alberich, Rosa | Vallvé Torrente, Joan Carles.

Main lines of research

- Atherogenic dyslipidaemia in diabetes, obesity and metabolic syndrome.
- The characterization of plasma lipoprotein subclasses by NMR, metabolomics and lipidomics.
- Adipose tissue dysfunction as a major determinant of AD.
- Fatty Acid-Binding Proteins (FABPs) and insulin resistance in different tissues.
- Fatty acids and adipokine-induced endothelial dysfunction.
- AD and subclinical atherosclerosis.
- FFA, extracellular matrix and artery wall dysfunction in diabetes.
- The epigenetics of atherosclerosis.
- The impact of nutrition on metabolic and cardiovascular risk.
- Nutrigenomics.

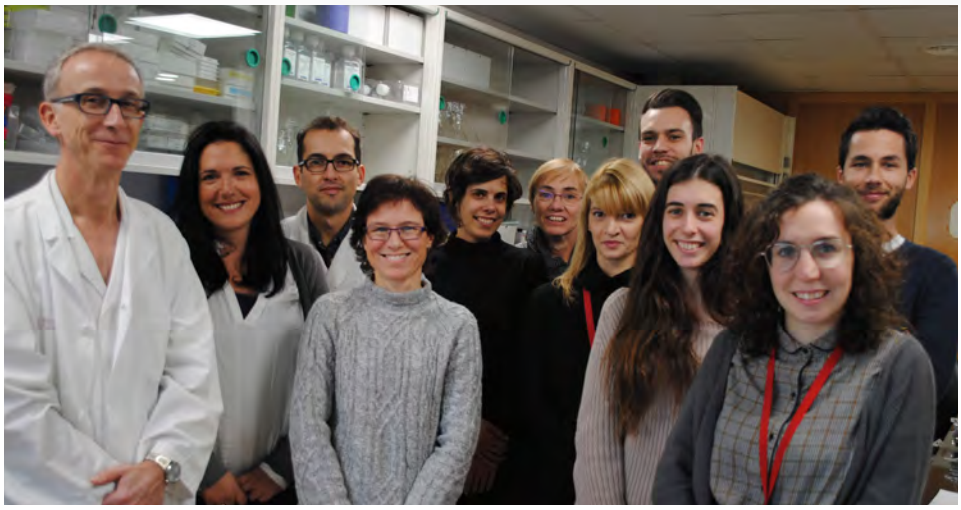
Institution: Fundación Institut d'Investigació Sanitària Pere Virgili · **Contact:** Universitat Rovira i Virgili
C/ Sant Llorenç, 21. Planta baja del edificio 4 de la Facultat de Medicina i Ciències de la Salut. 43201 Reus
E.mail: urla@iispv.cat · Website: http://www.iispv.cat/recerca/arees_de_recerca/15/unitat-de-recerca-en-lipids-i-arteriosclerosi-urla-unitat-vascular-i-del-metabolisme-uvasmet

Group of research into Diabetes and metabolism

Programme: **P2**

Lead Researcher: **Montanya Mias, Eduard**

Group members



STAFF MEMBERS: Estil·les Altamiras, Elisabet | Tellez Besoli, Noelia.

ASSOCIATED MEMBERS: Caballero Corchuelo, Jorge | Gómez Saez, José Manuel | Moreno Amador, José Luis | Nacher García, Montserrat | Pairo Delgado, María del Mar | Pérez Maraver, Manuel | Ramis Juan, Isabel | San José Terron, Patricia | Soler Ramón, Juan | Vilarrasa García, Nuria.

Main lines of research

The group has two main lines of research focused on diabetes and obesity:

- The research on the molecular and cellular biology of pancreatic islets has an essential component of pre-clinical research with a particular emphasis on its translation to the treatment of diabetes. The specific focus of research line on pancreatic islets are the mechanisms of destruction and regeneration of pancreatic beta cells with a particular interest in the cell therapy of diabetes and regenerative medicine. This research includes also some aspects more directly related to beta cell function and chronic complications in diabetic patients.
- The group has also a strong interest in the link between obesity and diabetes, and has focused its efforts in the study of the metabolic and molecular regulation of insulin resistance by adipose tissue, the impact of bariatric surgery glucose metabolism and the metabolic and non-metabolic complications of obesity..

Most relevant scientific articles

ROMAGUERA R., GÓMEZ-HOSPITAL J.A., GÓMEZ-LARA J., BRUGALETTA S., PINAR E., JIMÉNEZ-QUEVEDO P. ET AL. A Randomized Comparison of Reservoir-Based Polymer-Free Amphilimus-Eluting Stents Versus Everolimus-Eluting Stents with Durable Polymer in Patients with Diabetes Mellitus the RESERVOIR Clinical Trial. JACC: Cardiovascular Interventions. 2015;9(1):42-50.

MONTANYA E, FONSECA V, COLAGIURI S, BLONDE L, DONSMARK M, NAUCK MA. HbA1c improvement evaluated by baseline BMI: a meta-analysis of the liraglutide phase 3 clinical trial programme.Diabetes, obesity & metabolism. 2015.

NACHER M, ESTIL LES E, GARCÍA A, NADAL B, PAIRÓ M, GARCÍA C ET AL. Human serum versus human serum albumin supplementation in human islet pretransplantation culture. In vitro and in vivo assessment.Cell transplantation. 2015.

TEICHENNE J, MORRÓ M, CASELLAS A, JIMÉNEZ V, TELLEZ N, LEGER A ET AL. Identification of miRNAs Involved in Reprogramming Acinar Cells into Insulin Producing Cells.PloS one. 2015;10(12):e0145116.

AGUERA Z., GARCÍA-RUIZ-DE-GORDEJUELA A., VILARRASA N., SÁNCHEZ I., BANO M., CAMACHO L. ET AL. Psychological and personality predictors of weight loss and comorbid metabolic changes after bariatric surgery. European Eating Disorders Review. 2015;23(6):509-516.

Highlights

In 2015 we have established that human islets maintain a higher functional capacity and survival in a culture medium supplemented with human serum versus human albumin, which allows improving the prognostic when the islets are transplanted afterwards. We have continued the characterization of different aspects of medical and surgical treatment of diabetic patient, especially with morbid obesity. In a multicenter clinical assay in interventional cardiology, where we have participated as the only expert group in diabetes, we have demonstrated a similar efficacy between two types of stents in patients with diabetes and ischemic cardiopathy. The head of the group participated as Local Organization Committee and chairman of the international meeting at the 4th European Joslin-Sunstar Diabetes Education Iniciative (JSDEI) "Diabetes on Oral Health & Nutrition. Inter-relationships, Innovations & Interaction", sponsored by the Joslin Diabetes Center (Harvard Medical School) and the Sunstar Foundation.

Several investigators of the group are members of boards of different national and international scientific societies, such as the Islet Study Group of the EASD (Dr. Montanya), the Islet Group of the Spanish Diabetes Association (Dra. Téllez) or the Catalan Diabetes Association (Dr. Caballero). Regarding education, we have incorporated a new PhD student through competitive public financing (AGAUR), and two graduate students have completed their master's degree in our group. Regarding outreach, the head of the group is the current President of the Diabetes Advisory Board of Generalitat de Catalunya, and several members have participated on the Catalan autonomic television program, La Marató de TV3, a fundraising initiative for diabetes research. The Senior Basic Research award "Alberto Sols" of the Spanish Diabetes Association was conferred to the head of the group.

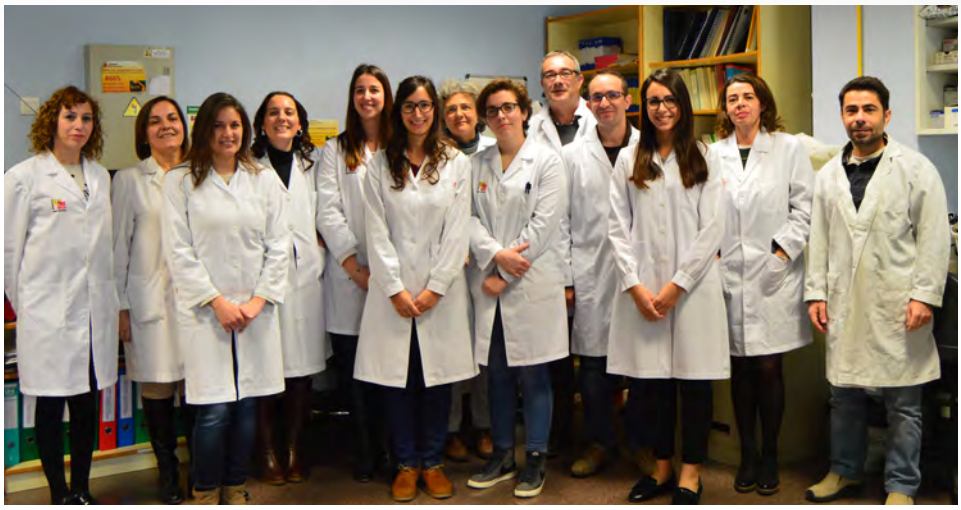
Institution: Fundación IDIBELL · **Contact:** Hospital Universitario de Bellvitge. C/ Freixa Larga s/n
08907 Hospitalet de Llobregat · Tel.: 93 260 25 73 · E.mail: montanya@ub.edu
Website: http://www.idibell.cat

Unit of Cell Physiology and Nutrition IB-UMH

Programme: **P2**

Lead Researcher: **Nadal Navajas, Ángel**

Group members



STAFF MEMBERS: Castellano Muñoz, Manuel | Navarro García, Mª Luisa.

ASSOCIATED MEMBERS: Alonso-Magdalena, Paloma | Arévalo Provencio, Marta | Fuentes Marhuenda, Esther | Irles Vidal, Esperanza | Lluesma Gómez, Mónica | Merino Antolín, Beatriz | Quesada Moll, Iván | Ripoll Orts, Cristina | Villar Pazos, Sabrina.

Main lines of research

- **We study the link between endocrine disruptors and type 2 diabetes.**

  We investigate the actions of oestrogens and environmental oestrogenic pollutants in the function of pancreatic alpha and beta cells with an emphasis on the molecular mechanisms involved.

- **Signal transduction pathways involved in the function and pathology of alpha and beta-cells.**

  Additionally, we investigate the adaptations of islet-cells to obesity and malnutrition states.

Most relevant scientific articles

GORE AC, CHAPPELL VA, FENTON SE, FLAWS JA, NADAL A, PRINS GS ET AL. EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals. Endocrine reviews. 2015;36(6):E1-E150.

VIEIRA E., MERINO B., QUESADA I.. Role of the clock gene Rev-erbα in metabolism and in the endocrine pancreas. Diabetes, Obesity and Metabolism. 2015;17(S1):106-114.

ALONSO-MAGDALENA P., GARCÍA-AREVALO M., QUESADA I., NADAL A.. Bisphenol-A treatment during pregnancy in mice: A new window of susceptibility for the development of diabetes in mothers later in life. Endocrinology. 2015;156(5):1659-1670.

MERINO B., ALONSO-MAGDALENA P., LLUESMA M., NECO P., GONZÁLEZ A., MARROQUI L. ET AL. Pancreatic alpha-cells from female mice undergo morphofunctional changes during compensatory adaptations of the endocrine pancreas to diet-induced obesity. Scientific Reports. 2015;5:-.

IRLES E., NECO P., LLUESMA M., VILLAR-PAZOS S., SANTOS-SILVA J.C., VETTORAZZI J.F. ET AL. Enhanced glucose-induced intracellular signaling promotes insulin hypersecretion: Pancreatic beta-cell functional adaptations in a model of genetic obesity and prediabetes. Molecular and Cellular Endocrinology. 2015;404:46-55.

Highlights

During 2015 we have shown that, at the intial steps of obesity induced by a high-fat diet, the pancreatic alpha cell undergoes several functional and structural changes, leading to hipoglucagonemia which could have a positive influence on the adaptations of the pancreas during obesity to maintain glucose homeostasis and prevent / delay the potential onset of diabetes.

In a second line of research, we have shown that exposure to endocrine disruptors during pregnancy increases the susceptibility of the mother to obesity and diabetes throughout her life. Within this line, we have participated in the preparation of the second official document of the Endocrine Society USA on Endocrine Disruptors (Gore et al, Endocrine Reviews 2015).

Institution: Universidad Miguel Hernández · **Contact:** Instituto de Bioingeniería · Edificio Vinalopo. Avda. De la Universidad S/N. 03202 Elche · Tel.: 96 522 20 02 · E.mail: nadal@umh.es
Website: http://diabetes.umh.es

Metabolic and molecular disturbances in diabetes

Programme: **P2**

Lead Researcher: **Novials Sardá, Anna Maria**

Group members

STAFF MEMBERS: Brugnara, Laura | Castaño Perez, Carlos | Murillo García, Serafín

ASSOCIATED MEMBERS: Alcarraz Vizán, Gema | Cadavez Trigo, Lisa | Ceriello, Antonio | García Rovés González, Pablo Miguel | Montane Mogas, Joel | Moreno Asso, Alba | Parrizas Jiménez, Marcelina | Servitja Duque, Joan Marc | Visa Majoral, Montse.

Main lines of research

- Mechanisms of pancreatic islet dysfunction in type 2 diabetes mellitus, in particular, the process of cytotoxicity as induced by amyloidogenesis.
- Signalling and transcriptional networks in the pancreatic beta cell, mainly related to the modulation of the transcriptional programme under stress conditions.
- Impact of lifestyle on diabetes: metabolic and molecular responses to exercise and nutrition in diabetic patients and animal models.
- Impact of glucose oscillations on cardiovascular complications of diabetes: mechanisms of endothelial dysfunction.

Most relevant scientific articles

PÁRRIZAS M, BRUGNARA L, ESTEBAN Y, GONZÁLEZ-FRANQUESA A, CANIVELL S, MURILLO S ET AL. Circulating miR-192 and miR-193b Are Markers of Prediabetes and Are Modulated by an Exercise Intervention.The Journal of clinical endocrinology and metabolism. 2015;100(3):E407-15.

ALCARRAZ-VIZÁN G, CASINI P, CADAVEZ L, VISA M, MONTANE J, SERVITJA JM ET AL. Inhibition of BACE2 counteracts hIAPP-induced insulin secretory defects in pancreatic β-cells.FASEB journal: official publication of the Federation of American Societies for Experimental Biology. 2015;29(1):95-104.

LA SALA L., PUJADAS G., DE NIGRIS V., CANIVELL S., NOVIALS A., GENOVESE S. ET AL. Oscillating glucose and constant high glucose induce endoglin expression in endothelial cells: the role of oxidative stress. Acta Diabetologica. 2015;52(3):505-512.

BRUGNARA L., MALLOL R., RIBALTA J., VINAIXA M., MURILLO S., CASSERRAS T. ET AL. Improving assessment of lipoprotein profile in type 1 diabetes by 1H NMR spectroscopy. PLoS ONE. 2015;10(8):-.

VISA M., ALCARRAZ-VIZAN G., MONTANE J., CADAVEZ L., CASTANO C., VILLANUEVA-PENACARRILLO M.L. ET AL. Islet amyloid polypeptide exerts a novel autocrine action in b-cell signaling and proliferation. FASEB Journal. 2015;29(7):2970-2979.

Highlights

Among the overall results of our scientific productivity in 2015, we highlight the description of a new mechanism of autocrine action of the pancreatic peptide IAPP on the proliferative capacity of the pancreatic beta-cell. The enzyme BACE2 plays a role in insulin secretory function, and our results point to its potential use as a therapeutic target. The line of research begun the previous year with the analysis of mirRNAs as markers of prediabetes has been fruitful, as we have identified a group of mirRNAs correlated with prediabetes and with fatty liver, both in human and animal models. We also demonstrated with these mirRNAs are modified after implementing an exercise program.

The group remains actively involved in clinical collaborations with European scientific societies. Of particular interest, it published an international consensus document on glycemic index, glycemic load and glycemic response.

Over the past year the group received funding from various sources: Health Research Fund (FIS) grant from the Carlos III Health Institute; Research Group Support (SGR) grant from the Government of Catalonia; an international grant from the European Foundation for the Study of Diabetes (EFSD); and participation in the European project, MEDIGENE (Genetic and environmental factors of insulin resistance syndrome and its long-term complications in immigrant Mediterranean populations). Also, a 3-year collaborative agreement with Grifols company was made to study the potential of one of its pharmaceutical products for treating diabetes.

Of note, 4 doctoral theses were defended in 2015, the results of which have been published during the current year.

Finally, we participated in several social outreach activities focusing on the importance of lifestyle in the control of diabetes, including a lecture during the high-impact, social media event, "Diabetes Experience Day", and the organization of a symposium geared toward young athletes with diabetes.

Institution: Institut d'Investigacions Biomèdiques August Pi i Sunyer · **Contact:** Centro Esther Koplowitz
C/Rosselló, 149. 08036 Barcelona · Tel.: 93 227 54 00 (ext. 4153) · E.mail: anovials@clinic.cat
Website: http://www.diabetes-obesity-research.org

Endocrinology and Nutrition Service

Programme: **P1**

Lead Researcher: **Rojo Martínez, Gemma**

Group members

STAFF MEMBERS: García Escobar, Eva | García Serrano, Sara | Linares Parrado, Francisca.

ASSOCIATED MEMBERS: Almaraz Almaraz, María Cruz | Bermúdez Silva, Francisco Javier | Colomo Rodríguez, Natalia | de Antonio Esteva, Isabel | Gómez Zumaquero, Juan Miguel | González Molero, Immaculada | González Romero, María Stella | Lago Sampedro, Ana María | Monastero, Roberto | Olveira Fuster, Gabriel | Rodríguez Pacheco, Francisca | Rubio Martín, Elehazara | Ruiz de Adana Navas, Soledad | Ruz Maldonado, Inmaculada | Valdés Hernández, Sergio.

Main lines of research

- The biomolecular epidemiology of diabetes, obesity and metabolic syndrome (Pizarra Study, Egabro Study, di@bet .es Study) .
- The study of insulin resistance in patients with extreme obesity undergoing bariatric surgery.
- Fatty acids, insulin resistance and adipocyte metabolism .
- Artificial nutrition and hiperglycaemia.
- New technologies applied to the treatment of type 1 diabetes .
- To study biomarkers in animal models and in vitro to elucidate the mechanisms of disease.

Most relevant scientific articles

MONASTERO R., GARCÍA-SERRANO S., LAGO-SAMPEDRO A., RODRÍGUEZ-PACHECO F., COLOMO N., MORCILLO S. ET AL. Methylation patterns of Vegfb promoter are associated with gene and protein expression levels: the effects of dietary fatty acids. European Journal of Nutrition. 2015;:1-12.

OLVEIRA G., TAPIA M.J., OCON J., CABREJAS-GÓMEZ C., BALLESTEROS-POMAR M.D., VIDAL-CASARIEGO A. ET AL. Prevalence of diabetes, prediabetes, and stress hyperglycemia: Insulin therapy and metabolic control in patients on total parenteral nutrition (prospective multicenter study). Endocrine Practice. 2015;21(1):59-67.

GARCÍA-SERRANO S., GUTIÉRREZ-REPISO C., GONZALO M., GARCÍA-ARNES J., VALDES S., SORIGUER F. ET AL. C-peptide modifies leptin and visfatin secretion in human adipose tissue. Obesity. 2015;23(8):1607-1615.

RUIZ-DE-ADANA M.S., DOMÍNGUEZ-LÓPEZ M.-E., GONZÁLEZ-MOLERO I., SORIGUER F., ANARTE M.T., ROJO-MARTÍNEZ G.. Comparison between a multiple daily insulin injection regimen (basal once-daily glargine plus mealtime lispro) and continuous subcutaneous insulin infusion (lispro) using continuous glucose monitoring in metabolically optimized type 1 diabetes patients: A randomized open-labelled parallel study. Medicina Clinica. 2015.

LAGO-SAMPEDRO A.M., GUTIÉRREZ-REPISO C., VALDES S., MALDONADO C., COLOMO N., ALMARAZ M.C. ET AL. Changes in thyroid function with age: Results from the Pizarra population-based longitudinal study. International Journal of Clinical Practice. 2015;69(5):577-587.

Highlights

DOCTORAL THESIS:

- "ISCI in people with type 1 diabetes. A biopsychosocial experience "(MªSoledad Ruiz de Adana, directed by Gemma Rojo and Federico Soriguer.
- "Impact on the metabolic control and quality of life of the addition of a system of real time continuous glucose monitoring in patients with type 1 DM in intensive treatment with insulin pump. (Marta Dominguez, directed by Stella González).
- "Evaluation of the usefulness of the bolus calculator in patients with type 1 diabetes treated with insulin multidose, in terms of metabolic control and psychological benefits." (Rosario Vallejo, directed by Stella González).

PROJECTS:

The group participates in several collaborative funded projects:

- "Incidence of type 2 diabetes in the di@bet.es study: role of fatty acid transport system regulated by VEGFB in the development of metabolic diseases (PI 14/00710, Rojo Martinez G IP) coordinated with 4 others subprojects, which together have been awarded more than 500000€ to study various biomarkers of risk for diabetes (di@bet.es study).
- "Understanding obesity (Ob), metabolic syndrome (MetS), type 2 diabetes (T2DM) and fatty liver disease (FL): a multidisciplinary approach" (PIE14/00031), excellence integrated project coordinated with other 11 CIBER groups with a budget of 660000€.
- The group currently participates in the DEDIPAC and ENPADASI actions of JPI "A Healthy Diet for a Healthy Life"
- In 2015 it has finished the project "Effects of dietary fatty acids on the expression and epigenetic changes in the fatty acids transport system mediated byVEGFB in rats" (PI12 / 01293, IP Eva Garcia Escobar, employed researcher by CIBERDEM).

Institution: Fundación Pública Andaluza para la Investigación de Málaga en Biomedicina y Salud (FIMABIS)
Contact: Hospital Universitario Carlos Haya · Plaza del Hospital Civil S/N. 29000 Málaga
E.mail: gemma.rojo.m@gmail.com

Diabetobe

Programme: **P1**

Lead Researcher: **Serrano Rios, Manuel**

Group members

STAFF MEMBERS: Pescador Sánchez, Nuria.

ASSOCIATED MEMBERS: Bernat Jiménez, Antonia | Caso Pita, Covadonga | Corbatón Anchuelo, Arturo | Fernández Pérez, Cristina | Fernández Represa, Jesús Álvarez | Martínez Larrad, Mª Teresa | Zabena Carina, Alejandra.

Main lines of research

- A genowide study of the Spanish population. Search for loci for FG, FI, HbA1C and others.
- A genomic, lipidomic and proteomic study of subcutaneous/ abdominal adipose tissue and its relationship to type 2 diabetes and obesity.
- Genes and inflammatory markers in children with obesity and/ or metabolic syndrome.
- Analysis of genetic markers, circulating adipokines and insulin- resistance status in obesity and associated metabolic disorders. Non coding microRNA. Target and Adipogenesis.
- The Segovia Study: a) The molecular and physiological determinants of lifestyle in diabetes/ obesity studies. b) Analysis of genetic-epigenetic association in obesity/type 2 diabetes mellitus. c) Circulating MicroRNA levels in obesity, Type 2 DM and related conditions.

Most relevant scientific articles

AMOR A.J., MASANA L., SORIGUER F., GODAY A., CALLE-PASCUAL A., GAZTAMBIDE S. ET AL. Estimating cardiovascular risk in spain by the European guidelines on cardiovascular disease prevention in clinical practice. Revista Espanola de Cardiologia. 2015;68(5):417-425.

PASTOR P, MORENO F, CLARIMÓN J, RUIZ A, COMBARROS O, CALERO M ET AL. MAPT H1 Haplotype is Associated with Late-Onset Alzheimer's Disease Risk in APOEε4 Noncarriers: Results from the Dementia Genetics Spanish Consortium.Journal of Alzheimer's disease: JAD. 2015;49(2):343-52.

Highlights

Three different studies were conducted:

A. To describe cause-specific morbidity and mortality risk factors in a previously well characterized population. (Segovia Study) after 10 years follow-up.

   • Design: Prospective population-based (10 years) follow-up survey of 900 subjects previously recruited in 2001-2003 in the province of Segovia (Autonomous Community of Castilla y León, Spain). 719 subjects from 12 out of 14 Primary Care centres included in the cross-sectional survey were invited to participate.The health status was checked through medical records. End-point of the study: diagnosis of cardiovascular disease (CVD), neoplasms and/or other major diseases or death.

   • Results: Total mortality: 7,4%. Causes of death: cancer (49%) cardiovascular events (21,6%); 16,1 % of subjects developed cardiovascular event, with stroke as the leading cause (24,8 %). iii) Conclusions: Neoplasia is the main cause of death in middle aged and elderly subjects considered together, followed by CVD. Stroke was the most frequent cardiovascular event.

B. Analysis of specific polymorphisms (SNPs: rs7789066 / rs11977021 / rs4730153) visfatin gene and its influence on cardiovascular risk in obesity and impaired glucose tolerance, as well as its relation to insulin sensitivity.

   Conclusion: For the first time we showed that genotype adenine-adenine (AA) of the SNP rs4730153 appears to be protects from cardiovascular disease (Framingham and SCORE criteria) in subjects with / without obesity.

C. Currently developing Project: to investigate the potential association of circulating levels of Retinol Binding Protein 4 (RBP4) with insulin sensitivity tissue estimated by different indexes (HOMA-IR, Stumvoll, Matsuda).

Institution: Servicio Madrileño de Salud · **Contact:** Hospital Clínico San Carlos. Avda. Complutense S/N 28040 Madrid · Tel.: 91 330 33 88 · E.mail: mserrano.hcsc@salud.madrid.org

Diabetes and Metabolism Research Group

Programme: **P1**

Lead Researcher: **Simó Canonge, Rafael**

Group members

STAFF MEMBERS: Bogdanov, Patricia Mónica | Corraliza Márquez, Lidia | García Ramírez, Marta | Ramos Pérez, Lorena.

ASSOCIATED MEMBERS: Ciudín, Andreea | Enquix Elena, Natalia | Hernández Pascual, Cristina | Lecube Torello, Albert | Martínez Selva, David | Mesa Manteca, Jorge | Sáez López, Cristina | Sola Adell, Cristina | Villena Delgado, Josep Antoni.

Main lines of research

1. Physiopathology of diabetic retinopathy : The main aim of this line of research is to identify new targets for the treatment of diabetic retinopathy (DR). In this regard it should be noted that we are co-ordinating the first clinical trial aimed at testing the effectiveness and safety of neuroprotective agents for the treatment of DR (EudraCT -2012-001200-38). This project has been funded by EC (EURO-CONDOR-HEALTH-2011- FP7-278040). In addition, is also noteworthy that we are partners of the project "Early Prevention of Diabetes Complications in people with hyperglycaemia in Europe" (e-PREDICE. FP7-279074) in which we are the responsible for measuring the biomarkers of DR.

2. Insulin resistance and obesity: new pathogenic candidates and the study of co-morbidities. The main objective is to investigate the pathogenic mechanisms of obesity and its co-morbidities and to find out new therapeutic targets. As a result of our recent findings we are giving priority to the role of sex hormone binding globulin (SHBG) and mitochondrial dysfunction in the pathogenesis of obesity, insulin-resistance and type 2 diabetes.

3. Endothelial dysfunction, dyslipideamia and cardiovascular disease in type 2 diabetes.: We are exploring non-classic cardiovascular risk factors. In this setting is worth mentioning our key participation in the project "Preventing cardiovascular ischemic events and arresting their consequences in type 2 diabetic population: a multidisciplinary clinical and experimental approach", which has been funded by the *Ministerio de Economía y Competitividad*.

4. Diabetes as a metabolic accelerator of Alzheimer's disease.: In this regard it should be noted that

we are developing the project "Retinal Neurodegeneration in Type 2 diabetes as biomarker for Alzheimer´s disease" funded by European Foundation for the Study of Diabetes (EFSD).

Most relevant scientific articles

SIMO R., SAEZ-LÓPEZ C., BARBOSA-DESONGLES A., HERNÁNDEZ C., SELVA D.M.. Novel insights in SHBG regulation and clinical implications. Trends in Endocrinology and Metabolism. 2015;26(7):376-383.

SIMO R., HERNÁNDEZ C.. Novel approaches for treating diabetic retinopathy based on recent pathogenic evidence. Progress in Retinal and Eye Research. 2015;48:160-180.

SAEZ-LÓPEZ C., RIVERA-GIMÉNEZ M., HERNÁNDEZ C., SIMO R., SELVA D.M.. SHBG-C57BL/ksJ-db/db: A new mouse model to study SHBG expression and regulation during obesity development. Endocrinology. 2015;156(12):4571-4581.

ZAMORA M., PARDO R., VILLENA J.A.. Pharmacological induction of mitochondrial biogenesis as a therapeutic strategy for the treatment of type 2 diabetes. Biochemical Pharmacology. 2015;98(1):16-28.

LECUBE A., SAMPOL G., HERNÁNDEZ C., ROMERO O., CIUDIN A., SIMO R.. Characterization of sleep breathing pattern in patients with type 2 diabetes: Sweet sleep study. PLoS ONE. 2015;10(3).

Highlights

The outstanding advances for research lines are the follows:

Pathophysiology of diabetic retinopathy (DR): We have characterized retinal neurodegeneration in db/db mice and we have found that this model reproduces the morphological and functional events that occur in the human diabetic eye. Therefore, the db/db mouse is very useful to gain new insights into the mechanisms that lead to the neurodegeneration of the retina induced by diabetes and to test neuroprotective agents for DR (Projects PI13/00603; FP7-278040; SAF2012-35562). Among the drugs tested, it should be noted the efficacy observed with GLP-1 administered in eye drops to prevent neurodegeneration and early microvascular damage in db/db mice. We are conducting the preclinical studies required for assessing GLP-1 use in humans (Project DTS15/00151). Our main objective is to use the knowhow and international leadership of the group in this field to be pioneers in the development of topical treatments and new drug formulations for early stages of RD.

Patents generated and managed in 2015 directly related to this topic:

- PCT/ES/2015/070415.
- PCT/EP2014/053787 and PCT/EP2013/058836 (2015: national phase entry).

Obesity, insulin resistance and comorbidities: Notably, within the study of new candidates involved in obsesity and potential therapeutic targets, we have shown that SHBG has lipolytic properties, and particularly in the liver (Project PI12/01357; PI15/00823).

Patent: PCT/EP2014/061218 (2015: national phase entry).

Cardiovascular disease in type 2 diabetes: We are defining a new cardiovascular risk score in type 2 diabetic population with special emphasis in the role of microangiopathy (PIE13/00027).

Diabetes as a risk factor for Alzheimer's disease (AD): We evaluated the usefulness of the study of neurodegeneration of the retina as a predictor of risk of developing AD (EFSD / Lilly-Mental Health and Diabetes Project Programme). We also investigated the common pathogenic mechanisms between diabetes and AD (Project PIE14/0061) and how we can to proceed for the early identification of prodromic AD in type 2 diabetic population (MOPEAD-IMI2-Horizon 2020).

Institution: Fundación Hospital Universitario Vall d'Hebron - Institut de Recerca (VHIR)
Contact: Hospital Vall d'Hebron. Passeig Vall d'Hebron, 119-129. 08035 Barcelona · Tel.: 93 489 41 72
E.mail: rafael.simo@vhir.org · Website: http://www.vhir.org

Transcriptional mechanisms of pancreatic function

Programme: P2

Lead Researcher: Vallejo Fernández de la Reguera, Mario

Group members

STAFF MEMBERS: Fernández Pérez, Antonio | Mirasierra Cuevas, Mercedes.

Main lines of research

- The characterization of phenotypic alterations of pancreatic islets in the absence of the homeoprotein Alx3.
- The requirement of Alx3 for the maintenance of glucose homeostasis and metabolic activity in vivo.
- The identification of transcriptional targets regulated by Alx3.
- Alx3 and diabetic pregnancy: the role of Alx3 in the regulation of the development of the neural tube and vulnerability to hyperglycaemic insult in its absence.

Most relevant scientific articles

RUIZ-DEDIEGO I., MELLSTROM B., VALLEJO M., NARANJO J.R., MORATALLA R.. Activation of DREAM (Downstream Regulatory Element Antagonistic Modulator), a calcium-binding protein, reduces L-DOPA-induced dyskinesias in mice. Biological Psychiatry. 2015;77(2):95-105.

Highlights

During 2015 we characterized in detail a molecular mechanism by which glucagon gene expression is suppressed in response to increases in blood glucose levels, thereby contributing to the maintenance of glucose homeostasis. The relevance of this finding lies in the recent recognition of the existence of abnormally high levels of glucagon in the blood of diabetic patients, even in conditions of hyperglycemia. Therefore a defect in these mechanisms, in which transcription factors Pax6 and Alx3 are involved, could contribute significantly to the pathogenesis of this disease (Mirasierra and Vallejo, Diabetologia, DOI 10.1007 / s00125-015-3849-4)

Our group oversees the management of the Indirect Calorimetry and Energy Metabolism Unit (UCIME), which provides the use of a Phenomaster system (TSE Systems) as a technology platform provided by CIBERDEM for evaluating energy metabolism in rodents.

Project granted: Transcriptional control of metabolic homeostasis at a multiorganic level by the homeodomain transcription factor Alx3. Ministerio de Economía y Competitividad, BFU2014-52149-R. Duration, 2015-2017.

Institution: Agencia Estatal Consejo Superior de Investigaciones Científicas
Contact: Instituto de Investigaciones Biomédicas Alberto Sols · C/ Arturo Duperier 4. 28029 Madrid
Tel.: 91 585 44 80 · E.mail: mvallejo@iib.uam.es
Website: http://www.iib.uam.es/portal/web/guest/investigacion/grupos

Pharmacological targets in inflammation and metabolic diseases

Programme: **P3**

Lead Researcher: **Vázquez Carrera, Manuel**

Group members

STAFF MEMBERS: Barroso Fernández, Emma de Juan | Montori Grau, Marta | Peña Moreno, María Lucía | Pizarro Delgado, Javier.

ASSOCIATED MEMBERS: Botteri, Gaia | Salvado Serra, Laia.

Main lines of research

Our main research topic is the study of the molecular mechanisms involved in the link between inflammation and insulin resistance. Specifically, we are interested in:

- Evaluating the molecular mechanisms by which PPAR agonists prevent inflammation and insulin resistance.
- Studying the molecular mechanisms responsible for metabolic alterations in diabetic cardiomyopathy.
- Studying how oleic acid prevents saturated fatty acid-induced insulin resistance.
- Assessing the links between insulin resistance and Alzheimer's disease.

Most relevant scientific articles

SALVADO L., PALOMER X., BARROSO E., VAZQUEZ-CARRERA M.. Targeting endoplasmic reticulum stress in insulin resistance. Trends in Endocrinology and Metabolism. 2015;26(8):438-448.

PALOMER X., CAPDEVILA-BUSQUETS E., BOTTERI G., DAVIDSON M.M., RODRÍGUEZ C., MARTÍNEZ-GONZÁLEZ J. ET AL. MiR-146a targets Fos expression in human cardiac cells. DMM Disease Models and Mechanisms. 2015;8(9):1081-1091.

BARROSO E., RODRÍGUEZ-RODRÍGUEZ R., CHACON M.R., MAYMO-MASIP E., FERRER L., SALVADO L. ET AL. PPARβ/δ ameliorates fructose-induced insulin resistance in adipocytes by preventing Nrf2 activation. Biochimica et Biophysica Acta - Molecular Basis of Disease. 2015;1852(5):1049-1058.

CHEHAIBI K, CEDÓ L, METSO J, PALOMER X, SANTOS D, QUESADA H ET AL. PPAR-β/δ activation promotes phospholipid transfer protein expression.Biochemical pharmacology. 2015;94(2):101-8.

PETROV D., PEDROS I., ARTIACH G., SUREDA F.X., BARROSO E., PALLAS M. ET AL. High-fat diet-induced deregulation of hippocampal insulin signaling and mitochondrial homeostasis deficiences contribute to Alzheimer disease pathology in rodents. Biochimica et Biophysica Acta - Molecular Basis of Disease. 2015;1852(9):1687-1699.

Highlights

RESULTS:

- Adipose tissue macrophage infiltration and inflammation as well as glucose intolerance are aggravated in fructose-fed PPARb/d-null mice via nuclear factor E2-related factor 2 (Nrf2).
- miR-146a might be a new and promising therapeutic tool for treating cardiac disorders associated with enhanced inflammation in the heart.
- PPAR-ß/d activation may modulate phospholipid transfer protein-mediated preß-HDL formation and macrophage cholesterol efflux.

DOCTORAL THESIS:

- Title: Adamentane-like scaffolds for a wide range of therapeutic targets. PhD candidate: Elena Valverde Murillo. Supervisors: Santiago Vázquez Cruz and Manuel Vázquez Carrera.
- Title: Curta administração de GW501516 melhora o estado inflamatório do tecido adiposo branco, o dano hepático e a inflamação renal de camundongos alimentados com dieta rica em frutose. PhD candidate: D'Angelo Carlo Magliano. Directores: Márcia Barbosa Águila, Mandarim de Lacerda and Manuel Vázquez-Carrera.

RESEARCH PROJECTS:

- Title: Cardiomiopatía diabética: a la búsqueda de una nueva diana terapéutica. La Marató de TV3. Ref. 201542.
- Title: Medicamentos para trastornos inflamatorios y cardiovasculares. CaixaImpulse.

PATENT.

Inventors: Santiago Vázquez Cruz, Elena Valverde Murillo and Manuel Vázquez Carrera. Title: Analogs of adamantylureas as soluble epoxide hydrolase inhibitors. Number: P3392EP00.

Institution: Universitat de Barcelona · **Contact:** Facultad de Farmacia.
Diagonal, 645. 08028 Barcelona · Tel.: 93 402 45 31 · E.mail: mvazquezcarrera@ub.edu
Website: http://www.ciberdem.org/grupo.php?id=29

Diabetes and Metabolic Associated Diseases Research Group

Programme: **P3**

Lead Researcher: **Vendrell Ortega, Joan Josep**

Group members

STAFF MEMBERS: Duran Sanmartí, Francesc Xavier | Keiran Fernández, Noelia | Maymó Masip, Elsa | Miranda Guardiola, Mercedes.

ASSOCIATED MEMBERS: Cerperuelo Mallafre, María Victoria | Ejarque Carbó, Miriam | Escoté Miró, Xavier | Fernández Veledo, Sonia | Gallart Millán, Lluís | Gutiérrez Fornés, Cristina | Llauradó Cabot, Gemma | Megia Colet, Anna | Näf Cortés, Silvia | Pachón Peña, Olga Gisela | Roche, Kelly | Rodríguez Chacón, Matilde | Serena Perelló, Carolina | Simón Muela, Inmaculada | Solano Fraile, Esther | Yáñez García, Rosa Elena.

Main lines of research

- Adipose tissue plasticity.
- Metabolic dysfunction as a trigger of adipose tissue derangement in obesity and type 2 diabetes mellitus.
- Inflammatory mechanisms in the context of obesity and insulin resistance.
- Metabolic derangement in the context of Gestational Diabetes (GD).
- Fat as a sensor of a worst inflammatory environment.
- Biomarkers of precocious atherosclerotic risk in type 1 Diabetes.

Most relevant scientific articles

LLAURADO G., SEVASTIANOVA K., SADEVIRTA S., HAKKARAINEN A., LUNDBOM N., ORHO-MELANDER M. ET AL. Liver fat content and hepatic insulin sensitivity in overweight patients with type 1 diabetes. Journal of Clinical Endocrinology and Metabolism. 2015;100(2):607-616.

CHENG Y.-S., SEIBERT O., KLOTING N., DIETRICH A., STRASSBURGER K., FERNÁNDEZ-VELEDO S. ET AL. PPP2R5C Couples Hepatic Glucose and Lipid Homeostasis. PLoS Genetics. 2015;11(10):-.

MORENO-NAVARRETE J.M., ESCOTE X., ORTEGA F., CAMPS M., RICART W., ZORZANO A. ET AL. Lipopolysaccharide binding protein is an adipokine involved in the resilience of the mouse adipocyte to inflammation. Diabetologia. 2015;58(10):2424-2434.

PERAIRE J., LÓPEZ-DUPLA M., ALBA V., BELTRAN-DEBON R., MARTÍNEZ E., DOMINGO P. ET AL. HIV/antiretroviral therapy-related lipodystrophy syndrome (HALS) is associated with higher RBP4 and lower omentin in plasma. Clinical Microbiology and Infection. 2015;21(7):711.e1-711.e8.

FADINI G.P., BONORA B.M., MARCUZZO G., MARESCOTTI M.C., CAPPELLARI R., PANTANO G. ET AL. Circulating stem cells associate with adiposity and future metabolic deterioration in healthy subjects. Journal of Clinical Endocrinology and Metabolism. 2015;100(12):4570-4578.

Highlights

RESEARCH PROJECTS

- Title: Central effects of GLP2-R activation: insights into a potential brain-gut-adipose tissue cross-talk. (European Foundation for the Study of Diabetes. 2015-2016). Principal Investigator: Dra. Sonia Fernández-Veledo
- Title: Estudio del efecto de las incretinas sobre la microbiota, la metainflamación y la plasticidad del tejido adiposo. Análisis prospectivo en una cohorte de sujetos obesos tras intervención dietética (PI14/00228). (ISCIII - 2015-2017). Principal Investigator: Dr. Joan Vendrell. Coordinated Project. Coordinator: Dr. Joan Vendrell
- Title: Identificación y caracterización de los microRNAs regulados por sTWEAK en el adipocito y su papel en la respuesta inflamatoria asociada a la Resistencia a la Insulina. Análisis de su utilidad (PI14/00465). (ISCIII. 2015-2017). Principal Investigator: Dra. Matilde Rodríguez
- Title: Identification of novel modulators of chronic inflammation in prevalent diseases: unveiling divergent mechanisms of disease (INFLAMES) (PIE14/00045). (ISCIII. 2015-2017). Principal Investigator: Dr. Joan Vendrell
- Title: Estudio de la expresión de miRNAs plasmáticos en la Diabetes Mellitus Gestacional (DMG). Análisis prospectivo gestacional y a los 4 años post-parto (PI13/000152). (ISCIII. 2014-2016). Principal Investigator: Dra. Inmaculada Simón
- Title: Función del metabolismo del glucógeno en el tejido adiposo: investigación translacional para la búsqueda de nuevas dianas terapéuticas en el tratamiento de la obesidad (SAF2012-36186). (ISCIII. 2013-2015). Principal Investigator: Dra. Sonia Fernández-Veledo
- Title: Papel de las metilaciones del ADN en la en la diabetes gestacional como predictor de alteraciones en el metabolismo hidrocarbonado post-parto (PI12/00717). (ISCIII. 2013-2015). Principal Investigator: Dra. Ana Megia

Institution: Fundación Institut d'Investigació Sanitària Pere Virgili · **Contact:** Hospital Universitario Juan XXIII
C/ Mallafre Guasch, 4. 43007 Tarragona · E.mail: diamet@iispv.cat · Website: http://www.diamet.org

Complex Metabolic diseases and Mitochondria

Programme: **P3**

Lead Researcher: **Zorzano Olarte, Antonio**

Group members

STAFF MEMBERS: Muñoz Neculman, Juan Pablo | Romero de Pablos, Montserrat | Saska, Ivanova | Sebastián Muñoz, David.

ASSOCIATED MEMBERS: Camprubí, Marta Camps | Castrillon Rodríguez, Ignacio | Díaz Ramos, Mª Àngels | Enciso Salas, Hilda Yuliana | Guma García, Ana Mª | Hernández Álvarez, María Isabel | Martínez Cristobal, Paula | Rodríguez Nuevo, Aida | Sabaté Pérez, Alba | Sánchez Feutrie, Manuela | Testar Ymbert, Xavier.

Main lines of research

The aim of our laboratory is to identify the mechanisms by which mitochondrial dysfunction is involved in the development of complex metabolic diseases such as obesity, insulin resistance or type 2 diabetes. In addition, our focus is the study of the processes that lead to mitochondrial dysfunction, as well as identifying new drugs targets in diabetes therapy. Our main lines of research are:

- Analysis of the role of proteins involved in mitochondrial dynamics on the development of metabolic diseases;
- Role of the interaction between autophagy, mitochondrial function and energy metabolism;
- Identification of new therapeutic targets, and development of new compounds for the treatment of metabolic diseases.

Most relevant scientific articles

ZORZANO A., HERNÁNDEZ-ÁLVAREZ M.I., SEBASTIÁN D., MUNOZ J.P.. Mitofusin 2 as a Driver That Controls Energy Metabolism and Insulin Signaling. Antioxidants and Redox Signaling. 2015;22(12):1020-1031.

SCHNEEBERGER M., GÓMEZ-VALADES A.G., ALTIRRIBA J., SEBASTIÁN D., RAMIREZ S., GARCÍA A. ET AL. Reduced α-MSH Underlies Hypothalamic ER-Stress-Induced Hepatic Gluconeogenesis. Cell Reports. 2015;12(3):361-370.

MORENO-NAVARRETE J.M., ESCOTE X., ORTEGA F., CAMPS M., RICART W., ZORZANO A. ET AL. Lipopolysaccharide binding protein is an adipokine involved in the resilience of the mouse adipocyte to inflammation. Diabetologia. 2015;58(10):2424-2434.

CHENG Y.-S., SEIBERT O., KLOTING N., DIETRICH A., STRASSBURGER K., FERNÁNDEZ-VELEDO S. ET AL. PPP2R5C Couples Hepatic Glucose and Lipid Homeostasis. PLoS Genetics. 2015;11(10).

ZAMUDIO-VAZQUEZ R., IVANOVA S., MORENO M., HERNÁNDEZ-ÁLVAREZ M.I., GIRALT E., BIDON-CHANAL A. ET AL. A new quinoxaline-containing peptide induces apoptosis in cancer cells by autophagy modulation. Chemical Science. 2015;6(8):4537-4549.

Highlights

During the year 2015 our group has been deeply involved in the implementation and coordination of the ISCIII-funded program project INFLAMES, constituted by 12 research teams belonging to four different areas of CIBER. The overall objective of this study is to identify the mechanistic basis for the distinct inflammatory profile in obese/type 2 diabetes and Crohn's disease patients, and to obtain proof of concept to enable novel therapeutic approaches. Our laboratory has been operating in 2015 thanks to to funds obtained from MINECO, ISCIII, FP7 (EU) and the Generalitat de Catalunya.

During 2015 we have published results indicating the regulatory role of the Mitofusin-2 protein in the insulin signaling in muscle and liver, promoting it as a therapeutic target in the treatment of type 2 diabetes. We have also reported a new mechanism controlling muscle mass in type 2 diabetic patients based on the activity of a regulatory autophagy protein in the muscle fiber. It is also noteworthy the demonstration we have obtained that the neuregulin protein exerts antidiabetic effects that improve glucose tolerance in an animal model of type 2 diabetes (diabetic ZDF rats).

In collaboration with Prof. Fernando Albericio (member of the CIBER-BBN), we have demonstrated the apoptotic activity of peptides containing quinoxaline, because of their inhibitory properties of autophagy. These results clarify the role of autophagy in cells and allow us to visualize some of the potential applications of its modulation.

As a result of our research activity, we have been invited to participate in five international Conferences / Symposia in 2015 allowing us a relevant visualization (The International Liver Congress 2015; Oxygen Club of California World Congress 2015; Symposium Diabetes & Exercise, EMBO Workshop on Mitochondrial DNA and neurodegeneration; Anger's Symposium on Mitochondrial Medicine).

Institution: Fundació Privada Institut de Recerca Biomèdica IRB · **Contact:** IRB-Barcelona
C/ Baldiri Reixac 10-12. 08028 Barcelona · Tel.: 93 403 71 97 · E.mail: antonio.zorzano@irbbarcelona.org
Web: http://www.irbbarcelona.org/index.php/es/research/programmes/molecular-medicine/molecular-pathology-and-therapy-in-heterogenic-and-polygenic-diseases

ciberdem

Centro de Investigación Biomédica en Red

Diabetes y Enfermedades Metabólicas Asociadas

MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD

Instituto de Salud Carlos III

Unión Europea

Fondo Europeo
de Desarrollo Regional
"Una manera de hacer Europa"

ciber

Centro de Investigación Biomédica en Red (CIBER)
Instituto de Salud Carlos III
C/ Monforte de Lemos 3-5. Pabellón 11
28029 Madrid
www.ciberisciii.es