Annual Report 2013

ciberdem

Centro de Investigación Biomédica en Red de
Diabetes y Enfermedades Metabólicas Asociadas

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Organization

Introduction

The Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM) is a public research consortium which was founded on December 3, 2007 under the funding of the Instituto de Salud Carlos III (ISCIII) and the Ministry of Economy and Competitiveness.

CIBERDEM is made up of 31 research groups of reference based in different hospitals, universities and research centres throughout Spain (the merger of two groups in 2013 reduced the number of groups to 30). The consortium is also formed by 19 other consortium institutions from 6 Autonomous Communities.

CIBERDEM's primary objective is to promote research on diabetes and associated metabolic disorders by identifying the genes making one more inclined to suffer said diseases and disorders and the environmental factors contributing to their development, to clarify the molecular mechanisms involved in the impairment of insulin secretion and signaling; to determine the molecular and cellular mechanisms of pancreatic beta cell formation and destruction; to study strategies for replacing said cell mass; and to conduct research on the signals linking obesity and diabetes. Research on the complications of diabetes and associated metabolic disorders is also of special interest.

To meet its objectives, CIBERDEM seeks to generate an attractive framework for the incorporation of basic and clinical research staff, as well as the development of biomedical platforms suitable for conducting research of excellence in diabetes and associated metabolic disorders. In turn, CIBERDEM promotes translational research, favoring the transfer of acquired diabetes knowledge to other disciplines, and vice versa.

CIBERDEM's mission is to lead the research effort of excellence in diabetes and associated metabolic disorders, and to speed up the translation of scientific results to clinical practice.

CIBERDEM conducted research activities relating to the following fields:

- Type 1 Diabetes Mellitus. Autoimmunity.
- Type 2 Diabetes Mellitus. Insulin signaling and resistance.
- Genetics of Diabetes Mellitus.
- Diabetes Mellitus. Microvascular complications.
- Dyslipidemia, inflammation and endothelial dysfunction.
- Pancreatic islet dysfunction, destruction and regeneration.
- Diabetes and Obesity. Biological interferences between tissues.

- Diabetes and associated metabolic disorders. Glucotoxicity and lipotoxicity.
- Metabolic syndrome. Physiopathology and epidemiology.

CIBERDEM enmarca su investigación en cuatro programas científicos:

P1

Molecular and physiological determinants of lifestyle in diabetes and obesity. Population studies for genetic-epigenetic association analysis in type 2 diabetes mellitus and related factors.

P2

Mechanisms promoting the development of diabetes and its vascular complications. Associated co-morbidities. Strategies for prevention and treatment.

P3

Impact of beta cell dysfunction and plasticity on diabetes. Development of new treatment strategies.

P4

Use of biomedical approach systems to develop personalized therapies for diabetes.

CIBERDEM's strategic lines of research are grouped into four categories:

- **Transverse research projects**
- **Technological platforms**, such as CIBERDEM Biobank and Metabolomics Platform.
- **Research support activities**, among which the "special actions", aid packages so that CIBERDEM groups can have access to cutting-edge technological services stand out.
- **Training plan**, such as organizing courses for CIBERDEM research community (pre-doctoral, etc.).

CIBERDEM's nature, purposes and operation are described in its By-laws published in the Boletín Oficial del Estado (BOE) (Official State Journal) no. 42, February 18, 2011.

List of groups and institutions

List of research groups and consortium institutions

NO.	PI NAME	GROUP CODE	CONSORTIUM INSTITUTION	AUTO. COMM.
01	Álvarez Escola, Carmen	CB07/08/0013	Universidad Complutense de Madrid	Madrid
02	Balsinde Rodríguez, Jesús	CB07/08/0004	Consejo Superior de Investigaciones Científicas	Castile and Leon
03	Benito de las Heras, Manuel R.	CB07/08/0001	Universidad Complutense de Madrid	Madrid
04	Blanco Vaca, Francisco	CB07/08/0016	Instituto de Investigación del Hospital de la Santa Cruz y San Pablo	Catalonia
05	Blázquez Fernández, Enrique	CB07/08/0010	Universidad Complutense de Madrid	Madrid
06	Bosh Tubert, Fátima	CB07/08/0037	Universidad Autónoma de Barcelona	Catalonia
07	Burks, Deborah	CB07/08/0043	Fundación Centro de Investigación Príncipe Felipe	Comm. of Valencia
08	Carmena Rodríguez, Rafael	CB07/08/0018	Fundacion Hospital Clínico Universitario de Valencia	Comm. of Valencia
09	Casimiro-Soriguer Escofet, Federico José	CB07/08/0019	Fundación Instituto Mediterráneo para el Avance de la Biotecnología Sanitaria	Andalusia
10	Castaño González, Luis	CB07/08/0025	Fundación Vasca de Innovación e Investigación Sanitarias	Basque Country
11	Correig Blanchar, Francesc Xavier	CB07/08/0014	Fundación Institut d'Investigació Sanitària Pere Virgili	Catalonia
12	Novials Sardà, Anna Maria	CBO7/08/2005	Instituto de Investigaciones Biomédicas August Pi i Sunyer	Catalonia
13	Escobar Morreale, Hector Francisco	CB07/08/0005	Servicio Madrileño de Salud	Madrid
14	Ferrer Marrades, Jorge	CB07/08/0021	Instituto de Investigaciones Biomédicas August Pi i Sunyer	Catalonia
15	Gómez Foix, Ana Maria	CB07/08/0011	Universitat de Barcelona	Catalonia
16	Gomis De Barbara, Ramon	CB07/08/0009	Instituto de Investigaciones Biomédicas August Pi i Sunyer	Catalonia
17	Guinovart Cirera, Joan Josep	CB07/08/0045	Fundació Privada Institut de Recerca Biomedica (IRB)	Catalonia
18	De Pablo Dávila, Flora *	CB07/08/0036	Consejo Superior de Investigaciones Científicas	Madrid
19	Ibáñez Toda, Lourdes	CB07/08/0044	Fundacion para la Investigación y Docencia Sant Joan de Deu	Catalonia
21	Martín Bermudo, Francisco	CB07/08/0006	Universidad Pablo de Olavide	Andalusia
22	Martínez Valverde, Angela Maria *	CB07/08/0033	Consejo Superior de Investigaciones Científicas	Madrid

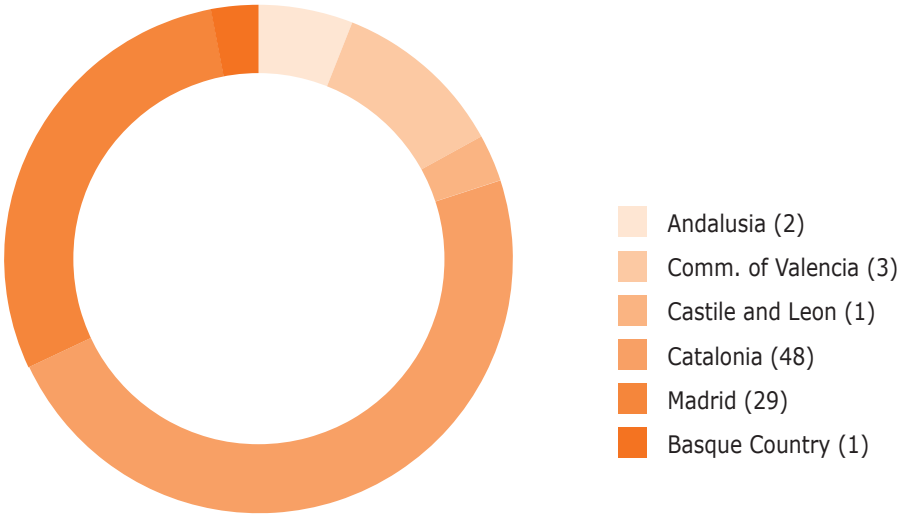
23	Masana Marín, Luis	CB07/08/0028	Fundación Institut d'Investigació Sanitària Pere Virgili	Catalonia
24	Montanya Mias, Eduard	CB07/08/0022	Fundación IDIBELL	Catalonia
25	Nadal Navajas, Ángel	CB07/08/0002	Universidad Miguel Hernández	Comm. of Valencia
26	Serrano Ríos, Manuel	CB07/08/0030	Servicio Madrileño de Salud	Madrid
27	Simo Canonge, Rafael	CB07/08/0024	Fundación Instituto de Investigación Valle de Ebron	Catalonia
28	Vallejo Fernández de la Reguera, Mario	CB07/08/0029	Consejo Superior de Investigaciones Científicas	Madrid
29	Vázquez Carrera, Manuel	CB07/08/0003	Universitat de Barcelona	Catalonia
30	Vendrell Ortega, Joan Josep	CB07/08/0012	Fundación Institut d'Investigació Sanitària Pere Virgili	Catalonia
31	Zorzano Olarte, Antonio	CB07/08/0017	Fundació Privada Institut de Recerca Biomèdica (IRB)	Catalonia
32	Villanueva-Peñacarrillo, María Luisa / Jesús Egido **	CB07/08/2007	Instituto de Investigación Sanitaria Fundación Jiménez Díaz	Madrid

Notes:

** Group 18 (CB07/08/0036), PI: Flora de Pablo, and Group 22 (CB07/08/0033), PI: Angela Martínez Valverde, merged in 2013.*

*** Group 32 (CB07/08/2007) PI changed to J Egido. Group CB07/08/0007 was dissolved in January 2011 so it is not indicated in the table.*

Territorial distribution of the research groups



CONSORTIUM INSTITUTIONS
1. Consejo Superior de Investigaciones Científicas (CSIC)
2. Universidad Pablo Olavide (UPO)
3. Fundación IDIBELL
4. Fundación Instituto de Investigación Valle de Hebrón
5. Fundación Instituto de Investigación Sanitaria Pere Virgili
6. Universidad de Barcelona (UB)
7. Universidad Autónoma de Barcelona (UAB)
8. Fundación Centro de Investigación Príncipe Felipe (CIPF)
9. Fundación Hospital Clínico Universitario de Valencia
10. Universidad Miguel Hernández (UMH)
11. Servicio Madrileño de Salud
12. Universidad Complutense de Madrid (UCM)
13. Fundación Vasca de Innovación e Investigación Sanitaria
14. Instituto de Investigaciones Biomédicas August Pi i Sunyer (IDIBAPS)
15. Instituto de Investigación del Hospital de la Santa Cruz y San Pablo
16. Fundación Instituto Universitario para el Avance de la Biotecnología Sanitaria (IMABIS)
17. Instituto de Investigación Sanitario Fundación Jiménez Díaz
18. Fundación para la Investigación y Docencia Sant Joan de Déu
19. Fundación Privada Institut de Recerca Biomédica (IRB)

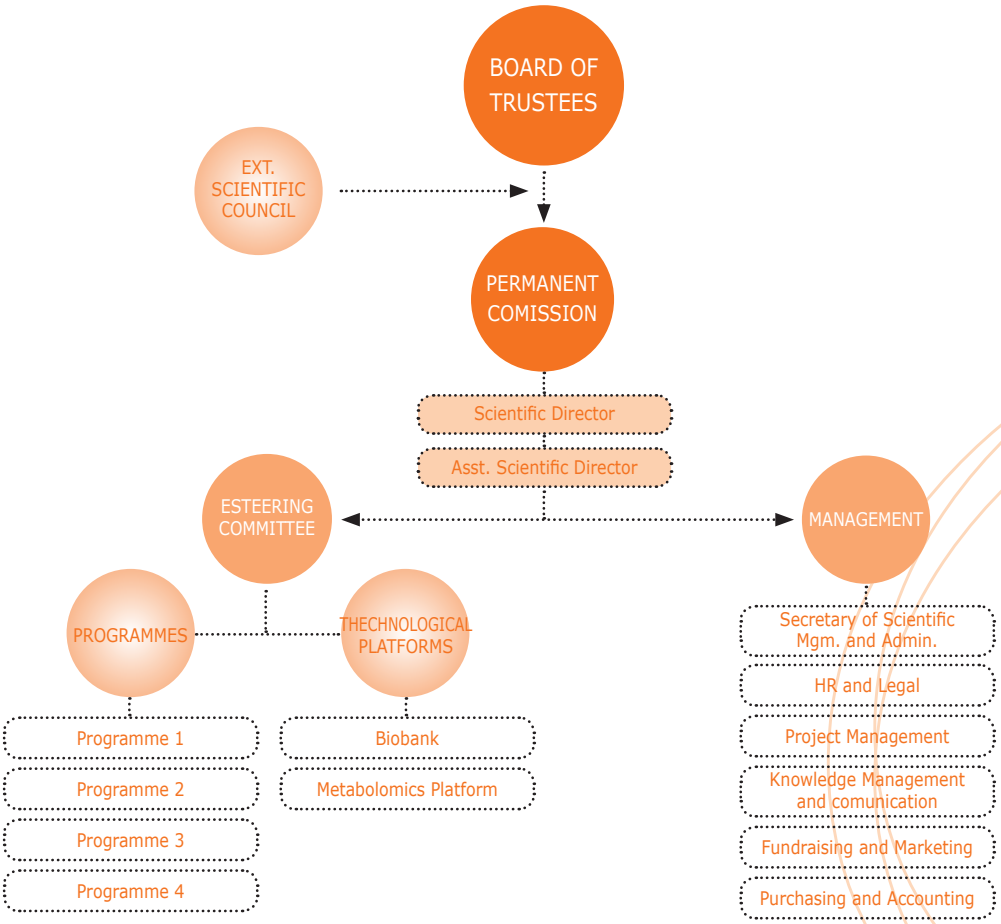
Organizational Structure

CIBERDEM's organizational structure is based on the strategic objectives and the By-laws governing the Consortium.

CIBERDEM's management and administration is made up the following bodies:

- Board of Trustees
- Permanent Commission
- Scientific Director
- External Scientific Advisory Council
- Steering Committee
- Scientific Management Office

Organizational Chart



Board of Trustees

The Board of Trustees is the highest body in the Consortium and is formed by three representatives from the Instituto de Salud Carlos III (ISCIII) and one representative from each of the 19 consortium entities, the CIBERDEM Director and CIBERDEM General Manager, acting as Secretary of the Board of Trustees.

The President of the Board of Trustees is the Director of the Instituto de Salud Carlos III. The main functions of the Board of Trustees are:

- To appoint members of the Board of Trustees who will be part of the Permanent Commission.
- To appoint and choose the members of the External Scientific Advisory Committee.
- To approve amendments of the Consortium's By-laws.
- To set the criteria for CIBERDEM's scientific and technological policy.
- To approve the strategic plan in the form of a multi-annual action plan every 4 years or when a sector initiative in biomedical and health sciences research is initiated.
- To approve the annual report of the Consortium and its Annual Action Plan.
- To approve the conditions of the appropriate contracts with senior management, scientific-technical staff and administrative staff.
- To approve staff policy and remuneration system every year, including staff undergoing training.
- To approve the policy to be followed by CIBERDEM in relation to scientific-technological infrastructures.
- To analyze the measures proposed by the External Scientific Advisory Committee.
- To approve collaboration agreements and association agreements with other entities.
- To approve and authorize agreements, works, service and supply contracts involving a committed expenditure equal to or greater than 300,000.01 €.
- To approve the creation of research programmes and their modifications. To approve the CIBERDEM annual budget and account statements.
- To represent the Consortium.

In 2013, the CIBERDEM Board of Trustees consisted of:

- President: **Antonio Andreu**, Director of the Instituto de Salud Carlos III (ISCIII).
- Vice-President: **Margarita Blázquez**, Subdirectora General de Redes y Centros de Investigación Cooperativa (ISCIII).
- Members-Consortium institutions:

  Dolores González, Consejo Superior de Investigaciones Científicas (CSIC).

  Rosa Valenzuela, Fundación Centro de Investigación Príncipe Felipe (CIPF).

  Rafael Carmena, Fundación Investigación Hospital Clínico Universitario de Valencia (FIHCUV).

  Emilià Pola, Fundación Institut d'Investigació Biomèdica de Bellvitge (IDIBELL).

  Francesc Vidal, Fundació Institut d'Investigació Sanitària Pere Virgili (IISPV).

  Joan X. Comella, Fundació Institut de Recerca Hospital Universitari Vall d'Hebron (FIR-HUVH).

Itziar Lourdes Ochotorena, Fundación Instituto Mediterráneo para el Avance de la Biotecnología y la Investigación Sanitaria (IMABIS).

Emili Bargalló, Fundación para la Investigación y Docencia Sant Joan de Déu (FSJD).

Juan Antonio Álvaro, Fundación Jiménez Díaz (FJD).

Joan J. Guinovart, Fundació Institut de Recerca Biomèdica (IRB Barcelona).

Carmen Garaizar, Fundación Vasca de Innovación e Investigación Sanitarias (BIOEF).

Jaume Kulisevsky, Institut de Recerca Hospital de la Santa Creu i Sant Pau (IRHSCSP).

Mª Carmen Fernández, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS).

Antonio Romero, Servicio Madrileño de Salud (SERMAS).

Anna Ripoll, Universitat Autònoma de Barcelona (UAB).

Dídac Ramírez, Universitat de Barcelona (UB).

Joaquín Plumet, Universidad Complutense de Madrid (UCM).

Fernando Borrás, Universidad Miguel Hernández (UMH).

Manuel Herrero, Universidad Pablo de Olavide (UPO).

- Secretary: **Johanna Rivera**, CIBERDEM General Manager.

Permanent Commission

The Permanent Commission consists of 4 members from the consortium entities, the Vice-President of the Board of Trustees who acts as the President, the CIBERDEM Scientific Director and CIBERDEM General Manager. It evaluates CIBERDEM's activities and approves the information that must be presented to the Board of Trustees. The members from the consortium entities are appointed by the Board of Trustees every year.

The main functions of the Permanent Commission are:

- To perform follow-up on the implementation of the decisions made by the Board of Trustees.
- To perform follow-up on CIBERDEM's budget execution.
- To approve agreements to be signed by CIBERDEM.
- To approve agreements with institutions not belonging to the consortium, when necessary, for carrying out projects.
- To prepare budgets, account statements and other mandatory reports to be presented to and approved by the Board of Trustees.
- To authorize works, service and supply contracts provided the amount thereof is equal to or more than 150,000.01 € and less than 300,000.01 €.
- To authorize the creation of files containing personal data and to authorize the registration thereof in the Spanish Data Protection Agency.

Members of the CIBERDEM Permanent Commission are:

- President: **Margarita Blázquez**, Subdirectora General de Redes y Centros de Investigación Cooperativa (ISCIII).

- **Four representatives from the consortium centres:**
  - Universidad Complutense de Madrid (UCM).
  - Fundación Vasca de Innovación e Investigación Sanitarias (BIOEF).
  - Fundación Investigación Hospital Clínico Universitario de Valencia (FIHCUV).
  - Fundació Institut d'Investigació Sanitària Pere Virgili (IISPV).
- Secretary: **Johanna Rivera**, CIBERDEM General Manager.

Scientific Management

The CIBER Scientific Director is an internationally renowned scientist in the CIBER's area of research who has extensive experience in carrying out and managing research projects. The Scientific Director is appointed by the Board of Trustees for a period of four years, extendable by agreement of the parties.

The main functions of the Scientific Director are:

- To run CIBERDEM's scientific activity.
- To present to the Board of Trustees action plans in relation to CIBERDEM's scientific, teaching and research policy.
- To prepare and present to the Permanent Commission and the Board of Trustees annual action plans and multi-annual action plans.
- To propose the appointment of Research Area Coordinators and the Teaching Programme Coordinator.
- To distribute the resources among CIBERDEM areas.

The Scientific Director in fiscal year 2012 was Dr. Luis Castaño. He was appointed by the CIBERDEM Permanent Commission as acting Scientific Director, and the appointment was ratified before the Board of Trustees by December 18, 2012.

Members of CIBERDEM's Scientific Management are:

- Scientific Director: **Luis Castaño**
- Adjunt Scientific Director: **Anna Novials**

Scientific Steering Committee

The Scientific Steering Committee is formed by the Scientific Director, the Coordinator of each research programme and the Teaching Coordinator. It is responsible for the CIBER's performance and establishes the multi-annual scientific action plan.

The main functions of the Scientific Steering Committee are:

- To give advice and support to the Scientific Director in carrying out his/her functions.
- To take part in the preparation, development and implementation of the research areas.
- To perform follow-up and to track the performance of the groups from the research areas.

Members of the Steering Committee are:

- **Luis Castaño**, Scientific Director and President of the Steering Committee.
- **Anna Novials**, Assistant Scientific Director and Programme 3 Coordinator.
- **Rafael Carmena**, Programme 1 Coordinator.
- **Manuel Benito**, Programme 2 Coordinator.
- **Antonio Zorzano**, Programme 4 Coordinator.
- **Fátima Bosh**, Teaching Programme Coordinator.
- **Johanna Rivera**, General Manager and Secretary of the Steering Committee.

Scientific Management Office

The Scientific Management Office is the administrative coordination and management unit responsible for assuring that the Consortium works properly. In fiscal year 2013, CIBERDEM's Scientific Management Office was re-structured as a result of centralizing the CIBER offices into a single office in Madrid as of January 1, 2014. For this reason, the management staff hired in 2013 was reduced by half, each department taking on more responsibilities and outsourcing some services, such as Human Resources.

Structure:

Management

The management is the responsible for the correct functioning of the administrative procedures which must assure optimal development of consortium activities for the purpose of optimizing resources and attaining optimal yield in quality, service and cost.

Main functions:

- To coordinate the correct functioning of technical unit departments to offer optimal service to CIBERDEM groups.
- To prepare and draw up annual account statements.
- To prepare the draft annual budget.
- Administrative management of CIBERDEM's budget.
- To authorize, together with the Scientific Director, works, service and supply contracts and any other contracts that may be established for achieving its purposes, provided that the amount of the contracts is equal to or more than 50,000.01 Euros and less than 150,000.01.
- To control the economic aspect of CIBERDEM projects and activities.
- To promote fundraising actions with enterprises for obtaining external funds.
- To sign agreements with public and private entities and to follow up same.
- To be responsible for staff management.

Secretary of Scientific Management and Administration

- To implement and to follow-up on, both in terms of organization and administration, the objectives and actions established by CIBERDEM's Scientific Management and Administration.

- To channel the information released by and received from Scientific Management and Administration.
- To organize scientific events such as the Annual Meeting, Congresses, Courses, among others, with the support of Management.
- To provide institutional support as the Secretary of the Follow-up Commission for the correct application of framework agreements with consortium entities.
- To provide support in the implementation and development of the CIBERDEM Teaching Programme.
- To manage CIBERDEM staff trips (travelling and housing expenses).

Project Management Department

- To manage the COFUND-DIATRAIN European Mobility Project.
- To manage internal and external (national/international) research projects.
- To disseminate calls for research projects and to advise CIBERDEM investigators on participation in European projects.
- To promote CIBERDEM in Europe (FP7).
- To prepare the necessary documentation for both internal and external scientific evaluations.

Purchasing and Accounting Department

- To manage purchases and procurements, inventory, follow-up and maintenance of CIBERDEM's tangible and intangible assets.
- To supervise and coordinate maintenance of CIBERDEM's Technical Office and its tangible assets.
- To process payments, expenses and reimbursements.
- To carry the Consortium's accounting books.

Administration

- To record incoming and outgoing information
- To act as reception
- To provide support to all departments in the office so that they all work properly
- To provide support in preparing events organized by CIBERDEM or events in which CIBERDEM collaborates

Human Resources Department (external)

- To manage CIBERDEM staff, hiring, employment policy development and application, depending on Scientific Management and Administration.
- To conduct public procurement procedures: calls for proposal and public tenders, negotiated procedures and certain small contracts.
- To control CIBERDEM staff vacations, leaves of absence, etc.

Communication Department (external)

- To manage internal and external CIBERDEM communication.
- To manage the knowledge generated in the Consortium.
- To build and monitor the corporate image.
- To prepare CIBERDEM's Annual Report.
- To update the web and social networks.

Finally, it must be indicated that all of CIBERDEM's legal issues are reviewed and approved by the State Legal Service.

External Scientific Committee

The External Scientific Advisory Committee is formed by prominent individuals in the health sciences field whose professional and scientific careers are in alignment with Consortium objectives. This Committee is a scientific advisory body that performs annual evaluation of CIBERDEM's activity and research groups. It consists of a President appointed by the President of the Board of Trustees, and 4 members appointed by the Board of Trustees.

The main functions of the External Scientific Advisory Committee are:

- To advise on scientific policy and institutional relations guidelines to be followed by CIBERDEM.
- To review and report on the proposed strategic plan, scientific reports and action plans.
- To report on programme, resource and skill suitability with respect to the Consortium's objectives.
- To advise on the research result transfer strategy.
- To advise on the scientific staff hiring policy.
- To report on the creation of research programmes.

CIBERDEM's External Scientific Advisory Committee Members:

President: **Jose M. Ordovas**, Universidad de Tufts, Boston (USA)

Director, Nutrition and Genomics Laboratory, Human Nutrition Research Center on Aging (HNR-CA) at Tufts University, Boston (Massachusetts) and Professor in Nutrition and Genetics, School of Medicine and Nutrition, Tufts University.

Mr. Jose M. Ordovas is a pioneer in research on the importance of diet and eating habits in relation to the genome. His work in the genetic field of cardiovascular diseases led to his appointment as the Head of Genetic Studies of the well-known Framingham Study. His articles have been published in the most prestigious journals with the greatest international impact on biomedical research, such as The New England Journal of Medicine, Science, JAMA, The Lancet, etc. His career in this field has earned him many awards, such as the Nutrition Science Award (2007) from the American Society for Nutrition, or the USDA Secretary's Honor Award (2006), the most important distinction awarded by the US Department of Agriculture (USDA), among others. In 2004, the Sociedad Española de Arteriosclerosis named him an Honorary Member.

Member: **F. Xavier Pi-Sunyer**, Universidad de Columbia, New York (USA)

Professor of Medicine at Columbia University (New York). Chief of Endocrinology, Diabetes and Nutrition Department of St. Luke's-Roosevelt Hospital Center and Director of the New York Obesity Research Center. He chaired the Committee of the National Heart, Lung and Blood Institute, defining and designing new governmental guidelines for the prevention and treatment of obesity. He also served as the President of the American Diabetes Association (ADA), the American Society for Clinical Nutrition and the North American Association for the Study of Obesity, and as a member of various diabetes and obesity advisory committees. He has written over 300 international articles and a number of book chapters. He served as the Editor of the International Journal of Obesity from 1994-2005 and as the Editor-in-Chief of Obesity Research from 1995-2000.

Member: **Decio Eizirik**, Universidad Libre, Bruselas (Bélgica)

Director, Experimental Medicine Laboratory, Université Libre, Brussels (ULB), Belgium. He has published over 220 articles in international journals and received many awards including, most importantly, the Juvenile Diabetes Research Foundation Award (JDRF), the Diabetes Care Research Award and the EASD/Eli Lilly Award. He is the coordinator of the Beta Cell Gene Expression Bank and of several competitive European projects in the field of diabetes. He served as the Honorary Scientific Secretary of the European Association for the Study of Diabetes (EASD) (2004-2007) and the Assistant Editor of the Diabetologia journal (1998-2004). He is currently the member of the Scientific Committee for the National Programme of Diabetes Research in France. His research interests focus on molecular mechanisms regulating beta cell apoptosis and the search for new approaches to prevent progressive cell mass loss in diabetes.

Member: **Antonio Vidal-Puig**, Universidad de Cambridge, Cambridge (UK)

M.D, PhD in Endocrinology. He completed his post-doctoral internship at Harvard and then lived out his research career there until 1999 when he moved to the University of Cambridge. He is now the Associate Professor of Metabolic Medicine and Honorary Consultant in Metabolic Medicine at the University of Cambridge. He is also the Assistant Director of the MRC-CORD Research Centre for Obesity and Related Diseases of the University of Cambridge and Director of Wellcome Trust's Mouse Programme. His areas of scientific interest include adipocyte biology, mitochondrial biology, lipotoxicity and genetically modified animal models.

Member: **Ele Ferrannini**, Universidad de Pisa, Pisa (Italia)

Professor of Internal Medicine, Università degli Studi di Pisa, Chief of the Metabolic Medicine Unit of the CNR (National Research Council), Instituto de Fisiología Clínica de Pisa, and Professor of Clinical Medicine, Diabetes Department, University de Texas, USA. He has published over 400 original articles in the field of diabetes, metabolic medicine and hypertension. He is a member of various scientific associations. His participation in the Executive Council of the European Association for the Study of Diabetes (EASD) as the President (2004-2008) and his role as the Editor-in-Chief of Diabetologia (1994-1998), the official journal of the EASD, must be given special mention. He now serves as the President of the European Group for the Study of Insulin Resistance.

Lines of research: insulin resistance and atherosclerosis, impact of oxidative stress and blood pressure on endothelial function, autoimmunity in adult-onset diabetes, physiopathology of insulin secretion, impact of hyperinsulinemia on the nervous system, pathogenesis of insulin resistance and hyperinsulinism in obesity, effect on weight loss; coronary atherosclerosis in diabetes, atherosclerosis in diabetes.

2013 CIBERDEM Budget

Item	Value
Programme 1	564.157,50 €
Programme 2	813.075,00 €
Programme 3	827.782,50 €
Programme 4	569.985,00 €
Metabolomics Platform	75.000,00 €
Biobank	75.000,00 €
Teaching	59.300,00 €
Total	2.984.300,00 €

One of the objectives in 2013 was to try to increase inflow of external funds to enhance funding/co-funding for staff and for research project development.

On the other hand, the budgets allocated for the Biobank and Metabolomics Platform were reduced compared to previous fiscal years. Therefore, CIBERDEM seeks to make better use of its resources and to encourage collaborative actions with enterprises.

2013 CIBERDEM Staff

The mean number of employees in the fiscal year ending December 31, 2013 distinguished by categories and sex are shown below.

2013						
Categories	No. of staff members 12-31-2012			Ave. no. of staff members 2013		
	Total	Male	Female	Total	Male	Female
Doctor	42,0	11,0	31,0	42,5	11,5	31,0
Graduate	3,0	2,0	1,0	3,0	2,0	1,0
Senior Technician	25,0	4,0	21,0	23,0	3,5	19,5
Technician	12,0	4,0	8,0	12,0	4,0	8,0
Administration	4,0	0,0	4,0	4,0	0,0	4,0
Grant Holder	0,0	0,0	0,0	1,0	0,0	1,0
Total	86,0	21,0	65	85,5	21,0	64,5

2012						
Categories	No. of staff members 12-31-2012			Ave. no. of staff members 2012		
	Total	Male	Female	Total	Male	Female
Doctor	43,0	12,0	31,0	43,8	11,6	32,2
Graduate	3,0	2,0	1,0	4,5	2,0	2,5
Senior Technician	21,0	3,0	18,0	21,9	3,4	18,5
Technician	12,0	4,0	8,0	11,6	4,1	7,5
Administration	4,0	0,0	4,0	3,7	0,0	3,7
Grant Holder	2,0	0,0	2,0	2,0	0,0	2,0
Total	85,0	25,0	83,0	87,5	21,1	66,4

2 Scientific Programmes

Programme 1

Molecular and physiological determinants of lifestyle in diabetes and obesity. Population studies for genetic-epigenetic association analysis in type 2 diabetes mellitus and related factors.

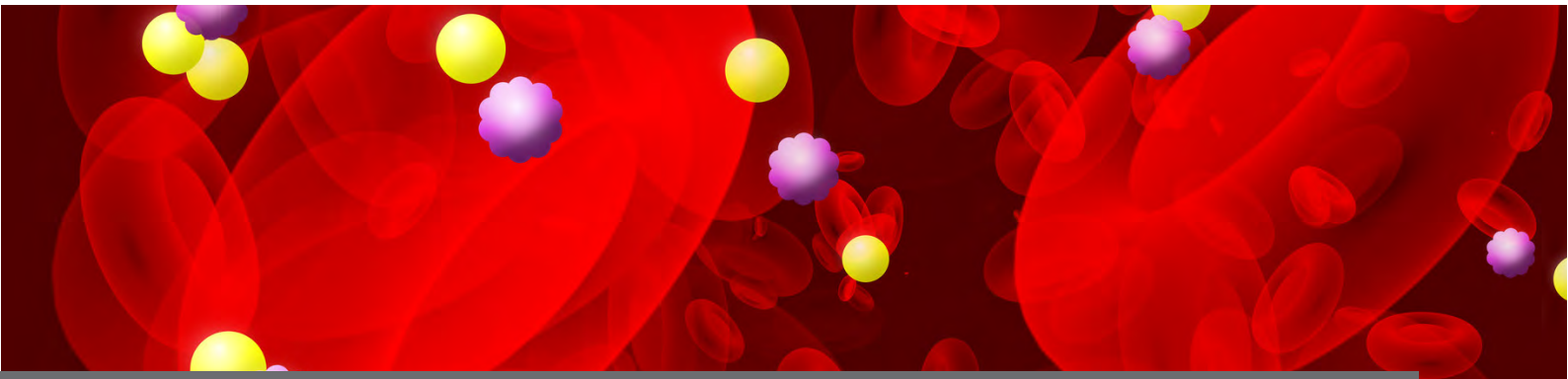
Coordinator: Dr. Rafael Carmena

Associated groups: 8

Objectives

- Strategies for establishing nutritional guidelines in lifestyle studies and in diabetes/obesity prevention.
- The impact of overnutrition, diabetes-obesity and malnutrition in energy homeostasis regulation in the central nervous system.
- Body fat amount and distribution in childhood and predisposition to type 2 diabetes.
- Environment, genes and prevalence of diabetes mellitus in Spain. Di@bet.es study.
- Cooperative-population and database studies for genetic association analysis in type 2 diabetes mellitus and related traits.
- Genetic and environmental factors of insulin resistance syndrome and its long-term complications in Mediterranean immigrant populations.
- Characterization of low HDL syndrome in type 2 diabetes.

PI Name	Consortium Institution	AUTO. COMM.
Álvarez Escola, Carmen	Universidad Complutense de Madrid	Madrid
Blázquez Fernández, Enrique	Universidad Complutense de Madrid	Madrid
Carmena Rodríguez, Rafael	Fund. Hospital Clínico Universitario de Valencia	Comm. of Valencia
Casimiro-Soriguer Escofet, Federico José	Fundación Instituto Mediterraneo para el Avance de la Biotecnología Sanitaria	Andalusia
Correig Blanchar, Francesc Xavier	Fund. Inst. d'Investigació Sanitària Pere Virgili	Catalonia
Novials Sardà, Anna Mª	Instituto de Investigaciones Biomédicas August Pi i Sunyer	Catalonia
Masana Marín, Luis	Fund. Inst. d'Investigació Sanitaria Pere Virgili	Catalonia
Serrano Ríos, Manuel	Servicio Madrileño de Salud	Madrid



Programme 2

Mechanisms involved in the development of diabetes and its vascular complications. Associated co-morbidities. Strategies for prevention and treatment.

Coordinator: Dr. Manuel Benito

Associated groups: 10

Objectives

- Identification of neurodegenerative mechanisms which promote the development of diabetic retinopathy: the role of insulin signaling and apoptosis.
- Glycogen-induced dysfunctions in the pancreas and retina and the involvement thereof in the etiopathogenesis of diabetes mellitus.
- Mechanisms of endothelial dysfunction in diabetes: the role of amylin and circulating endothelial cells.
- The influence of insulin resistance and the compensatory response of the endocrine pancreas on endothelial/vascular damage.

PI Name	Consortium Institution	AUTO. COMM.
Benito de las Heras, Manuel Román	Universidad Complutense de Madrid	Madrid
Blanco Vaca, Francisco	Instituto de Investigación del Hospital de la Santa Cruz y San Pablo	Madrid
Gomis de Bárbara, Ramón	Instituto de Investigaciones Biomédicas August Pi i Sunyer	Catalonia
Guinovart Cirera, Joan Josep	Fundació Privada Institut de Recerca Biomèdica (IRB)	Catalonia
De Pablo Dávila, Flora	Consejo Superior de Investigaciones Cientificas	Madrid
Martínez Valverde, Ángela María	Consejo Superior de Investigaciones Cientificas	Madrid
Masana Marin, Luis	Fund. Institut d'Investigació Sanitaria Pere Virgili	Catalonia
Simo Canonge, Rafael	Fund. Instituto de Investigación Valle de Hebrón	Catalonia
Vendrell Ortega, Joan J.	Fund. Institut d'Investigació Sanitaria Pere Virgili	Catalonia
Villanueva-Peñacarrillo, Mª Luisa/Jesús Egido	Instituto de Investigación Sanitario Fundación Jiménez Díaz	Madrid

Programme 3

Impact of beta cell dysfunction and plasticity on diabetes. Development of new treatment strategies.

Coordinator: Dra. Anna Novials

Associated groups: 10

Objectives

- Recovery of functionally impaired metabolic tissues.
- Clinical, genetic and functional characterization of monogenic diabetes: from bench to bedside.
- Production of monoclonal antibodies which selectively react with cell-surface molecules in human pancreatic beta cells.
- Comparative metabolomic analysis for detecting diabetes biomarkers.

PI Name	Consortium Institution	AUTO. COMM.
Bosh Tubert, Fátima	Universidad Autónoma de Barcelona	Catalonia
Burks, Deborah	Fund. Centro de Investigación Príncipe Felipe	Comm. of Valencia
Castaño González, Luis	Fundación Vasca de Innovación e Investigación Sanitarias	Basque Country
Novials Sardà, Anna Mª	Instituto de Investigaciones Biomédicas August Pi i Sunyer	Catalonia
Ferrer Marrades, Jorge	Instituto de Investigaciones Biomédicas August Pi i Sunyer	Catalonia
Gomis de Barbara, Ramón	Instituto de Investigaciones Biomédicas August Pi i Sunyer	Catalonia
Martín Bermudo, Francisco	Universidad Pablo de Olavide	Andalusia
Montanya Mias, Eduard	FUNDACIÓN IDIBELL	Catalonia
Nadal Navajas, Ángel	Universidad Miguel Hernández	Comm. of Valencia
Vallejo Fernández de la Reguera, Mario	Consejo Superior de Investigaciones Científicas	Madrid

Programme 4

Use of biomedical approach systems to develop personalized therapies for diabetes.

Coordinator: Dr. Antonio Zorzano

Associated groups: 10

Objectives

- Determinants of insulin resistance and glucose tolerance disorders (including diabetes) in severely obese individuals and their changes after bariatric surgery-induced weight loss .
- Adipose tissue-derived adult progenitor cells: the influence of clinical phenotype and fat depot origin on their biological properties .

PI Name	Consortium Institution	AUTO. COMM.
Balsinde Rodriguez, Jesús	Consejo Superior de Investigaciones Científicas	Castile and Leon
Escobar Morreale, Héctor Francisco	Servicio Madrileño de Salud	Madrid
Ferrer Marrades, Jorge	Instituto de Investigaciones Biomédicas August Pi i Sunyer	Catalonia
Gómez Foix, Ana María	Universitat de Barcelona	Catalonia
Ibañez Toda, Lourdes	Fundación para la Investigación y Docencia Sant Joan de Déu	Catalonia
Montanya Mias, Eduard	FUNDACIÓN IDIBELL	Catalonia
Simó Canonge, Rafael	Fund. Instituto de Investigación Valle de Ebron	Catalonia
Vázquez Carrera, Manuel	Universitat de Barcelona	Catalonia
Vendrell Ortega, Joan J.	Fund. Institut d'Investigació Sanitària Pere Virgili	Catalonia
Zorzano Olarte, Antonio	Fundació Privada Institut de Recerca Biomèdica (IRB)	Catalonia

3 Horizontal Programmes and Platforms

Platforms

CIBERDEM BIOBANK

http://www.ciberdem.org/biobanco.php

The objective of the CIBERDEM Biobank is to make well characterized and standardized biological samples of main metabolic disorders with a high added value available to the scientific community to promote, facilitate and develop biomedical research according to the laws in force.

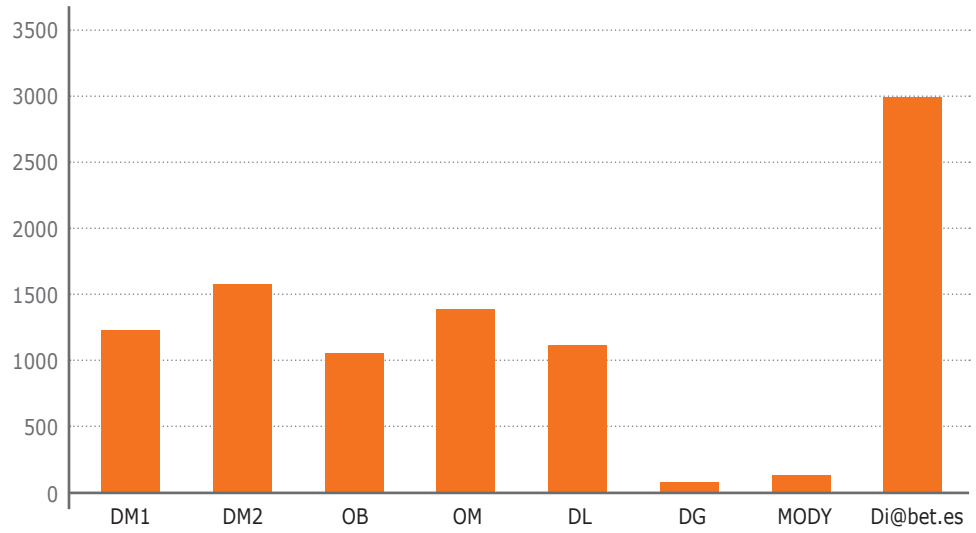
The CIBERDEM Biobank consists of CIBERDEM groups in the following centres:

- Hospital Clínic de Barcelona: Dr. Ramon Gomis and Dr. Anna Novials
- Hospital Joan XXIII: Dr. Joan Vendrell
- Hospital Sant Joan de Reus: Dr. Masana
- Hospital de Cruces: Dr. Luís Castaño
- Hospital Clínico de Madrid: Dr. Serrano-Ríos
- Hospital Clínico de Valencia: Dr. Carmena
- Hospital Carlos Haya de Málaga: Dr. C. Soriguer
- Hospital de la Santa Creu i Sant Pau: Dr. Blanco-Vaca

Donor information is stored in the BCGene computer platform. This application complies with the requirements of Organic Law on Personal Data Protection 15/1999 and will be accessible from all participating nodes to facilitate data entry by clinical teams.

In 2013, the sample collection was enlarged with the inclusion of diabetic patients with monogenic diabetes. Furthermore, a DNA bank of the ancient population of the Roman city of Tarraco was established in 2013 in the framework of the MEDIGENE project. This DNA Bank will be one-of-a-kind worldwide and will provide a basis for studying the origin and progression of many diseases. Likewise, individuals at risk for developing diabetes started to be included in the Predaps study (GDPS Network) **in order to determine the risk of diabetes and the risk of vascular complications in prediabetic patients and to identify the factors associated with those risks.**

Muestras Biobanco



METABOLOMICS PLATFORM

http://www.ciberdem.org/metabolomica.php

The Metabolomics Platform is a technological service platform created by the Universitat Rovira i Virgili (hereinafter URV) and the Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas (hereinafter CIBERDEM) by means of a collaboration agreement.

The main objective of the Metabolomics Platform is to work as an integrated laboratory, i.e., as a consultation point directly involved in metabolomics-related experiments proposed by the research groups. Our collaborations start with defining the objectives, dimension and characteristics of both the sample set and experiment designs. After that, the data is processed by our team and we are involved in the interpretation of results, delivering sound, significant and useful clinical conclusions for the different research groups.

The equipment currently available in the field of NMR and MS (GC-single quad, LC-TOF and LCQqQ) allows large-scale measurements of body fluids, for example, serum or urine, as well as tissues or biopsies from humans and/or animal models (such as rats, mice, etc).

The use of advanced statistics, chemometrics, multivariate and artificial-intelligence algorithms allows transforming a large dataset into metabolic fingerprints or continuous result profiles, and ultimately into clinical information. Our goal is to introduce metabolomics as a potential tool for clinical diagnostics and to clarify unknown mechanisms of associated diseases.

The Metabolomics Platform particularly focuses on the needs of CIBERDEM and URV research groups. However, its services and potential scientific collaborations are available to other biomedical research groups both in Spain and abroad.

Currently the Platform manages and has full access to the following NMR technology:

- 600 MHz Bruker Avance III + cryoprobe + ScanJet.
- 500 MHz Bruker Avance III + HR-MAS probe.

The Universitat Rovira I Virgili shares three mass spectrometers with the Metabolomics Platform, thus limiting CIBERDEM staff's access to the following equipment:

- LC ESI-TOF
- LC ESI-QqQ
- GC-single quad

Item	2010	2011	2012
Number of collaborations with CIBERDEM groups	12	10	11
Published articles	1	5	10 (Total IF=97)
Accepted articles	--	--	4

Note: Overall results: (pending update in 2013)

CIBERDEM and EU Funded Projects

TELEMEDICINE STUDY

http://www.ciberdem.org/estudio_telemed_diabetes.php

The **Telemed-diabetes** study developed by CIBERDEM is a multicentre study including the participation of Hospital Clínic de Barcelona, Hospital Carlos Haya de Málaga, Hospital Clínico de Madrid, Hospital de Cruces de Barakaldo and Hospital Clínico de Valencia, under the leadership of the Director of ISCIII.

CIBERDEM Groups: Dr. Rafael Carmena, Dr. Ramon Gomis, Dr. Manuel Serrano Ríos, Dr. Federico Soriguer and Dr. Luis Castaño.

The main objective of the project is to assess the impact of the Medical Guard Diabetes® telematic system on the efficiency of clinical and economic management of human resources and materials intended for a programme for optimizing metabolic control in patients with type 1 diabetes mellitus (DM1), taking into consideration the degree of metabolic control and quality of life of the patients. This telematic communication system allows transmitting results of capillary blood glucose, insulin dose, carbohydrate intake during meals and other events from the patient's home or anywhere else to the medical team through a web server

Patient inclusion took place between May and October 2011 and patient follow-up ended in April 2012. The results were analyzed in 2013 and a scientific report was prepared.

The distribution of patients per centre is as follows:

- Hospital Carlos Haya de Málaga: 34 patients
- Hospital Clínic de Barcelona: 33 patients
- Hospital de Cruces Barakaldo: 32 patients
- Hospital Clínico de Valencia: 29 patients
- Hospital Clínico de Madrid: 25 patients

The evolution of the metabolic control data, economic patient and medical equipment costs, the knowledge, quality of life and compliance with treatment corresponding to the follow-up of two groups of patients were studied:

- 80 patients in the control group (hospital visits)
- 80 patients in the intervention group (hospital visits replaced by telemedicine).

The project led to the hiring of 5 part-time nurses for the medical centres, of the Medical Guard telematic systems from Pulso Ediciones S.L., of CRO services from Insight Consulting & Research S.L. and of a data analyst. Furthermore, it also led to taking out liability insurance.

In April 2012, the database was closed with data from the first six months and the degree of compliance was evaluated as the study ended with 118 patients from the 153 who were initially included. The preliminary results analyzed at the end of 2012 suggest that telemedicine applied to DM1 patients who are being treated with MDI and inappropriate metabolic control is a valid strategy providing results that are comparable with hospital visits as regards the improvement in blood glucose control, acquisition of knowledge, quality of life and therapeutic compliance, with a significant time reduction time spent, especially for the patient. Final and more comprehensive results were presented in 2013.

STUDY DI@BET.ES

Estudio di@bet.es
Primer estudio de prevalencia de la diabetes en España

CIBERDEM Project

http://www.ciberdem.org/estudio_diabetes.php

Di@bet.es is a national population study having a cohort that is representative of the general Spanish population with the application of a homogenous methodology. The objective was primarily to investigate the association between the presence of metabolic impairments and health habits. The results were published in 2011 and 2012. However, in 2013 the group was working on scientific papers associated with data obtained from the project.

CIBERDEM groups: Dr. Federico Soriguer, Dr. Rafael Carmena, Dr. Joan Vendrell, Dr. Luis Castaño, Dr. Manuel Serrano Ríos and Dr. Ramon Gomis.

Primary Objectives: To determine the overall (known and unknown) prevalence of type 2 diabetes mellitus in Spain, in a representative sample of the Spanish population. To determine the degree of association between DM and physical activity and eating habits of individuals, and to make a scientific health evaluation instrument available for institutional health strategies on a national level.

Secondary Objectives: To determine the prevalence of impaired fasting glucose and impaired glucose tolerance, insulin resistance, arterial hypertension, dyslipidemia, obesity and metabolic syndrome. To determine the association of these impairments and physical activity and eating habits of individuals.

Tertiary Objectives: To make a biological sample collection containing a representative sample of the Spanish population available to the scientific community to allow conducting genotype-phenotype-environment interaction studies. To establish the basis for a future project to determine the incidence of metabolic disorder in this cohort.

The use of the information gathered in the field study allows providing more information about diabetes and other studied biomedical problems. Furthermore, it will allow implementing collaboration strategies with other national or international projects designed with similar objectives.

GLOBAL PREVALENCE DATA (DI@BET.ES STUDY)		
	% of affected individuals over 18 years of age	No. of affected individuals over 18 years of age
Known diabetes mellitus	7,78	3.111.641
Unknown diabetes mellitus	6,01	1.514.916
Total diabetes mellitus	13,79	4.626.557
Abnormal tolerance to glucose	9,21	3.028.706
Impaired fasting glucose	3.44	1.398.183
Obesity 1	28.21	10.863.431
Arterial hypertension	41.20	15.889.058
Metabolic syndrome	20.82	8.022.026
Smoking	27.81	10.724.238
Daily intake of alcoholic beverages	22.62	8.733.905
Intake of olive oil for frying	69.20	26.583.402
Sedentary lifestyle	50.31	19.400.237

According to the Di@bet.es study, the total prevalence of DM2 in Spain is 13.79%. It is worth highlighting that 6% of those suffering the disease are unaware of it. On the other hand, three out of every ten Spanish people suffer obesity and four out of every ten suffer arterial hypertension.

Most relevant publications in 2013

- Rojo-Martínez G, Valdés S, Colomo N, Lucena MI, Gaztambide S, Gomis R, Casamitjana R, Carmena R, Catalá M, Martínez-Larrad MT, Serrano-Ríos M, Castaño L, Vendrell J, Girbés J, Franch J, Vázquez JA, Mora-Peces I, Urrutia I, Pascual-Manich G, Ortega E, Menéndez E, Delgado E, Bordiú E, Castell C, López-Alba A, Goday A, Calle A, Bosch-Comas A, Soriguer F. Use of Drugs Related to the Treatment of Diabetes Mellitus and Other Cardiovascular Risk Factors in the Spanish Population. The Di@bet.es Study. Rev Esp Cardiol (Engl Ed). 2013 Nov;66(11):854-63. doi: 10.1016/j.rec.2013.05.027. Epub 2013 Sep 23. PubMed PMID: 24773992.
- Soriguer F, Rojo-Martínez G, Goday A, Bosch-Comas A, Bordiú E, Caballero-Díaz F, Calle-Pascual A, Carmena R, Casamitjana R, Castaño L, Castell C, Catalá M, Delgado E, Franch J, Gaztambide S, Girbés J, Gomis R, Gutiérrez G, López-Alba A, Teresa Martínez-Larrad M, Menéndez E, Mora-Peces I, Ortega E, Pascual-Manich G, Serrano-Rios M, Urrutia I, Valdés S, Antonio Vázquez J, Vendrell J. Olive oil has a beneficial effect on impaired glucose regulation and other cardiometabolic risk factors. Di@bet.es study. Eur J Clin Nutr. 2013 Sep;67(9):911-6. doi: 10.1038/ejcn.2013.130. Epub 2013 Jul 17. PubMed PMID: 23859999.
- Ortega E, Franch J, Castell C, Goday A, Ribas-Barba L, Soriguer F, Vendrell J, Casamitjana R, Bosch-Comas A, Bordiú E, Calle-Pascual A, Carmena R, Castaño L, Catalá M, Delgado E, Gaztambide S, Girbés J, López-Alba A, Martínez-Larrad MT, Menéndez E, Mora-Peces I, Pascual-Manich G, Rojo-Martínez G, Serrano-Rios M, Urrutía I, Valdés S, Vázquez JA, Gomis R. Mediterranean diet adherence in individuals with prediabetes and unknown diabetes: the Di@bet.es Study. Ann Nutr Metab. 2013;62(4):339-46. doi: 10.1159/000346553. Epub 2013 Jul 2. PubMed PMID: 23838479.
- Marcuello C, Calle-Pascual AL, Fuentes M, Runkle I, Rubio MA, Montañez C, Rojo-Martinez G, Soriguer F, Bordiu E, Goday A, Bosch-Comas A, Carmena R, Casamitjana R, Castaño L, Castell C, Catalá M, Delgado E, Franch J, Gaztambide S, Girbés J, Gomis R, Urrutia I, López-Alba A, Martínez-Larrad MT, Menéndez E, Mora-Peces I, Ortega E, Pascual-Manich G, Serrano-Rios M, Valdés S,

Vázquez JA, Vendrell J. Prevalence of the metabolic syndrome in Spain using regional cutoff points for waist circumference: the di@bet.es study. Acta Diabetol. 2013 Aug;50(4):615-23. doi: 10.1007/s00592-013-0468-8. Epub 2013 Mar 20. PubMed PMID: 23512475.

- Rojo-Martínez G, Soriguer F, Colomo N, Calle A, Goday A, Bordiú E, Delgado E, Menéndez E, Ortega E, Urrutia I, Girbés J, Castaño L, Catalá M, Gaztambide S, Valdés S; di@bet.es study group. Factors determining high-sensitivity C-reactive protein values in the Spanish population. Di@bet.es study. Eur J Clin Invest. 2013 Jan;43(1):1-10. doi: 10.1111/eci.12002. Epub 2012 Nov 7. PubMed PMID: 23134526.
- Gutiérrez-Repiso C, Rojo-Martínez G, Soriguer F, García-Fuentes E, Vendrell J, Vázquez JA, Valdés S, Urrutia I, Serrano-Rios M, Pascual-Manich G, Ortega E, Mora-Peces I, Menéndez E, Martínez-Larrad MT, López-Alba A, Gutiérrez G, Gomis R, Goday A, Girbés J, Gaztambide S, Franch J, Delgado E, Catalá M, Castell C, Castaño L, Casamitjana R, Carmena R, Calle-Pascual A, Bordiú E, Bosch-Comas A. Factors affecting levels of urinary albumin excretion in the general population of Spain: the Di@bet.es study. Clin Sci (Lond). 2013 Feb;124(4):269-77. doi: 10.1042/CS20120261. PubMed PMID: 22970892.

PILCHARDUS STUDY

CIBERDEM Project

Status: Development

PILCHARDUS is a clinical research project that aims to test the hypothesis that a sardine-rich diet can improve metabolic control in patients with type 2 diabetes mellitus.

CIBERDEM is the driving force behind this multicenter study with the participation of Hospital Clínic de Barcelona as the coordinator and Hospital de la Vall d'Hebrón de Barcelona and Hospital Carlos Haya de Málaga as associated centres.

Groups involved: R. Gomis (coordinator), R. Simó, F. Soriguer, A. Novials and X. Correig (Metabolomics Platform).

The objectives of the study are to evaluate the effects of a sardine-rich diet on blood glucose control, inflammation markers, blood pressure, lipid metabolism and intestinal microbiota in patients with recently diagnosed type 2 diabetes or patients not undergoing pharmacological treatment.

Sixty-two patients are to be included in the study. They will be randomly divided into two groups: the intervention group (sardine diet) and the control group (normal diet). The diet consists of replacing part of the daily protein intake with 100 g of sardines, five times a week for six months. Canned sardines or sardines processed in other ways are supplied. The Galician fish-canning company, Cerqueira, collaborated by providing all the canned sardines required for the study free of charge, and the food research centre Fundación Alícia, led by chef Ferran Adrià, designed sardine-based products to provide patients with a wide gastronomic variety of sardine-based meals and to prevent monotonous diets.

Indicators/results/status

In 2012 and 2013, informed consent forms for the study and case report forms were designed and printed, and the materials needed for carrying out the nutrition education sessions were prepared. Also, the sardine-based products developed by the Fundación Alícia, which is part of the PILCHARDUS study, were selected and their nutritional content was analyzed.

As regards study monitoring, the first monitoring visits were performed in the different participating hospitals and patient recruitment began.

Finalist in the Ecotendencias Cosmocaixa video competition.

The main results obtained from the study will determine the effect of long-term sardine intake on glucose levels and glycosylated hemoglobin values. They will also allow obtaining information on its effects on inflammation markers and cardiovascular risk factors associated with type 2 diabetes (blood pressure and lipid profile).

The study will generate new scientific knowledge in the field of nutrition in diabetes which will contribute to the consideration of future applications in the treatment of type 2 diabetes, allowing making sardine-based dietary recommendations for patients with diabetes and with other metabolic diseases associated with obesity.

The use of sardines in cooking will also be improved, with influences on the eating habits of patients, their relatives and society as a whole. Taking into consideration the expected increase in the prevalence of type 2 diabetes over the next few years, the results of this novel study will have an impact on public health because they will lay the foundations for new studies in the field of nutrition strategies in type 2 diabetes.

MEDIGENE STUDY

European Project

Estado: Development

The MEDIGENE Study is a study on the genetic and environmental factors influencing insulin resistance syndrome in Mediterranean immigrant populations. It is a 4-year collaborative project between CIBERDEM and other European institutions. It is subsidized by the European Commission under its FP7-Health-2011-two-stage framework programme with project number 279171 and coordinated by Dr. Florin Grigorescu of the Universitè Montpellier I, France.

Partners in the international consortium:

- University Montpellier 1 (UM1), UMR-204 NUTRIPASS Prévention des malnutritions et des pathologies associées. Montpellier, France.
- Universite Lyon 1 Claude Bernard, Fédération d'Endocrinologie, HOPITAL NEURO-CARDIO. Lyon-Bron, France.
- Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas (CIBERDEM), Laboratorio de Diabetes y Obesidad (IDIBAPS). Barcelona, España.
- Instituto Catalán de Arqueología Clásica. Tarragona, España.
- University Of Medicine And Pharmacy Carol Davila, National Institute of Endocrinology, Neuroendocrinology Laboratory. Bucharest, Romania.
- Alma Mater Studiorum-Universita Di Bologna, Division of Endocrinology, Department of Internal Medicine. Bologna, Italy.
- Magna Graecia University Of Catanzaro, Laboratory of Internal Medicine, Department of Experimental and Clinical Medicine. Catanzaro, Italy.
- Scientific Institute Casa Sollievo Della Sofferenza, Department of Clinical Science. Rome, Italy.

- Universita Degli Studi Di Roma Tor Vergata, Department of Internal Medicine. Rome, Italy.
- Ioannina University, Department of Endocrinology. Ioannina, Greece.
- Institute Of Biochemistry And Genetics, Ufa Scientific Center, Russian Academy of Sciences. Bashkortostan, Russia.
- Institut Pasteur de Tunis, Research Unit on Genetic Orphan Diseases. Tunis, Tunisia.
- Univesity Of Alger 1, Laboratoire de Biochimie Génétique (LABIOGEN). Alger, Algeria.
- Institut Pasteur Du Maroc, Laboratoire de Génétique Moléculaire Humaine. Casablanca, Morocco.
- University Hospital Of Tirana, Endocrinology Division. Tirana, Albania.
- BC Platforms Ltd.
- PersonMed Ltd, Hungary.
- Istanbul University, Dept. Internal Midicine, Millet Caddesi. Istanbul, Turkey.

The project began in fiscal year 2012 and continued in 2013. The total budget for the 4-year project is 371,644.00€ distributed as follows:

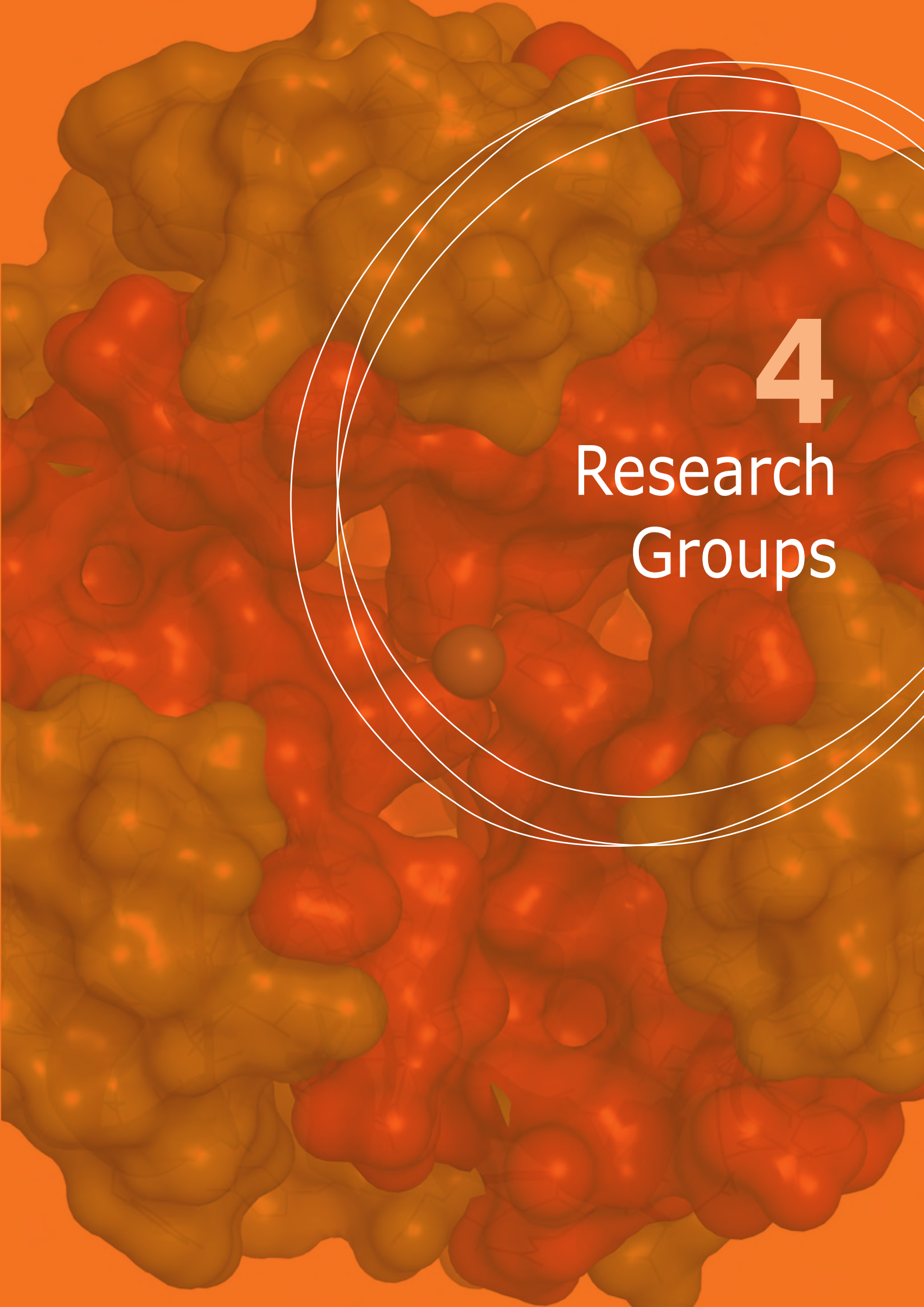
COST DISTRIBUTION			
	EU (75%)	CIBERDEM (25%)	PROJECT TOTAL
TOTAL CONTRIBUTION	278,733.00 €	92,911.00 €	371,644.00 €

CIBERDEM is involved in several work packages of the project and has various deliverables throughout its participation. CIBERDEM Biobank and several other Consortium groups, such as the groups led by Dr. Luis Castaño and Dr. Ramon Gomis, will contribute greatly to the project. In turn, the possible participation of other CIBERDEM groups is currently under study.

In 2013, work continued to be done on WP1 "Anthropological studies and GWAS in ethnic populations" and WP2 "Ancient DNA studies in Tarragona" of the project.

The work on WP1 consisted of selecting DNA samples from patients with metabolic syndrome and the respective controls existing in CIBERDEM Biobank databases and obtaining project approval from ethics committee. A total of 300 samples were obtained following strict selection criteria. These samples were analyzed through a genome-wide association study (GWAS) together with another 1500 samples collected from all over Europe and part of Africa by other MEDIGENE members.

CIBERDEM's work on WP2 also continued in 2013 and consisted of determining the genetics of ancient Roman populations in Tarragona and comparing it to modern populations of Catalonia and Italy as evidence of historical migrations and determining the prevalence of allelic variants. Various archaeological remains, primarily teeth, have been identified in collaboration with the Institut Català d'Arqueologia Clàssica (ICAC) of Tarragona, for obtaining ancient DNA samples. In 2013, CIBERDEM continued to work on extracting DNA from samples of teeth for subsequent sample amplification and analysis through NEXT-GEN genotyping in collaboration with the participants from Universitè Montpellier.



4 Research Groups

PROGRAMME: **P1**

Endocrinology and Metabolism

Group Members

STAFF MEMBERS
Fernández Millan, Elisa

ASSOCIATED MEMBERS
Escriva Pons, Fernando
Lizárraga Mollinedo, Esther
Martín Arribas, María Ángeles

Lead Researcher

Álvarez Escolá, Carmen

Contact:
Facultad de Farmacia. Univ. Complutense de Madrid.
Ciudad Universitaria, S/N. 28040 Madrid.
Phone: (+34) 91 394 18 57
E.mail: calvarez@farm.ucm.es · Website: http://www.ucm.es/biomol2

Main lines of research

The identification of the cellular and molecular mechanisms that link poor perinatal growth and increased risk of metabolic syndrome and type 2 diabetes in adult life through the use of animal models of nutritional manipulation: maternal undernutrition followed or not by overnutrition. To this end we have focused on:

- The effect of nutrients on the growth, death and function of pancreatic alfa and beta cells: involvement of different growth factors.
- The potential role of incretins (GLP-1 and GIP) in the relationship between intrauterine growth restriction and the development of type 2 diabetes in adulthood: study of the entero-insular axis.
- Changes in insulin/glucagon plasma levels and liver sensitivity associated with early undernutrition which could alter the available substrates for the growing brain.
- Impact of early undernutrition on the insulin and leptin hypothalamic responses and the hypothalamic expression of orexigenic and anorexigenic factors (NPY, POMC).
- The effect of early undernutrition followed by an overcaloric diet on the obesity risk and the white adipose tissue metabolism.

Most relevant scientific articles

- Lizárraga-Mollinedo E, Álvarez C, Fernández-Millán E, Escrivá F, González-Martín C, Salas E et al.. Undernutrition upregulates fumarate hydratase in the rat nucleus accumbens.Metab Brain Dis. 2013 Mar;28(1):111-5.
- Fernández-Millán E, de Toro-Martín J, Lizárraga-Mollinedo E, Escrivá F, Álvarez C. Role of endogenous IL-6 in the neonatal expansion and functionality of Wistar rat pancreatic alpha cells.Diabetologia. 2013 Feb 23;.
- Cordero-Herrera I, Martín MA, Bravo L, Goya L, Ramos S.. Cocoa flavonoids improve insulin signalling and modulate glucose production via AKT and AMPK in HepG2 cells. Mol Nutr Food Res. 2013 ;57(6):974-85.
- Martín MA, Fernández-Millán E, Ramos S, Bravo L, Goya L.. Cocoa flavonoid epicatechin protects pancreatic beta cell viability and function against oxidative stress.Mol Nutr Food Res.. 2013;.
- Martín MA, Ramos S, Cordero-Herrero I, Bravo L, Goya L. Cocoa phenolic extract protects pancreatic beta cells against oxidative stress.Nutrients. 2013 Jul 31;5(8):2955-68.

Highlights

FUNDING:

- Mecanismos moleculares y celulares implicados en la patogénesis de la obesidad y DM2 en ratas sometidas a subnutrición materna y posteriormente realimentadas con dieta grasa. MINECO. Ref.BFU 2011-25420. IP: Carmen Álvarez Escolá. (2012-2014).
- Estudio de los mecanismos de resistencia a insulina: implicaciones en obesidad, diabetes y síndrome metabólico (MOIR). Proyecto de la CAM. Ref.P2010/BMD-2423 Programas I+D en Biomedicina/2010. Coordinador Manuel Ros Pérez. URJC. Grupo Enmeper: IP: Fernando Escrivá Pons. (2012-2015)

PAPERS:

- Predominant role of GIP in the development of a metabolic syndrome-like phenotype in female Wistar rats submitted to forced catch-up growth. De Toro-Martín J, Fernández-Millán E, Lizárraga-Mollinedo E, López-Oliva E, Serradas P, Escrivá F, Álvarez C. Enviado a Endocrinology: MN: EN-13-2043 (segunda revisión).
- MA Mobasher, J de Toro-Martín, A González-Rodríguez, S Ramos, LG Letzig, LP James, J Muntané, C Álvarez and AM Valverde. Protein Tyrosine Phosphatase 1B modulates the cross-talk between acetaminophen and insulin signaling in hepatocytes. Enviado al JBC. MS ID#: JBC/2013/539189 en segunda revisión. En colaboración con la Dra. Valverde de CIBERDEM

CONGRESS:

- E. Lizárraga- Mollinedo et al. Obesogenic effect of hypercaloric diet on early undernourished rats; changes in centraland peripheral insulin sensitivity. 49th EASD Annual Meeting. Barcelona, 23-27 September 2013. Diabetología. 56:S1:528
- J. de Toro-Martín et al. "Catch-up growth after intrauterine growth retardation induces gender-specific deregulation of the entero-insular axis" 49th EASD Annual Meeting. Barcelona, September 2013. Diabetología. 56:S1:528-529
- M.A. Martín et al. Flavonol Metabolites produced by colonic microbiota improve glucose stimulated insulin secretion and protect pancreatic beta cells against oxidative damage. 49th EASD Annual Meeting. Barcelona, 23-27 September 2013. Diabetología. 56:S1:199
- E. Fernández-Millán et al. Predominant role of GIP in the development of a metabolic syndrome –like in Wistar rats submitted to forced catch-up growth. XII International Symposium on insulin Receptors and Insulin Action. Barcelona, Spain. November 7-9, 2013.

PROGRAMME: **P4**

The Eicosanoid Research Division

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Rubio Aranda, Julio Miguel

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Main lines of research

- Regulatory roles of eicosanoids in diabetes and obesity.
- Lipid profiling by mass spectrometry; lipidomic and metabolipidomic approaches.
- Biosynthesis and degradation of lipid droplets during cell activation.
- Regulation of omega-6 and omega-3 fatty acid availability; roles of phospholipases A2 and lipins.

Most relevant scientific articles

- Gil-de-Gómez L, Astudillo AM, Meana C, Rubio JM, Guijas C, Balboa MA, Balsinde J. A phosphatidylinositol species acutely generated by activated macrophages regulates innate immune responses.The Journal of Immunology. 2013;190(10):5169-5177.
- Fernández A, Matias N, Fucho R, Ribas V, Von Montfort C, Nuño N, Baulies A, Martínez L, Tarrats N, Mari M, Colell A, Morales A, Dubuquoy L, Mathurin P, Bataller R, Caballeria J, Elena M, Balsinde J, Kaplowitz N,García-Ruiz C, Fernández-Checa JC. ASMase is required for chronic alcohol induced hepatic endoplasmic reticulum stress and mitochondrial cholesterol loading.Journal of Hepatology. 2013;59(4):805-813.

Highlights

Discovery of novel molecular markers and lipid signatures specific for activated cells that could represent potential targets for pharmacological intervention. In particular, a promising novel arachidonate-containing lipid molecular species has been described that could be involved in the regulation of inflammatory responses.

PROGRAMME: **P2**

Diabetes and Cardiovascular

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Main lines of research

- Compensatory mechanisms to hepatic insulin resistance: Progression to type 2 diabetes:

  - The role of the liver-pancreas endocrine axis in triggering beta-cell hyperplasia.

  - The role of autophagy, mitophagy and ER stress in the regulation of beta-cell pancreatic mass and beta-cell failure.

- 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 IGF-1R and IGF-1R/IR DKO.

- New mouse models of browning: Brown adipose tissue-specific knockout of p85 alpha/PI 3 kinase.

- Molecular mechanisms of insulin resistance:

  - The role of IR isoforms in cardiomyocytes, endothelial and aortic vascular smooth muscle cells.

Most relevant scientific articles

- Bartolomé A, López-Herradón A, Portal-Núñez S, García-Aguilar A, Esbrit P, Benito M et al.. Autophagy impairment aggravates the inhibitory effects of high glucose on osteoblast viability and function.Biochem J. 2013 Nov 1;455(3):329-37.
- Gómez-Hernández A, Escribano Ó, Perdomo L, Otero YF, García-Gómez G, Fernández S et al.. Implication of insulin receptor A isoform and IRA/IGF-IR hybrid receptors in the aortic vascular smooth muscle cell proliferation: role of TNF-α and IGF-II.Endocrinology. 2013 Jul;154(7):2352-64.
- de las Heras N, Valero-Muñoz M, Ballesteros S, Gómez-Hernández A, Martín-Fernández B, Blanco-Rivero J et al.. Factors involved in rosuvastatin induction of insulin sensitization in rats fed a high fat diet.Nutr Metab Cardiovasc Dis. 2013 Nov;23(11):1107-14.
- Guillen C, Bartolome A, Vila-Bedmar R, García-Aguilar A, Gomez-Hernández A, Benito M. Concerted expression of the thermogenic and bioenergetic mitochondrial protein machinery in brown adipose tissue.J Cell Biochem. 2013 Oct;114(10):2306-13.
- Gómez-Hernández A, Perdomo L, Escribano Ó, Benito M. [Role of brown and perivascular adipose tissue in vascular complications due to obesity].Clin Investig Arterioscler. 2013 Jan-Mar;25(1):36-44.

Highlights

CURRENT PROJECTS IN 2013:

- Papel de la formación y función del tejido adiposo marrón sobre la patogénesis de la obesidad: recuperación de la función termogénica marrón como terapia antiobesidad. D.G.I.P.N., M.C.INN., SAF2011-22555, 2012 hasta 2014, Lead Researcher: Manuel R. Benito De las Heras
- Estudio de los mecanismos de resistencia a insulina: implicaciones en obesidad, diabetes y síndrome metabólico (MOIR). C.A.M. S2010/BMD-2423, 2012 hasta 2015, Lead Researcher Grupo Consorciado: Manuel R. Benito De las Heras

MOST RELEVANT RESULTS:

Throughout 2013, we have been able to generate the IGF-1R KO and IGF-1R/IR DKO. This is the first new generation of BAT-specific KO after BATIRKO in the two thousands. We have studied the development of BATIGFIRKO under standard diet. The ratio of brown fat mass/body weight did not change versus control upon a year development. However, lipid content and cell size increased in KO mice versus control as revealed by interscapular BAT histology. Western-blot analysis showed a huge increase of IR, IRS-1 and IRS-2 protein expression versus control, suggesting a compensatory mechanism by the insulin signaling upon IGFIR deletion. In addition, UCP-1 expression, the BAT thermogenic marker, was significantly decreased. However, Hsp-60 protein expression did not change in KO mice suggesting that the mitochondrial mass remained unchanged. Also, the expression of mitochondrial CPT-1 remained unchanged, suggesting that fatty acid oxidation capacity by BAT remained invariable. Conversely, the expression of ACC and FAS, lipogenic markers, increased very significantly in KO mice versus controls. These data support the accumulation of lipid that turned out in hypertrophic brown adipocytes as observed by BAT histology in the KO mice. However, the epigonadal white fat mass remained unchanged in the KO mice, with a significant reduction in the inguinal white fat mass. These data were confirmed by NMR studies at 1 year-old mice. Energy expenditure studies showed no significant changes in the KO mice versus controls, suggesting that diet-induced non-shivering thermogenesis was unaffected. However, the cold-induced non-shivering thermogenesis was much affected as revealed by the cold-acclimatation studies performed at 5 0C room temperature. Regarding MOIR project, we have developed new ADV carrying insulin receptor isoforms IRA or IRB. Gene therapy studies revealed that IRA, but not IRB, were able to impair or to revert the diabetic phenotype induced in iLIRKO mice by tamoxifen content diet.

PROGRAMME: **P2**

Metabolic Disease and Cardiovascular Risk

Group Members

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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

- Llaverias G, Escolà-Gil JC, Lerma E, Julve J, Pons C, Cabré A, Cofán M, Ros E, Sánchez-Quesada JL, Blanco-Vaca F. Phytosterols inhibit the tumor growth and lipoprotein oxidizability induced by a high-fat diet in mice with inherited breast cancer.J Nutr Biochem. 2013;24(1):39-48.
- Mendoza-Barberá E, Julve J, Nilsson SK, Lookene A, Martín-Campos JM, Roig R, Lechuga-Sancho AM, Sloan JH, Fuentes-Prior P, Blanco-Vaca F.. Structural and functional analysis of APOA5 mutations identified in patients with severe hypertriglyceridemia.Journal of Lipid Research. 2013;54(3):649-61.
- Escolà-Gil JC, Chen X, Julve J, Quesada H, Santos D, Metso J, Tous M, Jauhiainen M, Blanco-Vaca F.. Hepatic lipase- and endothelial lipase-deficiency in mice promotes macrophage-to-feces RCT and HDL antioxidant propertiesBiochimica Biophysica Acta (Mol Cell Biol Lipids). 2013;183(4):691-7.
- Lee-Rueckert M, Blanco-Vaca F, Kovanen PT, Escola-Gil JC.. The role of the gut in reverse cholesterol transport--focus on the enterocyte.Progress in Lipid Research. 2013;52(3):317-28.
- Julve J, Escolà-Gil JC, Rodríguez-Millán E, Martín-Campos JM, Jauhiainen M, Quesada H, Rentería-Obregón IM, Osada J, Sánchez-Quesada JL, Blanco-Vaca F. Methionine-induced hyperhomocysteinemia impairs the antioxidant ability of high-density lipoproteins without reducing in vivo macrophage-specific reverse cholesterol transport. Mol Nutr Food Res. 2013;57(10):1814-24.

Highlights

PUBLISHED RESEARCH RESULTS

We have demonstrated that: 1) Dietary phytosterols show a protective effect on breast cancer development; 2) rare apoA-V mutations can be responsible of some cases of familial hyperchylomicronemia; 3) hepatic lipase- and endothelial lipase-deficiency affect two well-known HDL antiatherogenic functions, thus constituting potential therapeutic targets; 4) the gut has an emerging role in reverse cholesterol transport; 5) hyperhomocysteinemia induced by a methionine rich-diet impair several HDL functions, a concept that links two different cardiovascular risk factors with protein intake.

BEGINNING OR FUNDING OF NOVEL PROJECTS DURING 2013

- Therapeutic and nutritional strategies based on improvement of antioxidant and anti-inflammatory HDL function in type 2 diabetes and breast cancer. FIS PI12/00291 (2013-15), PI: J.C. Escolà Gil. 198.440 euros.
- Efficacy and security in the management of hyperglycemia at hospital discharge. Spanish Diabetes Society-DIA, 2013-2014, PI: A. Pérez, 207.000 euros
- Sara Borrell Contract, ISCIII. Helena Quesada, 75.600 euros, 2013-15.
- Molecular studies on monogenic dislypidemias and construction of diagnostic and prognostic criteria in patients with familial hypercholesterolemia without identified mutation. PI: J. Julve, PI, Miguel Servet Program, 2014-18, 323.997 euros.

INTERNALIZATION AND TRAINING

Three of the main five selected publications of our group in 2013 include researchers from other countries (Sweden, Estonia, Finland, and USA).

The internalization activities have continued in COST-HDL BM0904 meetings, including assistance to summer schools and short visits to other laboratories of young researchers.

Two PhD thesis have been defended (directors, A. Pérez, and F. Blanco-Vaca), Universitat Autònoma de Barcelona.

CLINICAL PRACTICE GUIDELINES

A. Pérez is a coauthor in eight papers in seven national journals on the adoption of the new European guidelines on cardiovascular prevention to the clinical practice in our country.

PROGRAMME: **P1**

Brain Glucose Sensor, Satiety Control, Insulin Resistance and Type 2 Diabetes

Group Members

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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

- Verónica Hurtado-Carneiro, Isabel Roncero, Enrique Blázquez, Elvira Álvarez, Carmen Sanz. PAS kinase as a nutrient sensor in neuroblastoma and hypothalamic cells required for the normal expression and activity of other cellular nutrient and energy sensors Molecular Neurobiology. 2013;48(3):904-920.
- Verónica Hurtado, Isabel Roncero, Enrique Blázquez, Elvira Álvarez and Carmen Sanz. Glucagon-Like Peptide-1 and Its Implications in ObesityINTECH. HOT TOPICS IN ENDOCRINE AND ENDOCRINE-RELATED DISEASES. 2013;CHAPTER 7:165-195.
- Isabel Roncero, Elvira Álvarez, Carlos Acosta, Carmen Sanz, Pedro Barrio, Verónica Hurtado, Deborah Burks, Enrique Blázquez. Insulin-receptor substrate-2 (IRS-2) required for mantaining glucokinase and glucokinase regulatory protein expresion in mouse liverPloS one. 2013;8.

Highlights

PROJECTS AND COLLABORATIONS:

- Grant from Fundación Mutua Madrileña, awarded to Dr. Enrique Blázquez Fernández in 2013.
- Collaboration with Deborah Burks in studies with IRS-2 -/- animals.
- Collaboration with Prof. Lucia Sacchetti (Federico II University, Naples) in the analysis of mutations in the GK gene identified in children with MODY2 in southern Italy.
- Collaboration with Prof. Roland H. Wenger (Institute of Physiology, University of Zürich- Irchel) in the study of PASK-deficient animals.
- X Course for Postgraduates. Fundamentos Moleculares de la Medicina, organized by Dr. Enrique Blázquez Fernández, at RANM (May 2013).

CONGRESOS:

- Navas MA, Gutierrez-Nogués A, García-Herrero CM, Oriola J, Casamitjana R and Vincent O. FUNCTIONAL ANALYSIS OF MUTATIONS IN THE MODY2 NUCLEAR EXPORT SIGNAL OF GLUCOKINASE. Poster / Oral. 49th EASD Annual Meeting of the European Association for the Study of Diabetes . Diabetologia 56: S143. Barcelona.
- Gutierrez-Nogués A, García-Herrero CM, Castrillón-Correa AM, Vincent O y Navas MA. FUNCTIONAL ANALYSIS OF MUTATIONS ASSOCIATED WITH DIABETES MONOGENIC MODY2 LOCATED IN NUCLEAR SIGNAL DE EXPORTACIÓN glucokinase. Poster. CONGRESS: XXXVI Congress of the Spanish Society of Biochemistry and Molecular Biology. Madrid.
- Rosa Martínez Salazar, Ángel Gutiérrez-Nogués, María Ortiz, Inés Urrutia, Concepción Fernández, Amaia Vela, Mercedes Gil Campos, Joan Bel, Mª Teresa García Silva, Concepción Blanco, María Ángeles Navas y Luis Castaño. HYPERINSULINISM CAUSED BY ACTIVATING MUTATIONS IN GLUCOKINASE: NEW MUTATION AND FUNCTIONAL CHARACTERIZATION. Poster. XXVII National Congress of the Spanish Association of Human Genetics. Madrid.
- Enrique Blázquez Fernández. Assistance. 48th EASD Annual Meeting of the European Association for the Study of Diabetes. Barcelona. Master Thesis in Biochemistry, Molecular Biology and Biomedicine. Ana María Castrillón Correa. Effects of the mutations L309P and L309H, that cause familiar hyperglycemia or MODY2 on the regulation of glucokinase. Directed by Mª Ángeles Navas.

PROGRAMME: **P3**

Transgenic Animal Models and Gene Therapy Approaches for Diabetes

Group Members

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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

- McMurray F, Church CD, Larder R, Nicholson G, Wells S, Teboul L, Tung YC, Rimmington D, Bosch F, Jiménez V, Yeo GS, O'Rahilly S, Ashcroft FM, Coll AP, Cox RD. Adult onset global loss of the fto gene alters body composition and metabolism in the mousep. los Genetics. 2013 ;9(1):e1003166.
- Anguela XM, Tafuro S, Roca C, Callejas D, Agudo J, Obach M, Ribera A, Ruzo A, Mann CJ, Casellas A, Bosch F. Non-viral-mediated hepatic expression of igf-i increases treg levels and suppresses autoimmune diabetes in mice. Diabetes. 2013 ;62(2):551-560.
- Callejas D, Mann C, Ayuso E, Lage R, Grifoll I, Roca C, Andaluz A, Ruiz-de Gopegui R, Montané J, Muñoz S, Ferré T, Haurigot V, Zhou S, Ruberte J, Mingozzi F, High K, García F and Bosch F. Treatment of diabetes and long-term survival after insulin and glucokinase gene therapy. Diabetes. 2013;62 (5):1718-1729.
- Villacampa P, Ribera A, Motas S, Ramírez L, García M, De la Villa P, Haurigot V & Bosch F. Insulin-like growth factor i (igf-i)-induced chronic gliosis and retinal stress lead to neurodegeneration in a mouse model of retinopathy. Journal of Biological Chemistry. 2013;228(24):17631-42.
- Jiménez V, Muñoz S, Casaña E, Mallol C, Elias I, Jambrina C, Ribera A, Ferre T, Franckhauser F & Bosch F. In vivo aav-mediated genetic engineering of white and brown adipose tissue in adult mice. Diabetes. 2013;62(12):4012-22.

Highlights

Our group is participating in the EU, Programme "Capacities"-Call "FP7-INFRASTRUCTURES-2012-1 "The European infrastructure for phenotyping and archiving of model mammalian genomes (Infrafrontier-I3)", for high-throughput mouse phenotyping. We are also involved in the "International Mouse Phenotyping Consortium", initiative including Mouse Clinics around the world (Europe, United States, Canada, Australia and China).

We are part of the collaborative project BETASEL-"In vivo selection of genes and miRNAs improving betacell mass", funded by the Juvenile Diabetes Research Foundation, together with Dr. Mauro Giacca (Trieste, Italy), and Dr. Philippe Halban (Geneva, Switzerland).

On the other hand, our group is granted by European Foundation for the Study of Diabetes (EFSD)/MSD Programme 2013 for the project "Unravelling of novel factors capable of inducing Browning of WAT in vivo", aiming to identify new mechanisms involved in white adipose tissue browning, which may open the way for new treatment of diabetes and obesity. We also count with funds from Ministerio de Educación y Ciencia, Plan Nacional I+D+I (SAF2011-24698) "Ingeniería genética del músculo esquelético para expresar insulina y/o glucoquinasa para el tratamiento de la diabetes mellitus", a project aiming to develop new gene therapy approaches for the treatment of diabetes based on genetic engineering of the skeletal muscle to increase glucose uptake and produce insulin.

Our group, from the Autonomous University of Barcelona, together with Ciberdem and the German Center for Diabetes Research (DZD), organized the "XII INTERNATIONAL SYMPOSIUM ON INSULIN RECEPTORS AND INSULIN ACTION: NEW OPPORTUNITIES FOR THE PREVENTION AND TREATMENT OF DIABETES IN THE XXI CENTURY (IR2013)". This symposium, held in Barcelona form 7th to 9th of November 2013 follows a long tradition since 1981 and counts with the participation of the best international experts in the field. IR2013 has been a great success for the 300 participants.

PROGRAMME: **P3**

Laboratory of Molecular Endocrinology

Group Members

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Main lines of research

The incidence of diabetes and obesity is increasing at alarming rates throughout the world, creating a significant social and economic burden in industrialised countries. Defective expression or function of insulin signalling pathway components, such as the IRS (insulin receptor substrate) proteins, causes insulin resistance, which occurs with normal ageing but is also a hallmark of disease states such as diabetes. The overall aim of our research is to understand precisely how impaired insulin signalling contributes to metabolic diseases. Our research therefore focuses on several major themes:

- Regulation of the cell cycle in pancreatic beta cells.
- The role of IRS-2 signals in the differentiation of human pluripotent stem cells to progenitors of pancreas and liver.
- IRS-2 signalling in the regulation of neuronal function.
- The role of insulin/IGF-I signalling in diabetic retinopathy.
- The role of IRS2 in adipocyte progenitors and development of obesity.

Most relevant scientific articles

- Griffeth RJ, Carretero J, Burks DJ.. Insulin receptor substrate 2 is required for testicular development.PLoS One. 2013;May 31(8(5)):e62103.
- González-Navarro H, Vinué Á, Sanz MJ, Delgado M, Pozo MA, Serrano M, Burks DJ, Andrés V.. Increased dosage of Ink4/Arf protects against glucose intolerance and insulin resistance associated with aging.Aging Cell. 2013 ;Feb(12(1)):102-11.
- Isabel Roncero, Elvira Álvarez, Carlos Acosta, Carmen Sanz, Pedro Barrio, Verónica Hurtado, Deborah Burks, Enrique Blázquez. Insulin-receptor substrate-2 (IRS-2) required for mantaining glucokinase and glucokinase regulatory protein expresion in mouse liverPloS one. 2013;8.
- Hernández C, Simó R, European Consortium for the Early Treatment of Diabetic Retinopathy (EUROCONDOR). Somatostatin replacement: a new strategy for treating diabetic retinopathy.Curr Med Chem. 2013;20(26):3251-7.
- Arroba AI, Revuelta-Cervantes J, Menes L, González-Rodríguez Á, Pardo V, de la Villa P et al.. Loss of protein tyrosine phosphatase 1B increases IGF-I receptor tyrosine phosphorylation but does not rescue retinal defects in IRS2-deficient mice.Invest Ophthalmol Vis Sci. 2013 Jun 19;54(6):4215-25.

Highlights

In addition to the work published by our group in 2013 we have continued to work as active members of the European Consortium for the Early Treatment of Diabetic Retinopathy (EUROCONDOR, FP7-278040-2. FP7-HEALTH-2011: 2012-2015 Programme 3) and the "Innovative strategies to generate human hepatocytes" "InnovaLIV" consortium (FP7: 2011-2014, Programme 3). Veronica Moreno Viedma successfully defended her PhD thesis entitled "Role of IRS2 in Obesity and Adipogenesis" (May, 2013) and Dr Luke Noon performed a successful 1 year DIAbetes Transnational Research Advancement for INvestigators (DIATRAIN) Fellowship in the laboratory of Professor Scott Friedman at The Icahn School of Medicine at Mount Sinai (New York, USA).

PROGRAMME: **P1**

Dyslipidaemia, Inflammation and Endothelial Dysfunction

Group Members

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Main lines of research

- Study of genetic variations present in the exome related to development of type 2 diabetes and its consecuences.
- Study of insulin resistance and diabetes.
- Detection of genetic alterations (mutations or polymorphisms) involved in the development of complex diseases with high cardiovascular risk focused on genes related to the mitochondrial respiratory chain, oxidative stress, lipid metabolism and diabetes.
- Diagnosis, preventionand treatment of diabetic foot.
- Study of autosomal dominant hypercholesterolemias and familial combined hyperlipidemia.
- Effect of postprandial lipidemia on cardiovascular system, mainly on lipid profile, inflammatory markers and oxidative stress and the response of circulanting cells to stress caused by hyperlipidemia.
- Genetic factors involved in the regulation of Body Mass Index (BMI), waist circumference and obesity develpment.

Most relevant scientific articles

- Silbernagel G, Chapman MJ, Genser B, Kleber ME, Fauler G, Scharnagl H et al.. High intestinal cholesterol absorption is associated with cardiovascular disease and risk alleles in ABCG8 and ABO: evidence from the LURIC and YFS cohorts and from a meta-analysis.J Am Coll Cardiol. 2013 Jul 23;62(4):291-9.
- Soriguer F, Gutiérrez-Repiso C, Rubio-Martín E, García-Fuentes E, Almaraz MC, Colomo N et al.. Metabolically healthy but obese, a matter of time? Findings from the prospective Pizarra study.J Clin Endocrinol Metab. 2013 Jun;98(6):2318-25.
- Martín-Núñez GM, Cabrera-Mulero R, Rojo-Martínez G, Gómez-Zumaquero JM, Chaves FJ, de Marco G et al.. Polymorphisms in the SCD1 gene are associated with indices of stearoyl CoA desaturase activity and obesity: a prospective study.Mol Nutr Food Res. 2013 Dec;57(12):2177-84.
- Rojo-Martínez G, Soriguer F, Colomo N, Calle A, Goday A, Bordiú E et al.. Factors determining high-sensitivity C-reactive protein values in the Spanish population. Di@bet.es study.Eur J Clin Invest. 2013 Jan;43(1):1-10.
- Gutiérrez-Repiso C, Rojo-Martínez G, Soriguer F, García-Fuentes E, Vendrell J, Vázquez JA et al.. Factors affecting levels of urinary albumin excretion in the general population of Spain: the Di@bet.es study.Clin Sci (Lond). 2013 Feb;124(4):269-77.

Highlights

- Study of insulin resistance and diabetes. The aim is the early detection of insulin-resistance, identifying early markers and risk and inflammatory factors linked to this condition. Identification of the correlation between the levels of C-reactive protein and the incidence of type 2 diabetes and identification of the correlation between levels of homocysteine and diabetic neuropathy.
- Detection of genetic alterations (mutations or polymorphisms) involved in the development of complex diseases with high cardiovascular risk focused on genes related to the mitochondrial respiratory chain, oxidative stress, lipid metabolism and diabetes. We have studied the association of 65 polymorphisms found in 25 genes of the mitochondrial respiratory chain. We have identified several polymorphisms associated with significant risk of developing obesity and metabolic syndrome.ç
- Diagnosis, preventionand treatment of diabetic foot. Confirmation of our previous results connecting plasma homocysteine levels and risk for diabetic foot ulceration
- Study of autosomal dominant hypercholesterolemias and familial combined hyperlipidemia. An analysis of inflammation markers has been performed, as well as a comprehensive biochemical profile and a collection of clinical and genetic characteristics.
- Effect of postprandial lipidemia on cardiovascular system, mainly on lipid profile, inflammatory markers and oxidative stress and the response of circulanting cells to stress caused by hyperlipidemia. Studies of oral lipid overload in obese diabetic patients have been carried out to study cell response to fatty acid delivery. Expression of all genes present in the lymphomonocytes of these patients has been examined comparing with control subjects and the results are currently being analyzed.
- Genetic factors involved in the regulation of Body Mass Index (BMI), waist circumference and obesity develpment. Study of oxidative stress and other aspects of metabolism as factors able to modulate development of obesity. Levels of certain free radicals and oxidative stress regulate metabolism and energy homeostasis.

PROGRAMME: **P3**

Hospital de Cruces Endocrinology and Diabetes Research Group

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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 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 (both CGI and CGH approaches).
- 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

- Martín-Núñez GM, Cabrera-Mulero R, Rojo-Martínez G, Gómez-Zumaquero JM, Chaves FJ, de Marco G et al.. Polymorphisms in the SCD1 gene are associated with indices of stearoyl CoA desaturase activity and obesity: a prospective study.Mol Nutr Food Res. 2013 Dec;57(12):2177-84.
- Gutiérrez-Repiso C, Rojo-Martínez G, Soriguer F, García-Fuentes E, Vendrell J, Vázquez JA et al.. Factors affecting levels of urinary albumin excretion in the general population of Spain: the Di@bet.es study.Clin Sci (Lond). 2013 Feb;124(4):269-77.
- Moran A, Bundy B, Becker DJ, DiMeglio LA, Gitelman SE, Goland R et al.. Interleukin-1 antagonism in type 1 diabetes of recent onset: two multicentre, randomised, double-blind, placebo-controlled trials.Lancet. 2013 Jun 1;381(9881):1905-15.
- Cameron FJ, de Beaufort C, Aanstoot HJ, Hoey H, Lange K, Castano L et al.. Lessons from the Hvidoere International Study Group on childhood diabetes: be dogmatic about outcome and flexible in approach.Pediatr Diabetes. 2013 Nov;14(7):473-80.
- de Beaufort CE, Lange K, Swift PG, Aman J, Cameron F, Castano L et al.. Metabolic outcomes in young children with type 1 diabetes differ between treatment centers: the Hvidoere Study in Young Children 2009.Pediatr Diabetes. 2013 Sep;14(6):422-8.

Highlights

- Participation in international projects on diabetes prevention, either nutritional (TRIGR project-NIH 5U01HD040364-08) or about immunomodulation using antigens (Dyamid Project).
- Colaboration with the International Group of Pediatric Diabetes (Hvidore Group)
- Completion of Di@betes Study: study about the epidemiology of diabetes in Spain; completion of the Basque study about epidemiology of diabetes in the Basque Country (Basque Health Department GV2010111058)
- Participation in the Europen MEDIGENE Project (FP7-279171-1) about characterization of diabetes in Mediterranean populations.
- Development of projects about molecular characterization of monogenic diabetes (Basque Department of Education GV IT795-3; Basque Health Department GV 2010111185).

During the development of these projects, more than 16 articles have been published in several journals (i.e.: ,:Moran A, et al. Interleukin-1 antagonism in type 1 diabetes of recent onset: two multicenter, randomized, double-blind, placebo-controlled trials. Lancet. 2013 Jun 1;381(9881):1905-15)

PROGRAMME: **P1**

Metabolomics Platform

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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 NIMS (Nanostructure Initiator Mass Spectrometry).

Most relevant scientific articles

- Samino S, Revuelta-Cervantes J, Vinaixa M, Rodríguez MA, Valverde AM, Correig X. A (1)H NMR metabolic profiling to the assessment of protein tyrosine phosphatase 1B role in liver regeneration after partial hepatectomy.Biochimie. 2012 Dec 12;.
- Mallol R, Rodríguez MA, Brezmes J, Masana L, Correig X. Human serum/plasma lipoprotein analysis by NMR: application to the study of diabetic dyslipidemia.Prog Nucl Magn Reson Spectrosc. 2013 Apr;70:1-24.
- Catalán Ú, Rodríguez MÁ, Ras MR, Maciá A, Mallol R, Vinaixa M et al.. Biomarkers of food intake and metabolite differences between plasma and red blood cell matrices; a human metabolomic profile approach.Mol Biosyst. 2013 Jun;9(6):1411-22.
- Bondia-Pons I, Cañellas N, Abete I, Rodríguez MÁ, Perez-Cornago A, Navas-Carretero S et al.. Nutrimetabolomics: subtle serum metabolic differences in healthy subjects by NMR-based metabolomics after a short-term nutritional intervention with two tomato sauces.OMICS. 2013 Dec;17(12):611-8.
- Canellas N, Sola-Alberich R, Brezmes J, Mallol R, Valls RM, Rodríguez MA, Vinaixa M, Anguera A, Correig X. Use of multivariate chemometric algorithms on H-1 NMR data to assess a soluble fiber (Plantago ovata husk) nutritional interventionCHEMOMETRICS AND INTELLIGENT LABORATORY SYSTEMS. 2013;121:1-8.

Highlights

COLLABORATIONS WITH GROUPS FROM CIBERDEM

- Group J. Guinovart: Metabolomic study of neuronal cells under hypoxia
- Group R. Gomis: Metabolomic study of adipose tissue of obese animal models
- Group R. Simó: Metabolomic study in cells from the pigment epithelium of the retina in hyperglycemia and / or hypoxia
- Group L. Ibáñez: Metabolomic study in PCOS patients undergoing different treatments
- Group L. Masana: Study of diabetic dyslipidemia through advanced characterization of lipoproteins
- Group A.Novials: Study of the effects of exercise in T1DM
- Group A. Novials: Characterization of pancreatic islets in diabetic rats from images obtained by mass spectrometry (MALDI-TOF)
- Group J. Egido: Metabolomic study in patients with diabetic nephropathy
- Group G. Rojo: Metabolomics characterization of dairy products to assess their impact on health in T2DM patients
- Group A. Valverde: Metabolomic study on liver regeneration
- Participation in the project Pilchardus (transversal project CIBERDEM)

RELEVANT PROJECTS:

- 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:

- Creation and validation of an advanced method for lipoprotein characterization
- Identification of biomarkers of subclinical atherosclerosis in PCOS patients
- Identification of metabolic pathways altered by hyperglycemia and/or hypoxia in cells from the pigment epithelium of the retine
- Creation and validation of a new algorithm for the identification of unknown metabolites by mass spectrometry

INNOVATION

- Registration of two european patents relating to the creation of an advanced method for lipoprotein characterization (EP13382478.9) and for modeling of HDL in atherogenic dyslipidemia (EP13382477.1)
- Creation of Biosfer Teslab (http://biosferteslab.com/es/), an spin-off company of the University Rovira i Virgili to commercialize an advanced lipoprotein test (Liposcale)

PROGRAMME: **P2**

Division of Nephrology and Hypertension, Instituto de Investigaciones Sanitarias Fundación Jiménez Díaz

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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.

Most relevant scientific articles

- Rayego-Mateos S, Morgado-Pascual JL, Sanz AB, Ramos AM, Eguchi S, Batlle D, Pato J, Keri G, Egido J, Ortiz A, Ruiz-Ortega M. TWEAK transactivation of the epidermal growth factor receptorJournal of Pathology. 2013; 231: :480–494.
- González-Parra E, Herrero JA, Elewa U, Bosch RJ, Arduán AO, Egido J. Bisphenol A in Chronic Kidney DiseaseInternational Journal of Nephrology. 2013;2013(437857).
- Ramírez E, Klett-Mingo M, Ares-Carrasco S, Picatoste B, Ferrarini A, Rupérez FJ, Caro-Vadillo A, Barbas C, Egido J, Tuñón J, Lorenzo Ó. Eplerenone attenuated cardiac steatosis, apoptosis and diastolic dysfunction in experimental type-II diabetesCardiovascular Diabetology. 2013; 12:172.
- Moreno P, Mantey SA, Nuche-Berenguer B, Reitman ML, González N, Coy DH, Jensen RT.. Comparative pharmacology of bombesin receptor subtype-3, nonpeptide agonist MK-5046, a universal peptide agonist, and peptide antagonist Bantag-1 for human bombesin receptors.J Pharmacol Exp Ther. . 2013; 347:100-16.
- Portal-Núñez S, Cruces J, Gutiérrez-Rojas I, Lozano D, Ardura JA, Villanueva-Peñacarrillo ML, De la Fuente M, Esbrit P.. The vertebrae of prematurely aging mice as a skeletal model of involutional osteoporosis.Histol Histopathol. . 2013;28:1473-81.

Highlights

PROJECTS:

- Project Title: Diabetes Cancer Connect: Targeting common inflammatory markers and signaling pathways in cancer and diabetes mellitus. Role: Principal Investigator in the Integrated Project for Excellence in Research Institutes Accredited, Coordinated by Dr. Jesús Egido Rivers. Funding Agency: Institute of Health Carlos III (PIE 13/00051). Financing: 800.000 €. Duration (funding period): 3 years (2014-2016).
- Project Title: Study on the role of bombesin receptor subtype-3 in human adipose tissue: potential use as a therapeutic target in obesity and diabetes. Role: Principal Investigator. Funding Agency: Mutua Madrileña (12224/2). Funding: 20,000 €. Duration (funding period): 2 years (2013-2014).

PATENT PREPARATION:

- SOCS 1 derived peptide for use in chronic complications of diabetes. In collaboration with our center (Carmen Gomez-Guerrero and Jesus Egido) and the Diabetes Research Center of the Vall d'Hebron (Cristina Hernandez and Rafael Simó).

PROGRAMME: **P4**

Diabetes, Obesity and Human Reproduction

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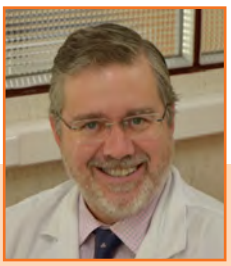

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Main lines of research

- Influence of the balance between androgens and oestrogens 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.

Most relevant scientific articles

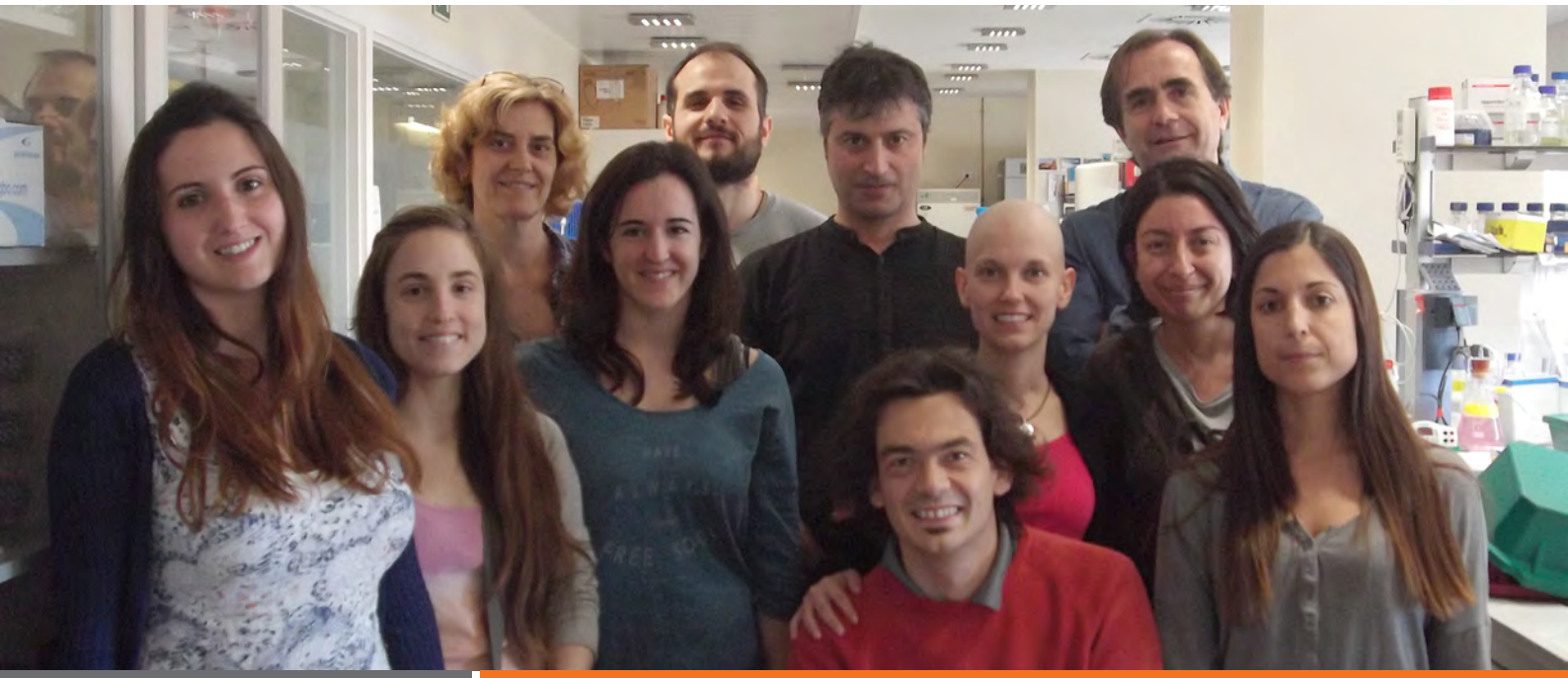
- Murri M, Luque-Ramírez M, Insenser M, Ojeda-Ojeda M, Escobar-Morreale HF. Circulating markers of oxidative stress and polycystic ovary syndrome (PCOS): a systematic review and meta-analysisHum Reprod Update. 2013;19(3):268-88.
- Martínez-García MÁ, Montes-Nieto R, Fernández-Durán E, Insenser M, Luque-Ramírez M, Escobar-Morreale HF. Evidence for masculinization of adipokine gene expression in visceral and subcutaneous adipose tissue of obese women with polycystic ovary syndrome (PCOS)J Clin Endocrinol Metab. 2013 Feb;98(2):E388–E396 .
- Montes-Nieto R, Insenser M, Martínez-García MA, Escobar-Morreale HF. A Nontargeted Proteomic Study of the Influence of Androgen Excess on Human Visceral and Subcutaneous Adipose Tissue ProteomesJ Clin Endocrinol Metab. 2013];98(3):E576-E585.
- Borruel S, Fernández-Durán E, Alpañés M, Martí D, Álvarez-Blasco F, Luque-Ramírez M, Escobar-Morreale HF. Global Adiposity and Thickness of Intraperitoneal and Mesenteric Adipose Tissue Depots Are Increased in Women With Polycystic Ovary Syndrome (PCOS).J Clin Endocrinol Metab. 2013;98(3):1254-1263.
- M. Luque-Ramírez, M. A. Martínez-García, R. Montes-Nieto, E. Fernández-Durán, M. Insenser, M. Alpañés, H. F. Escobar-Morreale. Sexual dimorphism in adipose tissue function as evidenced by circulating adipokine concentrations in the fasting state and after an oral glucose challengeHuman Reproduction. 2013;28(7):1908–1918.

Highlights

During 2013 we have studied the influence of sex steroids on the mechanisms implicated in abdominal adiposity and adipose tissue dysfunction. This line of research has lead to several scientific articles indicating that hyperandrogenic women have increased global adiposity and visceral fat when compared with control women. Though to a lesser extent, these women resemble men in their anthropometric and metabolic characteristics at the gene expression and protein abundance levels. We have also confirmed the existence of a sexual dimorphism in adipose tissue at these levels.

With the funding provided by a FIS grant (Intrasalud PI11/00357) we are carrying out a study in women with and without androgen excess and men with the aim to determine the hormonal, metabolic, inflammatory, oxidative stress responses to the different dietary macronutrients. The study of the polycystic ovary syndrome suggests that certain macronutrients, particularly soluble carbohydrates, induce unfavorable inflammatory and oxidative responses that may contribute to its association with insulin resistance, abdominal adiposity and cardiovascular risk.

Regarding collaborations, we have published the proteomic study of visceral adipose tissue in overweight patients with type 2 diabetes (Dr. Tinahones' group, CIBEROBN), we are currently collaborating with the groups of Drs. Pasquali (University of Bologna, Italy), Kelestimur (University of Erciyes, Turkey) and Pignatelli (University of Porto, Portugal) and participate in collaborative efforts addressing the study of polycystic ovary syndromeof the European Society of Endocrinology and the Androgen Excess & PCOS Society. Regarding clinical practice we have contributed to the clinical guideline "Definition and significance of polycystic ovarian morphology: a task force report from the Androgen Excess and Polycystic Ovary Syndrome Society. Hum Reprod Update. Epub 2013 Dec 16. doi: 10.1093/humupd/dmt061".



PROGRAMAS: **P3 y P4**

Genomic Programming of Beta Cells and Diabetes

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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

- van Arensbergen J, García-Hurtado J, Maestro MA, Correa-Tapia M, Rutter GA, Vidal M et al.. Ring1b bookmarks genes in pancreatic embryonic progenitors for repression in adult β cells.Genes Dev. 2013 Jan 1;27(1):52-63.
- Al-Hasani K, Pfeifer A, Courtney M, Ben-Othman N, Gjernes E, Vieira A et al.. Adult duct-lining cells can reprogram into β-like cells able to counter repeated cycles of toxin-induced diabetes.Dev Cell. 2013 Jul 15;26(1):86-100.
- van de Bunt M, Gaulton KJ, Parts L, Moran I, Johnson PR, Lindgren CM et al.. The miRNA profile of human pancreatic islets and beta-cells and relationship to type 2 diabetes pathogenesis.PLoS One. 2013;8(1):e55272.
- Jeliazkova P, Jörs S, Lee M, Zimber-Strobl U, Ferrer J, Schmid RM et al.. Canonical Notch2 signaling determines biliary cell fates of embryonic hepatoblasts and adult hepatocytes independent of Hes1.Hepatology. 2013 Jun;57(6):2469-79.

Highlights

- Dissection of the genetic mechanisms underlying the pathogenesis of human diabetes.

  Throughout the year 2013 the team has completed major projects that have addressed the importance of non-coding genomic defects in human diabetes. This has led to publications in which members of this team are first and senior authors (Pasquali et al, Nature Genetics 2014; Weedon, Cebola et al, Nature Genetics 2014). We have further collaborated in a study that describes human pancreatic islet miRNAs, and reports potential role in Type 2 diabetes (van de Bunt, Plos One 2013).

- Understanding the epigenome of pancreatic beta cells and its implications for the development, plasticity and growth of beta cells

  Our team has employed conditional mouse KOs, engineered cell lines, and epigenomic studies to clarify the role of an epigenetic regulator in the formation of pancreatic lineages (van Arensbergen et al, Genes and Development, 2013).

- Mouse genetic analysis of beta-cell gene regulation.

  The team has participated in an international study that used mouse and human models to show that Argonaute 2 and miR-184 play a central role in the proliferative response of beta cells to insulin resistance, and are thus relevant to the pathogenesis of Type 2 diabetes (Tattikota, Cell Metab, 2014)

- The regeneration of pancreatic beta cells.

  We have participated in international collaborative studies that have revealed novel mechanisms important for the regeneration (Al Hasani et al, Dev Cell, 2013; Baeyens et al, Nature Biotechnol, 2014) plasticity and tumorignesis (von Figura, Nature Cell Biol, 2014) of pancreatic cells.

  Team members have presented this work in invited seminars in prestigious international settings (Epigenetics Keystone Symposium in Monterrey, Gordon Research Conferences, Mount Holyoke, Wellcome Trust Sanger Institute, Kyoto Beta Cell Workshop, Dynamics of Stem Cell Decisions, Niels Bohr Institute, EMBO Pancreas and liver Biology Meeting, Cape Sounion, among others). The Team Leader has received a Senior Investigator Prize from the Spanish Society of Diabetes. Finally, the team has organized a CIBERDEM Symposium in Sitges, entitled Beta Cell Genome Regulation and Regeneration (October, 2014).

PROGRAMME: **P4**

Mechanisms Of Control Of Glucose And Fatty Acid Metabolism In Skeletal Muscle Cells And Metabolic Impairment In Atrophy

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Main lines of research

- Mechanisms of control of skeletal muscle glycogen metabolism: differential functionality of the protein phosphatase 1 glycogen-associated regulatory subunits and function of GNIP1 (glycogenin Interacting Protein 1) / TRIM7.
- Participation and identity of signaling molecules derived from palmitate metabolism in the impairment of muscle cell insulin response and induction of an inflammatory signal. Metabolic control by the fatty acid transport protein 1 (FATP1) in the context of high-fat diet induced diabetes.
- Role of secretable proteins predominant in adipose tissue and muscle, such as PTX3, CCDC80 or collagen VI, in the modulation of insulin signaling and glucose metabolism in adipocytes and muscle cells.
- Development of an electroporator device directly applicable to adherent cells cultured on standard multiwell plates to facilitate molecular transfer.

Most relevant scientific articles

- Montori-Grau M, Tarrats N, Osorio-Conles O, Orozco A, Serrano-Marco L, Vázquez-Carrera M et al.. Glucose dependence of glycogen synthase activity regulation by GSK3 and MEK/ERK inhibitors and angiotensin-(1-7) action on these pathways in cultured human myotubes.Cell Signal. 2013 May;25(5):1318-27.
- Paco S, Kalko SG, Jou C, Rodríguez MA, Corbera J, Muntoni F et al.. Gene expression profiling identifies molecular pathways associated with collagen VI deficiency and provides novel therapeutic targets.PLoS One. 2013;8(10):e77430.

Highlights

- Postdoctoral stay (01-09- 2012 / 11-31-2013) of Dr. Marta Montori (CIBERDEM researcher) in the laboratory of Dr. Solange Desagher (Institut de Génétique Moléculaire, Montpellier, France) to develop the project "Study of the biological activity and metabolic control role of Glycogenin-interacting protein (GNIP) / Tripartite motif-containing protein 7 (TRIM7) in skeletal muscle" granted by the DIAbetes Trans-national Research Advancement for INvestigators (DIATRAIN) enclosed under the FP7-People Co-funding of Regional, National and International Program (FP7-People-2010-COFUND) of the European Commission.
- Project SAF2012-37480 "Mechanisms of Control of glucose and fatty acid metabolism in skeletal muscle and transcriptome analysis and phenotype of cultured human myogenic cells derived from adult and embryonic stem cells." Funded by: Ministerio de Economía y Competitividad, España. IP: Ana M. Gómez Foix. Entity: Universitat de Barcelona. Duration: 01-01-2013 to 31-12-2015. Grant amount: € 93,600.
- Publications in collaboration: Oleate prevents saturated-fatty-acid-induced ER stress, inflammation and insulin resistance in skeletal muscle cells through an AMPK-dependent mechanism. Salvadó L, Coll T, Gómez-Foix AM, Salmerón E, Barroso E, Palomer X, Vázquez-Carrera M. Diabetologia. 2013 Jun;56(6):1372-82.
- Patent Publication: WO 2013/167185. Electrode assembly for generating electric field pulses to perform electroporation to a biological sample. Tomás García Sánchez, Xavier Rosell Ferrer, Ramon Bragós Bardia, Ana M. Gómez Foix, Maria Guitart De la Rosa, Beatriz Sánchez Ortiz. Release: November 14, 2013. Entities: Universitat Politècnica de Catalunya and Universitat de Barcelona. International application.
- Patent application: ES 201231787. Uso de colágeno VI soluble para la fabricación de un medicamento para el tratamiento de enfermedades asociadas a hiperglucemia, composición farmacéutica, método y uso de un medio líquido extracelular para incrementar la captura de glucosa. Cecilia Jimenez Mallebrera, Ana M. Gomez Foix y Oscar Osorio Conles. Priority date: November 19, 2012. Resubmitted PCT November 2013. Entity: Fundació Sant Joan de Deu. Priority country: Spain.

PROGRAMME: **P2 y P3**

Diabetes and Obesity: Biopathology and Cellular Plasticity

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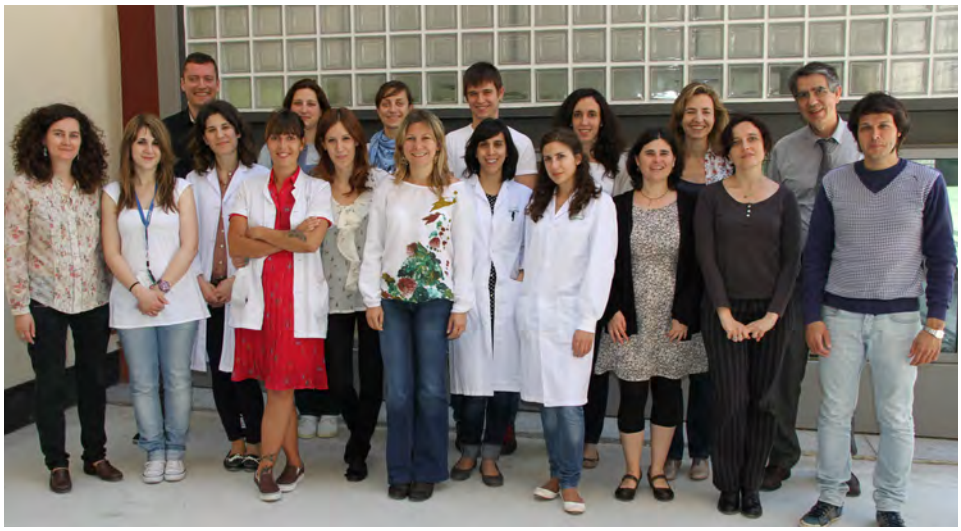
Conget Donlo, Ignacio
Esmatjes Mompo, Enrique
Fernández Rebollo, Eduardo
Flores Meneses, Lilliam
Gasa Arnaldich, Rosa María
Giménez Álvarez, Margarita
Hanzu, Felicia Alexandra
Martins de Sousa Maia Malpique, Rita M.
Mora Porta, Mireia
Nadal Belén
Nicod, Nathalie
Ortega Martínez de Victoria, Emilio C.
Papageorgiou, Aikaterini
Parrizas Jiménez, Marcelina
Pradas Marta
Schneeberger, Marc
Vidal Cortada, Josep



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Main lines of research

- The effects of pancreatic-mesenteric adipose tissue on beta-cell plasticity
- Crosstalk between adipose tissue and endothelium in obesity and type 2 diabetes: 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
- Metabolic and molecular targets of the antidiabetic effect of sodium tungstate
- 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

Most relevant scientific articles

- Rebuffat SA, Oliveira JM, Altirriba J, Palau N, García A, Esteban Y et al.. Downregulation of Sfrp5 promotes beta cell proliferation during obesity in the rat.Diabetologia. 2013 Nov;56(11):2446-55.
- Jiménez A, Perea V, Corcelles R, Moizé V, Lacy A, Vidal J. Metabolic Effects of Bariatric Surgery in Insulin-Sensitive Morbidly Obese Subjects.Obes Surg. 2013;.
- Jiménez A, Casamitjana R, Viaplana-Masclans J, Lacy A, Vidal J. GLP-1 action and glucose tolerance in subjects with remission of type 2 diabetes after gastric bypass surgery. Diabetes Care. 2013 Jul;36(7):2062-9.
- Ejarque M, Cervantes S, Pujadas G, Tutusaus A, Sánchez L, Gasa R. Neurogenin3 cooperates with Foxa2 to autoactivate its own expression.J Biol Chem. 2013 Apr 26;288(17):11705-17.
- Schneeberger M, Dietrich MO, Sebastián D, Imbernón M, Castaño C, García A et al.. Mitofusin 2 in POMC neurons connects ER stress with leptin resistance and energy imbalance.Cell. 2013 Sep 26;155(1):172-87.

Highlights

Three important projects stand out among the activities of our group during 2013:

a) the MEDIGENE project, funded by the European Commission, which focuses on understanding the environmental and genetic determinants that influence the incidence of diabetes in immigrant Mediterranean populations. During the second year of the project, many objectives have already been achieved, including the analysis of genes underlying susceptibility to metabolic syndrome in the Spanish population. We also created a biobank of genomic and mitochondrial DNA samples from the Roman necropolis in Tarragona, with the goal of reanalyzing T2D candidate genes in this ancestral population;

b) the Pilchardus project, funded by Fundació Catalunyacaixa, which seeks to investigate the impact of a diet rich in sardines on metabolic control in patients with type 2 diabetes. The results are promising, showing an improvement in inflammation markers and reduced insulin resistance, and publications and dissemination are now underway;

c) the development of a new coordinated project with high clinical impact, aimed at evaluating "New methods for the effective and safe use of an artificial pancreas at home in type 1 diabetes". These projects all have a high level of international scientific impact and represent important advancements in the study and treatment of diabetes. In addition, we have published highly competitive papers in transversal journals such as Cell and journals in our field, including Diabetes Care, Diabetologia and Endocrinology. We have also patented a diagnostic kit for gestational diabetes, commercialization pending, and have two more applications pending with the patent agency, which we hope will be approved and registered this year. Finally, we were the local organizers (Chairman of the Local Organising Committee) of the Annual Meeting of the European Association for the Study of Diabetes, as well as other international events.

PROGRAMME: **P2**

Metabolic Engineering and Diabetes Therapy

Group Members

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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

- Duran J, Saez I, Gruart A, Guinovart JJ, Delgado-García JM. Impairment in long-term memory formation and learning-dependent synaptic plasticity in mice lacking glycogen synthase in the brain. J Cereb Blood Flow Metab. 2013 Apr;33(4):550-6.
- von Wilamowitz-Moellendorff A, Hunter RW, García-Rocha M, Kang L, López-Soldado I, Lantier L et al.. Glucose-6-phosphate-mediated activation of liver glycogen synthase plays a key role in hepatic glycogen synthesis. Diabetes. 2013 Dec;62(12):4070-82.
- Zafra D, Nocito L, Domínguez J, Guinovart JJ. Sodium tungstate activates glycogen synthesis through a non-canonical mechanism involving G-proteins. FEBS Lett. 2013 Jan 31;587(3):291-6.
- Rodríguez-Hernández CJ, Llorens-Agost M, Calbó J, Murguia JR, Guinovart JJ. Sodium tungstate modulates ATM function upon DNA damage.FEBS Lett. 2013 May 21;587(10):1579-86.
- Villarroel-Espíndola F, Maldonado R, Mancilla H, vander Stelt K, Acuña AI, Covarrubias A et al.. Muscle glycogen synthase isoform is responsible for testicular glycogen synthesis: glycogen overproduction induces apoptosis in male germ cells. J Cell Biochem. 2013 Jul;114(7):1653-64.

Highlights

- Carrying out of the project from the European Foundation for the Study of Diabetes (EFSD-Novo Nordisk) for the study of the role of glycogen metabolism in the pancreatic beta-cell.
- Carrying out of the project from the Human Frontiers Sience Programme (HFSP) to study the role of glycogen accumulation in neurons.
- Tungstate treatment ameliorates experimental diabetes by increasing liver glycogen deposition through a new G-protein-dependent and Tyr-Kinase Receptor-independent mechanism. This result unveils a novel non-canonical signalling pathway that leads to the activation of glycogen synthesis and that could be exploited as an approach to treat diabetes.
- We have identified a key residue (Arg(582)) required for activation of liver glycogen synthase (GYS2) by glucose-6-phosphate (G6P). We have used GYS2 Arg(582)Ala knockin (+/R582A) mice in which G6P-mediated GYS2 activation had been profoundly impaired (60-70%), while sparing regulation through reversible phosphorylation. R582A mutant-expressing hepatocytes show significantly reduced glycogen synthesis with glucose and insulin or glucokinase activator, which results in channeling glucose/G6P toward glycolysis and lipid synthesis. GYS2(+/R582A) mice are modestly glucose intolerant and display significantly reduced glycogen accumulation with feeding or glucose load in vivo. These data show that G6P-mediated activation of GYS2 plays a key role in controlling glycogen synthesis and hepatic glucose-G6P flux control and thus whole-body glucose homeostasis.
- We have shown a key role of brain glycogen in the proper acquisition of new motor and cognitive abilities and in the underlying changes in synaptic strength. However, its over-accumulation in neurons induces neurodegeneration.

PROGRAMME: **P4**

Consequences of Prenatal and Perinatal Disorders on Postnatal Development. Disorders of Fetal Origin.

Group Members

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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

- Casano-Sancho P, Suárez L, Ibáñez L, García-Fructuoso G, Medina J, Febrer A. Pituitary dysfunction after traumatic brain injury in children: is there a need for ongoing endocrine assessment?Clin Endocrinol (Oxf). 2013 Dec;79(6):853-8.
- Ibáñez L, Díaz M, Sebastiani G, Marcos MV, López-Bermejo A, de Zegher F. Oral contraception vs insulin sensitization for 18 months in nonobese adolescents with androgen excess: posttreatment differences in C-reactive protein, intima-media thickness, visceral adiposity, insulin sensitivity, and menstrual regularity.J Clin Endocrinol Metab. 2013 May;98(5):E902-7.

- Díaz M, Bassols J, Aragonés G, Mazarico E, López-Bermejo A, Ibáñez L. Decreased placental expression of pre-adipocyte factor-1 in children born small-for-gestational-age: association to early postnatal weight gain.Placenta. 2013 Apr;34(4):331-4.
- de Zegher F, Sebastiani G, Diaz M, Gómez-Roig MD, López-Bermejo A, Ibáñez L. Breast-feeding vs formula-feeding for infants born small-for-gestational-age: divergent effects on fat mass and on circulating IGF-I and high-molecular-weight adiponectin in late infancy.J Clin Endocrinol Metab. 2013 Mar;98(3):1242-7.
- Prats-Puig A, Grau-Cabrera P, Riera-Pérez E, Cortés-Marina R, Fortea E, Soriano-Rodríguez P et al.. Variations in the obesity genes FTO, TMEM18 and NRXN3 influence the vulnerability of children to weight gain induced by short sleep duration.Int J Obes (Lond). 2013 Feb;37(2):182-7.

Highlights

RESEARCH GROUP:

Over 2013, the group has further developed the two main research lines:

- ovarian androgen excess;
- low birth weight and subsequent postnatal endocrine-metabolic and body composition abnormalities.

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

The results of the recent progress have been presented in invited lectures at international forums.

COLLABORATIONS:

Since 1998, the research group has developed joint research projects (and derived manuscripts) with the University of Leuven, Belgium (Profesor F. de Zegher), the University of Cambridge, UK (Prof. D.B. Dunger, Dr. K. Ong) and the University of Girona (Dr. A. López-Bermejo). During 2013, we have completed, among others, the results of the project entitled: Infant manifestations of adult obesity susceptibility genotypes [Barcelona, Cambridge, INSERM (Paris) & Leuven], supported by a research grant from the European Society for Paediatric Endocrinology (ESPE).

AWARDS:

Dr. Lourdes Ibáñez has received the prestigious ESPE 2013 Research Award

INNOVATION:

Biannual courses organized and coordinated by the group:

- II Update Course in Paediatric Endocrinology, Hospital Sant Joan de Déu.
- I Update Course: Small for Gestational Age (SGA) and Beyond. Postgraduate Course, SGA Working Group, Spanish Society for Paediatric Endocrinology (SEEP).

OTHER (DR. LOURDES IBÁÑEZ):

- *Coordination & Direction of the Master in Paediatric & Adolescent Endocrinology.*
- *Chair: Pediatric & Adolescent Gynecology Working Group, ESPE (www.eurospe.org) & SGA Working Group, SEEP (www.seep.es/privado/ctpubli6.asp).*
- *National Chair: CADET European project (Children and Adolescent Diabetes and Endocrine Trials Network), with the suport of EMA (European Medications Agency), ESPE, SLEP (Sociedad Latinoamericana de Endocrinología Pediátrica), APPES (Australasian Pediatric Endocrine Societies) & PES (Pediatric Endocrine Societies, USA).*

PROGRAMME: **P3**

Islet Cell and Stem Cell Physiology

Group Members

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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

- Delaspre F, Massumi M, Salido M, Soria B, Ravassard P, Savatier P, Skoudy A. Directed pancreatic acinar differentiation of mouse embryonic stem cells via embryonic signalling molecules and exocrine transcription factorsPlos One. 2013;8(1):e54243.
- Transcriptional control of mammalian pancreas organogenesis. Transcriptional control of mammalian pancreas organogenesis.Cell Mol Life Sci. 2013;18(1):1.
- Horrillo A, Pezzolla D, Fraga MF, Aguilera Y, Salguero-Aranda C, Tejedo JR, Martín F, Bedoya FJ, Soria B, Hmadcha A. Zebularine regulates early stages of mESC differentiation: effect on cardiac commitmentCell Death Dis. 2013;4(4):e570.
- Soria B, Gauthier BR. Dual Trade of Bcl-2 and Bcl-xL in islet physiology: balancing life and death with metabolism secretion couplingDiabetes. 2013;62(1):18-21.
- Acosta L, Hmadcha A, Escacena N, Pérez-Camacho I, de la Cuesta A, Ruiz-Salmeron R, Gauthier BR, Soria B.. Adipose mesenchymal stromal cells isolated from type 2 diabetic patients display reduced fibrinolytic activityDiabetes. 2013;62(12):4266-9.

Highlights

CLINICAL ASSAYS:

Title: Clinical assay phase I/II, multicentric, open, randomized and controlled for the use of stem cells as cell therapy in critical limb ischemia of insulinized type 2 diabetic patients: study of insulin requirements. Reference number and phase: CeTMMoTa/ICPDI/2010; 2010-019774-33; I/II. Promoter and period: Fundación Progreso y Salud; 01/01/2012 – 31/03/2015. Participants: Bernat Soria, Abdelkrim Hmadcha, Franz Martín

Title: Use of adipose tissue mesenchimal stem cells(CeTMAd) as cell regenerative therapy in the syndrome of chronic critical limb ischemia in diabetic patients. Reference number and phase: CeTMAd/ICPD/2008; 2008-001837-88; I/II. Promoter and period: Fundación Progreso y Salud; 09/12/2010 - 31/12/2014. Participants: Bernat Soria, Abdelkrim Hmadcha

PROJECTS:

Título: Obtention of insulin producing cells from pluripotent stem cells (diabetes mellitus cell therapy). Funding entity and reference number: Consejería de Innovación Ciencia y Empresa (Secretaria General de Universidades, Investigación y Tecnología); CTS-6505. Period: 01/01/2011-31/12/2014. Principal research: Bernat Soria; Associated researchers: Abdelkrim Hmadcha, Franz Martin. Funding: 184.643,00 €

Título: Diabetes mellitus cell therapy: role of intercellular signaling pathways and intracellular material transfer. Funding entity and reference number: Ministerio de Sanidad y Política Social (ISCIII); PI-10/00964. Period: 01/03/2010-31/12/2014. Principal research: Bernat Soria; Associated researchers: Abdelkrim Hmadcha; Franz Martín. Funding: 130.680,00 €

Título: Critical limb ischemia cell therapy in insulinized type 2 diabetic patients: study of insulin requirements. Funding entity and reference number: Ministerio de Sanidad y Política Social / Dirección General de terapias Avanzadas; TRA-120. Period: 10/02/2010-31/12/2013. Principal research: Bernat Soria; Associated researchers: Abdelkrim Hmadcha, Franz Martin. Funding: 433.500,00 €

PATENT:

Methods for predicting treatment response and test for safe use of mesenchymal stem cells on inflammatory diseases. Patent number: EP 13382315.3?Registration date: 01-08-2013;?Owners: Fundación Pública Andaluza Progreso y Salud;?Inventors: Bernat Soria Escoms, Abdelkrim Hmadcha, Mª Lourdes Acosta Lopez, Natalia Escacena Acosta.

PROGRAMME: **P2**

Molecular Mechanisms of Insulin Resistance, Insulin Sensitivity, Islet Development and Diabetic Complications

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Main lines of research

- Autophagy as a potential mediator of the progression of the non-alcoholic hepatic liver disease (NAFLD) in humans.
- Effect of fatty acids and lipid species in the cross-talk between inflammatory and insulin signalling in hepatocytes.
- Drug-mediated insulin resistance in peripheral tissues: effects of chronic pharmacologycal treatments on insulin signalling and glucose homeostasis
- 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.
- Analysis of the balance between stress and survival signalling pathways in diabetic retinopathy in humans.
- Study of the polarization of microglia in diabetic retinopathy.
- Characterization of diabetic nephropathy in IRS2-deficient mice: role of the critical nodes of the insulin signalling in podocytes.
- 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

- Hernández C, García-Ramírez M, Corraliza L, Fernández-Carneado J, Farrera-Sinfreu J, Ponsati B et al.. Topical administration of somatostatin prevents retinal neurodegeneration in experimental diabetes.Diabetes. 2013 Jul;62(7):2569-78.
- Arroba AI, Revuelta-Cervantes J, Menes L, González-Rodríguez Á, Pardo V, de la Villa P et al.. Loss of protein tyrosine phosphatase 1B increases IGF-I receptor tyrosine phosphorylation but does not rescue retinal defects in IRS2-deficient mice.Invest Ophthalmol Vis Sci. 2013 Jun 19;54(6):4215-25.
- Valverde AM, Miranda S, García-Ramírez M, González-Rodríguez A, Hernández C, Simó R. Proapoptotic and survival signaling in the neuroretina at early stages of diabetic retinopathy.Mol Vis. 2013;19:47-53.
- Hale LJ, Hurcombe J, Lay A, Santamaría B, Valverde AM, Saleem MA et al.. Insulin directly stimulates VEGF-A production in the glomerular podocyte.Am J Physiol Renal Physiol. 2013 Jul 15;305(2):F182-8.
- Vida M, Serrano A, Romero-Cuevas M, Pavón FJ, González-Rodríguez A, Gavito AL et al.. IL-6 cooperates with peroxisome proliferator-activated receptor-α-ligands to induce liver fatty acid binding protein (LFABP) up-regulation.Liver Int. 2013 Aug;33(7):1019-28.

Highlights

RESEARCH PROJECTS

PUBLIC FUNDINGS

- Inhibition of Protein tyrosine phosphatase 1B in the treatment of type 2 diabetes: effects in diabetic complications and cell proliferation. REFERENCE:SAF2012-33283 (2013-2015),MINECO, SPAIN. PI: Ángela Martínez Valverde
- Regulation and function of locus TH-INS in embrionary development and cell differentiation. REFERENCE: BFU-BMC 2010-15868 (2011-2014),MINECO, SPAIN. PI: Flora de Pablo Dávila.
- Study of the mechanisms of insulin resistance: implications in obesity, diabetes and metabolic syndrome. REFERENCE: S2010/BMD-2423 MOIR-CM (2012-2015), COMUNIDAD DE MADRID, SPAIN. PI: Ángela María Martínez Valverde. COORDINATOR: Manuel Ros (URJC, Madrid)
- 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 (2012-2014). PI WP5: Ángela María Martínez Valverde. COORDINATOR: Rafael Simó Canonge (Fundación Val´d Hebrón, Barcelona)
- Preclinical proof of concept of AF243 potency to prevent and/or treat sensorineural hearing loss (AFHELO). FP/-HEALTH.2012.2.4.5-1: Technological approaches to combating sensory impairments (2012-2015). PI AND COORDINATOR: Isabel Varela Nieto (IIB Alberto Sols,CSIC, Madrid).

PRIVATE FUNDINGS

- Study of new targets for treatment of acute liver failure by in vivo siRNA administration in mice. FUNDING COMPANY: Hoffann-LaRoche (Nutley, NJ, USA) (2010-2013). PI: Ángela Martínez Valverde.
- Effect of GLP-1 on the gut-to-liver axis in the hepatoprotection against non-alcoholic fatty liver disease. FUNDING ORGANIZATION: European Foundation for the Study of Diabetes (2011-2113). PI: Ángela Martínez Valverde.
- Role of Oxintomodulin in hepatic regeneration in a model of NASH. FUNDING COMPANY: MEDIMMUNE (Gaithersburg, MA, USA) (2012-). PI: Ángela Martínez Valverde.
- Validation of anti-gremlin antibody for kidney fibrosis: in vitro and in vivo approaches. FUNDING COMPANY: MEDIMMUNE (Gaithersburg, MA, USA) (2013-). PI: Ángela Martínez Valverde.

PROGRAMME: **P1 y P2**

Lipids and Arteriosclerosis Research Unit

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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.

Most relevant scientific articles

- Hegele RA, Ginsberg HN, Chapman MJ, Nordestgaard BG, Kuivenhoven JA, Averna M et al.. The polygenic nature of hypertriglyceridaemia: implications for definition, diagnosis, and management.Lancet Diabetes Endocrinol. 2013 Dec 23;.
- Català R, Cabré A, Hernández-Flix S, Ferré R, Sangenís S, Plana N et al.. Circulating FABP4 and FABP5 levels are differently linked to OSA severity and treatment.Sleep. 2013 Dec 1;36(12):1831-7.
- Girona J, Rosales R, Plana N, Saavedra P, Masana L, Vallvé JC. FABP4 induces vascular smooth muscle cell proliferation and migration through a MAPK-dependent pathway. PLoS One. 2013;8(11):e81914.
- Lázaro I, Ferré R, Masana L, Cabré A. Akt and ERK/Nrf2 activation by PUFA oxidation-derived aldehydes upregulates FABP4 expression in human macrophages.Atherosclerosis. 2013 Oct;230(2):216-22.
- Holmes MV, Simon T, Exeter HJ, Folkersen L, Asselbergs FW, Guardiola M et al.. Secretory phospholipase A(2)-IIA and cardiovascular disease: a mendelian randomization study.J Am Coll Cardiol. 2013 Nov 19;62(21):1966-76.

Highlights

- Publications: 32 articles with an impact factor of 158,062.
- We have developed two patents related determination by NMR lipoprotein profile.
- He has participated in the implementation of the Spin-Off "Biosfer Teslab".
- Were read four theses.
- Publication of a clinical guide to prevent coronary heart disease.

PROGRAMME: **P3 y P4**

Group of Research Into Diabetes and Metabolism

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Main lines of research

The group has two main lines of research focused on diabetes and obesity that are strongly interconnected. The group has developed for many years a research on the molecular and cellular biology of pancreatic islets that 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 is the mechanisms of destruction, protection 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 clinical chronic complications of diabetes. 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

- Vilarrasa N, Ruiz de Gordejuela AG, Gómez-Vaquero C, Pujol J, Elio I, San José P, Toro S, Casajoana SA, Gómez JM.. Effect of Bariatric Surgery on Bone Mineral Density: Comparison of Gastric Bypass and Sleeve GastrectomyObesity Surgery. 2013;23:2089-91.
- Pérez-Maraver M, Caballero-Corchuelo J, Boltana A, Insa R, Soler J, Montanya E. Comparison of human insulin and insulin analogues on hypoglycaemia and metabolic variability in type 1 diabetes using standardized measurements (HYPO score and Lability Index).Acta Diabetol. 2011 Aug 27;.
- King AB, Montanya E, Pratley RE, Blonde L, Svendsen CB, Donsmark M et al.. Liraglutide Achieves AIC Targets More Often than Sitagliptin or Exenatide when Added to Metformin in Patients with Type 2 Diabetes and a Baseline AIC <8.0%Endocr Pract. 2012 Nov 27;:1-28.
- Di Yacovo S, García-Vidal C, Viasus D, Adamuz J, Oriol I, Gili F et al.. Clinical features, etiology, and outcomes of community-acquired pneumonia in patients with diabetes mellitus.Medicine (Baltimore). 2013 Jan;92(1):42-50.

Highlights

The research of the group covers the pre-clinical and clinical aspects of diabetes, and has a strong translational orientation. The mixed composition of the group, with basic and clinical researchers makes this translational orientation particularly clear. The group has active collaborations with other research groups at the level of CIBERDEM with several collaborative projects, with groups from other CIBERs (CIBERESP and CIBERNED in particular), as well as with international groups and networks.. Specifically in the field of the translational activities, it is noticeable the participation of members of the group in the elaboration of clinical guidelines, such as, more recently the recommendations for the treatement of pacients with type 2 diabetes of the Spanish Diabetes Association (SED) or the guideline for the treatment of pacients with chronic kidney disease (contributing to the treatment of patients with diabetis) of several scientific societies. Several members of the group have elected positions in the excutive boards of national or international scientific societies, and the principal investigator of the group is the President of the Advisory Council about Diabetes of the Health Department of the Catalan Government (Generalitat de Catalunya). In year 2013, the group has organized, with the colaboration of CIBERDEM, the Meeting of the Islet Study Group of the European Association for the Study of Diabetes.

PROGRAMME: **P3**

Unit of Cell Physiology and Nutrition IB-UMH

Group Members

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ASSOCIATED MEMBERS

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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. We study the activation of signalling pathways by leptin receptors. Additionally, we investigate the adaptations of islet-cells to obesity and malnutrition states.

Most relevant scientific articles

- Alonso-Magdalena P, Ropero AB, García-Arévalo M, Soriano S, Quesada I, Muhammed SJ et al.. Antidiabetic actions of an estrogen receptor β selective agonist.Diabetes. 2013 Jun;62(6):2015-25.
- Gonzalez A, Merino B, Marroquí L, Ñeco P, Alonso-Magdalena P, Caballero-Garrido E et al.. Insulin hypersecretion in islets from diet-induced hyperinsulinemic obese female mice is associated with several functional adaptations in individual β-cells.Endocrinology. 2013 Oct;154(10):3515-24.
- Vieira E, Marroquí L, Figueroa AL, Merino B, Fernández-Ruiz R, Nadal A et al.. Involvement of the clock gene Rev-erb alpha in the regulation of glucagon secretion in pancreatic alpha-cells.PLoS One. 2013;8(7):e69939.
- Nadal A. Linking intermittent hypoxia, sympathetic response and metabolic disturbances.Acta Physiol (Oxf). 2013 Jun 19;.
- Nadal A. Obesity: Fat from plastics? Linking bisphenol A exposure and obesity.Nat Rev Endocrinol. 2013 Jan;9(1):9-10.

Highlights

RESEARCH GRANTS

- Ayuda complementaria al proyecto: Análisis de la función de la leptina y la resistencia a la leptina en células alfa y beta del islote de Langerhans. Principal Investigator: Ivan Quesada. Generalitat Valenciana: 2013. Autonomous Community project
- Functional and structural adaptations in the alpha-cell and changes glucagon action during obesity. Boehringer-Ingelheim Basic Programme on the Regulation of Secretion and Function of Non-insulin. Peptides from the Endocrine Pancreas, 94553 EFSD: 2012-2014. Principal Investigator: Ivan Quesada. European project.
- Análisis de la función de la leptina y la resistencia a la leptina en células alfa y beta del islote de Langerhans. MICINN, BFU2010-21773: 2011-2013. Principal Investigator: Ivan Quesada. National project.
- Efectos del Bisfenol-A en la homeostasis de la glucosa, la función del islote de Langerhans y la señalización de insulina en el ratón. BFU2011-28358, Ministerio de Economía y Competitividad: 2012-2014. Principal Investigator: Angel Nadal. National project.
- Caracterización del efecto insulinotrópico rápido de agonistas específicos del receptor de estrógenos ß: implicaciones en el tratamiento de la diabetes. Programa Prometeo para grupos de investigación de excelencia. Generalitat Valenciana, PROMETEO/2011/080: 2011-2014. Principal Investigator: Angel Nadal. Autonomous Community project.
- Exposure to endocrine disruptor chemicals during pregnancy: a possible mechanism involved in the premature ageing of maternal pancreatic B-cell. 94224 EFSD 2013-2015. Principal Investigator: Paloma Alonso-Magdalena. European project.

PhD THESES

- Adaptaciones funcionales y estructurales de la célula ß pancreática en un modelo de obesidad inducida por dieta rica en grasa. Author: Alejandro González Álvarez. Thesis advisor: Ivan Quesada and Sergi Soriano. University: Universidad Miguel Hernández. Thesis defense date: March 13, 2013
- Efecto de la exposición intraútero a bisfenol-A en la homeostasis de la glucosa en ratones. Author: Marta García-Arévalo Provencio. Thesis advisor: Ángel Nadal and Paloma Alonso-Magdalena. University: Universidad Miguel Hernández. Thesis defense date: December 20, 2013.

SCIENTIFIC COLLABORATIONS WITHIN CIBERDEM

The production of monoclonal antibodies which selectively react with cell surface molecules on human pancreatic beta cells. Coordinator: Juan Tejedo. CIBERDEM Groups: Nadal A, Martín F , Montanya E.

PROGRAMAS: **P1 y P3**

Metabolic and Molecular Disturbances in Diabetes

Group Members

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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

- Moreno-Asso A, Castaño C, Grilli A, Novials A, Servitja JM. Glucose regulation of a cell cycle gene module is selectively lost in mouse pancreatic islets during ageing. Diabetologia. 2013 May 18;.
- Ceriello A, Novials A, Ortega E, Canivell S, La Sala L, Pujadas G et al.. Glucagon-Like Peptide 1 Reduces Endothelial Dysfunction, Inflammation, and Oxidative Stress Induced by Both Hyperglycemia and Hypoglycemia in Type 1 Diabetes.Diabetes Care. 2013 Apr 5;.
- Ceriello A, Novials A, Ortega E, Canivell S, La Sala L, Pujadas G et al.. Vitamin C further improves the protective effect of glucagon-like peptide-1 on acute hypoglycemia-induced oxidative stress, inflammation, and endothelial dysfunction in type 1 diabetes.Diabetes Care. 2013 Dec;36(12):4104-8.
- Gutiérrez-Rojas I, Lozano D, Nuche-Berenguer B, Moreno P, Acitores A, Ramos-Álvarez I et al.. Amylin exerts osteogenic actions with different efficacy depending on the diabetic status.Mol Cell Endocrinol. 2013 Jan 30;365(2):309-15.
- Ceriello A, Novials A, Ortega E, Canivell S, Pujadas G, La Sala L et al.. Vitamin C further improves the protective effect of GLP-1 on the ischemia-reperfusion-like effect induced by hyperglycemia post-hypoglycemia in type 1 diabetes.Cardiovasc Diabetol. 2013 Jun 27;12(1):97.

Highlights

Among the global results of our scientific production during 2013, we highlight high-impact publications in our speciality, both in basic and clinical research: we described the transcriptional regulation of the cell cycle during ageing within the pancreatic beta-cell; also, we published various articles focused on studying the protective effect of molecules, such as vitamin C and GLP-1, on endothelial dysfunction in patients with type 1 diabetes.

Throughout the year, our group participated in 2 projects funded by the Health Research Fund of the Carlos III Health Institute, and another by the Spanish National R&D&I Plan of the Spanish Ministry of Economy and Competitiveness. The group also entered a three-year agreement with the company Grifols to study one of its pharmaceutical projects. It obtained a prestigious grant from the European Association for the Study of Diabetes (EASD) to research plasma miRNAs as potential biomarkers and mediators of tissue cross-talk in diabetes. Finally, as associate investigators, members of the group began work on a project funded by the Marató de TV3 to investigate progenitor cells (iPs) as therapeutic substitution for beta-cells.

In terms of social outreach activities, members of our group have performed various activities related to exercise and healthy lifestyle in the diabetic population; specifically, we have been involved in half-marathon races, educating young participants with diabetes. We have also conducted training courses to teach strategies for calculating insulin doses and carbohydrates for sports. We have presented various informative talks for diabetic associations.

Finally, part of our group participated in the local organization of the 49th EASD Annual Meeting in Barcelona. The principal investigator is, moreover, a member of the EASD Council and also Vice President of the Spanish Diabetes Society (SED).

PROGRAMME: **P1**

Endocrinology and Nutrition Service

Group Members

STAFF MEMBERS

García Escobar, Eva
García Serrano, Sara
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ASSOCIATED MEMBERS

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González Romero, María Stella
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Morcillo Espina, Sonsoles
Olveira Fuster, Gabriel
Rodríguez Pacheco, Francisca
Ruiz De Adana Navas, Soledad
Valdés Hernández, Sergio

Lead Researcher

Rojo Martínez, Gemma

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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

- Soriguer F, Gutiérrez-Repiso C, Rubio-Martín E, García-Fuentes E, Almaraz MC, Colomo N et al.. Metabolically healthy but obese, a matter of time? Findings from the prospective Pizarra study.J Clin Endocrinol Metab. 2013 Jun;98(6):2318-25.
- Martín-Núñez GM, Cabrera-Mulero R, Rojo-Martínez G, Gómez-Zumaquero JM, Chaves FJ, de Marco G et al.. Polymorphisms in the SCD1 gene are associated with indices of stearoyl CoA desaturase activity and obesity: a prospective study.Mol Nutr Food Res. 2013 Dec;57(12):2177-84.
- Rubio-Martín E, Soriguer F, Gutiérrez-Repiso C, Garrido-Sánchez L, de Adana MS, García-Fuentes E et al.. C-reactive protein and incidence of type 2 diabetes in the Pizarra study.Eur J Clin Invest. 2013 Feb;43(2):159-67.
- Gutiérrez-Repiso C, Rojo-Martínez G, Soriguer F, García-Fuentes E, Vendrell J, Vázquez JA et al.. Factors affecting levels of urinary albumin excretion in the general population of Spain: the Di@bet.es study.Clin Sci (Lond). 2013 Feb;124(4):269-77.
- Rojo-Martínez G, Soriguer F, Colomo N, Calle A, Goday A, Bordiú E et al.. Factors determining high-sensitivity C-reactive protein values in the Spanish population. Di@bet.es study.Eur J Clin Invest. 2013 Jan;43(1):1-10.

Highlights

We are a research group with epidemiological, clinical and experimental projects whose ultimate purpose is the study of the nature-nurture relationships in explaining the high prevalence of metabolic diseases such as diabetes. Our methodology is based on a continuous dialogue between clinical, experimental and epidemiological observations . The group operates from a holistic understanding of human biology, and tries to study the natural history of the disease in addition to intervention studies and evaluation of clinical practice to control risk factors, prevent diabetes, prevent the onset of complications or improve the quality of life of patients .

The group has participated in collaborative CIBERDEM projects: TELEMED , PILCHARDUS, di@bet.es , INGENFRED and contributed with samples to the CIBERDEM biobank. This year we have published much of the results of the di@bet.es study and also have made significant contributions in the field of artificial nutrition and telemedicine related to diabetes and other diseases.

Other lines of research (Pizarra study, Egabro study) have yielded important results about the risk of obesity and type 2 diabetes in the general population. The group has several projects based on the exploitation of the serum and DNA collections obtained from epidemiological studies, while other projects have studying biomarkers in animal models and in vitro to elucidate the mechanisms of disease. In 2013 we were awarded a contract with industry (CDTI) to study the nutritional properties of dairy goat milk and the relationship of these nutrients with metabolic diseases.

PROGRAMME: **P1**

DIABETOBE

Group Members

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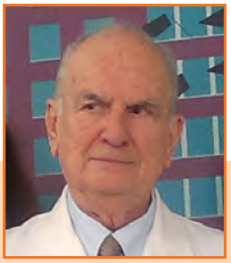
Fernández Pérez, Cristina
Lazcano Redondo, Yera
Martínez Larrad, María Teresa
Pérez Barba, Milagros

Lead Researcher

Serrano Ríos, Manuel



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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

- Pescador N, Pérez-Barba M, Ibarra JM, Corbatón A, Martínez-Larrad MT, Serrano-Ríos M. Serum circulating microRNA profiling for identification of potential type 2 diabetes and obesity biomarkersPlos One. 2013;8(10):8.
- Pueyo N, Ortega FJ, Mercader JM, Moreno-Navarrete JM, Sabater M, Bonàs S, Botas P, Delgado E, Ricart W, Martínez-Larrad MT, Serrano-Ríos M, Torrents D, Fernández-Real JM.. Common genetic variants of surfactant protein-D (SP-D) are associated with type 2 diabetesPLoS One. 2013;8(4):10.
- Marcuello C, Calle-Pascual AL, Fuentes M, Runkle I, Rubio MA, Montañez C, Rojo-Martínez G, Soriguer F, Bordiu E, Goday A, Bosch-Comas A, Carmena R, Casamitjana R, Castaño L, Castell C, Catalá M, Delgado E, Franch J, Gaztambide S, Girbés J, Gomis R, Urrutia I, López-Alba A, Martínez-Larrad MT, Menéndez E, Mora-Peces I, Ortega E, Pascual-Manich G, Serrano-Rios M, Valdés S, Vázquez JA, Vendrell J. Prevalence of the metabolic syndrome in Spain using regional cutoff points for waist circumference: the di@bet.es studyActa Diabetol. 2013;50(4):615-23.
- Rojo-Martínez G, Valdés S, Colomo N, Lucena MI, Gaztambide S, Gomis R, Casamitjana R, Carmena R, Catalá M, Martínez-Larrad MT, Serrano-Ríos M, Castaño L, Vendrell J, Girbés J, Franch J, Vázquez JA, Mora-Peces I, Urrutia I, Pascual-Manich G, Ortega E, Menéndez E, Delgado E, Bordiú E, Castell C, López-Alba A, Goday A, Calle A, Bosch-Comas A, Soriguer F. Use of Drugs Related to the Treatment of Diabetes Mellitus and Other Cardiovascular Risk Factors in the Spanish Population. The Di@bet.es StudyRevista Española de Cardiologia. 2013;11(5):10.
- Corbatón-Anchuelo A, Martínez-Larrad MT, Fernández-Pérez C, Vega-Quiroga S, Ibarra-Rueda JM, Serrano-Ríos M. Metabolic syndrome, adiponectin, and cardiovascular risk in Spain (the Segovia study): impact of consensus societies criteria.Metab Syndr Relat Disord. 2013;11(5):11.

Highlights

Integrated by Clinical basic and epidemiology Investigators with long experience of joint work; and original contributions to the field of Genetic epidemiology of the Metabolic syndrome the Segovia Study, a population-based prospective survey. Each member has specific areas of competence in genetic-epidemiologicy (M Serrano Rios, MT Martinez-Larrad, A Corbatón, C. Fernández ...), design and development of non-coding microRNA analysis (N Pescador, Y. Lazcano); biomarkers of inflammation, of several other techniques Elisa/RIA (M Pérez, A Asensio, N. del Prado, Adm. MM González).

PROJECTS

- Nutritional Primary Prevention of Type1 Diabetes in Children. NIH, QLK1-CT-2002-00372: 2001-2016. Principal Investigator: Manuel Serrano Ríos. European project. Programme 1
- Meta-analyses of Glucose and Insulin-Related Traits Consortium. MAGIC: 2008-2014 Principal Investigator: Manuel Serrano Ríos. European project. Programme 1
- Morbi-Mortalidad y caracterización genotípica en el ámbito rural y urbano de la provincia de Segovia. Lilly S.A.: 2012-2014 Principal Investigator: Manuel Serrano Ríos. Associate investigators: Arturo Corbatón Anchuelo, María Teresa Martínez Larrad, Cristina Fernández Pérez, Saturio Vega Quiroga, Nuria Pescador Sánchez. National project. Programme 1
- Estudio de los mecanismos de resistencia a insulina: Implicaciones de Obesidad, Diabetes y Síndrome Metabólico. S2010/BMD-2423: 2012-2015. Principal Investigator: Manuel Serrano Ríos Associate investigators: Arturo Corbatón Anchuelo, María Teresa Martínez Larrad, Cristina Fernández Pérez, Saturio Vega Quiroga, Nuria Pescador Sánchez. National project. Programme 1

INGENFRED: Cooperative population and database studies for genetic association analysis in T2DM and related traits. Coordinator: Felipe Javier Chaves Ciberdem groups: Serrano-Ríos M, Blanco-Vaca F, Carmena R, Soriguer F

IODURE: The impact of overnutrition, diabetes-obesity, and undernutrition on the regulation of energy homeostasis in the central nervous system. From animal models to humans. Coordinator: Manuel Serrano Ríos Ciberdem groups: Serrano-Ríos M, Álvarez C, Blázquez E, Burks D, Vallejo M.

Di@bet.es Study: 1st epidemiological study of the prevalence of type 2 diabetes in Spain Coordinator: Federico Soriguer Ciberdem groups: Serrano-Ríos M, Soriguer F, Carmena R, Castaño L, Gomis R, VendrellJ.

PROGRAMME: **P2 y P4**

Diabetes and Metabolism Research Group

Group Members

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Main lines of research

- 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 coordinating 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 (EUROCONDOR-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.
- 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.
- 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.
- 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

- Hernández C, García-Ramírez M, Corraliza L, Fernández-Carneado J, Farrera-Sinfreu J, Ponsati B et al.. Topical administration of somatostatin prevents retinal neurodegeneration in experimental diabetes.Diabetes. 2013 Jul;62(7):2569-78.
- Hernández C, García-Ramírez M, Simó R. Overexpression of hemopexin in the diabetic eye: a new pathogenic candidate for diabetic macular edema.Diabetes Care. 2013 Sep;36(9):2815-21.
- Barbosa-Desongles A, Hernández C, De Torres I, Munell F, Poupon MF, Simó R et al.. Diabetes protects from prostate cancer by downregulating androgen receptor: new insights from LNCaP cells and PAC120 mouse model.PLoS One. 2013;8(9):e74179.
- Hernández C, Simó R, European Consortium for the Early Treatment of Diabetic Retinopathy (EUROCONDOR). Somatostatin replacement: a new strategy for treating diabetic retinopathy.Curr Med Chem. 2013;20(26):3251-7.
- Valverde AM, Miranda S, García-Ramírez M, González-Rodríguez A, Hernández C, Simó R. Proapoptotic and survival signaling in the neuroretina at early stages of diabetic retinopathy.Mol Vis. 2013;19:47-53.

Highlights

CAPACITY FOR INNOVATION AND TRANSFERENCE TO CLINICAL PRACTICE

Our research is aimed at gaining new insights into the pathogenesis and treatment of diabetes and its associated complications and co-morbidities. The combination in our group of basic and clinical investigators permits us a rapid transference of the results to clinical practice.

In 2013 we have registered two patents addressed to protect therapeutic targets for DR (EP13382063.9) and hepatic steatosis/obesity (EP13382202.3), respectively. Notably, our project entitled "Development of eye drops to treat diabetic retinopathy: from experimental research to clinical application" has been awarded the Innovation-2013-Prize sponsored by VHIR-HUVH (Vall d'Hebron Research Institute-University Hospital Vall d'Hebron).

PROJECTS

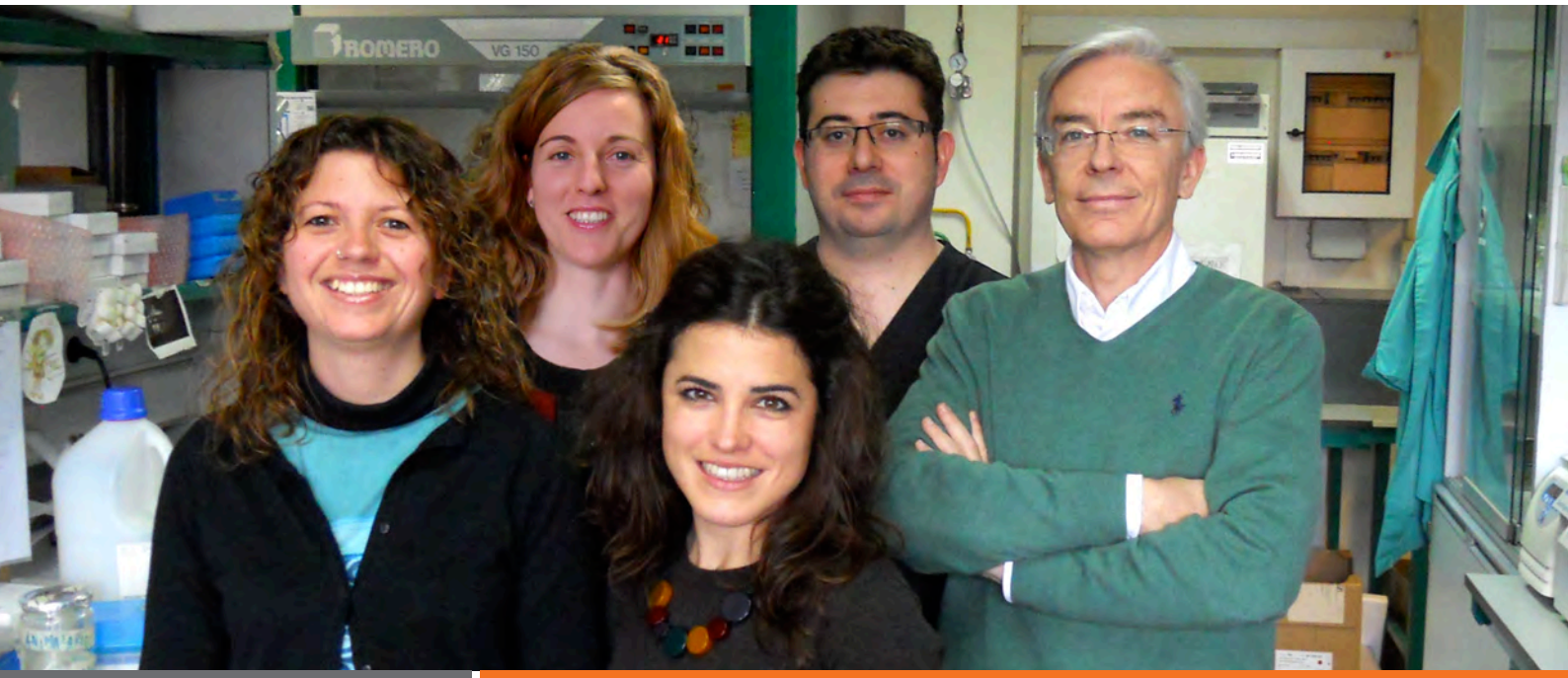
During 2013 our group has obtained the following competitive grants: 1) FIS (PI13/00603); 2) Ministerio de Economía y Competitividad (PIE13/00027); 3) European Foundation for the Study of Diabetes (EFSD/Lilly-Mental Diabetes and Health Program). We have also received grant funding from the Foundation of the Spanish Society of Endocrinology and Nutrition and the Catalan Society of Endocrinology and Nutrition. Moreover, we have established two research agreements with two companies of biomedicine (VIFOR Pharma and Bristol Myers Squibb).

RESULTS

Regarding the results obtained during the year under evaluation it should be underlined the publication in the journal Diabetes (Diabetes 2013;62:2569-78) of the pre-clinical results of the project funded by the EC (EUROCONDOR-FP7-278040).

OTHERS

The leader of our research group (Prof. Rafael Simó) is member of the EASDec (European Association for the Study of Diabetes-Eye Complications) board and has been the President of the local committee of the 23rd EASDec meeting which was held in Barcelona, 23-25th May, 2013.



PROGRAMME: **P3**

Transcriptional Mechanisms of Pancreatic Function

Group Members

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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

- García-Sanz P, Fernández-Pérez A, Vallejo M. Differential configurations involving binding of USF transcription factors and Twist1 regulate Alx3 promoter activity in mesenchymal and pancreatic cellsBiochemical Journal. 2013;450:199-208.

Highlights

During 2013 our group discovered the mechanism by which Alx3 plays a protective role against embryonic malformations generated during gestation in diabetic mothers. Our data show that maternal hyperglycemia induces Alx3 expression, which in turn stimulates the promoter of Foxo1. This is a key factor for the expression of genes that encode oxidative stress detoxifying enzymes (MnSOD, catalase and Gpx1). In the absence of Alx3, this defense response is inhibited, thus resulting in a significant increase in oxidative stress produced by high concentrations of glucose (García-Sanz P, Mirasierra M, Vallejo M: Increased susceptibility to intrauterine malformations during diabetic pregnancy in Alx3-deficient mice. Submitted).

Regarding our studies on the regulation of the Alx3 promoter, we determined that its expression in beta cells is under the control of Pdx1. This is an important finding because Pdx1 is a critical factor for pancreatic cell function, and it is involved in the etiopathogenic mechanisms of some types of diabetes. Therefore, a decrease in Alx3 gene expression can contribute to the phenotype generated by Pdx1 loss of function (Fernández-Pérez A, Vallejo M: Pdx1 and USF transcription factors regulate Alx3 gene expression in pancreatic beta cells. Submitted).

PROGRAMME: **P4**

Pharmacological Targets in Inflammation and Metabolic Diseases

Group Members

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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

- Salvadó L, Coll T, Gómez-Foix AM, Salmerón E, Barroso E, Palomer X et al.. Oleate prevents saturated-fatty-acid-induced ER stress, inflammation and insulin resistance in skeletal muscle cells through an AMPK-dependent mechanism.Diabetologia. 2013 Jun;56(6):1372-82.
- Palomer X, Capdevila-Busquets E, Álvarez-Guardia D, Barroso E, Pallàs M, Camins A et al.. Resveratrol induces nuclear factor-κB activity in human cardiac cells.Int J Cardiol. 2013 Sep 10;167(6):2507-16.
- Palomer X, Salvadó L, Barroso E, Vázquez-Carrera M. An overview of the crosstalk between inflammatory processes and metabolic dysregulation during diabetic cardiomyopathy.Int J Cardiol. 2013 Oct 9;168(4):3160-72.
- Barroso E, del Valle J, Porquet D, Vieira Santos AM, Salvadó L, Rodríguez-Rodríguez R et al.. Tau hyperphosphorylation and increased BACE1 and RAGE levels in the cortex of PPARβ/δ-null mice.Biochim Biophys Acta. 2013 Aug;1832(8):1241-8.
- Quintero-Fabián S, Ortuño-Sahagún D, Vázquez-Carrera M, López-Roa RI. Alliin, a garlic (Allium sativum) compound, prevents LPS-induced inflammation in 3T3-L1 adipocytes.Mediators Inflamm. 2013;2013:381815.

Highlights

Our research group, funded by CIBERDEM and the Spanish Ministerio de Economía y Competitividad (SAF2012-30708 project), has unveiled a new mechanism by which the monounsaturated fatty acid oleate could prevent saturated fatty acid-induced inflammation and insulin resistance in skeletal muscle cells (*Diabetologia* 2013, 56:1372-82). Specifically, our group has found that oleate inhibits palmitate-induced endoplasmic reticulum stress by activating AMPK. This fact is consistent with the increasing evidence that the Mediterranean diet has a protective effect on both obesity and diabetes, since this diet is characterized by a specific fatty acid pattern: it is low in saturated fatty acids (7-8% of energy) and high in monounsaturated fatty acids (over 20% of total energy), because the fat source consists primarily of olive oil.

Likewise, since 75% of people with diabetes die because of cardiovascular diseases, the study of new cardioprotective mechanisms is key for the health of these patients. Our research group has found a new mechanism by which resveratrol, through NF-κB activation, could activate antiapoptotic ways in murine and human cardiomyocytes. These changes might be involved in the cardioprotective effects of this compound (*International Journal of Cardiology* 2013, 167:2507-16).

Furthermore, the previous experience of our research group has allowed us to review the crosstalk between inflammatory processes and metabolic dysregulation during diabetic cardiomyopathy (*International Journal of Cardiology* 2013, 168:3160-72).

We are also interested in the study of the relationship between insulin resistance and Alzheimer's disease. Our group has observed that PPARβ/δ-deficient mice, which are glucose intolerant, show increased tau phosphorylation and higher levels of proteins involved in Alzheimer's disease (BACE1 and RAGE) (*Biochimica Biophysica Acta. Molecular Basis of Disease* 2013, 1832:1241-8).

PROGRAMME: **P2 y P4**

Diabetes and Metabolic Associated Diseases Research Group

Group Members

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Main lines of research

- Adipose Tissue Plasticity: Molecular basis of insulin resistance; Adipocyte apoptosis and proliferation during obesity; Adipose tissue-derived mesenchymal stem cells from obesity states; Browning capacity of white adipose tissue.
- Role of lipid metabolism in the functionality of adipose tissue during obesity. Study of the lipin protein family.
- Role of inflammation in obesity and insulin resistance.
- Metabolic disorders associated with Gestational Diabetes.
- Biomarkers of atherosclerotic risk in pathologies associated with a high cardiovascular morbidity and mortality.

Most relevant scientific articles

- Vázquez-Carballo A, Ceperuelo-Mallafré V, Chacón MR, Maymó-Masip E, Lorenzo M, Porras A, Vendrell J, Fernández-Veledo S.. TWEAK prevents TNF-α-induced insulin resistance through PP2A activation in human adipocytes.Am J Physiol Endocrinol Metab. . 2013;305(1):E101-12.
- Bassols J, Megia A, Soriano-Rodríguez P, Díaz M, Prats-Puig A, Gifre M, Simón-Muela I, Torrent S, Borrell AC, Riera-Socasau JC, Vendrell J, de Zegher F, Ibáñez L, López-Bermejo A.. A common gene variant in STK11 is associated with metabolic risk markers and diabetes during gestation.Fertil Steril.. 2013;100(3):788-92.
- Maymó-Masip E, Fernández-Veledo S, García España A, Vázquez-Carballo A, Tinahones FJ, García-Fuentes E, Garrifo-Sánchez L, Rodríguez Mdel M, Vendrell J, Chacón MR.. The rise of soluble TWEAK levels in severely obese subjects after bariatric surgery may affect adipocyte-cytokine production induced by TNFα.J Clin Endocrinol Metab.. 2013;98(8):E1323-33.
- Díaz-López A, Chacón MR, Bulló M, Maymó-Masip E, Martínez-González MA, Estruch R, Vendrell J, Basora J, Díez-Espino J, Covas MI, Salas-Salvadó J.. Serum sTWEAK concentrations and risk of developing type 2 diabetes in a high cardiovascular risk population: a nested case-control study.J Clin Endocrinol Metab.. 2013;98(8):3482-90.
- Simón-Muela I, Näf S, Ballesteros M, Vendrell J, Ceperuelo-Mallafre V, de la Flor M, Megia A.. Gender determines the actions of adiponectin multimers on fetal growth and adiposity.Am J Obstet Gynecol.. 2013;208(6):481.e1-7.

Highlights

ACTIVE RESEARCH PROJECTS DURING 2013:

- 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 - Ministerio de Economía y Competitividad). Duración: 2013-2015.
- Papel de las metilaciones del ADN en la diabetes gestacional como predictor de alteraciones en el metabolismo hidrocarbonado postparto (PI12/00717 - ISCIII). Duración: 2013-2015.
- Estudi del grau de metilació d' ADN en pacients amb diabetis gestacional i en gestants amb tolerància normal a la glucosa (Associació Catalana de Diabetis) Duración: 2013-2014.
- Estudio de los marcadores de tejido adiposo marrón y de los mecanismos de su diferenciación a partir de células madre mesenquimales del tejido adiposo blanco subcutáneo humano (PI11/00085 - ISCIII). Duración: 2012-2014.
- Estudio de TWEAK/CD163 como posibles biomarcadores de diabetes tipo 2 en la cohorte di@bet.es. Aspectos moleculares locales en el tejido adiposo (PI11/00049 - ISCIII). Duración: 2012-2014.
- Papel de las Fosfatifato Fosfatasas (PAP, Lipin) en la regulacion de funciones celulares por medio del control de la biosintesis de fosfolipidos y su relacion con la obesidad (PI10/00967 - ISCIII). Duración: 2011-2013.
- Grup de Recerca en Diabetis i Co-morbiditats Associades. DiReCor (2010PFR-URV-B2-54 - URV). Duración: 2011-2013.
- Papel de las isoformas circulantes de adiponectina en la diabetes gestacional. Relación con el metabolismo hidrocarbonado y el desarrollo antropométrico fetal (PI09/2152 - ISCIII). Duración: 2010 – junio 2013.
- Grup de Recerca en Diabetis i Co-morbiditats Associades. DiReCor (2009SGR1257 - AGAUR). Duración: 2009-2013.

The research group hosts three Researches from the "Miguel Servet" Program (CP06/00119, CP10/000438, CP11/00021 - ISCIII), one Postdoctoral Researcher within "Sara Borrell" program (CD10/00285 - ISCIII), and a Clinical Investigator with a "Río Hortega" contract (CM12/00044 - ISCIII).

PROGRAMME: **P4**

Heterogenic and Polygenic Diseases

Group Members

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Main lines of research

Molecular mechanisms involved in the development of insulin resistance and type 2 diabetes and identification of novel targets for diabetes therapy:

- Analysis of the role of mitochondrial dynamics proteins in metabolic homeostasis, in the control of insulin signalling, and in the response to cell stress,
- Role of interplay between autophagy, mitochondrial function and energy metabolism,
- Analysis of the metabolic role of neuregulins.

Most relevant scientific articles

- Schneeberger M, Dietrich MO, Sebastián D, Imbernón M, Castaño C, García A et al.. Mitofusin 2 in POMC neurons connects ER stress with leptin resistance and energy imbalance.Cell. 2013 Sep 26;155(1):172-87.
- Segalés J, Paz JC, Hernández-Álvarez MI, Sala D, Muñoz JP, Noguera E et al.. A form of mitofusin 2 (Mfn2) lacking the transmembrane domains and the COOH-terminal end stimulates metabolism in muscle and liver cells.Am J Physiol Endocrinol Metab. 2013 Nov 15;305(10):E1208-21.
- Muñoz JP, Ivanova S, Sánchez-Wandelmer J, Martínez-Cristóbal P, Noguera E, Sancho A et al.. Mfn2 modulates the UPR and mitochondrial function via repression of PERK.EMBO J. 2013 Aug 28;32(17):2348-61.
- Hernández-Álvarez MI, Paz JC, Sebastián D, Muñoz JP, Liesa M, Segalés J et al.. Glucocorticoid modulation of mitochondrial function in hepatoma cells requires the mitochondrial fission protein Drp1.Antioxid Redox Signal. 2013 Aug 1;19(4):366-78.
- Moreno-Navarrete JM, Escoté X, Ortega F, Serino M, Campbell M, Michalski MC et al.. A role for adipocyte-derived lipopolysaccharide-binding protein in inflammation- and obesity-associated adipose tissue dysfunction.Diabetologia. 2013 Nov;56(11):2524-37.

Highlights

THESIS DIRECTION:

Title: "Functional characterization of DOR protein in skeletal muscle "Ph.D. student: David Sala. Universidad de Barcelona. The Ph.D. was defended in 2013 and qualified with "Excellent cum laude".

Title: "Neuregulin reduces glycaemia by targeting liver metabolism". Ph.D. student: Katrin Niisuke. Universidad de Barcelona. The Ph.D. was defended in 2013 and qualified with Excellent "cum laude".

PROJECTS:

- Genetic determinants of obesity or diabetes type 2 metabolic alterations and insulin resistance. Secretaría de Estado de Universidades, MICINN (SAF2008-038). January 2009 to June 2014. IP: Antonio Zorzano.
- Mechanisms of prevention of type 2 diabetes by lifestyle intervention in subjects with pre-diabetes or at high-risk for progression. Union Europea (FP7). January 2012-june 2015. IP: Antonio Zorzano (Coordinator: John Nolan).
- Role of Mitofusin 2 as a link between hepatocellular carcinoma and insulin resistance. European Foundation for the Study of Diabetes (EFSD). January 2014-june 2015. IP: Antonio Zorzano.

PATENTS:

- Inventors: Julio Castro, Luc Marti, Antonio Zorzano, Silvia Garcia-Vicente, Alec Mian. Title: Pharmaceutical combinations including anti-inflammatory and antioxidant conjugates useful for treating metabolic disorders. Aplication number: WO 2013037985 A8. Publication date: 11 April 2013.

AWARDS:

- ICREA Academia 2013 (Antonio Zorzano).

RESULTS PRESENTED AT THE FOLLOWING INTERNATIONAL CONFERENCES AND RESEARCH CENTERS:

- Mitochondria, metabolic regulation and the Biology of Aging Conference. Lanzarote. Febrero 2013.
- Universidad de Cordoba. Febrero 2013.
- Gordon Research Conference. Les Diablerets. Suiza. Abril 2013.
- 197th ENMC workshop on Fusion/Fission. Naarden. Holanda. Abril 2013.
- International Cell Death Society. Malaga. Junio 2013.
- ECSS Congress. Barcelona. Junio 2013.
- Dynamito 2013. Okinawa – Japón. Octubre 2013.
- Congreso PABMB. Chile. Noviembre 2013.

Diseño: OnAccent.com · Fotografías: Archivo CIBERDEM; Fotolia

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