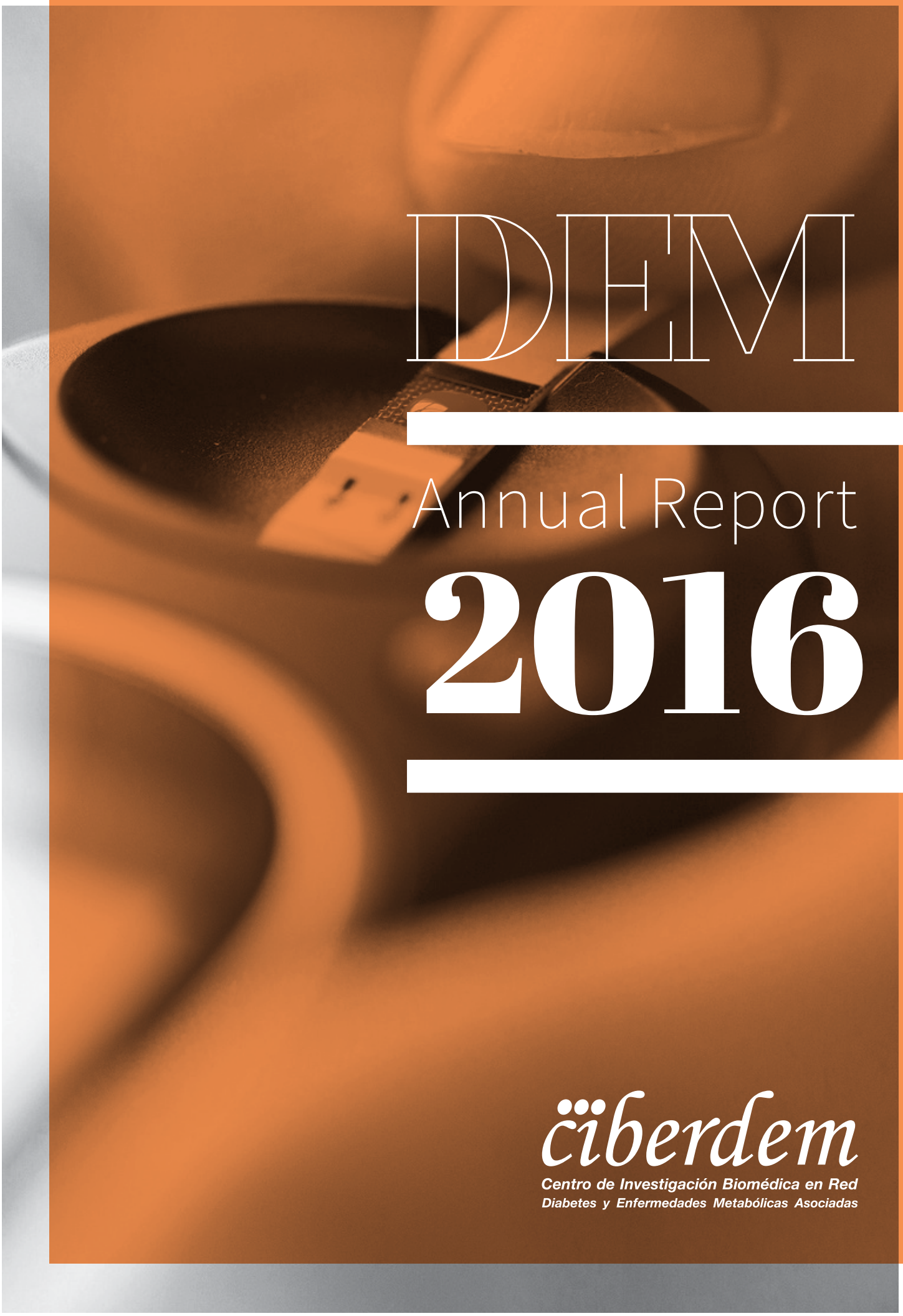


DEM

Annual Report

2016

ciberdem

Centro de Investigación Biomédica en Red

Diabetes y Enfermedades Metabólicas Asociadas

Index

Scientific Director's Presentation

2016 was a period involving the consolidation of organisational changes at CIBERDEM. The structure of the Research Programmes set up in 2015 was reinforced, agreements with platforms were renewed, adapting these to current legislation, and the Strategic Plan was almost completely drawn up to enable us to set the strategic approaches for the coming years. The evaluation of groups formed a major part of the organisational activity for 2016, and gave us an image of the work done by groups in the CIBERDEM context which will gradually be completed in coming assessments. Resuming our annual meeting has meant a particular satisfaction for me, as scientific director, since this allows us to share scientific concerns, point out or establish cooperation schemes and enjoy more personal contact.

In our own particular context, 2016 was a year of intense research activity, as displayed by both the large amount of scientific production (285 publications with CIBERDEM affiliation) and through its quality (28% of the publications in the first decile, 67% in the first quartile, average impact factor 5.1). The cooperation work done by CIBERDEM in the national and international spheres should be highlighted, with respective proportions of 76% and 36% of collaborative publications. The breakdown of the most relevant publications by each group is shown in the report. I would also like to stress the progress made in the Di@bet.es study, which will establish the incidence of diabetes in Spain and whose field study has already ended in one of the zones, and is making satisfactory progress in all the others.

In the balance for 2016 we should also point out the initiatives got under way in the Training Programme and that of Outreach. In the training area one could highlight the creation of the Mobility Aids, with the first call already issued in 2016, and which is continuing in the 2017 call, as well as the organisation of the Annual Session "Diabetes to debate 2016: Diabetes in the knowledge frontier" , in cooperation with MSD. The work done by the groups organising courses and seminars nationwide and abroad is worthy of mention, contributing to the training of researchers and the visibility of CIBERDEM. At the end of the year we made the formal application for the CIBERDEM to join EURADIA, *The Alliance for European Diabetes Research*, as member of the alliance, which will allow us to bolster the CIBERDEM's international presence in the institutional domain. Finally, with the aim of making our research work more visible and better known by society, we maintain our presence, through the CIBERDEM Space, in the DiabetesFEDE journal brought out by the Federación Española de Diabetes, we have begun cooperation with the DiabetesCero association and have taken part, amongst others, in the Diabetes Experience Day and in the Science Week, along with the many activities performed on regional or local levels by the different CIBERDEM groups.

The Report now being presented will give you more detailed knowledge about the activity and achievements of the CIBERDEM in 2016 and reflects the impact and quality of the research that we are doing. Please go ahead and consult this!

With best regards,

Eduard Montanya,
Scientific Director

2

Organisation

Organisational Structure

The CIBERDEM is one of the thematic areas forming the Centro de Investigación Biomédica en Red (CIBER), a Spanish research consortium in the field of biomedical research with great scientific potential, under the Instituto de Salud Carlos III (ISCIII) – Ministry of the Economy and Competitiveness. In 2016 this was made up of 8 thematic areas, extended to 11 in 2017.
The area of Diabetes and associated Metabolic Diseases is made up of 30 research groups, retaining its independence as regards scientific management. Its organisational structure is based on its research groups and its activity revolves around its Research Programmes and Transversal Programmes, there being a coordinator for each Programme belonging to the Steering Committee. Scientific decisions are made by the Scientific Director, advised by the Steering Committee and the External Scientific Committee.

MEMBERS OF THE STEERING COMMITTEE

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

Name	Post held
Eduard Montanya Mías	Scientific Director
Ángela Martínez Valverde	Coordinator of Programme 1
Franz Martín Bermudo	Coordinator of Programme 2
Antonio Zorzano Olarte	Coordinator of Programme 3
Ángel Nadal Navajas	Training Coordinator
Anna Novials Sardá	Coordinator of Outreach
Manuel Sánchez Delgado	Manager

Assistant Scientific Director: Isabel Ramis
Contact: http://www.ciberdem.org/en/about-us/contact

EXTERNAL ADVISORY SCIENTIFIC COMMITTEE

The External Advisory Scientific Committee is a body for scientific support and assessment, made up of relevant personalities in the field of health sciences standing out for their professional or scientific career in line with the centre's objectives. This is the body in charge of performing the annual assessment of the work done by CIBERDEM and its research groups.

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

The senior governing bodies of the CIBERDEM are the Governing Board and the Permanent Commission, common for all CIBER research areas.
The Governing Board is made up of three representatives of the ISCIII and one institutional representative of each of the centres in the consortium. This is presided over by the director of the ISCIII and meets every six months. The Permanent Commission is an executive committee, formed by the ISCIII and 8 members of the Governing Board, who can be renewed annually.
Both the operation and the purposes of the governing, support and assessment bodies are established in the statutes of the CIBER.

TECHNICAL UNIT

See list of personnel: http://www.ciberdem.org/en/about-us/structure/head-office

Directory of groups and institutions

Group leader	Institution	Centre	Centre Prov.
Álvarez Escola, Carmen	Universidad Complutense de Madrid	Facultad de Farmacia	Madrid
Ascaso Gimilio, Juan Francisco	Fund.para la Investigacion del Hospital Clínico de la Com. Valenciana (Fundación INCLIVA)	Instituto de Investigación sanitaria INCLIVA	Valencia
Balsinde Rodríguez, Jesús	Agencia Estatal Consejo Superior de Investigaciones Científicas	Instituto de Biología y Genética Molecular	Valladolid
Benito de las Heras, Manuel Román	Universidad Complutense de Madrid	Facultad de Farmacia	Madrid
Blanco Vaca, Francisco	Instituto de Investigacion del Hospital de la Santa Creu i Sant Pau	Inst. de investigación del Hospital de la Santa Creu i Sant Pau	Barcelona
Blázquez Fernández, Enrique	Universidad Complutense de Madrid	Facultad de Medicina	Madrid
Bosch Tubert, Fátima	Universidad Autónoma de Barcelona	Centro de biotecnología animal y terapia genética	Barcelona
Burks, Deborah	Fund. Centro de Investigación Príncipe Felipe	Centro de investigación Príncipe Felipe	Valencia
Calle Pascual, Alfonso Luis	Servicio Madrileño de Salud	Hospital Clínico San Carlos	Madrid
Castaño González, Luis	Asociación Instituto de Investigación Sanitaria de Biocruces	Hospital Universitario Cruces	Vizcaya
Correig Blanchart, Francesc Xavier	Fundación Instituto de Investigación Sanitaria Pere Virgili	Universidad Rovira i Virgili	Tarragona
Egido de los Ríos, Jesús	Fundación Instituto de Investigación Sanitaria Fundación Jiménez Díaz	Instituto de investigación sanitaria - Fundación Jiménez Díaz	Madrid
Escobar Morreale, Héctor Francisco	Servicio Madrileño de Salud	Hospital Ramón y Cajal	Madrid
Ferrer Marrades, Jorge	Instituto de Investigaciones Biomédicas August Pi i Sunyer	Centro Esther Koplowitz	Barcelona
Guinovart Cirera, Joan Josep	Fundación privada Instituto de Recerca Biomédica (IRB-Barcelona)	Fund. privada Instituto de Recerca Biomédica (IRB Barcelona)	Barcelona
Ibáñez Toda, Lourdes	Fundación para la Investigación y Docencia Sant Joan de Déu	Hospital Sant Joan de Déu	Barcelona
Martín Bermudo, Francisco	Universidad Pablo de Olavide	Centro andaluz de Biología Molecular y Medicina Regenerativa	Sevilla
Martínez Valverde, Ángela María	Agencia Estatal Consejo Superior de Investigaciones Científicas	Instituto de Investigaciones Biomédicas Alberto Sols	Madrid
Masana Marín, Luis	Fundación Instituto de Investigacion Sanitaria Pere Virgili	Universidad Rovira i Virgili	Tarragona
Mauricio Puente, Diego	Fundación Instituto de Investigacion Germans Trias i Pujol	Hospital Germans Trias i Pujol	Barcelona
Montanya Mías, Eduard	Fundación IDIBELL	Hospital universitario de Bellvitge	Barcelona
Nadal Navajas, Ángel	Universidad Miguel Hernández	Instituto de Bioingeniería	Alicante
Novials Sardá, Anna María	Instituto de Investigaciones Biomédicas August Pi i Sunyer	Centro Esther Koplowitz	Barcelona
Rojo Martínez, Gemma	Fundación Pública Andaluza para la Investigacion de Málaga en Biomedicina y Salud (FIMABIS)	Hospital Universitario Carlos Haya	Málaga
Simó Canonge, Rafael	Fundación Hospital Universitario Vall d'Hebron - Institut de Recerca (VHIR)	Hospital Vall d'Hebron	Barcelona
Vallejo Fernández de la Reguera, Mario	Agencia Estatal Consejo Superior de Investigaciones Científicas	Instituto de Investigaciones Biomédicas Alberto Sols	Madrid
Vázquez Carrera, Manuel	Universidad de Barcelona	Facultad de Farmacia. Universidad de Barcelona	Barcelona
Vendrell Ortega, Joan Josep	Fundación Instituto de Investigacion Sanitaria Pere Virgili	Hospital Universitario Juan XXIII	Tarragona
Vidal Cortada, Josep	Instituto de Investigaciones Biomédicas August Pi i Sunyer	Inst. de Investigaciones Biomédicas August Pi i Sunyer	Barcelona
Zorzano Olarte, Antonio	Fundación privada Instituto de Recerca Biomédica (IRB-Barcelona)	Fund. Privada Instituto de Recerca Biomédica (IRB Barcelona)	Barcelona

Budget

INCOME				
ISCIII TRANSFER	Grants Projects	Services	Other income	TOTAL
2.796.280,00	363.108,76	1.320,15	50,00	3.160.758,91

EXPENDITURE				
Project	Inventoriable	Supplies and other expenses for activity	Personnel	TOTAL
Scientific Management, Scientific Secretariat Communication	0,00	148.599,92	26.340,02	128.576,88
Groups	2.071,05	59.813,61	2.149.104,60	2.206.056,97
Training	0,00	540,00	0,00	540,00
Platforms	7,03	95.858,28	0,00	95.865,31
Intramural Projects	879,56	14.931,28	0,00	15.810,84
External Projects	8.289,11	200.749,83	207.194,76	415.623,60
TOTAL	**11.246,75**	**468.587,45**	**2.382.639,38**	**2.862.473,60**

Personnel

Personnel contracted during the year as of 31 December broken down by categories:

	MEN	WOMEN	Grand total
Diploma holders	-	3	3
Doctors	11	30	41
Graduates	3	26	29
Technical	4	11	15
TOTAL	18	70	88

Significant activities

Projects

NATIONAL

Financing Agency: Instituto de Salud Carlos III

Miguel Servet Contract -Characterization of the Lipin family in human adipocytes

Effects of fatty acids in the diet on the expression and epigenetic changes in the VEgf-b-mediated fatty acid transport system in rats

Rio Hortega Contract

Identification of novel modulators of chronic inflammation in prevalent diseases: unveiling divergent mechanisms of disease

Incidence of type 2 diabetes in Spain (Estudio di@bet.es II)

Financing Agency: Ministry of the Economy and Competitiveness

Aid from the Subprogramme of Research Staff Training

Ramón y Cajal Contract

Signalling insulin located in the liver

Reformulating the metabolism by identifying new metabolites and biochemical reactions using a new metabolomics tool

INTERNATIONAL EU

Genetic and environmental factors of insulin resistance syndrome and its long-term complications in immigrant Mediterranean populations (MEDIGENE)

European Nutrition Phenotype Assessment and Data Sharing Initiative (ENPADASI)

Determinants of Diet and Physical Activity; Knowledge Hub to integrate and develop infrastructure for research across Europe (DEDIPAC)

Transfer

One of the CIBER'S main aims is to pass on the knowledge generated by its researchers, so that the results of research are developed in protocols, services and products for improving clinical practice and the quality of people's life. To this end the Technology Transfer department of the CIBER acts as a link between our researchers and companies, private institutions, public research centres and other innovation agents to make cooperation with these effective and ensure that the results of research can manage to be applied. Work is done in several approaches to achieve this aim:

- Ongoing contact with our researchers to monitor their results and train them in the management of innovation.
  Hence, on 29 and 30 November 2016 a Technology Transfer Event was arranged as part of the 30th anniversary of the ISCIII. At this event experts in different fields shared their knowledge on industrial property, business creation, licence processes, venture capital, aid for internationalisation, etc.
- The protection of the results of research and management of cooperation with other agents, as vouched for by the application for patents and signing of licence contracts, amongst other agreements.
  Over 2016 eleven new applications for patents and a registration for software were presented at the CIBER. Seven inventions are in the patentability study stage and one is being drafted, and they are expected to be presented in early 2017.
  Apart from this, eight licence contracts have been signed. In 2016 furthermore, different negotiations expected to end successfully in the first quarter of 2017 were got under way.
  At CIBERDEM there are two inventions in the initial patentability study and the patents are expected to be presented in early 2017.

- The presentation of the results of research and technological capacities of our groups at technology transfer events. Amongst many other measures, and only as an example, CIBER had a stand and institutional presence at BIOSPAIN 2016 (28-30 September, Bilbao).
- The support for technology-based business creation stemming from groups at the CIBER.
- Other activities involving innovation, public-private cooperation and industrial and intellectual property.

Dissemination

In 2016 the CIBER'S Communication Department performed different measures for dissemination and disclosure in order to boost the Centre's visibility, as well as to make known the research work done by the groups in its eight thematic areas.

These are the main highlights of the CIBERDEM'S Communication work in 2016:

- **The CIBERDEM in the media:**
  In this period 347 appearances in the media were recorded:

2016	News	Audience
CIBERDEM	347	36.590.100

- **CIBER Newsletter**
  Five CIBER newsletters were drawn up and distributed, including relevant content about both the CIBERDEM and the other thematic areas. The digital newsletters were sent to nearly 4000 subscribers. http://www.ciberisciii.es/en/press/newsletter

- **CIBERDEM Newsletter**
  In 2016 the CIBERDEM newsletter was started up as a new tool for communication in this area. Every month, the newsletter contains an interview of a researcher and gives the news on the CIBERDEM for that period http://www.ciberdem.org/en/press/ciberdem-newsletter At present the newsletters are sent via e-mail to all the members of the area.

- **CIBERDEM Web**
  The CIBERDEM web published 45 news items and 31 events on the agenda in 2016.

Statistics on visits on the web 2016							
	No. of visits to page	Sessions*	Users	Pages/ session	Average duration of session	% rebound**	% new sessions
CIBERDEM	59.241	18.344	11.568	3,23	2:39	50,54	62,24

(*) **Sessions:** a session is a set of interactions taking place on this website in a certain period. For example, a single session may involve several pages being viewed.
(**) **Rebound:** the rebound percentage is the percentage of sessions of a single page, i.e. the sessions in which the user has left the site on the entry page without interacting with this.

- **Social Networks**
  Main indicators of the presence of CIBERDEM on twitter:

	Followers		Updates		Clout (Influence)	
	January	December	January	December	January	December
CIBERDEM	1097	1506	1052	1285	44	46

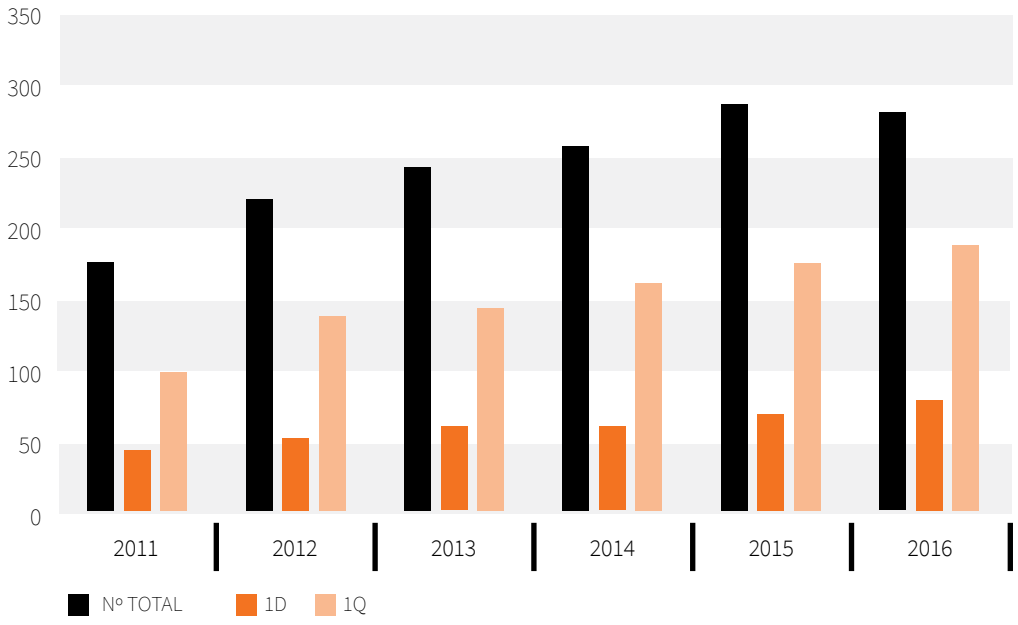
- **Annual CIBERDEM report**
  The CIBER Communication area, in cooperation with the CIBERDEM, coordinated the content of the CIBERDEM Report 2016 in Spanish/English, drawing up and disseminating 2 reports in interactive (flipbook) format and pdf. These reports have been distributed over the web page and through the Twitter account: http://www.ciberisciii.es/en/press/annual-report

Scientific Production

No. of publications

Nº of affiliated publications	2015	2016
Q1	177	190
D1	69	79
Total publications	316	285

EVOLUTION OF CIBERDEM PUBLICATIONS 2011-2016



Most relevant CIBERDEM publications in 2016 according to the impact factor

Publication	Impact factor
Mallarino R, Henegar C, Mirasierra M, Manceau M, Schradin C, Vallejo M, et Al. Developmental mechanisms of stripe patterns in rodents. Nature. 2016; 539(7630): 518–523.	38,138
Clemente-Casares X, Blanco J, Ambalavanan P, Yamanouchi J, Singha S, Fandos C, et Al. Expanding antigen-specific regulatory networks to treat autoimmunity. Nature. 2016; 530(7591):434-440.	38,138
Wright Rh, Lioutas A, Le Dily F, Soronellas D, Pohl A, Bonet J, et Al. ADP-ribose-derived nuclear ATP synthesis by NUDIX5 is required for chromatin remodeling. Science. 2016; 352(6290):1221-1225.	34,661
Akerman I, Tu Z2 Beucher A, Rolando Dm, Sauty-Colace C, Benazra M, et Al. Human Pancreatic β Cell lncRNAs Control Cell-Specific Regulatory Networks. Cell Metabolism. doi. org/10.1016/j.cmet. 2016.11.016.	17,303
Lagarrigue S, Lopez-Mejia Ic, Denechaud Pd, Escoté X, Castillo-Armengol J, Jimenez V, et Al. CDK4 is an essential insulin effector in adipocytes. Journal of Clinical Investigation. 2016; 126(1):335-48	12,575
López-Luque J, Caballero-Díaz D, Martinez-Palacián A, Roncero C, Moreno-Càceres J, García-Bravo M, et Al. Dissecting the role of epidermal growth factor receptor catalytic activity during liver regeneration and hepatocarcinogenesis. Hepatology. 2016; 63(2):604-619.	11,711
Slebe F, Rojo F, Vinaixa M, García-Rocha M, Testoni G, Guiu M, et Al. FoxA and LIPG endothelial lipase control the uptake of extracellular lipids for breast cancer growth. Nature Communications. 2016; 7:11199. doi: 10.1038/ncomms11199.	11,329
Ratajczak J, Joffraud M, Trammell Sa, Ras R, Canela N, Boutant M, et Al. NRK1 controls nicotinamide mononucleotide and nicotinamide riboside metabolism in mammalian cells. Nature Communications. 2016; 7:13103 7:13103. doi: 10.1038/ncomms13103.	11,329
Lordén G, Sanjuán-García I, De Pablo N, Meana C, Alvarez-Miguel I, Pérez-García Mt, et Al. Lipin-2 regulates NLRP3 inflammasome by affecting P2X7 receptor activation. The Journal of Experimental Medicine 2016; doi: 10.1084/jem.20161452	11,240
Nguan Soon T, Vázquez-Carrera M, Montagner A, Keat Sng M, Guillou H, Wahli W. Transcriptional control of physiological and pathological processes by the nuclear receptor PPARβ/δ. Progress in Lipid Research 2016; 64:98-122.	11.238

Publications per group

LEADER OF GROUP	TOTAL PUBLICATIONS	Q1	D1
Carmen Álvarez Escolá	6	6	2
Juan F. Ascaso Gimilio	13	8	7
Jesús Balsinde Rodríguez	4	4	0
Manuel R. Benito de las Heras	9	7	1
Francisco Blanco Vaca	15	8	1
Enrique Blázquez Fernández	-	-	-
Fàtima Bosch Tubert	6	4	3
Deborah Burks	6	5	1
Alfonso L. Calle Pascual	6	5	1

LEADER OF GROUP	TOTAL PUBLICATIONS	Q1	D1
Luis Castaño González	13	3	1
Francesc Xavier Correig Blanchar	16	16	10
Jesús Egido de los Ríos	15	11	3
Héctor F. Escobar Morreale	5	3	1
Jorge Ferrer Marrades	5	4	4
Joan J. Guinovart Cirera	5	3	2
Lourdes Ibáñez Toda	12	11	7
Francisco Martín Bermudo	12	8	5
Ángela M. Martínez Valverde	17	15	4
Luis Masana Marín	22	13	4
Diego Mauricio Puente	33	16	6
Eduard Montanya Mias	13	9	3
Ángel Nadal Navajas	9	7	3
Anna Maria Novials Sardà	32	20	6
Gemma Rojo Martínez	11	7	2
Rafael Simó Canonge	24	11	2
Mario Vallejo Fernández de la Reguera	2	2	2
Manuel Vázquez Carrera	5	5	3
Joan J. Vendrell Ortega	15	14	7
Josep Vidal Cortada	12	8	1
Antonio Zorzano Olarte	13	11	5

COOPERATION WORK

Number of intraCIBER publications 2016	48
Number of interCIBER publications 2016	102

Clinical guides and consensus documents

- Report from IPITA-TTS Opinion Leaders Meeting on the future of β-Cell Replacement. Bartlett St, Markmann Jf, Johnson P, Korsgren O, Hering BJ, et al. transplantation 2016; Suppl 2:S1-S44.
- Guidelines for the use and interpretation of assays for monitoring autophagy (3rd edition). Klionsky DJ, Abdelmohsen K, Abe A, Abedin MJ, Abeliovich H,et al. Autophagy. 2016; 12(1):1-222.
- Uppsala Consensus Statement on Environmental Contaminants and the global Obesity Epidemic. Lind L, Lind PM, Lejonklou MH, Dunder L, et al. Environmental Health Perspectives 2016; 124(5): A81-A83.
- Prevention, diagnosis, and treatment of obesity. 2016 position statement of the Spanish Society for the Study of Obesity. Lecube A, Monereo S, Rubio MÁ, Martínez-de-Icaya P et al. Endocrinol nutr 2016, pii: S1575-0922(16)30109-7. doi: 10.1016/j.endonu.2016.07.002.

3

Scientific Programmes

In 2016, the groups forming the programmes obtained financing from the Instituto de Salud Carlos III, from the Ministry of the Economy, Industry and Competitiveness, as well as from private institutions. The most relevant scientific milestones attained by the Programmes in 2016 are listed below, arranged on the basis of the main objectives for each Programme:

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

Coordinator: Ángela M Martínez Valverde

EPIDEMIOLOGY OF DIABETES MELLITUS, ITS CHRONIC COMPLICATIONS AND COMORBIDITIES

The di@bet.es epidemiological study was furthered to determine the incidence of diabetes in Spain. The field work began in all the zones and has already been completed in the southern zone. The data from the Di@bet.es study on prevalence has continued to be analysed and the influence of exercise on the risk of diabetes and the prevalence of hypertension has been described (Brugnara et al., PLOS ONE 2016).

Staff participated in a study on the association of the complete genome (gWAS) identifying two new loci of sensitivity to insulin (BCL2 and fAM19A2) and replicating variants associated with the sensitivity insulin (Walford et al., *Diabetes* 2016).

GENETICS, EPIGENETICS AND ENVIRONMENTAL FACTORS INVOLVED IN THE DEVELOPMENT OF DIABETES AND ITS COMPLICATIONS

The role of cytoplasmic transporters of fatty acids on the mechanisms inducing resistance to insulin in diverse tissues has been assessed, proving that these contribute to the induction of resistance to insulin on the hepatic level (Bosquet et al., *Atherosclerosis* 2016).

MOLECULAR MECHANISMS ASSOCIATED WITH THE APPEARANCE AND DEVELOPMENT OF CHRONIC COMPLICATIONS OF DIABETES: THERAPEUTIC STRATEGIES

The EUROCONDOR consortium funded by the European Union was coordinated, and the first clinical trial with neuroprotectors by topical ocular route for treatment of diabetic retinopathy was carried out (Trento et al., *Endocrine* 2016). It was shown that the neuroinflammation associated with diabetic retinopathy is reduced with GLP-1 analogues (Hernández et al., *Diabetes* 2016). During the progression of retinopathy in db/db mice there are changes in the polarisation of the microglia from M2 to M1 state, it being proposed that keeping the microglia in M2 state could be a therapeutic approach (Arroba et al., *Biochim Biophys Acta* 2016). Type 2 diabetic patients with diabetic retinopathy have been described as having an increase in the burden of cerebral small vessel disease. (Sanahuja et al., *Diabetes Care* 2016).

A work package has been led in the MOPEAD project (Models of Patient Engagement for Alzheimer's Disease) funded by IMI-2 to identify type 2 diabetic patients with the greatest risk of developing cognitive deterioration and a study was started in transgenic mice with Tau overexpression.

Biomarkers associated with heart failure in type 2 diabetes have been identified (Alonso et al., *Cardiovasc Diabetol* 2016).

It has been established that the Alx3 transcription factor is essential in the mechanism preventing congenital malformations during pregnancy in diabetic mothers. (García-Sanz et al., *Sci Rep* 2017, in press).

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

Coordinator: : Francisco Martín Bermudo

FUNCTION AND REGULATION OF PANCREATIC ISLETS: MOLECULAR AND CELLULAR BASES AND THERAPEUTIC TARGETS.

Different mechanisms increasing defence and improving the function and survival of β cells have been studied, such as the overexpression of endogenous chaperone PDI (Montane et al., *Mol Cell Endocrinol* 2016), the inhibition of microRnA-708; the use of gLP-1 (Fernández-Millán et al., *Free Radic Biol Med* 2016) and the reduction in the local expression of Igf-2.

As part of the function and adaptation of β cells a description was given of how a reduction in the expansion capacity of β mass is induced during ageing, caused by a limitation in its neogenesis and by a dedifferentiation of the β cell. At the same time the capacity for β cell hypertrophy and hyperplasia is maintained (Tellez et al., Am *J Physiol Endoc Metab* 2016). We have also characterised the mechanism used by TUDCA bile acid in the regulation of the function of β cells and we have generated a new animal model for in vivo study in real time of the role of IRS2 in β cells (Vettorazzi et al., *Metabolism* 2016).

The study of the molecular and cellular bases of the function and regulation of pancreatic islets has enabled us to find out that some lncRNAs display altered regulation of type 2 diabetes, showing a new type of molecular target (Akerman et al., *Cell Metab* 2017), that Wnt9a acts as a target gene of ngn3 and that the loss of gAtA6 in the β cell induces an intolerance to glucose on ageing (Pujadas et al., *Sci Rep* 2016).

MECHANISMS DAMAGING AND REGENERATING PANCREATIC ISLETS

Studies of the mechanisms damaging pancreatic islets have shown that exposure in the womb to bisphenol-A increases the mass of β cells during development, heightening the risk of developing diabetes as an adult (Garcia-Arevalo et al., *Endocrinology* 2016), and that administering taurine reverts the changes caused by a fat-rich diet on the circadian rhythm of mice (Figueroa et al., *Sci Rep* 2016).

PREVENTIVE AND THERAPEUTIC STRATEGIES IN REGENERATIVE MEDICINE, CELL THERAPY AND GENE THERAPY

A new protocol has been developed for obtaining insulin-producing cells responding to glucose from mouse embryo cells (Salguero-Aranda et al., Cell Transplant 2016).

A contribution was made to drafting the document of scientific associations International Pancreas and Islet transplant Association (IPITA) and Transplantation Society (TTS) on the future of the therapy for replacing β cells in diabetes (Markmann et al., Transplantation 2016).

Clinical trial NCT01257776 was completed, displaying the positive effects of intra-arterial administration of mesenchymal stem cells in the enhancement of clinical treatment for the diabetic foot.

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

Coordinator: Antonio Zorzano Olarte

DETERMINING FACTORS OF RESISTANCE TO INSULIN: MOLECULAR MECHANISMS INVOLVED

Prospective longitudinal monitoring of newborn babies with low weight for their gestational age (SGA) has shown that they experience fast and exaggerated postnatal recovery growth and develop early resistance to insulin and increase of visceral and hepatic fat which in turn conditions a greater risk for the future development of diabetes (Sebastiani et al., *Pediatr Obes* 2016).

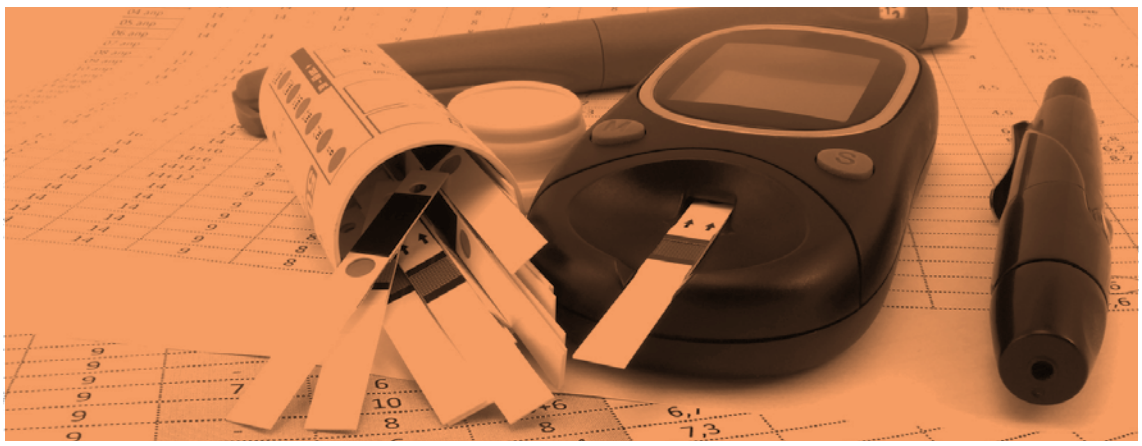
It has been shown that Mitofusin 2 (Mfn2) mitochondrial protein is repressed in the skeletal muscle of old mice, that knockout mice in which Mfn2 has been eliminated in the muscle display intolerance to glucose, mitochondrial dysfunction and muscular atrophy. This indicates that Mfn2 is a target for the development of new therapies for diabetes (Sebastián et al., *EMBO* J 2016).

Overexpression of Sirt1 in the skeletal muscle of the mouse has been proven to activate its oxidative capacity, but does not provide any protection against obesity and resistance to insulin (Vila et al., Mol Ther. Methods Clin Dev 2016). It has been described that an increase in the expression of Alox5ap can protect against obesity, inflammation, lipid steatosis and resistance to insulin (Elias et al. *Diabetes* 2016).

INFLAMMATION AS A PATHOGENIC PROCESS IN DIABETES MELLITUS: THE ROLE OF ADIPOSE TISSUE AND INTERACTION WITH OTHER TISSUES OR ORGANS

We have established new interrelations between lipid metabolism and inflammation. Lipin -2, a lipid metabolism protein which regulates the levels of phosphatidic acid and diacylglycerol, acts as a key regulator in macrophages in molecular assembly generating interleukin 1, known as inflammasome nLRP3. This provides a molecular explanation of Majeed syndrome and provides a connection between lipid metabolism and inflammation, with some interesting possibilities for therapeutic manipulation (Lordén et al., J *Exp Med* 2016).

We have shown that the hostile environment of chronic inflammation associated with obesity and type 2 diabetes alters the immunological functional properties of the stem cells residing in adipose tissue (Serena et al., *Stem Cells*. 2016).



IDENTIFICATION OF MOLECULAR MECHANISMS AND NEW THERAPEUTIC TARGETS FOR DEVELOPING PERSONALISED EARLY INTERVENTIONS IN DIABETES MELLITUS

For decades it had been discussed whether glycogen accumulation in beta cells of the pancreas had a major role in controlling glycaemia. By using genetic models with altered glycogen-accumulating capacity in the beta cells, we have proven that glycogen does not have a regulatory role (Mir-Coll et al., *Diabetologia* 2016).

Adipose tissue plays a major role in the control of energy consumption. It has been documented that selective ablation of IGFIR / IR (DKO) in brown adipose tissue induces severe atrophy of brown fat. DKO mice displayed an increase in body fat and a clear resistance to insulin, with no intolerance to glucose (Viana-Huete et al., *Endocrinology* 2016). These results indicate that the IGF-I receptor pathway is essential in the function of brown adipose tissue.

We have described that the activators of Heme-Regulated EIF2A kinase can revert intolerance to glucose and hepatic steatosis induced by a fat-rich diet due to its capacity to increase FGF21 (Ejaz et al., *Diabetes* 2016).

IDENTIFICATION OF RISK PROGRESSION BIOMARKERS IN DIABETES

A new inflammation marker has been identified in intracellular lipid droplets. Human peripheral blood monocytes contain an unusual isomer of palmitoleic acid, cis-7- hexadecenoic acid, in lipid droplets. This compound may prove useful as a biomarker of 'foamy monocytes' for early detection of cardiovascular diseases (Guijas et al., *Cell Chem Biol* 2016).

4

Transversal Programmes

Training Programme

Coordinator: Ángel Nadal Navajas

CIBERDEM had its 7th Annual Meeting from 11th to 13th May at the Hotel Campus, on the campus of the Universitat Autònoma de Barcelona in Cerdanyola del Vallés (Barcelona), with large numbers of participants and excellent scientific level of communications. In addition to sessions on each of the Research Programmes, there were sessions on CIBERDEM platforms, technology transfer at CIBER and a workshop on funding opportunities, intended for post-doctoral researchers.

In order to promote the training of researchers and interaction between groups, in 2016 CIBERDEM established a call for intraCIBERDEM and InterCIBER Mobility Aids.

CIBERDEM arranged the Annual Training Session entitled "Diabetes to debate 2016: Diabetes in the knowledge frontier" (Barcelona, 8th October) in the setting of its ongoing cooperation with the MSD company. The latest progress made in ground-breaking areas of obesity and cell and regenerative therapy in diabetes was discussed at the session. Along with this event there was also a programme of videoconferences on aspects of more applied research which was spread via WEB to Spain's endocrinology services.

Some of the training activities carried out by groups with CIBERDEM's participation were the following courses:

- *III Joint Worshop Tarraco-Malacca CIBERDEM-CIBEROBN*, (Hospital Universitario Juan XXIII and Hospital Universitario Carlos Haya, Lloret, 21 - 22 January).
- *Mass spectrometry imaging: a key technology for molecular histology* (Centre d'R+D+I en nutrició I Salut, Reus, 9 February).
- 7º Simposio sobre Diabetes, Dislipemias y Riesgo Cardiovascular (Calpe, 26 - 27 February).
- XIII Curso para Postgraduados: fundamentos Moleculares de la Medicina (Universidad Complutense de Madrid y Real Academia nacional de Medicina, Madrid, 25 – 26 May).
- *Cardiovascular Disease and Diabetes: Perspectives and Approaches* (Fundación SED, Madrid, 5 October, Barcelona, 6 October).
- VI Jornada Prometeo-GV: Avances en Diabetes y Obesidad (Universidad Miguel Hernández, Elche, 22 November).
- Course on "How to structure and present a clinical research project" (Instituto de Investigación sanitaria InCLIVA, Valencia, 19 -20 December).

Outreach Programme

Coordinator: Anna Novials Sardá

CIBERDEM goes on with its dual strategic aim of disclosing to society the scientific content generated by research groups to increase people's knowledge of diabetes and at the same time to enhance knowledge about CIBERDEM itself in national and international research community.

Some of the main outreach activities for social dissemination that could be mentioned are CIBERDEM's participation in:

- Diabetes Experience Day (13 February), a forum for people with diabetes, relatives and medicine professionals, where CIBERDEM made known its structure and organisation, as well as its lines of research. The meeting arranged by Canal Diabetes, a social channel with great diffusion capacity, brought over 1000 people together.
- World Diabetes Day (14 November), taking part in the activities arranged in Spain's different "autonomous communities".
- #Improciencia (16 November), a CIBER dissemination initiative as part of the Science Week, at which CIBERDEM presented the project entitled "Generation of Beta cells" in a theatre improvisation format.

CIBERDEM has close relations with the following patients' associations:

- Federación Española de Diabetes: CIBERDEM informs about its research activities in diabetes through the CIBERDEM Space in the journal entitled DiabetesFEDE. This year they had six interviews with principal CIBERDEM researchers.
- DiabetesCero, a movement of parents of children with diabetes and adults with the aim of monitoring and funding research into diabetes. A flow of information between CIBERDEM and DiabetesCERO has been set up. CIBERDEM groups with lines of research into type 1 diabetes prepared material on their lines of research which was made available to DiabetesCero and is currently found on its WEB page.
- Local and regional associations of patients with diabetes, with which CIBERDEM cooperated in different dissemination activities.

Some of the nationwide scientific communication activities worthy of mention are the presentation on the structure, organisation and scientific activities of CIBERDEM, given by the Scientific Director in the framework of the VII Reunión Anual Lilly en Diabetes held in Madrid on 1 October with the attendance of a large number of endocrinologists from all over the country.

On the international scale, and with the aim of reinforcing CIBERDEM'S presence in the scientific community, contact has been made this year with EURADIA, The Alliance for European Diabetes Research, a European alliance of scientific societies and pharmaceutical industry with a common interest in diabetes. CIBERDEM took part in the EURADIA *Summer Meeting* (13 July) and has applied to join as a member of the alliance.

5

Platforms

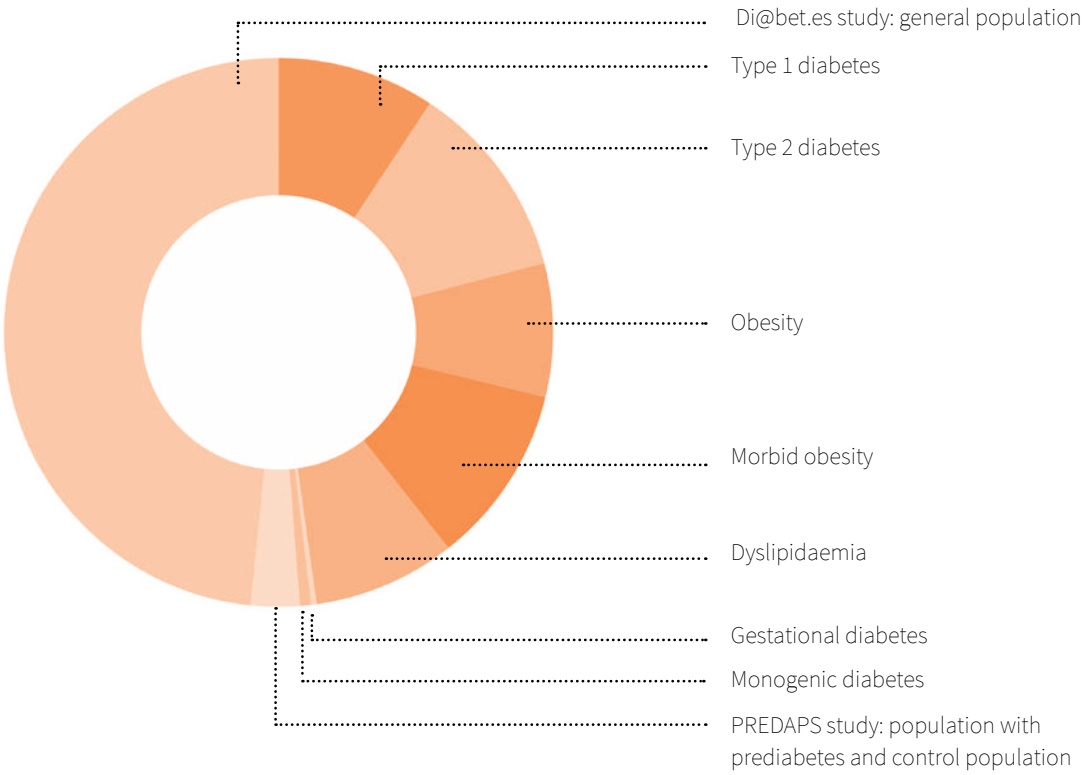
Biorepository for DIabetes and Metabolic Diseases CIBERDEM_IDIBAPS

Coordinator: **Anna Bosch** · Technical coordinator: **Verónica Fernández**

This is a mixed CIBER-IDIBAPS platform integrated in the IDIBAPS Biobank, with the aim of providing the scientific community with properly-characterised and standardised biological samples of the main metabolic diseases.

The Biorepository currently has a total number of 39,387 samples of whole blood, plasma, serum, DNA and lymphocytes from a total number of 11,545 persons with the following characteristics:

ORIGIN OF THE SAMPLES



In 2016 we continued to collect samples from donors belonging to the PREDAPS and Di@bet.es. projects. Most of the samples received from the PREDAPS study (131) were through follow-up of donors collected in previous years, with 76% being fourth donations. From the 2nd stage of the Di@bet.es project samples were received from 960 donors.

In 2016 aliquots were assigned for the following projects related to the Di@bet.es study:

- Incidence of type 2 diabetes in the di@bet.es study: role of fatty acids in the VEGFB-regulated transport system in the development of metabolic diseases.
- Genetic and environmental factors of insulin resistance syndrome and its long-term complications in immigrant Mediterranean populations.
- Understanding obesity, metabolic syndrome, type 2 diabetes and fatty liver disease: a multidisciplinary approach.
- Thyroid hormones and body weight. The role of variants in the alpha receptor gene of thyroid hormones in the risk of obesity.

Metabolomics Platform

Director: Xavier Correig · Coordinator: Òscar Yanes

http://www.metabolomicsplatform.com/

The Metabolomics Platform is a mixed CIBERDEM - Universitat Rovira i Virgili (URV) platform for giving technology services in the field of omic sciences. The main aim of the Metabolomics Platform is to work as an integrated laboratory for CIBERDEM groups, defining objectives, dimensions and characteristics of both the set of samples and of experimental designs. The equipment currently available in the NMR and LC/GC-MS field allows large-scale analyses of body fluids (for example, serum or urine) as well as tissues or biopsies of patients and/or animal models. The use of advanced statistics, chemometrics and multivariate algorithms enables a large set of data to be turned into metabolic profiles and ultimately into clinical information. The experimental data is processed by the platform team, facilitating the interpretation of results and providing sound and relevant clinical conclusions of use for different research groups.

The Metabolomics Platform particularly addresses to the needs of research groups from the CIBERDEM and the URV; however its services as well as potential scientific cooperation are available for other CIBER groups. In 2016 seven colaborations were carried out with CIBERDEM groups and four collaborations with groups from other thematic areas of the CIBER.

The platform's scientific activity in 2016 can be summed up as follows:

- Publications in indexed journals: 16
- Average impact factor: 8.27
- Participation in international conferences: 7
- Projects active in 2016: 3 national projects (BFU2014-57466-P, EUIN2015-62503 AND TEC2015- 69076-P) and 3 European projects (EU660034-MSCA-IF-ES-FT, 645758-TROPSENSE AND H2020-MSCA- ITN-2015).

Research lines active in 2016:

- Characterisation of lipoproteins by NMR for studying dyslipidaemias.
- Procedure for profiling serum for studying resistance to insulin and diabetes in population studies.
- Development and study of statistic algorithms, statistics, chemometrics, multivariates and artificial intelligence to enable the analysis of large sets of data.
- Non-radioactive isotopomers for studying metabolic profiles and their flow in cell cultures and animal models.
- Study of diabetic retinopathy.
- Study of molecular images of tissues and profiling of body fluid by means of nanostructured surfaces.
- Metabolomics study on the exposure to third-hand smoke (THS).

Relevant results in 2016:

- Development of a method for profiling glycoproteins in the blood by means of 1HRMN.
- Identification of metabolic markers in the vitreous humour of patients with diabetic retinopathy.
- Programming algorithms for flowomic experiments with mass spectrometry (LC-MS) and NMR.
- Creation and validation of a new algorithm for identifying unknown metabolites by means of mass spectrometry (GC-MS).
- Development of a methodology for obtaining and analysing metabolic images of mass spectrometry by cathodic spraying of metal nanoparticles (NP-LDI-MSI) on tissues of animal models.
- Development of a new computational approach based on the metabolic network of human metabolism to predict alterations in the abundance of metabolites based on quantitative proteomic data.

6

Research Groups

LEAD RESEARCHER

Álvarez Escola, Carmen

Universidad Complutense de Madrid

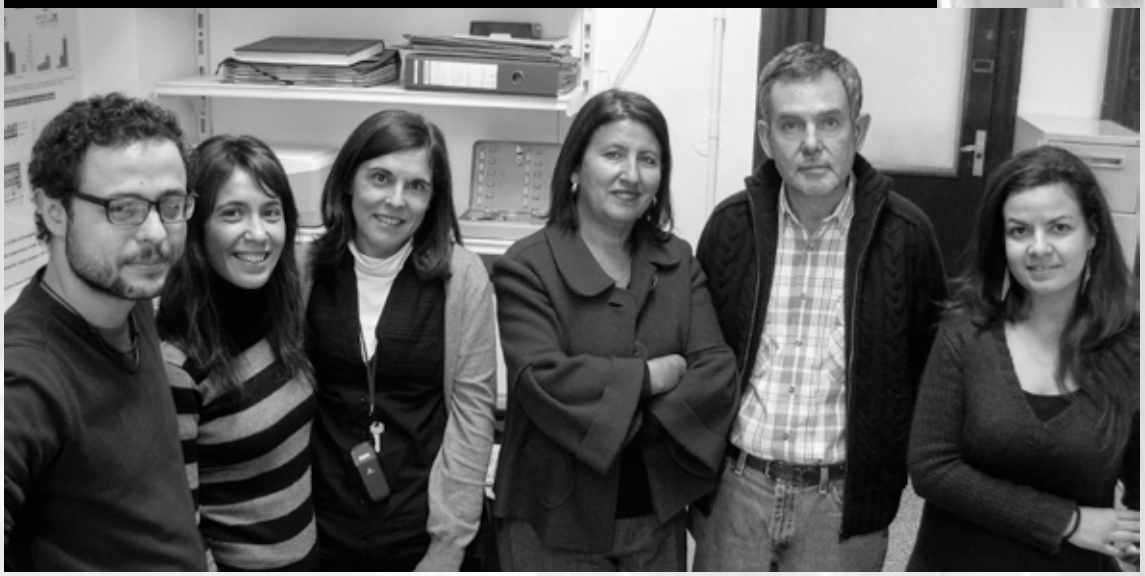
Facultad de Farmacia
Ciudad Universitaria, S/N
28040 Madrid

(+34) 91 394 18 57

calvarez@ucm.es

Group Website

PROGRAMME
P2



GROUP MEMBERS

Staff members: Fernández Millán, Elisa

Associated members: Escrivá Pons, Fernando | Lizarraga Mollinedo, Esther | Martín Arribas, María Ángeles

Main lines of research

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

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

Most relevant scientific articles

- Fernandez-Millan E., Martin M.A., Goya L., Lizarraga-Mollinedo E., Escriva F., Ramos S. et al. Glucagon-like peptide-1 improves beta-cell antioxidant capacity via extracellular regulated kinases pathway and Nrf2 translocation. Free Radical Biology and Medicine. 2016;95:16-26.
- Martin MÁ, Goya L, Ramos S, Álvarez Escola Carmen. Anti-diabetic actions of cocoa flavanols. Molecular nutrition & food research. 2016.
- Diaz-Castroverde S., Gomez-Hernandez A., Fernandez S., Garcia-Gomez G., Di Scala M., Gonzalez-Aseguinolaza G. et al. Insulin receptor isoform A ameliorates long-term glucose intolerance in diabetic mice. DMM Disease Models and Mechanisms. 2016;9(11):1271-1281.
- Goya L., Martin M.A., Sarria B., Ramos S., Mateos R., Bravo L. Effect of cocoa and its flavonoids on biomarkers of inflammation: Studies of cell culture, animals and humans. Nutrients. 2016;8(4).
- Fernandez-Gomez B., Ramos S., Goya L., Mesa M.D., del Castillo M.D., Martin M.A. Coffee silverskin extract improves glucose-stimulated insulin secretion and protects against streptozotocin-induced damage in pancreatic INS-1E beta cells. Food Research International. 2016.

Highlights

RESULTS

- The incretin GLP-1 effectively protects ß-cells from oxidative stress by improving their antioxidant capacity through the increased enzymatic activity of glutathione-peroxidase and -reductase via PKA-dependent activation of ERK and Nrf2 nuclear translocation.
- The blockage of autophagic activity in the endocrine pancreas seems to be required during postnatal remodeling in order to ensure the correct ß-cell turnover by apoptosis. This blockage might be associated to disappearance of islet IGF-2 expression since sustained IGF-2 stimulation of INS-1E cells inhibits mTORC1 activity and increases autophagy flux.
- Coffee silverskin extract improves glucose-stimulated insulin secretion and protects against streptozotocin-induced damage in pancreatic ß-cells.

FUNDING

- Molecular and cellular mechanisms involved in T2DM and obesity pathogenesis in rats submitted to maternal undernutrition and refed a high fat diet after weaning. MINECO. BFU 2011-25420. PI: Carmen Álvarez (2012-2016).
- Environmental factors involved in metabolic syndrome development: nutritional restriction and gut microbiota. MINECO Ref. BFU2016-77931-R. IP: Carmen Álvarez Escolá (2016-2019).

MEETINGS

- Fernández-Millán et al. Role of the (macro)autophagy in the postnatal regeneration of endocrine pancreas and its relationship with IGF-2. 52nd EASD Meeting (2016)
- Rodríguez-Rivera et al. Clusterin, a proposed biomarker of food addiction is upregulated in the Nucleus Accumbens of undernourished rats. 46th SfN's (Neurosciences) Meeting (2016)
- Fernández-Millán et al. Identification of new mechanisms involved in the postnatal regeneration of endocrine pancreas: role of the autophagy in beta-cells and its relationship with IGF-2. XXXIX Congreso de la SEBBM (2016). Invitación
- Rodríguez-Rivera et al. Sobre-expresión de la clusterina en el núcleo accumbens de ratas subnutridas. 25 Congreso Farmadrid (2016)

LEAD RESEARCHER

Ascaso Gimilio, Juan Fco.

Fundación para la Investigación del Hospital Clínico de la Comunidad Valenciana (Fund. INCLIVA)

Avd. Menéndez y Pelayo, 4 Acc. 46010 Valencia

(+34) 96 197 35 36

ascaso@uv.es

Group Website

PROGRAMME
P1

GROUP MEMBERS

Staff members: Benito Casado, Esther | García García, Ana Barbara | Peiros Signes, Marta

Associated members: Carmena Rodríguez, Rafael | Chaves Martínez, Felipe Javier | Martínez Hervás, Sergio | Real Collado, José Tomás

Main lines of research

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

Most relevant scientific articles

- Martinez-Hervas S., Artero A., Martinez-Ibanez J., Tormos M.C., González-Navarro H., Priego A. et al. Increased thioredoxin levels are related to insulin resistance in familial combined hyperlipidaemia. European Journal of Clinical Investigation. 2016;46(7):636-642.
- Martinez-Hervas S., Navarro I., Real J.T., Artero A., Peiro M., González-Navarro H. et al. Unsaturated oral fat load test improves glycemia, insulinemia and oxidative stress status in nondiabetic subjects with abdominal obesity. PLoS ONE. 2016;11(8).
- Marrachelli V.G., Rentero P., Mansego M.L., Morales J.M., Galan I., Pardo-Tendero M. et al. Genomic and metabolomic profile associated to clustering of cardio-metabolic risk factors. PLoS ONE. 2016;11(9).
- Andres-Blasco I., Vinue A., Herrero-Cervera A., Martinez-Hervas S., Nunez L., Piqueras L. et al. Hepatic lipase inactivation decreases atherosclerosis in insulin resistance by reducing LIGHT/lymphotoxin β-receptor pathway. Thrombosis and Haemostasis. 2016;116(2):379-393.
- Sánchez-Hernández RM, Civeira F, Stef M, Perez-Calahorra S, Almagro F, Plana N et al. Homozygous Familial Hypercholesterolemia in Spain: Prevalence and Phenotype-Genotype Relationship. Circulation. Cardiovascular genetics. 2016;9(6):504-510.

Highlights

The scientific activity of the research group during 2016 we wish to emphasize the the continuity of three research projects competitive and multidisciplinary led by the Dr. Ascaso, Dr. Real and Dr. Chaves. The Project led by Dr. Ascaso, entitled “Immunopharmacological modulation of the systemic inflammation associated to metabolic disorders. Search
for new therapeutic targets and synthesis of novel drugs”, studies the role of shaft CCL11/CCR3 in systemic inflammation associated with Familial Hypercholesterolemia and its immune modulation by oral lipid overload, as well as the study of the role of the axis CXCL16/CXCR6 in Ang-II-induced Endothelial dysfunction in subjects with metabolic síndrome. On the other hand, the main objetive of the project “Study of new infammatory and angiogenic mechanisms associated to severe morbid obesity: Role of CXCR3 axis and the nuclear receptors RORs” led by Dr. Real, is to explore the CXCR3 axis and RORs receptors in patients with severe morbid obesity with or without diabetes undergoing a gastric bypass. And finally, the main objetive of the project led by Dr. Chaves, “Identification of exome sequence variations alterations of methylation and hydroxymethylation associated with the development of type 2 diabetes”, evaluates the influence of sequence variations and methylation and hydroxymethylation of the coding and splicing regulatory sequences have on the development of T2DM.

LEAD RESEARCHER

Balsinde Rodríguez, Jesús

Ag. Estatal Consejo Superior de Investigaciones Científicas
Instituto de Biología y Genética Molecular
C/ Sanz y Fores S/N
47003 Valladolid
(+34) 98 342 30 62
jbalsinde@ibgm.uva.es
Group Website

PROGRAMME
P3

GROUP MEMBERS

Staff members: Meana González, Clara | Rubio Aranda, Julio Miguel

Associated members: Astudillo Del Valle, Alma | Balboa, María Ángeles | De Pablo Herranz, Nagore | Duque De Cela, Montserrat | Gil De Gómez Sesma, Luis | Guijas Maté, Carlos | Lebrero Fernández, Patricia | Lorden Losada, Gema | Montero Domínguez, Olimpio | Sanjuán García, Miren Itziar

Main lines of research

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

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

- Role of omega-3 fatty acid derivatives as deactivators of monocyte/macrophage activation via their antagonistic effects on inflammasome activation or other mechanisms of pathophysiological relevance.

Most relevant scientific articles

- Sala-Vila A., Navarro-Lérida I., Sánchez-Álvarez M., Bosch M., Calvo C., López J.A. et al. Interplay between hepatic mitochondria-Associated membranes, lipid metabolism and caveolin-1 in mice. Scientific Reports. 2016;6.
- Pena L., Meana C., Astudillo A.M., Lorden G., Valdearcos M., Sato H. et al. Critical role for cytosolic group IVA phospholipase A2 in early adipocyte differentiation and obesity. Biochimica et Biophysica Acta - Molecular and Cell Biology of Lipids. 2016;1861(9):1083-1095.
- Guijas C., Meana C., Astudillo A.M., Balboa M.A., Balsinde J. Foamy Monocytes Are Enriched in cis-7-Hexadecenoic Fatty Acid (16:1n-9), a Possible Biomarker for Early Detection of Cardiovascular Disease. Cell Chemical Biology. 2016;23(6):689-699.
- Lordén G, Sanjuán-García I, de Pablo N, Meana C, Álvarez-Miguel I, Pérez-García MT et al. Lipin-2 regulates NLRP3 inflammasome by affecting P2X7 receptor activation. The Journal of experimental medicine. 2016.

Highlights

GRANTS ACTIVE IN 2016

- "Lipid Pathways Regulating the Inflammasome: Role of Omega-3 Fatty Acids and Lipin-2". Ministry of Economy and Competitiveness (SAF2013-48201-R).
- "Positional Isomers and Oxygenated Derivatives of Palmitoleic Acid as New Mediators of Inflammation". Autonomous Government of Castile and Leon, Education Department ((JCYL CSI073U16).

RESEARCH CONTRACTS WITH PRIVATE COMPANIES

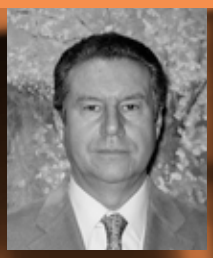
- FIV Recoletos, "Study of the role of the eicosanoids in implantation and in gestational diabetes".
- Mozo-Grau, "Fluids that promote or increase the osseointegration of implants in diabetic individuals".

MOST RELEVANT RESULTS

- Discovery that lipin-2, an enzyme of triglyceride and phospholipid metabolism, plays a key role in regulating interleukin-1ß production in macrophages through its effects on NLRP3 inflammasome assembly. These findings provide a molecular explanation for Majeed Syndrome, an autoinflammatory disease caused by inactivating mutations of the gene encoding for lipin-2.
- Description of the presence of an unusual isomer of palmitoleic acid, cis-7-hexadecenoic acid, in human peripheral blood monocytes. This fatty acid shows a strong anti-inflammatory character in vitro and in vivo, and its levels appear to be regulated by the activation state of the cells, which could be useful as a biomarker of 'foamy monocyes' for the early detection of cardiovascular disease.

TRAINING

- PhD thesis: "Regulation of lipid droplet formation by arachidonic acid in human monocytes. Relevance of the fatty acid 16:1n-9", Carlos Guijas Maté, University of Valladolid.
- PhD thesis: "Lipin-2 regulation of NLRP3 inflammasome activation in macrophages", Gema Lordén Losada, University of Valladolid.
- MSc thesis: "Levels of docosahexaenoic acid (22:6n-3) in mouse peritoneal macrophages", Laura Pereira de Blas, University of Valladolid.



LEAD RESEARCHER

Benito De las Heras, Manuel Román

Universidad Complutense de Madrid

Facultad de Farmacia
Ciudad Universitaria, S/N
28040 Madrid

(+34) 91 394 17 77

mbenito@ucm.es

Group Website

PROGRAMME
P3

GROUP MEMBERS

Staff members: Fernández López, Silvia | García Gómez, Gema | González Trujillos, Elena

Associated members: Bartolomé Herrainz, Alberto | Díaz-Castroverde Vicario, Sabela | Escribano Illanes, Óscar | Gómez Hernández, Almudena | Guillen Viejo, Carlos | Pedromo Loaiza, Liliana | Viana Huete, Vanesa

Main lines of research

- Compensatory mechanisms to hepatic insulin resistance: Progression to type 2 diabetes and the crossroad of autophagy and apoptosis in the pancreatic beta cells.
  A.- The role of the liver-pancreas endocrine axis in triggering beta-cell hyperplasia. The insulin receptor and its isoforms as gene therapy of the diabetic hyperglycemia.
  B.- The role of autophagy, mitophagy and ER stress in the regulation of beta-cell pancreatic mass and beta-cell failure.
  C.- The role of human amylin as a link between the pancreatic beta cell failure and neurodegeneration.
- Adipose organ inflammatory disease and the cardiovascular damage:
  D.- 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.
  E.1.- New mouse models to study energy imbalance and body weight regulation: Brown adipose tissue-specific knockout of IGFIR and IGFIR/IR DKO.
  E.2.- New mouse models of browning: Brown adipose tissue-specific knockout of p85 alpha/PI 3 kinase.
  E.3.- Role of IR and IGFIR in the mitochondrial dynamics in vitro and in vivo.

Most relevant scientific articles

- García-Aguilar A., Guillén C., Nellist M., Bartolomé A., Benito M. TSC2 N-terminal lysine acetylation status affects to its stability modulating mTORC1 signaling and autophagy. Biochimica et Biophysica Acta - Molecular Cell Research. 2016;1863(11):2658-2667.
- Díaz-Castroverde S., Baos S., Luque M., Di Scala M., González-Aseguinolaza G., Gómez-Hernández A. et al. Prevalent role of the insulin receptor isoform A in the regulation of hepatic glycogen metabolism in hepatocytes and in mice. Diabetologia. 2016;:1-9.
- Viana-Huete V, Guillén C, García-Aguilar A, García G, Fernández S, Kahn CR et al. Essential role of IGFIR in the onset of male brown fat thermogenic function: Regulation of glucose homeostasis by differential organ-specific insulin sensitivity.Endocrinology. 2016; en20151623.
- Beneit N, Fernández-García CE, Martín-Ventura JL, Perdomo L, Escribano Ó, Michel JB et al. Expression of insulin receptor (IR) A and B isoforms, IGF-IR, and IR/IGF-IR hybrid receptors in vascular smooth muscle cells and their role in cell migration in atherosclerosis. Cardiovascular diabetology. 2016;15(1):161.
- Díaz-Castroverde S., Gómez-Hernández A., Fernández S., García-Gómez G., Di Scala M., González-Aseguinolaza G. et al. Insulin receptor isoform A ameliorates long-term glucose intolerance in diabetic mice. DMM Disease Models and Mechanisms. 2016;9(11):1271-1281.

Highlights

Regarding to the ethiopathogenesis of type 2 diabetes, human amylin, but not rat amylin, through agregates formation in insulinoma cells overexpressing human amilin inhibited autophagy and enhanced the apoptosis susceptibility in response to induced ER stress. On the other hand, brown adipose tissue-specific knockout of IGFIR/IR (BATIGFIRDKO) induced a severe brown fat atrophy and mitochondrial crystae disruption, which turned out in an impaired cold-induced Drp-1-phophrylation fission mechanism, Overall DKO mice under HFD for 8 weeks showed an increased total body fat mass by NMR, overweight, a manifest insulin resistance, without glucose intolerance, a compensatory insulin secretion and finally, a severe hyperinsulinemia.

LEAD RESEARCHER

Blanco Vaca, Francisco

Instituto de Investigación del Hospital de la Santa Creu i Sant Pau

C/ S Antoni Mª Claret, 167
08025 Barcelona

(+34) 93 553 73 58

fblancova@santpau.cat

Group Website

PROGRAMME
P1

GROUP MEMBERS

Staff members: Cedo Gine, Lidia | Santos Palacios, David

Associated members: Escolá Gil, Juan Carlos | Julve Gil, Josep | Laura Errico, Teresa | Martín, Jesús | Pérez Pérez, Antonio | Roig Martínez, Rosa

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).
- Cholesterol homeostasis and human breast and epithelial thyroid cancer development.
- Relationship of epicardial fat, lipoprotein function and inflammation in the development of arteriosclerosis and diabetic cardiomyopathy.
- Evaluation of novel therapeutic and nutritional strategies for improving cardioprotective properties of HDL in mouse models of obesity, diabetes and cancer.

Most relevant scientific articles

- Salord N., Fortuna A.M., Monasterio C., Gasa M., Pérez A., Bonsignore M.R. et al. A randomized controlled trial of continuous positive airway pressure on glucose tolerance in obese patients with obstructive sleep apnea. Sleep. 2016;39(1):35-41.
- Julve J., Martín-Campos J.M., Escolà-Gil J.C., Blanco-Vaca F. Chylomicrons: Advances in biology, pathology, laboratory testing, and therapeutics. Clinica Chimica Acta. 2016;455:134-148.
- Fernández-Suárez M.E., Escolà-Gil J.C., Pastor O., Davalos A., Blanco-Vaca F., Lasuncion M.A. et al. Clinically used selective estrogen receptor modulators affect different steps of macrophage-specific reverse cholesterol transport. Scientific Reports. 2016;6.
- Cedo L., García-León A., Baila-Rueda L., Santos D., Grijalva V., Martínez-Cignoni M.R. et al. ApoA-I mimetic administration, but not increased apoA-I-containing HDL, inhibits tumour growth in a mouse model of inherited breast cancer. Scientific Reports. 2016;6.
- Amigó N, Mallol R, Heras M, Martínez-Hervás S, Blanco-Vaca F, Escolà-Gil JC et al. Lipoprotein hydrophobic core lipids are partially extruded to surface in smaller HDL: "Herniated" HDL, a common feature in diabetes. Scientific reports. 2016;6:19249.

Highlights

PROJECTS

- Coordinated project with other CIBERDEM groups funded by the Fundació La Marató de TV3 with the title: Preventing Premature Coronary Heart Disease in Catalonia by Expanding Familial Hypercholesterolemia Diagnosis.
- Coordinated project with other CIBERDEM groups funded by the Fundació La Marató de TV3 with the title Lipotoxicity and microvascular disease: Contribution to myocardial damage in clinical and experimental models of diabetes.
- Project funded by the Spanish Society of Arteriosclerosis with the title "Analysis of the effect of nicotinamide administration on the body weight and quantitative and qualitative properties of lipoproteins and its relationship with the development of atherosclerosis in experimental models."

RESULTS

- ApoA-I mimetic administration, but not increased apoA-I-containing HDL, inhibits tumor growth in a mouse model of inherited breast cancer and human breast adenocarcinoma MCF-7 cells.
- Continuous positive airway pressure treatment improves glucose tolerance in morbidly obese patients with severe obstructive sleep apnea.
- Obesity impairs the main cardioprotective HDL function, the macrophage-to-feces reverse cholesterol transport in obese db/db mice, by downregulating hepatic ABCG5/G8 transporters. A favorable upregulation of the hepatic levels of ABCG5/G8 is found in morbid obese patients undergoing Roux-en-Y gastric bypass surgery.
- The administration of nicotinamide (derived from vitamin B3) reduces weight gain concomitantly with lower adiposity and worse dietary caloric efficiency in a mouse model of obesity and insulin resistance.

LEAD RESEARCHER

Blázquez Fernández, Enrique

Universidad Complutense de Madrid

Facultad de Farmacia
Ciudad Universitaria, S/N
28040 Madrid

(+34) 91 394 14 43

eblazquez@med.ucm.es

Group Website

PROGRAMME
P1

GROUP MEMBERS

Staff members: Hurtado Carneiro, Verónica

Associated members: Álvarez García, Elvira | Navas Hernández, María de Los Ángeles | Roncero Rincón, Isabel | Ruiz Albusac, Juan Miguel | Sanz Miguel, Carmen | Velázquez Sánchez, Esther

Main lines of research

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

Highlights

- The most relevant findings of ours research team during 2016 were related with the reorganization of our group and the development of the different lines of research, especially with a new ones implied in the relationship between AD and T2DM, mainly focused on brain glucose hypometabolism and resistance to the action of insulin. Also, we have increased the number of scientific collaborations with other groups, such us L. Sacchetti, Universidad Federico II, Nápoles; J. Argente, Hospital Niño Jesús, Madrid; J. Oriola, Hospital Clinic, Barcelona; L. Castaño, Hospital de Cruces, Baracaldo, L. Wenger, Institute of Physiology, Zurich; D. Burks, Valencia; MA. Pozo, Madrid y R. Simó, Barcelona.
- We start the reorganization of the scientific team in order to hold the positions leave out by Drs. JA. Zueco and I. Roncero to one of them Dr. M. Pozo has been proposed to the Direction of Ciberdem. Besides the IP of our team communicate that he wants to end his work in this position, which was accepted by the group. Accordingly, during 2017 will be elected new IP.
- Also during 2016 the findings most relevants obtained were, the biological effects of GLP-2 on cell proliferation dependent of glucose concentrations and the demonstration that the functional characterization of MODY mutations may be of a great translational interest. Also have been of significant relevance the data obtained in the action of GLP-1 on brain metabolic sensors such us AMPK, mTOR, GK and PASK. Related with the last ones, have been very useful the studies on a mouse model PASK-deficient. In a similar way the experiment with on a transgenic mouse with hipperexpression of the Tau protein permit us to reproduce the brain glucose hypometabolism observed in AD patiens, wich in a near future open the door to the study with neuroprotector drugs, to test its potential therapeutic effect.
- Besides, it has been published a chapter in the book: “Tratado de Diabetes Mellitus (2ª Edicion) SED (Capítulo 14. Incretinas)” E. Blázquez and E. Velázquez
- Interview to Dr. Enrique Blázquez in the scientific Journal: “Diabetesfede (Federación Española de Diabetes) nº44, julio/Agosto 2016”
- Grant REF: RTC-2016-4823-1: GLAUKUS –SYLENTIS S.A.U. (2016). IP: Dra. Carmen Sanz
- Grant Artículo 83, UCM- SYLENTIS (Nov2015 –Nov 2016). IP: Dra. Carmen Sanz
- Grant Fundación Mutua Madrileña 25/09/2013-24/09/2016. IP: Dr. Enrique Blázquez
- Grant BFU2015-64440-P. Ministerio de Economía y Competitividad (2016-2018) IP: Ricardo Escalante y Olivier Vincent. Miembro del equipo investigador: Dra. María Ángeles Navas
- XIII Course Postgraduates: “Fundamentos Moleculares de la Medicina”, held in Madrid, May 2016. Director: Dr. Enrique Blázquez Fernández

LEAD RESEARCHER

Bosch Tubert, Fátima

Universidad Autónoma de Barcelona

Centro de Biotecnología Animal y Terapia Genética
Edificio H - Campus UAB
08193 Bellaterra - Barcelona

(+34) 93 581 41 82

fatima.bosch@uab.cat

Group Website

PROGRAMME
P2

GROUP MEMBERS

Staff members: Casellas Comallonga, Alba | Vilà Prats, Laia

Associated members: Barrero Victorio, Jennifer | Carretero Romay, Ana | Elias Puigdomenech, Ivet | Ferre Masferrer, María Del Tura | Franckhauser, Sylvie | García Martínez, Miguel | Haurigot, Virginia | Jiménez Cenzano, Verónica | León Madrenas, Xavier | Maggioni, Luca | Mallol Domínguez, Cristina | Melgarejo Bermúdez, Verónica | Molas Laplana, María | Morró Larrubia, Meritxell | Moya Martínez, Marta | Muñoz Forero, Sergio Antonio | Nacher García, Víctor | Navarro Beltrán, Marcos | Otaegui Goya, Pedro José | Pujol Altarriba, Anna | Ribera Sánchez, Albert | Roca Lecha, Carles | Ruberte Paris, Jesús | Zaguirre Sánchez, Mireia

Main lines of research

Study of causes and pathophysiological mechanisms of diabetes and obesity

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

Development of new gene therapy approaches for diabetes

- Gene therapy approaches for the treatment of type 1 diabetes centered on genetic engineering of skeletal muscle to produce insulin and/or increase glucose uptake.
- Gene therapy approaches for type 2 diabetes and obesity centered on genetic engineering of skeletal muscle and/or the liver.
- Study of in vivo pancreas regeneration in diabetic animals:
  Regeneration of endocrine pancreas by IGF-1
  Betasel: in vivo selection of genes to improve beta cell mass
- Development of new approaches for type 2 diabetes and obesity centered on genetic engineering of adipose tissue.

Most relevant scientific articles

- Elias I., Ferre T., Vila L., Munoz S., Casellas A., García M. et al. ALOX5AP overexpression in adipose tissue leads to LXA4 production and protection against diet-induced obesity and insulin resistance. Diabetes. 2016;65(8):2139-2150.
- Motas S, Haurigot V, Garcia M, Marcó S, Ribera A, Roca C et al. CNS-directed gene therapy for the treatment of neurologic and somatic mucopolysaccharidosis type II (Hunter syndrome). JCI insight. 2016;1(9): e86696.
- Vilà L, Roca C, Elias I, Casellas A, Lage R, Franckhauser S et al. AAV-mediated Sirt1 overexpression in skeletal muscle activates oxidative capacity but does not prevent insulin resistance. Molecular therapy. Methods & clinical development. 2016;5:16072.
- Albert V, Svensson K, Shimobayashi M, Colombi M, Muñoz S, Jiménez V et al. mTORC2 sustains thermogenesis via Akt-induced glucose uptake and glycolysis in brown adipose tissue. EMBO molecular medicine. 2016;.
- Lagarrigue S., López-Mejia I.C., Denechaud P.-D., Escote X., Castillo-Armengol J., Jiménez V. et al. CDK4 is an essential insulin effector in adipocytes. Journal of Clinical Investigation. 2016;126(1):335-348.

Highlights

In 2016, the second part of a project funded by the Juvenile Diabetes Research Foundation have been implemented: “BetaSel2 - Therapeutic efficacy of novel cytokines and growth factors selected to improve beta cell mass vivo”, in order to identify candidates to counteract type 1 diabetes. We have also obtained interesting results in the framework of the project funded by the Ministry of education and competitiveness (SAF2014-54866-R), “New approaches to gene therapy for type 2 diabetes and obesity based on the activation of brown adipose tissue and browning of white adipose tissue”. In addition, we have initiated a project funded by the EU, “Development of an innovative gene therapy platform for rare hereditary muscle disorders (MYOCURE)” to develop new approaches of gene therapy for rare muscular diseases, whose results will be of potential interest for the development of new strategies for the treatment of diabetes.
On the other hand, we participate in international initiatives such as the EU, “European infrastructure for phenotyping and archiving of model mammalian genomes (Infrafrontier-I3)” and the “Research Infrastructure for Phenotyping, Archiving and Distribution of Mouse Disease Models (IPAD-MD)”, or the Consortium “International Mouse Phenotyping Consortium (IMPC)” aiming at phenotyping, archiving and distributing mouse models to the scientific community. We also participate in the EU COST action “Development of a European network for preclinical testing of interventions in mouse models of age and age-related diseases (MouseAGE)”, in order to study aging in mice, and the EU COST action “European Network of Multidisciplinary Research and Translation of Autophaghy knowledge (TRANSAUTOPHAGHY)” to study the regulation of Autophagy.
Within the framework of the public / private partnership signed between UAB and Esteve, we are developing gene therapy approaches towards the clinic for rare inherited metabolic disorders (Mucopolysaccharidosis). In this field, we are also participating in the project “AAV-mediated gene therapy for the treatment of MPSIIID (Sanfilippo D)” financed by Association Française contre les Myopathies.

LEAD RESEARCHER

Burks, Deborah

Fundación Centro de Investigación Príncipe Felipe
C/ Eduardo Primo Yúfera, 3
46013 Valencia
(+34) 96 328 96 80
dburks@cipf.es
Group Website

PROGRAMME
P2

GROUP MEMBERS

Staff members: Acosta Umanzor, Carlos Rene | Arámbul Anthony, María José | Noon, Luke

Associated members: González Navarro, Herminia | Leal Tassias, Aránzazu | Moreno Gimeno, Inmaculada

Main lines of research

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

Our core research consists of 4 major lines:

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

4) Mechanisms of insulin resistance in the CNS. Aged Irs2-deficient mice present various manifestations of neurodegeneration including neuronal loss and deposits of hyperphosphorylated tau. Through the use of genomics and proteomics, we hope to identify new markers of neurodegeneration that are regulated by insulin signaling. Given that we seek to identify the molecular basis of obesity and insulin resistance, our research may provide the rational basis for the development of new and innovative strategies for the detection, treatment and prevention of metabolic disorders including lifestyle changes or drugs that promote IRS2 expression or function.

Most relevant scientific articles

- Martorell S., Hueso L., González-Navarro H., Collado A., Sanz M.-J., Piqueras L. Vitamin D Receptor Activation Reduces Angiotensin-II–Induced Dissecting Abdominal Aortic Aneurysm in Apolipoprotein E–Knockout Mice. Arteriosclerosis, Thrombosis, and Vascular Biology. 2016.
- Lao-Peregrin C., Ballesteros J.J., Fernández M., Zamora-Moratalla A., Saavedra A., Gómez Lázaro M. et al. Caffeine-mediated BDNF release regulates long-term synaptic plasticity through activation of IRS2 signaling. Addiction Biology. 2016.
- Andrés-Blasco I., Vinue A., Herrero-Cervera A., Martínez-Hervás S., Nunez L., Piqueras L. et al. Hepatic lipase inactivation decreases atherosclerosis in insulin resistance by reducing LIGHT/lymphotoxin β-receptor pathway. Thrombosis and Haemostasis. 2016;116(2):379-393.
- Martínez-Hervás S., Navarro I., Real J.T., Artero A., Peiro M., González-Navarro H. et al. Unsaturated oral fat load test improves glycemia, insulinemia and oxidative stress status in nondiabetic subjects with abdominal obesity. PLoS ONE. 2016;11(8).
- Martínez-Hervás S., Artero A., Martínez-Ibánez J., Tormos M.C., González-Navarro H., Priego A. et al. Increased thioredoxin levels are related to insulin resistance in familial combined hyperlipidaemia. European Journal of Clinical Investigation. 2016;46(7):636-642.

Highlights

During this year, our laboratory has received funding from the pharmaceutical industry to screen potential anti-diabetic compounds in the Irs2-deficient mouse model, a model of insulin resistance combined with pancreatic beta cell failure. One of these test drugs delayed the development of hyperglycemia in female Irs2-null mice and was associated with improved hepatic metabolism. However, the potential anti-diabetic properties of the other test drug may be dependent on IRS2 signaling since it had no beneficial effects in Irs2-deficient mice.

IRS2 signals are required for hepatic insulin action. Our recent studies suggest that local IRS2 signaling is also essential for hepatic regeneration in response to chronic injury. Irs2-deficiency undermines a full regeneration response that includes upregulation of inflammatory and repair genes. Our observations suggest that IRS2 may modulate a balance between regeneration and the uncontrolled proliferation of hepatocellular carcinoma.

We have also generated a new tool for studying the role of Irs2 in vivo: a transgenic mouse model where the expression of GFP and luciferase are under the control of the Irs2 promoter. Although IRS2 signals are critical for the development and function of the endocrine pancreas, little is known about the spatial/temporal expression during embryonic development and the regulation of the Irs2 gene in the adult pancreas. The new Irs2-GFP-luc model will permit us to define the spatiotemporal regulation of Irs2 during fetal and adult life and during the aetiology of metabolic disease. Additionally, this new mouse model will facilitate identification of compounds or drugs which protect and/or restore beta cell compensation as mediated by the IRS2 pathway.

LEAD RESEARCHER

Calle Pascual, Alfonso Luis

Servicio Madrileño de Salud
Hospital Clínico San Carlos
Avda. Complutense S/N
28040 Madrid
(+34) 91 394 18 57
Group Website

PROGRAMME
P1

GROUP MEMBERS

Staff members: Pescador Sánchez, Nuria

Associated members: Bernat Jiménez, Antonia | Caso Pita, Covadonga | Corbatón Anchuelo, Arturo | Fernández Pérez, Cristina | Fernández Represa, Jesús Álvarez | Martínez Larrad, María Teresa | Serrano Ríos, Manuel | Zabena Carina, Alejandra

Main lines of research

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

Most relevant scientific articles

- Martínez-Larrad M.T., Corbaton-Anchuelo A., Fernández-Pérez C., Lazcano-Redondo Y., Escobar-Jiménez F., Serrano-Ríos M. Metabolic syndrome, glucose tolerance categories and the cardiovascular risk in Spanish population. Diabetes Research and Clinical Practice. 2016;114:23-31.
- Martínez Larrad M.T., Corbaton Anchuelo A., Fernández-Pérez C., Pérez Barba M., Lazcano Redondo Y., Serrano Ríos M. et al. Obesity and cardiovascular risk: Variations in visfatin gene can modify the obesity associated cardiovascular risk. Results from the Segovia population based-study. Spain. PLoS ONE. 2016;11(5).
- Brugnara L., Murillo S., Novials A., Rojo-Martínez G., Soriguer F., Goday A. et al. Low physical activity and its association with diabetes and other cardiovascular risk factors: A nationwide, population-based study. PLoS ONE. 2016;11(8).
- García-Casarrubios E., de Moura C., Arroba A.I., Pescador N., Calderón-Domínguez M., García L. et al. Rapamycin negatively impacts insulin signaling, glucose uptake and uncoupling protein-1 in brown adipocytes. Biochimica et Biophysica Acta - Molecular and Cell Biology of Lipids. 2016;1861(12):1929-1941.
- Walford G.A., Gustafsson S., Rybin D., Stancakova A., Chen H., Liu C.-T. et al. Genome-wide association study of the modified stumvoll insulin sensitivity index identifies BCL2 and FAM19A2 as novel insulin sensitivity loci. Diabetes. 2016;65(10):3200-3211.

Highlights

- Genome-wide association studies (GWAS) have found few common variants that influence fasting measures of insulin sensitivity. We hypothesized that a GWAS of an integrated assessment of fasting and dynamic measures of insulin sensitivity would detect novel common variants. We performed a GWAS of the modified Stumvoll Insulin Sensitivity Index (ISI) within the Meta-Analyses of Glucose and Insulin-Related Traits Consortium.
  We identified two novel loci and replicated known variants associated with insulin sensitivity. Further studies are needed to clarify the causal variant and function at the BCL2 and FAM19A2 loci.
- Our aim was to investigate if genetic variations in the visfatin gene (SNPs rs7789066/ rs11977021/ rs4730153) could modify the cardiovascular-risk (CV-risk) despite the metabolic phenotype (obesity and glucose tolerance). In addition, we investigated the relationship between insulin sensitivity and variations in visfatin gene. This is the first study which concludes that the genotype AA of the rs4730153 SNP appear to protect against CV-risk in obese and non-obese individuals, estimated by Framingham and SCORE charts. Our results confirm that the different polymorphisms in the visfatin gene might be influencing the glucose homeostasis in obese individuals.
- We examined the prevalence of metabolic syndrome (MetS), glucose tolerance categories and risk factors of cardiovascular-disease (CVD) in the general Spanish population. Prevalence of MetS has not changed in the past decade in Spanish females, but has slightly increased in males. We found that subjects with IGT showed a higher risk of CVD than IFG and IFG/IGT according to the Framingham and SCORE. MetS increased the CVD-risk previously estimated by Framingham and SCORE.
- Di@bet.es Study. di@bet.es II is ongoing.

LEAD RESEARCHER

Castaño González, Luis

Asoc. Inst. de Investigación Sanitaria de Biocruces

Hospital Universitario Cruces
Pza. de Cruces, S/N
48903 Cruces (Barakaldo)
Vizcaya

(+34) 946 006 473

lcastano@osakidetza.eus

Group Website

PROGRAMME
P1

GROUP MEMBERS

Staff members: Martínez Salazar, Rosa María | Urrutia Echebarria, Inés María

Associated members: Aguayo Calcena, Anibal | Bilbao Catalá, José Ramón | Castellanos Rubio, Ainara | Cortázar Galarza, Alicia | Gaztambide Saenz, Sonia | González Frutos, Teba María Dolores | Pérez de Nanclares, Gustavo | Rica Etxebarría, Itxaso | Rivero, Sorkunde | Santamaría Sandi, Francisco Javier | Vázquez San Miguel, Federico | Vela, Amaia | Velayos Gainza, Teresa

Main lines of research

- 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.
- Study of enviromental factors and immune mediators of disease development, characterization of novel autoantigens/antibodies and cell populations in patients: Th1, Th2 and Th17 responses.
- Identification of new genes responsible for monogenic diabetes by genome wide analysis (array-CGH approach), whole exome sequencing and next generation sequencing panels of candidate genes.
- Molecular and clinical characterization of monogenic diabetes and new therapeutic strategies for KATP channel alterations.
- Prediction and prevention of type 1 diabetes.
- Control of diabetes complications.
- Epidemiology of diabetes.

Most relevant scientific articles

- Aguayo A., Urrutia I., González-Frutos T., Martínez R., Martínez-Indart L., Castano L. et al. Prevalence of diabetes mellitus and impaired glucose metabolism in the adult population of the Basque Country, Spain. Diabetic Medicine. 2016.
- Martínez R., Fernández-Ramos C., Vela A., Velayos T., Aguayo A., Urrutia I. et al. Clinical and genetic characterization of congenital hyperinsulinism in Spain. European Journal of Endocrinology. 2016;174(6):717-726.
- Brugnara L., Murillo S., Novials A., Rojo-Martínez G., Soriguer F., Goday A. et al. Low physical activity and its association with diabetes and other cardiovascular risk factors: A nationwide, population-based study. PLoS ONE. 2016;11(8).
- Fernández-Ramos C., Arana-Arri E., Jiménez-Huertas P., Vela A., Rica I. Incidence of childhood-onset type 1 diabetes in Biscay, Spain, 1990-2013. Pediatric Diabetes. 2016.
- Chico A., Herranz L., Corcoy R., Ramírez O., Goya M.M., Bellart J. et al. Glycemic control and maternal and fetal outcomes in pregnant women with type 1 diabetes according to the type of basal insulin. European Journal of Obstetrics Gynecology and Reproductive Biology. 2016;206:84-91.

Highlights

PROJECTS

- Endocrinology, Diabetes, Nutrition and Renal Alterations. Basque Government-IT 795-13. 2013-2018. L. Castaño.
- Incidence of diabetes and prevalence of monogenic-diabetes in the Di@bet.es study. ISCIII–PI14/01104. L. Castaño.
- Determinants of Diet and Physical Activity. DEDIPAC-KH (JPI) “Healthy Diet for Healthy Life” 2012-active. L. Castaño.
- European Nutrition Phenotype Assessment and Data Sharing Initiative. ENPADASI. “Healthy Diet for Healthy Life”. 2014-Luis Castaño.
- Prospective study: Incidence of diabetes and cardiovascular risk factors in Basque Country. Basque Government (2015111020) 2015-2017. Sonia Gaztambide.
- Functional characterization of the IDIN antiviral pathway: role in pancreatic ß-cell destruction and T1D progress. Basque Government (2015111068). 2015-2018. Izortze-Santin.
- Functional characterization of the genomic regions associated with celiac disease risk in cell populations of gut mucosa. (PI13/01201). 2014-2016. JR Bilbao.
- Functional study of candidate genes to celiac disease. Use as a diagnostic tool. Basque Government (2011111034). 2013-JR Bilbao.
- Genetic and environmental factors of insulin-resistance syndrome. Long-term complications in immigrant Mediterranean populations. MEDIGENE (FP7-279171-1). 2011-active, Luis Castaño.
- Centre Differences study in children aged under 11 years. Hvidore Study Group on childhood Diabetes. 2009-2015. Luis Castaño.
- TRIGR project: Trial to reduce IDDM in children at genetic risk. National Institute of Health. 2007-2016. Luis Castaño.
- BMBS COST Action BM1303. A systematic elucidation of differences of sex development (DSDnet). 2013-2017 Luis Castaño.
- Deep Osasuna: Knowledge-based personalized medicine (DEEPOS) KK-2015/00111_Elkartek and 2016222030_RIS3 proyects. Basque Government. Luis Castaño.
- Global obesity epidemic: Molecular and dynamic parameter characterization in order to develop diagnostic strategies and personalized therapies. Basque Government. Sonia Gaztambide.
- Multicentric, prospective, non-intervention study to investigate security and effectiveness of Insulin degludec in a population with type 1 and 2 diabetes mellitus. EudraCT: EPA2016012 (EPA-SP). Sonia Gaztambide.

ORGANISATION CONGRESS:

- Presidency and Organization of ISPAD Congress (International Society for Pediatric and Adolescent Diabetes) Valencia-2016, Luis Castaño. Sponsor/Partner: CIBERDEM.
- Presidency and Organization of SED Congress, Bilbao 2016. Sonia Gaztambide.

LEAD RESEARCHER

Correig Blanchart, Francesc Xavier

Fund. Inst. de Investigación Sanitaria Pere Virgili

Facultat de Medicina
C/ Sant Llorenç, 21
Edif. 4 · Planta baja
43201 Reus. Tarragona

(+34) 977 559 623

metabolomicsplatform@urv.cat

Group Website

PROGRAMME
P3

GROUP MEMBERS

Staff members: Capellades Tomás, Jordi | Navarro Sanz, Miriam | Yanes Torrado, Óscar

Associated members: Amigó Grau, Nuria | Brezmes Llecha, Jesús Jorge | Cañellas Alberich, Nicolau | Domingo Almenara, Xavier | Radu Ionescu, Radu | Ràfols Soler, Pere | Ramírez González, Noelia | Samino Gene, Sara | Vilalta Montlleo, Didac

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.
- 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.
- Study of diabetic retinopathy.
- Study of tissue imaging and body fluid profiling with laser desorption ionization mass spectrometry (LDI-MS).
- Thirdhand smoke (THS) exposition assesment with metabolomics and their effects on metabolic diseases.

Most relevant scientific articles

- Amigó N, Mallol R, Heras M, Martínez-Hervás S, Blanco-Vaca F, Escolà-Gil JC et al. Lipoprotein hydrophobic core lipids are partially extruded to surface in smaller HDL: "Herniated" HDL, a common feature in diabetes.Scientific reports. 2016;6:19249.
- Rafols P., Vilalta D., Brezmes J., Canellas N., del Castillo E., Yanes O. et al. Signal preprocessing, multivariate analysis and software tools for MA(LDI)-TOF mass spectrometry imaging for biological applications. Mass Spectrometry Reviews. 2016.
- Vinaixa M., Schymanski E.L., Neumann S., Navarro M., Salek R.M., Yanes O. Mass spectral databases for LC/MS- and GC/MS-based metabolomics: State of the field and future prospects. TrAC - Trends in Analytical Chemistry. 2016;78:23-35.
- Capellades J., Navarro M., Samino S., García-Ramírez M., Hernández C., Simo R. et al. GeoRge: A Computational Tool to Detect the Presence of Stable Isotope Labeling in LC/MS-Based Untargeted Metabolomics. Analytical Chemistry. 2016;88(1):621-628.
- Domingo-Almenara X., Brezmes J., Vinaixa M., Samino S., Ramírez N., Ramon-Krauel M. et al. ERah: A Computational Tool Integrating Spectral Deconvolution and Alignment with Quantification and Identification of Metabolites in GC/MS-Based Metabolomics. Analytical Chemistry. 2016;88(19):9821-9829.

Highlights

COLLABORATIONS

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

RELEVANT PROJECTS

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

H2020-MSCA-ITN-2015. Chromatin–metabolism interactions as targets for healthy living.

TEC2012-31074: Development of nanostructured surfaces and processing algorithms for obtaining and treatment of metabolic images measured by laser desorption ionization mass spectrometry (LDI-MS).

RELEVANT RESULTS ACHIEVED

- Development of a method for profiling of glycoproteins in blood measured by 1HNMR.
- Identification of metabolic markers in the vitreous humor of patients with diabetic retinopathy.
- Development of algorithms for fluxomics experiments based on LC-MS and NMR.
- Creation and validation of a new algorithm for the identification of unknown metabolites by GC-MS.
- Obtaining and processing metabolic images of mass spectrometry by metal nanoparticles (NP-LDI-MSI).

LEAD RESEARCHER

Egido De los Ríos, Jesús

Fundación Instituto de Investigación Sanitaria Fundación Jiménez Díaz

Avda. Reyes Católicos, 2
28040 Madrid

(+34) 91 550 48 00
(Ext. 3362/2294)

jegido@fjd.es

Group Website

PROGRAMME
P1

GROUP MEMBERS

Staff members: Civantos Martín, Esther

Associated members: Gómez Guerrero, Carmen | González Gómez, Nieves | Lorenzo González, Óscar | Martín Crespo, Estrella | Más Fontao, Sebastián | Oguiza Bilbao, Ainhoa | Recio Cruz, Carlota

Main lines of research

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

Most relevant scientific articles

- Tarín C., Fernández-Garcia C.E., Burillo E., Pastor-Vargas C., Llamas-Granda P., Castejón B. et al. Lipocalin-2 deficiency or blockade protects against aortic abdominal aneurysm development in mice. Cardiovascular Research. 2016;111(3):262-273.
- Rubio-Navarro A., Carril M., Padro D., Guerrero-Hue M., Tarín C., Samaniego R. et al. CD163-macrophages are involved in rhabdomyolysis-induced kidney injury and may be detected by MRI with targeted gold-coated iron oxide nanoparticles. Theranostics. 2016;6(6):896-914.
- Bosch-Panadero E, Mas S, Sánchez-Ospina D, Camarero V, Pérez-Gómez MV, Sáez-Calero I et al. The Choice of Hemodialysis Membrane Affects Bisphenol A Levels in Blood. Journal of the American Society of Nephrology: JASN. 2016;27(5):1566-74.
- Beneit N, Fernández-García CE, Martín-Ventura JL, Perdomo L, Escribano Ó, Michel JB et al. Expression of insulin receptor (IR) A and B isoforms, IGF-IR, and IR/IGF-IR hybrid receptors in vascular smooth muscle cells and their role in cell migration in atherosclerosis. Cardiovascular diabetology. 2016;15(1):161.
- Burillo E, Jorge I, Martínez-López D, Camafeita E, Blanco-Colio LM, Trevisan-Herraz M et al. Quantitative HDL Proteomics Identifies Peroxiredoxin-6 as a Biomarker of Human Abdominal Aortic Aneurysm. Scientific reports. 2016;6:38477.

Highlights

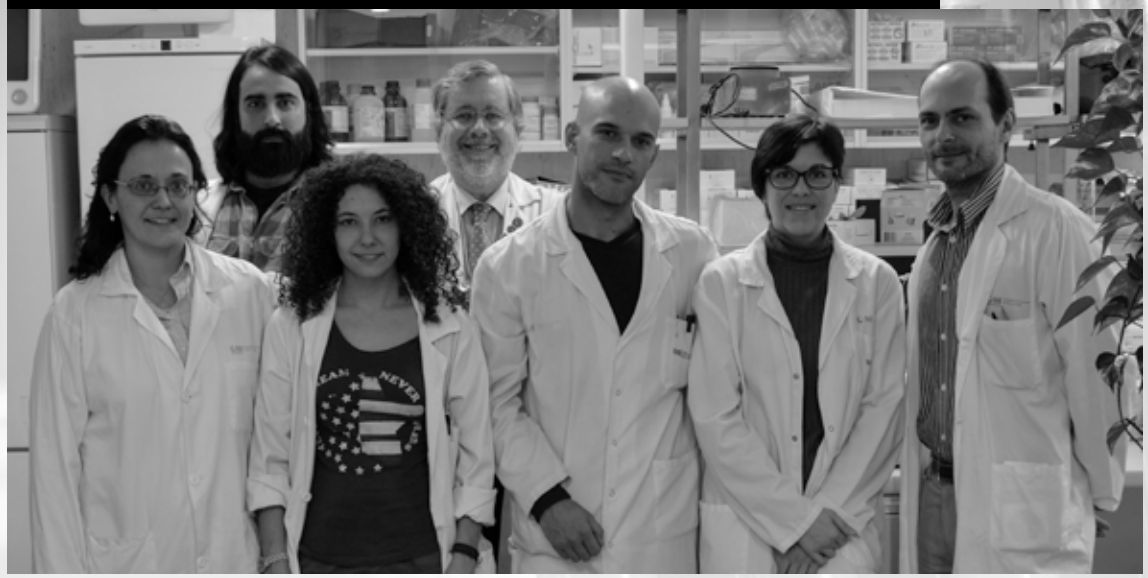
- Patent title: SOCS1-Derived peptide for use in chronic complications relating to diabetes. This patent has been filed in conjuction with professor Rafael Simó (CIBERDEM). In November 2016, this patent has been extended to 35 countries with the largest pharmaceutical market. Recently, we have got a grant from FIPSE to perform Viability Studies.
- Clinical trial supported by the 7th Program Early prevention of diabetes complications in people with hyperglycaemia in Europe (ePREDICE). Our group is involved in the recruitment of patients as well as running the WP4 on biomarkers. This is one of the first clinical trials assessing the effect of therapeutical intervention on prediabetes. The biobank is established in our institution.

LEAD RESEARCHER

Escobar Morreale, Héctor Francisco

Servicio Madrileño de Salud
Hospital Ramón y Cajal
Carretera de Colmenar, km 9.1
28034 Madrid
(+34) 91 336 90 29
elena.fenandezd@salud.madrid.org
Group Website

PROGRAMME
P3



GROUP MEMBERS

Staff members: Fernández Durán, Elena | Insenser Nieto, María Rosa | Martínez García, María Ángeles

Associated members: Álvarez Blasco, Francisco | Luque Ramírez, Manuel | Montes Nieto, Rafael | Roldán Martín, María Belén | San Millán López, José Luis

Main lines of research

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

Most relevant scientific articles

- Escobar-Morreale H.F., Roldán-Martín M.B. Type 1 diabetes and polycystic ovary syndrome: Systematic review and meta-analysis. Diabetes Care. 2016;39(4):639-648.
- Botella-Carretero J.I., Lafuente C., Montes-Nieto R., Balsa J., Vega-Pinero B., Garcia-Moreno F. et al. Serum Bioavailable Vitamin D Concentrations and Bone Mineral Density in Women After Obesity Surgery. Obesity Surgery. 2016;26(11):2732-2737.
- Luque-Ramírez M., Escobar-Morreale H.F. Adrenal hyperandrogenism and polycystic ovary syndrome. Current Pharmaceutical Design. 2016;22(36):5588-5602.
- Escobar-Morreale HF, Martínez-García MÁ, Montes-Nieto R, Fernández-Durán E, Temprano-Carazo S, Luque-Ramírez M. Effects of glucose ingestion on circulating inflammatory mediators: Influence of sex and weight excess. Clinical nutrition (Edinburgh, Scotland). 2016.

Highlights

During 2016, the group has focused on the execution of the following projects “Effects on cardiovascular risk factors of decreasing iron tissue deposits in women with polycystic ovary syndrome: a proof-of-concept study” (PI14/00649) and “Influence of sex and sex hormones on adipose tissue dysfunction and chronic metabolic disorders of complex etiology (SEXMETAB)” (PI15/01686). The SEXMETAB study, which includes animal and human experiments, will allow us to address the novel issue of gonadal dysfunction in men and its relation to metabolic dysfunction. Moreover, our previous project on the study of the hormonal, metabolic, inflammatory and oxidative stress response to dietary macronutrients and the influence of sex steroids is in its final phase of publication and dissemination (PI11/0357).
Also, in 2016, the group has received founding from an Excellence Integrated Project “Influence of sex and sex hormones on human chronic disorders of complex etiology -SEXCOMPLEX-” (PIE16/00050), which aim is to study the differences between women and men in several complex chronic diseases. The objective will focus on the mechanisms involved in the influence of sex and sexual steroids on the pathophysiology and clinical presentation of the proposed diseases. The group will coordinate the project in cooperation with six other groups of Instituto Ramón y Cajal de Investigación Sanitaria, three of them belong to other CIBERs.
In the field of training, our group got a post-doctoral contract Río Hortega Specialized Sanitary Training for the study of the prevalence of mutations in the INSR and LMNA genes in functional ovarian hyperandrogenism with insulin resistance.
Regarding scientific publications, the meta-analysis on the frequent association of polycystic ovarian syndrome and its signs and symptoms with type 1 diabetes, published in the journal Diabetes Care, should be highlighted. This study points to the importance of diagnosing and treating polycystic ovarian syndrome in women with type 1 diabetes as well as the inclusion of screening in clinical guidelines for the management of type 1 diabetes.

LEAD RESEARCHER

Ferrer Marrades, Jorge

Instituto de Investigaciones Biomédicas August Pi i Sunyer

Centro Esther Koplowitz
C/ Rossellón, 153, Planta 2
08036 Barcelona

(+34) 93 227 54 00 xt 4542

jferrer@clinic.ub.es

Group Website

PROGRAMME
P2

GROUP MEMBERS

Staff members: García Hurtado, Javier | Grau Martínez, Vanessa | López Díaz, Víctor | Maestro Garriga, Miguel Ángel | Sanahuja, Carme

Associated members: Akerman, Ildem | Armengol, Mar | Atla, Goutham | Miguel Escalada, Irene | Rovira Clusellas, Meritxell

Main lines of research

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

Most relevant scientific articles

- De Vas M., Ferrer J. Can Insulin Production Suppress β Cell Growth? Cell Metabolism. 2016;23(1):4-5.
- Akerman I, Tu Z, Beucher A, Rolando DM, Sauty-Colace C, Benazra M et al. Human Pancreatic β Cell lncRNAs Control Cell-Specific Regulatory Networks. Cell metabolism. 2016.
- Ferrer J., Real F.X. The cis-regulatory switchboard of pancreatic ductal cancer. EMBO Journal. 2016;35(6):558-560.
- Horikoshi M., Pasquali L., Wiltshire S., Huyghe J.R., Mahajan A., Asimit J.L. et al. Transancestral fine-mapping of four type 2 diabetes susceptibility loci highlights potential causal regulatory mechanisms. Human Molecular Genetics. 2016;25(10):2070-2081.
- Afelik S., Rovira M. Pancreatic β-cell regeneration: Facultative or dedicated progenitors? Molecular and Cellular Endocrinology. 2016.

Highlights

A study has been published that defines the function of long non-coding RNAs (lncRNAs) in genetic networks involved in type 2 diabetes.

LEAD RESEARCHER

Guinovart Cirera, Joan Josep

Fundación privada Instituto de Recerca Biomédica (IRB-Barcelona)

C/ Baldiri Reixac 10-12
08028 Barcelona

(+34) 93 403 71 63

guinovart@irbbarcelona.org

Group Website

PROGRAMME
P3

GROUP MEMBERS

Staff members: Duran Castells, Jordi | Veza Estévez, Emma

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

Main lines of research

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

Most relevant scientific articles

- Mir-Coll J., Durán J., Slebe F., García-Rocha M., Gomis R., Gasa R. et al. Genetic models rule out a major role of beta cell glycogen in the control of glucose homeostasis. Diabetologia. 2016:1-9.
- Slebe F., Rojo F., Vinaixa M., García -Rocha M., Testoni G., Guiu M. et al. FoxA and LIPG endothelial lipase control the uptake of extracellular lipids for breast cancer growth. Nature Communications. 2016;7.
- Díaz-Lobo M., Concia A.L., Gómez L., Clapes P., Fita I., Guinovart J.J. et al. Inhibitory properties of 1,4-dideoxy-1,4-imino-d-arabinitol (DAB) derivatives acting on glycogen metabolising enzymes. Organic and Biomolecular Chemistry. 2016;14(38):9105-9113.
- Maldonado R., Mancilla H., Villarroel-Espindola F., Slebe F., Slebe J.C., Mendez R. et al. Glycogen Synthase in Sertoli Cells: More Than Glycogenesis? Journal of Cellular Biochemistry. 2016.
- Krag T.O., Pinos T., Nielsen T.L., Durán J., García-Rocha M., Andreu A.L. et al. Differential glucose metabolism in mice and humans affected by McArdle disease. American Journal of Physiology - Regulatory Integrative and Comparative Physiology. 2016;311(2):R307-R314.

Highlights

- Glycogen accumulation in beta cells of diabetic patients has been proposed to partly mediate glucotoxicity-induced beta cell dysfunction. We studied glucose homeostasis in mice with (1) defective glycogen synthesis and (2) excessive glycogen accumulation in beta cells. Our results demonstrated that glycogen metabolism is not required for the maintenance of beta cell function. Furthermore, glycogen accumulation in beta cells alone is not sufficient to trigger the dysfunction or loss of these cells (Mir-Coll et al., Diabetologia 2016).
- To examine the involvement of the hepatic branch of the vagus nerve in the regulation of food intake and glucose homeostasis by liver glycogen, we performed vagotomy on mice that overaccumulate glycogen in the liver. Our results confirmed that this regulation of food intake and glucose homeostasis by liver glycogen is dependent on the hepatic branch of the vagus nerve (López-Soldado et al, second revision in Diabetologia).
- Glycogenin (GYG) is considered to be indispensable for the synthesis of glycogen, acting as primer of the glucose chain. We generated a GYG-KO mouse. Surprisingly, GYG-KO mice not only maintain their ability to synthesise glycogen, but accumulate high levels of the polysaccharide in skeletal and cardiac muscle. Recently, several patients with GYG1 loss of function that are affected by high glycogen storage in muscle fibers have been identified. Our results contribute to understanding this new type of glycogenosis and challenge the role of GYG in glycogen metabolism (Testoni et al, in revision in Cell Metabolism).
- We found that breast cancer cells are dependent on a mechanism to supply precursors for intracellular lipid production that are derived from extracellular sources and that the endothelial lipase LIPG fulfils this function. The downregulation of LIPG in transformed cells results in decreased proliferation and impaired synthesis of intracellular lipids (Slebe et al., Nature Communications 2016).

LEAD RESEARCHER

Ibáñez Toda, Lourdes

Fundación para la Investigación y Docencia Sant Joan de Deu

Hospital Sant Joan de Deu
C/ Santa Rosa, 39-57
08950 Esplugues de Llobregat

(+34) 93 280 40 00
(ext. 4424 ¸ 70205)

libanez@hsjdbcn.org

Group Website

PROGRAMME
P3

GROUP MEMBERS

Staff members: Díaz Silva, Marta | Quilez Moya, Jovita

Associated members: Casano Sancho, Paula | García Beltran, Cristina | Marcos Salas, María Victoria | Sebastiani, Giorgia

Main lines of research

- Metabolic endocrinology.
- Neonatal physiopathology.
- Childhood diabetes.

Most relevant scientific articles

- Mazarico E., Martínez-Cumplido R., Díaz M., Sebastiani G., Ibánez L., Gómez-Roig M.D. Postnatal anthropometric and body composition profiles in infants with intrauterine growth restriction identified by prenatal Doppler. PLoS ONE. 2016;11(3).
- De Zegher F., Díaz M., López-Bermejo A., Ibánez L. Recognition of a sequence: More growth before birth, longer telomeres at birth, more lean mass after birth. Pediatric Obesity. 2016.
- De Zegher F., Pérez-Cruz M., Sebastiani G., Díaz M., López-Bermejo A., Ibánez L. Large for Gestational Age Newborns from Mothers Without Diabetes Mellitus Tend to Become Tall and Lean Toddlers. Journal of Pediatrics. 2016;178:278-280.
- Díaz M, García C, Sebastiani G, de Zegher F, López-Bermejo A, Ibáñez L. Placental and Cord Blood Methylation of Genes Involved in Energy Homeostasis: Association with Fetal Growth and Neonatal Body Composition.Diabetes. 2016.
- Domingo-Almenara X., Brezmes J., Vinaixa M., Samino S., Ramírez N., Ramon-Krauel M. et al. ERah: A Computational Tool Integrating Spectral Deconvolution and Alignment with Quantification and Identification of Metabolites in GC/MS-Based Metabolomics. Analytical Chemistry. 2016;88(19):9821-9829.

Highlights

RESEARCH GROUP

Over 2016, the group has further developed the two main research lines:

- Ovarian androgen excess: follow-up of a clinical trial with novel therapies (PI15/01078); methylation and miRNAs exploration in hyperandrogenic adolescents.
- Low birth weight and postnatal endocrine-metabolic abnormalities: we have published the first part of the project related to methylation and gene expression in newborns of low birthweigth (PI11/02403). We are currently analyzing the persistence of this pattern ar age 12 months.

These are among the priority research lines of the Hospital Sant Joan de Déu, being part of a broader line entitled: Adult Diseases of Fetal Origin, coordinated by Dr. Lourdes Ibáñez since 2008 (UB; www.hsjdbcn.org). The results of the recent accomplishmetns have been presented in invited lectures at national and international forums, including those at the Endocrine Society (Boston), and ISPAD (Valencia), as well as ten update courses, twelve abstracts in international meetings and eight in national meetings.

COLLABORATIONS:

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

OTHER (DR. LOURDES IBÁÑEZ):

- PhD thesis: direction (Giorgia Sebastiani, September 2016).
- Chair of Research Group recognised and funded by the Agència de Gestió d'Ajuts Universitaris i de Recerca en Catalunya (2014SGR512)
- Research time (2015) funded by ISCIII-Departament de Salut, Generalitat de Catalunya (INT16/00121).
- Coordination & Direction of the Master in Paediatric & Adolescent Endocrinology and Diabetes (UB).
- Chair: Pediatric & Adolescent Gynecology Working Group, ESPE (www.eurospe.org) & SGA Working Group, SEEP (www.seep.es/privado/ctpubli6.asp).
- Participacion as expert and representative of the European Society for Paediatric Endocrinology in two Consensus Guidelines: Global Adolescent PCOS Consensus Statement & Evidence-based PCOS guidelines.

LEAD RESEARCHER

Martín Bermudo, Francisco

Universidad Pablo de Olavide
Centro Andaluz de Biología Molecular y Medicina Regenerativa
Avda. Américo Vespucio S/N
41092 Sevilla

(+34) 95 597 79 44

fmarber@upo.es

Group Website

PROGRAMME
P2

GROUP MEMBERS

Staff members: Araujo Legido, Raquel | Cardenas García, Antonio Manuel | Díaz Contreras, Irene | Hitos Prados, Ana Belén

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

Main lines of research

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

Most relevant scientific articles

- Tapia-Limonchi R., Cahuana G.M., Caballano-Infantes E., Salguero-Aranda C., Beltran-Povea A., Hitos A.B. et al. Nitric Oxide Prevents Mouse Embryonic Stem Cell Differentiation Through Regulation of Gene Expression, Cell Signaling, and Control of Cell Proliferation. Journal of Cellular Biochemistry. 2016.
- Soria B., Montanya E., Martín F., Hmadcha A. A role for the host in the roadmap to diabetes stem cell therapy. Diabetes. 2016;65(5):1155-1157.
- Munoz-Bravo J.L., Flores- Martínez A., Herrero-Martin G., Puri S., Taketo M.M., Rojas A. et al. Loss of pancreas upon activated Wnt signaling is concomitant with emergence of gastrointestinal identity. PLoS ONE. 2016;11(10).
- Jurado-Ruiz E., Varela L.M., Luque A., Berna G., Cahuana G., Martínez-Force E. et al. An extra virgin olive oil rich diet intervention ameliorates the nonalcoholic steatohepatitis induced by a high-fat "Western-type" diet in mice. Molecular Nutrition and Food Research. 2016.
- Fontan-Lozano A., Capilla-González V., Aguilera Y., Mellado N., Carrion A.M., Soria B. et al. Impact of transient down-regulation of DREAM in human embryonic stem cell pluripotency. The role of DREAM in the maintenance of hESCs.Stem Cell Research. 2016;16(3):568-578.

Highlights

A new differentiation protocol to obtain insulin secreting cells from mouse embryonic stem cells has been developed. In the new protocol, the biphasic pattern of Pdx1 expression has been induced by using nitric oxide and an inhibitor of p330.

The clinical assay ((AdMSC Diabetes; EudraCT: 2008-001837-88; ClinicalTrial.gov Identifier: NCT01257776) has been finished. This assay has demonstrated the positive effects of an intra-arterial injection of mesenchymal stem cells for diabetic food. The patients avoided the need for amputation, improved their vasculogenesis and their Rutheford Becker classification. Finally, the patients had a significant reduction of their ulcers and pain.

The loss of GAT6 in the function of beta cells induces a glucose intolerance after the fifth month of ages. It has been proven that GAT6 is key to insulin synthesis, the regulation of specific beta cell transcription factors and for the regulation of the genes involved insulin release.

In a mouse model of high-fat diet type 2 diabetes, it has been shown that the modification of the fats profile for monounsaturated rich-phenolics fats (coming from extra virgin olive oil) improve glucose homeostasis. The mechanisms for this improvement are: i) a decrease of insulin resistance; ii) a better stimulus-secretion coupling and iii) a decrease of beta cell apoptosis, as well as, an increase in beta cell mass.

LEAD RESEARCHER

Martínez Valverde, Ángela María

Agencia Estatal Consejo Superior de Investigaciones Científicas

Instituto de Investigaciones Biomédicas Alberto Sols
C/ Arturo Duperier 4
28029 Madrid

(+34) 91 585 44 97

avalverde@iib.uam.es

Group Website

PROGRAMME
P1

GROUP MEMBERS

Staff members: Abancéns Izcue, María | Ruiz Cañas, Laura | Valdecantos Jiménez De Andrade, María Pilar | Vázquez Pérez, Patricia

Associated members: Ahmed, Maysha | De Pablo Davila, Flora | Hernández Sánchez, Catalina | Rada Llano, Patricia | Rubio Caballero, Carmen | Santamaría Perez, Beatriz | Villar Lorenzo, Andrea

Main lines of research

- Study of the molecular mechanisms associated to the progression of non-alcoholic fatty liver disease (NAFLD):
  - Dual role of the protein tyrosine phosphatase 1B (PTP1B) in NAFLD: from intestinal inflammation to hepatic fibrosis.
  - Cross-talk between different liver cells (hepatocytes, Kuffer cells, stellate cells) in the context of NAFLD progression: molecular mechanisms involved.
  - Differential effects of single and dual agonists of glucagon-like peptide-1 receptor (GLP-1R) and glucagon receptor (GCGR) in the treatment of NAFLD at stages of non-alcoholic steatohepatitis (NASH).
  - Role of insulin receptor substrate 2 (IRS2) in the epithelial-mesenchymal transition (EMT) in hepatic cells in insulin resistant states.
- Differential therapeutic effects of single and dual agonists of glucagon-like peptide-1 receptor (GLP-1R) and glucagon receptor (GCGR) in the treatment of insulin resistance associated to obesity: effects of these drugs in the brown adipose tissue.
- Effect of low grade chronic inflammation on insulin and catecholamine sensitivity in brown adipocytes: molecular mechanisms involved and therapeutic strategies.

- Study of the polarization of microglia (M1/M2) in diabetic retinopathy (DR): targeting microglia polarization as a therapeutic approach at the early stages of DR.
- Physiological role of proinsulin and the consequences of inappropriately high levels during cardiogénesis.
- Involvement of Tyrosine Hydroxilase in the metabolic adaptations to diet and temperature stressors.

Most relevant scientific articles

- Arroba A.I., Alcalde-Estèvez E., García-Ramírez M., Cazzoni D., de la Villa P., Sánchez-Fernández E.M. et al. Modulation of microglia polarization dynamics during diabetic retinopathy in db/db mice. Biochimica et Biophysica Acta - Molecular Basis of Disease. 2016;1862(9):1663-1674.
- García-Casarrubios E., de Moura C., Arroba A.I., Pescador N., Calderón-Domínguez M., García L. et al. Rapamycin negatively impacts insulin signaling, glucose uptake and uncoupling protein-1 in brown adipocytes. Biochimica et Biophysica Acta - Molecular and Cell Biology of Lipids. 2016;1861(12):1929-1941.
- Hernández C, Bogdanov P, Corraliza L, García-Ramírez M, Solà-Adell C, Arranz JA et al. Topical Administration of GLP-1 Receptor Agonists Prevents Retinal Neurodegeneration in Experimental Diabetes. Diabetes. 2016;65(1):172-87.
- Isiegas C., Marinich-Madzarevich J.A., Marchena M., Ruiz J.M., Cano M.J., De La Villa P. et al. Intravitreal injection of proinsulin-loaded microspheres delays photoreceptor cell death and vision loss in the rd10 mouse model of retinitis pigmentosa. Investigative Ophthalmology and Visual Science. 2016;57(8):3610-3618.
- Arroba A.I., de la Rosa L.R., Murillo-Cuesta S., Vaquero-Villanueva L., Hurle J.M., Varela-Nieto I. et al. Autophagy resolves early retinal inflammation in Igf1-deficient mice. DMM Disease Models and Mechanisms. 2016;9(9):965-974.

Highlights

SCIENTIFIC PROJECTS

- "Identification of novel modulators of chronic inflammation in prevalent diseases: unveiling divergent mechanisms of disease". INFLAMES. PIE14/00045, Proyecto Integrado de Excelencia, Convocatoria 2014 de la Acción Estratégica en Salud 2013-16, ISCIII. Coordinator: Antonio Zorzano Olarte Principal Investigator of WP3: Ángela María Martínez Valverde. Total funding: 679.800 euros. From 01/01/2015 to 12/31/2017.
- "Inflammation associated with chronic metabolic damage in Type 2 diabetes and its complications. SAF 2015-65.267 RETOS (2016-2018) (MINECO/FEDER). Principal Investigator: Ángela María Martínez Valverde. Total funding: 180.000 euros and a predoctoral contract FPI. From 01/01/2016 to 12/31/2018.
- "Estrategias neuroprotectoras para la Retinosis Pigmentaria basadas en la modulación de la muerte celular y la inflamación". SAF2013-41059-R. Principal Investigators: Flora de Pablo y Enrique J. de la Rosa. Total funding: 295.999 euros. From 01/01/2014-to 30/09/2017.
- RESEARCH NETWORK IN NRF2 AS A NODE OF PATHOGENOSOME. SAF2015-71304-REDT (2016-2017) MINECO. Coordinator: Antonio Cuadro Pastor. Principal Investigator: Ángela Martínez Valverde. Cuantía TOTAL de la subvención: 35.000 euros. Fecha inicio/finalización: desde 01/01/2015 hasta 31/12/2017.

AWARDS

- AWARD CONSEJO DE COLEGIOS FARMACÉUTICOS. ROYAL NATIONAL ACADEMY OF PHARMACYREAL ACADEMIA NACIONAL DE FARMACIA (Scientific award 2016). Ángela Martínez Valverde and Ana I Arroba Espinosa. "Targeting microglia polarization: a new therapeutic approach in Diabetic Retinopathy".

LEAD RESEARCHER

Masana Marín, Luis

Fund. Inst. de Investigación Sanitaria Pere Virgili

Facultat de Medicina
C/ Sant Llorenç, 21
Edif. 4 · Planta baja
43201 Reus. Tarragona

(+34) 977 759 371

urla@iispv.cat

Group Website

PROGRAMME
P1

GROUP MEMBERS

Staff members: Martínez Micaelo, Neus | Rodríguez Calvo, Ricardo | Rosales Ribas, Roser

Associated members: Bosquet Agudo, Alba | Fernández Castillejo, Sandra | Ferré Vallés, Raimon | Girona Tell, Josefa | Guaita Esteruelas, Sandra | Guardiola Guionnet, Montserrat | Heras Ibáñez, Mercedes | Ibarretxe Guerediaga, Daiana | Plana Gil, Núria | Ribalta Vives, Josep | Solà Alberich, Rosa | Vallvé Torrente, Joan Carles

Main lines of research

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

Most relevant scientific articles

- Bosquet A., Guaita-Esteruelas S., Saavedra P., Rodríguez-Calvo R., Heras M., Girona J. et al. Exogenous FABP4 induces endoplasmic reticulum stress in HepG2 liver cells. Atherosclerosis. 2016;249:191-199.
- Girona J., Ibarretxe D., Plana N., Guaita-Esteruelas S., Amigo N., Heras M. et al. Circulating PCSK9 levels and CETP plasma activity are independently associated in patients with metabolic diseases. Cardiovascular Diabetology. 2016;15(1).
- Oliva I, Guardiola M, Vallvé JC, Ibarretxe D, Plana N, Masana L et al. APOA5 genetic and epigenetic variability jointly regulate circulating triacylglycerol levels. Clinical science (London, England: 1979). 2016;130(22):2053-2059.
- Guardiola M., Cofan M., de Castro-Oros I., Cenarro A., Plana N., Talmud P.J. et al. Corrigendum to "APOA5 variants predispose hyperlipidemic patients to atherogenic dyslipidemia and subclinical atherosclerosis" [Atherosclerosis 240/1 (2015) 98-104] DOI: 10.1016/j.atherosclerosis.2015.03.008. Atherosclerosis. 2016;250:190.
- Amigó N, Mallol R, Heras M, Martínez-Hervás S, Blanco-Vaca F, Escolà-Gil JC et al. Lipoprotein hydrophobic core lipids are partially extruded to surface in smaller HDL: "Herniated" HDL, a common feature in diabetes.Scientific reports. 2016;6:19249.

Highlights

CURRENT PROJECTS

- PI15/00627. Chaperonas lipídicas circulantes y estrés del retículo endoplásmico. Conexión clínica y patogénica entre obesidad, dislipemia aterógena y diabetes (Luis Masana). Instituto de Salud Carlos III.
- 12/C/2015. Preventing Premature Coronary Heart Disease in Catalonia by Expanding Familial Hypercholesterolemia Diagnosis (Luis Masana). Fundació La Marató de TV3. Coordinated project with Francisco Blanco Vaca.
- PI16/00507. Análisis lipídico avanzado para una mejor predicción del desarrollo tipo 2 y eventos cardiovasculares: estudio transversal y longitudinal de la cohorte Di@bet.es (Josep Ribalta; Montserrat Guardiola). Instituto de Salud Carlos III.

LEAD RESEARCHER

Mauricio Puente, Diego

Fundación Instituto de Investigacion Germans Trias i Pujol

Hospital Germans Trias i Pujol
Ctra. de Can Ruti.
Cami de les escoles, s/n
08916 Badalona. Barcelona

(+34) 93 497 88 60

ciberdembadalona@gmail.com

Group Website

PROGRAMME
P1

GROUP MEMBERS

Staff members: Real Gatius, Jordi | Sanjurjo Bouza, Lucía

Associated members: Aguilera Hurtado, Eva | Alonso Pedrol, Núria | Castelblanco Echavarria, Melida Esmeralda | Franch Nadal, Josep | Lucas Martín, Ana María | Mata Cases, Manel | Pasquali, Lorenzo | Pellitero Rodríguez, Ana Silvia | Puig Domingo, Manuel | Rubinat Arnaldo, Esther | Soldevila Madorell, Berta | Verdaguer Autonell, Juan | Vives Pi, Marta

Main lines of research

- Dysfunction and cell damage of the pancreatic beta cell.
- Complications of diabetes mellitus and study of associated metabolic conditions.
- Diabetes Research in Primary Care. Epidemiology of diabetes: studies with large databases.

Most relevant scientific articles

- Mata-Cases M, Franch-Nadal J, Real J, Mauricio D. Glycaemic control and antidiabetic treatment trends in primary care centres in patients with type 2 diabetes mellitus during 2007-2013 in Catalonia: a population-based study.BMJ open. 2016;6(10):e012463.
- Alonso N., Lupon J., Barallat J., de Antonio M., Domingo M., Zamora E. et al. Impact of diabetes on the predictive value of heart failure biomarkers. Cardiovascular Diabetology. 2016;15(1).
- Sanahuja J., Alonso N., Díez J., Ortega E., Rubinat E., Traveset A. et al. Increased burden of cerebral small vessel disease in patients with type 2 diabetes and retinopathy. Diabetes Care. 2016;39(9):1614-1620.
- Akerman I, Tu Z, Beucher A, Rolando DM, Sauty-Colace C, Benazra M et al. Human Pancreatic β Cell lncRNAs Control Cell-Specific Regulatory Networks.Cell metabolism. 2016.
- Mata-Cases M., Casajuana M., Franch-Nadal J., Casellas A., Castell C., Vinagre I. et al. Direct medical costs attributable to type 2 diabetes mellitus: a population-based study in Catalonia, Spain. European Journal of Health Economics. 2016.

Highlights

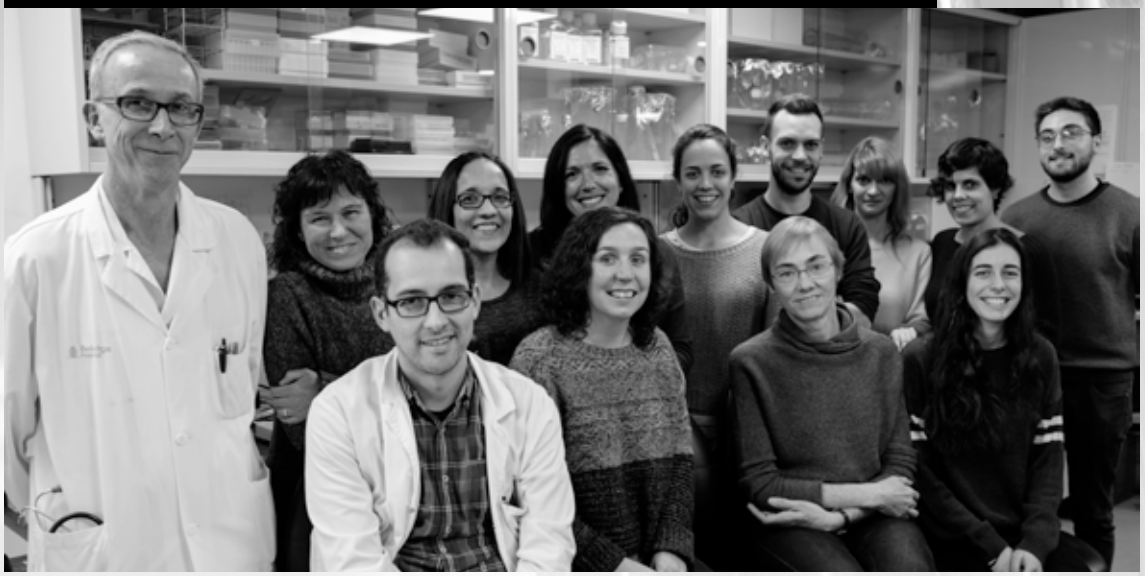
- **Beta cell dysfunction and damage**
  The development of nanotherapy against autoimmunity in type 1 diabetes continues, determining its effects on antigen-specific tolerance and addressing its translational aspect. We are also studying the humoral autoimmune mechanisms involved in the autoimmune diabetes model, i.e. NOD.
  We are actively collaborating with other CIBERDEM groups in elucidating the regulatory functions of the non-coding genome in diabetes and in identifying variants involved in the development of type 2 diabetes.
- **Complications of diabetes mellitus and associated metabolic conditions**
  We are working on the identification of markers of subclinical atheromatous disease and lipid metabolism abnormalities in patients with diabetes. The study of markers associated with heart failure in type 2 diabetes has also been initiated in a cohort of patients with heart failure. Competitive funding has been obtained to gain insight in the study of the role of lipotoxicity and microangiopathy in diabetic cardiomyopathy, in both type 1 and type 2 diabetes, in collaboration with another CIBERDEM group and an international group.
  A coordinated project with two other CIBERDEM groups on the role of the incretin pathway in obesity and the response to surgical treatment is still being carried out.
- **Epidemiology of diabetes: studies with large databases**
  Studies with databases of real clinical practice (SIDIAP database) are underway concerning aspects of complications, clinical inertia and modeling of the costs of type 2 diabetes being the focus of this research. The group is collaborating in the di@bet.es study. The follow-up of this study, in the framework of CIBERDEM on the incidence of diabetes in Spain, has been started. Our group is also leading a pragmatic clinical trial of several primary care centers in Catalonia.

LEAD RESEARCHER

Montanya Mías, Eduard

Fundación IDIBELL
Hospital Universitario de Bellvitge
C/ Freixa Larga, s/n
08907 Hospitalet de Llobregat. Barcelona
(+34) 93 260 25 73
montanya@ub.edu
Group Website

PROGRAMME
P2



GROUP MEMBERS

Staff members: Estil Les Altamiras, Elisabet | Ramis Juan, Maria Isabel | Tellez Besoli, Noelia

Associated members: Caballero Corchuelo, Jorge | Marín Cañas, Sandra | Moreno Amador, José Luis | Nacher García, Montserrat | Pairo Delgado, María del Mar | Pérez Maraver, Manuel | San José Terrón, Patricia | Vilarrasa García, Nuria

Main lines of research

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

Most relevant scientific articles

- Tellez N., Vilaseca M., Marti Y., Pla A., Montanya E. β-cell dedifferentiation, reduced duct cell plasticity, and impaired β-cell mass regeneration in middle-aged rats. American Journal of Physiology - Endocrinology and Metabolism. 2016;311(3):E554-E563.
- Soria B., Montanya E., Martín F., Hmadcha A. A role for the host in the roadmap to diabetes stem cell therapy. Diabetes. 2016;65(5):1155-1157.
- Vilarrasa N., de Gordejuela A.G.R., Casajoana A., Duran X., Toro S., Espinet E. et al. Endobarrier® in Grade I Obese Patients with Long-Standing Type 2 Diabetes: Role of Gastrointestinal Hormones in Glucose Metabolism. Obesity Surgery. 2016:1-9.
- Vilarrasa N., Rubio M.A., Minambres I., Flores L., Caixas A., Ciudin A. et al. Long-Term Outcomes in Patients with Morbid Obesity and Type 1 Diabetes Undergoing Bariatric Surgery. Obesity Surgery. 2016;1-8.
- Bartlett ST, Markmann JF, Johnson P, Korsgren O, Hering BJ, Scharp D et al. Report from IPITA-TTS Opinion Leaders Meeting on the Future of β-Cell Replacement. Transplantation. 2016;100 Suppl 2:S1-S44.

Highlights

We have described that aging is associated with a decrease in the ability of expansion of beta mass, with the contribution of both, limitation of neogenesis as well as de-differentiation of beta cells, whereas hypertrophy and beta cell hyperplasia capabilities are maintained. We have also reported that duodenal-yeyunal bypass liner, Endobarrier®, in type 2 diabetes patients with grade I obesity and poor metabolic control is associated with significant weight decrease and moderate reduction in HbA1c at month 12. The data do not support a role for GLP-1 in the metabolic improvement in this subset of patients. A collaborative clinical trial, of our own initiative, assessing the impact of the optimization of metabolic control in patient with type 1 diabetes mellitus on platelet reactivity has been completed. An observational study of preferences of patients in relation to the treatment of type 2 diabetes has also been completed.
The group has participated in the preparation of the document from de International Pancreas and Islet Transplant Association (IPITA) and Transplantation Society (TTS) “Report from the IPITA-TSS Opinion Leaders Meeting on the Future of Beta Cell Replacement”.
The group PI has been member of Organizer Committee of EASD Islet Study Group Meeting 2016. The group maintains a high presence in boards of national and international scientific institutions, among them, the Islet Study Group de la EASD, el Grupo de Islotes de la SED, y la Associació Catalana de Diabetes.
The group PI has been appointed coordinator of Program of Diabetes and Metabolism from the area of Translacional Medicine of IDIBELL. Regarding education, two students have completed their degree project and master project, respectively in 2016. The group has participated in the outreach activity Improciencia from Week of Science, with the presentation of the Project “Beta cells generation”.

LEAD RESEARCHER

Nadal Navajas, Ángel

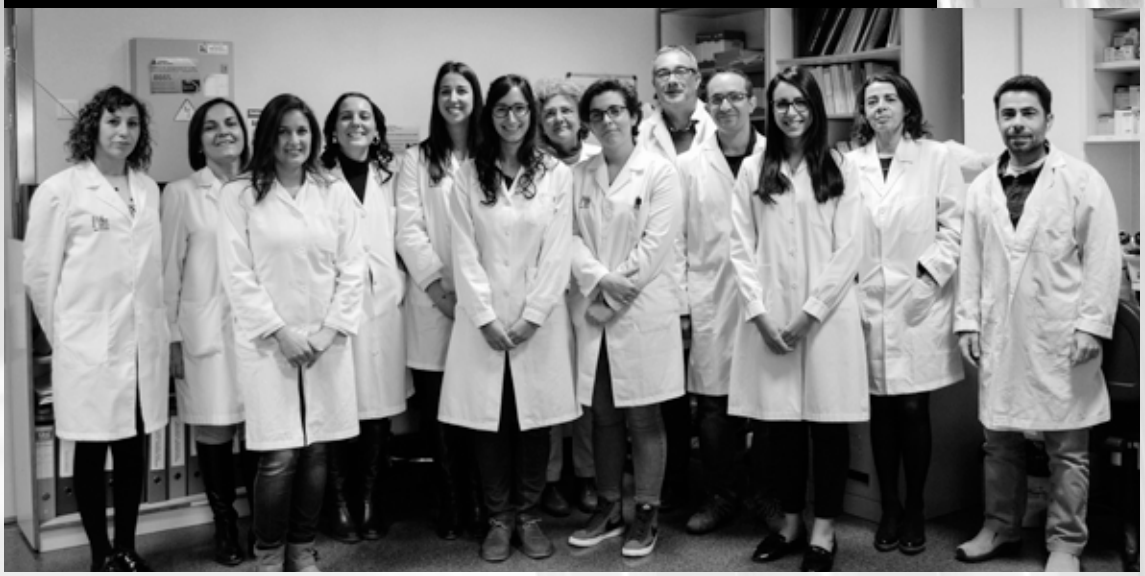
Univ. Miguel Hernández
Instituto de Bioingeniería
Edificio Vinalopo.
Avda. de la Universidad S/N
03202 Elche. Alicante

(+34) 96 522 20 02

nadal@umh.es

Group Website

PROGRAMME
P2



GROUP MEMBERS

Staff members: Castellano Muñoz, Manuel | Navarro García, María Luisa

Associated members: Alonso-Magdalena, Paloma | Boronat Belda, Talía | Fuentes Marhuenda, Esther | Quesada Moll, Iván | Ripoll Orts, Cristina | Villar Pazos, Sabrina

Main lines of research

- We study the link between endocrine disruptors and type 2 diabetes. We investigate the actions of oestrogens and environmental oestrogenic pollutants in the function of pancreatic alpha and beta cells with an emphasis on the molecular mechanisms involved.
- Signal transduction pathways involved in the function and pathology of alpha and beta-cells. Additionally, we investigate the adaptations of islet-cells to obesity and malnutrition states.

Most relevant scientific articles

- Garcia-Arévalo M., Alonso-Magdalena P., Servitja J.-M., Boronat-Belda T., Merino B., Villar-Pazos S. et al. Maternal exposure to bisphenol-A during pregnancy increases pancreatic β-cell growth during early life in male mice offspring. Endocrinology. 2016;157(11):4158-4171.
- Lind L., Mónica Lind P., Lejonklou M.H., Dunder L., Bergman A., Guerrero-Bosagna C. et al. Uppsala consensus statement on environmental contaminants and the global obesity epidemic. Environmental Health Perspectives. 2016;124(5):A81-A83.
- Vettorazzi J.F., Ribeiro R.A., Borck P.C., Branco R.C.S., Soriano S., Merino B. et al. The bile acid TUDCA increases glucose-induced insulin secretion via the cAMP/PKA pathway in pancreatic beta cells. Metabolism: Clinical and Experimental. 2016;65(3):54-63.
- Tuduri E., López M., Dieguez C., Nadal A., Nogueiras R. Glucagon-Like Peptide 1 Analogs and their Effects on Pancreatic Islets. Trends in Endocrinology and Metabolism. 2016;27(5):304-318.
- Mellado-Gil J.M., Jiménez-Moreno C.M., Martín-Montalvo A., Álvarez-Mercado A.I., Fuente-Martín E., Cobo-Vuilleumier N. et al. PAX4 preserves endoplasmic reticulum integrity preventing beta cell degeneration in a mouse model of type 1 diabetes mellitus. Diabetologia. 2016;:1-11.

Highlights

During 2016, we have shown in mice that maternal exposure to the endocrine disruptor bisphenol-A during gestation increases beta cell mass in offspring from the first day of birth. This is associated to alterations in the expression of genes related to cell growth, favoring an increase in the proliferation and a decrease of apoptosis of the pancreatic beta cell in offspring. We have also described that the bile acid TUDCA is able to regulate insulin secretion from beta cells through the protein kinase A pathway. During this year we have been involved in the development of a consensus document on the contribution of environmental contaminants to the epidemics of obesity.
At the end of 2016, we began to study the role of pancreatic alpha cells and glucagon secretion in glucose homeostasis during aging, a National Plan project granted this year.
The researchers of the group have been invited to the congresses: XXVII National Congress of the Spanish Society of Diabetes, Bilbao, April 2016; Environmental Endocrine Disruptors, Gordon Research Conference, Sunday River, Maine, June 2016; XIV International Congress of Toxicology Merida-Mexico, October 2016.

LEAD RESEARCHER

Novials Sardá, Anna María

Instituto de Investigaciones Biomédicas August Pi i Sunyer
Centro Esther Koplowitz
C/ Rossellón, 153, Planta 2
08036 Barcelona
(+34) 93 227 54 00 (ext. 4153)
anovials@clinic.cat
Group Website

PROGRAMME
P2

GROUP MEMBERS

Staff members: Brugnara, Laura | Castaño Pérez, Carlos | De Pablo Pons, Sara | Murillo García, Serafín | Parrizas Jiménez, Marcelina

Associated members: Alcarraz Vizán, Gema | Ceriello, Antonio | Montane Mogas, Joel | Servitja Duque, Joan Marc | Visa Majoral, Montse.

Main lines of research

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

Most relevant scientific articles

- Montane J., de Pablo S., Obach M., Cadavez L., Castano C., Alcarraz-Vizan G. et al. Protein disulfide isomerase ameliorates β-cell dysfunction in pancreatic islets overexpressing human islet amyloid polypeptide. Molecular and Cellular Endocrinology. 2016;420:57-65.
- Parrizas M., Novials A.. Circulating microRNAs as biomarkers for metabolic disease. Best Practice and Research: Clinical Endocrinology and Metabolism. 2016;30(5):591-601.
- Brugnara L., Murillo S., Novials A., Rojo-Martínez G., Soriguer F., Goday A. et al. Low physical activity and its association with diabetes and other cardiovascular risk factors: A nationwide, population-based study. PLoS ONE. 2016;11(8).
- Ceriello A., De Nigris V., Pujadas G., La Sala L., Bonfigli A.R., Testa R. et al. The simultaneous control of hyperglycemia and GLP-1 infusion normalize endothelial function in type 1 diabetes. Diabetes Research and Clinical Practice. 2016;114:64-68.
- La Sala L., Cattaneo M., De Nigris V., Pujadas G., Testa R., Bonfigli A.R. et al. Oscillating glucose induces microRNA-185 and impairs an efficient antioxidant response in human endothelial cells. Cardiovascular Diabetology. 2016;15(1).

Highlights

During 2016, we made advancements in our attempts to formulate new strategies for reversing pancreatic islet dysfunction induced by amyloid deposits. In particular, we demonstrated that the overexpression of the endogenous chaperone PDI enables the recovery of beta-cell function in mice expressing human IAPP. We also continued exploring the role that microRNAs play in the pathophysiology of diabetes, identifying a microRNA (miR-185) involved in the reduction of antioxidant response in human endothelial cells. In clinical studies, we participated in a study of the prevalence of sedentariness in the Spanish population, establishing associations between low physical activity and diabetes, along with other cardiovascular risk factors.

Our research group actively collaborates with other CIBERDEM groups, as well as other groups belonging to other CIBER thematic areas. Of special mention is our participation in an integrated project of excellence funded by the Carlos III Health Institute (ISCIII), which seeks to identify the molecular mechanisms common to both diabetes and neurodegenerative disorders.

Throughout 2016, our group continued work on projects funded by national, regional and European agencies including: the Health Research Fund (FIS) of ISCIII; the Research Groups Support grant (SGR) from the Government of Catalonia; and the European Commission for the MEDIGENE project, which ended in 2016. Moreover, we continue to collaborate with the Grífols company, conducting research on anti-inflammatory strategies for treating diabetes.

In terms of social outreach, an activity that stands out is our talk presented within the framework of the large-scale, social networking event, “Diabetes Experience Day”. Finally, our group participated in the activities organized by the AstraZeneca Chair in Diabetes Innovation at IDIBAPS, with the collaboration of CIBERDEM, including the presentation of the book, Sketching Diabetes, and the initiative, Living Lab, “Diabetes: fighting against sedentary lifestyles.”

LEAD RESEARCHER

Rojo Martínez, Gemma

FIMABIS
Hospital Universitario Carlos Haya
Plaza del Hospital Civil S/N
29000 Málaga
gemma.rojo.m@gmail.com
Group Website

PROGRAMME
P1

GROUP MEMBERS

Staff members: García Escobar, Eva | García Serrano, Sara | Linares Parrado, Francisca

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

Main lines of research

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

Most relevant scientific articles

- Menéndez E, Delgado E, Fernández-Vega F, Prieto MA, Bordiú E, Calle A et al. Prevalence, Diagnosis, Treatment, and Control of Hypertension in Spain. Results of the Di@bet.es Study. Revista española de cardiología (English ed.). 2016;69(6):572-8.
- Olveira G., Tapia M.J., Ocon J., Cabrejas-Gómez C., Ballesteros-Pomar M.D., Vidal-Casariego A. et al. Hypoglycemia in noncritically ill patients receiving total parenteral nutrition: A multicenter study. (Study group on the problem of hyperglycemia in parenteral nutrition; Nutrition area of the Spanish Society of Endocrinology and Nutrition). Nutrition. 2016;31(1):58-63.
- Bermúdez-Silva F.J., Romero-Zerbo S.Y., Haissaguerre M., Ruz-Maldonado I., Lhamyani S., El Bekay R. et al. The cannabinoid CB1 receptor and mTORC1 signalling pathways interact to modulate glucose homeostasis in mice. DMM Disease Models and Mechanisms. 2016;9(1):51-61.
- Brugnara L., Murillo S., Novials A., Rojo-Martínez G., Soriguer F., Goday A. et al. Low physical activity and its association with diabetes and other cardiovascular risk factors: A nationwide, population-based study. PLoS ONE. 2016;11(8).
- Balfego M., Canivell S., Hanzu F.A., Sala-Vila A., Martínez-Medina M., Murillo S. et al. Effects of sardine-enriched diet on metabolic control, inflammation and gut microbiota in drug-naïve patients with type 2 diabetes: A pilot randomized trial. Lipids in Health and Disease. 2016;15(1).

Highlights

During 2016, the field work of the di@bet.es study has been organized and launched. This project will determine the incidence of diabetes and associated metabolic diseases in Spain.
The integrated project of excellence PIE14/00031 that will determine the metabolic profiles associated with the presence of metabolic syndrome in several clinical projects has been developed.
A project has also been initiated on the beneficial actions of phenolic compounds of extra virgin olive oil in pancreatic islets and their impact on the prevention of type 2 diabetes, with regional funding.
One Research Contract (Service Agreement) has been signed with INSERM regarding collaboration with Dr. Daniela Cota (U1215, Bordeaux, France).
The group participates in the European Union's DEDIPAC and ENPADASI actions.

LEAD RESEARCHER

Simó Canonge, Rafael

Fundación Hospital Universitario Vall d'Hebron - Institut de Recerca (VHIR)

Hospital Vall d'Hebron
Passeig Vall D'hebron, 119-129
08035 Barcelona

(+34) 93 489 41 72

rafael.simo@vhir.org

Group Website

PROGRAMME
P1

GROUP MEMBERS

Staff members: Bogdanov, Patricia Mónica | García Ramírez, Marta | Gutiérrez Carcedo, Patricia Carlota | Ramos Pérez, Lorena | Turch Anguera, Miriea

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

Main lines of research

- **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.
  In the setting of the new pathogenic candidates, we are investigating the role of sex hormone binding globulin (SHBG), as well as mitochondrial dysfunction.
  Regarding co-morbidities, we are examining the mechanisms by which the lung can be considered a new target of diabetes complications.
- **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, Bogdanov P, Corraliza L, García-Ramírez M, Solà-Adell C, Arranz JA et al. Topical Administration of GLP-1 Receptor Agonists Prevents Retinal Neurodegeneration in Experimental Diabetes. Diabetes. 2016;65(1):172-87.
- Simo R., Hernández C. New Treatments for Type 2 Diabetes Mellitus and Cardiovascular Disease. The Revolution Has Begun. Revista Espanola de Cardiologia. 2016;69(11):1005-1007.
- Lecube A., Sánchez E., Gómez-Peralta F., Abreu C., Valls J., Mestre O. et al. Global assessment of the impact of type 2 diabetes on sleep through specific questionnaires. A case-control study. PLoS ONE. 2016;11(6).
- Pardo R., Blasco N., Vila M., Beiroa D., Nogueiras R., Canas X. et al. EndoG knockout mice show increased Brown adipocyte recruitment in white adipose tissue and improved glucose homeostasis. Endocrinology. 2016;157(10):3873-3887.
- Lecube A., Valladares S., López-Cano C., Gutiérrez L., Ciudin A., Fort J.M. et al. The role of morbid obesity in the promotion of metabolic disruptions and non-alcoholic steatohepatitis by helicobacter pylori. PLoS ONE. 2016;11(11).

Highlights

SCIENCE. The most important milestone has been the demonstration that topical administration of somatostatin is able to arrest the progression of retinal neurodegeneration in type 2 diabetic patients. This is the main result of the EUROCONDOR project (see below). The baseline results are under review in Diabetes and we are preparing the manuscript regarding the longitudinal study to be published in a top journal. In addition, 26 manuscripts have been published, and the most important results have been presented in international meetings.

It should be noted that we have stablished an intramural collaboration with CIBER-BBN in the setting of the project "Microfluidic model of retinal microvascular unit to identify therapeutic targets in diabetic retinopathy" (CIB16-BI012).

PROJECTS. We have finished the EUROCONDOR project (FP7-278040, Coordinator: R. Simó) in due time. In addition, the following collaborative international projects are ongoing: e-Predice (FP7-279074), two projects granted by the EFSD (European Foundation for the Study of diabetes), and MOPEAD (H2020-IMI2-115985). Moreover, we are implementing the following national projects: PI13/00603, DTS15/00151, LIRALUNG, PIE13/00027, and PIE14/0061 (Excellence Inter-CIBER). Furthermore, 3 new national projects have been founded (PI16/00541, SAF2016-77784, Fundació Marató TV3).

INNOVATION. We currently deal with 4 patents (PCT/EP2014/053787; PCT/EP2014/053787; P201430796; EP13382202.3; P3572EP00). The first 3 have already entry in national phases. It should be underlined that 1 of them (P201430796) has been as the result of a fruitful collaboration with another group of CIBERDEM (PI: J. Egido).

ACADEMY/TRAINING. In this setting it should be underlined that 2 doctoral thesis related to diabetes have been finished. The PI of the group has been involved in the organization of the annual general session of CIBERDEM. Finally, our group has been pioneer in organizing internal sessions in our hospital linked with relevant of CIBERDEM.

LEAD RESEARCHER

Vallejo Fernández De la Reguera, Mario

Agencia Estatal Consejo Superior de Investigaciones Científicas

Instituto de Investigaciones Biomédicas Alberto Sols
C/ Arturo Duperier
28029 Madrid

(+34) 91 585 44 80

mvallejo@iib.uam.es

Group Website

PROGRAMME
P2

GROUP MEMBERS

Staff members: Fernández Pérez, Antonio | Mirasierra Cuevas, Mercedes

Main lines of research

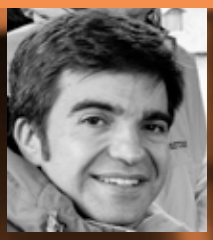
- The characterization of phenotypic alterations of pancreatic islets in the absence of the homeoprotein Alx3.
- The requirement of Alx3 for the maintenance of glucose homeostasis and metabolic activity in vivo.
- The identification of transcriptional targets regulated by Alx3.
- Alx3 and diabetic pregnancy: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

Most relevant scientific articles

- Mirasierra M, Vallejo M. Glucose-dependent downregulation of glucagon gene expression mediated by selective interactions between ALX3 and PAX6 in mouse alpha cells. Diabetologia. 2016.
- Mallarino R, Henegar C, Mirasierra M, Manceau M, Schradin C, Vallejo M et al. Developmental mechanisms of stripe patterns in rodents.Nature. 2016;539(7630):518-523.

Highlights

We discovered a mechanism by virtue of which the transcription factor Alx3 downrrgulates the expression of glucagon in pancreatic islets in response to elevations in the concentrations of glucose. This mechanism is important for the maintenance of glucose homeostasis, and may have implications in the etiopathogenesis of diabetes, in patients showing paradoxically hyperglucagonemia accompanying hyperglycemia. Notably, the mechanism of action of Alx3 at the molecular level appears to be conserved in other systems, for example in the inhibition by Alx3 of the expression of genes that are important for the differentiation of melanocytes in the skin.



LEAD RESEARCHER

Vázquez Carrera, Manuel

Universidad de Barcelona
Facultad de Farmacia
Diagonal, 645
08028 Barcelona
(+34) 93 402 45 31
mvazquezcarrera@ub.edu
Group Website

PROGRAMME
P3

GROUP MEMBERS

Staff members: Barroso Fernández, Emma De Juan | Montori Grau, Marta | Peña Moreno, María Lucía

Associated members: Botteri, Gaia | Palomer Tarrida, Francisco Javier

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

- Zarei M., Barroso E., Leiva R., Barniol-Xicota M., Pujol E., Escolano C. et al. Heme-regulated eIF2α kinase modulates hepatic FGF21 and is activated by PPARβ/δ deficiency. Diabetes. 2016;65(10):3185-3199.
- Tan N.S., Vazquez-Carrera M., Montagner A., Sng M.K., Guillou H., Wahli W. Transcriptional control of physiological and pathological processes by the nuclear receptor PPARβ/δ. Progress in Lipid Research. 2016;64:98-122.
- Vazquez-Carrera M.. Unraveling the Effects of PPARβ/δ on Insulin Resistance and Cardiovascular Disease. Trends in Endocrinology and Metabolism. 2016.

Highlights

During 2016 we have discovered that HRI (*Heme-regulated eIF2alpha kinase*) activators might be useful for the prevention and treatment of type 2 diabetes mellitus and additional metabolic diseases due to its ability to increase hepatic levels of FGF21 (*Fibroblast growth factor 21*). This finding allowed us to file the patent "*HRI activators useful for the treatment of metabolic diseases*". Likewise, we have obtain research funds from the Fundación Bosch i Gimpera of the University of Barcelona to perform a proof of concept with new HRI activators to prove their efficacy in an animal model of type 2 diabetes mellitus.

LEAD RESEARCHER

Vendrell Ortega, Joan Josep

Fund. Instituto Investigación Sanitaria Pere Virgili

Hospital Universitario Juan XXIII
C/ Mallafre Guasch, 4
43007 Tarragona

diamet@iispv.cat

Group Website

PROGRAMME
P3

GROUP MEMBERS

Staff members: Ceperuelo Mallafre, María Victoria | Ejarque Carbo, Miriam | Keiran Fernández, Noelia | Maymo Masip, Elsa | Núñez Roa, Catalina

Associated members: Calvo Manso, Enrique | Da Silva Madeira, Ana | Fernández Veledo, Sonia | Gallart Millán, Lluís | González Clemente, José Miguel | Gutiérrez Fornes, Cristina | Llaurado Cabot, Gemma | Megia Colet, Anna | Näf Cortés, Silvia | Pachón Peña, Olga Gisela | Roche, Kelly | Rodríguez Chacón, Matilde | Serena Perello, Carolina | Simón Muela, Inmaculada | Solano Fraile, Esther

Main lines of research

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

Most relevant scientific articles

- Serena C., Keiran N., Ceperuelo-Mallafre V., Ejarque M., Fradera R., Roche K. et al. Obesity and Type 2 Diabetes Alters the Immune Properties of Human Adipose Derived Stem Cells. Stem Cells. 2016.
- Martínez-Pérez B., Ejarque M., Gutiérrez C., Nunez-Roa C., Roche K., Vila-Bedmar R. et al. Angiopoietin-like protein 8 (ANGPTL8) in pregnancy: a brown adipose tissue–derived endocrine factor with a potential role in fetal growth. Translational Research. 2016;178:1-12.
- Ceperuelo-Mallafre V., Ejarque M., Serena C., Duran X., Montori-Grau M., Rodríguez M.A. et al. Adipose tissue glycogen accumulation is associated with obesity-linked inflammation in humans. Molecular Metabolism. 2016;5(1):5-18.
- Pachon-Pena G., Serena C., Ejarque M., Petriz J., Durán X., Oliva-Olivera W. et al. Obesity determines the immunophenotypic profile and functional characteristics of human mesenchymal stem cells from adipose tissue. Stem Cells Translational Medicine. 2016;5(4):464-475.
- Lagarrigue S., López-Mejía I.C., Denechaud P.-D., Escote X., Castillo-Armengol J., Jiménez V. et al. CDK4 is an essential insulin effector in adipocytes. Journal of Clinical Investigation. 2016;126(1):335-348.

Highlights

COMPETITIVE FUNDING FOR RESEARCH PROJECTS

In 2016 our research group DIAMET has been funded by 5 projects from the “Fondo de Investigaciones Sanitaria (FIS), ISCIII” (PI15/00045, PI13/00152, PI14/00465, PI15/00143 and PI15/01562) and a project funded by the “Programa Estatal de I+D+i Orientada a los Retos de la Sociedad del MINECO” (SAF2015-65019R); all of them led by members of our research group. Our group has also become part of the “Red de Investigación de Excelencia “Adipoplast”” funded by MINECO (BFU2015-70454-REDT).

To highlight that in 2016 DIAMET was awarded with two projects of the “Fundació La Marató de TV3” with the co-directors of the group, Joan Vendrell and Sonia Fernández-Veledo, as principal investigators of each of them.

COMPETITIVE FUNDING FOR HUMAN RESOURCES

The DIAMET research group currently comprises clinical and basic researchers; some of them funded through competitive training and senior fellowships from the MINECO (FJCI-2014-23060, RYC2013-13186) and FIS (CD15-00173, CPII16/00008). To note that in 2016 our group was awarded with a training fellowship (BES-2016-077745) and a postdoctoral fellowship (IJCI-2015-24157), both of which supported by MINECO.

TRAINING

The researchers of our group has also experience in teaching undergraduate and post-graduate studens in the field of Medicine, Nutrition and Biochemistry, as full and associate professors. More specifically, Dr. Vendrell directed a doctoral thesis in 2016. To emphasize the annual intra-CIBER training workshop organized by our group in 2016 “TARRACO-MALACCA III JOINT WORKSHOP. Up to date on the etiopathogenesis of type 2 diabetes and obesity. Local and systemic events in the insulin-resistance process. “carried out in Lloret de Mar.

LEAD RESEARCHER

Vidal Cortada, Josep

Instituto de Investigaciones Biomédicas August Pi i Sunyer
C/ Rosselló 149-153, planta 5
08036 Barcelona
jovidal@clinic.cat
Group Website

PROGRAMME
P2

GROUP MEMBERS

Staff members: Esteban Romero, María Yaiza | Fernández Ruiz, Rebeca | Freitas Simoes, Tania Marisa | García Alamán, Ainhoa | González Ruano, Elena | Katte, Kimberly | Viaplana Masclans, Judith

Associated members: Canivell Fusté, Silvia | Claret Carles, Marc | Conget Donlo, Ignacio | Esmatjes Mompo, Enrique | Flores Meneses, Lilliam | Gasa Arnaldich, Rosa María | Giménez Álvarez, Margarita | Gomis de Barbará, Ramon | Hanzu, Felicia Alexandra | Martins De Sousa Maia Malpique, Rita María | Mora Porta, Mireia | Papageorgiou, Aikaterini | Pradas Juni, Marta | Schneeberger Pane, Marc

Main lines of research

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

Most relevant scientific articles

- Figueroa A.L.C., Figueiredo H., Rebuffat S.A., Vieira E., Gomis R. Taurine Treatment Modulates Circadian Rhythms in Mice Fed A High Fat Diet. Scientific Reports. 2016;6.
- Pujadas G., Cervantes S., Tutusaus A., Ejarque M., Sánchez L., García A. et al. Wnt9a deficiency discloses a repressive role of Tcf7l2 on endocrine differentiation in the embryonic pancreas. Scientific Reports. 2016;6.
- Ejarque M., Mir-Coll J., Gomis R., German M.S., Lynn F.C., Gasa R. Generation of a conditional allele of the transcription factor Atonal Homolog 8 (Atoh8). PLoS ONE. 2016;11(1).
- Conget I., Mauricio D., Ortega R., Detournay B. Characteristics of patients with type 2 diabetes mellitus newly treated with GLP-1 receptor agonists (CHADIG Study): A cross-sectional multicentre study in Spain. BMJ Open. 2016;6(7).
- Mir-Coll J., Duran J., Slebe F., Garcia-Rocha M., Gomis R., Gasa R. et al. Genetic models rule out a major role of beta cell glycogen in the control of glucose homeostasis. Diabetologia. 2016;:1-9.

Highlights

Among the major achievements of our group throughout 2016 we can stand out the concession of a "Consolidator grant" awarded by the European Research Council (ERC) for the study of the different neural populations which regulate the energetic status of the organism.
Several courses addressed to clinical specialists have been organized, among which we can highlight New Tools in Diabetes Management (University of Barcelona), Clinical Excellence (Hospital Clínic), Preceptorship in Diabetes for Primary Care Clinicians (for Spanish and Portuguese medical doctors) (IDIBAPS-Hospital Clínic).
During this year, the group has performed several science broadcasting events including the launch of the new research line on dietary intervention with sardine in order to prevent and improve the diabetic state – in the framework of the science communication lectures "After work science" at La Pedrera-. Worth mentioning also the concession of the award to the Best Ideas of the Year, in the category of patronage and solidarity, to the project Living Lab Diabetes, granted by Diario Clínico. Another notable achievement during 2016 has been the recognition to the teaching and scientific trajectory of Prof. Dr. Ramon Gomis by awarding him the Honoris Causa recognition by the Rovira i Virgili University. Moreover, Prof. Dr. Ramon Gomis has been recently nominated President of the Research and Innovation Advisory Board of the Government of Catalonia.

LEAD RESEARCHER

Zorzano Olarte, Antonio

Fundación privada Instituto de Recerca Biomédica (IRB-Barcelona)

C/ Baldiri Reixac, 10-12
08028 Barcelona

(+34) 93 403 71 97

antonio.zorzano@irbbarcelona.org

Group Website

PROGRAMME
P3

GROUP MEMBERS

Staff members: Muñoz Neculman, Juan Pablo | Romero De Pablos, Montserrat | Saska, Ivanova | Sebastián Muñoz, David

Associated members: Camprubí, Marta Camps | Castrillón Rodríguez, Ignacio | Díaz Ramos, Maria Ángels | Enciso Salas, Hilda Yuiliana | Guma García, Ana María | Hernández Álvarez, María Isabel | Martínez Cristobal, Paula | Rodríguez Nuevo, Aida | Sabate Pérez, Alba | Sánchez Feutrie, Manuela | Testar Ymbert, Xavier

Main lines of research

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

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

Most relevant scientific articles

- Sebastián D., Sorianello E., Segales J., Irazoki A., Ruiz-Bonilla V., Sala D. et al. Mfn2 deficiency links age-related sarcopenia and impaired autophagy to activation of an adaptive mitophagy pathway. EMBO Journal. 2016.
- Sebastián D., Zorzano A. When MFN2 (mitofusin 2) met autophagy: A new age for old muscles. Autophagy. 2016;:1-2.
- Naon D., Zaninello M., Giacomello M., Varanita T., Grespi F., Lakshminaranayan S. et al. Critical reappraisal confirms that Mitofusin 2 is an endoplasmic reticulum-mitochondria tether. Proceedings of the National Academy of Sciences of the United States of America. 2016;113(40):11249-11254.
- Soro-Arnaiz I., Li Q.O.Y., Torres-Capelli M., Meléndez-Rodríguez F., Veiga S., Veys K. et al. Role of Mitochondrial Complex IV in Age-Dependent Obesity. Cell Reports. 2016;16(11):2991-3002.
- Maria I.H.-A., Kulkarni S.S., Joffraud M., Boutant M., Ratajczak J., Gao A.W. et al. Mfn1 deficiency in the liver protects against diet-induced insulin resistance and enhances the hypoglycemic effect of metformin. Diabetes. 2016;65(12):3552-3560.

Highlights

During 2016, our research group has published 15 scientific articles. Thus, we have shown that mitochondrial protein Mitofusin 2 (Mfn2) is repressed in the skeletal muscle of old mice. This repression is associated with insulin resistance, and reduced muscle mass. In parallel to these observations, knockout mice in which Mfn2 has been specifically deleted in skeletal muscle show impaired glucose tolerance, mitochondrial dysfunction, and muscle atrophy. These results allow us to propose a relevant role of muscle Mfn2 protein in the development of insulin resistance associated with aging, and additionally indicate that mfn2 is a target for the development of new diabetes therapies (Sebastián et al., EMBO Journal 2016).
In addition, our laboratory has demonstrated that liver deficiency in Mfn1 mitochondrial protein in mice causes increased mitochondrial respiratory capacity and increased lipid consumption. Mfn1 KO mice are protected against insulin resistance induced by a high fat diet. In addition, under these conditions, liver deficiency of Mfn1 increased the abundance of the respiratory chain I complex, and mice showed increased sensitivity to treatment with the hypoglycemic compound metformin. These results suggest that inhibition of Mfn1 could improve glucose homeostasis in obese patients and increase the effectiveness of metformin (Kulkarni et al., Diabetes 2016).
In addition to these scientific contributions, our research team has obtained funding through 3 different proposals in 2016 (Plan Nacional Ministerio de Economía y Competitividad, Fundación Marató TV3, and Fundación Areces). Finally, we want to mention that our group has participated in a guide for the precise measurement of autophagic activity (Klionsky et al., 2016).

DEYM

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

MINISTERIO DE ECONOMÍA, INDUSTRIA Y COMPETITIVIDAD
Instituto de Salud Carlos III

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

ciber

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