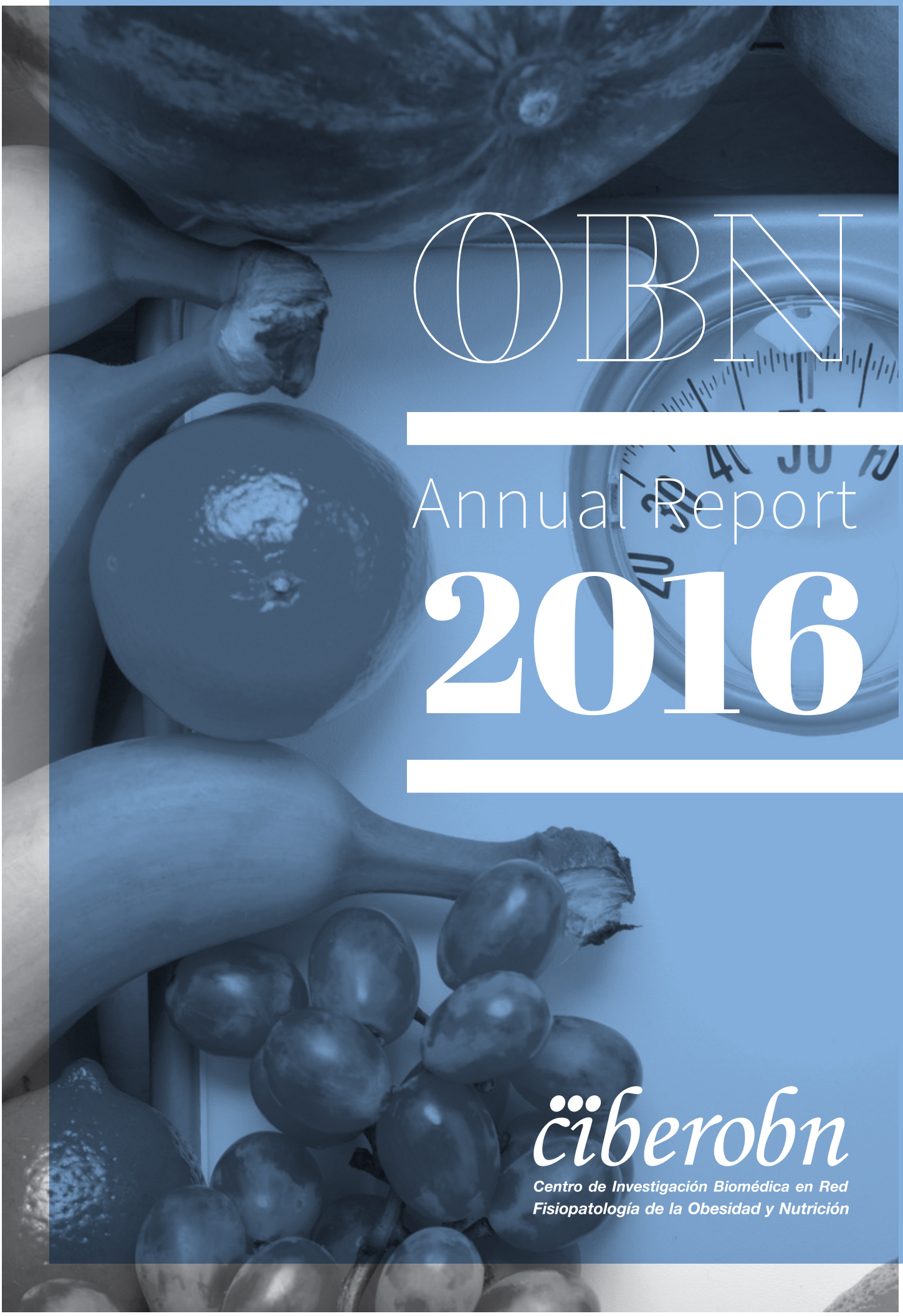

OBN

Annual Report

2016

ciberobn

Centro de Investigación Biomédica en Red
Fisiopatología de la Obesidad y Nutrición

Index

Carlos Diéguez, Scientific Director

Scientific Director's Presentation

It is a pleasure for me to be presenting the annual report on the CIBEROBN'S activity, representing the scientific work done in the field of Obesity and Nutrition in the CIBER public consortium. 2016 was a year of transition in strategic terms, through being the last one in the last strategic plan and the year in which the new plan, to be in force until 2020, was drawn up. All the thinking done for designing the new plan led to some relevant changes. It was decided that the scientific work would be focussed on just two programmes, "Nutrition" and "Obesity", through considering that there was a great deal of overlapping between the six hitherto existing. This does not mean any loss of focus on the themes tackled in the programmes beforehand but, on the contrary, represents an attempt to ensure greater integration and greater scientific ambition as regards tackling prevention strategies, knowledge of physiopathological mechanisms and therapies of pathologies connected with the CIBEROBN'S field. In other words, we believe that this is the right time to foster the generation of new synergies between the different groups forming the CIBEROBN. To this end we have also attempted to further application for international projects with the joint participation of several groups and have implemented a new instrument, which is the call for intramural projects.

The report being presented represents the work done by a total number of 33 groups, in which we should mention two new groups which joined the CIBEROBN in 2016 with the aim of reinforcing the child obesity line and who are already perfectly integrated in the organisation.

With regard to the contents of this report I would like to make the following points. An outstanding level of scientific production has been obtained. Although the total number of publications has remained fairly stable (>500), there has been a noteworthy increase, 25%, in the number of D1 articles, which correlates with an increase in the total FI. This is a sign that CIBEROBN is becoming consolidated as one of the European organisations with greatest scientific production in the field of obesity and nutrition. Even though this data is outstanding, one aspect that should not go unmentioned is the fact that this is also associated with a considerable increase, almost 20%, in the number of publications carried out in cooperation with several CIBEROBN groups, as well as a similar increase in interCIBER cooperation. We should also lastly mention that the CIBEROBN continues to extend its internationalisation, as is vouched for by the increase in the number of publications with international groups, which now make up almost 40% of these, and an increase in the application for, and obtaining of, projects financed in international calls. We should emphasise the fact that the financing obtained by CIBEROBN researchers in national or international projects increases year by year regardless of their management.

This scientific production data indicates a high degree of excellence as regards the generation of knowledge and translation, oriented towards solving healthcare problems in benefit of the national healthcare system (SNS) and improving people's quality of life. As evidence of the demonstrable quality of the work done in this field, in both national and international spheres, such milestones have been achieved as the recognition of the Mediterranean Diet as a regime standard effective in primary prevention of cardiovascular disease in American Diet Guides; in the primary prevention of cerebrovascular accidents in American Guides on primary prevention of strokes; or in the prevention of type 2 diabetes mellitus in

Australian Guides on diabetes. In this context we should stress that in 2016 we managed to get under way the PREDIMEDPLUS project with the randomisation of over six thousand patients. This thus opens up a new, even more ambitious and promising stage. as regards its scientific and healthcare repercussions. In short, what has been accomplished this year should act as a spur to attain even greater heights of success resulting in an improvement in the prevention of diseases in our population and better healthcare for patients, the ultimate reason for the existence of CIBERs.

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Organisation

Organisational Structure

The CIBEROBN 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 capacity, under the Instituto de Salud Carlos III (ISCIII) – Ministry of the Economy and Competitiveness. In 2016 it was made up of 8 thematic areas, these being extended to 11 in 2017.

The Area of Physiopathology of Obesity and Nutrition consists of 33 research groups, retaining its own independence in respect of its scientific management. Its organisational structure is based on the research groups belonging to this and its work is done through Research Programmes and Transversal Programmes, with a coordinator for each Programme belonging to the Management Committee. Scientific decisions are made by the Scientific Director, advised by the Management Committee and the External Scientific Committee.

The senior administrative bodies of the CIBEROBN are the Governing Body and the Permanent Commission, common for all the CIBER research areas. The Governing Body is made up of three representatives of the ISCIII and one institutional representative of each of the centres in the consortium. It is presided over by the Director of the ISCIII and meets every six months. The Permanent Commission is an executive committee made up of the ISCIII and 8 members of the Governing Body, who can be renewed annually. Both the operation and the purposes of the governing, support and advisory bodies are defined in the statutes of the CIBER.

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

Members of the Management Committee

Name	Post
Carlos Diéguez González	Scientific Director
Jordi Salas Salvadó	Nutrition Programme
Dolores Corella Piquer	Nutrition Programme
Gema Frühbeck Martínez	Adipobiology Programme
Francisco Tinahones Madueño	Complications of Obesity Programme
Fernando Fernández Aranda	Neurocognition and Environmental-Biological Factors Programme
Andreu Palou Oliver	New Strategies and Biomarkers Programme
Francesc Villarroya Gombau	Physiopathology of Body Weight Homeostasis Programme
José Manuel Fernández Real	Scientific Platforms
Manuel Tena Sempere	Training Programme
Manuel Sánchez Delgado	Manager of the CIBER

Attached to Scientific Director: Leticia Álvarez Mangas

Contact: http://www.ciberobn.es/en/about-us/contact

External Advisory Scientific Committee

The External Advisory Scientific Committee is a body for scientific support and assessment, made up of internationally significant researchers of special relevance in the field of health sciences who are prominent for their professional or scientific careers, in line with the centre's objectives.

Name	Institution
Xavier Pi-Sunyer	Department of Medicine, St. Luke's/Roosevelt Hospital Center
Antonio Vidal-Puig	University of Cambridge Metabolic Research Laboratories, Institute of Metabolic Science
José C. Florez	Center for Human Genetic Research/Diabetes Unit Massachusetts General Hospital
José M. Ordovás	Professor Nutrition and Genetics JM-USDA-HNRCA at Tufts University
Lluis Fajas	Research Director Metabolism and Cancer Laboratory - Montpellier - France

Technical Unit

List of personnel http://www.ciberobn.es/en/about-us/structure/head-office

Directory of groups and institutions

Group Leader	Institution	Centre	Centre Prov.
Argente Oliver, Jesús	Servicio Madrileño de Salud	Hospital Infantil Universitario Niño Jesús	Madrid
Arós Borau, Fernando	Fundación Vasca de Innovación e Investigación Sanitarias	Hospital Universitario Araba. Sede Txagorritxu	Álava
Botella Arbona, Cristina	Universidad Jaume I	Facultad de Ciencias de la Salud	Castellón
Casanueva Freijo, Felipe	Servicio Gallego de Salud	Complejo Hospitalario Universitario Santiago	A Coruña
Corella Piquer, Dolores	Universidad de Valencia	Facultad de Medicina de Valencia	Valencia
Diéguez González, Carlos	Universidad de Santiago de Compostela	CIMUS	A Coruña
Estruch Riba, Ramón	Hospital Clínic de Barcelona	Hospital Clínic de Barcelona	Barcelona
Fernández Aranda, Fernando	Fundación IDIBELL	Hospital Universitario de Bellvitge	Barcelona
Fernández-Real Lemos, José Manuel	Fundación Instituto de Investigación Biomédica de Girona	Hospital Josep Trueta	Girona
Fiol Sala, Miguel	Universidad de las Islas Baleares	Facultad de Ciencias de Mallorca	Illes Balears
Fitó Colomer, Montserrat	Consorci Mar Parc Salut de Barcelona	Consorcio Mar Parc de Salut de Barcelona	Barcelona
Frühbeck Martínez, Gema	Universidad de Navarra	Clínica Universitaria de Navarra	Navarra
Gil Campos, María Mercedes	Fundación para la Investigación Biomédica de Córdoba (FIBICO)	Hospital Universitario Reina Sofía	Córdoba
Lamuela-Raventós, Rosa María	Universidad de Barcelona	Facultad de Farmacia.	Barcelona
Lapetra-Peralta, José	Fund.Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla	Distrito sanitario atención primaria de Sevilla	Sevilla

Group Leader	Institution	Centre	Centre Prov.
Lasunción Ripa, Miguel Ángel	Servicio Madrileño de Salud	Hospital Ramón y Cajal	Madrid
López Miranda, José	Fundación para la Investigación Biomédica de Córdoba (FIBICO)	Hospital Universitario Reina Sofía	Córdoba
Lurbe Ferrer, Empar	Consorcio Hospital General Universitario Valencia	Hospital General Universitario Valencia	Valencia
Martínez González, Miguel Ángel	Universidad de Navarra	Universidad de Navarra	Navarra
Martínez Hernández, José Alfredo	Universidad de Navarra	Universidad de Navarra	Navarra
Moreno Aznar, Luis Alberto	Fundación Instituto de Investigación Sanitaria Aragón	Fundación instituto de investigación sanitaria Aragón	Zaragoza
Osada García, Jesús de la	Universidad de Zaragoza	Universidad de Zaragoza	Zaragoza
Palou Oliver, Andreu	Universidad de las Islas Baleares	Facultad de Ciencias de Mallorca	Illes Balears
Pintó Sala, Xavier	Fundación IDIBELL	Hospital universitario de Bellvitge	Barcelona
Portillo Baqueda, Mª del Puy	Universidad del País Vasco	Facultad de Farmacia	Álava
Remesar Betlloch, Xavier	Universidad de Barcelona	Facultad de Biología.	Barcelona
Ros Rahola, Emilio	Hospital Clínic de Barcelona	Hospital Clínic de Barcelona	Barcelona
Salas Salvadó, Jordi	Fundación Instituto de Investigación Sanitaria Pere Virgili	Universidad Rovira i Virgili	Tarragona
Serra Majem, Lluis	Universidad de las Palmas de Gran Canaria	Universidad de las Palmas de Gran Canaria	Las Palmas
Tena Sempere, Manuel	Universidad de Córdoba	Facultad de Medicina.	Córdoba
Tinahones Madueño, Francisco	Fundación Pública Andaluza para la Investigación de Málaga en Biomedicina y Salud (FIMABIS)	Hospital Universitario Carlos Haya	Málaga
Tur Mari, Josep Antoni	Universidad de las Islas Baleares	Facultad de Ciencias de Mallorca	Illes Balears
Villarroya Gombau, Francesc	Universidad de Barcelona	Facultad de Biología.	Barcelona

Budget

INCOME					
ISCIII transfer	Grants projects	Services rendered	Other income	Carryovers	TOTAL
2.887.230,00	481.282,08	20.854,70	30.000,00	331.464,95	3.750.831,73

EXPENDITURE				
Project	Inventoriable	Provisions and other activity expenses	Personnel	TOTAL
Scientific management, Scientific Secretariat, Communication	3.497,27	32.392,29	45.548,16	81.437,72
Groups	261.099,63	728.421,78	1.606.136,36	2.595.657,86
Training-Capacity Building	0,00	43.730,98	0,00	43.730,98
Programmes	0,00	63.798,38	50.209,34	114.007,76
Platforms	297.960,19	5.781,88	10.138,77	313.880,84
Transfer	0,00	440,30	0,00	440,30
Intramural projects	59.505,01	51.756,36	0,00	111.261,37
External projects	3.085,84	124.948,71	362.380,35	490.414,90
TOTAL	**625.147,94**	**1.051.270,68**	**2.074.412,98**	**3.750.831,73**

Personnel

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

	MEN	WOMEN	Total
Diploma holders	1	13	14
Doctors	9	9	18
Graduates	15	31	46
Technical staff	2	13	15
TOTAL	27	66	93

Significant activities

Projects

NATIONAL

Financing agency: Instituto de Salud Carlos III

Miguel Servet contract ("Cell membrane changes induced by dietary long-chain omega-3 fatty acids and their link to chronic disease development").

FIS Project: "Walnuts as an antiatherogenic food. Clinical and experimental assessment".

FIS Project: "Epigenetic changes in the evolution of the metabolically healthy obese. Search for new biomarkers. Prospective and intervention study".

FIS Project: "Study of the biosynthesis of H2S in human adipose tissue and its possible effect on adipogenesis and on sensitivity to insulin".

Predimed Cohorts.

Other financing agencies:

CDTI-CIEN: "Smartfoods"

Fundación La Marató: "Liposicity, hepatic steatosis and hepatocellular carcinoma: function of the armc10/armcx mitochondrial protein family".

INTERNATIONAL PROJECTS EU

Long-term effects of an energy-restricted Mediterranean diet on mortality and cardiovascular disease: the PREDIMED PLUS Study"

EhcoBUTLER

Joint Action (CE+ISCIII): Dedipac JPIHDHL (CE+ISCIII): Enpadasi

ERAB: "Health effects of the ethanol and polyphenol content in beer: Evaluation of the effects of moderate beer consumption on cardiovascular system. A metabolomic approach".

ERAB: "Evaluation of moderate daily intake of beer in reducing menopausal symptoms. Estrogenic effect of hop prenylflavonoids".

ERAB: "Risks and benefits of moderate beer intake (with and without alcohol) on osteoporosis in postmenopausal women".

Technology Transfer

One of the CIBER'S main objectives is to transfer the knowledge generated by its researchers, so that their research results can be developed in protocols, services and products for improving clinical practice and people's quality of life. For this purpose the CIBER Technology Transfer department acts as a link between our researchers and companies, private institutions, public research centres and other innovation agents to make cooperation with them more effective and ensure that the results of research are actually applied. Work is done in several lines in order to achieve this aim:

- Continuous contact with our researchers to monitor their results and train them in innovation management.
- On 29 and 30 November 2016 a Technology Transfer Session was organised to this end as part of the 30th anniversary of ISCIII. At this event experts in different areas shared their knowledge on industrial property, company creation, licencing processes, venture capital, grants for internationalisation, etc...

- Protection of the results of research and management of cooperation with other agents, as shown by the application for patents and signing licence contracts, amongst other agreements.
- Hence, in 2016 eleven new patent applications and a registration of software were submitted at the CIBER. Seven inventions are also in the patentability study and one in the drafting stage, and these are expected to be submitted in early 2017.
- Apart from this, eight licence contracts have been signed. In 2016 different negotiations expected to come to a successful conclusion in the first quarter of 2017 were also got under way.
- In the Obesity and Nutrition area one priority patent and one registration of software were applied for in 2016. Three inventions are in the patentability study stage and it is expected that the applications will be presented in early 2017.
- The presentation of the results of our groups' research and technological capacities in technology transfer sessions. Just as an example of the many measures taken, CIBER had a stand with institutional presence at BIOSPAIN 2016 (28-30 September, Bilbao).
- Support for technology-based company creation stemming from CIBER groups.
- Other activities connected with innovation, public-private cooperation and industrial and intellectual property: as an example:

  -Call for CaixaImpulse Projects 2016: one project was awarded (CIBERES) and another got to the final stage (CIBEROBN).

  -The assignment of the PREDIMED trademark to the CIBER is being managed.

  -Participation in internal and external forums and conferences.

Dissemination

In 2016 the CIBER'S Communication Department took different dissemination and disclosure action in order to raise awareness about the Centre, as well as to spread knowledge about the research work done by the groups in its eight thematic areas.
The main highlights of the Communication work done by CIBEROBN in 2016 are as follows:

- **The CIBEROBN in the media:**
  67 CIBER press releases were issued over this period, 23 of these from CIBEROBN and one in cooperation between several CIBER areas.

Date	Title	Researcher/s
02/02/2016	El CIBEROBN demuestra por primera vez la relación directa entre las variantes del gen reloj y la diabetes tipo 2	Dolores Corella
01/04/2016	Más del 50% de los trabajadores españoles son metabólicamente sanos	Albert Goday
21/04/2016	Reemplazar la carne roja por carne blanca, pescado y legumbres o huevos reduce el riesgo de síndrome metabólico	Nerea Becerra-Tomás, Nancy Babio y Jordi Salas- Salvadó
27/04/2016	No es necesario ayunar antes de una prueba de colesterol	Emilio Ros
30/04/2016	La Realidad virtual ayuda a que los niños obesos disfruten más de la actividad física	Asiás Cebolla
03/05/2016	La dieta mediterránea podría atenuar los efectos nocivos de las acylcartinas elevadas en sangre, factor de riesgo en enfermedades cardiovasculares	Jordi Salas
15/04/2016	Investigadores del CIBEROBN evidencian la existencia de personas delgadas metabólicamente enfermas	Francisco J. Tinahones
23/05/2016	Investigadores del Imibic y la UCO descubren nuevos mecanismos cerebrales de control de la pubertad	Manuel Tena-Sempere
28/05/2016	La dieta de los celíacos es más desequilibrada en cuanto a los azúcares añadidos, la grasa y el contenido de micronutrientes	Jordi Salas y Nancy Babio
07/06/2016	Una dieta mediterránea rica en grasas saludables no lleva a un aumento de peso.	Ramón Estruch
13/06/2016	Descubren un mecanismo cerebral que abre la puerta a curar la enfermedad del hígado graso.	Rubén Nogueiras.
22/06/2016	Aumento proteína hipotálamo disminuye masa corporal en ratas obesas.	Miguel López
4/06/2016.	Cáncer de colon y obesidad infantil, premios Lilly de Investigación Biomédica.	Luis Moreno Aznar
08/07/2016	El consumo frecuente de bebidas endulzadas, light y zumos de fruta aumenta el riesgo de síndrome metabólico	Jordi Salas-Salvadó, Nancy Babio y Cíntia Ferreira-Pêgo
25/08/2016	Guía Europea Hipertensión Pediátrica	Empar Lurbe.
16/09/2016	El consumo de lácteos no se asocia con un incremento del riesgo cardiovascular	Dolores Corella
29/09/2016	Grasa parda como órgano endocrino	Francesc Villarroya

02/11/2016	Los obesos, los adictos al juego y los adictos a sustancias comparten rasgos neuropsicológicos	Fernando Fernández-Aranda
27/11/2016	El Imibic acoge desde este lunes el congreso internacional 'Nuevas fronteras de investigación en obesidad'	CIBEROBN
28/11/2016	Más de 140 expertos se reúnen en Córdoba para abordar nuevos retos en la investigación de la obesidad	CIBEROBN
21/12/2016	El CIBEROBN descubre que la exposición a andrógenos en las primeras horas de vida puede inducir	Francisco J. Tinahones
16/11/2016	El CIBER acerca su investigación a la sociedad de la mano de la improvisación teatral en #ImproCiencia	VARIOS CIBER

2068 appearances in the media were also recorded:

2016	News items	Audience
CIBEROBN	2.068	246.837.000

- **CIBER Newsletter**
  This year five CIBER newsletters were published and disseminated, including relevant content about the CIBEROBN and other thematic areas. The digital newsletters were sent to about 4000 subscribers. http://www.ciberisciii.es/en/press/newsletter

- **CIBEROBN Web page**
  In 2016 60 news items and 32 events on the agenda were published on the CIBEROBN web page.

Statistics on visits on the web page 2016							
	No. of visits to page	Sessions*	Users	Pages / session	Average duration of session	% rebound**	% new sessions
CIBEROBN	84.814	44.526	32.484	1,90	1:18	75,27	72,30

(*) 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 looked at.
(**) 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 CIBEROBN presence on Twitter:

	Followers		Updates		Klout (Influence)	
	January	December	January	December	January	December
CIBEROBN	527	901	405	648	46	44

- **CIBEROBN Annual Report**
  The CIBER Communication area, in cooperation with the CIBEROBN, coordinated the content of the CIBEROBN Report 2015 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

- **CIBER Science Week #ImproCiencia**
  The #ImproCiencia dissemination event, held on 16 November in Madrid, combined science and theatre improvisation to give an entertaining explanation of the biomedical research work done by the CIBER in its eight thematic areas. From the CIBEROBN, Empar Lurbe went onto the stage to explain one of the projects being developed by their group for detecting the risk undergone by new-born babies of suffering from obesity, diabetes or cardiovascular diseases later on in life.

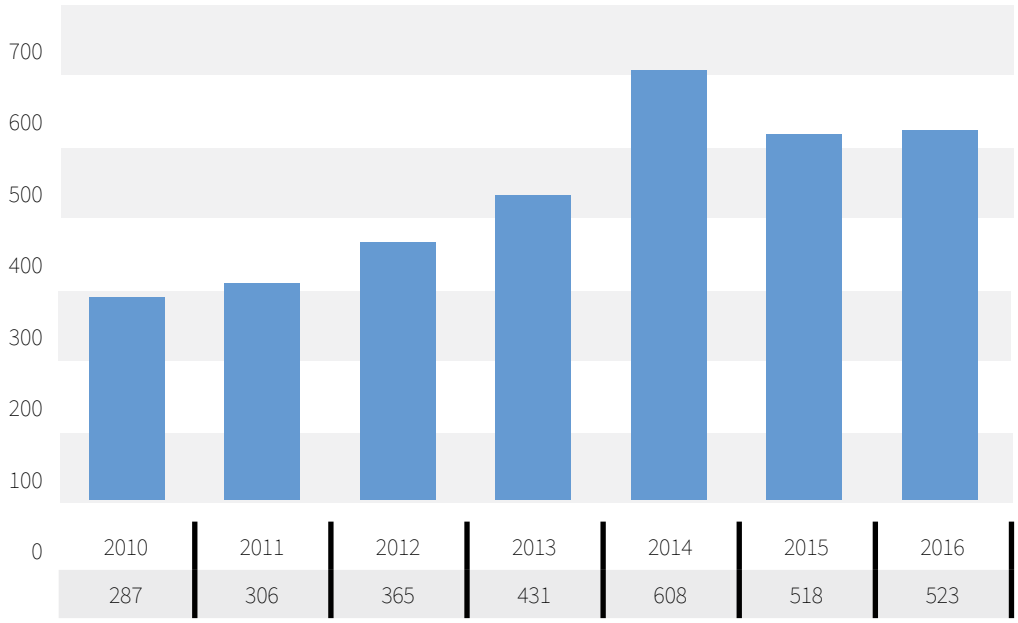
Scientific Production

The graphic evolution of CIBEROBN publications can be seen from the following graphs, in which the data is analysed for 2010 to 2016. This also details the publications per group for this year, as well as interCIBER and intraCIBER cooperation work.

Publications

No. of affiliated publications	2015	2016
Q1	298	340
D1	88	110
Total Publications	535	523

EVOLUTION OF PUBLICATIONS 2010-2016



Most relevant publications of the CIBEROBN in 2016 according to impact factor

Publication	impact factor
Worldwide trends in diabetes since 1980: A pooled analysis of 751 population-based studies with 4.4 million participants	44,002
Management of obesity	44,002
Genetic identification of thiosulfate sulfurtransferase as an adipocyte-expressed antidiabetic target in mice selected for leanness	30,357
FTO genotype and weight loss: systematic review and meta-analysis of 9563 individual participant data from eight randomised controlled trials.	19,697
Liver X Receptor Regulates Triglyceride Absorption Through Intestinal Down-regulation of Scavenger Receptor Class B, Type 1	18,187
A microRNA switch regulates the rise in hypothalamic GnRH production before puberty	16,724
Effect of a high-fat Mediterranean diet on bodyweight and waist circumference: A prespecified secondary outcomes analysis of the PREDIMED randomised controlled trial	16,320
The role of astrocytes in the hypothalamic response and adaptation to metabolic signals	13,177
CDK4 is an essential insulin effector in adipocytes	12,575
Hypothalamic kappa opioid receptor mediates both diet-induced and melanin concentrating hormone-induced liver damage through inflammation and endoplasmic reticulum stress.	11,711

No. of publications per group

Group Leader	Publications	Q1	D1
Argente Oliver, Jesús	16	7	3
Arós Borau, Fernando	21	16	4
Botella Arbona, Cristina	25	15	2
Casanueva Freijo, Felipe	43	24	11
Corella Pique, Dolores	36	25	7
De la Osada García, Jesús	13	7	2
Diéguez González, Carlos	25	23	7
Estruch Riba, Ramón	31	21	5
Fernández Aranda, Fernando	29	22	4
Fernández Real, José Manuel	26	22	11
Fiol Sala, Miquel	34	22	9
Fitó Colomer, Monserrat	56	39	10
Frühbeck Martínez, Gema	28	21	7
Gil Campos, Mercedes	20	7	0
Lamuela Raventós, Rosa Maria	23	14	5

Group Leader	Publications	Q1	D1
Lapetra Peralta, José	25	15	4
Lasunción Ripa, Miguel Ángel	11	5	1
López Miranda, José	29	26	8
Lurbe Ferrer, Empar	19	12	5
Martínez González, Miguel Ángel	50	33	12
Martínez Hernández, José Alfredo	39	26	7
Moreno Aznar, Luis Alberto	12	8	3
Palou Oliver, Andreu	11	8	3
Pintó Salas, Xavier	16	6	2
Portillo Baquedano, María del Puy	8	2	0
Remesar Betlloch, Xavier	13	9	1
Ros Rahola, Emilio	43	32	10
Salas Salvadó, Jordi	40	26	7
Serra Majem, Lluis	54	37	11
Tena Sempere, Manuel	31	22	3
Tinahones Madueño, Francisco José	44	34	9
Tur Mari, Josep A	40	23	4
Villarroya Gombau, Francesc	16	15	9

COLLABORATION

Collaboration	2015	2016
IntraCIBER publications	113	130
InterCIBER publications	99	125

Patents with CIBER ownership 2016

APPLIED FOR

- Pharmaceutical composition comprising 5-dodecanolid, its preparation and use.
- Method for predicting and/or preventing excess weight, obesity and/or its complications by gene expression analysis.

GRANTED

- Method for predicting and/or preventing excess weight, obesity and/or its complications by gene expression analysis.

Clinical guidelines

Scope	Title
International	Guide and Position of the International Society of Nutrigenetics/Nutrigenomics on Personalised Nutrition: Part 1 – Fields of Precision Nutrition
National	Guía para la Promoción del Desayuno Saludable
National	Guía para la Promoción de Estilos de Vida Saludables
National	Guía Práctica Clínica de Asesoramiento Periconcepcional
National	Diabetes mellitus and cardiovascular risk: Working group recommendations of Diabetes and Cardiovascular Disease of the Spanish Society of Diabetes (SED, 2015)
International	Fasting is not routinely required for determination of a lipid profile: clinical and laboratory implications including flagging at desirable concentration cut-points-a joint consensus statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine
International	Indications for Surgery for Obesity and Weight-Related Diseases: Position Statements from the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO).
International	2015 Milan Declaration: A Call to Action on Obesity - an EASO Position Statement on the Occasion of the 2015 EXPO.
National	Consensus document of the Spanish Society of Arteriosclerosis on indications of inhibitors of PCSK9
National	Iniciativas para una alimentacion saludable en Euskadi
International	Metabolic Surgery in the Treatment Algorithm for Type 2 Diabetes: A Joint Statement by International Diabetes Organizations
International	Metabolic Surgery Enters the T2DM Treatment Algorithm.
National	ESPGHAN 2012 Guidelines for Coeliac Disease Diagnosis: Validation Through a Retrospective Spanish Multicentric Study
International	Guide and Position of the International Society of Nutrigenetics/Nutrigenomics on Personalised Nutrition: Part 1 - Fields of Precision Nutrition
National	Guías alimentarias para la población española (SENC, diciembre 2016); la nueva pirámide de la alimentación saludable
National	Postura científica del Col·legi de Dietistes-Nutricionistes de Catalunya y de la Federació Catalana d'Entitats contra el Càncer SOBRE EL CONSUMO DE LÁCTEOS Y LA INCIENCIA DEL CÁNCER "Asociación entre el consumo de lácteos y el riesgo de cáncer de colon, estómago, mama, ovario, próstata y vejiga: revisión de tipo sistemática."
International	2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents.
National	Guía práctica para el manejo de la hipertensión arterial
International	Guide and Position of the International Society of Nutrigenetics/Nutrigenomics on Personalized Nutrition: Part 2 - Ethics, Challenges and Endeavors of Precision Nutrition
International	Guide and Position of the International Society of Nutrigenetics/Nutrigenomics on Personalised Nutrition: Part 1 - Fields of Precision Nutrition
International	EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease_Journal of Hepatology
International	EASL-EASD-EASO Clinical Practice Guidelines for the Management of Non-Alcoholic Fatty Liver Disease_Obesity Facts
International	EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease_Diabetologia
National	Desmitificando las resinas. Tratamiento de la dislipemia en el Paciente con diabetes tipo 2

3

Scientific Programmes

P1. Nutrition

Coordinators: **Jordi Salas Salvadó** and **Dolores Corella Piquer**

The major highlights in this programme in 2016 were as follows:

PREDIMED

- The publication of the PREDIMED study in NEJM 2013 was the one most cited for over 2 years and is at present in third place (Altmetric www.altmetric.com/details/1261724#score)
- The Mediterranean Diet (DMed) is recognised as an effective diet standard for:

Primary prevention of cardiovascular disease in American Diet Guides.
The primary prevention of cerebrovascular accidents in American Guides on primary prevention of strokes. (Stroke 2014;45:3754-832).
The prevention of type 2 diabetes mellitus in Australian Guides on diabetes.

- The results are published in relation to the effects of DMed on weight and waist size: The DMed is slightly superior to the low fat diet in terms of adiposity (Lancet Diabetes Endocrinol 2016;4:666-76).
- A study reveals the importance of omega-3 fatty acids (fish) to prevent retinopathy complications in diabetic patients (JAMA Ophthalmol 2016;134:1142-9).
- PREDIMED is taking part in a genetic meta-analysis including over 197,000 individuals in weight and high blood pressure.
- The first results on metabolites predicting cardiovascular disease are published as a result of a NIH project in Navarre in cooperation with Harvard.
- A meta-analysis on FTO genotype and weight loss is published, including eight clinical trials, in the British Medical Journal.
- A European ERA-NET HDHL project was obtained (López-Miranda and Martínez-González) “Metabolism of fatty acids-bridge between diet and cardiometabolic health”.
- Organisation of the 1st World Conference on the Mediterranean Diet. 6-8 e 2016, Milan, Italy (IP: Serra-Majem).
- Different international projects are requested from the NHI, H2020.

PREDIMED Plus:

- Over 6900 participants randomised.
- >3000 participants have been followed up for over 1 year.
- The first PREDIMED-PLUS work is published.
- A H2020 project is obtained with cognitive function in a subgroup of PREDIMED-PLUS participants.
- PREDIMED PLUS is accepted by the NIH of the United States to join the NHI Consortium for GWAs in clinical trials for weight loss.

SUN project (Universidad de Navarra):

- Article accepted by World Psychiatry (IF>20).
- 22600 participants with 16-year follow-up in the SUN cohort.

Estudio WAHA (Hospital Clínico de Barcelona):

- After completing the WAHA (WAlnuts and Healthy Aging) study, recruiting 700 elderly but cognitively healthy volunteers at the Hospital Clínic de Barcelona and Loma Linda University to compare a diet of walnuts as compared with a control, on cognitive impairment and macular degeneration.

CARDIOPREV

- Publication of the design of the study, whose aim is to display the effectiveness of a DMed rich in extra virgin olive oil on the incidence of recurrence in coronary disease (Am Heart J. 2016;177:42-50).
- Several studies on nutrigenetic analyses are published at CORDIOPREV (Clin Nutr. 2016. pii: S0261-5614(16)31352-8 and J Gerontol A Biol Sci Med Sci. 2016).
- New applications for the test on tolerance to oral fat are established (J Clin Lipidol. 2016;10(5):1163-71).
- First results published on intestinal microbiota-diet (J Nutr Biochem. 2016;27:27-31 and J Clin Endocrinol Metab. 2016;101:233-42).

Other clinical trials

- The results of a clinical trial on cognitive training plus epigallocatechin-3-gallate in patients with Down syndrome are published (The Lancet Neurology. 2016;15(8):801-810).
- Metabolic-nutritional effects on virgin olive oil and its components: SOE1/P1/E0123. Funding body EU-SUDOE. From 2016 to 2018. PI: M. Jesús Rodríguez Yoldi.

Guides

- Guides of the International Society of Nutrigenetics/Nutrigenomics on Personalised Nutrition.

P 2. Adipology

Coordinator: **Gema Frühbeck Martínez**

The research work done in the Adipobiology Programme is outstanding for both its quality and quantity. It should also be stressed that this comprises both intra- and inter- CIBER cooperation work, as well as work done with groups of acknowledged international prestige, which enables taking on much more ambitious and extensive projects, which would otherwise not have been possible and which have materialised in findings of great scientific importance (MORTON ET AL Nat Med 2016;22:771 / MESSINA ET AL Nat Neurosci 2016;19:835 / LAGARRIGUE ET AL J Clin Invest 2016;126:335 / QUESADA-LÓPEZ ET AL Nat Commun 2016;7:13479 / IMBERNON ET AL Hepatology 2016;64:1086). Other relevant accomplishments are having gone further into the knowledge on the contribution made by adipose fat not only to ponderal control, but also overall metabolic control, in its different facets (TULIPANI ET AL Obesity 2016;24:2451 / CATALÁN ET AL Diabetes 2016;65:3636 / FUCHO ET AL FASEB J. 2016 Dec 21. pii: fj.201601156R), as well as its response to surgical and/or diet interventions (PÉREZ-MARTÍNEZ J Clin Lipidol 2016;10:1163 / RANGEL-ZÚÑIGA ET AL Exp Gerontol 2016;83:56 / YUBERO-SERRANO ET AL Atherosclerosis 2016;253:178 / LEÓN-ACUÑA ET AL Cardiovasc Diabetol 2016;15:68 / GRACIA ET AL Food Funct. 2016;7:1680). It should be stressed that the cooperation between groups has extended to take on transversal projects between different CIBERs (Inter-CIBER Inflames Project), as well as between different programmes of the CIBEROBN, as is vouched for in the case of the microbiota study (LELOUVIER ET AL Hepatology 2016;64:2015) or the accumulated and synergic effect with the Neurocognition programme.

Progress has also been made in the knowledge of the effects of adipose tissue browning and central control of energy homeostasis, fields in which different CIBEROBN groups are genuine world leaders (GAVALDÀ-NAVARRO ET AL Diabetología 2016;59:2208 / MARTINS ET AL Cell Rep 2016 23;16:2231 / LÓPEZ ET AL Nat Rev Endocrinol 2016;12:421 / MANFREDI-LOZANO ET AL Mol Metab 2016;5:844 / LEÓN ET AL Sci Rep 2016;6:19206). A contribution has also been made to proving the dynamic endocrine functionality of adipose tissue, for example in the case of the effect of GLP-1 (EL BEKAY ET AL Br J Pharmacol 2016;173:1820) or of the growth factors of fibroblasts (EJAZ ET AL Diabetes 2016;65:902 / ZAREI ET AL Diabetes 2016;65:3185 / OLIVA-OLIVERA ET AL J Clin Endocrinol Metab 2016 14:jc20162256).

Other translation activities should be added to this prolific and significant publishing work, such as obtaining resources for creation of the ADIPOPLAST Excellence Network, led by Prof. Villarroya, in which other groups from the Adipobiology programme are taking part, along with different groups of acknowledged national prestige. One major translational aspect also involves drafting clinical guides and positioning documents concerning obesity and excess adiposity, in particular as a centre of attention. The groups forming part of Programme 2 have furthermore taken part in the formation of international consortiums (see participation in European projects) and pursued the development of patents.

P3. Complications of Obesity and Child Obesity

Coordinator: **Francisco Tinahones Madueño**

Milestones achieved in 2016*

Milestone1. The CordioPrev study continues to provide results:

1.1.-Genetic variables in Telomerase RNA Component interact with the response to Mediterranean diet.

1.2 Genetic variables of TNFA are related with an inflammatory state.

1.3 Demonstrating the close relationship between metabolic disease and carotid atherosclerosis.

Milestone 2. An article has been published in Journal 'Clinical Investigation' as a result of cooperation between CIBEROBN and CIBERDEM.

Milestone 3. The metagenomics platform has been got under way, performing four hundred determinations of our own, interciber and intraciber projects in the last quarter of 2016.

Milestone 4. We have continued to provide data for explanation of discordant phenotypes of obesity - diabetes:

4.1.-We have proven that thin subjects with metabolic syndrome have increased inflammation and drop in the lipogenic capacity in the subcutaneous adipose tissue.

4.2 We have proven that the mesenchymal cells of the obese with metabolic syndrome have lower angiogenic capacity.

Milestone 5. We have provided information on the relationship of the microbiota with metabolic illness (two patents have been registered with mixes of probiotics which will be tested in clinical trials). The changes arising in the microbiota with hygiene-diet interventions such as the Mediterranean diet or the intake of polyphenols from red wine have also been described.

Milestone 6. Participation in a collaborative study in which it was shown for the first time that a microbiota profile is associated with hepatic fibrosis in obese subjects.

Milestone 7. New data has been provided on the relationship between endotoxaemia and the development of brown adipose tissue in animal and human models. This line of research is producing collaborative work in the study of the relationship between microbiota and brown adipose fat in humans.

OBESITY-CANCER SUB-PROGRAMME

Milestone 8. The analysis of the methylome in breast and colon cancer has been completed in both tumour and adipose tissue. At the present time two manuscripts are being prepared and a patent has been applied for to protect a diagnostic and prognostic biomarker of colon cancer.

CHILD OBESITY SUB-PROGRAMME

Milestone 9. It has been discovered that prepuberal children with resistance to insulin have a different metabolomic profile to children sensitive to insulin. Above all, metabolites connected with bile salts are affected.

Milestone 10. European guides on treatment of high blood pressure in children and adolescents have been led by a CIBEROBN researcher.

*The 10 most important milestones achieved have been registered.

P4. Neurocognition and environmental-biological factors

Coordinator: **Fernando Fernández Aranda**

The result and participation of groups in our programme are excellent, both a regards inter-group cooperation and external cooperation with other CIBERs (CIBERSAM, CIBERDEM and CIBERESP) and international cooperation. Dialogue between groups is constant and generating synergies in the CIBER itself and on international scale.

Some of the most outstanding results which reflect this positive valuation are:

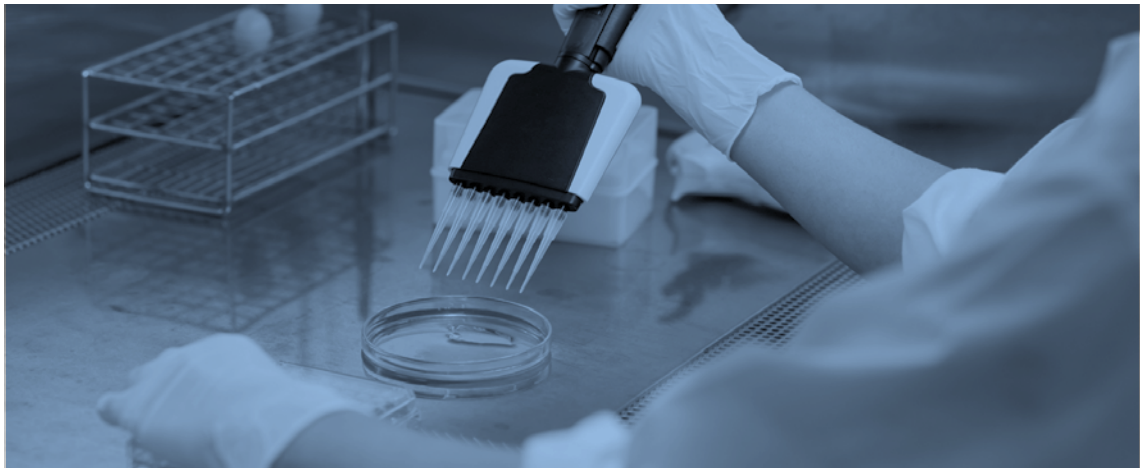
- Increase in **publications and scientific dissemination** on the subjects covered by the CIBEROBN study (Total publications in the programme: 38; in the last year, 2016, a total number of 11 articles, all in Q1).
- Participation in drawing up the **Guide on Eating Disorders through participation in the International Agreement on** "Substance Use Disorders in Eating Disorders"- 2016 (Authors: Dr F. Fernández Aranda and Dr S. Jiménez-Murcia)- Encyclopaedia of Feeding and Eating Disorders | book-chapter | Springer; DOI: 10.1007/978-981-287-087-2_19-1
- Greater **internationalisation** through participation in consortiums: Playmancer; GWAS on Anorexia Nervosa and Abnormal Eating Conduct; Psychiatric GWAS; COST-EU-BM1105)
- Increase in applications for and **procurement of resources** for research: Participation as a cooperating group in the Excellence Network (26/ 11/ 2014)- State Secretariat for Research, Development and Innovation - MINECO / PSI2014-56303-REDT, of two groups from our Programme; and granting of an EU project to two members of our Programme (H2020 EhcoButtler- H2020-643566 /2014-16); FIS PI14/00290. Obtaining H2020 (H2020-SFS-2016-2) Effects of Nutrition and Lifestyle on Impulsive, Compulsive, and Externalizing behaviours/ Eat2beNICE (Ref 728018) IP F. Fernández-Aranda.
- Increase of **dissemination**: Increase in visibility, general dissemination and social diffusion of the subjects studied by the CIBEROBN in the media (opinion letter in The Lancet journal: The neglect of eating disorders. Giel K, Schmidt U, Fernández-Aranda F, Zipfel S. Lancet. 2016 Jul 30; 388(10043):461-2. doi: 10.1016/S0140-6736(16)31154-0/printed media, radio, TV and Internet); Five lectures sponsored with visiting foreign professors in our programme (2 UK; 1 Germany; 1 Austria; 1 USA)
- Increase in the production of **doctoral theses:** this year a total number of 7 doctoral theses have been published on the subject covered by our programme (three of these international).

P5. New strategies and Biomarkers

Coordinator: **Andreu Palou Oliver**

In 2016 progress was made in identifying obesity biomarkers and eating behaviour in children as part of the European project I. FAMILY. In rodents, early blood markers of nutritional alterations, risk of obesity and associated medical complications were also identified. In this period one patent was accepted and published (P201430428) which defines the nutrigenomic biomarker in the blood able to predict the predisposition to develop obesity in early stages and the international patent was extended to Russia. We should also stress the identification of markers connecting hepatic steatosis associated with the intake of unbalanced diets with a greater risk of lesions in the liver, including liver cancer. Progress has also been made in the identification of the importance of epigenetic regulation, of microRNA and of the genotype in obesity and weight loss in humans. Guides have been written on personalised nutrition and studies are being carried out on humans intended to develop nutrigenetic-based tests to facilitate control of body weight and weight loss. Of interest in the field of functional nutrition, new methods of identification of bioactive compounds of food (antioxidant compounds) in the blood and urine have been published, of use for analysing their positive effects on health. Some interesting properties from the standpoint of obesity control of bioactive compounds of food, such as glycosaminoglycans, have also been identified. Apart from this, studies which display the positive effects of breast-feeding in children with low weight when born have been carried out. Also with children, as part of the ETIOBE project, based on the implementation of e-therapy for dealing with child obesity, an innovative mathematical method ("self-organizing map") has been used for analysing data of self-registers of eating habits. Protocols have also been established for measuring physical activity habits in obese children and adolescents, which enable obtaining profiles used for designing personalised physical exercise. In this respect the physical activity programme (PAIDO programme) has been implemented, with the addition of the *Marchando con mi Pediatra* (Walking with my Doctor), enabling patients and families to go on fast walks in leisure areas supervised by paediatric doctors. The platform has also been prepared for its implementation in the adult population.

In July 2016 the *VII Seminario sobre Alimentación y Estilos de Vida Saludables* was arranged: "The declarations of healthy properties one decade later and New Food in the European Union" in Palma de Mallorca. The seminar was a joint activity of the excellence network MARCASALUD (MINECO) and of the Programme for New Strategies and Biomarkers (CIBER), and different groups associated with the programme took an active part in the event as speakers.



P6. Body Weight Homeostasis Physiopathology

Coordinator: **Francesc Villarroya Gombau**

The Programme went on with its activities in 2016 and the results of its work were excellent. Over the year nearly 40 international publications focussing on the objectives of the programme were produced by CIBEROBN teams. Apart from the relevant contributions based on the research work done by the groups forming part of the programmes, we should stress the work done in cooperation intended to achieve the programme's transversal objectives. Some of the most noteworthy of these are mentioned below, either because of their impact or in particular through being based on cooperative aspects in implementation of the Programme.

As part of the sub-programmes under way, one relevant area of research is the determination of gonadotropic determining factors and the interaction of puberal development with obesity. One highly relevant contribution in this sphere is the publication entitled "Defining a novel leptin-melanocortin-kisspeptin pathway involved in the metabolic control of puberty" by MANFREDI-LOZANO M ET AL. in Mol Metab. 2016, 5:844-57, as a result of the cooperation between 2 CIBEROBN teams (M. Tena-Sempere; C, Diéguez) in the Programme. The identification of new factors of systemic action involved in the control of adiposity is also being investigated in the Programme. We should stress in this respect the publication about the role of LBP protein, as a result of the cooperation between two CIBEROBN teams involved in the programme (J.M. Fernández Real and F.Villarroya): "Lipopolysaccharide-binding protein is a negative regulator of adipose tissue browning in mice and humans" GAVALDÀ-NAVARRO A ET AL. Diabetologia. 2016, 59:2208-18. Mention should also be given to the joint participation of two CIBEROBN groups from the Programme (C. Diéguez and F. Casanueva) in the publication of "Uroguanylin Action in the Brain Reduces Weight Gain in Obese Mice via Different Efferent Autonomic Pathways." FOLGUEIRA C, ET AL. Diabetes. 2016, 65:421-32.

Apart from the scientific contributions materialised in the publications, in 2016 the Programme has been performing different actions for energising and coordinating work. Support has continued to be given for importing and transferring model animals between the groups, especially mice with genetic modifications, relevant for the study of obesity. The internal database of animal models available is being kept up. New cooperation schemes between several CIBEROBN groups have been started for new objectives of the programme (for example, the coordinated study of new circulating factors in obesity and diabetes associated with environmental management and determinants, in coordination between the groups of F. Tinahones, F. Villarroya and M. Fitó). General meetings for annual coordination and scientific exchange have also been held. To this end the internal meetings of the Programme were usefully combined with sessions involving participation of scientists from other international spheres, a highly successful system already tried out in previous years. In 2016 we should stress the meeting "Emerging model systems and obesity research", held in March 2016 at the Universidad de Barcelona, with the participation of international experts and members of all the groups in the Programme, at which the use of non-conventional animal models for studies of the physiopathology of obesity was discussed.

4

Transversal Programmes

Training Programme

Coordinator: **Manuel Tena Sempere**

The CIBEROBN Training Programme is founded on the premise that continuous training is a key element for sustaining research work. As in previous years, the basic feature of the programme has focussed on the youngest members of the teams, its objectives being to promote the training of researchers in obesity and nutrition (especially emerging and in the consolidation process), to favour their mobility and help to consolidate their professional careers as independent researchers in this thematic area. Another part of the same approach involved thematic training activities being carried out in cooperation with other CIBER thematic areas and other national and international institutions, in the sphere of biomedical research and obesity, intended to bolster our CIBER's commitment to the continuous training of its members.

In keeping with the programme's trajectory the main training measures used the vehicle of financing training stays of CIBEROBN members at other national and international reference research groups. Since it started the programme has had an open and dynamic system of applications to this end, enabling it, after assessment by scientific management and the manager, to grant economic aid for going on training stays at CIBEROBN groups (other than the ones located in the city where the applicant group is based) other CIBER groups and groups not within the CIBER structure (both national and international). From our accumulated experience, these stays have proved to be extremely useful for the progress of our programmes, since the young investigators are trained in specific techniques which they then immediately apply to studies of the group in the CIBEROBN.

More specifically, over the year in 2016, a total number of 8 applications for training stays of CIBEROBN researchers were carried out (two of which will finally be materialised in 2017), most of these involving a duration of roughly or nearly 3 months (which is the maximum time allowed for financing per group and year by the programme). In spite of this representing a slight drop as compared with the number of applications for the previous year (10), we should stress the positive side of the large percentage of internationalisation (ALL except for one of the stays applied for were at distinguished foreign centres in Europe and America) and involved an extended average stay, of special interest from the standpoint of acquiring knowledge, establishing scientific relationships and developing new techniques and cooperation work.

As well as the aforementioned mobility activities, the programme has been involved in the organisation and support for complementary training activities more intensively than in previous years. Three initiatives should be pointed out in this context:

(a) Participation, with financing of two persons from CIBEROBN, at the Encuentro de Doctorado de Excelencia, in Mahón, promoted by the CIBERESP;

(b) Support for the thematic Workshop entitled "How to tackle the Obesity epidemic in European children", with the participation of several international speakers and of the CIBEROBN, held in Saragossa from 19-20 September 2016; and particularly (c) the scientific meeting "New Frontiers in Obesity Research", an initiative jointly arranged with the European Society of Endocrinology, held in Cordova from 28 - 30 November, which was attended by 150 people with 25 high-level international speakers, with over 65 members of the CIBEROBN going to this. This set of activities has enabled complementing the training components of the programme, extending its scope to practically all the groups in the CIBEROBN. Scientific Management's strategy is to go on in this approach, and joint training courses are already being prepared with other thematic areas of the CIBER, such as CIBERDEM, as well as renewing cooperation with the CIBERESP in the Doctorate School.

Lastly, and as a training feature of the very greatest importance, we should point out here that a total number of 129 Doctoral theses (30 of these international) were completed in 2016, which represents the consolidation of a growing tendency in this important training activity, with a figure doubling the number of theses defended in 2011.

The overall financing assigned in this programme in 2016 came to 39,884 EUR. This means a very considerable increase, of almost 70%, in the funds used as compared with the previous year. Put into perspective, it may be considered that the training and mobility programme of the CIBEROBN has been consolidated, and due to its flexibility has become a valuable tool not only in the professional development of researchers (especially younger ones) but also in the reinforcement of international connections and collaboration of the groups forming part of our CIBER. In this setting, this programme made a very considerable contribution to reinforcing the interest and synergies of the combination of universities and hospitals in the CIBER, with very good results in the training of research staff. Similarly, and without being reflected in terms of financing, the training programme has covered stays of post-doctoral researchers at the centres in the consortium of our CIBEROBN, as well as of doctoral candidates who have received grants from other countries to do their doctoral theses at CIBEROBN groups. All of this has had a very decisive effect on consolidating our CIBER'S position as an international benchmark in Obesity and Nutrition.

5

Platforms

Platforms Coordinator: **José Manuel Fernández-Real**

"FATBANK" Platform

The platform's noteworthy accomplishments in 2016 were as follows:

- The 5 Nodes of the Platform signing the internal agreement regulating cooperation, between them, and stressing:

  The legal and regulatory definition governing this.

  Minimum characteristics for a donor to be able to be included in the collection. Minimum commitments of the Nodes in respect of the Platform.

  Regulation of the Internal Scientific Committee.

  Conditions in the event of drafting scientific articles that are published thanks to the use of samples coming from the FATBANK.
- Exhaustive review of all the information associated with the donors and samples of the coordinating node.
- Exhaustive check of storage of ALL the samples on an I.T. basis by the coordinating node.
- Starting to collect a new type of adipose tissue mode: intra-osseous adipose tissue.

			MUESTRAS 2016						
Nodo	Nº Donantes acumulados 2009-2016	DONANTES 2016	SUERO	PLASMA EDTA	BUFFY COAT	TA VIS-CERAL	TA PARIETAL	TA TIROIDAL	HECES
Girona	464	78	1280	2528	616	70	69	22	239
Málaga	199	32	0	0	0	0	0	0	0
Pamplona	277	75	205	782	133	132	43	0	0
Santiago	153	28	328	852	166	54	27	0	0
Córdoba	88	0	0	0	0	0	0	0	0
Total	1181	213	1813	4162	915	256	139	22	239

Metagenomics Platform

The Metagenomics Platform is a system shared by the IBIMA and the CIBEROBN. In the first six months of 2016 the tender and acquisition of the structure took place. The use of the platform is being managed by the CIBEROBN research group led by Dr Tinahones and forms part of the ECAI (Common Support Structures for Research) in genomics of the IBIMA.

From October 2016 the technical staff working at the platform were given training by the Thermo Fisher Scientific (company in charge of installing the equipment).

In December 2016 the platform was already operative and the analyses of the following projects started:

- Analysis of the samples of stools of patients undergoing bariatric surgery, comparing responders and non-responders (cooperative study with CIBERDEM, Hospital Clinic Dr. Pep Vidal's group).
- Analysis of samples of the of cooperation agreement with Pronakal company. Intervention with high-calorie, high-protein diet with and without added probiotic.

Epigenomics-Obesity Platform

The Epigenomics-Obesity Platform is a system shared by the Fundación Ramón Domínguez and the CIBEROBN.

- In the first quarter of 2016 the measures required were taken for putting out the public tender for an array scanner which was published in the State Gazette on 13 February 2016.
- On 8 February 2016 the documents were sent for the application for technical staff associated with the CIBER in the call for Technical Support Staff of the MINECO (State Gazette of 7 December 2015). Financing for this application was not granted (resolution 01/05/2016).
- In April 2016 a call was issued for one place for a predoctoral researcher associated with the CIBER and a predoctoral researcher joined us on 1 June to carry out the epigenetic techniques and perform her doctoral thesis in this area.
- In September 2016 a specific agreement was signed for cooperation between the CIBER and the Fundación Ramón Domínguez for promoting and furthering research in the thematic area of Physiopathology of Obesity and Nutrition. The agreement materialises in joint cooperation by creating the Platform for Epigenomics of Obesity by the joint contribution of media by the Foundation and the CIBER. Under this agreement the Foundation will supply the installations and support resources and the CIBER will provide the ILLUMINA Array HiScan plus the components required for manual processing of the Infinium tests described in the Infinium Option Starter Package 220V, as well as the technical staff required for the management and development of the platform.
- In September 2016 the HiScan equipment for methylation arrays was installed.
- In December 2016 the researchers and technical staff of the Epigenomics of Obesity Platform were given training by ILLUMINA in order to carry out the protocols required for analysis of the samples in the HiScan Equipment.
- The following scientific work has been done since the establishment of the platform:

  1. Data has been generated on a piece of research work done in cooperation between the Casanueva and Fernández-Real groups of the CIBEROBN on the methylation pattern in visceral adipose tissue associated with resistance to insulin in patients with morbid obesity. The following publication was a result of this work: CRUJEIRAS AB, DIAZ-LAGARES A, MORENO-NAVARRETE JM, SANDOVAL J, HERVAS D, GOMEZ A, RICART W, CASANUEVA FF, ESTELLER M, FERNÁNDEZ-REAL JM. Genome-wide DNA methylation pattern in visceral adipose tissue differentiates insulin-resistant from insulin-sensitive obese subjects. Transl Res. 2016 Dec;178:13-24.e5.
  2. The study of "Evaluation of epigenetic changes in breast cancer associated with obesity" was carried out. The methylome of these samples was analysed with the HiScan equipment, the bioinformatic and statistical analyses were performed and the results were compiled for a publication which is currently being reviewed in the Endocrine-related Cancer journal. The Casanueva and Tinahones group of the CIBEROBN cooperated in this .
  3. Different coordination meetings were held between the group of Casanueva and Tinahones of the CIBEROBN to carry out the study on "Evaluation of the colon cancer epigenome associated with obesity" in the framework of the Complications of Obesity Programme of the CIBEROBN. At present the data on the methylome of the samples in this study were generated with the HiScan equipment, now awaiting the bioinformatic and statistical analysis.
  4. Epigenetic analyses have been performed cooperating in a study on cancer which has given rise to the following publication: DÍAZ-LAGARES A, CRUJEIRAS AB, ET AL. Epigenetic inactivation of the p53- induced long noncoding RNA TP53 target 1 in human cancer. Proc Natl Acad Sci U S A. 2016 Nov 22;113(47):E7535-E7544.

6

Research Groups

LEAD RESEARCHER

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PROGRAMMES
P2 | P3 | P5 | P6

GROUP MEMBERS

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Main lines of research

- Severe early onset childhood obesity: metabolic, hormonal, genetic, genomic, metabolomic and microbiota aspects. Clinical follow-up and study of more than 1300 children with severe early onset obesity.
- Relationship genotype/phenotype in the development of secondary complications of obesity. Studies analyzing the impact of sex, ethnic group, etc., on the development of lipid, cardiac and carbohydrate metabolism disorders.
- Importance of the GH/IGF-I axis in growth and body composition. Description and study of the first patients with mutations in the metaloprotease PAPP-A2 and its effects on the GH/IGF-I axis. Studies analyzing the role of proteases (PAPP-A and PAPP-A2) specific for certain IGF binding proteins in controlling the balance of the GH/IGF-I system in obese children.
- The role of hypothalamic astrocytes in physiological and pathophysiological metabolic control. Analysis of the effect of metabolic factors (ghrelin and leptin) and nutritional factors (fructose and fatty acids) on hypothalamic astrocytes and how this affects the neuroendocrine control of metabolism and the possible development of leptin and insulin resistance. Determination of the protective effects of sex steroids, IGF-I and resveratrol on astrocytes.

- Long-term metabolic effects of early dietary and hormonal modifications. Studies involving the effects of maternal and/or neonatal nutrition, stress and modifications in hormones (leptin and sex steroids) on adult metabolism.
- Interaction of leptin and insulin signaling pathways in the development of obesity associated complications.

Most relevant scientific articles

- Dauber A., Munoz-Calvo M.T., Barrios V., Domene H.M., Kloverpris S., Serra-Juhe C. et al. Mutations in pregnancy-associated plasma protein A2 cause short stature due to low IGF-I availability. EMBO Molecular Medicine. 2016.
- Munoz-Calvo M.T., Barrios V., Pozo J., Chowen J.A., Martos-Moreno G.A., Hawkins F. et al. Treatment with recombinant human insulin-like growth factor-1 improves growth in patients with PAPP-A2 deficiency. Journal of Clinical Endocrinology and Metabolism. 2016;101(11):3879-3883.
- Mastrangelo A., Martos-Moreno G.A., García A., Barrios V., Rupérez F.J., Chowen J.A. et al. Insulin resistance in prepubertal obese children correlates with sex-dependent early onset metabolomic alterations. International Journal of Obesity. 2016;40(10):1494-1502.
- Fuente-Martín E., García-Cáceres C., Argente-Arizón P., Díaz F., Granado M., Freire-Regatillo A. et al. Ghrelin Regulates Glucose and Glutamate Transporters in Hypothalamic Astrocytes. Scientific Reports. 2016;6.
- Chowen J.A., Argente-Arizón P., Freire-Regatillo A., Frago L.M., Horvath T.L., Argente J. The role of astrocytes in the hypothalamic response and adaptation to metabolic signals. Progress in Neurobiology. 2016.

Hightlights

Our discovery of a new syndrome, characterized by growth failure and skeletal abnormalaties, due to a mutation in the gene for the protease PAPP-A2 has led to a better understanding of the IGF-I system in human growth and development. This discovery has been filed for patent approval in the USA. We have also obtained data regarding the response to exogenous IGF-I treatment, including not only longitudinal growth, but also metabolic factors. Funding of new project has been obtained to further analyze this new mechanism in human physiology. This project is a coordinated project with collaborators in Málaga and will include a close collaboration with groups in Denmark and Canada.
Our genetic and genomic studies have resulted in the identification of new genes involved in human obesity and these genes and their functions are currently under investigation.
Metabolomic studies have identified biomarkers that may be more useful for the prediction of the onset of insulin resistance in obese children than the currently used methods in the clinical setting. These studies have also identified sex differences in the metabolic markers even in prepubertal children.

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PROGRAMMES
P1

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Main lines of research

- Effect of Mediterranean Diet on primary prevention of cardiovascular disease.
- Secondary prevention of ischemic heart disease. Cardiac rehabilitation. Lifestyle.
- Exercise testing in stable coronary artery disease.
- Exercise phisiology in obese patients.
- Cardiac imaging in obesity.

Most relevant scientific articles

- Estruch R., Martínez-González M.A., Corella D., Salas-Salvadó J., Fito M., Chiva-Blanch G. et al. Effect of a high-fat Mediterranean diet on bodyweight and waist circumference: A prespecified secondary outcomes analysis of the PREDIMED randomised controlled trial. The Lancet Diabetes and Endocrinology. 2016.
- Ruiz-Canela M., Toledo E., Clish C.B., Hruby A., Liang L., Salas-Salvadó J. et al. Plasma branched-chain amino acids and incident cardiovascular disease in the PREDIMED Trial. Clinical Chemistry. 2016;62(4):582-592.
- Guasch-Ferre M., Zheng Y., Ruiz-Canela M., Hruby A., Martínez-González M.A., Clish C.B. et al. Plasma acylcarnitines and risk of cardiovascular disease: Effect of Mediterranean diet interventions. American Journal of Clinical Nutrition. 2016;103(6):1408-1416.
- Sala-Vila A., Guasch-Ferre M., Hu F.B., Sánchez-Tainta A., Bullo M., Serra-Mir M. et al. Dietary α-linolenic acid, marine ω-3 fatty acids, and mortality in a population with high fish consumption: Findings from the PREvención con DIeta MEDiterránea (PREDIMED) Study. Journal of the American Heart Association. 2016;5(1).
- Chiva-Blanch G., Suades R., Crespo J., Vilahur G., Arderiu G., Padro T. et al. CD3+/CD45+ and SMA-α+ circulating microparticles are increased in individuals at high cardiovascular risk who will develop a major cardiovascular event. International Journal of Cardiology. 2016;208:147-149.

Hightlights

The core activity of the Group has been focused on the multicenter PREDIMED PLUS study finished the recruitment phase in November 30, 2016. Our node has recruited a whole of 274 patients and we have continued our substudy, within the general study, on echocardiographic changes and variations in the response to exercise with weight loss.

On the other hand, Dr. Arós Borau (group's IP) has continued coordinating the events Clinical Adjudication Committees of the PREDIMED PLUS and PREDIMED studies (events committees are different in one and another study). In the PREDIMED study clinical follow-up is still done every two years since the main publication (2013) while in the PREDIMED PLUS the cuts are annual. Dr. Alonso Gómez, member of the group, is also involved in both committees.

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Main lines of research

- Virtual Reality.
- Augmented Reality.
- Internet and Web technologies.
- Mobile Devices.
- Serious Games.
- Psychological Treatments.
- Health Psychology.
- Physical activity, health and wellness.
- Positive Psychology.
- Emotional Regulation.
- Cognitive Ergonomics.

Most relevant scientific articles

- Banos R.M., Escobar P., Cebolla A., Guixeres J., Alvarez Pitti J., Lisón J.F. et al. Using virtual reality to distract overweight children from bodily sensations during exercise. Cyberpsychology, Behavior, and Social Networking. 2016;19(2):115-119.
- Mensorio M.S., Cebolla A., Lisón J.F., Rodilla E., Palomar G., Miragall M. et al. Emotional eating as a mediator between anxiety and cholesterol in population with overweight and hypertension. Psychology, Health and Medicine. 2016;1-8.
- Barrada J.R., van Strien T., Cebolla A. Internal Structure and Measurement Invariance of the Dutch Eating Behavior Questionnaire (DEBQ) in a (Nearly) Representative Dutch Community Sample. European Eating Disorders Review. 2016.
- Fleming T.M., de Beurs D., Khazaal Y., Gaggioli A., Riva G., Botella C. et al. Maximizing the impact of E-Therapy and Serious Gaming: Time for a paradigm shift. Frontiers in Psychiatry. 2016;7(APR).

Hightlights

During this 2016 we have achieved several milestones:

- The European project MEAL has successfully ended (Modifying eating attitudes and actions through learning; 531229-LLP-2012-UK-KA3-KA3MP). This project had as objective the development and validation of a tool to train nutritionists and school teachers providing them with nutritional skills in order to use them with 9 to 12-year-old kids. Last July the student Alejandro Domínguez-Rodríguez defended his PhD thesis entitled "Design, development and validation of an online platform addressed to teachers and nutritionists to provide nutritional education to children: MEAL".
- The project "Vivir mejor" (trial: NCT02445833) has finished. Its objective was the development and validation of a self-applied treatment through the Internet in order to change the life style and weigh loss among obese hypertensive adults. Results were very promising, detecting anthropometric changes at the end of the program, and even some improvement at one year follow-up.
- The ACTIOVE Project has finished (New technologies and promotion of the physical activity among children: variables that influence at adherence and its potential in the treatment of children obesity PSI2011-25767).
- The ETIOBE Project (PSI2008-04392) has resulted in the publication of self-records data on children's habits through a very innovative mathematical methodology, altogether with Professor Emilio Soria.
- We have kept working with the Dutch Eating Behaviour Questionnaire (DEBQ) altogether with Professor Tatjana Van Strien, with a validation study in a Dutch normative sample.
- The "Mindful eating" (Comer atento) project has finished, in collaboration with the Basque Culinary Cente, at Donostia. The objective of this project was to develop a research to validate the effect of eating in an attentive way, when selecting food.

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Main lines of research

- Adipobiology.
- Obesity and Cancer.
- Nanotechnology applied to obesity.
- Development and validation of anti-obesity treatments.
- Influence of obesity in models of cerebral ischemia.
- Obesidomic: identification and characterization of new signals released by adipose and muscle tissue involved in the regulation of energy homeostasis: Proteomic Analysis of visceral and subcutaneous adipose tissue and its implications in the development and maintenance of obesity.
- Development and adaptation of proteomic technologies (quantitative proteomics: DIGE, CILAIR) study these secretome of muscle and adipose tissue.
- Analysis of skeletal muscle secretome for the identification of regulatory signals of energy homeostasis.
- Characterization of Fetuin-A and Musclin/Osteocrin as new peripheral signals involved in energy homeostasis.
- Study of the role of hormone irisin as a new target for the treatment of obesity and type 2 diabetes.

- Study of the physiological mechanisms responsible for the regulation of energy balance in the gastrointestinal tract. Role of ghrelin nesfatin a-1, gastricendogenous cannabinoid, signaling pathway activated by FNDC5 andmTOR/S6k1.
- Study of the effect of lactation on metabolism. Study of lipid metabolism in adipose tissue and gastrointestinal mechanisms.

Most relevant scientific articles

- Fagundo A.B., Jiménez-Murcia S., Giner-Bartolomé C., Aguera Z., Sauchelli S., Pardo M. et al. Modulation of irisin and physical activity on executive functions in obesity and morbid obesity. Scientific Reports. 2016;6.
- Barja-Fernández S., Folgueira C., Castelao C., Al-Massadi O., Bravo S.B., García-Caballero T. et al. FNDC5 is produced in the stomach and associated to body composition. Scientific Reports. 2016;6.
- Zhou B., Lu Y., Hajifathalian K., Bentham J., Di Cesare M., Danaei G. et al. Worldwide trends in diabetes since 1980: A pooled analysis of 751 population-based studies with 4.4 million participants. The Lancet. 2016;387(10027).
- Di Cesare M., Bentham J., Stevens G.A., Zhou B., Danaei G., Lu Y. et al. Trends in adult body-mass index in 200 countries from 1975 to 2014: A pooled analysis of 1698 population-based measurement studies with 19.2 million participants. The Lancet. 2016;387(10026):1377-1396.
- Díaz-Lagares A., Méndez-González J., Hervás D., Saigi M., Pajares M.J., García D. et al. A novel epigenetic signature for early diagnosis in lung cancer. Clinical Cancer Research. 2016;22(13):3361-3371.

Hightlights

The research group has published 51 articles with a cumulative impact factor in them of 250,60. Has managed 2 new clinical trials. It is also worth mentioning the development of a project financed by the FEDER-INNTERCONECTA concerning nutritional intervention with products developed from mushrooms and fish on the evolution of patients with pre-diabetic metabolic syndrome.
Implementation of a platform within the CIBER for the study of epigenetics in cancer and obesity. The main objective of this platform is the use of high-throughput epigenomic technology for research and clinical practice on metabolic pathologies and cancer. In addition, it will lend support to different lines of research within and outside the IDIS in the implementation of epigenetic approaches, both in the research of new mechanisms involved in the pathogenesis and in new biomarkers involved in diagnostic, prognostic and response to the treatment of complex diseases with great relevance in our society.
Has developed research focused on the search for new effective therapies against obesity based on oral treatments with antioxidants whose results will be published soon. A regional multidisciplinary consortium has also been created for the search of therapies against various diseases (obesity, cancer and neurodegenerative diseases) based on the development of nanostructures.
In the project The Obesity Paradox, with an overall balance of 7 articles already submitted for publication. Obtainment of a new research project of the ISCIII and has requested a new European Patent Application.

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Main lines of research

- Mediterranean diet and health.
- Genetic and Molecular Epigemiology of Obesity and Cardiovascular Diseases.
- Gene-environment interactions and Gene-Diet Interactions.
- Research Methods in Genomics and Epigenomics.
- Nutrigenomics of eye diseases.
- Bionformatics and Genomics.
- Computational Medicine.
- Taste and cardiovascular risk factors and obesity.
- MicroRNAs, methodology and association with cardiovascular diseases and obesity.
- Meta-analysis.
- Gene expression and modulation by diet and physical activity.
- Healhty ageing.

Most relevant scientific articles

- Estruch R., Martínez-González M.A., Corella D., Salas-Salvadó J., Fito M., Chiva-Blanch G. et al. Effect of a high-fat Mediterranean diet on bodyweight and waist circumference: A prespecified secondary outcomes analysis of the PREDIMED randomised controlled trial. The Lancet Diabetes and Endocrinology. 2016.
- Smith C.E., Coltell O., Sorli J.V., Estruch R., Martínez-González M.A., Salas-Salvado J. et al. Associations of the MCM6-rs3754686 proxy for milk intake in Mediterranean and American populations with cardiovascular biomarkers, disease and mortality: Mendelian randomization. Scientific Reports. 2016;6.
- Corella D., Coltell O., Sorli J.V., Estruch R., Quiles L., Martínez-González M.A. et al. Polymorphism of the transcription factor 7-like 2 gene (TCF7L2) interacts with obesity on type-2 diabetes in the Predimed study emphasizing the heterogeneity of genetic variants in type-2 diabetes risk prediction: Time for obesity-specific genetic risk scores. Nutrients. 2016;8(12).
- Barragan R., Coltell O., Asensio E.M., Francés F., Sorli J.V., Estruch R. et al. MicroRNAs and drinking: Association between the pre-miR-27a rs895819 polymorphism and alcohol consumption in a mediterranean population. International Journal of Molecular Sciences. 2016;17(8).
- Corella D., Asensio E.M., Coltell O., Sorli J.V., Estruch R., Martínez-González M. et al. CLOCK gene variation is associated with incidence of type-2 diabetes and cardiovascular diseases in type-2 diabetic subjects: Dietary modulation in the PREDIMED randomized trial. Cardiovascular Diabetology. 2016;15(1).

Hightlights

Our research group has obtained important results in the study of the genetics of obesity and its interaction with environmental factors, through its participation in different national and international projects, that will be published in 2017. Among the published results, we would like to highlight the report for the first time regarding the use of stratum-specific genetic risk scores (GRS) to increase the predictive value of these markers. Specifically, we have published that the best GRS to predict type 2 diabetes are different depending on whether the person is obese or not. Also in our pioneer work, we have demonstrated the association between variations in the clock gene and the incidence of type-2 diabetes and stroke. In addition, we have conducted an international study of Mendelian randomization and participated in other international consortia such as CHARGE in other Medellan randomization works. In these studies, we have used genetic markers as instrumental variables of food consumption. In parallel, we have described for the first time a genetic marker in a microRNA associated with alcohol consumption. We have expanded the line of epigenetics by obtaining several funded projects through which we are studying the effect of DNA methylation on obesity and cardiovascular risk, as well as the influence of diet and physical activity on changes in methylation. We have participated in new clinical trials with the industry, as well as in the development of clinical guidelines. Participation in conferences through invited lectures has been remarkable, both nationally and internationally. Moreover, we have carried out extensive scientific outreach activities in television, radio and press media. The group has carried out training activities giving several specific courses and masters, including the defense of 4 Doctoral Theses. Dr. Corella, coordinator of the Healthy Campus at the University of Valencia, has participated in several health promotion activities.

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Main lines of research

- Identification of new drug targets at the CNS for Obesity and associated comorbilities.
- Search for new therapeutic agents against complicated obesity by reprofiling existing drugs.
- The Integrated Neurobiology of Food Intake and food reward.
- Central Control of peripheral lipid metabolism.
- Gender and energy homeostasis.
- Energy sensors and energy balance.
- Molecular Metabolism.

Most relevant scientific articles

- López M., Nogueiras R., Tena-Sempere M., Diéguez C. Hypothalamic AMPK: A canonical regulator of whole-body energy balance. Nature Reviews Endocrinology. 2016;12(7):421-432.
- Imbernon M, Sánchez-Rebordelo E, Romero-Picó A, Kalló I, Chee MJ, Porteiro B et al. Hypothalamic kappa opioid receptor mediates both diet-induced and melanin concentrating hormone-induced liver damage through inflammation and endoplasmic reticulum stress.Hepatology (Baltimore, Md.). 2016;64(4):1086-104.
- Folgueira C, Beiroa D, Callon A, Al-Massadi O, Barja-Fernández S, Senra A et al. Uroguanylin Action in the Brain Reduces Weight Gain in Obese Mice via Different Efferent Autonomic Pathways.Diabetes. 2016;65(2):421-32.
- Tuduri E., Lopez M., Diéguez 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.
- Álvarez-Crespo M., Csikasz R.I., Martínez-Sánchez N., Diéguez C., Cannon B., Nedergaard J. et al. Essential role of UCP1 modulating the central effects of thyroid hormones on energy balance. Molecular Metabolism. 2016;5(4):271-282.

Hightlights

One of the most rewarding aspects of 2016 was the great recognition obtained by the emerging researchers of the Group in different forums. In this regard, it is worth mentioning that Miguel López obtained the Biomedical Research Prize for the best young researcher in our country awarded by atresmedia. This award of great prestige and a generous economic endowment allow the development of a project during the next four years. Similarly, Rubén Nogueiras obtained two prizes, from the Rising Star Award by the European Diabetes Society as well as the Astra-Zeneca Foundation Award for Best Young Investigator in Diabetes / Metabolism. Again, the prestige of all of them and the associated economic endowment will allow CIBEROBN to be more recognized both nationally and internationally in addition to the further economic support.

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Main lines of research

- Effects of the Mediterranean diet on the prevention of cardiovascular disease, cancer and neurodegenerative diseases.
- Effects of the Mediterranean diet of classical and novel cardiovascular risk factors.
- Effects of olive oil, nuts, tomato and cocoa effects on lipid profile, oxidative stress and biomarkers related to atherosclerosis.
- Effects of chronic alcohol consumption on cardiovascular system, liver and nervous system.
- Mechanism of the effects on moderate consumption of wine or beer: effect on the expression and function of adhesion molecules and chemokines associated with the development of atherosclerosis.
- Effects of different types of alcoholic beverages on the immune system.

Most relevant scientific articles

- Estruch R., Martínez-González M.A., Corella D., Salas-Salvadó J., Fito M., Chiva-Blanch G. et al. Effect of a high-fat Mediterranean diet on bodyweight and waist circumference: A prespecified secondary outcomes analysis of the PREDIMED randomised controlled trial. The Lancet Diabetes and Endocrinology. 2016.
- Casas R, Sacanella E, Urpí-Sardà M, Corella D, Castañer O, Lamuela-Raventós RM et al. Long-Term Immunomodulatory Effects of a Mediterranean Diet in Adults at High Risk of Cardiovascular Disease in the PREvención con DIeta MEDiterránea (PREDIMED) Randomized Controlled Trial.The Journal of nutrition. 2016;146(9):1684-93.
- Ruiz-Canela M., Toledo E., Clish C.B., Hruby A., Liang L., Salas-Salvadó J. et al. Plasma branched-chain amino acids and incident cardiovascular disease in the PREDIMED Trial. Clinical Chemistry. 2016;62(4):582-592.
- Guasch-Ferre M., Zheng Y., Ruiz-Canela M., Hruby A., Martínez-González M.A., Clish C.B. et al. Plasma acylcarnitines and risk of cardiovascular disease: Effect of Mediterranean diet interventions. American Journal of Clinical Nutrition. 2016;103(6):1408-1416.
- Sala-Vila A., Díaz-López A., Valls-Pedret C., Cofan M., García-Layana A., Lamuela-Raventós R.-M. et al. Dietary marine ω-3 fatty acids and incident sight-threatening retinopathy in middle-aged and older individuals with type 2 diabetes: Prospective investigation from the PREDIMED trial. JAMA Ophthalmology. 2016;134(10):1142-1149.

Hightlights

Currently, we participate in the PREDIMED Plus study; it would assess the effect on adiposity, cardiovascular risk factors and quality of life of an intensive weight loss intervention based on a low calorie Mediterranean diet, physical activity and behavioral therapy, the effects of the Mediterranean diet on the primary prevention of cardiovascular disease, now framed in the CIBEROBN. In parallel, we are carrying out a study to reduce body weight with a natural plant extracts, participate in the InterCIBER INFLAMES Project and designing a new randomized parallel group controlled intervention trial on the protective effects of moderate alcohol consumption on cardiovascular disease (MACH 14 trial) that will have included 20 centers from USA, Europe, Africa, Australia and South America. Also, we participate in collaboration with the Department of Nutrition and Food Science School of Pharmacy of University of Barcelona in a study to know the nutritional benefits of following diet based on ecological products, so as a study to know the alcohol benefits on menopausal women and osteoporosis disease. On the other side, our group has published over 150 research papers in journals such as New England Journal of Medicine, Annals of Internal Medicine, JAMA, Archives of Medicine, Annals of Neurology and Archives of Neurology, American Journal of Clinical Nutrition and the Journal of Nutrition or Lancet Diabetes Endocrinol.

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Main lines of research

- Environmental and genetic risk factors in eating disorders and abnormal eating behaviors.
- Neurocognitive, sensorial, and activity related factors and their interaction with biological correlates in extreme weight conditions.
- New technology and emotion regulation strategies in eating disorders and behavioral addictions: effectiveness and underlying brain-physiological correlates.
- fMRI studies in obesity and related eating disorders considering specific stimulus and emotional states.
- Food behavior and addictive patterns in eating disorders, obesity and non-substance related addictions.
- Development and application of new technologies for the management of eating disorders, obesity and behavioral addictions.
- Treatment outcome and related clinical-cognitive-biological correlates in obesity and related eating disorders.

Most relevant scientific articles

- Sauchelli S, Jiménez-Murcia S, Sánchez I, Riesco N, Custal N, Fernández-García JC et al. Orexin and sleep quality in anorexia nervosa: Clinical relevance and influence on treatment outcome. Psychoneuroendocrinology. 2016;65:102-108.
- Via E., Goldberg X., Sánchez I., Forcano L., Harrison B.J., Davey C.G. et al. Self and other body perception in anorexia nervosa: The role of posterior DMN nodes. World Journal of Biological Psychiatry. 2016;1-15.
- Fagundo A.B., Jiménez-Murcia S., Giner-Bartolome C., Aguera Z., Sauchelli S., Pardo M. et al. Modulation of irisin and physical activity on executive functions in obesity and morbid obesity. Scientific Reports. 2016;6.
- Maillard A.M., Hippolyte L., Rodríguez-Herreros B., Chawner S.J.R.A., Dremmel D., Aguera Z. et al. 16p11.2 Locus modulates response to satiety before the onset of obesity. International Journal of Obesity. 2016;40(5):870-876.
- Davies H., Wolz I., Leppanen J., Fernández-Aranda F., Schmidt U., Tchanturia K. Facial expression to emotional stimuli in non-psychotic disorders: A systematic review and meta-analysis. Neuroscience and Biobehavioral Reviews. 2016;64:252-271.

Hightlights

- Increase in the number of publications and scientific dissemination of subjects related to CIBEROBN study objectives. Total publications this year: 35; higher percentage of Q1 publications (total 77%).
- Participation in the completion of the international Eating Disorders Treatment Guide on “Substance Use Disorders in Eating Disorders”- 2016 (Authors: Dr. F Fernández Aranda and Dra. S. Jiménez-Murcia)- Encyclopedia of Feeding and Eating Disorders | book-chapter |Springer; DOI: 10.1007/978-981-287-087-2_19-1.
- Participation in the expert WHO Guide on addictive behaviors.
- Greater internationalization through participation in the following consortiums: Playmancer; GWAS in anorexia nervosa and normal eating behavior; GWAS in psychiatry; COST-EU-BM1105.
- Increase in the solicitation and acquisition of research resources: Participation in Excellence in Research Network Participation (26/ 11/ 2014) – State Research, Development and Innovation program - MINECO / PSI2014-56303-REDT, two groups from our program; and EU grants for two members of our program (H2020 EhcoButtler- H2020-643566 /2014-16); FIS PI14/290. Acquisition of H2020 (H2020-SFS-2016-2) Effects of Nutrition and Lifestyle on Impulsive, Compulsive, and Externalizing behaviors/ Eat2beNICE (Ref 728018) IP F. Fernandez-Aranda, in collaboration with Predimed-Plus.
- Increase in dissemination: Greater visibility, general dissemination and social awareness of subjects related to CIBEROBN study objectives in the media: (opinion letter in the journal Lancet: The neglect of eating disorders. Giel K, Schmidt U, Fernandez-Aranda F, Zipfel S. Lancet. 2016 Jul 30;388(10043):461-2. doi: 10.1016/S0140-6736(16)31154-0./ Written press, radio, TV and internet); Five invited conferences and professors within our group(2 UK; 1 Germany; 1 Austria; 1 USA).
- Increase in the production of doctoral theses: last year 8 doctoral theses were presented from our group (three international).

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Main lines of research

- Inflammation and insulin resistance.
- Iron metabolism and insulin resistance.
- Biomarkers of obesity, insulin resistance and type 2 diabetes.
- Bone as an endocrine organ.
- Vascular disease and inflammation.
- Proteomics in adipose tissue.
- Microbiota, insulin resistance and NASH.
- PEPPER (Patient empowerment through predictive Pernsonalized Desicion Support).

Most relevant scientific articles

- Moreno-Navarrete J.M., Jove M., Ortega F., Xifra G., Ricart W., Obis E. et al. Metabolomics uncovers the role of adipose tissue PDXK in adipogenesis and systemic insulin sensitivity. Diabetologia. 2016;59(4):822-832.
- Prats-Puig A., Moreno M., Carreras-Badosa G., Bassols J., Ricart W., López-Bermejo A. et al. Serum Ferritin Relates to Carotid Intima-Media Thickness in Offspring of Fathers with Higher Serum Ferritin Levels. Arteriosclerosis, Thrombosis, and Vascular Biology. 2016;36(1):174-180.
- Morton N.M., Beltram J., Carter R.N., Michailidou Z., Gorjanc G., McFadden C. et al. Genetic identification of thiosulfate sulfurtransferase as an adipocyte-expressed antidiabetic target in mice selected for leanness. Nature Medicine. 2016;22(7):771-779.
- 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.
- Lelouvier B., Servant F., Païsse S., Brunet A.-C., Benyahya S., Serino M. et al. Changes in blood microbiota profiles associated with liver fibrosis in obese patients: A pilot analysis. Hepatology. 2016;64(6):2015-2027.

Hightlights

Our group has been awarded with the Best of JCEM prize, in recognition of the best article in the area of Obesity published in "*Journal of Clinical Endocrinology and Metabolism*" during the year 2015 (Serrano M, Moreno M, Bassols J, Moreno-Navarrete JM, Ortega F, Ricart W, Fernández-Real JM. *Coxsackie and adenovirus receptor is increased in adipose tissue of obese subjects: a role for adenovirus infection?* J Clin Endocrinol Metab. 2015 Mar;100(3):1156-63), and invited to give a conference in the Annual Congress of the Endocrine Society in Boston (April 2016).

Our group has also been awarded with the prize of the Spanish Society of Endocrinology (SEEN), in recognition of the best article in the area of Obesity (Fernandez-Real JM, Serino M, Blasco G, Puig J, Daunis-i-Estadella J, Ricart W, Burcelin R, Fernández-Aranda F, Portero-Otin M. *Gut Microbiota Interacts With Brain Microstructure and Function*. J Clin Endocrinol Metab. 2015 Dec;100(12):4505-13.

In this year, we have begun with new projects from the Instituto de Salud Carlos III (FIS) and from the European Union (Horizon 2020). Furthermore, 2016 has been a succesful year in the obtention of several funds (four projects from the Marató de TV3, with an overall budget over one million euros).

The group has also begun a new project on *Imagenomics*, planned to study 2,000 subjects from the general population.

We have filled an international patent application for the detection of liver fibrosis using circulating microbiota composition.

It is also of note the publication in *Nature Medicine* (in collaboration with the University of Edimburgh), in *Hepatology* (University of Toulose), in *Cell Reports* (University of Madrid), as well as articles leadered by our goup and published in *Arterioscl Thromb Vasc Biol*, *Diabetologia*, *J Clin Endocrinol Metab*, *Transl Res*, *Mol Nutr Food Res*, *Ped Res*, *Surg Obes Relat Dis*, *Clin Endocrinol and Obesity*.

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Main lines of research

Cardiovascular risk factors (nutrition, diabetes, obesity, high blood pressure, lipid levels, smoking, etc.) affect cardiovascular disease incidence through several physio-pathological pathways.
Our group investigates some of these pathways in these research lines:

- **The role of diet on intermediate markers of cardiovascular risk**
  - Evaluation of the effect of a Mediterranean diet on the primary prevention of cardiovascular disease (Predimed Study).
  - Phytate intake, coronary calcification and risk of cardiovascular disease.
  - Change in cardiovascular risk score and metabolic syndrome after an intervention based on the Mediterranean diet.
- **Phatological implications of obesity**
  - Valuation of an intensive lifestyle intervention based on a low calorie Mediterranean diet, physical activity and conductual treatment on weight loss and cardiovascular disease prevention (PredimedPlus study).
  - Molecular basis of sexual dimorphism on the energy metabolism and mitocondrial function; pathological implications.

- Nutritional and genetic determinants of the development of different obesity phenotypes; association of these phenotypes with diseases risk and mortality.

- **Nutrition, diet and cancer**
  - Pro-oxidant and antioxidant nutritional factors and their influence on carcinogenesis: the role of estrogens.
  - Dietary patterns defined a priori and a posteriori and incidence and recurrence of cancer.

Most relevant scientific articles

- Ruiz-Canela M., Toledo E., Clish C.B., Hruby A., Liang L., Salas-Salvadó J. et al. Plasma branched-chain amino acids and incident cardiovascular disease in the PREDIMED Trial. Clinical Chemistry. 2016;62(4):582-592.
- Cordani M., Oppici E., Dando I., Butturini E., Dalla Pozza E., Nadal-Serrano M. et al. Mutant p53 proteins counteract autophagic mechanism sensitizing cancer cells to mTOR inhibition. Molecular Oncology. 2016.
- Estruch R., Martínez-González M.A., Corella D., Salas-Salvadó J., Fito M., Chiva-Blanch G. et al. Effect of a high-fat Mediterranean diet on bodyweight and waist circumference: A prespecified secondary outcomes analysis of the PREDIMED randomised controlled trial. The Lancet Diabetes and Endocrinology. 2016.
- Navarrete-Munoz E.M., Wark P.A., Romaguera D., Bhoo-Pathy N., Michaud D., Molina-Montes E. et al. Sweet-beverage consumption and risk of pancreatic cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC). American Journal of Clinical Nutrition. 2016;104(3):760-768.
- Di Cesare M., Bentham J., Stevens G.A., Zhou B., Danaei G., Lu Y. et al. Trends in adult body-mass index in 200 countries from 1975 to 2014: A pooled analysis of 1698 population-based measurement studies with 19.2 million participants. The Lancet. 2016;387(10026):1377-1396.

Hightlights

During 2016 our group has completed the recruitment of participants for the PREDIMED-PLUS study, recruiting a total of 335 individuals. Within the PREDIMED-PLUS study, we continued to lead the *Core Laboratory of Electrocardiography*, collecting and interpreting all electrocardiograms generated for the entire PREDIMED-PLUS study and participated in the sub-studies of densitometry and echocardiography. We have requested numerous research projects, including an NIH project R1 (USA) in collaboration with other CIBER-OBN groups and researchers from the University of Atlanta (Dr. Alvaro Alonso), to study the atrial fibrillation substrate in participants Of the PREDIMED-PLUS study (not yet granted). We have also obtained funding through the Ministry of Economy and Competitiveness (MINECO) to initiate the project ESTROGENE MODULATOR EFFECT ON THE FUNCTIONALITY OF THE ADIPOSE TISSUE AND ITS INFLUENCE ON THE CARDIOVASCULAR RESPONSE IN AN INFLAMMATORY ENVIRONMENT (SAF2016-80384-R). We are currently conducting statistical analyses to publish two articles with PREDIMED-1 data related to diet and obesity, and we have two approved proposals for analysis with data from the PREDIMED-PLUS study once data is available. The Principal Investigator of the group, Dr. Fiol, continues as Scientific Director of the Institute of Health Research of the Balearic Islands.

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Main lines of research

The Mediterranean diet, its foods and the interaction among different nutrients, has healthy effects on morbidity and mortality related to chronic degenerative diseases, such as cardiovascular and neurodegenerative. Into this context, the main objective of our research is to determine the benefit of a healthy diet pattern and some of characteristic food (olive oil and wine among others) on different cardiovascular risk factors, in healthy and in patients. To establish the cellular and molecular mechanisms that contribute to these benefits is also a key part of our research activity. Based on the knowledge of these underlying mechanisms of the benefit of the diet, progress is being achieved in research of the classical and emergent risk factors for cardiovascular and neurodegenerative diseases together with in the establishment of future risk biomarkers.

To achieve these goals, we are working at present in the following research lines:

- Nutrition intervention studies on the cardiovascular and neurodegenerative risk.
- Classical and emergent risk factors for cardiovascular and neurodegenerative diseases, including imaging biomarkers.

- Molecular and cellular mechanisms related with risk and protective factors for cardiovascular and neurodegenerative disease. Role of high density lipoproteins (HDLs) and low density (LDL), the interaction between diet and intestinal flora, and nutrigenomics.
- Nutritional Epidemiology and Epidemiology and Obesity and Diabetes management.

Most relevant scientific articles

- Hernáez A., Farras M., Fito M. Olive oil phenolic compounds and high-density lipoprotein function. Current Opinion in Lipidology. 2016;27(1):47-53.
- Martín-Peláez S., Castaner O., Sola R., Motilva M.J., Castell M., Pérez-Cano F.J. et al. Influence of phenol-enriched olive oils on human intestinal immune function. Nutrients. 2016;8(4).
- De la Torre R., de Sola S., Hernández G., Farré M., Pujol J., Rodríguez J. et al. Safety and efficacy of cognitive training plus epigallocatechin-3-gallate in young adults with Down's syndrome (TESDAD): A double-blind, randomised, placebo-controlled, phase 2 trial. The Lancet Neurology. 2016;15(8):801-810.
- Goday A., Calvo E., Vázquez L.A., Caveda E., Margallo T., Catalina-Romero C. et al. Prevalence and clinical characteristics of metabolically healthy obese individuals and other obese/non-obese metabolic phenotypes in a working population: Results from the Icaria study. BMC Public Health. 2016;16(1).
- Fito M., Konstantinidou V. Nutritional genomics and the mediterranean Diet's effects on human cardiovascular health. Nutrients. 2016;8(4).

Hightlights

The incorporation of two pre-doctoral students (contract i-PFIS and AGAUR) have been achieved the present year.

With regard projects, mention should be made of the granting of a European project linked to the PREDIMED-plus study on impulsivity and cognitive performance (coordination: Dr. Fernández de Aranda, co-coordinator Dr. Salas-Salvador) in the framework of CIBEROBN. In this regard, one of the researchers belongs to CARIN group.

On the other hand, in the context of the PREDIMED-plus Study, two sub-projects are being led on:

- Functionality of HDL: highlight the recent publication in Circulation journal on the benefits of a Mediterranean diet pattern, particularly when it is rich in olive oil, on the functionality of HDL.
- "Halo" effect (coordinators Dr. Goday and Dra. Castañer) on the relatives of participants in clinical trials on lifestyle. The expected results would be that a lifestyle intervention, basically diet and physical activity practice, can also affect the lifestyle of the relatives of the participants to the trial. This project is currently being developed in different scenarios: a / the 10-year follow-up of the PREDIMED Study in the centers of Barcelona (Hospital-Clinic and IMIM); B / in 6 centers of the PREDIMEDplus Study (IMIM, URV, Bellvitge Hospitals and Clinic of Barcelona, and the Epidemiology and Nutrition Centers of the University of Navarra); And c / within the family of patients who will undergo bariatric surgery.

Finally, the project on the effect of green tea components on the cognitive performance of children and adolescents with Down syndrome led by Dr. de la Torre, whose results in the Lancet Neurology had a great impact on the scientific community and media.

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Main lines of research

- Study of the changes in energy balance and metabolism following bariatric surgery.
- Influence of adipokines, myokines, hepatokines and osteokines in the development of obesity and its comorbidities.
- Implication of aquaglyceroporins in energy homeostasis and metabolic control.
- Importance of adipose tissue extracellular matrix remodelling in obesity and its comorbidities.
- Influence of immune cells in the development of obesity-associated adipose tissue inflammation.
- Adipose tissue dysregulation and colon carcinogenesis promotion.

Most relevant scientific articles

- Bray G.A., Fruhbeck G., Ryan D.H., Wilding J.P.H. Management of obesity. The Lancet. 2016;387(10031):1947-1956.
- Moncada R., Landecho M.F., Fruhbeck G. Metabolic Surgery Enters the T2DM Treatment Algorithm. Trends in Endocrinology and Metabolism. 2016;27(10):678-680.
- Gómez-Ambrosi J., Pascual-Corrales E., Catalán V., Rodríguez A., Ramírez B., Romero S. et al. Altered concentrations in dyslipidemia evidence a role for ANGPTL8/betatrophin in lipid metabolism in humans. Journal of Clinical Endocrinology and Metabolism. 2016;101(10):3803-3811.
- Catalán V., Gómez-Ambrosi J., Rodríguez A., Ramírez B., Valentí V., Moncada R. et al. Increased interleukin-32 levels in obesity promote adipose tissue inflammation and extracellular matrix remodeling: Effect of weight loss. Diabetes. 2016;65(12):3636-3648.
- Ezquerro S., Méndez-Giménez L., Becerril S., Moncada R., Valentí V., Catalán V. et al. Acylated and desacyl ghrelin are associated with hepatic lipogenesis, β-oxidation and autophagy: Role in NAFLD amelioration after sleeve gastrectomy in obese rats. Scientific Reports. 2016;6.

Hightlights

RESEARCH PROJECTS:

- Prospective study of the changes in energy expenditure after bariatric surgery. FIS_INTRASALUD-ISCIII_ Frühbeck.
- Identification of novel modulators of chronic inflammation in prevalent diseases: unveiling divergent mechanisms of disease (INFLAMES). FIS-ISCIII.
- Study of the implication of osteopontin in colon cancer development in the context of obesity. FIS-ISCIII_Gómez Ambrosi.
- Study of the regulation of aquagliceroporins in insulin-sensitive tissues in an obesity and insulin resistance context. Dept. Salud, GobNav_Rodríguez.
- Implication of ghrelin isoforms in the development of steatosis and non-alcoholic steatohepatitis associated with obesity and insulin resistance. FIS-ISCIII_Rodríguez.
- Identification of novel modulators of chronic inflammation in prevalent diseases: unveiling divergent mechanisms of disease. FIS-ISCIII.
- Role of interleukin-32 in the regulation of macrophage polarization in adipose tissue. Involvement in the obesity-associated inflammation and comorbidities. FIS-ISCIII_Catalán.

CLINICAL GUIDELINES:

- EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol. 2016 Jun;64(6):1388-402.
- EASL-EASD-EASO Clinical Practice Guidelines for the Management of Non-Alcoholic Fatty Liver Disease. Obes Facts. 2016;9(2):65-90.
- EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. Diabetologia. 2016 Jun;59(6):1121-40.
- 2015 Milan Declaration: A Call to Action on Obesity - an EASO Position Statement on the Occasion of the 2015 EXPO. Obes Facts. 2016;9(4):296-8.
- Prevención, diagnóstico y tratamiento de la obesidad. Posicionamiento de la Sociedad Española para el Estudio de la Obesidad de 2016 Endocrinol Nutr. 2016 Aug 16.
- Indicators for Surgery for Obesity and Weight-Related Diseases: Position Statements from the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO). Obes Surg. 2016 Aug;26(8):1659-96. https://www.ncbi.nlm.nih.gov/pubmed/27412673
- Metabolic Surgery in the Treatment Algorithm for Type 2 Diabetes: A Joint Statement by International Diabetes Organizations. Diabetes Care. 2016 Jun;39(6):861-77.

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Main lines of research

- **Child obesity:**
  Life habits, body composition and cardiovascular risk factors in prepubertal and pubertal children.
    Study of body composition through DEXA or bioimpedanciometry.
    Study of the physical condition, physical activity and sedentarism.
    Study of metabolic, inflammatory, oxidative and cardiovascular risk biomarkers.
  Prevention and treatment of childhood obesity.
  Genomics, metabolomics, metagenomics and proteomics in obesity.
  Study of white and brown adipose tissue.
- **Infant nutrition:** development of probiotics and prebiotics and study of functional components and nutritional status of the child in chronic pathologies and innate errors of metabolism.
- **Development of omics related to human nutrition.**

Most relevant scientific articles

- Barja-Fernández S., Folgueira C., Castelao C., Al-Massadi O., Bravo S.B., García-Caballero T. et al. FNDC5 is produced in the stomach and associated to body composition. Scientific Reports. 2016;6.
- Rangel-Huerta O.D., Aguilera C.M., Pérez-de-la-Cruz A., Vallejo F., Tomás-Barberán F., Gil A. et al. A serum metabolomics-driven approach predicts orange juice consumption and its impact on oxidative stress and inflammation in subjects from the BIONAOS study. Molecular Nutrition and Food Research. 2016.
- Nissensohn M., Sánchez-Villegas A., Ortega R.M., Aranceta-Bartrina J., Gil A., González-Gross M. et al. Beverage consumption habits and association with total water and energy intakes in the Spanish population: Findings of the ANIBES study. Nutrients. 2016;8(4).
- Ruiz-Ojeda F.J., Rupérez A.I., Gómez-Llorente C., Gil A., Aguilera C.M. Cell models and their application for studying adipogenic differentiation in relation to obesity: A review. International Journal of Molecular Sciences. 2016;17(7).
- Sáez-Lara M.J., Robles-Sánchez C., Ruiz-Ojeda F.J., Plaza-Díaz J., Gil A. Effects of probiotics and synbiotics on obesity, insulin resistance syndrome, type 2 diabetes and non-alcoholic fatty liver disease: A review of human clinical trials. International Journal of Molecular Sciences. 2016;17(6).

Hightlights

Research activity with projects with competitive public funding and other projects are being realized through agreements with companies, in the development of new products.
They stand out among them: EPIC Spain and BIORICA, financing of FIS-ISCIII. This year, funding has been granted for the coordinated group project of CIBEROBN: PUBMEP, financing of ISCIII FIS 2016.
In addition, it has carried out other projects through agreements with companies, in the development of new products, such as probiotics, products with healthy fats, or technological development of tools for use in nutrition or physical activity in children. Among them, the following stand out with funding from the Feder Interconecta program:
"Potentiation of functional biomolecules in food products of Galician origin through agrobiotechnological research" (BIOFUNCIOGAL).
"Design and development of nutritionally balanced, attractive and comfortable / easy to handle food specific for the third and fourth age" (GOLDENFOOD).
"GR2020 - ADVANCED FAT DEVELOPMENT: Development of new food products supplemented with active ingredients, derived from by-products obtained in agroindustrial processes, which will reduce the risk of cardiovascular diseases in children and the elderly" (FUNZIONA).
Of the call Reto, highlights the funding obtained in 2016 from: VOLUMETRIC MEASUREMENT SYSTEM - VoluMea.
Prizes in the group: the Childhood Prize of the Fundació Agrupació and the Prize to the Scientific Path "Dr. Carles Henneberg "by the Danone Institute.
Coordination and assistance of group members in the workshop: How to tackle the obesity epidemic in european children? Course organized by the Ibero-American Nutrition Foundation and CIBEROBN. Zaragoza, 19-20 September 2016.
Coordination and attendance of joint meeting members CIBEROBN. NEW FRONTIERS IN OBESITY RESEARCH event, held in Cordoba November 28 to 30, 2016.
Two specific meetings for groups of CIBEROBN have been carried out for the development of an intervention project with Mediterranean diet and physical activity in childhood obesity.

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Main lines of research

- **Study of food bioactive compounds (polyphenols, carotenoids and vitamins)**
  - Polyphenols, carotenoids and vitamins in food, intrinsic and extrinsic factors that modify the presence therefore. Influence of cultural factors, technology, processing and storage in the levels of these compounds.
  - The matrix effect on the bioavailability of such compounds.
- **Nutritional studies of bioactive compounds: clinical trials and epidemiological studies**
  - The relationship between the consumption of bioactive compounds in the prevention and reduction of chronic diseases.
  - Bioavailability and Bioaccessibility tests, effect of food matrix on the absorption and efficacy of such compounds.
  - Studies of nutritional biomarkers.
  - Nutrikinetics and pharmacokinetics analysis. Effect of consumption of polyphenols and other bioactive compounds in primary prevention and obesity (PREDIMED and PREDIMEDPLUS).

Most relevant scientific articles

- Martínez-Huelamo M., Vallverdu-Queralt A., Di Lecce G., Valderas-Martínez P., Tulipani S., Jauregui O. et al. Bioavailability of tomato polyphenols is enhanced by processing and fat addition: Evidence from a randomized feeding trial. Molecular Nutrition and Food Research. 2016.
- Quifer-Rada P., Choy Y.Y., Calvert C.C., Waterhouse A.L., Lamuela-Raventós R.M. Use of metabolomics and lipidomics to evaluate the hypocholestreolemic effect of Proanthocyanidins from grape seed in a pig model. Molecular Nutrition and Food Research. 2016.
- Ruiz-Lozano T., Vidal J., De Hollanda A., Canteras M., Garaulet M., Izquierdo-Pulido M. Evening chronotype associates with obesity in severely obese subjects: Interaction with CLOCK 3111T/C. International Journal of Obesity. 2016;40(10):1550-1557.
- Lamuela-Raventós R.M., Quifer-Rada P. Effect of dietary polyphenols on cardiovascular risk. Heart. 2016.
- Colman-Martínez M., Martínez-Huelamo M., Miralles E., Estruch R., Lamuela-Raventós R.M. A new method to simultaneously quantify the antioxidants: Carotenes, xanthophylls, and Vitamin A in human plasma. Oxidative Medicine and Cellular Longevity. 2016;2016.

Hightlights

During the 2016 the group has been working in the next projects:

- The study PREDIMED and PREDIMED+ where the effect of consumption of polyphenols and other bioactive compounds in primary prevention and obesity is being evaluated.
- Bioactive components of “sofrito”. Metabolomic study and mechanisms involved in the control of oxidative stress and inflammation (ref. AGL2013-49083-C3-1-R). The clinical trial has ended and the resulting data is being analyzed.
- Probiotics increase the presence of phenolic bioactive compounds in the body and decrease cardiovascular risk parameters (Danone Institute call 2014). This project has ended.
- A new research project granted by the “Generalitat de Catalunya” which objective is to demonstrate the nutritional benefits of following an organic vs. conventional diets using “omics technologies” (ref.53 05012 2016). A clinical trial has been done in young healthy volunteers. The clinical trial has almost ended and the samples analysis will start once it has ended.
- Three projects granted by the European Foundation for Alcoholic Reserach ERAB (EA 15 14, EA 15 15 y EA 15 17) has been started, those projects are being managed by CIBER.

During the year 2016, two competitive projects have been awarded and they will start in 2017:

- School-based educational intervention to face obesity and promote Cardiovascular health among Spanish adolescents: a cluster-randomized controlled trial. Funded by “Fundació La Marató de TV3”.
- Effect of diet polyphenols on the insulin sensitivity, inflammation markers and diabetes mellitus type 2. Funded by the “Ministerio de Economía y competitividad”, reference AGL2016-79113.

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Main lines of research

- Diet, nutrition, and disease prevention.
- Cardiovascular epidemiology.
- Hypertension and ambulatory blood pressure monitoring.
- Health related quality of life.

Most relevant scientific articles

- Estruch R., Martínez-González M.A., Corella D., Salas-Salvadó J., Fito M., Chiva-Blanch G. et al. Effect of a high-fat Mediterranean diet on bodyweight and waist circumference: A prespecified secondary outcomes analysis of the PREDIMED randomised controlled trial. The Lancet Diabetes and Endocrinology. 2016.
- Baena-Diez J.M., Penafiel J., Subirana I., Ramos R., Elosua R., Marín-Ibánez A. et al. Risk of cause-specific death in individuals with diabetes: A competing risks analysis. Diabetes Care. 2016;39(11):1987-1995.
- Ruiz-Canela M., Toledo E., Clish C.B., Hruby A., Liang L., Salas-Salvadó J. et al. Plasma branched-chain amino acids and incident cardiovascular disease in the PREDIMED Trial. Clinical Chemistry. 2016;62(4):582-592.
- Sala-Vila A., Díaz-López A., Valls-Pedret C., Cofan M., García-Layana A., Lamuela-Raventós R.-M. et al. Dietary marine ω-3 fatty acids and incident sight-threatening retinopathy in middle-aged and older individuals with type 2 diabetes: Prospective investigation from the PREDIMED trial. JAMA Ophthalmology. 2016;134(10):1142-1149.
- Guasch-Ferre M., Zheng Y., Ruiz-Canela M., Hruby A., Martínez-González M.A., Clish C.B. et al. Plasma acylcarnitines and risk of cardiovascular disease: Effect of Mediterranean diet interventions. American Journal of Clinical Nutrition. 2016;103(6):1408-1416.

Hightlights

- Public defense, in February 2016, of two Doctoral Thesis: a) “Efficacy of a Mediterranean diet in the primary prevention of heart failure and atrial fibrillation in hypertensive patients at high cardiovascular risk”. PhD Student: Jesus Lozano Rodríguez. Directors: José Lapetra, Manuel Ortega-Calvo and José Manuel Santos-Lozano. Rating: Sobresaliente. b) “Effects of a Mediterranean diet on health-related quality of life in high-risk cardiovascular patients: PREDIMED-Sevilla results”. PhD Student: Yolanda Corchado. Directors: José Lapetra and Manuel Ortega-Calvo. Rating: Sobresaliente Cum Laude.
- Ending of the PREDIABOLE Study: “Effect of olive oil enriched in oleanolic acid in the prevention of diabetes in pre-diabetic patients” (ISRCT03372660), carried out in collaboration with the Instituto de la Grasa (Consejo Superior de Investigaciones Cientificas).

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Main lines of research

- Alterations of intracellular cholesterol homeostasis and its repercussion in reverse cholesterol transport
- Role of cholesterol metabolism in cell cycle progression and DNA replication.
- Study of the mechanisms and in vivo significance of xenobiotic-induced changes in intracellular lipid trafficking and its prevention by polyphenols.
- Role of lipids in male infertility associated to metabolic diseases. Study of its mechanisms and prevention by diet.
- Metabolic effects of bariatric surgery in the morbidly obese patient.
- Gene polymorphisms and gene expression in the obese patient and their relation with cardiometabolic affectation.
- Lipidomics for the study of the metabolic alterations associated with human diseases.

Most relevant scientific articles

- Fernández-Suárez M.E., Escolá-Gil J.C., Pastor O., Davalos A., Blanco-Vaca F., Lasunción M.A. et al. Clinically used selective estrogen receptor modulators affect different steps of macrophage-specific reverse cholesterol transport. Scientific Reports. 2016;6.
- Casado M.E., Pastor O., García-Seisdedos D., Huerta L., Kraemer F.B., Lasunción M.A. et al. Hormone-sensitive lipase deficiency disturbs lipid composition of plasma membrane microdomains from mouse testis. Biochimica et Biophysica Acta - Molecular and Cell Biology of Lipids. 2016;1861(9):1142-1150.
- Botella-Carretero J.I., Lafuente C., Montes-Nieto R., Balsa J., Vega-Pinero B., García-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.
- Canfrán-Duque A., Barrio L.C., Lerma M., de la Pena G., Serna J., Pastor O. et al. First-generation antipsychotic haloperidol alters the functionality of the late endosomal/lysosomal compartment in vitro. International Journal of Molecular Sciences. 2016;17(3).
- Briand O., Touche V., Colin S., Brufau G., Davalos A., Schonewille M. et al. Liver X Receptor Regulates Triglyceride Absorption Through Intestinal Down-regulation of Scavenger Receptor Class B, Type 1. Gastroenterology. 2016;150(3):650-658.

Hightlights

During 2016, the CNO group was involved in the study cholesterol metabolism, the actions and effects of certain components of the diet and the complications of obesity, such as infertility. In the context of secondary alterations in lipid metabolism by xenobiotics, we have shown that certain antipsychotics alkalinize lysosomes, which explains the cellular retention of cholesterol they produce. Likewise, selective estrogen receptor modulators reduce cholesterol efflux from macrophages and alter the cholesterol reverse transport. Regarding the mechanisms of male infertility, we showed that HSL lipase deficiency produces large changes in the composition and functionality of lipid rafts, cell membrane microdomains where several receptors and signaling proteins are localized. In addition, a high throughput peptide microarray has been developed to identify food allergen epitopes. This group has been awarded with three projects from the AES ISCIII call (PI16 / 00154, Study of the role of lipid homeostasis in male infertility associated with obesity and its possible resolution after surgery and diet; PI16-00205, Effect of the intervention 'Milk ladder' in the development of tolerance and recognition of B-cell epitopes in children allergic to cow's milk proteins; DTS16 / 00131, Validation and implementation of a tool to predict the efficacy and safety of the treatment of allergy to cow's milk proteins by oral immunotherapy), the MINECO project SAF2015-70747-R has been initiated (Study of the mechanisms and in vivo significance of xenobiotic-induced changes in intracellular lipid trafficking and its prevention by polyphenols) and the ALIBIRD-CM consortium (functional foods and effective nutritional strategies for the prevention and treatment of chronic diseases) is maintained.

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Main lines of research

During the year 2016 we have continued to examine various research areas thanks to the CordioPrev Study. In the gene-diet interaction, results are published that demonstrate the beneficial effect of chronic consumption of a Mediterranean diet as a function of simple nucleotide polymorphisms (SNPs) that interact with the diet, in patients of high cardiovascular risk, modify intermediate markers of the Disease, such as parameters of systemic inflammation, lipid metabolism and glucose (Garcia-Rios A, Clin Nutr. 2016:5614(16)31352-8; Gomez-Delgado F, J Gerontol A Biol SciMed Sci. 2016 Oct 5). Similarly, it is also validated in two intervention studies, CORDIOPREV and GOLDN, the association between a variant of the S100A9 gene (SNP rs3014866), insulin resistance and type 2 diabetes mellitus is validated in two intervention studies, CORDIOPREV and GOLDN, Blanco-Rojo R, Am J Clin Nutr. 2016 Aug; 104 (2): 508-17.
It is established that the oral fat tolerance test could be used in clinical practice as a tool to identify postprandial hyperlipidemia in patients with fasting triglyceride values between 1-2 mmol/l (89-180 mg/dL), through its validation in the intervention studies CORDIOPREV and GOLDN.
In addition, this methodology is used to demonstrate that patients with prediabetes have a lower metabolic flexibility with higher postprandial hypertriglyceridemia than non-diabetic patients. (Perez-Martinez P, Assessment of postprandial triglycerides in clinicalpractice: Validation in a general population and coronary

heart disease patients. J Clin Lipidol. 2016 Sep-Oct;10(5):1163-71. -Leon-Acuña A, et al., Hepatic insulin resistance both in prediabetic and diabetic patients determines postprandial lipoprotein metabolism: from the CORDIOPREV study. Cardiovasc Diabetol. 2016 Apr 19;15:68).
Finally, results are published showing that the consumption of the two healthy diets administered in the CORDIOPREV study modify the composition of the intestinal microbiota. On the one hand, it is shown that the consumption of the Mediterranean diet counteracts the decrease of the saccharolytic flora observed in patients with metabolic syndrome (J Nutr Biochem. 2016 Jan;27:27-31.),
As well as increases the abundance of Roseburia, whereas the low fat diet favors the growth of F. prausnitzii, whose abundance is low in diabetic people (J Clin Endocrinol Metab. 2016 Jan;101(1):233-42).

Most relevant scientific articles

- Blanco-Rojo R., Alcalá-Díaz J.F., Wopereis S., Pérez-Martínez P., Quintana-Navarro G.M., Marín C. et al. The insulin resistance phenotype (muscle or liver) interacts with the type of diet to determine changes in disposition index after 2 years of intervention: the CORDIOPREV-DIAB randomised clinical trial. Diabetología. 2016;59(1):67-76.
- López-Moreno J., Quintana-Navarro G.M., Delgado-Lista J., García-Ríos A., Delgado-Casado N., Camargo A. et al. Mediterranean Diet Reduces Serum Advanced Glycation End Products and Increases Antioxidant Defenses in Elderly Adults: A Randomized Controlled Trial. Journal of the American Geriatrics Society. 2016;64(4):901-904.
- Blanco-Rojo R., Delgado-Lista J., Lee Y.-C., Lai C.-Q., Pérez-Martínez P., Rangel-Zuniga O. et al. Interaction of an S100A9 gene variant with saturated fat and carbohydrates to modulate insulin resistance in 3 populations of different ancestries. American Journal of Clinical Nutrition. 2016;104(2):508-517.
- Pérez-Martínez P., Alcalá-Diaz J.F., Kabagambe E.K., García-Ríos A., Tsai M.Y., Delgado-Lista J. et al. Assessment of postprandial triglycerides in clinical practice: Validation in a general population and coronary heart disease patients. Journal of Clinical Lipidology. 2016.
- Haro C., Montes-Borrego M., Rangel-Zuniga O.A., Alcalá-Díaz J.F., Gámez-Delgado F., Pérez-Martínez P. et al. Two healthy diets modulate gut microbial community improving insulin sensitivity in a human obese population. Journal of Clinical Endocrinology and Metabolism. 2016;101(1):233-242.

Hightlights

During the year 2016 our group has maintained the high level of excellence, accredited in the past. This fact is supported by the following milestones:
We have published 41 articles (JCR), with a high percentage of leadership in these publications, and an index of more than 140 points cumulative impact. In addition, during the year of 2016, we have developed a total of 7 research projects of national competitive calls, and a European project (Power2DM), and we have obtained the financing of a new European project (PCIN-0156-2016). Within the catchment of the Group's resources, it should be noted the creation of 2 new clinical trials as well as the participation in 14 clinical trials. From the point of view of mobility, we have been receiving several visiting researchers. In relation to the human resources we currently enjoy a contract PFIS, FPI, Sara Borrell, Juan de la Cierva, two Miguel Servet, one Nicolás Monarde, a contract with internal medicine to enhance the research work of the UGC and eight PhD theses have been defended with the highest rating, which indicates the quality of training of our group. Moreover, we have also participated in the development of a consensus document. Finally, highlight that we have finished an electronic platform for the management of research projects "Virtual platform for the management and exploitation of research projects, with application to nutritional intervention studies (Pad-CRD)", with copyright registration code RPI201599902441360 (Spain). This tool is added to the preliminary patents of previous years, which are still on.

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Main lines of research

The group has established a number of research areas that focus on various aspects of childhood obesity and the study of cardiometabolic and renal complications both in children and in adults.
In the area of childhood obesity:

- Study of risk factors for development of obesity, focusing on the impact of intrauterine life, nutrition, postnatal growth and environmental factors (tobacco, metals).
- Identification of molecular mechanisms involved in cardiometabolic risk to better understand its mechanisms and search for biomarkers.
- Study of the association of metabolic factors, dyslipidemia, insulin resistance and hyperuricemia, hemodynamics (blood pressure, vessels).
- Comprehensive prevention and treatment focused on physical exercise with the implementation of new technologies for personalized treatment leading to the creation of PEDITEC (JOINT RESEARCH UNIT FOR TECHNOLOGICAL INNOVATION IN PEDIATRICS -PEDITEC- FACING CHILD WELFARE) together with the Polytechnic University of Valencia (VLCCampus).
- Technology transfer, with the creation of integrated software for cardio respiratory fitness and autonomic activity for personalized exercise.

- Programmes for personalized physical activity present at the hospital and in areas of free time supervised by pediatricians. Programmes for personalized home physical activity implemented via telematics.

In the study area of cardiometabolic and renal complications:

- Study of biomarkers of cardiometabolic risk.
- Study of the mechanisms of podocyte damage as the origin of renal damage in obesity.
- Study of genetic markers (epigenetics, proteomics, genomics) in the risk of developing obesity and its complications.

Most relevant scientific articles

- Lurbe E., Agabiti-Rosei E., Cruickshank J.K., Dominiczak A., Erdine S., Hirth A. et al. 2016 European Society ofHypertension guidelines for themanagement of high blood pressure in children and adolescents. Journal of Hypertension. 2016;34(10):1887-1920.
- Redon P., Grassi G., Redon J., Álvarez-Pitti J., Lurbe E. Sympathetic neural activity, metabolic parameters and cardiorespiratory fitness in obese youths. Journal of Hypertension. 2016.
- Lurbe E., Torro M.I., Álvarez-Pitti J., Redon P., Redon J. Central blood pressure and pulse wave amplification across the spectrum of peripheral blood pressure in overweight and obese youth. Journal of Hypertension. 2016;34(7):1389-1395.
- Lurbe E., Redon J. Isolated Systolic Hypertension in Young People Is Not Spurious and Should Be Treated: Con Side of the Argument. Hypertension. 2016;68(2):276-280.
- Urdinguio R.G., Torro M.I., Bayon G.F., Álvarez-Pitti J., Fernández A.F., Redon P. et al. Longitudinal study of DNA methylation during the first 5 years of life. Journal of Translational Medicine. 2016;14(1).

Hightlights

SCIENTIFIC:

a) An applied methodology for our population of obese children and adolescents has been developed for the evaluation of the vascular phenotype, ambulatory blood pressure, peripheral as well as aortic, activity of the sympathetic nervous system and metabolic evaluation (insulin resistance, hyperglycemia, metabolomics); b) application of genomic, epigenetic, metabolomics and proteomics techniques in the umbilical cord for searching biomarkers on the evaluation of the risk of obesity and cardio metabolic alterations.

INNOVATION AND TRANSFER:

a) Development of algorithms of the cardiorespiratory fitness for the personalised physical activity of overweight, children and adults, using “wearables” without using calorimeter. This development lead to the participation within the BIOTEI-LAB, belonging to the KIC eit-HEALTH in the node of the Polytechnic University of Madrid. This technology, currently being registered, is going to be applied in the 4-year project PROMETEO (Funding of 268.000€) for the study of the temporal evolution of metabolic alterations and the activity of the sympathetic nervous system. b) Achievement of the European project within the call IMI2 named Big Data4Big Heart, using methodology of big data for a better knowledge and segmentation of cardio metabolic alterations.

GUIDELINES:

There have been two participations in European Guidelines. The European Guidelines of Hypertension in Children and Adolescents of the European Society of Hypertension have been coordinated by the group leader (J Hypertens 2016). Apart from that there has been a participation as an author in the European Guidelines of the Evaluation of Cardiovascular Risk of the European Society of Cardiology (Eur Heart Journal, 2016).

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Colaboradores: Sánchez Adán, David

Main lines of research

- Mediterranean diet and cardiovascular disease.
- Mediterranean diet and other chronic diseases.
- Lifestyles and obesity.
- Lifestyles and chronic diseases.
- Metabolic profile and cardiovascular disease.
- Dietary patterns, quality of life and depression.
- Lifestyles, genetics and cognitive decline.
- Metabolomic profile and cardiovascular disease.
- Metabolomic profile and diabetes.
- Nutritional and lifestyle factors and breast cancer.

Most relevant scientific articles

- Livingstone KM, Celis-Morales C, Papandonatos GD, Erar B, Florez JC, Jablonski KA et al. FTO genotype and weight loss: systematic review and meta-analysis of 9563 individual participant data from eight randomised controlled trials. BMJ (Clinical research ed.). 2016;354:i4707.
- Estruch R., Martínez-González M.A., Corella D., Salas-Salvadó J., Fito M., Chiva-Blanch G. et al. Effect of a high-fat Mediterranean diet on bodyweight and waist circumference: A prespecified secondary outcomes analysis of the PREDIMED randomised controlled trial. The Lancet Diabetes and Endocrinology. 2016.
- Martínez-González M.A. Benefits of the Mediterranean diet beyond the Mediterranean Sea and beyond food patterns. BMC Medicine. 2016;14(1).
- Ruiz-Canela M., Toledo E., Clish C.B., Hruby A., Liang L., Salas-Salvadó J. et al. Plasma branched-chain amino acids and incident cardiovascular disease in the PREDIMED Trial. Clinical Chemistry. 2016;62(4):582-592.
- Grosso G., Micek A., Godos J., Sciacca S., Pajak A., Martínez-González M.A. et al. Coffee consumption and risk of all-cause, cardiovascular, and cancer mortality in smokers and non-smokers: a dose-response meta-analysis. European Journal of Epidemiology. 2016;1-15.

Hightlights

In May 2016, our research group co-organized the International Symposium on “Omics: Advances, Applications, and Translation in Nutrition” at the Harvard T.H. Chan School of Public Health (05/9-10/2016, Boston). World-known scientists in the area participated in the conference, including Robert Gerszten, José Florez, Frank Hu and José Ordovás. Four members of our group, Miguel A. Martínez-González, Miguel Ruiz-Canela, Estefanía Toledo and Cristina Razquin, gave one or more speeches at the symposium.
In 2016, Miguel A. Martínez-González, gave three important lectures at the highest international level: 42nd Rankin-Skatrud Lecture (7th of April) at the University of Wisconsin, Medical Grand Rounds (12nd of May) at the Massachusetts General Hospital and Richard Doll Seminar (23th of November) at the Oxford University. In September, was appointed Adjunct Professor by the Harvard University. He was invited as speaker in 12 conferences in the US. One of them was an initiative of the NIH and he was the only European invited speaker.
https://www.nhlbi.nih.gov/research/reports/national-heart-lung-and-blood-institute-workshop-toward-testing-effects-mediterranean-dietary
From the cohorts that our group has set up (SUN, PREDIMED, PREDIMEDPLUS, SENDO, Monkole…), PREDIMEDPLUS is currently the most important. Our group was the unique center that started the recruitment in 2013 and was the one with the highest number of included participants, 628 randomized subjects (>10% of the total) compared to the rest of 23 centers.
We have received funding sources to set up three new cohorts and trials aimed at analyze the potential effects of the Mediterranean diet in the prevention of breast cancer, atrial fibrillation (funded by the Navarra Government) and depression (funded by the FIS).
We obtained funding by national (FIS) and European public institutions (ERA-HDHL) for the ongoing projects, and we have applied for international calls (US-NIH) that are still pending.
Our group publishes, by mean, one new article per week with an increased trend to a higher rate.

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Collaborators: Jimeno Moreno, Beatriz

Main lines of research

- Obesity and inflammation.
- Personalized nutrition and diet therapy in metabolic syndrome.
- Mechanisms involved in energy homeostasis.
- Metabolic biomarkers in obesity.
- bioactive compounds.

Most relevant scientific articles

- Solas M., Milagro F.I., Martínez-Urbistondo D., Ramírez M.J., Martínez J.A. Precision Obesity Treatments Including Pharmacogenetic and Nutrigenetic Approaches. Trends in Pharmacological Sciences. 2016;37(7):575-593.
- Morell-Azanza L., García-Calzón S., Rendo-Urteaga T., Martín-Calvo N., Chueca M., Martínez J.A. et al. Serum oxidized low-density lipoprotein levels are related to cardiometabolic risk and decreased after a weight loss treatment in obese children and adolescents. Pediatric Diabetes. 2016.
- Livingstone K.M., Celis-Morales C., Navas-Carretero S., San-Cristoba R., MacReady A.L., Fallaize R. et al. Effect of an Internet-based, personalized nutrition randomized trial on dietary changes associated with the Mediterranean diet: The Food4Me Study. American Journal of Clinical Nutrition. 2016;104(2):288-297.
- Mansego M.L., García-Lacarte M., Milagro F.I., Martí A., Martínez J.A. DNA methylation of miRNA coding sequences putatively associated with childhood obesity. Pediatric Obesity. 2016.
- Nicoletti C.F., Nonino C.B., de Oliveira B.A.P., Pinhel M.A.S., Mansego M.L., Milagro F.I. et al. DNA Methylation and Hydroxymethylation Levels in Relation to Two Weight Loss Strategies: Energy-Restricted Diet or Bariatric Surgery. Obesity Surgery. 2016;26(3):603-611.

Hightlights

The most relevant milestones in the group include the participation in the production of two international clinical guidelines: “Guide and Position of the International Society of Nutrigenetics/Nutrigenomics on Personalised Nutrition: Part 1 - Fields of Precision Nutrition” and “Guide and Position of the International Society of Nutrigenetics/Nutrigenomics on Personalized Nutrition: Part 2 - Ethics, Challenges and Endeavors of Precision Nutrition” and the implementation of three new clinical trials (Development of a Nutrigenetic Test for Personalized Prescription of Body Weight Loss Diets (Obekit)),(Hígado graso no alcohólico en población navarra obesa: abordaje multidisciplinar/nutricional desde el punto de vista clínico y científico). One of them is international and multicentric (Evaluation of the consumption of a medical device on body weight and glycaemic control in overweight and obese subjects with impaired fasting glucose or mild type 2 diabetes: a 2-arms, placebo-controlled intervention study)
The group has also participated in coordinated projects such as PREDIMED-PLUS or INCOMES and other European ones such as PREVIEW or Food4Me.
The number of indexed publications has been 55, in addition to a letter to the editor in New England Journal of Medicine (FTO Obesity Variant and Adipocyte Browning in Humans, N Eng J Med, 2016, 374: 190-1) and another collaborative paper in British Medical Journal (FTO genotype and weight loss: systematic review and meta-analysis of 9563 individual participant data from eight randomised controlled trials, BMJ, 2016, 254: i4707)
We can also highlight a Summer Course organized by the University of the Basque Country entitled “Progresses in understanding, preventing and managing obesity and diabetes: PREVIEW updates”.

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Main lines of research

The CB15 / 00043 Group of the Foundation Institute of Health Research in Aragon has as main objective to investigate the main determinants of children and adolescents' health and their impact on the health of adults in the future. Chronic diseases related to nutrition and lifestyles represent the main causes of mortality and morbidity in developed countries, such as Spain. From the fetal period, nutrition and lifestyles, including physical activity, influence the development and characteristics of the newborn future. The first 1000 days of life (from conception to the end of the second year) have been identified as the most important period for the correct programming of the physiological mechanisms that predict the onset of chronic diseases. The rapid growth rate from birth to the end of this period, determines the subsequent appearance of obesity and other diseases related to it. During the preschool, school and adolescent years, the lifestyles that usually persist throughout life are established. For this reason, their identification and improvement are a strategy that will improve the health of the population in the future.
Our research group main activity is to investigate the principal determinants of the appearance of obesity and to develop the most effective strategies that allow its prevention.

To achieve this goals we focus our work on the following lines of research:

- Childhood Obesity. Epidemiology and Prevention.
- Nutrition Programming.
- Physical activity.
- Applied Nutrition.

Most relevant scientific articles

- Cashman K.D., Dowling K.G., Skrabakova Z., González-Gross M., Valtuena J., De Henauw S. et al. Vitamin D deficiency in Europe: Pandemic?. American Journal of Clinical Nutrition. 2016;103(4):1033-1044.
- Santos-Lozano A., Pareja-Galeano H., Sanchís-Gomar F., Quindos-Rubial M., Fiuza-Luces C., Cristi-Montero C. et al. Physical Activity and Alzheimer Disease: A Protective Association. Mayo Clinic Proceedings. 2016;91(8):999-1020.
- De Miguel-Etayo P., Muro C., Santabarbara J., López-Antón R., Morande G., Martin-Matillas M. et al. Behavioral predictors of attrition in adolescents participating in a multidisciplinary obesity treatment program: EVASYON study. International Journal of Obesity. 2016;40(1):84-87.
- García-Calzón S., Moleres A., Gómez-Martínez S., Díaz L.E., Bueno G., Campoy C. et al. Association of telomere length with IL-6 levels during an obesity treatment in adolescents: Interaction with the-174G/C polymorphism in the IL-6gene. Pediatric Obesity. 2016.
- Lauria F., Siani A., Pico C., Ahrens W., Bammann K., De Henauw S. et al. A common variant and the transcript levels of MC4R gene are associated with adiposity in children: The IDEFICS study. Journal of Clinical Endocrinology and Metabolism. 2016;101(11):4229-4236.

Hightlights

The most relevant activity of the Group focuses on its research projects funded by the European Commission for the implementation of the coordinated project I. Family (FP7-KBBE-2010-4; Contract FP-266044) and the project "Developing and implementing a community -based intervention to create more supportive social and physical environment for lifestyle changes to prevent diabetes in vulnerable families across Europe (FEEL4DIABETES) "(I-2014/032, Contract HCO-05-2014). In addition, we have projects funded by the Ministry of Health, such as the "Maternal and Child Health and Development Network" (SAMID) (RD08 / 0072). We also work on the analysis of data on the fluid intake of children and adolescents (2014/0525) through data from the HELENA and IDEFICS studies, the promotion of healthy eating in children and the effect of family meals on health and dairy consumption in a healthy diet and lifestyle. In addition, the effect on short-term appetite satisfaction and satiety of different plant compositions in children and adolescents is evaluated, as well as physical fitness in preschool children and their usefulness as a marker of current and future diseases, such as obesity and osteoporosis. In the same way, we are members of the RedPRYS (Livestock production systems in the Pyrenean region and consumer health, 229392 TPR6 / 13).

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PROGRAMMES

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Main lines of research

- Olive oil and fatty liver.
- Olive oil and intestinal physiopathology.
- Nuts and atherosclerosis.
- Expandability of adipose tissue.

Most relevant scientific articles

- Sevelsted Moller L., Fialla A.D., Schierwagen R., Biagini M., Liedtke C., Laleman W. et al. The calcium-Activated potassium channel KCa3.1 is an important modulator of hepatic injury. Scientific Reports. 2016;6.
- Arbones-Mainar J.M., Johnson L.A., Torres-Pérez E., García A.E., Pérez-Díaz S., Raber J. et al. Metabolic shifts toward fatty-acid usage and increased thermogenesis are associated with impaired adipogenesis in mice expressing human APOE4. International Journal of Obesity. 2016;40(10):1574-1581.
- Gamundi-Segura S., Torres-Pérez E., Sanz-Paris A., Arbones-Mainar J.M. Interaction of apolipoprotein E gene polymorphisms on miscarriage risk in black and white American women. Fertility and Sterility. 2016.
- Sanz-París A., Gómez-Candela C., Martín-Palmero A., García-Almeida J.M., Burgos-Peláez R., Matia-Martín P. et al. Application of the new ESPEN definition of malnutrition in geriatric diabetic patients during hospitalization: A multicentric study. Clinical Nutrition. 2016.
- García-Moreno E., Tomas A., Atrian-Blasco E., Gascón S., Romanos E., Rodríguez-Yoldi J.M. et al. In vitro and in vivo evaluation of organometallic gold(i) derivatives as anticancer agents. Dalton Transactions. 2016;45(6):2462-2475.

Hightlights

PROJECTS

- *Project: Search for molecular mechanisms of squalene action in vitro and in vivo.* Funding body: Ministerio de Economía y Competitividad SAF2016-75441-R. From: 2016 to: 2018. PI: JESUS DE LA OSADA GARCIA.
- *Project: Technological alliance to complete the cycle of agroindustrial and forestproduction.* Reference: SOE1/P1/E0123. Funding body UE-SUDOE. From 2016 to 2018. PI: M. JESÚS RODRÍGUEZ YOLDI.

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Main lines of research

- Nutrition, genes and pathologies. Obesity and diabetes.
- Nutrigenomics and personalized nutrition.
- Biomarkers of health.
- Functional foods. Health claims.
- Food security and quality.

Most relevant scientific articles

- Díaz-Rua R., Van Schothorst E.M., Keijer J., Palou A., Oliver P. Isocaloric high-fat feeding directs hepatic metabolism to handling of nutrient imbalance promoting liver fat deposition. International Journal of Obesity. 2016.
- Lauria F., Siani A., Pico C., Ahrens W., Bammann K., De Henauw S. et al. A common variant and the transcript levels of MC4R gene are associated with adiposity in children: The IDEFICS study. Journal of Clinical Endocrinology and Metabolism. 2016;101(11):4229-4236.
- Castro H., Pomar C.A., Palou A., Pico C., Sánchez J. Offspring predisposition to obesity due to maternal-diet-induced obesity in rats is preventable by dietary normalization before mating. Molecular Nutrition and Food Research. 2016.
- Reynes B., Serrano A., Petrov P.D., Ribot J., Chetrit C., Martínez-Puig D. et al. Anti-obesity and insulin-sensitising effects of a glycosaminoglycan mix. Journal of Functional Foods. 2016;26:350-362.
- Cifre M., Díaz-Rua R., Varela-Calvino R., Reynes B., Pericas-Beltran J., Palou A. et al. Human peripheral blood mononuclear cell in vitro system to test the efficacy of food bioactive compounds: Effects of polyunsaturated fatty acids and their relation with BMI. Molecular Nutrition and Food Research. 2016.

Hightlights

During the year 2016, the group headed by Prof. Andreu Palou has participated in different projects and research networks of excellence mainly focused in the identification of predictive biomarkers of obesity and nutrition, and in the effects of food bioactive compounds useful for substantiation of functional claims. As part of the European project I.FAMILY the group has contributed to the identification of obesity biomarkers in children. In the National Plan, the group has initiated the INTERBIOBES project (AGL2015-67019-P) in which interaction between nutrients and food bioactives for prevention of obesity and its complications is being analysed. The group is also involved in three private projects with Alimentómica S.L. (two of them with the direct implication of CIBER), in two national excellence research networks (MARCASALUD and CaRed) and in a COST Action on carotenoid research and applications in agro-food and health (EUROCAROTEN). Moreover, they group has worked in 4 projects from the University of the Balearic Islands aimed to the research on biomarkers useful in obesity and functional food studies, and to the use of bioinformatics tools in the identification of these biomarkers (BIOTHERM, IBIFLEX, MECALI y BIOBIP). During this period, a patent (P201430428) in which the group identifies a nutrigenomic biomarker, in blood, able to predict since early ages predisposition to develop obesity has been accepted; this patent has been deposited in Russia. In addition, during this period two human studies have been initiated, METAHEALTH-test and COLEX-test, aimed to identify biomarkers of clinical interest in blood cells.

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Main lines of research

- Observational study of the effect in clinical practice of anti-PCSK9 monoclonal antibodies.
- Study of number and size of lipoprotein particles by NMR in patients with premature ischaemia.
- Clinical studies about the diagnosis and treatment of lipoprotein metabolism disorders, including the degree of control of dyslipidemia and the related factors.
- Effect of an intensive intervention on lifestyle with an hipocaloric Mediterranean diet, physical activity and behavior therapy for primary prevention of cardiovascular disease in patients with obesity and high cardiovascular risk.
- Influence of diet and changes in body weight on changes in hepatic fat (steatosis) assessed by nuclear magnetic resonance (NMR) and biochemical parameters of liver inflammation (Esteatohepatitis). Assessing the relationship between changes in biomarkers of oxidative stress and inflammation, and changes in hepatic fat content and biochemical signs of hepatitis.
- Study of the relationship between changes in body weight and the variations in the parameters of platelet aggregation.
- Study variants of genes of lipid metabolism that may be related with the etiology of familial and polygenic hypercholesterolemia and severe hypertriglyceridemia.
- Study of the relationship between cardiovascular risk factors of Arterial and Venous Vascular Disease.

- Study the relationship between cardiovascular risk factors, diet and drug treatments on erectile function.
- Relationship between nutritional factors and lifestyle with plasma homocysteine concentrations.

Most relevant scientific articles

- Estruch R., Martínez-González M.A., Corella D., Salas-Salvadó J., Fito M., Chiva-Blanch G. et al. Effect of a high-fat Mediterranean diet on bodyweight and waist circumference: A prespecified secondary outcomes analysis of the PREDIMED randomised controlled trial. The Lancet Diabetes and Endocrinology. 2016.
- Sala-Vila A., Díaz-López A., Valls-Pedret C., Cofan M., García-Layana A., Lamuela-Raventós R.-M. et al. Dietary marine ω-3 fatty acids and incident sight-threatening retinopathy in middle-aged and older individuals with type 2 diabetes: Prospective investigation from the PREDIMED trial. JAMA Ophthalmology. 2016;134(10):1142-1149.
- Sala-Vila A., Guasch-Ferre M., Hu F.B., Sánchez-Tainta A., Bullo M., Serra-Mir M. et al. Dietary α-linolenic acid, marine ω-3 fatty acids, and mortality in a population with high fish consumption: Findings from the PREvención con DIeta MEDiterránea (PREDIMED) Study. Journal of the American Heart Association. 2016;5(1).
- Tresserra-Rimbau A., Guasch-Ferre M., Salas-Salvadó J., Toledo E., Corella D., Castaner O. et al. Intake of total polyphenols and some classes of polyphenols is inversely associated with diabetes in elderly people at high cardiovascular disease risk. Journal of Nutrition. 2016;146(4):767-777.
- Downer M.K., Gea A., Stampfer M., Sánchez-Tainta A., Corella D., Salas-Salvadó J. et al. Predictors of short- and long-term adherence with a Mediterranean-type diet intervention: The PREDIMED randomized trial. International Journal of Behavioral Nutrition and Physical Activity. 2016;13(1).

Hightlights

- Achievement of the recruitment objectives of the PREDIMEDplus Study.
- Guide to high-intensity lipid-lowering therapy in high-risk cardiovascular patients.
- Guide for the diagnosis and treatment of abdominal aortic aneurysm.
- Guide of the Spanish Society of Arteriosclerosis on indications of PCSK9 inhibitors.
- Guide on pharmacological treatment of atherogenic dyslipidemia with statin-fenofibrate combination therapy.
- Guideline on the management of dyslipidemia in patients with impaired glucose metabolism.

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Main lines of research

- Functional foods and obesity.
- Fuctional food and diabetes.
- Mediterranean diet and health.
- Childhood obesity.
- Epigenetic: obesity markers.
- Assessment of dietary habits and nutritional state of population.
- Design and validation of nutritional education programs.
- Assessment of gluten in food. Accredited laboratory.

Most relevant scientific articles

- Arias N., Macarulla M.T., Aguirre L., Milton I., Portillo M.P. The combination of resveratrol and quercetin enhances the individual effects of these molecules on triacylglycerol metabolism in white adipose tissue. European Journal of Nutrition. 2016.
- Arias N., Aguirre L., Fernández-Quintela A., González M., Lasa A., Miranda J. et al. MicroRNAs involved in the browning process of adipocytes. Journal of Physiology and Biochemistry. 2016;1-13.
- Carpene C., Hasnaoui M., Balogh B., Matyus P., Fernández-Quintela A., Rodríguez V. et al. Dietary Phenolic Compounds Interfere with the Fate of Hydrogen Peroxide in Human Adipose Tissue but Do Not Directly Inhibit Primary Amine Oxidase Activity. Oxidative Medicine and Cellular Longevity. 2016;2016.
- Gracia A., Miranda J., Fernández-Quintela A., Eseberri I., García-Lacarte M., Milagro F.I. et al. Involvement of miR-539-5p in the inhibition of de novo lipogenesis induced by resveratrol in white adipose tissue. Food and Function. 2016;7(3):1680-1688.
- Fernández-Quintela A., Carpene C., Fernández M., Aguirre L., Milton-Laskibar I., Contreras J. et al. Anti-obesity effects of resveratrol: comparison between animal models and humans. Journal of Physiology and Biochemistry. 2016;1-13.

Hightlights

During 2016 we have continued working on the Project (AGL2015-65719-R; 2016-2019), supported by the Spanish Government. Moreover, we have two new projects, supported by the Dpt. of Health from the Basque Government: “Obesity, global epidemic: molecular characterization and dynamic parameters for the development of diagnostic and therapeutic estartegies”.
As far as the traslational activities are concerned, we continue implementing a program devoted to promote fruit and vegetable consumption among scholars in Vitoria-Gasteiz, supported by the City Hall. We have written one Guide “Practical Guide for the management of arterial hypertension. Contreras, A. Fernández-Quintela, L. Aguirre, M.P. Portillo. Ed. University of the Basque Country. Bilbao, 2016, ISBN:978-84-9860-282-0, and we have spread a previous Guide “Practical Guide for the management of type 2 diabetes 2” J. Contreras, A. Fernández-Quintela, L. Aguirre, M.P. Portillo. Ed. University of the Basque Country. Bilbao, 2015., ISBN:078-84-9082-280-7, thanks to a contract with Roche Laboratories.
Moreover, two members of our group have participated in the elaboration of the Feeding Plan 2015-2018 for Basque population (Dpt. Health. Basque Government).
Finally, the IP of the group has participated in the elaboration of the “Guide and Position of the International Society of Nutrigenetics/Nutrigenomics on Personalised Nutrition: Part 1 - Fields of Precision Nutrition. Ferguson LR, De Caterina R, Görman U, Allayee H, Kohlmeier M, Prasad C, Choi MS, Curi R, de Luis DA, Gil Á, Kang JX, Martin RL, Milagro FI, Nicoletti CF, Nonino CB, Ordovas JM, Parslow VR, Portillo MP, Santos JL, Serhan CN, Simopoulos AP, Velázquez-Arellano A, Zulet MA, Martinez JA. J Nutrigenet Nutrigenomics. 9:12-27 (2016).

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PROGRAMMES
P6

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Main lines of research

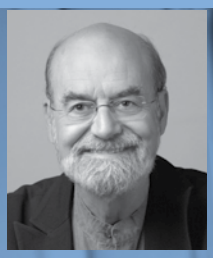
- Role of CPT1 in the development of insulin resistance induced by obesity and type 2 diabetes.
- Role of overexpression of CPT1 in mice in which obesity has been induced by high-fat diet.
- Role of the different CPT1A and CPT1C isoforms in the hypothalamus and its role in the control of ingestion and energy expenditure.
- Action of C75 derivatives as potential anti-obesity drugs and their interaction with CPT1 in vitro, and in vivo in the hypothalamus.
- Role of deficiency in the expression of CBG in lipid metabolism and how this lack of expression is regulated against diets of different caloric content.
- Activity of the urea cycle in adipose tissue: role and meaning. Effect of hyperlipidic diets.
- Metabolism of adipocytes isolated in primary culture. Relationship of its metabolic activity with that of other cell types of the tissue.

Most relevant scientific articles

- Gulfo J., Ledda A., Serra E., Cabot C., Esteve M., Grasa M. Altered lipid partitioning and glucocorticoid availability in CBG-deficient male mice with diet-induced obesity. Obesity. 2016;.
- Calderón-Domínguez M., Sebastián D., Fucho R., Weber M., Mir J.F., García-Casarrubios E. et al. Carnitine palmitoyltransferase 1 increases lipolysis, UCP1 protein expression and mitochondrial activity in brown adipocytes. PLoS ONE. 2016;11(7).
- Arriaran S., Agnelli S., Remesar X., Alemany M., Fernández-López J.A. White adipose tissue urea cycle activity is not affected by one-month treatment with a hyperlipidic diet in female rats. Food and Function. 2016;7(3):1554-1563.
- Casals N., Zammit V., Herrero L., Fado R., Rodríguez-Rodríguez R., Serra D. Carnitine palmitoyltransferase 1C: From cognition to cancer. Progress in Lipid Research. 2016;61:134-148.
- Sabater D., Agnelli S., Arriaran S., Romero M.M., Fernández-López J.A., Alemany M. et al. Cafeteria diet induce changes in blood flow that are more related with heat dissipation than energy accretion. PeerJ. 2016;2016(3).

Hightlights

Role of CPTI in the development of obesity-induced insulin resistance and type 2 diabetes. We study that enhancing fatty acid oxidation in liver, in brown adipose tissue can be new therapies against obesity.
In the study of the effect of overexpression of CPT1 in animal models prone to obesity prevention and treatment of obesity, it has been observed that in mice in which obesity is induced by fat diet and which has the CPT1A overexpressed exhibit a reversal of hyperinsulinemia, hyperglycemia and an almost complete reversal of hepatic steatosis accompanied by a slight decrease in weight of the animals.
We also study the role of CPT1A and CPT1C in the hypothalamus in the control of food intake and energy expenditure.
We study of C75 derivatives as potential drugs against obesity by their interaction with CPT1 at the hypothalamus.
CBG deficiency promotes the redistribution of lipids from the subcutaneous tissue to the visceral tissue in a context in which excess lipids modulate the expression of the 11-beta hydroxy steroid dehydrogenase and hence the activity of the glucocorticoids.
We have described the presence of all the enzymes of the urea cycle in adipose tissue, although there are differences depending on their body location and their response to energy availability. In any case, adipose tissue, although dispersed organ, seems to be subject to uniform control.
The incubation of cells isolated from adipose tissue, in periods of up to 48 hours, has allowed us to determine its high capacity to produce lactate and glycerol. But we have also been able to determine that the active cell volume of the adipocytes (non-fatty) represents only 1.3% of the tissue.



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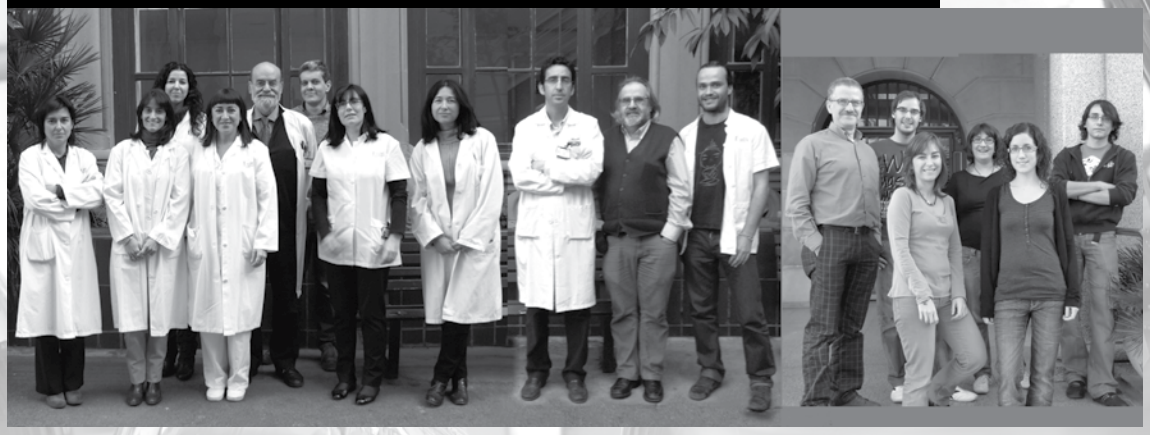
PROGRAMMES
P1



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Main lines of research

- Study of variants in genes of lipid metabolism that might illustrate the etiology of familial and polygenic hypercholesterolemia.
- Carotid ultrasound examination: a) associations between preclinical atherosclerosis and classical and emergent risk factors and dietary biomarkers; b) preclinical atherosclerosis in the pre-diabetic stage.
- Functionality of whole foods and dietary patterns: effects on the serum lipoprotein profile, 24-h ambulatory blood pressure, insulin resistance, markers of cholesterol absorption and synthesis, and dietary biomarkers.
- Specific projects within the PREDIMED study, for which the Group directed the nutritional intervention. Effects of PREDIMED diets on: a) cognitive decline alter intervention for 4 y; b) 5-y incidence of dementia; c) consumption of alpha-linolenic acid and mortality; d) fructose intake and mortality; e) changes in carotid plaque by ultrasound and MRI after intervention for 2 y.
- Randomized controlled trial WAHA (WAlnuts and Healthy Aging): effects of a diet enriched with walnuts (15% of energy) for 2 y in comparison with a control diet on age-related cognitive decline and macular degeneration in 700 older persons. Other outcomes: 2-y changes in brain structure and function by functional MRI, carotid atherosclerosis, body composition, bone mineral density, 24-h ambulatory blood pressure, lipid profile and circulating inflammation markers, telomere length, and miRNAs related to lipid metabolism.
- Cognitive function evaluated by neuropsychological tests and functional brain MRI in familial hypercholesterolemia compared to moderate hypercholesterolemia and normolipidemia.
- Cholesterol absorption and synthesis as assessed by determination of plasma non-cholesterol sterols: quantification, genetic determinants, and effect on cardiovascular risk.

- Associations of fatty acids profiles in total blood, total plasma and phospholipid fractions with cardiometabolic risk factors; carotid preclinical atherosclerosis; composition of "mitochondria-associated membranes" and intracellular signal transduction.
- Investigation of receptors heterodimeric with RXR (PPAR, FXR, LXR, etc.) and other nuclear receptors participating in energy metabolism in liver, adipose, and skeletal muscle tissues and in macrophages.
- Experimental models of metabolic syndrome in fructose-fed rats and rodent models of senescence. Molecular characterization.

Most relevant scientific articles

- Estruch R., Martínez-González M.A., Corella D., Salas-Salvadó J., Fito M., Chiva-Blanch G. et al. Effect of a high-fat Mediterranean diet on bodyweight and waist circumference: A prespecified secondary outcomes analysis of the PREDIMED randomised controlled trial. The Lancet Diabetes and Endocrinology. 2016.
- Sala-Vila A., Díaz-López A., Valls-Pedret C., Cofan M., García-Layana A., Lamuela-Raventós R.-M. et al. Dietary marine ω-3 fatty acids and incident sight-threatening retinopathy in middle-aged and older individuals with type 2 diabetes: Prospective investigation from the PREDIMED trial. JAMA Ophthalmology. 2016;134(10):1142-1149.

Hightlights

PROJECTS

- Title: Effect of daily ingestion of walnuts for 2 years on age-related cognitive decline and macular degeneration in healthy elderly subjects: A randomized, single blind, dual center, controlled trial. WAHA study. PI: Emilio Ros. Funding Agency: California Walnut Commission. Budget: 695.640 euros. Duration 01/JAN/2012 – 31/DEC/2016 (5 years)
- Title: Walnuts as an antiatherogenic food. Clinical and experimental assessment. PI: Aleix Sala Vila. Funding Agency: Instituto de Salud Carlos III. Budget: 110.715 euros. Duration: 01/01/2016 - 31/12/2018 (3 años). Contract number: PI15/01014.
- Title: Cell membrane changes induced by dietary long-chain omega-3 fatty acids and their link to chronic disease development. PI: Aleix Sala Vila. Funding Agency: Instituto de Salud Carlos III (programa Miguel Servet). Budget: 60.000 euros. Duration: 01/06/2013 - 31/12/2017 (4 años y 7 meses). Contract number: CP12/03299.

RESULTS

- The WAlnuts and Healthy Aging (WAHA) study was succesfully completed after follow-up for 2 years of 350 older participants submitted to a walnut dieta or a control diet. Data are being analyzed for publications in 2017.
- The PREDIMED database keeps providing insight into the associations between the Mediterranean diet and various health outcomes. During this year we have analysed the effects of the PRDIMED diets on an important health outcome, incident dementia, and the resulting paper has been submitted.
- The group has continued with the productive line of research of associations of fructose intake with cardiometablic risk.
- The PI has participated in important clinical guidelines (consensus document) of the European Atherosclerosis Society and the European Federation of Clinical Chemistry and Laboratory Medicine, which recommends non fasting for blood lipid analyses and has had a great impact inclinical laboratories worldwide.

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Main lines of research

- Mediterranean diet and cardiovascular disease.
- Public health and epidemiology in relation to nutrition and nutrition related diseases.
- Clinical trials to assess the effect of diet and diet components on health or disease and its mechanisms.
- Evaluation of the relation between obesity, inflammation and co morbidities associated to obesity.
- Effect of the interactions of genetics and nutrition on health.
- Influence of the nutritional status on fertility and the effect on pregnancy on the pregnant and its offspring.
- Metabolic and biochemical biomarkers of diabetes and cardiovascular disease.

Most relevant scientific articles

- Hernández-Alonso P., Salas-Salvadó J., Ruiz-Canela M., Corella D., Estruch R., Fito M. et al. High dietary protein intake is associated with an increased body weight and total death risk. Clinical Nutrition. 2016.
- Becerra-Tomás N., Babio N., Martínez-González M.A., Corella D., Estruch R., Ros E. et al. Replacing red meat and processed red meat for white meat, fish, legumes or eggs is associated with lower risk of incidence of metabolic syndrome. Clinical Nutrition. 2016.
- Guasch-Ferre M., Zheng Y., Ruiz-Canela M., Hruby A., Martínez-González M.A., Clish C.B. et al. Plasma acylcarnitines and risk of cardiovascular disease: Effect of Mediterranean diet interventions. American Journal of Clinical Nutrition. 2016;103(6):1408-1416.
- Guasch-Ferre M., Hruby A., Toledo E., Clish C.B., Martínez-González M.A., Salas-Salvadó J. et al. Metabolomics in prediabetes and diabetes: A systematic review and meta-analysis. Diabetes Care. 2016;39(5):833-846.
- Ferreira-Pego C., Babio N., Bes-Rastrollo M., Corella D., Estruch R., Ros E. et al. Frequent consumption of sugar- and artificially sweetened beverages and natural and bottled fruit juices is associated with an increased risk of metabolic syndrome in a mediterranean population at high cardiovascular disease risk. Journal of Nutrition. 2016;146(8):1528-1536.

Hightlights

PROJECTS AND RESULTS:

- **Predimed-Plus.** Project Coordinators. 460 subjects were recruited, few of them starting the 3rd year of intervention. Samples for the pilot study were searched.
- **CIBER Cohort-projects.** A higher physical activity and lower watching TV time is associated with a better cardiometabolic profile in the PREDIMED-PLUS study subjects (manuscript sent)
- **SATIN.** End of intervention, a great part of metabolomic and biochemical markers were done. We are currently working in to evaluate the effect of intervention on the metabolic profile.
- **Fertinuts.** End of the intervention period and a great part of analytical measurements. A review article was sent for its publication.
- **METADIET study.** Starting the protocol to demonstrate the effect of a nutritional intervention with nuts on changes in gut microbiota and metabolic risk factors.
- **PIE14/0003.** Metabolomic analysis already and statistical analysis already done demonstrating whether changes in the blood lipid composition are associated to the progression of liver disease.
- **ExoRNA Study (Ramón Areces Foundation).** To evaluate in a PREDIMED subcohort, the modulatory effect of the diet on exosomal miRNAs and its relationship with metabolic diseases.
- **Glyndiet.** End of cell membrane fatty acid composition analysis (article already sent). Currently working on the effect of nutritional interventions and changes in body weight on miRNAs at circulating and adipose tissue levels.
- **Novel predictors of coronary heart diseases.** Identification, selection and searcjeng of blood samples in the PREDIMED biobanks. Set uo of methodologies regarding the cell isolation and metabolomic approach for its implementation to the overall study population
- **T2D NIH-project.** Currently working in the analysis of gut microbiota metabolites and its relationship with glucose/insulin metabolism and T2D.

CLINICAL GUIDE AUTHORING:

- Prevention and reduction of mycotoxins throughout the food chain. Catalonia Public Health Agency.
- CODINUCAT Scientific Position on Dairy Consumption and Cancer Incidence. College of Dietitians-Nutritionists of Catalonia.

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PROGRAMMES
P1 | P3 | P4

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Main lines of research

- Assessment of nutritional status in different populations in the context of Public Health Nutrition. Nutritional adequacy methodology in populations and individuals and its repercussions on health.
- Epidemiology and obesity determinants in different populations: children, adolescents and pregnant women.
- Mediterranean diet, chronic diseases and mental disorder. SUN and PREDIMED studies. Effect of an intensive lifestyle intervention with an energy-restricted Mediterranean diet, increased physical activity, and behavioural treatment on the primary prevention of cardiovascular diseases: the PREDIMED-PLUS randomized clinical trial.
- PLANT food supplements: Levels of Intake, Benefit and Risk Assessment: PLANTLIBRA.
- Role of Zinc in neurodevelopment and growth. EURRECA.
- European Network of Excellence developing methodologies to standardise the process of setting micronutrient recommendations. EURRECA NoE.
- Incentives and new technologies in the promotion of Mediterranean Diet and physical activity (Credits4Health).

- Interaction of the genetic load with the metabolism of selected micronutrients and with the load of POPs (Persistent Organic Pollutants), and the development of the obesity and other chronic diseases.
- Body composition estimated by bioelectrical impedance and Mediterranean diet.
- Study of the dietary glycaemic index and dietary glycaemic load in the Mediterranean Diet.
- Quality of life and Mediterranean diet.
- Effect of the Mediterranean diet on the development of pregnancy and intrauterine growth.
- Hydration and health in Europe: validation of questionnaires for beverage intake.

Most relevant scientific articles

- Álvarez-Pérez J., Sánchez-Villegas A., Díaz-Benítez E.M., Ruano-Rodríguez C., Corella D., Martínez-González M.A. et al. Influence of a Mediterranean Dietary Pattern on Body Fat Distribution: Results of the PREDIMED–Canarias Intervention Randomized Trial. Journal of the American College of Nutrition. 2016;:1-13.
- Estruch R., Martínez-González M.A., Corella D., Salas-Salvadó J., Fito M., Chiva-Blanch G. et al. Effect of a high-fat Mediterranean diet on bodyweight and waist circumference: A prespecified secondary outcomes analysis of the PREDIMED randomised controlled trial. The Lancet Diabetes and Endocrinology. 2016.
- Nissensohn M., Sánchez-Villegas A., Ortega R.M., Aranceta-Bartrina J., Gil A., González-Gross M. et al. Beverage consumption habits and association with total water and energy intakes in the Spanish population: Findings of the ANIBES study. Nutrients. 2016;8(4).
- Serra-Majem L. Head and neck cancer: smoking, drinking, eating and…sexual practices. European Journal of Epidemiology. 2016;31(4):333-335.
- Schroder H., Serra-Majem L., Subirana I., Izquierdo-Pulido M., Fito M., Elosua R. Association of increased monetary cost of dietary intake, diet quality and weight management in Spanish adults. British Journal of Nutrition. 2016;115(5):817-822.

Hightlights

Recruitment and follow up of 269 patients from the PREDIMED PLUS study at the Canarian Health Service Centers of Guía and San José. Follow up of 59 patients after 16 months of the bariatric surgery in a study of neurocognition, microbiota and environmental endocrine disruptors.
Coordination of a Consensus Expert Meeting on Food, Community Nutrition and Sustainability, 7-9 April 2016 in Las Palmas de Gran Canaria. As a result, the Declaration of Gran Canaria 2016: a Decalogue for a Sustainable Nutrition in the Community was drawn, with the edition of a video in English and Spanish (https://youtu.be/_91m8N85cBk)
Direction of the 1st World Conference on the Mediterranean Diet. 6-8 July 2016, in Milano Italy. http://www.ifmed.org/the-foundation with a special session on PREDIMED-CIBER OBN. Coordination and Launching of the Call for Action for the Revitalization of the Mediterranean Diet under the auspices of CIHEAM and FAO, and the support of more than 40 international organizations.
Four Clinical Guides and Consensus were published:

- Coordination of the Healthy Kids Network Report 2016: Physical Activity among children and adolescents in Spain.
- Coordination de Dietary Guidelines for the Spanish population SENC 2016, The new Food pyramid for a healthy eating.
- Coordination of the Decalogue for a Food Sustainability in the Community: Declaration of Gran Canaria.
- ESPGHAN 2012 Guidelines for Celiac Disease Diagnosis.

Member of the Expert Group of Nutrition and Food Systems of the High-Level Panel of Experts (HPLE) of the Food and Agricultural Organization (FAO).
Coordination and edition of the Special Issue Beverage Consumption Habits around the World: Association with Total Water and Energy Intakes in Nutrients with a total 0f 25 articles on the subject.

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Main lines of research

Our group implements integral analyses of various aspects of the pathophysiology of obesity and its complications, by the use of state-of-the-art techniques and cellular and animal models, as well as human samples. Our major research lines are:

- **Adipobiology.** We conduct proteomic analyses directed to the identification of novel molecular targets that are altered in the adipose tissue in obesity, with special interest in the characterization of the differential proteomic profile of the various fat depots and their different components (mature adipocytes vs. stromal-vascular fraction). These studies aim also at the identification of novel molecular markers of adipocyte differentiation and insulin resistance.
- **Adipose hormone signaling.** We aim to characterize the receptors and signaling cascades of key adipokines, with special attention to the characterization of the receptors and intracellular signaling of adiponectin.
- **Neuroendocrinology of metabolic alterations.** We aim to characterize the endocrine and metabolic alterations of suitable preclinical models of deregulated energy balance, with special attention to the analysis of the contribution of somatostatin/cortistatin, ghrelin, GH/IGF-1, insulin, their receptors and related molecules, involved in the neuro-hormonal mechanisms responsible for the control of food intake, glucose homeostasis and metabolism.

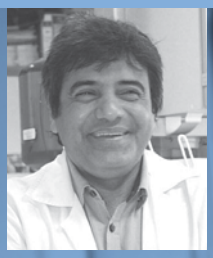
- **Puberty, reproduction and obesity.** We aim to characterize the alterations of puberty and reproductive function in conditions of energy imbalance, with special attention to the impact of obesity on puberty onset, gonadotropic function and fertility. Our interest is also covering the pathophysiology of early onset obesity and its link with pubertal disorders, addressed by the use of suitable preclinical models.
- **Gonadal factors and obesity.** We study the metabolic alterations associated to gonadal and reproductive dysfunction, with special attention to the analysis of the influence of nutritional and gonadal factors in the generation of obesity, as studies by the use of preclinical models of sequential obesogenic insults.
- **Obesity and cancer.** We aim to evaluate the alterations induced by obesity in the generation and progression of hormone-dependent cancers, such as breast, ovarian and prostate cancers, using both human samples and suitable animal models, with special attention to the analysis of neuroendocrine metabolic and inflammatory markers.

Most relevant scientific articles

- Manfredi-Lozano M., Roa J., Ruiz-Pino F., Piet R., García-Galiano D., Pineda R. et al. Defining a novel leptin–melanocortin–kisspeptin pathway involved in the metabolic control of puberty. Molecular Metabolism. 2016;5(10):844-857.
- Castellano J.M., Tena-Sempere M. Metabolic control of female puberty: potential therapeutic targets. Expert Opinion on Therapeutic Targets. 2016;20(10):1181-1193.
- Moreno-Castellanos N., Rodríguez A., Rabanal-Ruiz Y., Fernández-Vega A., López-Miranda J., Vázquez-Martínez R. et al. The cytoskeletal protein septin 11 is associated with human obesity and is involved in adipocyte lipid storage and metabolism. Diabetologia. 2016;1-12.
- Luque R.M., Córdoba-Chacón J., Pozo-Salas A.I., Porteiro B., De Lecea L., Nogueiras R. et al. Obesity- and gender-dependent role of endogenous somatostatin and cortistatin in the regulation of endocrine and metabolic homeostasis in mice. Scientific Reports. 2016;6.
- Córdoba-Chacón J., Gahete M.D., Pozo-Salas A.I., De Lecea L., Castano J.P., Luque R.M. Cortistatin is a key factor regulating the sex-dependent response of the GH and stress axes to fasting in mice. Endocrinology. 2016;157(7):2810-2823.

Hightlights

The scientific activities of the group have continued and expanded ongoing research lines focusing on topics of some of the major Scientific Programs of CIBEROBN, including prominently adipocyte biology, obesity-cancer interactions, early onset obesity and pubertal alterations, as well as pathophysiological mechanisms for the control of body weight and related body functions (e.g., reproduction), as well as their potential alterations. In this context, during 2016 the group has made important contributions towards (i) the elucidation of the mechanism of the metabolic control of puberty, which will help to explain the basis for pubertal alterations associated to obesity and other metabolic disorders (see highlighted articles 1 and 2), (ii) the characterization of the molecular basis for the connection between obesity, metabolic signals and cancer (with different papers being published in prestigious journals, such as Scientific Reports, Oncotarget and Oncogene), (iii) the understanding of fundamental aspects of adipocyte biology, and its alteration in conditions of metabolic distress, such as obesity and insulin resistance, as well as adipose responses to interventions (e.g., bariatric surgery; see highlighted article 3); and (iv) the evaluation of the multi-faceted mechanisms whereby metabolic signals participate in the integral control of body weight, metabolism and related body functions (with different publications in reference journals, such as Endocrinology, Scientific Reports and Molecular Cellular Endocrinology; for a representative example see highlighted articles 4 and 5). In addition, the group has kept active collaborations with other CIBEROBN teams, which have materialized in numerous joint publications during 2016, including invited authoritative reviews (e.g., in Nature Reviews in Endocrinology) and original articles. Finally, our group was invited to write a commemorative article on the occasion of the centennial of the prestigious journal Endocrinology, on the topic of hormones and obesity.



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Main lines of research

- **Obesity and related diseases.** Our group is studying the relationship between obesity and its related metabolic diseases. We try to elucidate the mechanisms that protect some particular obese individuals who do not develop metabolic diseases or do it lately. Within these related diseases, we are focused on diabetes, postprandial lipidemia and cancer.
- **Adipose tissue biology.** Our group is studying the expansion capacity of the adipose tissue and its relationship with insulin resistance. Thus, we are studying the neogenic capacity of the mesenchymal cells from adipose tissue, the necrosis predisposition, autophagy and apoptosis as well as the pro-fibrotic capacity of the tissue, relating these factors to metabolic pathologies. Moreover, the group is studying lipogenic and angiogenic capacities of the different factors that modulate the expansion capacity of the adipose tissue and its relationship with the metabolic diseases.
- **Study of the gut microbiota and related diseases.** We are studying the bacterial profiles of the gut microflora within different pathologic situations in order to establish its role in their origins and developments. Moreover, we are also studying the microbiota changes that interventions with polyphenols cause and the changes produced by the radiotherapy in oncologic patients.

- **Study of the epigenetic profiles according to their relationships with obesity-diabetes and cancer-obesity.** We are studying the epigenetic modifications of the genes implicated in the molecular mechanisms of expression repression and of the transcription factors implicated in obesity and insulin resistance, associated to the development of tumors in humans.
- **PREDIMED+ Study.** In this line, we are focused on the study of a Mediterranean diet intervention with olive oil and nuts (pistachios and almonds), in order to prevent the cardiovascular disease in overweight/obese metabolic syndrome patients.

Most relevant scientific articles

- Moreno-Indias I., Sánchez-Alcoholado L., Sánchez-Garrido M.A., Martín-Nunez G.M., Pérez-Jiménez F., Tena-Sempere M. et al. Neonatal androgen exposure causes persistent gut microbiota dysbiosis related to metabolic disease in adult female rats. Endocrinology. 2016;157(12):4888-4898.
- Rosenstock J., Guerci B., Hanefeld M., Gentile S., Aronson R., Tinahones F.J. et al. Prandial options to advance basal insulin glargine therapy: Testing lixisenatide plus basal insulin versus insulin glulisine either as basal-plus or basal-bolus in type 2 diabetes: The GetGoal Duo-2 Trial. Diabetes Care. 2016;39(8):1318-1328.
- El Bekay R., Coin-Araguez L., Fernández-García D., Oliva-Olivera W., Bernal-López R., Clemente-Postigo M. et al. Effects of glucagon-like peptide-1 on the differentiation and metabolism of human adipocytes. British Journal of Pharmacology. 2016;173(11):1820-1834.
- Moreno-Indias I., Oliva-Olivera W., Omiste A., Castellano-Castillo D., Lhamyani S., Camargo A. et al. Adipose tissue infiltration in normal-weight subjects and its impact on metabolic function. Translational Research. 2016;172:6-17.
- 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.

Hightlights

PATENTS: As result of the microbiota and metabolic disease research lines, two patents have been generated with the aim of the clinical use of probiotics. Currently, they are in internationalization phase and there are some companies interested in them. The collaborative research line with Dr. Casanueva has also generated a new patent in order to protect the finding of new biomarkers for colon cancer diagnosis and prognostic in obese patients.

TRANSLATION: The node participates in a number of clinical trials and it has been published four articles in high-impact journals in 2016 that has been authored by some researchers of our node. The results of some of these clinical trials will change the clinical practice in patients with obesity and diabetes.

COLLABORATIONS AND SYNERGY: Our node organizes every year networking meetings with other groups of the CIBERDEM and guest European researchers. The fourth meeting has taken place in 2017. As result of these interactions the number of collaborative works with groups form the CIBERdem has been increased, and among them it worth mentioning the article published in the Journal Clinical Investigation.

METAGENOMIC PLATFORM START-UP: This platform has been launched in 2016. In the last three months, more than 400 analyses have been done with samples from projects of this node, interCIBER and intraCIBEROBN.

NODE CRITICAL MASS INCORPORATION IN 2016: Two contracts from the Juan de la Cierva program and one contract from Sara Borrel program has been obtained in 2016. In addition, a new Miguel Servet contract has been incorporated in the node.

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Main lines of research

- Characterization and monitoring of the dietary pattern of the population, the prevalence of obesity and its comorbidities.
- Longitudinal intervention study of the effect of an intensive lifestyle intervention by adopting a healthy lifestyle based on an energy-restricted Mediterranean diet, promoting physical activity and behavioral support on the prevention of cardiovascular diseases (PREDIMED PLUS study).
- Evaluation of the effect of physical activity on health and quality of life.
- Search of strategies to enhance antioxidant defenses.
- Functional food and sports performance.

Most relevant scientific articles

- Ripoll-Vera T., Gámez J.M., Govea N., Gómez Y., Nunez J., Socias L. et al. Clinical and Prognostic Profiles of Cardiomyopathies Caused by Mutations in the Troponin T Gene. Revista Espanola de Cardiología. 2016;69(2):149-158.
- Sureda A., Bibiloni M.D.M., Martorell M., Buil-Cosiales P., Martí A., Pons A. et al. Mediterranean diets supplemented with virgin olive oil and nuts enhance plasmatic antioxidant capabilities and decrease xanthine oxidase activity in people with metabolic syndrome: The PREDIMED study. Molecular Nutrition and Food Research. 2016;60(12):2654-2664.
- Busquets-Cortes C., Capo X., Martorell M., Tur J.A., Sureda A., Pons A. Training Enhances Immune Cells Mitochondrial Biosynthesis, Fission, Fusion, and Their Antioxidant Capabilities Synergistically with Dietary Docosahexaenoic Supplementation. Oxidative Medicine and Cellular Longevity. 2016;2016.
- Del Mar Bibiloni M., Ozen A.E., Pons A., González-Gross M., Tur J.A. Physical activity and beverage consumption among adolescents. Nutrients. 2016;8(7).
- Capo X., Martorell M., Sureda A., Riera J., Drobnic F., Tur J.A. et al. Effects of almond- and olive oil-based docosahexaenoic- and vitamin E-enriched beverage dietary supplementation on inflammation associated to exercise and age. Nutrients. 2016;8(10).

Hightlights

In the framework of the research project PI11/01791, completed in 2015, we have analysed the impact of physical activity and sedentarism on hydration status and fluid intake in Spanish older adults, and as well the independent association between body composition and lipid profile and on the serum 25-hydroxyvitamin D (25(OH)D) status. In the framework of the research project PI14/00636 (PREDIMED+DM), which assesses the effect of an intensive lifestyle intervention by adopting a healthy lifestyle based on an energy-restricted Mediterranean diet, promoting physical activity and behavioral support on the prevention of cardiovascular diseases (PREDIMED PLUS study), we overcome the marked objective and recruiting 270 participants, which are being followed intensely as planned. In collaboration with the Autonomous University of Nuevo León (Mexico), the prevalence of dyslipidemia and components in adolescents aged 11-16 years in Northern Mexico was assessed. In the framework of the NutriOx European network, the COST Association awarded our research project OC-2016-1-20695, entitled "Personalized Nutrition in aging society: redox control of major age-related diseases". The Board of the Fundació La Marató of TV3 funded our research project 549/U/2016, entitled "Prevention and reversion of non-alcoholic fatty liver disease (NAFLD) among obese patients by means of customized nutritional and physical activity intervention". In January 2016, we have started with the patent application of a product with anti-inflammatory properties. Our scientific activity received 4 awards in 2016. Finally, Dr. Tur, member of the Scientific Committee of the Spanish Agency of Consumption, Food Safety and Nutrition (AECOSAN), participated in 4 technical reports in 2016.

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Main lines of research

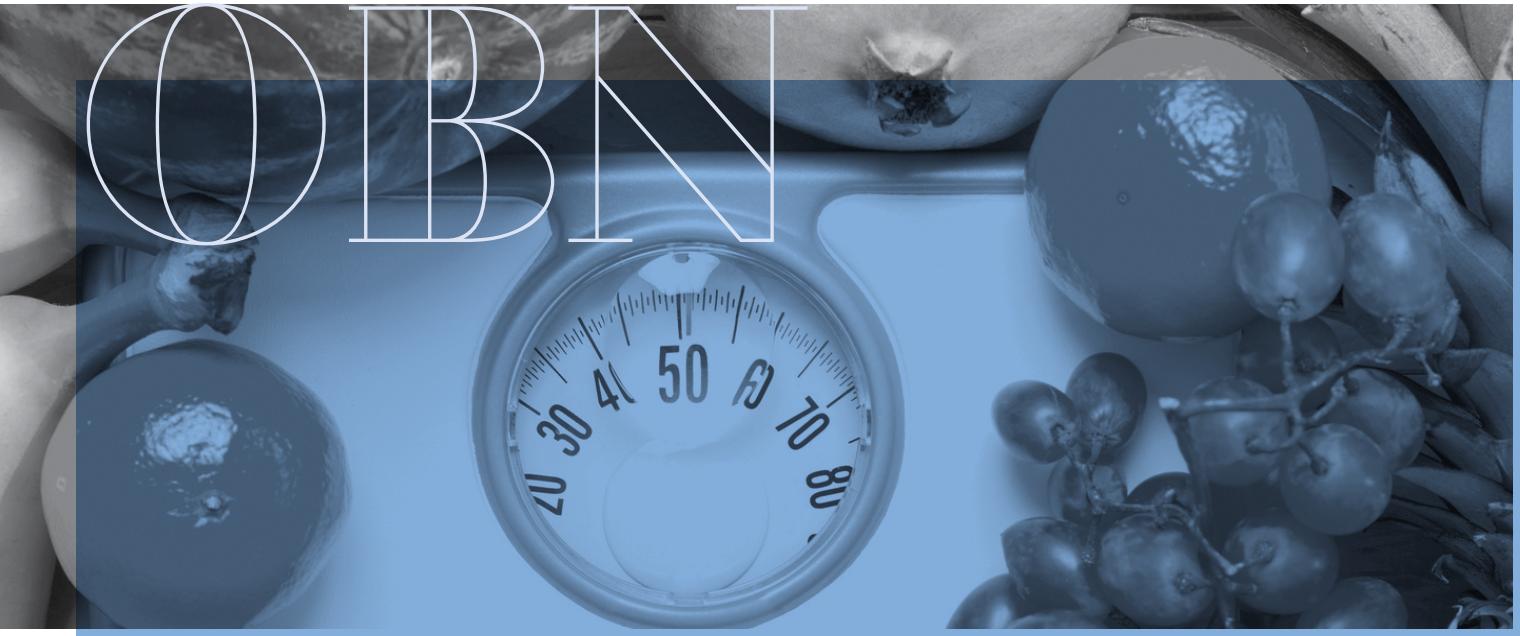
Our research group specializes in the study of the molecular and physiological basis that controls energy metabolism, and how this relates to human pathologies. We study the molecular mechanisms of adipocyte gene control, muscle and hepatic differentiation in relation to metabolism as well as fat functionality. Also, new metabolic and endocrine functions of cells, tissues and organs, and its control by hormones and nutrients are characterized. This involves the development of models at the sub-cellular, cellular and animal levels, and the study of biological material from patients with obesity and other metabolic diseases.

Most relevant scientific articles

- Quesada-López T., Cereijo R., Turatsinze J.-V., Planavila A., Cairo M., Gavalda-Navarro A. et al. The lipid sensor GPR120 promotes brown fat activation and FGF21 release from adipocytes. Nature Communications. 2016;7.
- Gavalda-Navarro A., Moreno-Navarrete J.M., Quesada-López T., Cairo M., Giralt M., Fernández-Real J.M. et al. Lipopolysaccharide-binding protein is a negative regulator of adipose tissue browning in mice and humans. Diabetologia. 2016;:1-11.
- Moure R., Domingo P., Gallego-Escuredo J.M., Villarroya J., Gutiérrez M.D.M., Mateo M.G. et al. Impact of elvitegravir on human adipocytes: Alterations in differentiation, gene expression and release of adipokines and cytokines. Antiviral Research. 2016;132:59-65.
- Villarroya F., Cereijo R., Villarroya J., Giralt M.. Brown adipose tissue as a secretory organ. Nature Reviews Endocrinology. 2016.
- Redondo-Angulo I, Mas-Stachurska A, Sitges M, Giralt M, Villarroya F, Planavila A. C/EBPβ is required in pregnancy-induced cardiac hypertrophy.International journal of cardiology. 2016;202:819-28.

Hightlights

In 2016, several researchers from the group have achieved funding of relevant competitive projects. The project '' Identification of molecular mediators of signaling from intestine to insulin sensitization and adipose tissue browning: role of LBP and FGF15 / 19'', coordinated by M. Giralt, researcher of our group, in collaboration with JM Moreno-Navarrete from JM Fernández-Real group, was one of the awarded projects in the call for obesity and diabetes of the TV3 Marathon. Also, A. Planavila, Ramón y Cajal researcher of the group, obtained the project "Meteorin-like, a new cardiomyoquine for the detection and treatment of heart disease "awarded by the Spanish Society of Cardiology. Within the scope of contracts with the private sector, two new projects have been developed with Lucta based on studies of metabolism and nutrition in porcine species. The group has carried out activities to disseminate relevant results, including the coordination by F. Villarroya of the special issue of the SEBBM journal of December 2016 on obesity research, with the participation of other CIBEROBN and international groups. Although awarded at the end of 2015, during 2016 the group has coordinated the activities of the MINECO Thematic Network of excellence "Adipose plasticity and associated pathologies" ("Adipoplast") in which national groups of several CIBER and other specialized institutions participate in studies of adipobiology.



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Centro de Investigación Biomédica en Red
Fisiopatología de la Obesidad y Nutrición

MINISTERIO DE ECONOMÍA, INDUSTRIA Y COMPETITIVIDAD

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