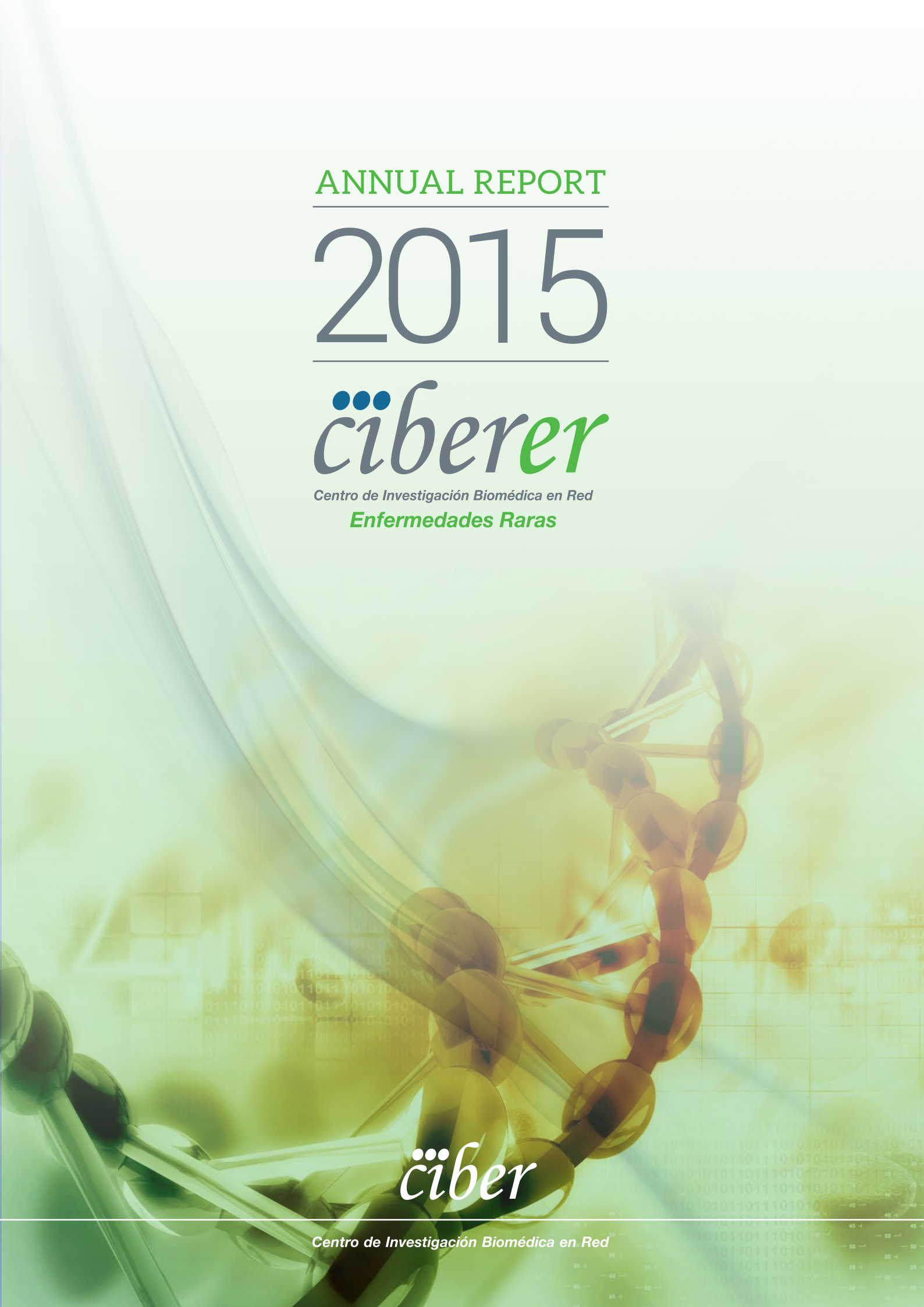
ANNUAL REPORT

2015

ciberer

Centro de Investigación Biomédica en Red

Enfermedades Raras



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Centro de Investigación Biomédica en Red

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Scientific Director's Presentation

2015 was a year of hard work, going on with the main strategic measures which were specified in the Action Plan. We continued to consolidate our endeavours as a national and international benchmark in research into rare diseases (RD). All this is done through cooperation of the different organisations in the consortium and research groups forming the CIBERER, but also thanks to the committed work of national and international policies in the field of infrequently found diseases.

With this in mind, there are a number of tools that we continue to consider essential for our network activity in RD to be effective and to respond to the mission that we have been entrusted with, which is innovation and cooperation on all levels.

Innovation is a fundamental aim of our translational research. That is why our work takes a comprehensive approach ranging from diagnostic developments and new therapies to healthcare organisational models. We could stress the application for three European patents for new therapeutic developments in RD and obtaining the designation of orphan drugs by the European Medicines Agency for bazedoxifene acetate, indicated for Hereditary Haemorrhagic Telangiectasia (HHT), led by Carmelo Bernabeu (U707). As far as diagnosis is concerned, Federico Pallardó's group (U733) has patented a new diagnostic method for idiopathic scoliosis. A large number of tools have been developed for new generation diagnosis and thanks to our ENoD programme (Undiagnosed Rare Diseases) and the BIER platform, the implication of new genes in many minority disorders has been discovered.

As regards cooperative networking I would like to stress several achievements. First of all, CIBERER's participation in the Joint Action on Rare Diseases (RD Action) financed by the European Commission, as a basic instrument for implementing information processing with the Orphanet and Community policies on RD. The second is the culmination of the TREAT-CMT project, made up of a multidisciplinary team of twelve groups and financed by the ISCIII in the framework of the IRDiRC. As regards scientific findings we should highlight the implication of the MORC2 gene in Charcot-Maire-Tooth neuropathy led by the groups of Juan Vílchez (U763) and Francesc Palau (U732). Thirdly, our commitment to our own projects such as the eleven new Cooperative and Complementary Intramural Actions (ACCI) and the two translational research projects led by our linked clinical groups, reinforcing our orientation towards providing solutions that are useful in clinical practice.

I would lastly like to highlight the fact that two new groups which are doubtlessly going to bolster our leadership in RD over the coming years have joined our network. These are the group led by Josep Dalmau of the IDIBAPS in Barcelona, focussing on the identification and description of autoimmune processes of the nervous system, and the group led by Vicente Vicente from the Instituto Murciano de Investigación Biosanitaria, a reference in the typification and characterisation of RD such as thrombopathies and inherited thrombophilia.

Francesc Palau,
Scientific Director of CIBERER.

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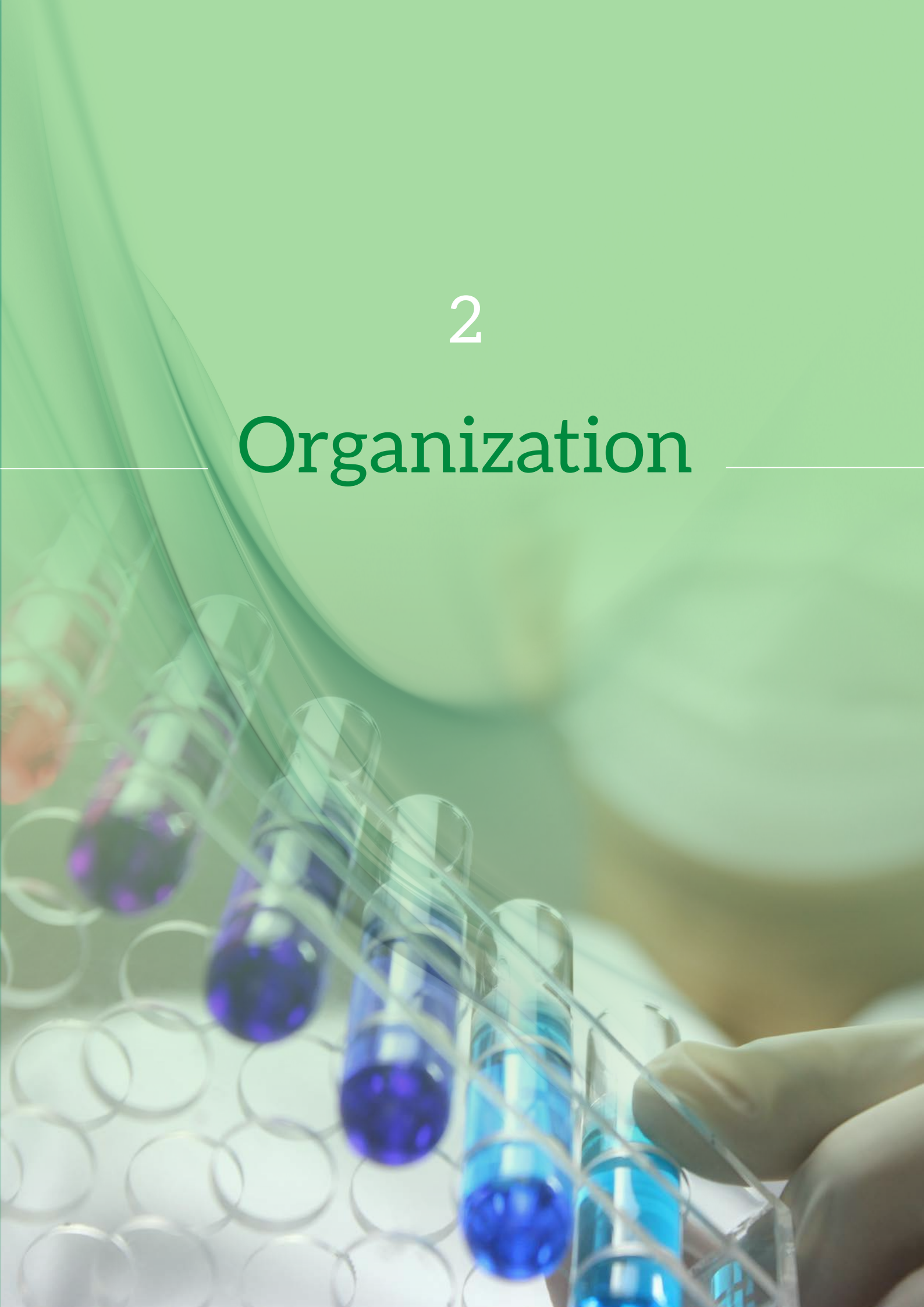
Organization



Organisational Structure

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

The Rare Disease area is made up of 60 research groups, keeping its independence as regards scientific management. Its organisational structure is based on the research groups belonging to this and its activity revolves around the Research Programmes and Transversal Programmes, with a coordinator for each Programme belonging to the Steering Committee. Scientific decisions are made by the Scientific Director, advised by said Steering Committee and the External Scientific Committee.

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

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

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

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

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

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

Members of the Steering Advisory Committee of CIBERER

NAME	POST HELD
Francesc Palau	Scientific Director
José María Millán	Assistant Scientific Director
Guillermo Antiñolo	Genetic Medicine
Antonia Ribes	Inherited Metabolic Medicine
Miguel A. Martín	Mitochondrial and Neuromuscular Medicine
Pablo Lapunzina	Paediatric and Developmental Medicine
Carmen Ayuso	Sensorineural Pathology
Susan Webb	Endocrine Medicine
Jordi Suralés	Inherited Cancer, Haematological and Dermatological Diseases
Luis Pérez Jurado	Training Programme
Manuel Sánchez	Managing Director

Scientific Director Assistant: Ingrid Mendes.

CIBERER External Advisory Scientific Committee

NAME	INSTITUTION
Josep Torent Farnel	Fundació Dr. Robert, Universitat Autònoma de Barcelona
Ségolène Aymé	Instiut de la Santé et Recherche Médicale, Paris
Jean-Jacques Casiman	Catholic University of Leuven, Bélgica
Jean-Marie Saudubray	Hôpital Pité-Salpêtrière, Paris
Mª Rita Passos-Bueno	Centro de Estudos do Genoma Humano, São Paulo

Scientific Management

Beatriz Gómez	Programmes Manager
Monica Bescós	Programmes Manager
Juan Luque	Programmes Manager
Andrés Medrano	Head of Training and Programmes Manager

Technical Unit

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

Directory of groups and institutions

Group leader	Institution	Centre	Province
Martí Seves, Ramón	Fundación Hospital Universitario Vall d'Hebron - Institut de Recerca (VHIR)	Hospital Vall d'Hebron	BARCELONA
Antiñolo, Guillermo	Fund. Púb. Andaluza para la Gestión de la Investigación en Salud de Sevilla	Hospital Virgen del Rocío	SEVILLA
Artuch Iriberri, Rafael	Fundación para la Investigación y Docencia Sant Joan de Déu	Hospital Sant Joan de Deu	BARCELONA
Ayuso, Carmen	Instituto de Investigación Sanitaria Fundación Jiménez Díaz	Hospital Fundación Jiménez Díaz	MADRID
Baiget Bastús, Montserrat	Instituto de Investigación del Hospital de la Santa Cruz y San Pablo	Hospital de la Santa Creu i Sant Pau	BARCELONA
Benítez, Javier	Fundación Centro Nacional de Investigaciones Oncológicas	Fundación Centro Nacional de Investigaciones Oncológicas	MADRID
Bernabéu, Carmelo	Agencia Estatal Consejo Superior de Investigaciones Científicas	Centro de Investigaciones Biológicas	MADRID
Bernal, Juan	Agencia Estatal Consejo Superior de Investigaciones Científicas	Instituto de Investigaciones Biomédicas Alberto Sols	MADRID
Bovolenta, Paola	Agencia Estatal Consejo Superior de Investigaciones Científicas	Centro de Biología Molecular Severo Ochoa	MADRID
Bueren, Juan Antonio	Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas	Centro de Investigaciones Energeticas, Medioambientales y Tecnológicas	MADRID
Carracedo, Ángel	Universidad de Santiago de Compostela	Facultad de Medicina	A CORUÑA
Carrascosa, Antonio	Fundación Hospital Universitario Vall d'Hebron - Institut de Recerca (VHIR)	Hospital Vall d'Hebron	BARCELONA
Cuezva, José Manuel	Universidad Autónoma de Madrid	Centro de Biología Molecular Severo Ochoa	MADRID
Del Río Nechaevsky, Marcela	Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas	Centro de Investigaciones Energeticas, Medioambientales y Tecnológicas	MADRID
Dopazo Blázquez, Joaquín	Fundación Centro de Investigación Príncipe Felipe	Centro de Investigación Principe Felipe	VALENCIA
Fillat, Cristina	Instituto de Investigaciones Biomédicas August Pi i Sunyer	Instituto de Investigaciones Biomédicas August Pi I Sunyer	BARCELONA
Garesse, Rafael	Universidad Autónoma de Madrid	Universidad Autónoma de Madrid	MADRID
González Duarte, Roser	Universitat de Barcelona	Facultad de Biología. Universitat de Barcelona	BARCELONA
Gratacós, Eduard	Hospital Clínic de Barcelona	Instituto de Investigaciones Biomédicas August Pi I Sunyer	BARCELONA
Grinberg, Daniel	Universitat de Barcelona	Facultad de Biología	BARCELONA
Knecht, Erwin	Fundación Centro de Investigación Príncipe Felipe	Centro de Investigación Príncipe Felipe	VALENCIA
Cardellach López, Francesc	Hospital Clínic de Barcelona	Hospital Clínic de Barcelona	BARCELONA
Martín Casanueva, Miguel Ángel	Servicio Madrileño de Salud	Hospital 12 de Octubre	MADRID
Martínez Frías, Mª Luisa	Asociación Española para el Registro y Estudio de las Malformaciones Congénitas (ASEREMAC)	Centro de Investigación Sobre Anomalias Congenitas	MADRID
Castaño González, Luis	Asociación Instituto de Investigación Sanitaria de Biocruces	Hospital Cruces	VIZCAYA
Milá, Montserrat	Hospital Clínico y Provincial Barcelona	Hospital Clínico y Provincial Barcelona	BARCELONA
Montoya Villarroya, Julio	Universidad de Zaragoza	Facultad de Veterinaria	ZARAGOZA
Moreno Pelayo, Miguel Á.	Servicio Madrileño de Salud	Hospital Ramon y Cajal	MADRID

Group leader	Institution	Centre	Province
Navas, Plácido	Universidad Pablo de Olavide	Centro Andaluz de Biología Molecular y Medicina Regenerativa	SEVILLA
Nunes, Virginia	Fundación IDIBELL	Hospital Duran y Reynals	BARCELONA
Palacín, Manuel	Fundación privada Instituto de Recerca Biomédica (IRB-Barcelona)	Fundación Privada Instituto de Recerca Biomédica (IRB Barcelona)	BARCELONA
Palau Martínez, Francesc	Fundación para la Investigación y Docencia Sant Joan de Deu	Hospital Sant Joan de Deu	BARCELONA
Pallardó Calatayud, Federico	Universidad de Valencia	Facultad de Medicina de Valencia	VALENCIA
González Manchón, Consuelo	Agencia Estatal Consejo Superior de Investigaciones Científicas	Centro de Investigaciones Biológicas	MADRID
Pérez Jurado, Luis	Universidad Pompeu Fabra	Facultad de Ciencias Experimentales y de la Salud	BARCELONA
Ribes, Antonia	Hospital Clínic de Barcelona	Instituto de Bioquímica Clinica	BARCELONA
Rodríguez de Córdoba, Santiago	Agencia Estatal Consejo Superior de Investigaciones Científicas	Centro de Investigaciones Biológicas	MADRID
Rubio Zamora, Vicente	Agencia Estatal Consejo Superior de Investigaciones Científicas	Instituto de Biomedicina de Valencia	VALENCIA
Salido, Eduardo	Fundación Canaria de Investigación Sanitaria (FUNCANIS)	Hospital de Canarias	SANTA CRUZ DE TENERIFE
Sánchez Jiménez, Francisca	Universidad de Málaga	Facultad de Ciencias	MALAGA
Sanz, Pascual	Agencia Estatal Consejo Superior de Investigaciones Científicas	Inst. de Biomedicina de Valencia	VALENCIA
Satrústegui Gil Delgado, Jorgina	Universidad Autónoma de Madrid	Centro de Biología Molecular Severo Ochoa	MADRID
Serratosa, José	Instituto de Investigación Sanitaria Fundación Jiménez Díaz	Hospital Fundación Jiménez Díaz	MADRID
Surrallés, Jordi	Universidad Autónoma de Barcelona	Facultad de Biociencias	BARCELONA
Pérez González, Mª Belén	Universidad Autónoma de Madrid	Centro de Biología Molecular Severo Ochoa	MADRID
Webb, Susan	Instituto de Investigación del Hospital de la Santa Creu i Sant Pau	Hospital de la Santa Creu i Sant Pau	BARCELONA
Fernández Piqueras, José	Universidad Autónoma de Madrid	Centro de Biología Molecular Severo Ochoa	MADRID
Estévez Povedano, Raúl	Universitat de Barcelona	Facultad de Medicina	BARCELONA
Giraldo Castellano, Pilar	Instituto Aragonés de Ciencias de la Salud	Hospital Miguel Servet	ZARAGOZA
Lapunzina Badía, Pablo Daniel	Servicio Madrileño de Salud	Hospital La Paz	MADRID
López Trascasa, Margarita	Servicio Madrileño de Salud	Hospital La Paz	MADRID
Millán Salvador, José María	Fundación para la Investigación del Hospital la Fe	Hospital de La Fe	VALENCIA
Montoliú José, Lluis	Agencia Estatal Consejo Superior de Investigaciones Científicas	Centro Nacional de Biotecnología	MADRID
Perona Abellón, Rosario	Agencia Estatal Consejo Superior de Investigaciones Científicas	Instituto de Investigaciones Biomédicas Alberto Sols	MADRID
Posada de la Paz, Manuel	Instituto de Salud Carlos III	Instituto de Investigación en Enfermedades Raras	MADRID
Pujol Onofre, Aurora	Fundación IDIBELL	Hospital Duran y Reynals	BARCELONA
Ruiz Pérez, Víctor Luis	Agencia Estatal Consejo Superior de Investigaciones Científicas	Instituto de Investigaciones Biomédicas Alberto Sols	MADRID
Varela Nieto, Isabel	Agencia Estatal Consejo Superior de Investigaciones Científicas	Instituto de Investigaciones Biomédicas Alberto Sols	MADRID
Illa Sendra, Isabel	Instituto de Investigación del Hospital de la Santa Creu i Sant Pau	Hospital de la Santa Creu i Sant Pau	BARCELONA
Vílchez Padilla, Juan Jesús	Fundación para la Investigación del Hospital la Fe	Hospital de La Fe	VALENCIA

Budget

INCOME	7.712.043,68
NOMINAL ISCIII GRANT	4.785.860,00
INCOME FROM NEW GROUPS	120.000,00
AGREEMENTS AND CONTRACTS	478.412,25
OWN FUNDS	2.327.771,43

EXPENDITURE	6.091.722,71
GROUPS	3.332.325,72
RESEARCH PROGRAMMES	892.384,20
TRAINING	128.548,26
TECHNICAL OFFICE	220.000,00
SCIENTIFIC MANAGEMENT AND MANAGEMENT COMMITTEE	50.141,46
COORDINATION AND DISSEMINATION	99.318,77
DRAFT AGREEMENT FEES	69.582,22
SCIENTIFIC CONFERENCE	53.623,68
EPIDISEASE	4.328,18
PLATFORMS	269.506,30
COMPETITIVE PROJECTS	971.963,92

Personnel

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

Category	Permanent	Temporary	Works & service	Post-doctoral	Main Total
Diploma holder	1				1
Doctor	52	1	7	11	71
Graduate	18	1	17		36
Technical	16		3		19
TOTAL	**87**	**2**	**27**	**11**	**127**

Significant Activities

Projects

The projects active in 2015 were as follows:

NATIONAL PROJECTS

Financing Agency: Instituto de Salud Carlos III:

- Genetics and Disease Mechanisms in inherited peripheral neuropathies.
- Mitochondrial alterations in cell models of Parkinson's disease (LRRK2 and Parkin): Therapeutic potential of modulators of the mitochondrial function.
- Translational Research Experimental Medicine and Therapeutics on Charcot-Marie-Tooth. Translational Research and disease mechanisms in inherited peripheral neuropathies.
- Study of the channels involved in autism spectrum disorders: functional consequences of genetic and epigenetic variants.
- Progress made in McArdle's disease: New therapeutic approaches and development of a new non-invasive diagnostic model in patients.

Financing Agency: Ministry of the Economy and Competitiveness:

- Platform for supporting internationalisation of the CIBER-BBN/ER/RES.
- Regulation of the replication of mitochondrial DNA in human pathology: Importance of the homeostasis of the pool of dNTPs.

Otros:

- Generalitat Valenciana: Study of the specificity and sensitivity of a method based on the detection of the histones circulating in plasma as biomarkers of severe sepsis and septic shock.
- Fundació La Maratò – TV3: Regenerative medicine for Fanconi anaemia: generation of disease-free patient-specific iPS cells, and iPSC-derived hematopoietic progenitors and platelets.
- Fundación ARECES:

  - Generation of iPS cells for the study of neurodevelopment diseases: Autism and Williams Syndrome.

  - Allan-Herndon-Dudley Syndrome: Molecular mechanisms and therapeutic approach in the murine model of the disease.

We should stress the CIBERER's participation in one of the CIBER interdisciplinary excellence projects financed by the AES. The project led by the CIBER-BBN has the aim of identifying common molecular mechanisms between diabetes and neurodegenerative diseases.

INTERNATIONAL PROJECTS EU

- *European network and registry for homocystinurias and methylation defects (E-HOD).*
- *EUCERD Joint Action: working for rare diseases (EJA).*
- *Promoting Implementation of Recommendations on Policy, Information and Data for Rare Diseases (RD-ACTION).*

Transfer

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

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

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

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

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

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

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

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

  The CIBER has since 2014 taken part in Epidisease (http://www.epidisease.com/es/) which it continued to support in 2015. Epidisease is the first Spin-off to have been produced by the CIBER area. This company offers services based on epigenetics to provide solutions for human diseases. This year it was given an award of aid from the VLC/ Campus Start Up programme.

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

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

- **In this period CIBERER applied for three priority patents and signed two licences.**

Dissemination activities

In 2015 CIBER's Communication Department carried out different measures for dissemination and disclosure in order to improve the Centre's visibility, as well as publicising the research work done by the groups in its eight thematic areas. We now detail the 2015 milestones in CIBERER Communication.

THE CIBERER IN THE MEDIA:

During the 2015 period 50 CIBER press releases were issued, seven of these from the CIBERER and four in cooperation between several CIBER areas.

Date	Thematic Area	Title
January	SEVERAL CIBER	El CIBER pone en marcha tres proyectos de excelencia interdisciplinares financiados con casi 2 millones de euros por la AES
February	SEVERAL CIBER	Investigadores del CIBER identifican diversos factores de riesgo de sufrir cáncer
January	SEVERAL CIBER	El CIBER acerca su investigación al público de la mano de la improvisación teatral en #ImproCiencia
February	SEVERAL CIBER	Investigadores del CIBER identifican diversos factores de riesgo de sufrir cáncer
February	CIBERER	Investigadores y afectados exponen su colaboración en diversas enfermedades raras en una jornada en Valencia
April	CIBERER	La nueva plataforma Rare Commons une a investigadores y familias de pacientes para avanzar en el conocimiento de las enfermedades raras
April	CIBERER	Identifican en dos familias españolas un nuevo gen asociado a retinosis pigmentaria
May	CIBERER	Familias e investigadores se unen para avanzar en el conocimiento de la enfermedad de Menkes
August	CIBERER	Identifican una nueva posible causa genética de microftalmia
October	CIBERER	CIBERER pone en marcha un mapa interactivo de los proyectos de investigación sobre enfermedades raras en España
December	CIBERER	El Group de referencia en enfermedades raras hematológicas que lidera el doctor Vicente Vicente se incorpora al CIBER

1141 appearances in the media were registered over this period:

CIBERER	NEWS	AUDIENCE
Internet	1.034	136.050.800
Press	107	11.405.000
Total	**1.141**	**147.455.800**

NEW WEB PAGE OF THE CIBERER:

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

http://www.ciberer.es/en

CIBER NEWSLETTER

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

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

SOCIAL NETWORKS

Main indicators of CIBERER's presence on Twitter:

UPDATES		FOLLOWERS		FOLLOWING		KLOUT (influence, values between 1 and 100)	
JANUARY	DECEMBER	JANUARY	DECEMBER	JANUARY	DECEMBER	JANUARY	DECEMBER
2490	3001	2696	3800	187	198	55	52

CIBERER´S ANNUAL REPORT

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

CIBER #IMPROCIENCIA SCIENCE WEEK

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

Games and improvisations were alternated with live connections with CIBER researchers during the event. As far as the CIBERER is concerned, we should stress José Luis García's part in this, explaining from Valencia the CIBER's first spin-off - Epidisease, for research into diagnoses and therapies based on epigenetics (the switches which control and modify the expression of our genes).

Scientific Production

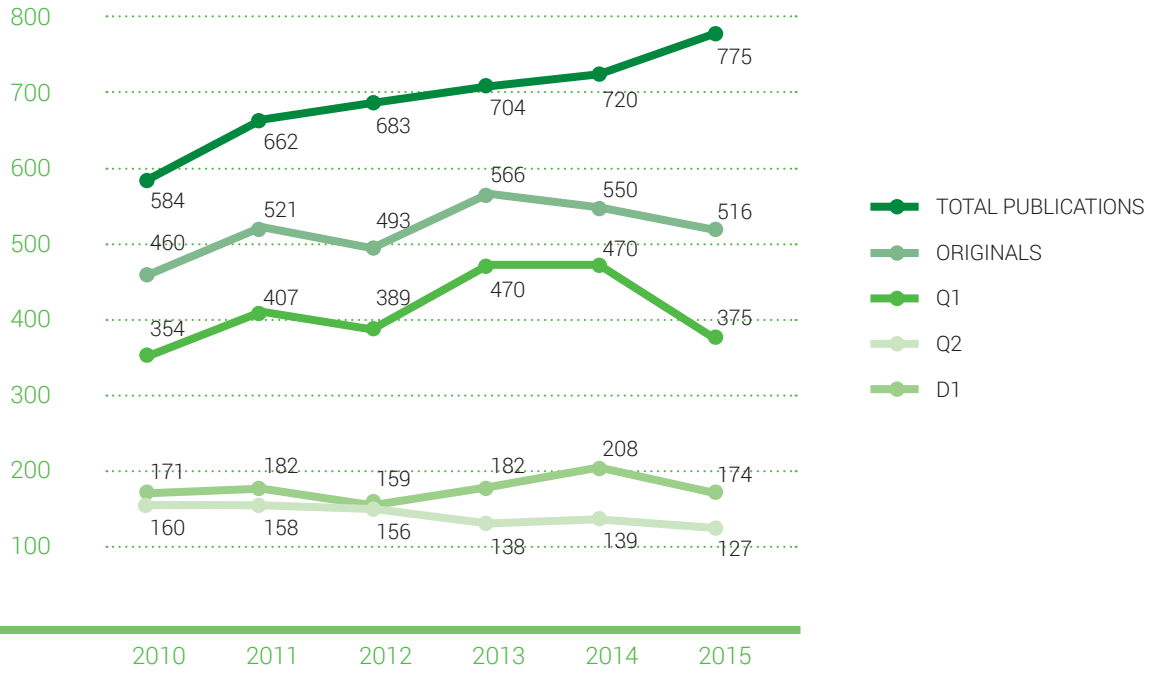
The evolution of CIBERER publications can be seen from the following graphs in which the data from 2010 to 2015 is analysed.

The publications are also detailed by group for this year, as well as the interCIBER e intraCIBER cooperation.

Publications:

No. of affiliated publications 2015	
Total publications	**516**
First quartile	375
First decile	174

EVOLUTION OF CIBERER PUBLICATIONS 2010-2015



MOST RELEVANT CIBERER PUBLICATIONS IN 2015 BY IMPACT FACTOR

Publication	Impact Factor
ZHENG HF, FORGETTA V, HSU YH, ESTRADA K, ROSELLO-DIEZ A, LEO PJ ET AL. Whole-genome sequencing identifies EN1 as a determinant of bone density and fracture. Nature. 2015 Oct 1;526(7571):112-7.	42.351
REDDY P, OCAMPO A, SUZUKI K, LUO J, BACMAN SR, WILLIAMS SL ET AL. Selective elimination of mitochondrial mutations in the germline by genome editing. Cell. 2015 Apr 23;161(3):459-69.	33.116
KUCHENBAECKER KB, RAMUS SJ, TYRER J, LEE A, SHEN HC, BEESLEY J ET AL. Identification of six new susceptibility loci for invasive epithelial ovarian cancer. Nat Genet. 2015 Feb;47(2):164-71.	29.648
SYRBE S, HEDRICH UB, RIESCH E, DJÉMIÉ T, MÜLLER S, MØLLER RS ET AL. De novo loss- or gain-of-function mutations in KCNA2 cause epileptic encephalopathy. Nat Genet. 2015 Apr;47(4):393-9.	29.648

Publication	Impact Factor
BAIXAULI F, ACÍN-PÉREZ R, VILLARROYA-BELTRÍ C, MAZZEO C, NUÑEZ-ANDRADE N, GABANDÉ-RODRIGUEZ E ET AL. Mittelbrunn M. Mitochondrial Respiration Controls Lysosomal Function during Inflammatory T Cell Responses.Cell Metab. 2015 Sep 1;22(3):485-98.	16.747
SEGUÍ N, MINA LB, LÁZARO C, SANZ-PAMPLONA R, PONS T, NAVARRO M ET AL. Germline Mutations in FAN1 Cause Hereditary Colorectal Cancer by Impairing DNA Repair.Gastroenterology. 2015 Sep;149(3):563-6.	13.926
CALVETE O, MARTINEZ P, GARCIA-PAVIA P, BENITEZ-BUELGA C, PAUMARD-HERNÁNDEZ B, FERNANDEZ V ET AL. A mutation in the POT1 gene is responsible for cardiac angiosarcoma in TP53-negative Li-Fraumeni-like families.Nat Commun. 2015 Sep 25;6:8383.	10.742
SEVILLA T, LUPO V, MARTÍNEZ-RUBIO D, SANCHO P, SIVERA R, CHUMILLAS MJ ET AL. Mutations in the MORC2 gene cause axonal Charcot-Marie-Tooth disease. Brain. 2016 Jan;139(Pt 1):62-72.	10.226
PANZA E, ESCAMILLA-HONRUBIA JM, MARCO-MARÍN C, GOUGEARD N, DE MICHELE G, MORRA VB, LIGUORI R ET AL. ALDH18A1 gene mutations cause dominant spastic paraplegia SPG9: loss of function effect and plausibility of a dominant negative mechanism. Brain. 2016 Jan;139(Pt 1):e3.	10.226
RECALDE S, TORTAJADA A, SUBIAS M, ANTER J, BLASCO M, MARANTA R, ET AL. Molecular Basis of Factor H R1210C Association with Ocular and Renal Diseases. J Am Soc Nephrol. 2016 May;27(5):1305-11.	9.466

	PUBLICATIONS 2015		
Group – Name of PI	**Total**	**1D**	**1Q**
(U701) - Martí Seves, Ramón	7	2	5
(U702) - Antiñolo, Guillermo	6	2	2
(U703) - Artuch Iriberri, Rafael	14	1	6
(U704) - Ayuso, Carmen	13	2	13
(U705) - Baiget Bastús, Montserrat	2	1	2
(U706) - Benítez, Javier	46	18	36
(U707) - Bernabéu, Carmelo	6	-	3
(U708) - Bernal, Juan	4	2	2
(U709) - Bovolenta, Paola	6	3	5
(U710) - Bueren, Juan Antonio	8	2	6
(U711) - Carracedo, Ángel	22	9	19
(U712) - Carrascosa, Antonio	4	-	-
(U713) - Cuezva, José Manuel	3	1	3
(U714) - Del Río Nechaevsky, Marcela	4	1	2
(U715) - Dopazo Blázquez, Joaquín	6	3	3
(U716) - Fillat, Cristina	14	7	10
(U717) - Garesse, Rafael	6	2	3
(U718) - González Duarte, Roser	2	-	1
(U719) - Gratacós, Eduard	27	10	20
(U720) - Grinberg, Daniel	13	4	10
(U721) - Knecht, Erwin	3	1	3
(U722) - Cardellach López, Francesc	7	3	4
(U723) - Martín Casanueva, Miguel Ángel	5	1	3

	PUBLICATIONS 2015		
Group – Name of PI	**Total**	**1D**	**1Q**
(U724) - Martínez Frías, María Luisa	6	1	3
(U726) - Milá, Montserrat	19	7	14
(U727) - Montoya Villarroya, Julio	4	1	1
(U728) - Moreno Pelayo, Miguel Ángel	3	2	3
(U729) - Navas, Plácido	19	8	13
(U730) - Nunes, Virginia	1	-	1
(U732) - Palau Martínez, Francesc	6	2	4
(U733) - Pallardó Calatayud, Federico	2	-	2
(U734) - González Manchón, Consuelo	6	-	6
(U735) - Pérez Jurado, Luis	7	2	5
(U737) - Ribes, Antonia	4	1	1
(U738) - Rodríguez de Córdoba, Santiago	9	2	2
(U739) - Rubio Zamora, Vicente	2	1	1
(U741) - Sánchez Jiménez, Francisca	5	2	5
(U742) - Sanz, Pascual	5	1	3
(U743) - Satrústegui Gil Delgado, Jorgina	2	1	1
(U744) - Serratosa, José	3		1
(U745) - Surrallés, Jordi	3	1	2
(U746) - Pérez González, María Belén	9	-	4
(U747) - Webb, Susan	11	-	2
(U748) - Díaz Nido, Javier	3	1	2
(U749) - Fernández Piqueras, José	1	1	1
(U750) - Estévez Povedano, Raúl	3	2	3
(U751) - Giménez Martín, Cecilio	2	1	2
(U752) - Giraldo Castellano, Pilar	5	-	4
(U753) - Lapunzina Badía, Pablo Daniel	16	3	8
(U754) - López Trascasa, Margarita	7	1	3
(U755) - Millán Salvador, José María	2	1	1
(U756) - Montoliú José, Lluis	6	4	4
(U757) - Perona Abellón, Rosario	1	-	1
(U758) - Posada de la Paz, Manuel	7	2	5
(U759) - Pujol Onofre, Aurora	4	2	4
(U760) - Ruiz Pérez, Víctor Luis	1	-	1
(U761) - Varela Nieto, Isabel	10	3	8
(U762) - Illa Sendra, Isabel	4	2	4
(U763) - Vilchez Padilla, Juan Jesús	2	-	1

COOPERATION:

No. of intraCIBER publications 2015: **88**

No. of interCIBER publications 2015: **87**

3

Scientific Programmes

Genetic Medicine

The Genetic Medicine Programme continues to lead the initial implementation of Next Generation Sequencing (NGS) and other OMICS applications in diagnostic practice in hospitals. This enables us to go on discovering new genes involved in Rare Diseases (RD). Some examples of this are discoveries such as mutations in XPR1 which cause familial brain calcifications associated with alterations in the export of phosphates, published by Dr Carracedo's group (U711). (Legati A, et al *Nat Genet*. 2015 Jun;47(6):579-81), and the works on epilepsies by Dr Serratosa's group (U744) with mutations in KCNA2 and SLC13A5 which cause epileptic encephalopathy. (*Brain*. 2015 Nov;138(Pt 11): 3238-50 and *Nat Genet.* 2015 Apr;47(4):393-9).

Apart from this the first catalogue of genetic variation of the healthy Spanish population has been published. This work was jointly produced by Dr Dopazo's group (U715) and Dr Antiñolo's unit (U702). Dopazo et al, *Mol Biol Evol*. 2016 Jan 13.

Another of the programme's aims is to back preclinical research into rare epilepsies and related diseases, including Lafora's disease. We should stress the works published by Dr Giménez's group (U751) on the molecular aspects of glycine transporters 1 and 2 and their implication in hereditary Hyperekplexia. (*Neuropharmacology*. 2015 Feb;89:245-54 and *J Biol Chem*. 2015 Jan 23;290(4):2150-65), and the work done by Dr Sanz's group (U742) on the structural mechanisms of the laforin function implied in Lafora's disease (*Mol Cell.* 2015 Jan 22;57(2):261-72). Another accomplishment of Dr Sanz's group was the application for patent ref: P201531786 for treatment and prevention of diseases or disorders regulated by AMPK, as is Lafora's disease.

The programme also furthers physiopathological study for its therapeutic and diagnostic application in vascular and complement-mediated rare diseases. In this line of work we should stress the studies on complemented-mediated diseases done by Dr. Rodríguez de Córdoba's groups (U738) describing a new relationship of hybrid gene CFHR1/CFH with the atypical haemolytic uremic syndrome (SHUa) (*J Am Soc Nephrol*. 2015 Jan; 26(1):209-19), and the work done in cooperation with Dr López Trascasa (U754) for risk haplotypes (*Mol Immunol*. 2015 Oct;67(2 Pt B):276-86).

Other findings of this kind include the work on Haemorrhagic Hereditary Telangiectasia (HHT) of Dr Bernabeu's group (U707), which has postulated the involvement of endoglin in integrin-mediated cell adhesion as the pathogenic mechanism in HHT (*Cell Mol Life Sci*. 2015 Dec 8) and has obtained the designation of bazedoxifene acetate as an orphan drug by the European Medicines Agency.

Dr González Manchón (U734) has completed the phenotypic characterisation of a mouse model with podocalyxcin ablation (Podxl) in the vascular endothelium which represents an excellent tool for studying diseases occurring with an increase in vascular permeability, including systemic vasculitis.

Inherited Metabolic Medicine

In 2015 the 12 groups forming the Programme obtained relevant scientific results and got a large number of strategic actions under way to tackle RD whose main aspect is the alteration of homeostasis caused by mutations in genes connected with intermediary metabolism.

First of all, we have the results on **new genes and applications for better diagnosis of this group of diseases.** We could stress the discovery of mutations in the ALDH18A1 gene which cause dominant or recessive inherited diseases depending on the lesion of the gene, work done by Dr. Rubio's group (U739).

The identification by Dr Ribes's group (U737) of a new biomarker (Cholestane-3ß,5a, 6ß-triol) for Niemann-Pick type C disease, Cerebrotendineous xanthomatosis and lysosomal acid lipase deficiency and the implementation by Dr Giraldo's group (U752) of enzymatic determination in dried blood spots for screening lysosomal acid lipase (LAL) deficit and the Chitotriosidase biomarker.

There has also been cooperative work between several units in the Programme to prepare guides and recommendations for improving the neonatal screening of homocystinurias and methylmalonic aciduria, in the group "Newborn screening working group" in the framework of European project E-HOD (European Network and Registry for Homocystinurias and Methylation Disorders).

The programme has developed new models of disease to find out the physiopathological bases of these diseases. For example, Dr. Grinberg's group (U720) has completed a neuronal model by means of iPS cells for Sanfilippo C disease and successfully carried out fibroblast treatment using RNA interference. Dr Palacín's group (U731) has, in cooperation with Dr. Artuch (U703), made progress in phenotyping the first animal model of lysinuric protein intolerance (LPI).

As regards the progress made in molecular aspects of these diseases, we should stress the determination of the structure of human CPS1 whose deficiencies produce congenital hyperammonaemia and the characterisation of the effects of clinical mutations of the CPS1-regulating domain by Dr. Rubio's group (U739). In the context of MLC disease Dr Estévez's group (U750), in cooperation with unit (U730) under Dr Nunes, have taken steps forward in the understanding of the structure-function relationship of GlialCAM and the modulation of the functional properties of the ClC-2 chloride channel.

Lastly, we would like **to stress the achievements in the therapeutic and clinical aspects** of these diseases such as the identification of new therapeutic targets as controllers of mitochondrial biogenesis (Sirt1/PGC-1/PPAR axis) and the autophageal flow (via mTOR) in adrenoleukodystrophy (Dr Pujol U759), or the study of Dr Salido's group (U740) on the safety and effectiveness of the reduction of substrate in primary hyperoxalurias by glycolate oxidase inhibition with two approaches; siRNA and small molecules.

Mitochondrial and Neuromuscular Medicine

2015 was a year which involved several structural changes mainly stemming from the transfer of two new groups from the CIBER de Enfermedades Neurodegenerativas in 2014. These were the groups led by Dr Isabel Illa and Dr Vilchez respectively, which joined the one which became known as the Mitochondrial and Neuromuscular Medicine Programme; this was also due to a group in this programme leaving the CIBERER and another being included through the corresponding call of the Acción Estratégica de Salud (AES) of the Instituto de Salud Carlos III (ISCIII), led by Dr Josep Dalmau, whose real integration will become effective in 2016.

The 12 groups forming the Programme have obtained major scientific results, in dissemination and cooperation with patients' associations, both individually and in cooperation with other CIBERER groups, either in the programme itself or in other programmes.

On the scientific level we should stress the progress made in tackling diseases with mitochondria as the physiopathological target and affecting the individual's bioenergy balance. This was done by studying genome-mitochondria communication and the physiopathology and disease mechanisms in cell models and iPSC, the promotion of translational research into neuromuscular diseases and therapeutic research through the development of animal models to the preclinical stage, biomarkers, especially in neuromuscular pathologies. The most important publications and research projects of the groups are covered in the specific section for each of the groups included in this report.

As regards cooperation, we should stress that over 2015 the PdI participated in 4 projects in the ACCI Call: Cooperative and Complementary Intramural Actions (ACCI), 4 of these ending in 2015 and the other 4 being granted in the 2015 call. It is significant that three of these were coordinated by groups in the Programme. 9 of the 12 groups participated in an ACCI in 2015.

Its 3rd Annual Scientific Meeting was held on 15th December at Madrid's Hospital 12 de Octubre, where the work done was pooled, concentrating on studies of mitochondrial dysfunction and physiopathogeny in models of disease, as well as on aspects of genetic-molecular identification (NGS), biomarkers and therapeutic approaches in mitochondrial and neuromuscular pathology. The groups had also met beforehand in the framework of the Annual CIBERER meeting.

In 2015 the "*Translational Research Experimental Medicine and Therapeutics on Charcot-Marie-Tooth Disease*" project, financed by the ISCIII as part of the IRDiRC, concluded. This had started in 2012, with the participation of 12 reference research groups, 6 of these belonging to the CIBERER and specifically 4 from this programme.

As regards the transversal contribution to the CIBERER as a whole, we should stress the coordination by U713 led by Dr José Manuel Cuezva, from the PROTEOmAB Platform for phenotyping energy metabolism.

The groups in the programme also cooperated with patients' associations, such as AEPMI (Asociación de Enfermos de Patologías Mitocondriales) or ASEM (Federación Española de Enfermedades Neuromusculares).

Paediatric and Developmental Medicine

We will now summarise the main activities and results in line with the objectives defined in the Action Plan 2015:

To foster the development of genomic diagnosis tools for the diseases of interest in the programme:

- The identification of mutations in JMJD1C contributing to the development of Rett's syndrome, intellectual disability and/or autism. The units led by Dr Milà (U726) and Dr Pérez Jurado (U735) took part in this research.
- The characterisation of large structural genetic mosaicisms in human autosomes Am J Hum Genet. 2015 Mar 5; 96(3):487-97 and integrated studies of the full genome and transcriptome in diseases of the autism spectrum Mol Autism. 2015 Apr 15; 6:21 by U735, and the extensive study on the genetic causes of intellectual disability carried out by Dr Tejada's linked group Hum Mutat. 2015 Dec;36(12):1197-204.
- Molecular approaches for diagnosis of Beckwith-Wiedemann and Silver-Russell syndromes by Dr Lapunzina, U753, Eur J Hum Genet. 2015 Oct 28.
- The discovery of mutations in gene WDR35 causing a differentiated form of Ellis-van Creveld syndrome by groups U760 and U753. Hum Mol Genet. 2015 Jul 15;24(14):4126-37.
- The identification of TWIST2 gene as cause of Barber-Say and Ablepharon-Macrostomia syndromes, by groups U724 under Dr Martínez Frías.

To lead CIBERER research in innovative therapies, with special emphasis on gene and foetal therapy with the work of Dr Fillat (U716) on the development of new adenoviruses controlled by miRNA for the development of new gene therapies. ***Oncotarget***. 2015 Mar 20; 6(8).

To further clinical research thanks to the close cooperation with national benchmark hospitals:

In order to foster cooperation with experts from all over the country and abroad, numerous specialised workshops and conferences were arranged, such as the first Jornada Científica de la Asociación 11q in Spain last 11th July and the first Jornadas del Síndrome de Beckwith-Wiedemann for relatives, persons affected and healthcare professionals, which took place at the Hospital La Paz. There was also an event for those affected by 22q11 and professionals, an encounter with relatives of those affected by 5p- syndrome, the *2nd International Conference of FMR1 premutation*, and the spring and autumn dysmorphology conferences.

To develop tools for epidemiological research in rare diseases:

We should highlight the National Registry of Rare Diseases of the Instituto de Salud Carlos III (ISCIII), which is coordinated and directed by Dr Posada's group (U758) and the work done by the ECEMC (Estudio Colaborativo Español de Malformaciones Congénitas) and by the Servicios de Información Telefónica SITTE and SITE (both with regard to risks for prenatal development), led by Dr Martínez Frías (U724).

Sensorineural Pathology

In 2015 the seven groups in the Programme obtained major results in the scientific field, and as regards dissemination and cooperation with patients' associations, both independently and in cooperation with other CIBERER groups, either in the programme itself or in other programmes.

As far as the scientific level is concerned, we should stress the development of cell and animal models of RD, above all orientated towards leadership in preclinical research into sensorineural RD as well as the development of genomic and diagnostic tools and the discovery of new genes. The groups' most important publications and research projects are set forth in the specific section for each of the groups in this report.

As regards cooperation, we should stress that the programme took part in seven projects in the ACCI call, three of which ended in 2015 and the remaining four granted in the 2015 call. In 2015 all the groups took part in at least one ACCI and several of these were even participating in three of these.

Special mention should be given to the fact that the seven groups in the Programme are taking part in a new intramural project: MODCELANI_CRISPR New animal models of rare sensorineural diseases generated by means of CRISPR-Cas9 technology. This project came into being at the meeting of the programme held as part of the Annual Meeting of the CIBERER in El Escorial this same year, in which it was agreed to submit a joint project in which the seven units in the programme take part, so as to reinforce the strategic positioning and the cooperation already existing between the groups forming part of this.

The programme held its 5th Annual Scientific Meeting on 26th and 27th at the Centro Nacional de Biotecnología (CNB-CSIC), as well as the encounter held as part of the Annual CIBERER Meeting mentioned above.

The groups in the programme arranged five scientific events with CIBERER financing, two International Symposia deserving special mention; Hereditary Hearing Impairment: from diagnosis to therapy (Fundación Ramón Areces, 5th and 6th March, Madrid) and Understanding human disease: New tools for new challenges (Universitat de Barcelona, 23rd November, Barcelona). There were also several other scientific events put on with their own financing at which their membership of CIBERER was clearly visible.

With regard to the training area, two groups in the programme arranged CIBERER courses, one on animal phenotyping (arranged by the SEFALER platform, coordinated by unit U761 and which U756 also forms part of) and another one on alternative models to the mouse.

The groups in the programme also cooperated with patients' associations such as ASANOL (Asociación sobre la Atrofia del Nervio Óptico de Leber), ALBA (Asociación de personas con Albinismo) or FIAPAS (Confederación Española de Familias de Personas Sordas).

A cooperation agreement promoted through the programme was also signed by the CIBERER and the Red Temática de Investigación Cooperativa de Enfermedades Oculares "Oftared".

Endocrine Medicine

In 2015 the Endocrine Medicine programme was clearly strengthened by the three Linked Clinical Groups which joined this:

- Irene Halperin Ravinovich, from the Servicio de Endocrinología y Nutrición at the Hospital Clínic de Barcelona.
- Antonio Picó Alfonso from the Servicio de Endocrinología y Nutrición at the Hospital General Universitario de Alicante.
- Manuel Puig Domingo from the Servicio de Endocrinología y Nutrición at the Hospital Universitario Germans Trías i Pujol de Badalona.

This Research Programme, made up of only three research groups in their own right and a fourth associated group, lacked the critical mass to take on some measures. The new situation means they can, for example, get under way the project funded by the CIBERER as part of its call for Translational Research Projects: "Silent Corticotroph adenomas: Are these a subtype of non-functioning pituitary adenomas with more aggressive clinical behaviour?" This project is a transversal endeavour by all the groups involved in the research into this type of pathologies, combining the best national groups by pooling their collections of clinical cases to review the classification of this type of adenomas.

The Endocrine Programme arranged the "Simposio Internacional sobre Enfermedades Raras Endocrinas, de la Investigación al Manejo Clínico" sponsored by the Fundación Ramón Areces and the CIBERER itself. This Symposium was led by doctors Webb and Resmini (U747). It was of use as an encounter for updating and discussing pituitary and thyroidal rare diseases, monogenic diabetes and sexually developed rare diseases, from their causes to their clinical management. Doctors Bernal (U708), Castaño (U725A) and Audí (U712) took part in this. Another event, coordinated by the U712 through Dr Audí, was the XV encuentro de GrApSIA at the Hospital Universitario Miguel Servet de Zaragoza, an association which provides support for young people and adults with androgen insensitivity syndrome (AIS) and other related syndromes.

Inherited Cancer, Haematological and Dermatological Diseases

2015 was a year in which different groups from this programme went on fronting the development of new therapies through clinical trials of gene therapy. We should highlight the work coordinated by Dr. Bueren's unit U710 in cooperation with other CIBERER units and with Linked Clinical Groups (Niño Jesús and Vall d' Hebrón Hospitals) as well as with the Fundación Jiménez Díaz, with which the Unidad Mixta de Terapias Avanzadas was set up. There was also the first Sala GMP Nacional, approved by the Agencia Española del Medicamento y Productos Sanitarios for developing protocols for gene therapy with haematopoietic stem cells. This work has put the group among the world leaders in gene therapy projects in rare diseases affecting blood cells.

As a collaborative project, funded from CIBERER in its call for Translational Research Projects, we should stress the one got under way under the coordination of Dr Sevilla (GCV19) "New diagnostic approaches to hereditary syndromes with bone marrow failure for treatment with innovative therapies". Different groups took part in this project, such as Dr Bueren's U710; unit U745 under Dr Surrallés, Dr Lapunzina's U753, the U757 led by Dr Perona; Dr Badell's GCV16, unit GCV17 led by Dr Beléndez and Dr Catalá's GCV18. This project will allow the integration of clinical information on cases in the same clinical register already developed for Fanconi anaemia. A proposal for an intramural project has also been led: "Drug repurposing in Fanconi anemia", which involves groups U710 and U745, to be started up in 2016.

As well as the works taken on in the form of clinical trials for treatment of gene therapy of Fanconi anaemia, we should mention the progress made in pyruvate kinase deficiency therapy by means of gene edition in haematopoietic progenitors. This meant definite progress for transfer to the production sector could be established for both pathologies.

In the same line of advanced therapies we can stress the progress made by U757 in the therapy for rescuing telomerase activity and the genetic improvement of products such as nanoparticles and gene therapy vectors for the treatment of diseases with telomere shortening.

Lastly, new discoveries of genes associated with rare diseases have been made, such as that of gene MDH2 as cause for familial Paraganglioma (U706) and work has gone on in the description of the imbrication of genetic instability syndromes such as Fanconi anaemia and different types of cancer, such as breast and inherited colon cancer.

4

Transversal Programmes

Training Programme

The CIBERER Training Programme carried out its main work in 2015 in three overall approaches:

- Courses: Organisation and calls for aid for grants for attendance.
- Mobility grants.
- Pre-doctoral grants 2014-15.

Courses: Organisation and calls for attendance grants

Course on Applied Medical Genetics and Genomics, 9th to 13th March 2015. EUROFORUM, San Lorenzo de El Escorial, Madrid. Coordinated by Doctors Lapunzina (U753) and Pérez-Jurado (U735). This international course, arranged by CIBERER, was a venue for experts in clinical genetics from seven Latin American countries to meet, including teachers and students, and for discussion as to how to apply new diagnostic methodologies to clinical genetics.

MDA course on Next Generation Sequencing Data Analysis, 28th to 30th September 2015, Centro de Investigación Príncipe Felipe, Valencia. This was a CIBERER course arranged by the BER platform (U715). It provided training for 20 researchers in methods for filtration of genetic variants and interpretation of their meaning as regards potential causes of pathology.

CIBERER Training Course on Phenotyping of Animal Models, 16-20th November 2015, Facultad de Veterinaria UCM-Hospital Clínico Veterinario UCM, Madrid. Arranged by CIBERER's SEFALER platform and coordinated by Doctors Varela and Murillo (U761). It provided practical training with diverse models, mainly murine, basic knowledge for characterising physiopathology of RD and appraisal of therapies in models of disease.

Course on functional assays in alternative models to the mouse in Biomedical Research, 28th to 30th October 2015, Hospital Ramón y Cajal-IRICYS, Madrid. This was the first edition of this course arranged by the CIBERER's U728 unit, led by Doctors Moreno and Morín. The availability of a huge amount of genetic information contrasts with the difficulty of validating the clinical significance of new variants, which is why it is increasingly necessary to find out how to handle alternative models for this process.

Mobility grants

In 2015 CIBERER went on with its mobility programme to foster the training of researchers and cooperation between groups in the network. More specifically, 14 applications for mobility grants were able to be catered for in 2015, 11 of these intramural, one for a Linked Clinical Group and 2 international grants.

Pre-doctoral grants 2014-15

CIBERER pre-doctoral grants are a specific tool for attracting recent graduates to CIBERER groups. In 2015 it was not possible to issue any call. The 2014 call was completed, with its 13 beneficiaries, 9 of whom remained in research groups after this financing had ended.

Knowledge Application Programme

Cooperative and Complementary Intramural Actions (ACCI) are competitive collaborative research projects financed with CIBERER's own funds. The aim of this is to encourage cooperative research on RD, and thus be able to increase knowledge, technical capacity, diagnostic development or therapeutic progress. The projects granted in 2015 which started in 2016 are as follows:

Title	P.I.	Coord. unit.	Units taking part	Programme
New animal models of sensorineural rare diseases generated by means of CRISPR-Cas9 technology	Montoliu José, Lluis	756	704, 709, 718, 728, 755, 761	Sensorineural Pathology
Genetic diagnosis and possible treatment of albinism	Carracedo Álvarez, Ángel	711	704, 756	Genetic Medicine
Diagnostic biomarkers of Mitochondrial Diseases affecting the OXPHOS system	Martín Casanueva, Miguel Ángel	723	701, 713	Mitochondrial and Neuromuscular Medicine
Pathogenic mechanisms in rare and common diseases associated with complement deregulation	Rodríguez de Córdoba, Santiago	738	709, 754	Genetic Medicine
Development of a platform for diagnosis by new generation sequencing	Dopazo Blázquez, Joaquín	715	702, 704, 728, 735, 746, 753, 755	Genetic Medicine
The landscape between Phenotyping and Genotyping in Neurological Developmental Diseases: Validation of a Model of Clinical Functional Biology	Palau Martínez, Francesc	732	703, G19CIBERSAM	Mitochondrial and Neuromuscular Medicine
Analysis of a new function of endoglin in cell adhesion and its relevance in the physiopathology of Hereditary Haemorrhagic Telangiectasia	Bernabéu Quirante, Carmelo	707	734, +external	Genetic Medicine
Treatment of mitochondrial diseases with NAD+ precursors	Navas Llobet, Plácido	729	717, 727, +external	Mitochondrial and Neuromuscular Medicine
Drug repurposing in Fanconi anemia	Surrallés Calonge, Jordi	745	710, +external	Inherited Cancer, Haematological and Dermatological Diseases
Development and initial characterisation of animal models of Bartter syndrome	Estévez Povedano, Raúl	750	730	Inherited Metabolic Medicine
Implementation of massive sequencing in the study of Congenital Myopathies and congenital Myasthenic Syndromes: a model of translational research in rare diseases.	Gallano Petit, Pia	705	711, 732, GCV01, GCV02, GCV03, GCV04	Genetic Medicine

Translation

Cooperation was underpinned with the twenty Linked Clinical Groups (GCV), spread over nine Spanish administrative regions and sixteen National Health Service (NHS) hospitals. In order to foster translation at the CIBERER a Call for Translational Research Projects was launched, in which Linked Clinical Groups and CIBERER units took part. Ten expressions of interest were submitted and two projects were financed.

CIBERER backed the preparation of clinical practice guides through different measures such as the Grupo Español de Trabajo sobre Cáncer en Síndromes Genéticos Polimalformativos (GT-CSGP), coordinated by Dr Martínez-González-U753. Apart from presenting its new web site (http://www.csgpgrupo.org/) it published a new guide on the Tuberous Sclerosis Complex (TSC). Another example was the CIBERER's cooperation in the good clinical practice guide into Imprinting Disorders, which include chapters on different pathologies in this group of RD: These guides were published by Doctors Pérez de Nanclares and Lapunzina-U753.

CIBERER has gone on with its work in consultancy and promotion for the designation of orphan drugs stemming from its research groups. For example, in 2015 work was done on a new application for designation of EMA, for adrenoleukodystrophy with Doctors Pujol-U759 and Knecht-U721.

Apart from this CIBERER continues to take part in the "National Health Service Strategy for Rare Diseases", whose scientific coordinator is Dr Palau. In 2015 the Ministry of Health, Social Services and Equality officially presented the eight Health Service Good Practices in RD, four of which belonged to CIBERER groups.

Mention should be given to getting under way the new Joint Action on Rare Diseases (RD Action) co-funded by the European Union Health Programme, in which all the EU member states are involved, and which CIBERER is a member of. This Joint Action is intended to ensure continuity for Orphanet and EUCERD Joint Action.

Lastly, support continues to be given to different registries of patients for clinical research, such as: State RD Registry, Fanconi Anaemia Database, E-IMD European registry and network for Intoxication type Metabolic Diseases, E-HOD European network and registry for homocystinurias and methylation defects, NMD-ES Spanish Registry for Neuromuscular Diseases, aHUS/C3G Registry, Glycogenosis type V Registry, amongst others.

Transfer

Four patents were applied for in 2015, three of these European:

- Kit and method for diagnosis and prognosis of scoliosis developed by the U733 in cooperation with CIBER spin-off Epidisease S.R.L. (EP15382319).
- A number of spirane compounds derived from oxindol-pyrazole [3,4-b] pyridinone and its therapeutic uses, developed by Dr Sanz's group - U742 (P201531786).
- Use of nucleosides in the treatment of mitochondrial diseases developed by Dr Martí's group - U701 (EP15170825).
- Use of induced pluripotent cells (iPSCs) derived from PBMCs developed by the team under Dr Segovia - U710 (EP15382545 5).

Internationalisation Programme

Last 11th May 2015 the CIBER programme for supporting internationalisation was set up, as a joint initiative of the areas of Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN), Rare Diseases (CIBERER) and Respiratory Diseases (CIBERES), of the Centro de Investigación Biomédica en Red (CIBER). Its purpose is to reinforce and coordinate endeavours intended to promote its researchers' participation in European programmes and to create a common structure for encouraging internationalisation and leadership of research and innovation in these three thematic areas.

Over these first six months of its action the platform has focussed its work on establishing a relationship of trust with the research groups. This started by holding bilateral interviews with the groups and the area leaders to get first-hand information on the research done and the internationalisation potential of the CIBER groups. The platform has also created profiles of specific area capacities so as to have a simple and comprehensive document acting as an introductory letter for the research done at the CIBER. This could be used at the different events for seeking partners. Likewise, the CIBER register of different tools for seeking existing partners has been completed (Cordis, IMI…).

As regards improving CIBER's international visibility, the CIBER has worked hard by attending over sixteen events (including conferences, infodays and partner-seeking events). One of the greatest accomplishments in this field was CIBER's invitation by CDTI to form part of the CDTI-SOST Manager Specialisation Course (CDTI, Brussels, BE). This course is intended to boost the international presence of invited organisations by substantially improving their international network of contacts and knowledge on H2020 programmes. The platform also placed special stress on establishing smooth relations with the different national representatives, national points of contact by means of specific meetings, acting as a point of encounter on an institutional level.

The platform has also given awareness-raising talks on the relevance of internationalisation as part of the area conferences. The success of these events can be seen in the form of a significant increase in the number of enquiries from researchers: (twenty specific enquiries, six requests for support for presentation, six requests for partnering, and six requests for valuing research proposals). This means the platform is already seen as an effective tool for aid and a reference point for settling doubts involving international programmes.

In the field of backing for submission of proposals, the platform has drawn up specific material providing support for writing and managing proposals. This year a practical drafting guide has been drafted, entitled "How to write a European Proposal" as well as a practical guide for management and the "Quick guide for third parties" in order to provide researchers with understandable and reliable consultation material. As part of the support material the platform has also drawn up models and specific templates for managing and applying for H2020 proposals. These include the budget calculator, models of hour sheets, letters for acceptance of participation in proposals, support letters, CIBER profile for European proposals as a partner and as third party and different forms for compiling all the data required for submitting a proposal. This material is intended to facilitate the process of submitting proposals for all our researchers. Thanks to this, in these six months of 2015 the CIBER has submitted four new proposals (three of these coordinated) while expressions of interest for the submission of ten new proposals have been received. In this area it should also be stressed that CIBER has received five new contacts from research groups or companies with the aim of reaching agreements for joint submission of proposals in the H2020 framework. For the time being two of these contacts have materialised in actual presentation of two H2020 proposals.

Scientific-Social Dissemination Programme

Through its scientific-social dissemination programme, CIBERER gives society an ongoing presentation of the work done by its research groups, its projects, the diseases which are being worked on and the new knowledge generated.

CIBERER has worked hard to turn its web page (www.ciberer.es) into an effective instrument. This is shown by the Scopus ranking, which places it as one of the most important scientific web pages.

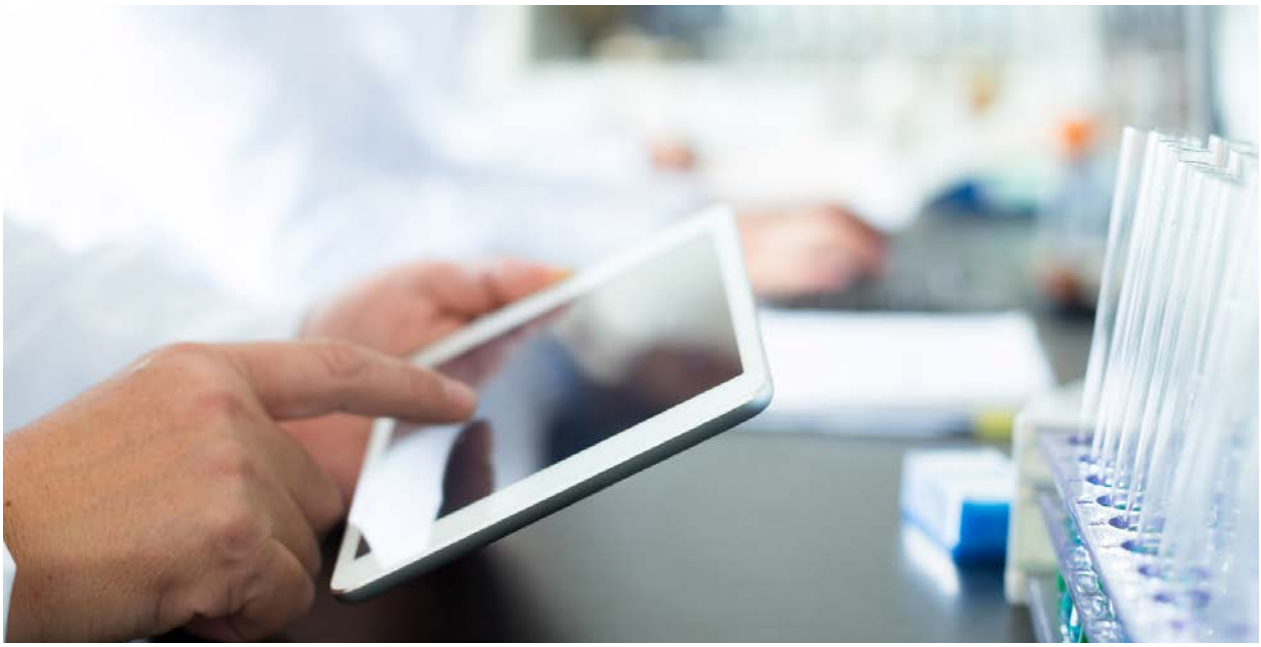
Mention should also be given to the issue of CIBERER's newsletter, a highly effective publication which both publicises the research work done in Rare Diseases (RD) by CIBERER and also sends all the information of interest on RD to the researchers contracted by and attached to our Institution. In 2015, knowledge of the different parties involved was improved and cooperation has been enhanced by means of the eight scientific and six social newsletters issued.

Lastly, CIBERER arranged several encounters for outreach to people affected over the year, some examples of which are given below:

- In February researchers and people affected presented their cooperation in different rare diseases at the Investigar es Avanzar (Research means Progress) events in Valencia.
- In March, the International Symposium on hereditary hearing imparment was held in Madrid. in cooperation with the Fundación Ramón Areces de Madrid.
- The 8th Annual Meeting of the CIBERER, where over 200 members of the thematic area presented the progress made in translational research in RD in San Lorenzo de El Escorial in March.
- In May, CIBERER organised an encounter to tackle the current situation of Centros de Expertos y Redes de Referencia en ER in Madrid.
- The CIBERER supported the Intenational Symposium on rare endocrine diseases in Madrid in October.

CIBERER also co-organised an exhibition on the research into "Less rare" rare diseases which was shown at the Hospital Universitari Vall d'Hebron, La Fe Hospital in Valencia and Reina Sofía Hospital in Cordoba over the year.

Lastly, CIBERER had 1141 impacts in the media. This indicator clearly shows that it has become a social reference in the field of research into Rare Diseases.



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Platforms


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CIBERER BIOBANK

We now sum up the main activities and results in line with the objectives defined in the 2015 Action Plan:

OBJECTIVE 1: TO SUPPLY THE BIOBANK WITH BIOLOGICAL SAMPLES

The total number of samples of RD collected at the end of 2015 is over 400, covering more than 30 different pathologies. (http://www.ciberer-biobank.es).

OBJECTIVE 2: TO FURTHER A PLAN OF STRATEGIC ALLIANCES AND DISSEMINATION

Cooperation:

- Member of the Red Valenciana de Biobancos (RVB).
- Cooperation Agreement with the FISABIO biobank for Biomedical Research and Public Health.
- Framework agreement with the National DNA Bank.
- Member of several work groups of the Red Nacional de Biobancos.
- Agreement with the Fundación FEDER for contracting technical staff for backing the development of the technique for generating human iPS.
- Contract with ABF Pharmaceutical Services GmbH.

Measures for publicising the work done by the Biobank:

'Investigar es Avanzar', 8th Annual CIBERER Meeting, 4th Scientific Meeting of TREAT-CMT, 6th National Congress of Biobanks, Master in Biobanks at the UCV and the RNB.

OBJECTIVE 3: GENERATING ADDED VALUE FOR CIBERER GROUPS.

Services provided

In 2015 the Biobank made ready new services for analysing the integrity of DNA and traceability (genetic fingerprint) provided at no cost to CIBERER researchers along with the services that it had already been providing (processing and custody of samples, ethical-legal advice, management of collection, implementation of quality management systems, etc.).

It has also gone on working on the development of other services (myoblast cultures, generating iPS cells, etc.).

In 2015 22 samples were provided and a wide range of services for processing and keeping samples, cell immortalisation and advice for CIBERER groups were given.

OBJECTIVE 4: FOSTERING AND SUPPORTING NEW LINES OF ACTION IN RARE DISEASES

Participation in projects:

- FP7 HEALTH 2012-INNOVATION: RD-Connect: An integrated platform connecting registries, biobanks and clinical bioinformatics for RD.
- Translational Research, Experimental Medicine and Therapeutics on Charcot Marie Tooth, TREAT-CMT. In cooperation with CIBERER units U732, U755, U733, U713, U743, processing a good deal of the associated samples.
- Participation, along with CIBERER unit U730 in an international project for studying Wolfram syndrome, assuming responsibility for managing samples.
- Influence of epigenetic factors on the development of Adolescent Idiopathic Scoliosis. Dr García (U733). Call for 2012 Grants by the Fundación Mapfre.
- AMER – Acción Multidisciplinar en Enfermedades Raras y Medicina Personalizada. FEDER-INNTERCONECTA Programme. 2012-14. The Biobank is taking part in PT2: Registers of patients, biobanks and knowledge management.
- Spanish Exomes Project, SPANEX. This project is financed with CIBERER funds involving 9 CIBERER groups, giving logistics support for collecting and storing samples, as well as advice on ethical/legal aspects.
- Development and validation of possible biomarkers and therapeutic targets for Friedreich's ataxia. IP: Dr Díaz-Nido (U748). Participating groups: U732 and U733. The Biobank cooperates by providing samples and giving advice in ethical/legal aspects.

SEFALer

The **"Servicio de fenotipado de animales de laboratorio en red"** (SEFALer) has the following objectives: I) Functional and histological phenotyping of animal models of human diseases; II) The archive of genetically modified mice; III) Continuous training; IV) Specialised and expert advice in phenotyping; and V) Scientific dissemination and disclosure.

SEFALer has specifically offered the following range of services in 2015:

- **Auditory, vestibular, respiratory and renal phenotyping, general pathological anatomy, neuro-behavioural (motor, cognitive and emotional), haematological and coagulation system, of demyelising diseases and motor coordination**. As a result of this work publications have been brought out with participation in research projects. Mention should be given to the COST-BM1402 MouseAGE action (http://www.cost.eu/COST_Actions/bmbs/BM1402).
- **Archiving and revitalisation** of mutants in the Spanish node of EMMA/Infrafrontier (www.infrafrontier.eu).

SEFALer arranged the annual **training** course with Madrid's Association of Veterinary Surgeons and the Facultad-Hospital Clínico Veterinario (UCM), with academic recognition and accreditation by the Continuous Training Commission of Healthcare professions of the Madrid area. The educational resources generated are available online. SEFALer units have also taken part in conferences, congresses, seminars, scientific meetings and university education (UAM, UCM, UAB, ULL).

SEFALer also gave **information and advice through** sefaler@ciberer.es and http://www.ciberer.es/plataformas/sefaler, updating of links, information and news. It has an **extensive network of national groups** expert in phenotyping.

SEFALer took part in **scientific dissemination activities** (Researchers' Night, Science Week, Brain Awareness Week...) and in sessions with patients' associations.

The following achievements of SEFALer units are worthy of mention:

- I) Organisation of the 6th Sessions on Training in Phenotyping of Animal Models;

  II) Participation in projects (FP7-AFHELO, FP7-TARGEAR and CDTI) for preclinical assessment of new drugs and development of cochlear implants for treating hearing loss.
- I) Giving services for pathological anatomy and phenotyping of the rental function, though without any significant increase in demand; II) Speaker at the 6th Sessions on Training in Phenotyping Animal Models.
- I) Development of Behavioural phenotyping techniques with predictive value for translational studies and on latest generation video-analysis techniques; II) Development of a system for analysis and display of Behavioural Big Data.
- I) Implementation of new protocols for the study of platelet function in flow conditions; II) Speaker at the 6th Sessions on Training in Phenotyping Animal Models.
- Assessment of the locomotor phenotype (Treadmi- ll, Bar-cross, Clasping) and of axonal (immunohistochemistry) in the model of X-linked adrenoleukodystrophy (double knockout Abcd1 and Abcd2 Abcd1-/Abcd2-/- mice) for Medday company, to test the MD1003 drug, with some very positive results. We go on with functional and molecular analysis of this promising treatment for X-ALD.
- I) Implementation of ultra-superovulation technology (Kumamoto University, Japan), which quintuplicates the production of oocytes, reducing the number of animals required for in vitro fertilisation/cryopreservation of embryos; II) Incorporation of Van Gieson and Sirius Red stains for detecting elastin and collagen fibres in histological preparations.

ORPHANET

The activities performed this year by the Orphanet Platform are as follows:

COLLECTION AND UPDATING OF DATA:

At the end of 2015, the total number of Spanish activities reflected in the Orphanet database was as shown below:

Total Spanish activities in 2015	
Specialised clinical consultations	360
Patients' associations	277
Diagnostic tests	7.860
Clinical trials	921
Research projects	380
Registries / Biobanks	68

TRANSLATIONS:

A total number of 100 abstracts of diseases and 179 names of new Rare Diseases (RD) have been translated into Spanish and uploaded onto the web page, along with the modification of 613 names of RD.

In order to contribute to the translation of the Orphanet Encyclopaedia for Patients, a number of texts containing a great deal of information on many RD in language accessible to all readers have been translated and six articles have been translated and published in 2015.

FURTHERING THE ACTIVE PARTICIPATION OF THE SCIENTIFIC COMMITTEE (SC)

In 2015 the members of the SC have been involved in different tasks such as the review of summaries of diseases, of clinical guides and the directories of expert centres, as well as in replies to patients' enquiries.

FURTHERING THE COMMUNICATION AND DISSEMINATION PLAN:

- Participation in the event entitled "Rare Disease Day 2015" at Valencia University.
- Translation and production of dissemination material on the Orphanet.
- Sponsorship of the III Jornadas Científicas de Técnicos Superiores Sanitarios, Barcelona 5-7 June.
- Contributions to the Orphanews Europe newsletter.
- Maintenance of the Orphanet Spain web site: the web page of Orphanet-Spain, created by the Spanish team of documentarists, published roughly 70 news items over 2015. In cooperation with patents' associations, it publicised events on RD in Spain and gave access to documents in Spanish on these diseases, such as the different guides compiled in "The Orphanet-Spain Encyclopaedia" or specific documentary resources.
- In cooperation with the communication department of the CIBERER, the news items published on the Orphanet-Spain web site further its visibility through its Twitter service. The most prominent ones dealing with the Orphanet portal itself are published on the CIBERER web site and in its institutional newsletter.

FURTHERING THE RESULTS SHARED BY CIBERER-ORPHANET, WORKING TO ENSURE THAT THE RELATIONSHIP BETWEEN THE TWO INSTITUTIONS REPRESENTS ADDED VALUE FOR THEIR RESPECTIVE PROJECTS.

- The list of rare diseases which CIBERER works on been reviewed and updated.
- Cooperation has been provided for the Patients' Care Service in handling enquiries and requests for information by those affected.
- Cooperation with the managers of CIBERER in preparing proposals for projects in which the Orphanet is involved.
- The list of diseases assigned to the projects listed in the MAPER has been reviewed.
- Cooperation in the different areas (Research Programmes, PdI) of the CIBERER in updating activities in the CIBERER database that have been dumped in Orphanet.

BIER

Last year 2015, the BiER platform kept up its hard work in cooperation with CIBERER groups, at first in the framework of the intramural sequencing projects and later on in its groups' own sequencing projects.

BiER has provided a service for technological-bioinformatic advice and support in 22 projects from 15 CIBERER groups, in the programmes of Genetic Medicine, Inherited Metabolic Medicine, Endocrine Medicine, Sensorineural pathology, Mitochondrial and Neuromuscular Medicine and Inherited Cancer, Haematological and Dermatological Diseases. The strategies developed were applied to data from high-performance technologies, tackling transcriptomic and genomic studies (exomes and gene panels). It has worked on the development of new methods for transcriptomic analysis in the context of signalling routes and analyses of functional enrichment of microRNAs.

It has taken an active part in intra-group cooperation with the reception of 11 researchers and held the "NGS course: from reads to candidate genes" training activity which was attended by 25 participants from different CIBERER groups.

The results of these bioinformatic analyses and developments have generated 25 cooperative scientific publications.

Apart from this, systems for assistance in discovering new disease variants have been developed by the BiER in support of the CIBERER's sequencing projects.

- The BiERapp (http://bierapp.babelomics.org) is a tool for analysing individual genome or exome sequences or from families or cases/controls. BiERapp enables the interactive application of heuristic filtration to rule out variants incompatible with the disease.
- The CIBERER Spanish Variant Server tool. (CSVS) which is a database of frequencies of Spanish variants (http://csvs.babelomics.org). The CSVS currently has 578 individuals, including 267 healthy controls for the Medical Genome Project and a growing amount of data on the CIBERER sequencing projects, as well as data on individuals from Spain in the 1000G project.
- Lastly, TEAM is described (http://team.babelomics.org). This is a specific software for designing panels of genes for NGS diagnosis reporting the diagnostic findings and optionally also unexpected findings and variants of uncertain significance.
- Other tools developed in the group are: CellMaps (http://cellmaps.babelomics.org), Babelomics (http://babelomics.org) and Genome Maps (http://genomemaps.org).

PROTEOmAb

The aim of this platform is to transfer metabolism to the field of RD for identifying new pathology biomarkers and possible therapeutic targets. Quantitative methods are applied for the assessment of the expression of enzymes controlling metabolic activities using the technology of reverse phase protein microarrays. The procedure involves antibodies validated against glycolytic enzymes, the pentose phosphate cycle, decarboxylation of pyruvate, Krebs cycle, β-oxidation, shuttles, the electron transport chain, oxidative phosphorylation, mitochondrial structure and dynamics, antioxidant system, etc.

The milestones reached this year focus on three activities:

IDENTIFICATION OF NEW DIAGNOSIS BIOMARKERS AND PROGRESS OF THE PATHOLOGY IN BIOPSIES OF PATIENTS AFFECTED BY RD.

- Myopathies: In cooperation with unit U723 new diagnosis biomarkers have been identified in Duchenne (DMD) and Becker (BMD) muscular dystrophies, carriers of DMD and BMD (Xp21 carriers), type 2 C hip dystrophy (LGMD2C), neuronal ceroid lipofuscinosis (NCL), type V glycogenosis (McArdle), myopathies through complex I deficiencies or by admittance to the intensive care unit (***Journal of Translational Medicine*** 2015 Feb 18; 13:65). The corresponding patent (2432653) owned by CIBERER/UAM was granted on 10/09/2015.
- Peripheral neuropathies. In the framework of the TREAT-CMT project and in cooperation with units U732 and U763 it has been identified in skin biopsies of patients with Charcot-Marie-Tooth (CMT) 1A that proteins of the OXPHOS system, of the antioxidant system and of the β-oxidation provide new biomarkers for progression of the disease (Plasma-metabolite and skin-protein signatures of Charcot-Marie-Tooth 1 A provide novel biomarkers of disease. Soldevilla B, Cuevas-Martín C, Ibáñez C, Al- berti MA, Simó C, Santacatterina F, Casasno- vas C., Márquez C, Sevilla T, Pascual S, Sán- chez-Aragó M, Espinós C, Palau F and Cuezva JM. (submitted) (2016).

PHENOTYPING OF ANIMAL MODELS OF RD.

In cooperation with unit U732 an analysis has been made of the metabolic phenotype of the different tissues of the knockout mouse for gene Gdap1, which is a murine model of CMT disease. It has been verified that the expression of proteins of glycolysis, OXPHOS and of mitochondrial dynamics are specifically reduced in peripheral nerves (***PLoS Genetics***, 2015 Apr 10;11(4):e1005115).

IDENTIFICATION OF BIOMARKERS OF RESPONSE TO THERAPY IN MODELS OF RD.

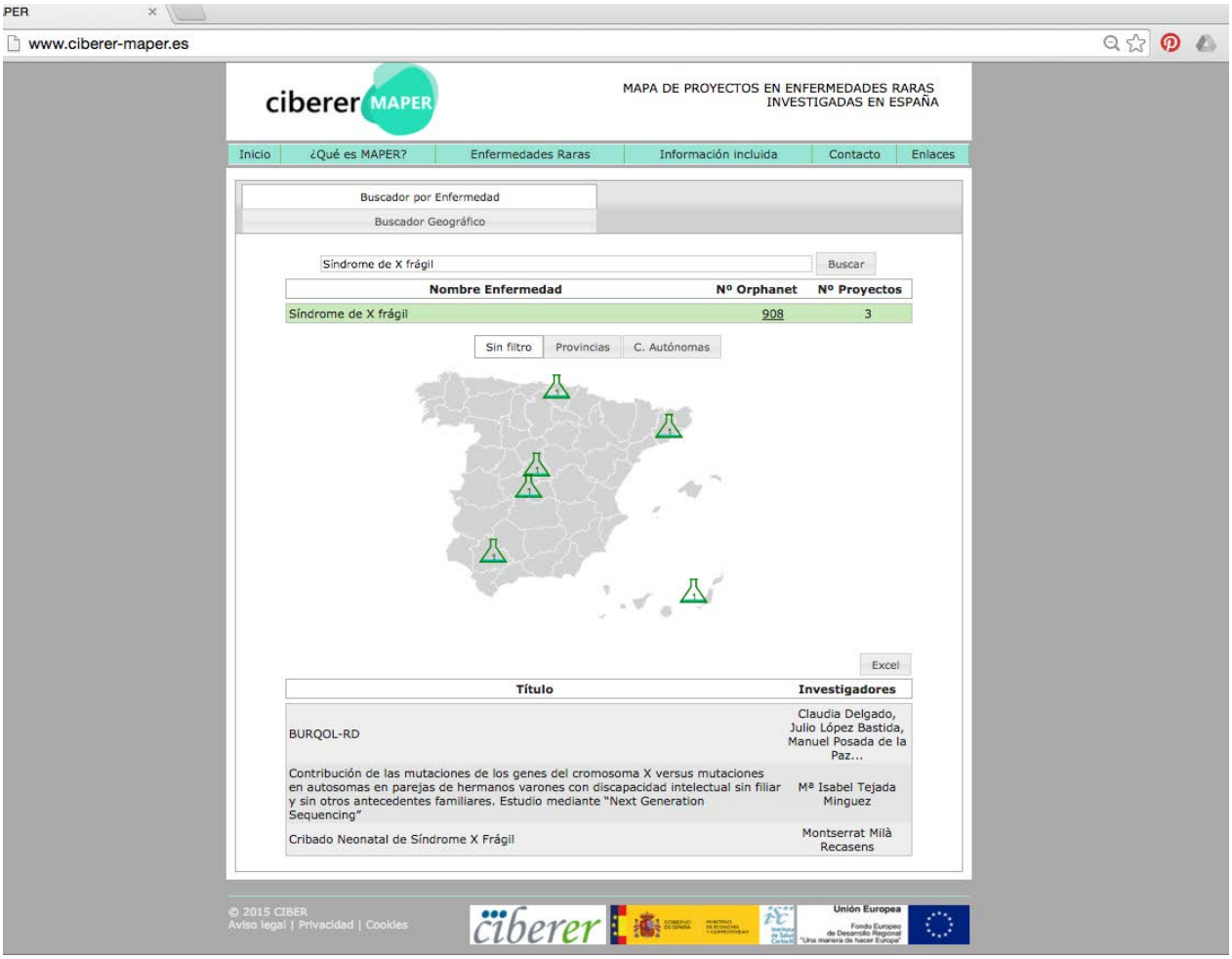
In cooperation with unit U755 an analysis of the phenotype of the mouse model of human retinitis pigmentosa (rd10) and of the response to treatment by the Adalimumab antibody has been made, identifying metabolic markers of therapeutic response preventing the death of photoreceptors (***Scientific Reports***, 2015 Jul 14; 5:11764).

MAPER

MAPER was got under way in 2015, as an interactive map developed by the CIBERER with information on the biomedical research projects which are running in Spain on rare diseases.

To draw up this map, information was compiled on competitive biomedical research and social-healthcare field projects on RD financed by the main public and private funding agencies. Apart from the accessible public information, this had the data provided by the Committee of the Strategy on Rare Diseases of the National Health Service. A large number of researchers have also cooperated with MAPER by voluntarily providing this information. The data on research projects validated and accessible over the MAPER web in 2015 is as follows:

- 396 biomedical research projects active in RD.
- 57 financing agencies participate in financing research into RD.
- Financing close to 90,000,000 €.
- 364 Principal Investigators included in the database.
- 260 RD included in the registry.
- 13 Spanish administrative regions (25 provinces) where these projects are active.



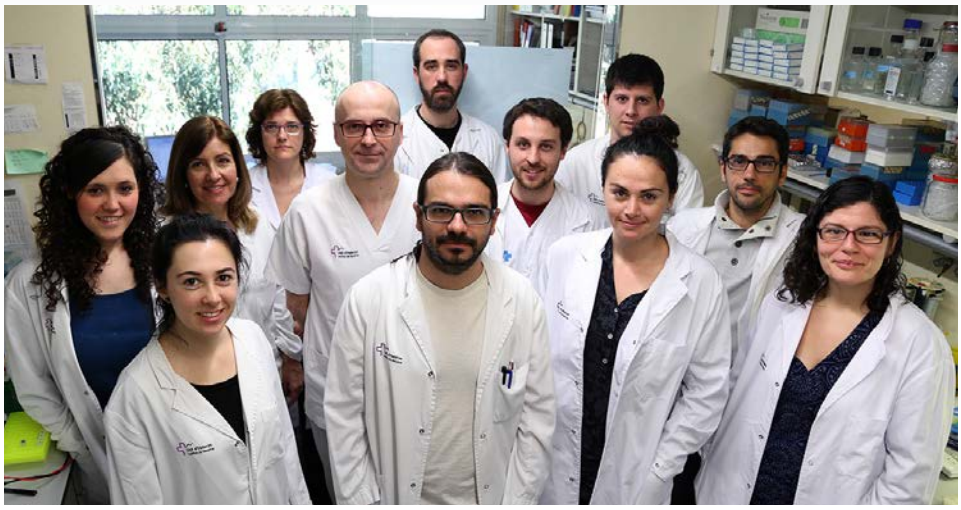
6

Research Groups

Group U701

Programme: Mitochondrial and Neuromuscular Medicine
Lead Researcher: Martí Seves, Ramón

Group members



STAFF MEMBERS: Cámara Navarro, Yolanda | Pinós Figueras, Tomás.

ASSOCIATED MEMBERS: Andreu Périz, Antonio Luis | Brull Cañagueral, Astrid | Carreño Gago, Lidia | García Arumi, Elena | Meliá Grimal, María Jesús | Ortega González, Francisco Javier | Torres Torronteras, Javier.

Main lines of research

- Mechanisms of pathogenicity of mtDNA structural gene mutations.
- Genetic and biochemical study of mitochondrial DNA depletion syndromes: MNGIE, depletion due to TK2 or dGK deficiency and other. Implications in the control of the nucleotide pool.
- Therapeutic approaches for MNGIE and other mitochondrial DNA depletion syndromes.
- McArdle disease: study of pathomechanisms and potential therapeutic approaches.
- Characterization and study of the pathomechanisms involved in the limb-girdle muscular dystrophy caused by mutations in the TNPO3 gene (LGMD1F).

Most relevant scientific articles

CAMARA Y, CARREÑO-GAGO L, MARTÍN MA, MELIÀ MJ, BLÁZQUEZ A, DELMIRO A, ET AL. Severe TK2 enzyme activity deficiency in patients with mild forms of myopathy. Neurology. 2015;In press.

HALTER J, SCHUPBACH WM, CASALI C, ELHASID R, FAY K, HAMMANS S, ET AL. Allogeneic hematopoietic SCT as treatment option for patients with mitochondrial neurogastrointestinal encephalomyopathy (MNGIE): a consensus conference proposal for a standardized approach. Bone Marrow Transplant. 2011 Mar;46(3):330-7.

BRULL A, DE LUNA N, BLANCO-GRAU A, LUCIA A, MARTIN MA, ARENAS J, ET AL. Phenotype consequences of myophosphorylase dysfunction: insights from the McArdle mouse model. J Physiol. 2015 Jun 15;593(12):2693-706.

DE LUNA N, BRULL A, GUIU JM, LUCIA A, MARTIN MA, ARENAS J, ET AL. Sodium valproate increases the brain isoform of glycogen phosphorylase: looking for a compensation mechanism in McArdle disease using a mouse primary skeletal-muscle culture in vitro. Dis Model Mech. 2015 May;8(5):467-72.

NOGALES-GADEA G, BRULL A, SANTALLA A, ANDREU AL, ARENAS J, MARTIN MA, ET AL. McArdle Disease: Update of Reported Mutations and Polymorphisms in the PYGM Gene. Hum Mutat. 2015 Jul;36(7):669-78.

Highlights

During 2015 our group has achieved important scientific goals on the field of mitochondrial genetics, mtDNA replication defects and McArdle disease. We have made a significant advance towards bringing our research from bench to bedside.

In the field of mitochondrial genetics we have established a coordinated strategy to identify the molecular and genetic causes of the diseases of the mitochondrial OXPHOS system integrating genetic and genomic methods.

Regarding the mtDNA replication defects, we have continued our pre-clinical studies on deoxyribonucleoside administration using cell and mouse models (TK2 knockout mouse donated by Dr. Karlsson, Karolinska Institutet, Stcokholm, Sweden). We have also strengthened our interaction with physicians and patient associations. Due to this interaction we have contributed broadening the clinical spectrum of TK2 mutations. We have recently obtained important results indicating that deoxyribonucleoside supply may be effective for many other mtDNA replication defects. This resulted in a registered patent at the European and American agencies. Our collaborative project including pre-clinical studies and the follow-up of patients undergoing compassionate treatment has been awarded by ISCIII (Personalized Medicine Call).

We have also continued our work on gene therapy for MNGIE by developing vectors that drive thymidine phosphorylase expression and ensure the safety and efficiency requirements. We have consolidated an international consortium aimed to conduct a clinical trial using our orphan-drug designated AAV and coordinated a proposal to the H2020 call with this goal.

Concerning McArdle disease we have continued the characterization of the knockin murine model. We have found that the main enzymes involved in glycogen metabolism are distinctly affected in metabolically different types of muscle (glycolytic versus oxidative). Additionally, we have evaluated the efficacy of valproic acid (VPA) as a treatment for McArdle disease. Finally, we have consolidated our collaboration with the Neuromuscular Research Unit, Rigshospitalet (Copenhagen, Denmark), to understand the physiopathologic mechanisms involved in the disease.

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Group U702

Programme: Genetic Medicine

Lead Researcher: Antiñolo, Guillermo

Group members

STAFF MEMBERS: Luzón Toro, Berta | Méndez Vidal, Cristina.

ASSOCIATED MEMBERS: Borrego López, Salud | Bravo Gil, Nereida | Enguix Riego, María del Valle | Fernández García, Raquel María | González del Pozo, María | Lozano Arana, María Dolores | Marcos Luque, Irene | Moya Jiménez, María José | Navarro González, Elena | Peciña López, Ana María | Sánchez García, Francisco Javier | Santoyo López, Javier | Torroglosa González, Ana.

Main lines of research

- Inherited retinal dystrophies
- Hirschsprung disease
- Thyroid cancer
- Breast and ovarian cancer
- Fetal therapy
- Preimplantatory Genetic Diagnosis (PGD)
- Next-Generation Sequencing and Bioinformatics

Most relevant scientific articles

JIANG Q, ARNOLD S, HEANUE T, KILAMBI KP, DOAN B, KAPOOR A, ET AL. Functional loss of semaphorin 3C and/or semaphorin 3D and their epistatic interaction with ret are critical to Hirschsprung disease liability. American journal of human genetics. 2015 Apr 2;96(4):581-96. PubMed PMID: 25839327. Pubmed Central PMCID: 4385176.

LUZON-TORO B, BLEDA M, NAVARRO E, GARCÍA-ALONSO L, RUIZ-FERRER M, MEDINA I, ET AL. Identification of epistatic interactions through genome-wide association studies in sporadic medullary and juvenile papillary thyroid carcinomas. BMC medical genomics. 2015;8:83. PubMed PMID: 26690675. Pubmed Central PMCID: 4685628.

LUZON-TORO B, ESPINO-PAISAN L, FERNÁNDEZ RM, MARTIN-SÁNCHEZ M, ANTINOLO G, BORREGO S. Next-generation-based targeted sequencing as an efficient tool for the study of the genetic background in Hirschsprung patients. BMC medical genetics. 2015;16:89. PubMed PMID: 26437850. Pubmed Central PMCID: 4595130.

LUZON-TORO B, GUI H, RUIZ-FERRER M, SZE-MAN TANG C, FERNÁNDEZ RM, SHAM PC, ET AL. Exome sequencing reveals a high genetic heterogeneity on familial Hirschsprung disease. Scientific reports. 2015;5:16473. PubMed PMID: 26559152. Pubmed Central PMCID: 4642299.

POZO MG, BRAVO-GIL N, MENDEZ-VIDAL C, MONTERO-DE-ESPINOSA I, MILLAN JM, DOPAZO J, ET AL. Re-evaluation casts doubt on the pathogenicity of homozygous USH2A p.C759F. American journal of medical genetics Part A. 2015 Jul;167(7):1597-600. PubMed PMID: 25823529.

Highlights

The group has received funding from external agencies in national projects (ISCIII: PI13/01560 and the Intrasalud project PI11/02923), from the Autonomous Government of Andalusia (Consejería de Salud, PI-0105–2011 and Consejería de Economía, Innovación, Ciencia y Empleo, projects of excellence, CTS-7447 and CTS-1664), and a project of the Foundation Ramon Areces (CIVP16A1856). Within the cooperation agreement in the "Multidisciplinary action on rare diseases and personalized medicine" granted by CDTI-FEDER Innterconecta (EXP000528 87/ITC-20111037), the group has developed a personalized medicine tool, using Inherited Retinal Dystrophies as a model. This tool integrates a full bioinformatics analysis with the automatic generation of a diagnostic report that links to the digital clinical history. It is also worth mentioning, a study showing that the common allele of the USH2A gene, p.C759F, is not pathogenic in homozygosis. These results indicate the need of re-evaluating all families genetically diagnosed with this mutation.

In the context of cooperative activity, the group has published six articles, two of them as a result of international collaboration, one within the International Consortium of Hirschsprung disease. The remaining four are the result of different collaborations with CIBERER units (U706, U715 and U735).

In addition, we have been first to perform whole exome sequencing in families with Hirschsprung disease (HSCR). This study showed a remarkable degree of genetic heterogeneity. This helps to understand the problematic behind genetic counselling in HSCR. In addition, we have designed and validated a panel of genes associated with HSCR, as an efficient tool for a preliminary genetic screening in patients.

As for the thyroid cancer research line, two significant epistatic gene interactions in medullary thyroid cancer and three in juvenile papillary thyroid cancer (formed by a ncRNA and a gene), both tumors with a poor molecular characterization.

Finally, preimplantation genetic diagnosis has been applied in families with hemophilia and in affected couples of X-fragile Syndrome, representing a reproductive option for affected families and an achievement for the public healthcare system in these pathologies.

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Group U703

Programme: Inherited Metabolic Medicine
Lead Researcher: Artuch Iriberri, Rafael

Group members

STAFF MEMBERS: Molero Luis, Marta | Montero Sánchez, Raquel.

ASSOCIATED MEMBERS: Armstrong Moron, Judith | Campistol Plana, Jaume | Fons Estupiña, María del Carmen | García Cazorla, María Ángeles | Jiménez Mallebrera, Cecilia | Jou Muñoz, Cristina | Martorell Sampol, Loreto | Nascimento Osorio, Andres | Ormazabal Herrero, Aida | Pérez Dueñas, Belén | Serrano Gimaré, Mercedes.

Main lines of research

- Phenylketonuria and other aminoacidopathies.
- Mitochondrial diseases through oxidative phosphorylation defects and coenzyme Q10 deficiency.
- Neurometabolic disorders in the synthesis of neurotransmitters, pterins and glucose transport defects. Since 2003 we have implemented the study of neurometabolic diseases, offering this service to different centres in Spain, Portugal, Greece, Argentina, Chile, La India and Turkey.
- Muscular dystrophies in childhood.
- Congenital disorders of glycosylation.
- Movement disorders in childhood.

Most relevant scientific articles

REDDY P, OCAMPO A, SUZUKI K, LUO J, BACMAN SR, WILLIAMS SL, SUGAWARA A, OKAMURA D, TSUNEKAWA Y, WU J, LAM D, XIONG X, MONTSERRAT N, ESTEBAN CR, LIU GH, SANCHO-MARTÍNEZ I, MANAU D, CIVICO S, CARDELLACH F, DEL MAR O'CALLAGHAN M,CAMPISTOL J, ZHAO H, CAMPISTOL JM, MORAES CT, IZPISUA BELMONTE JC. Selective elimination of mitochondrial mutations in the germline by genome editing. Cell. 2015 Apr 23;161(3):459-69.

ORMAZABAL A, CASADO M, MOLERO-LUIS M, MONTOYA J, RAHMAN S, AYLETT SB, HARGREAVES I, HEALES S, ARTUCH R. Can folic acid have a role in mitochondrial disorders?. Drug Discov Today. 2015 Nov;20(11):1349-54.

SERRANO M, DE DIEGO V, MUCHART J, CUADRAS D, FELIPE A, MACAYA A, VELÁZQUEZ R, POO MP, FONS C, O'CALLAGHAN MM, GARCÍA-CAZORLA A, BOIX C, ROBLES B, CARRATALÁ F, GIRÓS M, BRIONES P, GORT L, ARTUCH R, PÉREZ-CERDÁ C, JAEKEN J, PÉREZ B, PÉREZ-DUEÑAS B. Phosphomannomutase deficiency (PMM2-CDG): ataxia and cerebellar assessment. Orphanet J Rare Dis. 2015 Oct 26;10:138.

KÖLKER S, VALAYANNOPOULOS V, BURLINA AB, SYKUT-CEGIELSKA J, WIJBURG FA, TELES EL, ZEMAN J, DIONISI-VICI C, BARIĆ I, KARALL D, ARNOUX JB, AVRAM P, BAUMGARTNER MR, BLASCO-ALONSO J, BOY SP, RASMUSSEN MB, BURGARD P, CHABROL B, CHAKRAPANI A, CHAPMAN K, CORTÈS I SALADELAFONT E, COUCE ML, DE MEIRLEIR L, DOBBELAERE D, FURLAN F, GLEICH F, GONZÁLEZ MJ, GRADOWSKA W, GRÜNEWALD S, HONZIK T, HÖRSTER F, IOANNOU H, JALAN A, HÄBERLE J, HAEGE G, LANGEREIS E, DE LONLAY P, MARTINELLI D, MATSUMOTO S, MÜHLHAUSEN C, MURPHY E, DE BAULNY HO, ORTEZ C, PEDRÓN CC, PINTOS-MORELL G, PENA-QUINTANA L, RAMADŽA DP, RODRIGUES E, SCHOLL-BÜRGI S, SOKAL E, SUMMAR ML, THOMPSON N, VARA R, PINERA IV, WALTER JH, WILLIAMS M, LUND AM, GARCÍA CAZORLA A. The phenotypic spectrum of organic acidurias and urea cycle disorders. Part 2: the evolving clinical phenotype. J Inherit Metab Dis. 2015 Nov;38(6):1059-74.

ASENCIO C, RODRÍGUEZ-HERNÁNDEZ MA, BRIONES P, MONTOYA J, CORTÉS A, EMPERADOR S, GAVILÁN A, RUIZ-PESINI E, YUBERO D, MONTERO R, PINEDA M, O'CALLAGHAN MM, ALCÁZAR-FABRA M, SALVIATI L, ARTUCH R, NAVAS P. Severe encephalopathy associated to pyruvate dehydrogenase mutations and unbalanced coenzyme Q10 content. Eur J Hum Genet. 2016 Mar;24(3):367-72.

Highlights

During 2015, our group has got different reasearcg grants, since all of our principal investigators are developing research projects funded by public agencies, such a the ISCIII. Noteworthy, 2 new young principal researchers have got, for the first time, funds from FIS, for developing their projects in the area of rare diseases (Drs. Serrano and Ormazabal). Namely, one project is about congenital disorders of glycosylation and the other is about new biomarkers for neurometabolic diseases.

Regarding the research results of the group, we have reach a similar level of scientific publications when compared with previous years, with a remarkable traslational and collaborative component (at national and international levels). For example, Dr. García-Cazorla has leaded an international colaborative article about the results from an European registry for genetic-metabolic diseases. As a result, practical recommendations and guidelines have been developed.

As regards our relationships with patients and families associations, we have paticipated in the first meeting of a new Spanish association for patients with inborn errors of neurotransmission This meeting hold in valencia during 2015 was registered in the CIBERER web page.

Lastly, our Hospital is experiencing a deep transformation, especially in the area of rare diseases. A new pediatric Institute for rare diseases has been launched, with the incorporation of Dr. Francesc Palau, who will be the person in charge of leading this ambiciuos project.

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Group U704

Programme: Sensorineural Pathology
Lead Researcher: Ayuso, Carmen

Group members

STAFF MEMBERS: Gomez Sánchez, Clara Isabel | Sánchez Alcudia, Rocío | Zurita Muñoz, Olga.

ASSOCIATED MEMBERS: Blanco Kelly, Fiona | Bustamante Aragones, Ana | Cardero Merlo, Rocío de la Libertad | Cortón Pérez, Marta | Díaz Recasens, Joaquín | Fernández Moya, José María | Fernández San José, Patricia | Gallego Merlo, Jesús | García Sandoval, Blanca | Giménez Pardo, Ascension | Infantes Barbero, Fernando | Lorda Sánchez, Isabel | Martín Mérida, Inmaculada | Pérez Carro, Raquel | Perlado Marina, Sara | Plaza Arranz, Francisco Javier | Ramos Corrales, Carmen | Riveiro Álvarez, Rosa | Rodríguez de Alba Freiria, Marta | Sánchez Navarro, Iker | Trujillo Tiebas, María José | Villaverde Montero, Cristina.

Main lines of research

- Hereditary retinal dystrophies: identification of new genes and mutational mechanisms, genotype–phenotype correlation, genetic epidemiology, modifying genetic factors and development of algorithms.
- Complex neurodegenerative diseases: omic approach models.
- Pharmacogenetics.
- Quality control over genetic and genomic studies. Ethical aspects and informed consent.
- Infertility: Genetic and chromosomal factors.
- Non-invasive prenatal diagnosis applied to Mendelian and aneuploidy disorders.
- Genetic cardiovascular diseases: sudden death and cardiomyopathy.
- Ocular malformations, aniridia, anophthalmia, glaucoma and others.
- Neuromuscular and neurological diseases.
- Congenital skeletal abnormalities.
- Therapeutic aspects: Pharmacogenetics, IPSC and Clinical Trials.

Most relevant scientific articles

AVILA-FERNÁNDEZ A, PÉREZ-CARRO R, CORTÓN M, LÓPEZ-MOLINA MI, CAMPELLO L, GARANTO A ET AL. Whole-exome sequencing reveals ZNF408 as a new gene associated with autosomal recessive retinitis pigmentosa with vitreal alterations. Hum Mol Gen 2015 Jul 15;24(14):4037-48 doi: 10.1093/hmg/ddv140. PMID: 25882705

NIKOPOULOS K, AVILA-FERNÁNDEZ A, CORTON M, LÓPEZ-MOLINA MI, PEREZ-CARRO R, BONTADELLI L, ET AL. Identification of two novel mutations in CDHR1 in consanguineous Spanish families with autosomal recessive retinal dystrophy. Sci Rep. 2015 Sep 9;5:13902. PMID: 26350383

AYUSO C, MILLAN JM, DAL-RE R. Management and return of incidental genomic findings in clinical trials. Pharmacogenomics J. 2015 Feb;15(1):1-5. doi: 10.1038/tpj.2014.62. PMID: 25348616

LUKOVIC D, ARTERO-CASTRO A, DELGADO AB, BERNAL M DE L, LUNA PELÁEZ N, DÍEZ LLORET A ET AL,. Human iPSC derived disease model of MERTK-associated retinitis pigmentosa. Sci Rep. 2015 Aug 11;5:12910. PMID: 26263531

CASTRO-SÁNCHEZ S, ÁLVAREZ-SATTA M, CORTÓN M, GUILLÉN E, AYUSO C, VALVERDE D. Exploring genotype-phenotype relationships in Bardet-Biedl syndrome families. J Med Genet. 2015 Aug;52(8):503-13. PMID: 26082521

Highlights

PROJECTS

IP. C. AYUSO

1. "Identification of new molecular mechanisms in retinal dystrophies, translation to diagnosis and development of new gene and cell therapies." ISCIII (PI13 / 00226).
2. "Molecular and functional characterization of sporadic or autosomal dominant retinal dystrophies. Combined molecular mapping and exomic sequencing strategies" ACCI (ER15PR05ACCI14-704).
3. CONSYN: "Challenging the molecular diagnosis of Complex and Rare Diseases: WES analysis for Congenital Syndromes". CNAG-Call: 300 exomes to elucidate rare diseases.
4. "Clinical and molecular characterization in Spanish families with adDR using Next Generation Sequencing (NGS). Searching for new genes and algorithms design for molecular diagnosis". ONCE 2014.
5. "Clinical exome sequencing as a proxy for clinical and genetic characterization of Spanish families affected syndrome retinal Distrophies (sRD)". ONCE 2015.

IP-WP. C. AYUSO

6. "SPANEX (Spanish Exomes Project). A web-based database of variants of the normal monitoring healthy population of 1000 Spanish people". CIBERER-ISCIII.
7. "Beyond the Genome;. Training the next generation of ophthalmic Researchers EyeTN" (Marie Curie International Training Network).

IP. M. CORTÓN

9. "Towards a better understanding of the genetic basis of congenital eye malformations using high-throughput genomic technologies". Miguel Servet 2013.
10. "Molecular Study of Aniridia and other congenital eye malformations: Find new genetic mechanisms by NGS" (SAF2013-46943-R).
11. "Application of NGS techniques to genetic study of aniridia and other anterior segment dysgenesis." Mutua Madrileña Foundation.

BOOK "Gestión de datos genómicos con finalidad clínica y de investigación. Grupo de trabajo en gestión de datos genómicos". External Reviewer: Carmen Ayuso. Roche Farma Idemm Institute and S.L. ISBN: 978-84-944589-1-0 Legal Deposit: B 28474-2015.

WORKING GROUP Guía de Práctica Clínica sobre Distrofias de Retina" Ministry of Health.

ORGANIZATION OF COURSES / SEMINARS: "Pharmacogenetics"; "Genetic Medicine"; "DNA-day"; "Research on rare and common diseases"; "CNAG Symposium"; "Albino Day"; "Genomics C. Madrid"; "XLVIII L. Conmemorativa Jiménez Díaz".

Institution: Fundación Instituto de Investigación Sanitaria Fundación Jiménez Díaz.
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Group U705

Programme: Genetic Medicine

Lead Researcher: Baiget Bastús, Montserrat

Group members

STAFF MEMBERS: Alías Andreu, Laura | González Quereda, Lidia | Salazar Blanco, Juliana.

ASSOCIATED MEMBERS: Gallano Petit, María Pía | Lassa Laborde, Adriana | Páez López-Bravo, David | Tizzano Ferrari, Eduardo.

Main lines of research

- Study of clinical and genetic heterogeneity of limb-girdle muscular dystrophy of autosomal recessive inheritance and autosomal dominant transmission.
- Spinal muscular atrophy and SMN genes: 1. Studies of the molecular pathology, disease mechanisms and expression of SMN gene. 2. Identification of modifier genes. 3. Study of biological markers for validation of treatment for spinal muscular atrophy. 4. Study of the neuromuscular junction in human development.
- Hereditary breast cancer and BRCAs genes: 1. Identification of mutations and genetic variants. 2. Molecular characterization of circulating tumor cells (CTCs) through expression profiling in breast cancer patients. 3. Analysis of free circulating tumor DNA (cfDNA) as a predictor of response to treatment of breast cancer.
- Pharmacogenetics: Adverse drug reactions.
- Congenital coagulopathies: molecular pathology of haemofilias.
- Duchenne and Becker muscle dystrophies: molecular pathology of DMD gene.
- Elaboration of molecular diagnostic panels in hereditary monogenic pathology by means of the nanofluid system and massive sequencing.

Most relevant scientific articles

JUAN-MATEU J , GONZÁLEZ-QUEREDA L , RODRÍGUEZ MJ, BAENA M, VERDURA E, NASCIMENTO A, ET AL. DMD Mutations in 576 Dystrophinopathy Families: A Step Forward in Genotype-Phenotype Correlations. PlosOne. 2015;10(8): e0135189.

PARÉ-BRUNET L, SEBIO A, SALAZAR J, BERENGUER-LLERGO A, RÍO E, BARNADAS A ET AL. Genetic variations in the VEGF pathway as prognostic factors in metastatic colorectal cancer patients treated with oxaliplatin-based chemotherapy.Pharmacogenomics J. 2015;15(5):397-404.

MARTÍN-BLANCO A, FERRER M, SOLER J, ARRANZ MJ, VEGA D, CALVO N, ET AL. Therole of hypothalamus-pituitary-adrenal genes and childhood trauma in border line personality disorder. Eur Arch Psychiatry Clin Neurosci. 2015.

BOZA-MORÁN MG, MARTÍNEZ-HERNÁNDEZ R, BERNAL S, WANISCH K, ALSO-RALLO E, LE HERON A, ET AL. Decay in survival motor neuron and plastin 3 levels during differentiation of iPSC-derived human motor neurons. Sci Rep. 2015;5:11696.

SEBIO A, SALAZAR J, PÁEZ D, BERENGUER-LLERGO A, DEL RÍO E, TOBEÑA M, ET AL. EGFR ligands and DNA repair genes: genomic predictors of complete response after capecitabine-based chemoradiotherapy in locally advanced rectal cancer. Pharmacogenomics J. 2015;15(1):77-83.

Highlights

The U705 has maintained its high level of production and quality in research and clinical diagnosis of rare diseases during 2015.

In the evaluated period, the Unit has published a large number of papers in international scientific journals with good impact factors and has participated in the writing of the guidelines “Manual de Práctica Clínica en Senología”. Due to this scientific production, the Unit has attracted new funding from the competitive agencies FIS/ISCIII, ACCI and Mutua Madrileña Foundation, and also through donations from private companies (Ecogen and Gebro Pharma). Many of the projects funded will be conducted in collaboration with other CIBERER Units and linked clinical groups (U732, U703, GCV01, GCV02, GCV03 and GCV04).

Clinical trials in SMA and Pharmacogenetics, international registries –the DMD Registry (TREAT-NMD) and the National Registry of SMA patients-, and collaborations with scientific societies and patient associations –the ASEM and the SEN- which were started in previous years are still active. This is in addition to our continuing participation in clinical committees on genodermatoses and pediatrics in Sant Pau Hospital, and interhospital meetings on neuromuscular diseases in which the U703 and U732 Units also collaborate.

Regarding training, the Unit has organized the “Jornada CIBERER: actualización en Hemofilia”, the “VII Curso Teórico-práctico: Aplicación de las nuevas tecnologías al diagnóstico genotípico” and has initiated a seminar cycle in which researchers of CIBERER Units (U703, U732, U745, U726 and U747) participate. The mobility grant awarded to one of our CIBER employees permitted collaboration with U715 in analyzing and interpreting the NGS results generated by the CIBERER platform (U702) in the Program of Genetic Medicine. In 2015, a Rio Hortega-funded researcher led by the IP Unit defended her PhD thesis obtaining the highest qualification.

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Group U706

Programme: Inherited Cancer, Haematological & Dermatological Diseases
Lead Researcher: Benítez, Javier

Group members

STAFF MEMBERS: Gayarre Navarro, Javier | Inglada Pérez, Lucía.

ASSOCIATED MEMBERS: Cascón Soriano, Alberto | Fernández de Gabriel, Victoria | García Pérez, María José | García Aznárez, Francisco Javier | Martínez Delgado, Beatriz | Osorio Cabrero, Ana Laura | Robledo Batanero, Mercedes | Rodríguez González de Antona, Cristina | Urioste Azcorra, Miguel

Main lines of research

- Hereditary breast cancer.
- Cromosomal instability syndrome.
- Genetic Epidemiology.
- Cromosomal alterations.
- Hereditary colorectal cancer.
- Familial endocrine cancer.
- Pharmacogenetics and cancer.
- Hereditary ovarian cancer.

Most relevant scientific articles

CASCÓN A, COMINO-MÉNDEZ I, CURRÁS-FREIXES M, DE CUBAS AA, CONTRERAS L, RICHTER S, PEITZSCH M, MANCIKOVA V, INGLADA-PÉREZ L, PÉREZ-BARRIOS A, CALATAYUD M, AZRIEL S, VILLAR-VICENTE R, ALLER J, SETIÉN F, MORAN S, GARCÍA JF, RÍO-MACHÍN A, LETÓN R, GÓMEZ-GRAÑA Á, APELLÁNIZ-RUIZ M, RONCADOR G, ESTELLER M, RODRÍGUEZ-ANTONA C, SATRÚSTEGUI J, EISENHOFER G, URIOSTE M, ROBLEDO M. Whole-Exome Sequencing Identifies MDH2 as a New Familial Paraganglioma Gene. J Natl Cancer I 2015; 107, djv053.

DE CUBAS AA, KORPERSHOEK E, INGLADA-PÉREZ L, LETOUZÉ E, CURRÁS-FREIXES M, FERNÁNDEZ AF, COMINO-MÉNDEZ I, SCHIAVI F, MANCIKOVA V, EISENHOFER G, MANNELLI M, OPOCHER G, TIMMERS H, BEUSCHLEIN F, DE KRIJGER R, CASCON A, RODRÍGUEZ-ANTONA C, FRAGA MF, FAVIER J, GIMÉNEZ-ROQUEPLO AP, ROBLEDO M. DNA Methylation Profiling in Pheochromocytoma and Paraganglioma Reveals Diagnostic and Prognostic Markers. Clin Cancer Res 2015;21, 3020-3030.

CALVETE O, MARTÍNEZ P, GARCÍA-PAVIA P, BENITEZ-BUELGA C, PAUMARD-HERNÁNDEZ B, FERNÁNDEZ V, DOMINGUEZ F, SALAS C, ROMERO-LAORDEN N, GARCÍA-DONAS J, CARRILLO J, PERONA R, TRIVIÑO JC, ANDRÉS R, CANO JM, RIVERA B, ALONSO-PULPON L, SETIEN F, ESTELLER M, RODRÍGUEZ-PERALES S, BOUGEARD G, FREBOURG T, URIOSTE M, BLASCO MA, BENÍTEZ J. A mutation in the POT1 gene is responsible for cardiac angiosarcoma in TP53-negative Li-Fraumeni-like families. Nat Commun 2015;6, 8383.

MATAMALA N, VARGAS MT, GONZÁLEZ-CÁMPORA R, MIÑAMBRES R, ARIAS JI, MENÉNDEZ P, ANDRÉS-LEÓN E, GÓMEZ-LÓPEZ G, YANOWSKY K, CALVETE-CANDENAS J, INGLADA-PÉREZ L, MARTÍNEZ-DELGADO B, BENÍTEZ J. Tumor MicroRNA Expression Profiling Identifies Circulating MicroRNAs for Early Breast Cancer Detection. Clin Chem 2015;61, 1098-1106.

PEREA J, CANO JM, RUEDA D, GARCÍA JL, INGLADA L, OSORIO I, ARRIBA M, PÉREZ J, GASPAR M, FERNÁNDEZ-MIGUEL T, RODRÍGUEZ Y, BENÍTEZ J, GONZÁLEZ-SARMIENTO R, URIOSTE M. Classifying early-onset colorectal cancer according to tumor location: new potential subcategories to explore. Am J Cancer Res 2015; 5, 2308-2313.

Highlights

The U706 aims to identify genetic alterations conferring cancer susceptibility, and to translate our discoveries into clinical practice. The Unit attends patients with suspected genetic susceptibility to cancer at our consultancy in the Medical Oncology Service of the Hospital Universitario de Fuenlabrada (HUF). Discussions of protocols and clinical guidelines are held monthly conducted by the hospital's Hereditary Cancer Clinical Committee, created in March 2015.

We have doubled the number of patients visited in our consultancy at HUF (318 versus 163 during 2014). 328 genetic diagnostic studies were performed (314 in 2014). Analysis of the SMARCE1 gene, associated with familial meningiomas, was incorporated into our catalogue of services.

The Unit actively contributed to the search for new genes implicated in cancer susceptibility through the Familial Cancer Exome Project that we are conducting. Mutations in MDH2, responsible for familial paragangliomas, in FAN1 causing familial colorectal cancer type X, in POT1 as cause of hereditary cardiac angiosarcoma or in ATP4a as cause of gastric carcinoide, are some of our findings.

We are interested in the identification of modifier genes that modulate age of onset, disease evolution and cancer risk, and in polymorphisms that improve the quality of life for cancer patients (Pharmacogenetics). Neuropathy limits dose and efficacy of these drugs, and diminishes the quality of life of the patients, sometimes permanently. To note our findings on the role of miRNAs as early diagnostic biomarkers of breast cancer.

Establishing relationships with cancer patient associations is another goal. During 2015, the Unit strengthened its relationships with ASACO (Asociación de Afectados por Cáncer de Ovario) and AEAS (Asociación de Afectados por Sarcomas).

PATENT

Perea-García J., González-Sarmiento R., Urioste-Azcorra M., Rueda-Fernández, D., Arriba-Domènech, M., García-Hernández J.L., Pérez-García. J (2015). *Biomarcador para el diagnóstico, pronóstico y seguimiento de cáncer colorectal de aparición precoz*. ES201531891.

Institution: Fund. Centro Nacional de Invest. Oncológicas · **Contact:** C/ Melchor Fernández Almagro, 3. 28029 Madrid · Tel.: 91 224 69 65 /91 732 80 00 · E.mail: jbenitez@cnio.es · Website: www.cnio.es

Group U707

Programme: Genetic Medicine

Lead Researcher: Bernabéu, Carmelo

Group members

STAFF MEMBERS: Ruiz Llorente, Lidia.

ASSOCIATED MEMBERS: Botella Cubells, Luisa María | Gallardo Vara, Eunate | Langa Poza, Carmen | Morales Angulo, Carmelo | Zarrabeitia Puente, Roberto.

Main lines of research

- Studies of expression, function and structure of endoglin and its relevance in hereditary hemorrhagic telangiectasia and other pathologies such as preeclampsia.
- Genetic and cellular studies on the Spanish population with hereditary hemorrhagic telangiectasia.
- Molecular diagnostics and characterization of pathogenic mechanisms of hereditary hemorrhagic telangiectasia in the TGF-beta signaling pathway.
- Cellular and animal models for studying the function of endoglin and ALK1 in physiopathology.
- New therapies for hemangioblastomas and carcinomas from the von Hippel Lindau (VHL) disease, produced by constitutive expression of hypoxia inducible factor (HIF).

Most relevant scientific articles

BLANCO FJ, OJEDA-FERNÁNDEZ L, ARISTORENA M, GALLARDO-VARA E, BENGURIA A, DOPAZO A, LANGA C, BOTELLA LM, BERNABEU C. Genome-wide transcriptional and functional analysis of endoglin isoforms in the human promonocytic cell line U937. J. Cell Physiol. (2015) Apr; 230(4): 947-958. doi: 10.1002/jcp.24827.

DEL CASTILLO G, SÁNCHEZ-BLANCO E, MARTÍN-VILLAR E, VALBUENA-DIEZ AC, LANGA C, PÉREZ-GÓMEZ E, RENART J, BERNABÉU C, QUINTANILLA M. Soluble endoglin antagonizes Met signaling in spindle carcinoma cells. Carcinogenesis. (2015) Feb; 36(2): 212-222. doi: 10.1093/carcin/bgu240.

ROSSI E, LÓPEZ-NOVOA JM, BERNABEU C. Endoglin involvement in integrin-mediated cell adhesion as a putative pathogenic mechanism in Hereditary Hemorrhagic Telangectasia type 1 (HHT1). Front. Genet. (2015) January 2015, volume 5, article 457, pages 1-5. doi: 10.3389/fgene.2014.00457.

BOTELLA LM, ALBIÑANA V, OJEDA-FERNÁNDEZ L, RECIO-POVEDA L, BERNABÉU C. Research on potential biomarkers in hereditary hemorrhagic telangiectasia. Front. Genet. (2015) March 31; volume 6: article 115, pages 1-9. doi: 10.3389/fgene.2015.00115.

ALBIÑANA V, VILLAR GÓMEZ DE LAS HERAS K, SERRANO-HERAS G, SEGURA T, PERONA-MORATALLA AB, MOTA-PÉREZ M, DE CAMPOS JM, BOTELLA LM. Propranolol reduces viability and induces apoptosis in hemangioblastoma cells from von Hippel-Lindau patients. Orphanet J. Rare Dis. 2015 Sep 22; 10(1): 118. doi: 10.1186/s13023-015-0343-5.

Highlights

HHT NETWORK. We have made advances to create a Spanish network of clinical units in Hereditary Hemorrhagic Telangiectasia (HHT), reaching agreements regarding HHT assessment protocols. The link-up request to join CIBERER from two HHT clinical groups has been processed: i) Dr. Antoni Riera Mestre (Hospital de Bellvitge, Barcelona); and ii) Dr. José Luis Patier (Hospital Universitario Ramón y Cajal, Madrid).

ORPHAN DRUG. After obtaining the designation by the EMA (European Medicines Agency) of Bazedoxifene acetate (Conbriza) as an orphan drug for HHT, a maintenance report corresponding to 2015 has been issued, as requested by EMA.

PATHOGENIC MECHANISM. The involvement of endoglin in integrin-mediated cell adhesion has been postulated as a pathogenic mechanism in HHT and the reported biomarkers for this disease have been analyzed. Progress has been made in understanding the role of membrane endoglin (mutated protein in HHT1). It has been demonstrated that propranolol reduces viability and induces apoptosis in hemangioblastoma cells from von Hippel-Lindau patients.

PARTNERSHIPS AND OTHERS. We have maintained an active collaboration with the the Spanish Patient Association of HHT, FEDER, European associations of HHT through EURORDIS and the American international HHT association. We have actively participated in several scientific conferences, especially in the "11th International Hereditary Hemorrhagic Telangiectasia Scientific Conference", Captiva, Florida, USA (11-14 June, 2015) and the VIII Meeting of the Spanish HHT Association, Fundación ONCE, Madrid (9-10 October, 2015). Two doctoral theses have been presented by contracted/affiliated CIBERER members: i) Maria Luisa Ojeda Fernandez; Plasma biomarkers and impaired immune response in Hereditary Hemorrhagic Telangiectasia (HHT). December 18, 2015. ii) Roberto Zarrabeitia Puente; Epidemiology of HHT in Spain: Experience in the specialized unit of the Hospital Sierrallana (2003-2013). December 15, 2015.

Institution: Agencia Estatal Consejo Superior de Investigaciones Científicas
Contact: Centro de Invest. Biológicas · Ramiro de Maeztu, 9. 28040 Madrid · Tel.: 91 837 31 12 ext 4246

Group U708

Programme: Endocrine Medicine
Lead Researcher: Bernal, Juan

Group members

STAFF MEMBERS: Morte Molina, Beatriz.

ASSOCIATED MEMBERS: Bárez López, Soledad | Gil Ibáñez, Pilar | Guadaño Ferraz, Ana Cristina | Martín Belinchón, Mónica.

Main lines of research

- CONGENITAL HYPOTHYRODISM: Mechanisms of action of the thyroid hormone in the brain. Physiopathology of neural alterations over thyroid hormone deprivation during the fetal and neonatal periods. Influence of maternal thyroid hormones and consequences of maternal hypotiroxinemia over gene expression in the fetal brain.
- SLC16A2 MUTATIONS: Physiopathology of the Allan-Herndon-Dudley syndrome and deficiency of T3 transport in the syndrome using transporter knock out mice. Development of new therapeutic approaches based on thyroid hormone analogues with alternative transport. Histopathological studies from MCT8-deficient human brains. Study of patients with MCT8-like syndromes but without SLC16A2 mutations.
- THYROID HORMONE RESISTANCE: Alteration mechanisms in mental retardation and attention deficit- hyperactivity disorder as a consequence of beta type T3 receptor mutations.

Most relevant scientific articles

GIL-IBAÑEZ P, GARCÍA-GARCÍA F, DOPAZO J, BERNAL J, MORTE B. Global Transcriptome Analysis of Primary Cerebrocortical Cells: Identification of Genes Regulated by Triiodothyronine in Specific Cell Types. Cereb Cortex. 2015 Nov 2. pii: bhv273. [Epub ahead of print]

BERNAL J, GUADAÑO-FERRAZ A, MORTE B. Thyroid hormone transporters--functions and clinical implications. Nat Rev Endocrinol. 2015; 11(7):406-17.

BRABANT G, PEETERS RP, CHAN SY, BERNAL J, BOUCHARD P, SALVATORE D, BOELAERT K, LAURBERG P. Management of subclinical hypothyroidism in pregnancy: are we too simplistic? Eur J Endocrinol. 2015; 173(1):1-11.

AGUILERA Ó, GONZÁLEZ-SANCHO JM, ZAZO S, RINCÓN R, FERNÁNDEZ AF, TAPIA O, CANALS F, MORTE B, CALVANESE V, ORGAZ JL, NIELL N, AGUILAR S, FREIJE JM, GRAÑA O, PISANO DG, BORRERO A, MARTÍNEZ-USEROS J, JIMÉNEZ B, FRAGA MF, GARCÍA-FONCILLAS J, LÓPEZ-OTÍN C, LAFARGA M, ROJO F, MUÑOZ A. Nuclear DICKKOPF-1 as a biomarker of chemoresistance and poor clinical outcome in colorectal cancer. Oncotarget. 2015; 6(8):5903-5917.

Highlights

The group continues the studies on the pathogenesis of Allan-Herndon-Dudley Syndrome due to MCT8 mutations. In January Morte, Guadaño-Ferraz, and Bernal, attended a meeting supported by the Sherman Family, from Australia, that took place in Marina del Rey, California, together with groups investigating this disease, and parents of patients, to discuss recent advances in the study of the syndrome.

Dr. Bernal was invited to the European Endocrine Congress in Dublin, and to the International Thyroid Meeting in Orlando. Dr. Bernal was nomitated by the Spanish Society of Endocrinlogy as a candidate for the European Endocrine Societies medal. Dr. Guadaño was invited to the Prometeo-Generalitat Valenciana workshop on nuclear receptors, organized by Miguel Hernández University, Elche. Dr. Morte co-organized with Dr. Resmini (U747) an International Symposium of the Areces Foundation (Rare Endocrine Diseases: from Resarch to Clinical Management), with the participation of Dr. Bernal as speaker. Dr. Morte was on sabbatical at the Maine Medical Center Research Institute, Maine, USA, from June through December, 2015. Data on CGH arrays, performed as a collaboration between Dr. Morte and Dr. Moreno (INGEM, La Paz), and supported by a prize from the Madrid Endocrine Society, were presented in the annual meeting of the Society. Dr. Daniela Lopez Espindola presented her Doctoral Thesis on the Pathology of the brain in MCT8 patients.

The group continues to provide diganosis of RTH and MCT8 mutations, and the collaboration with Drs. Heuer (Germany) and Appelbaum (Israel) in the frame of an E-Rare-2 project. Drs. Bernal and Guadaño as IP have been awarded a new project from the Plan Nacional (SAF2014-54919-R: Mecanismos de enfermedad en el síndrome de Allan-Herndon-Dudley).

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Group U709

Programme: Sensorineural Pathology
Lead Researcher: Bovolenta, Paola

Group members

STAFF MEMBERS: Sandonís Consuegra, África.

ASSOCIATED MEMBERS: Cardozo Ruiz, Marcos Julián | Cavodeassi Madarro, Florencia | Esteve Pastor, Pilar.

Main lines of research

- Determination of the transcriptional network regulating ocular development and its implication in congenital developmental disorders.
- Study of the molecular basis for hereditary retinal dystrophies and generation of animal models.
- Study of the function of the Shh and Wnt signaling pathways in axon guidance and its implications in congenital visual system disorders.
- Regulation of metalloprotease activity in nervous system development and its implications in congenital developmental disorders and cell homeostasis.
- Study of the physiopathological basis for Lafora and Alzheimer Diseases.

Most relevant scientific articles

MARCOS S., NIETO-LÓPEZ F., SANDONIS A., DI MARCO, F., CARDOZO M., ESTEVE, P. AND BOVOLENTA P. Secreted Frizzled Related Proteins modulate pathfinding and fasciculation of mouse retina ganglion cell axons by direct and indirect mechanisms. J. Neurosci. 2015; 35, 4729-4740 (cover caption article)

GÓMEZ-MARÍN C, TENA JJ, ACEMEL RD, LÓPEZ-MAYORGA E NARANJO S, DE LA CALLE-MUSTIENES E, MAESO I, BECCARI L, ANEAS, I, VIELMAS E, BOVOLENTA P., NOBREGA, M.A, CARVAJAL JJ, GÓMEZ-SKARMETA JL Evolutionary comparison reveals that diverging CTCF sites are signatures of ancestral topológical associating domains borders. Proc. Natl. Acad. Sci. USA. 2015. 112, 7542-7547.

MARCOS, S. GONZÁLEZ, M., BECCARI, L., CARRAMOLINO, L., MARTIN-BERMEJO MJ, AMARIE O, MATEOS-SAN MARTÍN D., TORROJA C, BOGDANOVIC O, DOOHAN R., PUK O, HRABĚ DE ANGELIS M, GRAW J, GOMEZ-SKARMETA JL, CASARES F, TORRES M.*, AND BOVOLENTA P.* Meis1 coordinates a network of genes implicated in eye development and microphthalmia. Development. 2015. 142, 3009-3020.

BECCARI L., MARCO-FERRERES R., TABANERA N., SOUREN M., WITTBRODT B., CONTE I, WITTBRODT J. AND BOVOLENTA P. A trans-regulatory code for the forebrain expression of Six3.2 in the medaka fish. J. Biol. Chem. 2015. 290, 26927-26942

HERNÁNDEZ-BEJARANO, M*, GESTRI G*, SPAWLS, L., NIETO-LÓPEZ F, PICKER A, TADA M, BRAND M, BOVOLENTA P., WILSON SW, AND CAVODEASSI F. Opposing Shh and Fgf signals initiate nasotemporal patterning of the retina. Development. 2015. 142, 3933-3942.

Highlights

Our group investigates the mechanisms that control the early development of the vertebrate nervous system, mostly focusing on the visual system. We are particularly interested in those aspects that may help pinpointing the causes of congenital malformations or those related to the onset of neurodegenerative diseases. Besides the publications that have highlighted in this report, during this year we made progress in the study of Cdon, a component of the Shh signaling pathway, defining its likely implications in congenital developmental defects. This advance has been possible thanks to the collaboration with different clinical groups, including the U704. We have also extended our studies on the morphogenesis of the eye field with a particular focus on the specification of the retinal pigment epithelium. Furthermore, we have established collaborations with different neurologists to progress in the study of the involvement of the protein Secreted Frizzled Related Protein 1 (Sfrp1) in Alzheimer's Disease. For this project we have obtained, among others, the support of the "Fundacion Tatiana Perez de Guzmán el Bueno". Our studies have also provided support for a strong implication of Sfrp1 in the inflammatory processes associated to neurodegeneration. In collaboration with the U738 we have advanced in the analysis of the neural phenotype that characterize murine models of Lafora disease, which has led to the defense of a doctoral thesis. Our group is leading a national network of ten laboratories studying the development of the nervous system (ReDevNeural), for which we have been granted a MINECO project (BFU2014-55738-REDT). At the international level and within the ERA-Net Neuron II call, we are leading the project "ImprovVision", aimed at the study and treatment of congenital defects of the visual system.

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Group U710

Programme: Inherited Cancer, Haematological & Dermatological Diseases
Lead Researcher: Bueren, Juan Antonio

Group members

STAFF MEMBERS: Hernando Rodríguez, Miriam | Sánchez Domínguez, Rebeca.

ASSOCIATED MEMBERS: Aldea García, Montserrat | Almarza Novoa, Elena | Álvarez Ramos, Lara | Casado Olea, José Antonio | Cerrato Carrasco, Laura | Chinchón Córdoba, Raquel | Díez Cabezas, Begoña | Fernández García, Raquel Mª| García Bravo, María | Garín Ferreira, Marina Inmaculada | Güenechea Amurrio, Guillermo | Lamana Luzuriaga, Mª Luisa | León Rico, Diego | López Santalla, Mercedes | Lozano Vinagre, Mª de la Luz | Moleiro San Emeterio, Victoria | Navarro Ordoñez, Susana | Orman Bernal, Israel | Quintana Bustamante, Oscar | Río Galdo, Paula | Rodríguez Fornes, Fatima | Román Rodríguez, Fco. José | Segovia Sanz, José Carlos | Yañez González, Rosa Mª.

Main lines of research

- Gene and cell therapy for rare diseases.
- Research and applications of stem cells.
- Investigation of the molecular and genetic basis of rare diseases affecting the hematopoietic system.
- Biology hematopoietic transplantation.

Our work is focused on the development of innovative therapies for rare diseases that primarily affect blood cells. These include congenital bone marrow failures, as well as congenital anemias and immunodeficiencies. In particular, along 2015 we have worked in the following research areas:

- Gene therapy, gene editing and cell reprogramming in bone marrow failure sundromes, mainly Fanconi anemia.
- Gene therapy, gene editing and cell reprogramming in anemias associated with a deficit in erythrocyte pyruvate kinase (PKD).
- Lentiviral gene therapy in the congenital immunodeficiency, leukocyte adhesion deficiency type 1 (LAD-1).
- Applications of mesenchymal stromal cells in the treatment of rare diseases.

During 2015 our activity has been focused on the development of research projects of the National Plan for Research and the 7th Framework Programme of the EU (EUROFANCOLEN Project). Also we have participated in the Transatlantic Gene Therapy Consortium, and have established collaborations with biotech companies, with which we hope to achieve important cooperation agreements. Our interests in conducting translational biomedical research is reflected in the launch of the first National GMP labo-

ratory approved by the Spanish Agency of Medicines and Medical Devices for the development of gene therapy protocols with hematopoietic stem cells.

The work done by our research team - in collaboration with other groups from the CIBER, including Linked Clinical Groups (i.e. H. Niño Jesús and H. Vall d'Hebron) and the Hospital Fundación Jimenez Diaz (with whom we have formed a Joint Unit for Advanced Therapies) - is allowing us to lead global gene therapy programs on rare diseases that affect blood cells. Additionally we offer collaboration with other researchers from the CIBER to develop new advanced therapies for rare diseases.

Most relevant scientific articles

CUESTA-DOMINGUEZ A, LEON-RICO D, ALVAREZ L, DIEZ B, BODEGA-MAYOR I, BANOS R, ET AL. BCR-JAK2 drives a myeloproliferative neoplasm in transplanted mice. J Pathol. 2015 Jun;236(2):219-28. PubMed PMID: 25664618.

FERNÁNDEZ-GARCÍA M, YANEZ RM, SÁNCHEZ-DOMINGUEZ R, HERNANDO-RODRÍGUEZ M, PECES-BARBA M, HERRERA G, ET AL. Mesenchymal stromal cells enhance the engraftment of hematopoietic stem cells in an autologous mouse transplantation model. Stem Cell Res Ther. 2015;6:165. PubMed PMID: 26345192. Pubmed Central PMCID: PMC4562358.

GARATE Z, QUINTANA-BUSTAMANTE O, CRANE AM, OLIVIER E, POIROT L, GALETTO R, ET AL. Generation of a High Number of Healthy Erythroid Cells from Gene-Edited Pyruvate Kinase Deficiency Patient-Specific Induced Pluripotent Stem Cells. Stem Cell Reports. 2015 Dec 8;5(6):1053-66. PubMed PMID: 26549847. Pubmed Central PMCID: PMC4682065.

LÓPEZ-SANTALLA M, MANCHENO-CORVO P, MENTA R, LÓPEZ-BELMONTE J, DELAROSA O, BUEREN JA, ET AL. Human Adipose-Derived Mesenchymal Stem Cells Modulate Experimental Autoimmune Arthritis by Modifying Early Adaptive T Cell Responses. Stem Cells. 2015 Dec;33(12):3493-503. PubMed PMID: 26205964.

MOLINA-ESTEVEZ FJ, NOWROUZI A, LOZANO ML, GALY A, CHARRIER S, VON KALLE C, ET AL. Lentiviral-Mediated Gene Therapy in Fanconi Anemia-A Mice Reveals Long-Term Engraftment and Continuous Turnover of Corrected HSCs. Curr Gene Ther. 2015;15(6):550-62. PubMed PMID: 26415575.

Highlights

In March 2015, the Spanish Agency of Medicines and Medical Devices (AEMPS) has certified that the lab "CliniStem" at the CIEMAT complies with the requirements of Good Manufacturing Practices for the production of advanced therapy medicinal products under research. Besides, Begoña Díez presented her doctoral thesis on gene editing in hematopoietic stem cells as a potential therapeutic approach for Fanconi anemia.

In the field of Fanconi anemia, the safety of lentiviral vector LV-FANCA has been demonstrated and we have also carried out the validation of the FANCOLEN gene therapy protocol, allowing the approval of the clinical protocol by the AEMPS in March 2015.

With respect to erythrocyte pyruvate kinase deficiency (PKLR) we have developed tools for genetic editing to correct the gene defect in human hematopoietic progenitors. Therefore, we have also developed a partnership with an USA company to fund a clinical trial of gene therapy for deficiency PKLR, expected to be signed during the first quarter of 2016.

A lentiviral vector for gene therapy of leukocyte adhesion deficiency type I (LAD-I) has been developed, which was part of the doctoral thesis of Diego León Rico, and obtained cum laude qualification with international mention.

Preclinical studies with mesenchymal stromal cells (MSCs) have shown that intravenous administration of MSCs significantly improve the graft of hematopoietic stem cells in autologous transplantation models in mice, which will be applied in gene therapy protocols.

In collaboration with the biotech company Tigenix, cellular responses underlying the therapeutic effect of MSCs in a preclinical model of rheumatoid arthritis induced by collagen have been described. Furthermore, we have demonstrated that MSCs infused by intralymphatic route can modulate experimental collagen induced arthritis.

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Group U711

Programme: Genetic Medicine
Lead Researcher: Carracedo, Ángel

Group members

STAFF MEMBERS: Brea Fernández, Alejandro José | Cruz Guerrero, Raquel | Santamariña Pena, Marta.

ASSOCIATED MEMBERS: Álvarez Fernández, Vanesa | Amigo Lechuga, Jorge | Barros Angueira, Francisco | Blanco Arias, Patricia | Blanco Pérez, Ana | Fachal Vilar, Laura | Fernández Prieto, Montserrat | García Murias, María | Quintans Castro, Beatriz | Ruiz Ponte, Clara | Sobrido Gómez, María Jesús | Vega Gliemmo, Ana Paula.

Main lines of research

- Genetics of neurological and neuromuscular diseases.
- Genetics of hereditary colorectal cancer.
- Genetics of hereditary breast and ovarian cancer.
- Pharmacogenetics: Adverse drug reactions.
- Genetics of ocular diseases.
- Genetics of cardiovascular diseases.
- Genetics of serious microorganism-host interactions.
- Characterization of new genes, mutations and genotype-phenotype relation in ataxias and hereditary spastic paraplegias.
- Bioinformatic tools for genetic databases.
- Integration of genetic and environmental data in models of RD etiology by means of geographic information systems (ecogeographic genetic epidemiology). Analysis of spatial patterns of rare diseases.
- Neurocognitive aspects in rare genetic diseases genetic: Williams syndrome and Smith-Magenis syndrome.

Most relevant scientific articles

LEGATI A, GIOVANNINI D, NICOLAS G, LÓPEZ-SÁNCHEZ U, QUINTÁNS B, OLIVEIRA JR, SEARS RL, RAMOS EM, SPITERI E, SOBRIDO MJ, CARRACEDO Á, CASTRO-FERNÁNDEZ C, CUBIZOLLE S, FOGEL BL, GOIZET C, JEN JC, KIRDLARP S, LANG AE, MIEDZYBRODZKA Z, MITARNUN W, PAUCAR M, PAULSON H, PARIENTE J, RICHARD AC, SALINS NS, SIMPSON SA, STRIANO P, SVENNINGSSON P, TISON F, UNNI VK, VANAKKER O, WESSELS MW, WETCHAPHANPHESAT S, YANG M, BOLLER F, CAMPION D, HANNEQUIN D, SITBON M, GESCHWIND DH, BATTINI JL, COPPOLA G. Mutations in XPR1 cause primary familial brain calcification associated with altered phosphate export. Nat Genet. 2015 Jun;47(6):579-81. doi: 10.1038/ng.3289. Epub 2015 May 4.PMID: 25938945.

MANCIKOVA V, CRUZ R, INGLADA-PÉREZ L, FERNÁNDEZ-ROZADILLA C, LANDA I, CAMESELLE-TEIJEIRO J, CELEIRO C, PASTOR S, VELÁZQUEZ A, MARCOS R, ANDÍA V, ÁLVAREZ-ESCOLÁ C, MEORO A, SCHIAVI F, OPOCHER G, QUINTELA I, ANSEDE-BERMEJO J, RUIZ-PONTE C, SANTISTEBAN P, ROBLEDO M, CARRACEDO A. Thyroid cancer GWAS identifies 10q26.12 and 6q14.1 as novel susceptibility loci and reveals genetic heterogeneity among populations. Int J Cancer. 2015 Oct 15;137(8):1870-8. doi: 10.1002/ijc.29557. Epub 2015.

BALBOA-BELTRÁN E, CRUZ R, CARRACEDO A, BARROS F. Delimiting Allelic Imbalance of TYMS by Allele-Specific Analysis. Medicine (Baltimore). 2015 Jul;94(27):e1091. doi: 10.1097/MD.0000000000001091. PMID:26166093.

BALBOA-BELTRÁN E, DURAN G, LAMAS MJ, CARRACEDO A, BARROS F. Long Survival and Severe Toxicity Under 5-Fluorouracil-Based Therapy in a Patient With Colorectal Cancer Who Harbors a Germline Codon-Stop Mutation in TYMS. Mayo Clin Proc. 2015 Sep;90(9):1298-303. doi: 10.1016/j.mayocp.2015.05.005. Epub 2015 Jul 22. PMID: 26210704.

BRION M, SOBRINO B, MARTÍNEZ M, BLANCO-VEREA A, CARRACEDO A. Massive parallel sequencing applied to the molecular autopsy in sudden cardiac death in the young. Forensic Sci Int Genet. 2015 Sep;18:160-70. doi: 10.1016/j.fsigen.2015.07.010. Epub 2015 Jul 23. PMID: 26243589.

Highlights

During 2015 we have increased our scientific production to about 50 papers, which is our historical record in number of papers, although we have decreased the number of publications in top journals with only two with an IF>30. However 75% of the papers are still in the first quartile.

We have increased the publication of case reports most of them related with specific microstructural chromosome disorders dealing with autism cases.

The activity related with the genetics of rare adversary drug reaction has also increased, while the line of research related with the genetics of complex traits and particularly cancer (breast, colorectal cancer and thyroid cancer) is also yielding excellent results with new genes involved in colorectal and thyroid cancer being discovered.

Next-generation sequencing (NGS) is allowing the discovery of the new genes involved in rare disorders and the discovery of mutations in XPR1 that cause primary familial brain calcification associated with altered phosphate export, published in Nature Genetics, is a good example of the applications of NGS in gene discovery.

The line of research related with cardiac sudden death is also in a good progress, as well as the ones related with psychiatric diseases especially in the childhood that have an important genetic component.

The activity of the group in national and international consortia has also increased with two H2020 European projects awarded, PANCANRISK leaded by our group for cancer stratification and prediction and B-CAST, also for breast cancer prediction where the group is leading the working package on genetic biomarker discovery through massive sequencing of tumors and normal tissue.

Finally the translation of the research to clinical practice has been important for us, with an special effort last year in pharmacogenomics and personalized medicine, including actions for early drug discovery through the platform INNOPHARMA and the contributions of other groups of the CIBERER.

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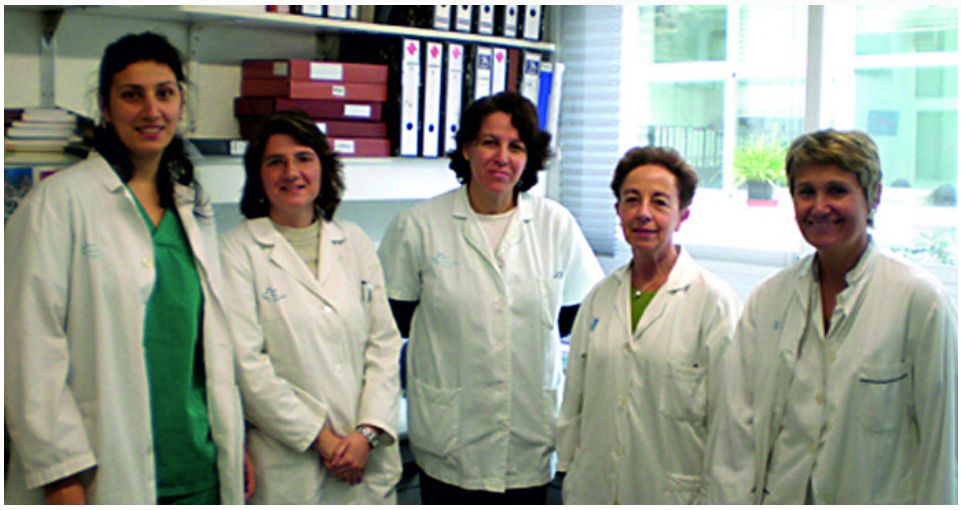
Group U712

Programme: Endocrine Medicine

Lead Researcher: Carrascosa, Antonio

Group members



STAFF MEMBERS: Fernández Cancio, Mónica.

ASSOCIATED MEMBERS: Andaluz López, Pilar | Audi Parera, Laura | Clemente León, Maria | Gussinye Canadell, Miquel | Torán Fuentes, Nuria | Yeste Fernández, Diego.

Main lines of research

- Genetic regulation of growth in control an delayed growth populations: genes GH1, GHR, GHRHR, IGF-1, IGF1R, VDR.
- Hormone and growth factor regulation of proliferation and gene expression in growing human cartilage.
- Analysis of new genes involved in human sex differentiation: AR, SRD5A2, HSD17B3, CYP17A1, CYP19A1, StAR, SF1, MAMLD1, GATA4. Search of new genes.
- Genes involved in congenital isolated glucocorticoid deficiency: genes MC2R, MRAP, StAR, CYP11A1.
- Epidemiological and genetic factors involved in raquitism. Genes VDR, MC1R, TYR1, TYRP1-1, TYRP1-2, OCA2-1, OCA2-2, SLC45A2-1, SLC45A2-2, SLC24A5-1, KITLG-1.

Most relevant scientific articles

CAMATS N, FERNÁNDEZ-CANCIO M, AUDÍ L, MULLIS PE, MORENO F, GONZÁLEZ CASADO I, LÓPEZ-SIGUERO JP, CORRIPIO R, BERMÚDEZ DE LA VEGA JA, BLANCO JA, FLÜCK CE. Human MAMLD1 Gene Variations Seem Not Sufficient to Explain a 46,XY DSD Phenotype. PLoS One. 2015 Nov 16;10(11):e0142831. doi: 10.1371/journal.pone.0142831. eCollection 2015. PubMed PMID: 26580071; PubMed Central PMCID: PMC4646284.

CAMATS N, AUDÍ L, FERNÁNDEZ-CANCIO M, ANDALUZ P, MULLIS PE, CARRASCOSA A, Flück CE. LRH-1 May Rescue SF-1 Deficiency for Steroidogenesis: An in vitro and in vivo Study. Sex Dev. 2015;9(3):144-54. doi: 10.1159/000381575. Epub 2015 Apr 17. PubMed PMID: 25896302.

RODRÍGUEZ-SUREDA V, VILCHES Á, SÁNCHEZ O, AUDÍ L, DOMÍNGUEZ C. Intracellular oxidant activity, antioxidant enzyme defense system, and cell senescence in fibroblasts with trisomy 21. Oxid Med Cell Longev. 2015;2015:509241. doi: 10.1155/2015/509241. Epub 2015 Mar 17. PubMed PMID: 25852816; PubMed Central PMCID: PMC4380103.

BERMÚDEZ DE LA VEGA JA, FERNÁNDEZ-CANCIO M, BERNAL S, AUDÍ L. Complete androgen insensitivity syndrome associated with male gender identity or female precocious puberty in the same family. Sex Dev. 2015;9(2):75-9. doi: 10.1159/000371617. Epub 2015 Jan 29. PubMed PMID: 25633053.

CANDEL PAU J, CASTILLO SALINAS F, PERAPOCH LÓPEZ J, CARRASCOSA LEZCANO A, SÁNCHEZ GARCÍA O, LLURBA OLIVÉ E. [Perinatal outcome and cardiac dysfunction in preterm growth-restricted neonates in relation to placental impairment severity]. An Pediatr (Barc). 2015 May 13. pii: S1695-4033(15)00119-8. doi: 10.1016/j.anpedi.2015.03.014. [Epub ahead of print] Spanish. PubMed PMID: 25982472.

Highlights

During 2015, Group activity has been oriented towards translational medicine in the aspects of patient management, diagnoses and specialized consultations on RD related to pediatric endocrinology. Of major impact are fields related to skeletal growth, disorders of sex development, familial glucocorticoid deficiency and rickets predisposing factors. Collaborative actions with SEEP, SEEN, SEQC and ESPE were active for the creation and revision of Recommendations and Guidelines for protocols of clinical, biochemical and genetic diagnoses.

Our centre is the reference centre for the Programmme of Neonatal Screening of Congenital Hypothyroidism in Catalunya. The Group collaborates with the Working Groups in the SEEP, the SEEN and ESPE for the study and databases of Disorders of Sex Development (DSD) Registries. Our Group also collaborates with the International database (I-DSD) and the COST Project BM1303 for the collaboraive study of DSD.

L. Audí is member of the Orphanet Spanish Scientific Committee. Our Group has a collection of Pediatric Endocrinology samples in the Vall d'Hebron Research Institute Biobank (BBHUVH).

In 2015, we have implemented new techniques of next generation sequencing which afforded obtaining molecular diagnoses in paediatric endocrinology patients previously lacking it.

We maintained clinical and research collaborations with other pediatric groups in our hospital that also work on RD (pediatric neumology, neurology, immunology, metabolic and other genetic diseases).

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Group U713

Programme: Mitochondrial and Neuromuscular Medicine

Lead Researcher: Cuezva, José Manuel

Group members

STAFF MEMBERS: Núñez de Arenas Flores, Cristina.

ASSOCIATED MEMBERS: Formentini, Laura | García Bermúdez, Javier | Martínez Jover, Estefanía | Nuevo Tapioles, Cristina | Santacatterina, Fulvio | Soldevilla Navarro, Beatriz.

Main lines of research

- Alterations of biogenesis and/or mitochondrial functions in human pathology due to genetic or epigenetic causes.
- Biosynthesis, assembling and degradation of the mitochondrial oxidative phosphorylation Complex V. Identification and functional characterization of the mRNA binding proteins from the beta-F1-ATPasa subunit.
- Development of cellular and mouse models of disease with alterations in mitochondrial oxidative phosphorylation.
- Development of proteomic platforms for the identification of molecular markers of diagnosis in rare diseases related to energy metabolism.
- Protein expression and development of monoclonal antibodies against mitochondrial proteins and energy metabolism to be used in mitochondrial pathologies diagnostic kits.

Most relevant scientific articles

GARCÍA-BERMÚDEZ J, SÁNCHEZ-ARAGÓ M, SOLDEVILLA B, DEL ARCO A, NUEVO-TAPIOLES C, CUEZVA JM. PKA Phosphorylates the ATPase Inhibitory Factor 1 and Inactivates Its Capacity to Bind and Inhibit the Mitochondrial H(+)-ATP Synthase. Cell Rep. 2015 Sep 29;12(12):2143-55.

SANTACATTERINA F, CHAMORRO M, DE ARENAS CN, NAVARRO C, MARTÍN MA, CUEZVA JM, SÁNCHEZ-ARAGÓ M. Quantitative analysis of proteins of metabolism by reverse phase protein microarrays identifies potential biomarkers of rare neuromuscular diseases. J Transl Med. 2015 Feb 18;13:65.

CASCAJO MV, ABDELMOHSEN K, NOH JH, FERNÁNDEZ-AYALA DJ, WILLERS IM, BREA G, LÓPEZ-LLUCH G, VALENZUELA-VILLATORO M, CUEZVA JM, GOROSPE M, SIENDONES E, NAVAS P. RNA-binding proteins regulate cell respiration and coenzyme Q biosynthesis by post-transcriptional regulation of COQ7. RNA Biol. 2015 Dec 21:0. [Epub ahead of print]

MARTÍNEZ-FERNÁNDEZ DE LA CÁMARA C, HERNÁNDEZ-PINTO AM, OLIVARES-GONZÁLEZ L, CUEVAS-MARTÍN C, SÁNCHEZ-ARAGÓ M, HERVÁS D, SALOM D, CUEZVA JM, DE LA ROSA EJ, MILLÁN JM, RODRIGO R. Adalimumab Reduces Photoreceptor Cell Death in A Mouse Model of Retinal Degeneration. Sci Rep. 2015 Jul 14;5:11764.

BARNEO-MUÑOZ M, JUÁREZ P, CIVERA-TREGÓN A, YNDRIAGO L, PLA-MARTIN D, ZENKER J, CUEVAS-MARTÍN C, ESTELA A, SÁNCHEZ-ARAGÓ M, FORTEZA-VILA J, CUEZVA JM, CHRAST R, PALAU F. Lack of GDAP1 induces neuronal calcium and mitochondrial defects in a knockout mouse model of charcot-marie-tooth neuropathy. PLoS Genet. 2015 Apr 10;11(4):e1005115.

Highlights

We have discovered that IF1 regulates the ATP synthetic activity of the mitochondrial ATP synthase. The activity of IF1 is regulated by phosphorylation mediated by a mitochondrial cyclic AMP-dependent protein kinase A. Phosphorylation of S39 in IF1 hampers its binding to the synthase and prevents the inhibition of the enzyme activity (Cell Rep; CIBERER collaboration). We have demonstrated the clinical utility of the PROTEOmAb platform for the identification of new biomarkers in myopathy affected patients (J Transl Med and Patent; CIBERER collaboration). Moreover, we have contributed to the translation of the PROTEOmAb platform for phenotyping a murine model of Charcot-Marie-Tooth disease (PLoS Genet; CIBERER collaboration) and as a powerful tool to evidence the therapeutic response to treatment in a murine model of retinitis pigmentosa (Sci Rep; CIBERER collaboration). In addition, we have contributed in the characterization of the RNABPs that regulate the biosynthesis of CoQ (RNA Biol; CIBERER collaboration). Dr. Sánchez-Aragó contracted personal of unit 713 of CIBERER up to June 2015, has actively contributed in four of these contributions.

Project: "Función oncogénica de IF1, el inhibidor de la H+ATP sintasa de la mitocondria". Financed by: Fundación Ramón Areces. Duration from: Juny 2015. To: May 2018. Amount: 125.760 €. PI: José Manuel Cuezva Marcos.

Project: ACCI. CIBERER 2015. Biomarcadores Diagnóstico de Enfermedades Mitocondriales que afectan al sistema OXPHOS. Amount: 60.000 €. PIs: E. García Arumi (701), JM Cuezva (713) y MA Martín (723).

Granted Patent Entitled: "Procedimiento y kit de diagnóstico diferencial de una enfermedad que cursa con afectación muscular". Authors: Fulvio Santacatterina, María Sánchez Aragó y José M. Cuezva. Number: ES2432653 Date of publication: 14/12/2013 Date granted: 10/09/2015. Owners: Universidad Autónoma de Madrid y CIBERER.

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Group U714

Programme: Inherited Cancer, Haematological & Dermatological Diseases

Lead Researcher: Del Río Nechaevsky, Marcela

Group members

STAFF MEMBERS: Escamez Toledano, María José | Gómez Llames, Sara María.

ASSOCIATED MEMBERS: Carretero Trillo, Marta | Duarte González, Blanca | García Díez, Marta | Guerrero Aspizua, Sara | Holguín Fernández, Almudena | Illera Esteban, Nuria | Larcher Laguzzi, Fernando | Meana Infiesta, Alvaro | Murillas Angoiti, Rodolfo | Retamosa Cervantes, María Luisa | Zapatero Solana, Elisabet.

Main lines of research

- Design and development of new therapeutic tools for rare skin diseases based on cell and gene therapy.
- Adult epidermal stem cell biology and its use in regenerative medicine.
- Cutaneous regeneration: study of the molecular mechanisms involved in wound repair and identification of new therapeutic targets.
- Study of the molecular basis of inherited ampollous diseases: Epidermolisis Bullosa and Kindler síndrome.
- Development of humanized animal models of rare skin diseases.
- Bone regeneration through tissue engineering.

Most relevant scientific articles

MENCÍA A, GARCÍA M, GARCÍA E, ET AL. Identification of two rare and novel large deletions in ITGB4 gene causing epidermolysis bullosa with pyloric atresia. Exp Dermatol 2016 [Epub ahead of print].

PEREZ CJ, MECKLENBURG L, JAUBERT J, ET AL. Increased Susceptibility to Skin Carcinogenesis Associated with a Spontaneous Mouse Mutation in the Palmitoyl Transferase Zdhhc13 gene. J Invest Dermatol. 2015;135:3133-43.

LLAMES S, GARCÍA-PÉREZ E, MEANA Á, ET AL. Feeder Layer Cell Actions and Applications. Tissue Eng Part B Rev 2015; 21:345-53.

LARCHER F, DEL RÍO M. Innovative therapeutic strategies for recessive dystrophic epidermolysis bullosa. Actas Dermosifiliogr 2015; 106:376-82.

GUERRERO-ASPIZUA S, LARCHER F, DEL RÍO M, ET AL. Tumor initiation by skin Ha-ras-ment. Exp Dermatol 2015; 24:252-3.

Highlights

During 2015 we highlight two new clinical trials in which the U714 started to be involved. One at the European level, "Study of immune tolerance and capacity for wound healing of Patients with Recessive Dystrophic Epidermolysis Bullosa" (EBGene-NCT01874769) and the other at national level: "Study of safety and preliminary efficacy of mesenchymal stem cell derived from adipose tissue for treating recessive dystrophic epidermolysis bullosa "(EudraCT 2015-001272-21). It is also to distinguish that during 2015, 3 COMPASSIONATE USE using a product developed by our team (http://patentscope.wipo.int/search/en/WO2002072800) were approved by the AEMPS and applied in Plató and Vall d'Hebron hospitals for the treatment of chronic ulcers in patients with epidermolysis bullosa.

It is also necessary to highlight our activity in the molecular diagnosis of genodermatosis (http://www.orpha.net). As well as in patient registries integrated in SpainRDR. In addition, since 2015, the U714 is part of "EB-Clinet - EB Clinical Network of Centres and Experts" (http://www.eb-clinet.org) and has strengthen the collaboration with other patient organizations, in this case, Berritxuak (http://www.berritxuak.org). Finally, we participated along with other researchers and dermatologists in the creation of the "European Xeroderma Pigmentosum (XP) Society" which was presented in October 2015 and is recognized by European Academy of Dermatology and Venereology.

Related to competitive funding, we emphasize during 2015 the following grants: 2 AES (PI014 / 00931 and ICI14 / 00363 PI: MJ.Escámez CIBERER postdoc contract), 1 Plan Estatal (SAF2013-43475- R), 1 INNPACTO and 2 Autonomic projects. As for private financing, we underline that granted by Berritxuak patient association. In 2015 the European project NanoSmell H2020-FETOPEN-2014-2015-RIA Project reference: 662629 was also funded.

Finally, we also like to point out the most important collaborations within CIBERER such as those including U716 and U710 for the preparation of the chapter: "Advanced Therapies for Rare Diseases" Revista Arbor, with the U704 for the development of a clinical guideline, with the U758 for patient registry and with U726 in the context of an ACCI project.

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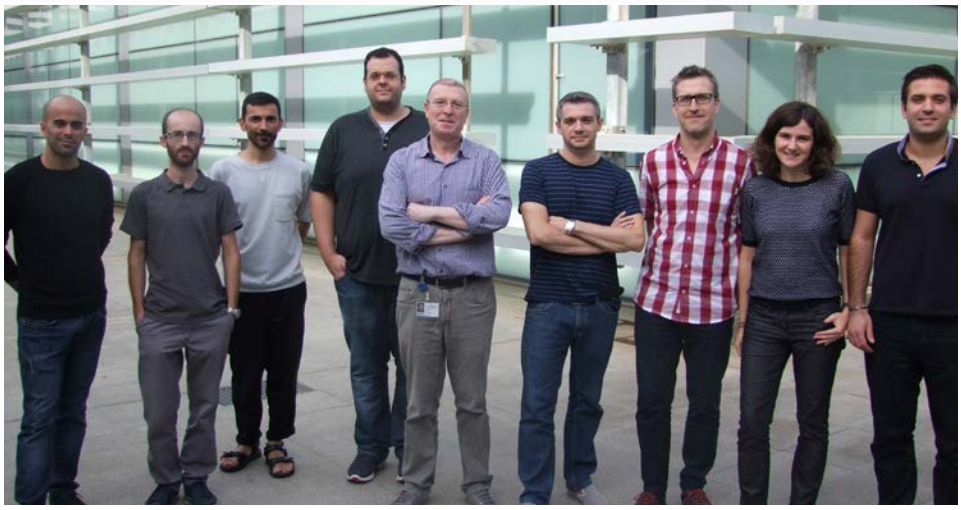
Group U715

Programme: Genetic Medicine

Lead Researcher: Dopazo Blázquez, Joaquín

Group members



STAFF MEMBERS: Alemán Ramos, Alejandro | Salavert Torres, Francisco.

ASSOCIATED MEMBERS: García García, Francisco | Montaner González, David | Tarraga Giménez, Joaquín.

Main lines of research

- Transcriptomics: Microarrays and ultra-sequencing data analysis.
- Genotyping (GWAS) from both microarrays and ultra-sequencing.
- Functional analysis of data from genomic experiments from the systems biology perspective. Use of non structured functional modules such as Gene Ontology (GO) and structured such as pathways, protein interaction networks or transcriptional networks.
- Development of software for the analysis and integration of genomic data. Projects Babelomics (http://www.babelomics.org), BiERapp (http://bierapp.babelomics.org), TEAM (http://team.babelomics.org) and the database of Spanish variability.
- Systems biology approach to the study of rare diseases.
- Analysis and use of different ultra-sequencing data. In addition to transcriptomics (RNA-seq) and variation analysis, Chip-seq, copy number variation (CNV) and other chromosome alterations (translocations, inversions...) are studied.

Most relevant scientific articles

PORTA-PARDO E, GARCÍA-ALONSO L, HRABE T, DOPAZO* J, GODZIK* A. (*co-corresponding). A Pan-Cancer Catalogue of Cancer Driver Protein Interaction Interfaces. PLoS Comput. Biol. 2015;11(10):e1004518.

HERNANSAIZ-BALLESTEROS RD, SALAVERT F, SEBASTIÁN-LEÓN P, ALEMÁN A, MEDINA I, DOPAZO J. Assessing the impact of mutations found in next generation sequencing data over human signaling pathways. Nucleic Acids Res.. 2015;43:W270-W275.

AVILA-FERNÁNDEZ A, PEREZ-CARRO R, CORTON M, LÓPEZ-MOLINA MI, CAMPELLO L, GARANTO A, FERNADEZ-SÁNCHEZ L, DUIJKERS L, LÓPEZ-MARTÍNEZ MA, RIVEIRO-ALVAREZ R, DA SILVA LRJ, SÁNCHEZ-ALCUDIA R, MARTIN-GARRIDO E, REYES N, GARCÍA-GARCÍA F, DOPAZO J, GARCÍA-SANDOVAL B, COLLIN RW, CUENCA N, AYUSO C. Whole Exome Sequencing Reveals ZNF408 as a New Gene Associated With Autosomal Recessive Retinitis Pigmentosa with Vitreal Alterations. Hum. Mol. Genet. 2015;24:4037-4048.

LUZÓN-TORO B, GUI H, RUIZ-FERRER M, SZE-MAN TANG C, FERNÁNDEZ RM, SHAM P-C, TORROGLOSA A, KWONG-HANG TAM P, ESPINO-PAISÁN L, CHERNY SS, BLEDA M, ENGUIX-RIEGO MDV, DOPAZO J, ANTIÑOLO G, GARCÍA-BARCELÓ M-M, BORREGO S. Exome sequencing reveals a high genetic heterogeneity on familial Hirschsprung disease. Sci Rep. 2015;5:16473.

AMADOZ A, SEBASTIAN-LEON P, VIDAL E, SALAVERT F, DOPAZO J. Using activation status of signaling pathways as mechanism-based biomarkers to predict drug sensitivity. Sci Rep. 2015;5:18494.

Highlights

The most remarkable during 2015 has been the study on Spanish contol population and the building of a database of allelic frequencies of the Spanish population (http://www.ciberer.es/plataformas/ciberer-spanish-variant-server). It consists on a unique resource very helpful to search for disease genes.

In addition, we have provided consulting and bioinformatic support in 22 projects from 15 different CIBERER groups. We have actively participated in the innter-group collaboration by hosting 11 researchers from other CIBERER groups. Finally, we carried out the course “NGS course: from reads to candidate genes” to which 25 delegates from different CIBERER groups attended.

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Group U716

Programme: Paediatric and Developmental Medicine
Lead Researcher: Fillat, Cristina

Group members

STAFF MEMBERS: Luna Cornado, Jeronimo

ASSOCIATED MEMBERS: Arato Arato, Krisztina | Arbones de Rafael, María Lourdes | Balducci, Elisa | Bofill de Ros, Xavier | de la Luna Gargantilla, Susana | Di Vona, Chiara | Dierssen Sotos, María del Mar | José Segarra-Martínez, Ana Isabel | Martínez de Lagran Cabredo, María | Najas Sales, Sonia | Raya Vaquera, Alicia | Sobrevals Sobrevals, Luciano Matías

Main lines of research

- Gene therapy.
- Characterization of factors associated with familial pancreatic cancer.
- Mouse models for neuropsychiatric disorders.
- Neurodegeneration.
- Mental retardation.
- Molecular and cellular basis of chromosome 21 aneuploidies.

Most relevant scientific articles

DI VONA C, BEZDAN D, ISLAM AB, SALICHS E, LÓPEZ-BIGAS N, OSSOWSKI S, DE LA LUNA S. Chromatin-wide profiling of DYRK1A reveals a role as a gene-specific RNA polymerase II CTD kinase. Mol Cell. 2015;57(3):506-20.

NAJAS S, ARRANZ J, LOCHHEAD PA, ASHFORD AL, OXLEY D, DELABAR JM, COOK SJ, BARALLOBRE MJ, ARBONÉS ML. DYRK1A-mediated Cyclin D1 Degradation in Neural Stem Cells Contributes to the Neurogenic Cortical Defects in Down Syndrome. EBioMedicine. 2015;2(2):120-34.

BOFILL-DE ROS X, SANTOS M, VILA-CASADESÚS M, VILLANUEVA E, ANDREU N, DIERSSEN M, FILLAT C. Genome-wide miR-155 and miR-802 target gene identification in the hippocampus of Ts65Dn Down syndrome mouse model by miRNA sponges. BMC Genomics. 2015;16:907.

CATUARA-SOLARZ S, ESPINOSA-CARRASCO J, ERB I, LANGOHR K, NOTREDAME C, GONZÁLEZ JR, DIERSSEN M. Principal Component Analysis of the Effects of Environmental Enrichment and (-)-epigallocatechin-3-gallate on Age-Associated Learning Deficits in a Mouse Model of Down Syndrome. Front Behav Neurosci. 2015 Dec 11;9:330.

BOFILL-DE ROS X, VILLANUEVA E, FILLAT C. Late-phase miRNA-controlled oncolytic adenovirus for selective killing of cancer cells. Oncotarget. 2015;6(8):6179-90.

Highlights

The group focuses its research on the study of the molecular basis, the physiopathological mechanisms and therapeutical approaches of neurodevelopmental genetic diseases with a special interest on aneuploidies associated to human chromosome 21 (HSA21), and towards the development of therapeutic strategies for rare tumours. Recently the group, in collaboration with U737, has initiated a new project for the development of a gene therapy approach for the glutaric aciduria, based on genome editing.

In 2015, team members have identified a new role for the DYRK1A protein kinase as a regulator of specific transcriptional programs, due to the ability of DYRK1A to phosphorylate the C-terminal end of the RNA polymerase II. Such novel activity enlarges the potential effectors that can be modulated upon changes in the kinase levels, as occurs in trisomies or monosomy conditions. Furthermore, it has been demonstrated that DYRK1A regulates cell division (proliferation vs differentiation) in neuronal progenitors during development, throughout a process that involves cyclin D1 phoshorylation by DYRK1A, thus contributing to the defect of excitatorial neurons in the cortex of the Ts65Dn mouse model of Down syndrome (DS). In this model we have also been able to show an association between the extra dose of miRNA-155 and miRNA-802 with the deregulation of a set of genes with implications in the DS phenotype. Finally, we have demonstrated the beneficial effects of a combined treatment base on (-)-epigallocatechin-3-gallate (EGCG) and the environmental enrichment for the amelioration of age-related cognitive decline in DS and fragile-X syndrome.

With respect to the development of novel therapies for rare tumors we have developed novel oncolytic adenovirus, and generated two patents.

During this year the group has also contributed to the SEFALER Unit.

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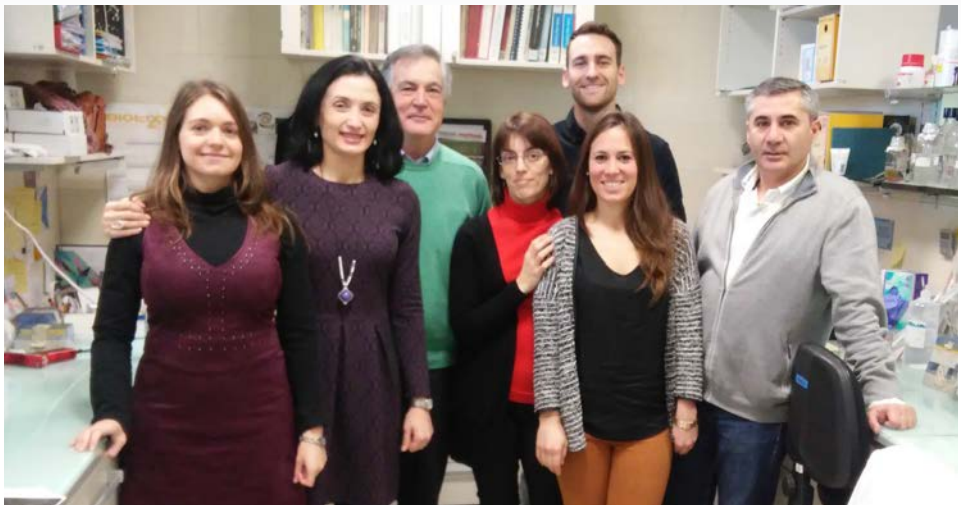
Group U717

Programme: Mitochondrial and Neuromuscular Medicine
Lead Researcher: Garesse, Rafael

Group members



STAFF MEMBERS: Gallardo Pérez, María Esther.

ASSOCIATED MEMBERS: Bornstein Sánchez, Belén | Fernández Moreno, Miguel Ángel | Galera Monge, Teresa | Zurita Díaz, Francisco

Main lines of research

- Identification and characterization of new proteins involved in the regulation of the OXPHOS system.
- Functional analysis by means of transmitochondrial cybrids of mutations identified in the mitochondrial genome associated with LHON and neurosensorial deafness.
- Molecular characterization of patients with intergenomic communication defects.
- Mitochondrial diseases with predominant phenotypic expression in cardiac muscle: Molecular characterization and analysis by means of transmitochondrial cybrids of new mutations identified in the mitochondrial genome.
- Development of animal models of mitochondrial diseases in Drosophila melanogaster.
- Generation of iPS cells harboring mutations in structural and regulator genes of the OXPHOS function.

Most relevant scientific articles

CRUZ-BERMÚDEZ A, VALLEJO CG, VICENTE-BLANCO RJ, GALLARDO ME, FERNÁNDEZ-MORENO MÁ, QUINTANILLA M ET AL. ENHANCED TUMORIGENICITY BY MITOCHONDRIAL DNA MILD MUTATIONS. ONCOTARGET. 2015; 6(15):13628-43.

MARTÍNEZ-MORENTIN L, MARTÍNEZ L, PILOTO S, YANG H, SCHON EA, GARESSE R ET AL. CARDIAC DEFICIENCY OF SINGLE CYTOCHROME OXIDASE ASSEMBLY FACTOR SCOX INDUCES P53-DEPENDENT APOPTOSIS IN A DROSOPHILA CARDIOMYOPATHY MODEL. HUM. MOL. GENET. 2015; 24(13):3608-22.

GONZÁLEZ-LÓPEZ E, GALLEGO-DELGADO M, GUZZO-MERELLO G, DE HARO-DEL MORAL FJ, COBO-MARCOS M, ROBLES C ET AL. WILD-TYPE TRANSTHYRETIN AMYLOIDOSIS AS A CAUSE OF HEART FAILURE WITH PRESERVED EJECTION FRACTION. EUR. HEART J. 2015; 36(38):2585-94.

DELGADO-ALVARADO M, DE LA RIVA P, JIMÉNEZ-URBIETA H, GAGO B, GABILONDO A ET AL. PARKINSONISM, COGNITIVE DEFICIT AND BEHAVIOURAL DISTURBANCE CAUSED BY A NOVEL MUTATION IN THE POLYMERASE GAMMA GENE. J NEUROL SCI. 2015; 350(1-2):93-7.

CÁMARA Y, CARREÑO-GAGO L, MARTÍN MA, MELIÀ MJ, BLÁZQUEZ A ET AL. SEVERE TK2 ENZYME ACTIVITY DEFICIENCY IN PATIENTS WITH MILD FORMS OF MYOPATHY. NEUROLOGY. 2015; 84(22):2286-8.

Highlights

During 2015, the unit U717 has been funded by four research projects: one from ISCIII (PI13/00556), one from the CAM (S2010/BMD-2402), one from ACCI (CIBERER 14-03) and one from MINECO (BIO2013-50346-EXP). The main aims of the CIBERER U717 unit have been focused on the study of different aspects of the mitochondrial physiopathology. Among them: 1) Biochemical characterization of transmitochondrial cybrids from patients with different mitochondrial diseases (MD). 2) Molecular and functional characterization of nuclear and mtDNA mutations in patients with mitochondrial cardiomyopathies. 3) From a clinical translational point of view, several diagnosis platforms are being implemented. Among them, one for the diagnosis of the POLG gene (we are reference center for this type of disorders) and other for sarcomeric genes involved in cardiomyopathies. Likewise, in collaboration with other CIBERER units, we have participated in a) the development of a normalized method for the mtDNA quantification and b) the standardization of clinical diagnosis of human mitochondrial respiratory chain defects. 4) Identification and characterization of new genes involved in the OXPHOS function. Up to now, we have identified and characterized several new genes. Some of them have been identified using the CRISPR/CAS9 genomic edition tool. 5) Generation of induced pluripotent stem cells (iPSC) like a model for the study of MD and like a therapeutical approximation. Until now, several iPSCs have been generated. Among them iPSCs from: a) controls, b) patients with Leigh syndrome caused by mutations in the mtDNA, c) patients with plus-optic atrophy caused by mutations in OPA1, d) a patient with a mutation in POLG and e) a patient with a severe mitochondrial encephalopathy produced by mutations in the GFM1 gene. This research line and another whose main aim is the identification of new OXPHOS genes will be the main research lines of our group in the next years.

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Group U718

Programme: Sensorineural Pathology
Lead Researcher: González Duarte, Roser

Group members

STAFF MEMBERS: Andrés Ventura, Maria Rosa.

ASSOCIATED MEMBERS: De Castro Miró, Marta | Marfany Nadal, Gemma | Sava, Florentina.

Main lines of research

- Study of the genetic and molecular basis for inherited retinal dystrophies (IRD).
- Genetic diagnosis by WES and targeted sequencing of the genes responsible for hereditary retinal dystrophies.
- Search for new genes causing retinal dystrophies and functional studies.
- Functional analysis of CERKL and other relevant IRD causative genes by generating cell lines and animal models constructed by morpholino knockdown in zebrafish as well as Cerkl -/- knockout by Cre/LoxP and CRISPR/Cas-genome editing approaches in mice.

Most relevant scientific articles

ABAD-MORALES V, DOMÈNECH EB, GARANTO A, MARFANY G. mRNA expression analysis of the SUMO pathway genes in the adult mouse retina. Biology Open 2015; 4(2):224-232.

Marfany G, Gonzàlez-Duarte R. Clinical applications of high-throughput genetic diagnosis in inherited retinal dystrophies: Present challenges and future directions. World J Med Genet. 2015; 5(2):14-22.

BOLOC D, CASTILLO-LARA S, MARFANY G, GONZÀLEZ-DUARTE R, ABRIL JF. Distilling a visual network of Retinitis Pigmentosa gene-protein interactions to uncover new disease candidates. PLoS One 2015; 10(8):e0135307.

MASOUMI KC, MARFANY G, WU Y, MASSOUMI R. Putative role of SUMOylation in controlling the activity of deubiquitinating enzymes in cancer. Fut Oncol 2016; 12(4):565-74.

Highlights

The research activity of the group U718 has been centered in the genetic and functional study of inherited retinal dystrophies (IRDs). One of our research topics aims to identify novel genes and devise efficient genetic diagnostic tools. This is achieved by merging in-house SNP-chips, whole exome sequencing (WES) and optimized bioinformatic analysis. Concerning the functional analysis of IRD causing genes, mainly CERKL and NR2E3, the group has focused the research on the generation of cellular and animal models.

Along 2015, the group has not only performed WES to identify the disease causing gene in RD families, but implemented a web-interactive tool, RPGnet, available to researchers that gathers all the biochemical, molecular and genetic data for 110 major IRD genes. This information allows to unveil new hubs in celular pathways, identifiy the proteins involved and so inspire the identification of novel clues to highlight unexpected functional retinal candidates for therapy.

A research line dealing with primary retinal cell cultures and organotypic cultures of murine retinas has been devised and the tisular transfection strategies have been improved. The assays in primary cell cultures nicely complement the functional assays that we are gathering through the study of animal models, among those, zebrafish with morpholino silencing approaches, and knockdown (through the Cre/LoxP approach) and knockout through the CRISPR/Cas methodology.

Funding: SAF2013-49069-C2-1-R (2014-2016) and La Marató TV3 (2014-2017), award with the recognition of a competitive research group under the Generalitat de Catalunya (SGR2014-0932). Six PhD research students are now supervised in the group.

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Group U719

Programme: Paediatric and Developmental Medicine
Lead Researcher: Gratacós, Eduard

Group members

STAFF MEMBERS: González Tendero, Ana | Rodríguez Sureda, Víctor Manuel.

ASSOCIATED MEMBERS: Borrel Vilaseca, Antoni | Cararach Ramoneda, Vicente | Casals Font, Elena | Cobo Cobo, Teresa | Crispi Brillas, Fatima | Domínguez Luengo , Mª del Carmen | Eixarch Roca, Elisenda | Figueras Retuerta, Francesc | Martínez Crespo, José Mª | Palacio Riera, Monserrat | Puerto Navarro, Bienvenido | Sanz Cortés, Magdalena.

Main lines of research

- Fetal and perinatal neurological damage.
- Diseases of placental origin and fetal programming of post-natal cardiac dysfunction.
- Highly complex fetal surgery: complications of monochorial twin pregnancy and congenital diaphragmatic hernia.
- Prenatal diagnosis of genetic and chromosomal abnormalities.
- Inherited metabolic diseases (IMD).
- Oxidative stress, antioxidant potential and premature cellular senescence in Down syndrome and Cockayne syndrome.
- Research on the pathogenic mechanisms of lysosomal disease.

Most relevant scientific articles

TRIUNFO S, PARRA-SAAVEDRA M, RODRÍGUEZ-SUREDA V, CROVETTO F, DOMINGUEZ C, GRATACÓS E & FIGUERAS F. Angiogenic Factors and Doppler Evaluation in Normally Growing Fetuses at Routine Third-Trimester Scan: Prediction of Subsequent Low Birth Weight. Fetal Diagn. Ther. (2015). doi:10.1159/000440650.

EIXARCH E, MUÑOZ-MORENO E, BARGALLO N, BATALLE D & GRATACOS E. Motor and cortico-striatal-thalamic connectivity alterations in intrauterine growth restriction. Am. J. Obstet. Gynecol. (2015). doi: 10.1016/j.ajog.2015.12.028.

SIMÕES R V., CRUZ-LEMINI M, BARGALLÓ N, GRATACÓS E & SANZ-CORTES M. Brain Metabolite Differences in One-Year-Old Infants Born Small at Term and its Association with Neurodevelopmental Outcome. Am. J. Obstet. Gynecol. 213, 210.e1–210.e11 (2015).

CRUZ-LEMINI M, CRISPI F, VALENZUELA-ALCARAZ B, FIGUERAS F, SITGES M, BIJNENS B & GRATACÓS E. Fetal cardiovascular remodelling persists at 6 months of life in infants with intrauterine growth restriction. Ultrasound Obstet. Gynecol. (2015). doi:10.1002/uog.15767.

RODRÍGUEZ-LÓPEZ M, OSORIO L, ACOSTA R, FIGUERAS J, CRUZ-LEMINI M, FIGUERAS F, BIJNENS B, GRATACOS E & CRISPI F. Influence of breastfeeding and postnatal nutrition on cardiovascular remodeling induced by fetal growth restriction. Pediatr. Res. (2015). doi:10.1038/pr.2015.182.

Highlights

Unit 719 combines an interdisciplinary team of clinical, basic and technological researchers specialized in Fetal Medicine. Many fetal disorders and pregnancy complications are classified as rare diseases. Our research aims to (1) pathophysiological mechanisms and fetal programming, (2) biochemical and imaging biomarkers, (3) development of therapies.

Some of our major scientific and translational milestones achieved in 2015 include:

- Improve the prediction of pregnancy complications: coordination of a study aiming to improve the classification and diagnosis of fetal diseases with long-term consequences such as brain damage or effects in the cardiovascular system. We will evaluate not only the use of ultrasound markers and standards but also new biological biomarkers (nutritional status, hypoxia, hormones, function / placental and toxic environmental aging), among other parameters.
- Perinatal brain damage biomarkers: use of MR diffusion-tractography and computer analysis of cortical development to characterize the effects of preeclampsia and congenital heart disease.
- Fetal Cardiology: coordination of several studies aiming to characterize fetal programming and changes in the cardiovascular system over time (fetal life, childhood, adolescence and adulthood), together with studies in experimental and computational models aiming to revert these changes.
- Clinical calculators that integrate the management of various rare diseases are available on the web, in addition to all our clinical protocols, most of them on rare diseases.
- Collaboration with Perkin Elmer for the development of new set of biomarkers for predicting growth restriction and preeclampsia in the third trimester of pregnancy.
- New quantitative image analysis method for predicting neonatal respiratory distress risk. In collaboration with our spin-off TMB, both the patent and the product (Quantus FML) are in the market since 2014.

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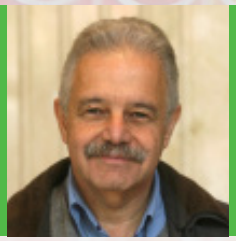
Website: http://www.ciberer.es/index.php?option=com_wrapper&Itemid=120&lang=spanish

Group U720

Programme: Inherited Metabolic Medicine
Lead Researcher: Grinberg, Daniel



Group members

STAFF MEMBERS: Cózar Morillo, Mónica | Fernández Castillo, Noelia | Urreizti Frexedas, Roser.

ASSOCIATED MEMBERS: Balcells Comas, Susana | Canals Montferrer, Isaac | Cormand Rifa, Bru | Corominas Castiñeira, Roser | Gómez Grau, Marta | Rodríguez Pascau, Laura | Serra Vinardell, Jenny | Sintas Vives, Celia | Toma Toma, Claudio | Torrico Avilés, Bárbara | Vilageliu Arques, Lluïsa.

Main lines of research

- Study of the genetic and molecular basis of lysosomal diseases.
- Study of the genetic and molecular basis of the Costello syndrome.
- Homocysteine and pathology.
- Genetic basis of bone pathologies.
- Genetic basis of neurologic diseases.
- Genetic study of hereditary multiple hereditary multiple exostoses.
- Identification of the gene responsible for Opitz C syndrome by whole exome sequencing.

Most relevant scientific articles

CANALS I, SORIANO J, ORLANDI JG, TORRENT R, RICHAUD-PATIN Y, JIMÉNEZ-DELGADO S, ET AL. Activity and High-Order Effective Connectivity Alterations in Sanfilippo C Patient-Specific Neuronal Networks. Stem cell reports. 2015;5(4):546–57.

CANALS I, BENETÓ N, COZAR M, VILAGELIU L, GRINBERG D. EXTL2 and EXTL3 inhibition with siRNAs as a promising substrate reduction therapy for Sanfilippo C syndrome. Sci Rep. 2015;5:13654.

ZHENG H, FORGETTA V, HSU Y, ESTRADA K, ROSELLO-DIEZ A, LEO PJ, ET AL. Whole-genome sequencing identifies EN1 as a determinant of bone density and fracture. Nature. 2015;526(7571):112–7.

FERNÀNDEZ-CASTILLO N, CABANA-DOMÍNGUEZ J, SORIANO J, SÀNCHEZ-MORA C, RONCERO C, GRAU-LÓPEZ L, ET AL. Transcriptomic and genetic studies identify NFAT5 as a candidate gene for cocaine dependence. Transl Psychiatry. 2015;5:e667.

TOMA C, TORRICO B, HERVÁS A, SALGADO M, RUEDA I, VALDÉS-MAS R, ET AL. Common and rare variants of microRNA genes in autism spectrum disorders. World J Biol Psychiatry. 2015;1–11.

Highlights

Within the lysosomal diseases research line, an iPS-based neuronal model for Sanfilippo C diseases has been completed and a successful treatment on patients' fibroblasts using interference RNA has been performed. A project on the generation of an iPS-derived osteoblast model for Gaucher disease is nearly finished. Besides, mouse models bearing a pseudoexon-generating splicing mutation, responsible for Niemann-Pick C disease have been generated and characterized.

Within the bone disease research line, the FLJ42280, WNT16, DKK1 and SOST genes, previously found to be involved in osteoporosis, have been resequenced. Functional studies for relevant variants have been started. We have participated in a multicentric study that identified EN1 as a novel osteoporosis related gene. Exome sequencing allowed the identification of mutations involved in atypical fractures in patients treated with bisphosphonates. Finally, a miRNA profile has been performed in normal and osteoporotic bone.

In the field of neurological diseases, large scale studies have been performed to characterize the genetic landscape shared by and specific to different psychiatric disorders, including autism, ADHD, and drug dependence, focused on common and rare variants, including point mutations and CNVs. Additionally, transcriptomic studies in drug-abuse animal and cellular models have been performed.

Finally, a whole exome sequencing has been performed on Opitz C syndrome and Bohring-Opitz syndrome patients. A mutation, very likely pathogenic, has been identified in the MAGEL2 gene in one patient, and a mutation in the FOXP1 gene has been found in another patient. These two genes had not been previously associated with the disease. Additionally, a mutation in the ASXL1 gene (in a Bohring-Opitz patient) and two mutations in the RYR1 gene (in two sibs re-diagnosed as congenital myopathy patients) have been found.

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Group U721

Programme: Genetic Medicine
Lead Researcher: Knecht, Erwin

Group members

STAFF MEMBERS: Aguado Muñoz, Carmen.
ASSOCIATED MEMBERS: Armengod González, María Eugenia.

Main lines of research

- Functional characteristics of CLN2 and CLN3, two variants of neuronal ceroid lipofuscinosis.
- Molecular basis of Lafora disease.
- Function of CERKL, a protein that causes retinitis pigmentosa.
- Role of mitochondrial tRNAs modification enzymes in MELAS and other OXPHOS syndromes.
- Alterations in intracellular protein degradation in X-linked adrenoleukodistrophy.

Most relevant scientific articles

LAUNAY N*, AGUADO C*, FOURCADE S, RUIZ M, GRAU L, RIERA J, GUILERA C, GIRÒS M, FERRER I, KNECHT E, PUJOL A (2015). Autophagy induction halts axonal degeneration in a mouse model of X-adrenoleukodystrophy. Acta Neuropathol, 29(3): 399-415. *equal contribution.

MACÍAS-VIDAL J, GUERRERO M, ESTANYOL JM, AGUADO C, KNECHT E, COLL MJ, BACHS O (2015). Identification of lysosomal Npc1-Binding Proteins: Cathepsin D activity is regulated by NPC1. Proteomics, oct 28.

MARTÍNEZ-ZAMORA A, MESEGUER S, ESTEVE JM, VILLARROYA M, AGUADO C, ENRÍQUEZ JA, KNECHT E, ARMENGOD MA (2015). Defective expression of the mitochondrial-tRNA modifying enzyme GTPBP3 triggers AMPK-mediated adaptive responses involving complex I assembly factors, uncoupling protein 2, and the mitochondrial pyruvate carrier. PLoS One. 2015 Dec 7;10(12): e0144273.

ROMÁ-MATEO C*, AGUADO C*, GARCÍA-GIMÉNEZ JL*, IBÁÑEZ-CABELLOS JS, SECO-CERVERA M, PALLARDÓ FV, KNECHT E, SANZ P (2015). Increased Oxidative Stress and Impaired Antioxidant Response in Lafora Disease. Mol Neurobiol, 51(3):932-946. *equal contribution.

ROMÁ-MATEO C*, AGUADO C*, GARCÍA-GIMÉNEZ JL*, KNECHT E, SANZ P, PALLARDÓ FV (2015). Oxidative stress, a new hallmark in the pathophysiology of Lafora progressive myoclonus epilepsy. Free Rad Biol & Med, 88:30-41. *equal contribution.

Highlights

Our CiberER group is funded by MINECO (projects SAF2014-54604-C3-2-R y BFU2014-58673-P). The most outstanding results obtained this year have been:

- Lafora disease. The fibroblasts from patients present a decrease in autophagic mitochondrial degradation that would explain the previously observed accumulation of damaged mitochondria and the consequent increase in the production of ROS. In collaboration with: U733 and U742.
- X-adrenoleukodystrophy. In all models analyzed of this pathology there is an impairment of autophagy that is restored by an inhibitor of mTOR. This treatment improves the neurological phenotype in mouse models of the disease. We are also analyzing in spinal cords from these mice the effect on autophagy of other treatments. In collaboration with: U759.
- Retinitis pigmentosa. The CERKL protein, involved in retinitis pigmentosa, but not its pathological mutants, interacts with mRNAs from humanin-like peptides and with non-coding RNA RN7SL2. CERKL would bind to the mRNAs from humanin-like peptides in the nucleus and, once in the cytoplasm, other proteins of the translational machinery and the non-coding RNA RN7SL2 would join them to form compact ribonucleoprotein particles. They move, via microtubules, to the plasma membrane where co-translational synthesis and secretion of the humanin-like peptides probably occurs. These peptides play an antiapoptotic role. In collaboration with: U718.
- Mitochondrial diseases. We study here GTPBP3, an evolutionarily conserved protein involved in mitochondrial tRNA modification. In a GTPBP3 stable silenced cell model we found a decrease in mitochondrial size and in their fractional volume, which would be related to an increase in autophagy due to activation of AMPK.
- Finally, we collaborate with Dr. Coll. (Hospital Clinic, Barcelona) in the study of a lysosomal storage disease, Niemann Pick type C, caused by mutations in the NPC1 gene. The work has allowed the identification of several proteins that interact with NPC1.

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Group U722

Programme: Medicina Mitocondrial y Neuromuscular
Lead Researcher: Cardellach López, Francesc

Group members

STAFF MEMBERS: Garrabou Tornos, Gloria.

AT THE EXPENSE OF THE PROJECT: González Casacuberta, Ingrid.

ASSOCIATED MEMBERS: Catalán García, Marc | Grau Junyent, José María | Guitart Mampel, Mariona | Moren Núñez, Constanza.

Main lines of research

The activity of U722 is framed within the clinical practice and the biomedical patient-oriented translational research. It is integrated by a multidisciplinar group of medical doctors and basic investigators whose labor is centered in the diagnosis and clinical follow up of patients with rare diseases (RD), but also on the investigation of its molecular basis and the development of prognostic/diagnostic biomarkers and potential treatments. Main research lines:

- Creation of the Group for Medical Assistance of Adult Patients with Rare Diseases (basically of metabolic, mitochondrial and muscular origin, among others): diagnosis and management of patients, training of specialized staff, clinical and experimental data base recruitment and biobank management.
- Establishment of etiological bases, putative diagnostic/prognostic biomarkers and potential therapeutic targets in:

- Muscular Pathology: mitochondrial, inflammatory, autoimmune and toxic. Special focus in inclusion body myositis and myopathy secondary to statin treatment. / Mitochondrial toxicity induced by drugs (antiretrovirals, antibiotics, antipsychotics) or toxic agents (HIV, CO, tobacco) that cause clinic manifestations characteristics of mitochondrial diseases (lipodystrophy, hyperlactatemia, peripheral neuropathy, infertility, obstetric problems, myopathy). / Neurodegenerative and psychiatric diseases: Parkinson disease (especially the one associated to mutations in Parkin and LRRK2 genes), X-Fragile syndrome, Huntington disease and schizophrenia. / Obstetric problems (especially intrauterine growth restriction and cardiovascular fetal remodeling or preeclampsia). / Cardiac disease. / Gene therapy in MNGIE.

The investigators of our group participate in mobility programmes, workshops and CIBER meetings, diffusion in magazines and international congresses of their activity and they attend questions of RD patients addressed from the CIBERER/Orphanet. The group has centred its efforts to broadcast both to

the scientific community and the general population all the activity related to the investigation and medical research on RD. For instance, through the commemoration of the "Annual meeting on rare diseases in adulthood".

Most relevant scientific articles

CATALÁN-GARCÍA M, GARRABOU G, MORÉN C, GUITART-MAMPEL M, GONZÁLEZ-CASACUBERTA I, HERNANDO A, GALLEGO-ESCUREDO J, YUBERO D, VILLAROYA F, MONTERO R, O-CALLAGHAN AS, CARDELLACH F, GRAU J. BACE-1, PS-1 and sAPPβ levels are increased in plasma from sporadic inclusion body myositis patients: surrogate biomarkers among inflammatory myopathies. Mol Med. 2015 Nov 3. doi: 10.2119/molmed.2015.00168.

CÁMARA Y, CARREÑO-GAGO L, MARTÍN MA, MELIÀ MJ, BLÁZQUEZ A, DELMIRO A, GARRABOU G, MORÉN C, DÍAZ-MANERA J, GALLARDO E, BORNSTEIN B, LÓPEZ-GALLARDO E, HERNÁNDEZ-LAIN A, SAN MILLÁN B, CANCHO E, RODRÍGUEZ-VICO JS, MARTÍ R, GARCÍA-ARUMÍ E. Severe TK2 enzyme activity deficiency in patients with mild forms of myopathy.Neurology. 2015 Jun 2;84(22):2286-8. doi: 10.1212/WNL.0000000000001644. Epub 2015 May 6.

BOSCH M, FAJARDO A, ALCALÁ-VIDA R, FERNÁNDEZ-VIDAL A, TEBAR F, ENRICH C, CARDELLACH F, PÉREZ-NAVARRO E, POL A. Hepatic Primary and Secondary Cholesterol Deposition and Damage in Niemann-Pick Disease. Am J Pathol. 2016 Jan 16. pii: S0002-9440(15)00693-8. doi: 10.1016/j.ajpath.2015.12.002.

HERNÁNDEZ-RODRÍGUEZ J, RUÍZ-ORTIZ E, TOMÉ A, ESPINOSA G, GONZÁLEZ-ROCA E, MENSA-VILARÓ A, PRIETO-GONZÁLEZ S, ESPÍGOL-FRIGOLÉ G, MENSA J, CARDELLACH F, GRAU JM, CID MC, YAGÜE J, ARÓSTEGUI JI, CERVERA R. Clinical and genetic characterization of the autoinflammatory diseases diagnosed in an adult reference center. Autoimmun Rev. 2016 Jan;15(1):9-15. doi: 10.1016/j.autrev.2015.08.008. Epub 2015 Aug 21. Review.

REDDY P, OCAMPO A, SUZUKI K, LUO J, BACMAN SR, WILLIAMS SL, SUGAWARA A, OKAMURA D, TSUNEKAWA Y, WU J, LAM D, XIONG X, MONTSERRAT N, ESTEBAN CR, LIU GH, SANCHO-MARTÍNEZ I, MANAU D, CIVICO S, CARDELLACH F, DEL MAR O'CALLAGHAN M, CAMPISTOL J, ZHAO H, CAMPISTOL JM, MORAES CT, IZPISUA BELMONTE JC. Selective elimination of mitochondrial mutations in the germline by genome editing. Cell. 2015 Apr 23;161(3):459-69. doi: 10.1016/j.cell.2015.03.051.

Highlights

In 2015 we have participated in: (i) PIBER-1 on genomics medicine with the rest of PdI groups (Neurology article); (ii) PIBER-2 on patophysiology of RD, specifically on mtDNA maintenance syndromes (together with U701,U717,U723,U727: Neurology article); (iii) PIBERs 3 and 4 on clinical and therapeutical investigation in the following categories: (a) muscular pathology (Mol Med and Rheumatol Int articles and collaboration with U713,U703); (b) mitochondrial toxicity (Pedatr Infect Dis, J AntimicrobChemother, AIDS articles); (c) neurodegenerative and psychiatric diseases: X-fragile syndrome (FIS with U726); familial Parkinson's Disease (PD) (FIS with CIBERNED); common aetiopathology between PD, diabetes and Alzheimer's disease (InterCIBER) and mitochondrial basis of schizophrenia; (d) obstetric disorders: intrauterine growth restriction (3 FIS projects with U719, 2 in 2015, Pedatr Infect Dis and AIDS articles); (e) myocardiopathies (Marató of TV3 2015, Cardiovasc Res article); (f) mitochondrial genetic disorders: gene therapy on MNGIE (ACCI with U701,U714) and TALENs for assisted reproduction techniques (Cell article). Many projects are conducted by CIBER and have allowed funding for human resources; the grants given by CELLEX foundation for infrastructure and staff have also been fundamental. Finally, we are working in the development of 2 orphan drugs for rare myopaties and Pompe disease.

Our participation in the PITER-1 is focused in: (a) diagnosis of RD (with U701,U729,U717); (b) translation to the health system of diagnostic methods (with U717, U737, U701, U723, U727, U729); (c) clinical guidelines elaboration and (d) creation of the "Group for Medical Assistance of Adult Patients with Rare Diseases" and the "Attention unit for patients with inborn errors of metabolism", formed by U703,U737,U722 and diverse services from the Hospital Clinic of Barcelona (intramural/CIBERER-2010, 2 medical residents in internship and papers including AmJPathol, AutoimmunRev, ClinExpRheumatol, JAmGeriatrSoc articles). Regarding PITER-2 we have participated by handing biologic samples to CIBER-biobank and on PITER-3 in the mentoring and teaching of students.

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Group U723

Programme: Mitochondrial and Neuromuscular Medicine
Lead Researcher: Martín Casanueva, Miguel Ángel

Group members

STAFF MEMBERS: Blázquez Encinar, Alberto | Jiménez García, Sara.

ASSOCIATED MEMBERS: Atencia Cibreiro, María Gabriela | Delmiro Magdalena, Aitor | Dominguez González, Cristina | Esteban Pérez, Jesús | García Consuegra Galiana, Inés | García Redondo, Alberto | García Silva, María Teresa | Hoyo Gordillo, Pilar del | Juárez Rufián, Alexandra | Martínez Azorín, Francisco | Morán Bermejo, María Jesús | Rubio Muñoz, Juan Carlos | Rufián Vázquez, Laura | Ugalde Bilbao, Cristina.

Main lines of research

- Mitochondrial diseases and exercise intolerance: Development and standardization of biochemical and genetic/genomic methods to improve the biochemical and genetic diagnosis. Identification of new disease-causing genes and novel mutations.
- Biochemical and molecular basis of mitochondrial respiratory chain complex I and complex III deficiencies.
- Assessment of OXPHOS complexes assembly by BN_PAGE and its clinical translation
- Neuromuscular diseases research lines: Metabolic Exercise Intolerance: i) Patient's registries, natural history and genotype-phenotype correlations of type V glycogenosis (GSDV- McArdle disease), ii) Amyotrophic Lateral Sclerosis: identifications of novel mutations, evaluation of pathophysiology of ALS using cell and animal models, and patient's clinical trials.
- Mitochondrial dynamics and autophagy: i) Role of mitochondrial dynamics and autophagy (and mitophagy) in cell models of mitochondrial disorders; ii) mitochondrial disturbances and autophagy pathway evaluation in a mouse model of graft vs host disease.
- Oxygen consumption as in vivo marker of mitochondrial disorders.
- Identification and validation of biomarkers in mitochondrial disorders.

Most relevant scientific articles

HERNÁNDEZ-LAÍN A, GUERRERO AM, DOMÍNGUEZ-GONZÁLEZ C, FERNÁNDEZ-VÁZQUEZ I, MAYA DG, DELMIRO A, ET AL. A novel RRM2B gene variant associated with Telbivudine-induced mitochondrial myopathy. J Neurol Sci. 2015;358(1-2):481-3.

BAIXAULI F, ACÍN-PÉREZ R, VILLARROYA-BELTRÍ C, MAZZEO C, NUÑEZ-ANDRADE N, GABANDÉ-RODRÍGUEZ E, ET AL. Mitochondrial Respiration Controls Lysosomal Function during Inflammatory T Cell Responses. Cell Metab. 2015;22(3):485-98.

BRULL A, DE LUNA N, BLANCO-GRAU A, LUCIA A, MARTIN MA, ARENAS J, ET AL. Phenotype consequences of myophosphorylase dysfunction: insights from the McArdle mouse model. J Physiol. 2015;593(12):2693-706.

CÁMARA Y, CARREÑO-GAGO L, MARTÍN MA, MELIÀ MJ, BLÁZQUEZ A, DELMIRO A, ET AL. Severe TK2 enzyme activity deficiency in patients with mild forms of myopathy. Neurology. 2015;84(22):2286-8

MARÍN-BUERA L, GARCÍA-BARTOLOMÉ A, MORÁN M, LÓPEZ-BERNARDO E, CADENAS S, HIDALGO B, ET AL. Differential proteomic profiling unveils new molecular mechanisms associated with mitochondrial complex III deficiency. J Proteomics. 2015;113:38-56.

Highlights

A clinical-translational level we have become a center and reference unit (CSUR) for mitochondrial and inherited metabolic diseases (Coordinator Dr. Garcia-Silva). The implementation of massive parallel sequencing-based methodologies (MPS-NGS), from a previous research project, has led to identification of new mutations in genes associated with depletion_deletion syndromes of mitochondrial DNA (MDDS). In this regard and in close collaboration with the U701_CIBERER (Dr. Martí), we were able to establish new genotype-phenotype correlations expanding the phenotypic spectrum of those disorders caused by mutations in the gene thymidine kinase 2 (TK2). These results have contributed and allowed the granting of a multicenter ISCIII-FIS project coordinated by us regarding personalized medicine. In addition, we have identified in this group of genes, a possible gene-mutation (RRM2B) that could be a modifier of certain antiviral effects. Dr. Martínez-Azorín identified by NGS-exome novel mutations associated with new phenotypes OXPHOS (genes SERAC1 and CHKB). We have collaborated with U713_CIBERER (Dr. Cuezva) to detect protein bioenergetic biomarkers in neuromuscular diseases. Following this research line, we have been granted with a CIBERER intramural project about biomarkers of mitochondrial PEO phenotype. In this proteomic context, Dr. Ugalde has characterized at the proteomic level the isolated complex III deficiencies of OXPHOS system. In collaboration with the group of Dr. Mittelbrunn (CNIC), currently in our Institute, we have participated in the work that has revealed the role of mitochondrial respiration in the control of the function of the lysosome in the inflammatory T cell response.

In McArdle disease we have continued with the EHAC-EU European Patients' Registry (EUROMAC) project, and have published several articles on the genetics, pathophysiology and intervention with physical exercise following our longstanding partnership with U701_CIBERER and groups IGTIP (Dr. Nogales-Gadea) and UEM (Prof. Lucia).

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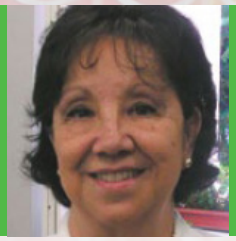
Group U724

Programme: Paediatric and Developmental Medicine
Lead Researcher: Martínez Frías, María Luisa



Group members

STAFF MEMBERS: Martínez Fernández, Mª Luisa.

ASSOCIATED MEMBERS: Arroyo Carrera, Ignacio | Barcia Ruiz, José María | Bermejo Sánchez, María Eva | Beseler Soto, Beatriz | Calvo Aguilar, María José | Canduela Martínez, Víctor Manuel | Centeno Malfaz, Fernando | Colli Lista, Gloria | Cuevas Catalina, Lourdes | Esteban Marfil, María Victoria | Felix Rodríguez, Valentín José | Foguet Vidal, Antoni | Galán Gómez, Enrique | Gallardo Hernández, Francisca Luisa | García Álix Perez, Alfredo | García González, María del Mar | García Martínez, María José | García Vicent, Consuelo | García García, Ángel | Gómez Martin, Hilario | González de Dios, Javier | Lara Palma, Ana María | Martín Sanz, Feliciano | Martínez Guardia, Nieves | Marugan Isabel, Víctor Manuel | Mayoral González, Begoña | Ochoa Sangrador, Carlos | Pi Castan, Graciela | Rodríguez Pando, María del Carmen | Rosal Roig, Jaime | Rota Zapata, Lucia | Sánchez Estévez, Carlos | Sanchís Calvo, María Desamparados | Silveira Cancela, Manuel | Zuazo Zamalloa, Ester.

Main lines of research

- Research on cytogenetics and molecular genetics of infants born with malformations and other congenital defects.
- Research for the identification of teratogenic risk factors in humans and environmental causes of congenital defects in newborn infants.
- Research on the clinical and etiological aspects of infants born with malformations and other congenital defects.
- Research on the descriptive and analytical epidemiological aspects of infants born with malformations and other congenital defects.

Most relevant scientific articles

MARTÍNEZ-FERNÁNDEZ ML, FERNÁNDEZ-TORAL J, LLANO-RIVAS I, BERMEJO-SÁNCHEZ E, MARTÍNEZ-FRÍAS ML. Delineation of the clinically recognizable 17q22 contiguous gene deletion syndrome in a patient carrying the smallest microdeletion known to date. Am J Med Genet A. 2015 Apr; 167A(9):2034-41. doi: 10.1002/ajmg.a.37117. PMID: 25899082.

ARROYO-CARRERA I, DE ZALDÍVAR TRISTANCHO MS, BERMEJO-SÁNCHEZ E, MARTÍNEZ-FERNÁNDEZ ML, LÓPEZ-LAFUENTE A, MACDONALD A, ZÚÑIGA Á, LUIS GÓMEZ-SKARMETA J, LUISA MARTÍNEZ-FRÍAS M. Deletion 1q43-44 in a patient with clinical diagnosis of Warburg-Micro syndrome. Am J Med Genet A. 2015 Jun;167(6): 1243-51. doi: 10.1002/ajmg.a.36878. PMID: 25899426.

MARCHEGIANI S, DAVIS T, TESSADORI F, VAN HAAFTEN G, BRANCATI F, HOISCHEN A, HUANG H, VALKANAS E, PUSEY B, SCHANZE D, VENSELAAR H, VULTO-VAN SILFHOUT AT, WOLFE LA, TIFFT CJ, ZERFAS PM, ZAMBRUNO G, KARIMINEJAD A, SABBAGH-KERMANI F, LEE J, TSOKOS MG, LEE CC, FERRAZ V, DA SILVA EM, STEVENS CA, ROCHE N, BARTSCH O, FARNDON P, BERMEJO-SÁNCHEZ E, BROOKS BP, MADURO V, DALLAPICCOLA B, RAMOS FJ, CHUNG HY, LE CAIGNEC C, MARTINS F, JACYK WK, MAZZANTI L, BRUNNER HG, BAKKERS J, LIN S, MALICDAN MC, BOERKOEL CF, GAHL WA, DE VRIES BB, VAN HAELST MM, ZENKER M, MARKELLO TC. Recurrent Mutations in the Basic Domain of TWIST2 Cause Ablepharon Macrostomia and Barber-Say Syndromes. Am J Hum Genet. 2015 Jul;97(1):99-110. doi: 10.1016/j.ajhg.2015.05.017. PMID: 26119818.

MARTÍNEZ F, MARÍN-REINA P, SANCHIS-CALVO A, PEREZ-AYTÉS A, OLTRA S, ROSELLÓ M, MAYO S, MONFORT S, PANTOJA J, ORELLANA C. Novel mutations of NFIX gene causing Marshall-Smith syndrome or Sotos-like syndrome: one gene, two phenotypes. Pediatr Res. 2015 Nov;78(5):533-9. doi: 10.1038/pr.2015.135. PMID: 26200704.

ARROYO CARRERA I, DE ZALDÍVAR MS, MARTÍN R, BEGEMANN M, SOELLNER L, EGGERMANN T. Microdeletions of the 7q32.2 imprinted region are associated with Silver-Russell syndrome features. Am J Med Genet A. 2015 Dec 10. doi: 10.1002/ajmg.a.37492. [Epub ahead of print] PMID: 26663145.

Highlights

- Maintenance of ECEMC (Spanish Collaborative Study of Congenital Malformations) Clinical Network (> 400 physicians throughout Spain) • Clinical-dysmorphological evaluation of 1,016 newborns and fetuses with congenital defects (CD) in Spain • Cytogenetic study (high resolution and molecular): 155 samples from ECEMC • Attending medical consultations by telephone:501 to SITTE (Teratology Information Service, Spain) and 2,148 to SITE (Teratology Information Service for general public) • Epidemiological Surveillance of CD in Spain • European Surveillance of CD in the EUROCAT network (www.eurocat-network.eu) • Worldwide epidemiological surveillance of CD in the ICBDSR network (www.icbdsr.org) • Chair of the Executive Committee of ICBDSR • Participation in the constitution of the EUROCAT Association of European Registries of Congenital Anomalies • Participation in activities of the Joint Research Centre-EUROCAT • Participation in the organisation of World Birth Defects Day • Start of a research project on descriptive aspects and genotype-phenotype correlation in patients with 5p- syndrome. Sponsored by the "Fundación 5p-". PI: M.L. Martínez-Frías • Development of the research project: "Research on the clinical and etiological aspects of atypical congenital craniofacial clefts". IP: E. Bermejo-Sánchez. PI12/00759 • Teaching part of the Official Master "Current knowledge on Rare Diseases". Universidad Internacional de Andalucía • Teaching activities and attendance of national and international conferences in the CD field • Organisation of the "XXXvIII ECEMC Annual Meeting" and "Update Course in research on CD". Aviles, 15-17 October 2015 [2,2 CME credits Madrid-NHS. File: 07-AFOC-04710.2/2015] • Participation and organisation of the "42nd Annual Meeting of the International Clearinghouse for Birth Defects, Surveillance and Research", Spoleto (Italy), 10-14 September 2015 • Two editions of the "Clinical Teratology Conference". Organised by the Training Service of the General Directorate (GD) of Human Resources and the Public Health Observatory of the Public Health GD, Health Administration of Castilla and Leon, and the Research Centre on Congenital Anomalies (CIAC).Valladolid and Palencia • Publication of 3 "Propositus: ECEMC Information Factsheets" http://www.fundacion1000.es/boletines-ecemc.

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Associated Group U725

Programme: Endocrine Medicine

Lead Researcher: Castaño González, Luis

Group members

ASSOCIATED MEMBERS: Bilbao Catalá, José RamÓn | Cortazar Galarza, Alicia | Gaztembide Sáenz, Sonia | Rica Etxebarria, Itxaso | Vázquez San Miguel, Federico | Vela Desojo, Amaia.

Main lines of research

- Pseudohypoparathyroidism: molecular characterization of locus GNAS.
- Search of new candidate genes in monogenic diabetes, neonatal diabetes, maturity onset diabetes of the young (MODY) and mitochondrial diabetes.
- Study of genes affecting sexual differentiation.
- Genetic and phenotypic characterization and differential immunohistochemistry in type 1 multiple endocrine neoplasia.
- Prediction and prevention of autoimmune disorders (celiac disease and diabetes).
- Genetic and phenotypic characterization of obesity.
- Genetic alterations in rare diseases of endocrine origin.
- Genetic alterations in Hirchsprung disease.

Most relevant scientific articles

PLAZA-IZURIETA L, FERNÁNDEZ-JIMÉNEZ N, IRASTORZA I, JAUREGI-MIGUEL A, ROMERO-GARMENDIA I, VITORIA JC, BILBAO JR. Expression analysis in intestinal mucosa reveals complex relations among genes under the association peaks in celiac disease (2015) Eur. J Hum Genet 23: 1100-1105. doi:10.1038/ejhg.2014.244. IF: 4.23.

PEREZ-NANCLARES G, VELAYOS T, VELA A, MUNOZ-TORRES M, CASTANO L. Pseudohypoparathyroidism Type Ib Associated with Novel Duplications in the GNAS Locus. Plos One. Feb 2015. (10) 2. IF: 3.23.

ONENGUT-GUMUSCU S, CHEN WM, BURREN O, COOPER NJ, QUINLAN AR,MYCHALECKYJ JC, FARBER E, BONNIE JK, SZPAK M, SCHOFIELD E. Tipo 1 Genetic Diabetes Consortium(..... Castano L.....) Fine mapping of type 1 diabetes susceptibility loci and evidence for colocalization of causal variants with lymphoid gene enhancers.Nature Genetics. Apr 2015(47)4 (381-U199). IF: 29.35.

FALORNI A, BINI V, BETTERLE, C, BROZZETTI A, CASTANO L, FICHNA M, KAMPE O, MELLGREN, G, PETERSON P, CHEN S. Determination of 21-hydroxylase autoantibodies: inter-laboratory concordance in the Euradrenal International Serum Exchange Program. Clinical Chemistry of Pediatrics. Oct 2015 (53) 11:1761-1770. IF: 2.71.

CABRERA SM, WANG X, CHEN YG, JIA S, KALDUNSKI ML, GREENBAUM CJ. Type 1 Diabetes TrialNet Canakinumab Study Group, Mandrup-Poulsen T, AIDA Study Group (..... Castano L.....), Hessner MJ. Eur J Immunol Dec 2015. IF: 4.034.

Highlights

- Study of the global prevalence of vitamin D levels in healthy pediatric population of the Goierri-Urola-Gipuzkoa region" Basque Government (2011111107). 2012-2015. Luis Castaño.
- Endocrinology, Diabetes, Nutrition and Renal Alterations".Basque Government (IT 795-13). 2013-2018. Luis Castaño.
- Researchers: Incidence of diabetes and prevalence of monogenic diabetes in the di@bet.es study. ISCIII – PI14/01104. Luis Castaño.
- Determinants of Diet and Physical Activity; Knowledge Hub to integrate and develop infrastructure for research across Europe. DEDIPAC KH. (JPI) "A Healthy Diet for a Healthy Life" 1/12/2012. Luis Castaño.
- The European Nutrition Phenotype Assessment and Data Sharing Initiative. ENPADASI. A Healthy Diet for a Healthy Life.01/04/2014. Luis Castaño.
- Clinical and Molecular characterization of pituitary tumors in children and adolescents. Fundación Salud 2000-15- EP-004. Luis Castaño.
- Prospective study of the incidence of diabetes mellitus and cardiovascular risk factors in Basque Country. Basque Government 2015111020. Sonia Gaztambide. 2016-2018.
- Functional characterization of the genomic regions associated with celiac disease risk in cell populations of the gut mucosa. ISCIII-MICINN (PI13/01201). José Ramón Bilbao. 2014-2016.
- Functional study of candidate genes to celiac disease and its possible use as a diagnostic tool. Basque Government (2011111034). José Ramón Bilbao. 2013-2015.
- Role of the cell cycle regulators E2F1 and E2F2 in the pathogenesis and prognosis of the hepatic disease: from Fatty Liver Disease to Hepatocellular carcinoma. State Research Program. 2015 Call (SAF2015-64352-R). Sonia Gaztambide.
- Genetic and environmental factors of insulin resistance syndrome and its long-term complications in immigrant Mediterranean populations. MEDIGENE (FP7-279171-1). Luis Castaño. 2011-active.
- Centre Differences study in children aged under 11 years. Hvidore Study Group on childhood Diabetes. Luis Castaño. 2009-2015.
- TRIGR project: Trial to reduce IDDM in children at genetic risk. National Institute of Health. Luis Castaño. 2007-2016.
- Role of the gut microbiota in metabolic syndrome and persistent inflammation in Cushing syndrome at remission. PI2015139. Sonia Gaztambide. 2015.

Institution: Asociación Inst. de Investigación Sanitaria de Biocruces · **Contact:** Hospital Universitario Cruces Pza. de Cruces, S/N. 48903 Barakaldo · Tel.: 946 006 473 · E.mail: lcastano@osakidetza.net

Group U726

Programme: Paediatric and Developmental Medicine

Lead Researcher: Milá, Montserrat

Group members

STAFF MEMBERS: Álvarez Mora, Mª Isabel | Giménez Xavier, Pol | Tell Martí, Gemma.

ASSOCIATED MEMBERS: Aguilera Peiro, Paula | Badenas Orquín, Celia | Carrera Álvarez, Cristina | Jiménez Sánchez, María Dolores | Madrigal Bajo, Irene | Malvehy Guilera, Josep | Margarit Torrent, Esther | Puig Sardá, Susana | Rodríguez-Revenga Bodi, Laia | Sánchez Díaz, María Aurora | Soler Casas, Anna Maria.

Main lines of research

- Intelectual disability of genetic origin.
- Familial cutaneous melanoma.
- Genodermatosis.
- Autism.
- Fragile X síndrome.
- FMR1 premutated disorders (FXTAS, FXPOI and others...).

Most relevant scientific articles

TELL-MARTI G, PUIG-BUTILLE JA, POTRONY M, BADENAS C, MILÀ M, MALVEHY J, MARTÍ MJ, EZQUERRA M, FERNÁNDEZ-SANTIAGO R, PUIG S. The MC1R melanoma risk variant p.R160W is associated with Parkinson disease. Ann Neurol. 2015 May;77(5):889-94

PUIG S, POTRONY M, CUELLAR F, PUIG-BUTILLE JA, CARRERA C, AGUILERA P, NAGORE E, GARCÍA-CASADO Z, REQUENA C, KUMAR R, LANDMAN G, COSTA SOARES DE SÁ B, GARGANTINI REZZE G, FACURE L, DE AVILA AL, ACHATZ MI, CARRARO DM, DUPRAT NETO JP, GRAZZIOTIN TC, BONAMIGO RR, REY MC, BALESTRINI C, MORALES E, MOLGO M, BAKOS RM, ASHTON-PROLLA P, GIUGLIANI R, LARRE BORGES A, BARQUET V, PÉREZ J, MARTÍNEZ M, CABO H, COHEN SABBAN E, LATORRE C, CARLOS-ORTEGA B, SALAS-ALANIS JC, GONZÁLEZ R, OLAZARAN Z, MALVEHY J, BADENAS C. Characterization of individuals at high risk of developing melanoma in Latin America: bases for genetic counseling in melanoma. Genet Med. 2015 Dec 17.

SÁEZ MA, FERNÁNDEZ-RODRÍGUEZ J, MOUTINHO C, SÁNCHEZ-MUT JV, GOMEZ A, VIDAL E, PETAZZI P, SZCZESNA K, LÓPEZ-SERRA P, LUCARIELLO M, LORDEN P, DELGADO-MORALES R, DE LA CARIDAD OJ, HUERTAS D, GELPÍ JL, OROZCO M, LÓPEZ-DORIGA A, MILÀ M, PEREZ-JURADO LA, PINEDA M, ARMSTRONG J, LÁZARO C, ESTELLER M. Mutations in JMJD1C are involved in Rett syndrome and intellectual disability. Genet Med. 2015 Jul 16

RIBERO S, DAVIES JR, REQUENA C, CARRERA C, GLASS D, RULL R, VIDAL-SICART S, VILALTA A, ALOS L, SORIANO V, QUAGLINO P, TRAVES V, NEWTON-BISHOP JA, NAGORE E, MALVEHY J, PUIG S, BATAILLE V. High nevus counts confer a favorable prognosis in melanoma patients. Int J Cancer. 2015 Oct 1;137(7):1691-8

TORRICO B, FERNÀNDEZ-CASTILLO N, HERVÁS A, MILÀ M, SALGADO M, RUEDA I, BUITELAAR JK, ROMMELSE N, OERLEMANS AM, BRALTEN J, FREITAG CM, REIF A, BATTAGLIA A, MAZZONE L, MAESTRINI E, CORMAND B, TOMA C. Contribution of common and rare variants of the PTCHD1 gene to autism spectrum disorders and intellectual disability. Eur J Hum Genet. 2015 Dec;23(12):1694-70

Highlights

During 2015 the U726 group has been working on the genetic aspects of rare diseases within the framework of our scientific projects. We obtained funding for a new three-year project entitled "Identification of modifier gene penetrance in rare inherited diseases through massive sequencing" (PI15 / 00483). In addition, the group has also been granted funding to start a new research line on the molecular factors associated with the development of Giant Congenital Nevus. In collaboration with the CIBERER we organized the "2nd International Conference on FMR1 Premutation: Basic Mechanisms and Clinical Involvement, which took place in September 2015 in Barcelona. The PI group has been part of a commission appointed by the Generalitat de Catalunya in order to organize genetic testing and genetic counseling in Catalunya. We work in two CSURs of "Spastic Ataxia and Paraparesia" and another in "Movement Disorders" We have actively collaborated with the Catalan Association of Fragile X Syndrome in various conferences and specifically in 2nd National Fragile X Congress. The group has been active in the creation of the European Society of Xeroderma Pigmentosum which aims to promote progress on issues Syndrome Xeroderma Pigmentosum. The group was responsible for presenting the Society at the 73rd Meeting of the American Academy of Dermatology and the 24th Annual Congress of the European Academy of Dermatology and Venereology. The PI has edited the book entitled "Allelic forms of the FMR1 gene: Fragile X Syndrome, Primary Ovarian Insufficiency and Tremor Ataxia Syndrome among others" ISBN 978-1-63321-914-4 which involved the collaboration of several group members and other Linked Clinical Groups. The results of the research carried by U726 are evident with the 25 manuscripts published in indexed journals.

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Group U727

Programme: Mitochondrial and Neuromuscular Medicine
Lead Researcher: Montoya Villarroya, Julio

Group members

STAFF MEMBERS: Emperador Ortiz, Sonia | López Gallardo, Ester.

ASSOCIATED MEMBERS: Llobet Sese, Laura | López Pérez, Manuel José | Ruiz Pesini, Eduardo.

Main lines of research

- Genetic and molecular diagnosis of mitochondrial disorders and study of the physiopathogenic mechanism of mutations. Rescue of the normal phenotype by transfection of the patient fibroblast wit the wild-type gene.
- Study of mtDNA population genetic variants conferring susceptibility to multifactorial diseases.
- Characterization of environmental or genetic factors interacting with the genetic pool in susceptibility development.
- Search of drugs acting on the OXPHOS system.
- Human chronic fatigue and pain syndromes.
- Use of stem cell as a model for he study of physiopatologic mechanism of the new mutations in the mitochondrial DNA.
- mtDNA variation and neurodegenerative diseases.
- Improvement of the model of cybrids for the study of pathological mutations.

Most relevant scientific articles

O'CALLAGHAN MM, EMPERADOR S, PINEDA M, LÓPEZ-GALLARDO E, MONTERO R, YUBERO D, JOU C, JIMÉNEZ-MALLEBRERA C, NASCIMENTO A, FERRER I, GARCÍA-CAZORLA A, RUIZ-PESINI E, MONTOYA J, ARTUCH R. "Mutation loads in different tissues from six pathogenic mtDNA point mutations". Mitochondrion 2015; 22(May): 17-22.

LLOBET L, MONTOYA J, LÓPEZ-GALLARDO E, RUIZ-PESINI E. "Side effects of culture media antibiotics on cell differentiation". Tissue Engineering Part C 2015; 21(11): 1143-47.

LORENTE L, MARTÍN MM, LÓPEZ-GALLARDO E, BLANQUER J, SOLÉ-VIOLÁN J, LABARTA L, DÍAZ C, JIMÉNEZ A, MONTOYA J, RUIZ-PESINI E. "Decrease of OXPHOS function in severe septic patients". Journal of Critical Care 2015; 30(5): 935-9.

ORMAZABAL A, CASADO M, MOLERO M, MONTOYA J, RAHMAN S, AYLETT SB, HARGREAVES I, HEALES S, ARTUCH R. "Can folic acid have a role in mitochondrial disorders?". Drug Discov Today 2015; 20(11): 1349-54.

LLOBET J, TOIVONEN, J M, MONTOYA J, RUIZ-PESINI E, LÓPEZ-GALLARDO E. "Xenobiotics that affect oxidative phosphorylation alter differentiation of human adipose-derived setem cells at concentrations that are found in human blood". Disease Models & Mechanisms. 2015; 8(11): 1441-55.

Highlights

RESEARCH PROJECTS

1. "New mutations in the mitochondrial DNA associated with diseases: Characterization in differentiated neurons and myocytes transmitocondriales cybrids". PI: Julio Montoya. Instituto de salud Carlos III FIS PI14/00005. 2015-20172

2. "Mitochondrial Pharmacogenomics in Alzheimer's disease". PI:Eduardo Ruiz Pesini. Instituto de Salud Carlos III FIS PI14/00070. 2015-20173.

3. Cconsolidated Group of applied research of Biogenesis and pathology mitochondrial B33. PI: Julio Montoya. 2014-2016. Diputacion General Aragon.

RESULTS.

Molecular-genetic Studies on mitocondrial DNA: sequencing of full mtDNA of 19 patients and other 14 specific genes. Found 3 new mutations (1 in a mitochondrial gene coding for protein and 2 in mt-tRNAs).

Construction of transmitochondrial cybrids of 3 patients with mutations candidates to be pathological. Application of the Blue Native-PAGE technique, 1D and 2D, and measurement of the activity of the OXPHOS complexes "in gel".

Analysis of mutations in new patients: analyzed 77 patients and 43 family membres. Found 46 mutations who correspond a: 12 of the 3243 mutation, 13 of the 3460, 5 of the 1555, 1 of the 13513, 2 depletions and 9 deletions. The rest of the positive samples belonged to new or described mutations in very few cases.

Study of mutations in nuclear genes that cause mitochondrial pathology: patients without any mutation in mtDNA were analizad for the presence of mutations nuclear genes panels (in collaboration with another CIBERER center). Mutations have been found in several nuclear genes that may explain the pathology of these patients. The normal phenotype was rescued by transfection of the patient fibroblasts with the gene wild-type gene. These studies have been conducted successfully in a patient whose results are in the way of publication.

Seminars and conferences: 5 national and international.

Institution: Universidad de Zaragoza · **Contact:** Facultad de Veterinaria. Miguel Servet, 117. 50013 Zaragoza
Tel.: 976 761 640 · E.mail: jmontoya@unizar.es

Group U728

Programme: Sensorineural Pathology

Lead Researcher: Moreno Pelayo, Miguel Ángel

Group members

STAFF MEMBERS: Garrido Martínez, Gema | Gómez Rosas, Elena | Morín Rodríguez, Matías.

ASSOCIATED MEMBERS: Borreguero Escribano, Lucía | Del Castillo Fernández del Pino, Francisco Javier | Del Castillo Fernández del Pino, Ignacio | Domínguez Ruiz, María | Gandia Ferri, Marta | Hernández Chico, Concepción | Hernández Imaz, Elisabete | Martín Santo Domingo, Yolanda | Mayo Merino, Fernando | Pardo Merino, Beatriz | Santos Serrao de Castro, Luciana | Villamar López, Manuela.

Main lines of research

- Hereditary (syndromic and non-syndromic) hearing loss: identification of new genes, genetic epidemiology by means of OMIC approaches (NGS and aCGH), functional studies and generation of murine models.
- Hereditary basis for glaucoma and for the pathology of anterior segment of the eye.
- Hidradenitis suppurativa: identification of the genes responsible for it, genetic epidemiology and functional studies.
- SAPHO syndrome (chronic recurrent multifocal osteomyelitis): identification of the gene responsible for it.
- Neurofibromatosis type 1 and 2 and neuro-cardio-facial-cutaneous syndromes.
- Spinal muscular atrophy.
- microRNA cure: Modulation of microRNAs to eliminate latency reservoirs in HIV patients.
- Genetic-molecular basis for Chiari syndrome.
- Study of primary immunodeficiencies associated with the TCR/CD3 complex and with DNA repair defects.

Most relevant scientific articles

ZAZO SECO C, SERRÃO DE CASTRO L, VAN NIEROP JW, MORÍN M, JHANGIANI S, VERVER EJ, ET AL. Allelic Mutations of KITLG, Encoding KIT Ligand, Cause Asymmetric and Unilateral Hearing Loss and Waardenburg Syndrome Type 2. Am J Hum Genet. 2015 Nov 5;97(5):647-60. Incluye contratado CIBERER. Q1 Genetics & Heredity (6/167). IF= 10.931.

ROJNUEANGNIT K, XIE J, GOMES A , SHARP A, CALLENS T, LIU Y, ET AL. High Incidence of Noonan Syndrome Features including short stature and Pulmonic Stenosis in patients carrying NF1 Missense Mutations affecting p.Arg1809: Genotype-Phenotype Correlation. Hum Mutat. 2015 Nov 36(11):1052-63. Q1 Genetics & Heredity (25/167). IF= 5.340.

SECO CZ, OONK AM, DOMÍNGUEZ-RUIZ M, DRAAISMA JM, GANDÍA M, OOSTRIK J, NEVELING K, KUNST HP, HOEFSLOOT LH, DEL CASTILLO I, PENNINGS RJ, KREMER H, ADMIRAAL RJ, SCHRADERS M. Progressive hearing loss and vestibular dysfunction caused by a homozygous nonsense mutation in CLIC5. Eur J Hum Genet. 2015; 23(2):189-94. Q1 Genetics & Heredity (36/167). IF= 4,349.

HERNÁNDEZ-IMAZ E, MARTÍN Y, DE CONTI L, MELEAN G, VALERO A, BARALLE E, HERNÁNDEZ-CHICO C. Functional analysis of splicing mutations in NF1 exon 9 reveals the presence of several splicing regulatory elements. PLoS One. 2015 Oct 28;10(10):e0141735. Q1 Multidisciplinary Sciences (9/57). IF=3.234.

SANTARELLI R, DEL CASTILLO I, CAMA E, SCIMEMI P, STARR A. Audibility, speech perception and processing of temporal cues in ribbon synaptic disorders due to OTOF mutations. Hear Res. 2015; 330(Pt B):200-12. Q1 (primer decil) Otorhinolaryngology (2/44). IF= 2,968.

GANDÍA M, FERNÁNDEZ-TORAL J, SOLANELLAS J, DOMÍNGUEZ-RUIZ M, GÓMEZ-ROSAS E, DEL CASTILLO FJ, VILLAMAR M, MORENO-PELAYO MA, DEL CASTILLO I. Mutations in PRPS1 causing syndromic or nonsyndromic hearing impairment: intrafamilial phenotypic variation complicates genetic counseling. Pediatr Res. 2015; 78(1):97-102. Q1 Pediatrics (29/120) Incluye contratado CIBERER IF= 2,314.

Highlights

The group continues to work actively on translational research on rare diseases in the field of sensorineural disorders studying the genetic-molecular basis and the mechanisms of pathogenesis behind hereditary hearing loss and disorders of the anterior segment of the eye. Other research interests include studies of neurofibromatosis type I and II. During the 2015 annuity we want to highlight the following achievements:

- Identification of a new gene for hereditary hearing loss, KITLG, being the first to be associated with unilateral and asymmetric deafness.
- Participation in 3 intramural actions financed (ACCI): A) Spänex; B) Development of a diagnostic platform for next generation sequencing and C) New cellular and animal models of neurosensory rare diseases generated by CRISPR.
- Organization and numerous teaching and training activities related to rare diseases:

  A) International Symposium on hereditary hearing loss Ramón Areces Foundation.

  B) Course CIBERER on functional assays as alternative to mouse models.

  C) 1st day of Human Genome Heritage.

  D) 3rd day clinical genetics of the Community of Madrid.

  E) Biomedical Technologies Master in Management and Development of the UC3M.

  F) Specialization Postgraduate Course in Clinical Genetics at the University of Alcala de Henares.
- Contracts and commercial exploitation licenses in progress with various companies: Genycell, Genome Systems, SECUGEN and ATOS / BULL.
- The U728 has seven active research projects funded by public and private (5 projects FIS, 1 draft the Ramón Areces Foundation and 1 draft ONCE.

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Group U729

Programme: Mitochondrial and Neuromuscular Medicine

Lead Researcher: Navas, Plácido

Group members

STAFF MEMBERS: Cascajo Almenara, María Victoria | Gavilán Naranjo, Angela | Sánchez Cuesta, Ana Mª.

ASSOCIATED MEMBERS: Arroyo Luque, Antonio | Asencio Salcedo, Claudio | Ballesteros Simarro, Manuel Angel | Brea Calvo, Gloria Teresa | García Testón Paez, Elena | Jiménez Hidalgo, María Auxiliadora | López Lluch, Guillermo | Moreno Fernández-Ayala, Daniel José | Rodríguez Aguilera, Juan Carlos | Rodríguez Hernández, María de los Angeles | Sánchez Alcazar, José Antonio | Santos Ocaña, Carlos | Vázquez Fonseca, Luis

Main lines of research

- Mitochondrial diseases due to coenzyme Q deficiencies.
- Mechanisms of regulation of coenzyme Q biosynthesis.
- Molecular structure of CoQ biosynthesis complex and its role in secondary deficiency.
- Other lines extramitochondrial:

  - Metabolism and aging

  - Epigenetic changes induced by both nutritional interventions and exercise.

Most relevant scientific articles

BREA-CALVO G, HAACK TB, KARALL D, OHTAKE A, INVERNIZZI F, CARROZZO R, ET AL. COQ4 mutations cause a broad spectrum of mitochondrial disorders associated with CoQ10 deficiency. Am J Hum Genet. 2015;96(2):309-17.

CASCAJO MV, ABDELMOHSEN K, NOH JH, FERNÁNDEZ-AYALA DJ, WILLERS IM, BREA G, ET AL. RNA-binding proteins regulate cell respiration and coenzyme Q biosynthesis by post-transcriptional regulation of COQ7. RNA Biol. 2015:0.

DESBATS MA, VETRO A, LIMONGELLI I, LUNARDI G, CASARIN A, DOIMO M, ET AL. Primary coenzyme Q10 deficiency presenting as fatal neonatal multiorgan failure. Eur J Hum Genet. 2015;23(9):1254-8.

YUBERO D, MONTERO R, O'CALLAGHAN M, PINEDA M, MEAVILLA S, DELGADILLO V, ET AL. Coenzyme Q and Pyridoxal Phosphate Deficiency Is a Common Feature in Mucopolysaccharidosis Type III. JIMD Rep. 2015.

YUBERO D, MONTERO R, RAMOS M, NEERGHEEN V, NAVAS P, ARTUCH R, ET AL. Determination of urinary coenzyme Q10 by HPLC with electrochemical detection: Reference values for a paediatric population. Biofactors. 2015;41(6):424-30.

Highlights

The research group starts 2015 with the proyect *Molecular mechanisms related to the secondary deficiency of coenzime Q associated to defects in oxidative phosphorylation*. This project has been granted by the Spanish Ministery of Economy and competitivity, Carlos III insdtitute. This is a three years project in which the group will study the molecular mechanisms associated to the diseases related with coenzyme Q deficiency.

On the other hand, the group continues during 2015 working on the project *Therapy of the Syndrome of Coenzyme Q10*, granted by the Andalusia Government into its excelence program. In this project the group is working in the study of different putative compouds able to be used in the therapy of human diseases associated with the coenzyme Q deficiency syndrome.

Our group is working in the central service of the university that offer the determination of coenzyme Q levels and the analysis of the deficiency of mitochondrial activities to hospitals from the sanitary network in Andalucía and rest of Spain.

The scientific production of the group has been fruitfull having published several works in collaboration with other groups of the CIBERER or alone. These works are based on the study of different mutations related with the deficiency of coenzyme Q. We deep into the metabolic changes producing some primary deficiencies que produce severe damages at the general level in the body.

IN 2015, the group has actively participated in the presentation of results related with the deficiency in coenzyme Q and the PI has organized the congress of the International Coenzyme Q10 association in Bolonia, Italia that contained section related with the deficiency of coenzyme Q and associated pathologies.

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Group U730

Programme: Inherited Metabolic Medicine
Lead Researcher: Nunes, Virginia

Group members

STAFF MEMBERS: González Simarro, Laura | López de Heredia Alonso, Miguel.
ASSOCIATED MEMBERS: Prat Pedrola, Esther | Vilches Caubet, Clara.

Main lines of research

- Bases moleculares de la reabsorción renal de aminoácidos.
- Implicación de los transportadores heteroméricos de aminoácidos (HAT) en enfermedades hereditarias humanas.
- Cistinuria: Búsqueda de genes moduladores de la litiaisis de cistina y posibles terapias.
- Caracterización del fenotipo muscular ratón knockout para el transportador LAT-2.
- Generación y caracterización del ratón doble knockout LAT-2/TAT1.
- Bases moleculares de la Leucoencefalopatía Megalencefálica con quistes subcorticales (MLC).
- Identificación del interactoma de MLC1.
- Puesta a punto de un estudio funcional para mutaciones en WFS1.

Most relevant scientific articles

ESPINO M, FONT-LLITJÓS M, VILCHES C, SALIDO E, PRAT E, LÓPEZ DE HEREDIA M, PALACÍN M, NUNES V. Digenic Inheritance in Cystinuria Mouse Model. PLoS One. 2015 Sep 11;10(9):e0137277. doi: 10.1371/journal.pone.0137277. eCollection 2015.(PMID:26359869)

MATSOUKAS MT, ARANGUREN-IBÁÑEZ Á, LOZANO T, NUNES V, LASARTE JJ, PARDO L, PÉREZ-RIBA M. Identification of small-molecule inhibitors of calcineurin-NFATc signaling that mimic the PxIxIT motif of calcineurin binding partners. Sci Signal. 2015 Jun 23;8(382):ra63. doi: 10.1126/scisignal.2005918. (PMID:26106221)

NAGAMORI S, WIRIYASERMKUL P, ESPINO-GUARCH M, OKUYAMA H, NAKAGOMI S, TADAGAKI K, NISHINAKA Y, BODOY S, TAKAFUJI K, OKUDA S, KUROKAWA J, OHGAKI R, NUNES V, PALACÍN M, KANAI Y. Novel cystine transporter in renal proximal tubule identified as a missing partner of cystinuria-related plasma membrane protein rBAT/SLC3A1. Proc Nat Acad Sciences 2016, www.pnas.org/cgi/doi/10.1073/pnas. 1519959113 (Trabajo acceptado el 11 de Diciembre de 2015, publicado el 7 de Enero 2016)

Highlights

During 2015, the group has continued working to understand the basis of the amino acids renal reabsorption in kidney by using the mouse knockout models for different heteromeric amino acid transporters. Together with Manuel Palacin´s group (U731), we have described: a) cystinuric digenia in mouse (Espino et al., 2015); b) a new cystine renal transporter, AGT1; responsible for the 10-15% cystine renal reabsorption (Nagamori yet al., 2016), that could be considered a putative new cystinuria gene; c) the cooperation between LAT2/4Fhc and TAT1 transporters in the neutral amino acids reabsorption, with the participation of Rafa Artuch´s team (U703). We have also studied the possible involvement of LAT2 transporter in different diseases as aged-related deafness (in collaboration with Isabel Varela´s group (U761)) and the occurrence of cataracts (in collaboration with Prof. Verrey in Zurich)

We have also worked in our FIS project aimed to demonstrate the roll of a compound as a cystine lithiasis modulator and we are analyzing the implication of AGT1 in cystinuria families.

We have been developing our intramural project together with Manuel Palacín (U731) and Antonia Ribes groups (U737); in which we have analyzed organic acids in knockout mice models with aminoacidurias, showing hiperexcretion of Krebs cycle intermediates in those models for basic amino acids basolateral transporters.

In collaboration with Raul Estevez's group (U751), we have been searching for other proteins involved in MLC by using transcriptomic analyses of Mlc1-/- mouse model cerebellum samples (project granted by ELA). We are also using this model to test the therapeutical possibilities of a compound for MLC (project partially granted by "La Sonrisa de Hugo" patients' association).

We have participated in a charity dinner organized by "La Sonrisa de Hugo" with an informative talk about our research on MLC.

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Group U731

Programme: Inherited Metabolic Medicine
Lead Researcher: Palacín, Manuel

Group members

STAFF MEMBERS: Bartoccioni, Paola Chiara | Fort Baixeras, Joana.

ASSOCIATED MEMBERS: Bodoy Salvans, Susana | Cano Crespo, Sara | Rosell Febres, Albert.

Main lines of research

- Mechanism of pathology in lysinuric protein intolerance.
- Molecular bases of renal re-absorption of amino acids.
- Pathology associated to Heteromeric Amino acid Transporters (HAT).
- Structure / Function of Heteromeric Amino acid Transporters (HAT).

Most relevant scientific articles

NAGAMORI S, WIRIYASERMKUL P, GUARCH ME, OKUYAMA H, NAKAGOMI S, TADAGAKI K, NISHINAKA Y, BODOY S, TAKAFUJI K, OKUDA S, KUROKAWA J, OHGAKI R, NUNES V, PALACÍN M, KANAI Y. Novel cystine transporter in renal proximal tubule identified as a missing partner of cystinuria-related plasma membrane protein rBAT/SLC3A1. Proc Natl Acad Sci U S A. 2016 Jan 19;113(3):775-80. doi: 10.1073/pnas.1519959113. Epub 2016 Jan 6.

ESPINO M, FONT-LLITJÓS M, VILCHES C, SALIDO E, PRAT E, LÓPEZ DE HEREDIA M, PALACÍN M, NUNES V. Digenic Inheritance in Cystinuria Mouse Model. PLoS One. 2015 Sep 11;10(9):e0137277. doi: 10.1371/journal.pone.0137277. eCollection 2015.

Highlights

Our activity has been focused in four research lines. At first instance, in collaboration with Rafael Artuch (U-703) we have progressed in phenotyping the first animal model of lysinuric Protein Intolerance (LPI). Tamoxifen-induced conditional knockout of y+LAT1 mimics the metabolic derangement of human LPI. In addition, this murine model shows immune abnormalities like altered iron metabolism in macrophages. We are trying at present to elucidate the involved molecular mechanism.

Secondly, in collaboration with Virginia Nunes (U-730) and Antonia Ribes (U-737) we have improved our knowledge on the molecular bases of renal re-absorption of amino acids. We had demonstrated digenic inheritance in rBAT- and b0,+AT-genetic ablation in mouse (Espino et al. 2015 PLoS One). We have also identified a second transporter (AGT1) that heterodimerizes with rBAT in kidney (Nagamori et al., 2016 PNAS). Because b0,+AT/rBAT and AGT1/rBAT transports cystine, this second transporter is a candidate gene to be mutated in non-explained cases of cystinuria. Moreover, murine models with double loss-of-function of LAT2 and TAT1, but not the single genetic ablation models, showed a dramatic hyperexcretion of neutral amino acids in urine suggesting functional cooperation of LAT2/4F2hc and TAT1 in renal reabsorption. We have also detected urine hyperexcretion of organic acids in mouse models with aminoacidurias. Specifically, genetic ablation of basolateral transporters of cationic amino acids results in hyperexcretion of Krebs cycle intermediates in urine.

In third place, we have identified, in collaboration with Virginia Nunes (U-730) and Isabel Varela (U-761), a HAT transporter involved in age related hearing loss. Genetic ablation of this transporter in mouse and functional mutations in human causes hearing loss.

Finally, we have identified a HAT transporter (vertebrate vLAT1/4F2hc) with high stability and promising properties to solve the structure of a HAT transporter at subnanometric resolution.

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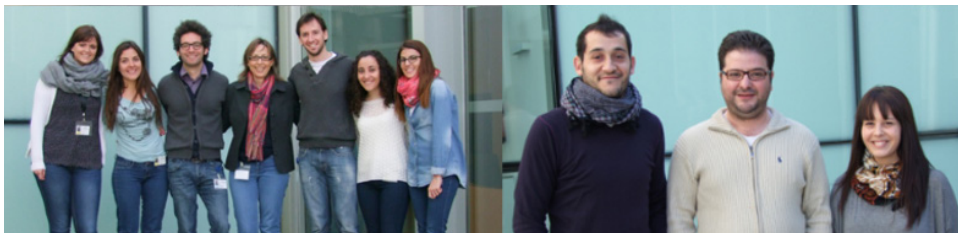
Group U732

Programme: Mitochondrial and Neuromuscular Medicine

Lead Researcher: Palau Martínez, Francesc

Group members



STAFF MEMBERS: López López, Dolores | Pilar González Cabo | Molla Moliner, Belén

AT THE EXPENSE OF THE PROJECT: Civera Tregon, Azahara | Domínguez Berzosa, Laura | Lupo Barretta, Vincenzo | Pérez Santamarina, Estela | Riveiro Arjomil, Fátima

AT THE EXPENSE OF MIGUEL SERVET: Espinós Armero, Carmen.

ASSOCIATED MEMBERS: Alarcón Hernandis, Benito | Barneo Muñoz, Manuela | Capilla Villanueva, Amalia | Galindo Orozco, Máximo Ibo.

Main lines of research

- Neurobiology and cellular pathophysiology of mitochondrial Charcot-Marie-Tooth neuropathy, Friedreich's ataxia and Duchenne muscular dystrophy.
- Genetics and genomics neurological and pediatric rare diseases.
- The clinical map of neurodevelopment: interaction between phenotype, genes and biological networks in neurological disorders of human development in children.

Most relevant scientific articles

PLA-MARTÍN D, CALPENA E, LUPO V, MÁRQUEZ C, RIVAS E, SIVERA R, SEVILLA T, PALAU F*, ESPINÓS C*. Junctophilin-1 is a modifier gene of GDAP1-related Charcot-Marie-Tooth disease. Hum Mol Genet 2015; 24: 213-229 (portada del número 1, vol 24)

BARNEO-MUÑOZ M, JUÁREZ P, CIVERA-TREGÓN A, YNDRIAGO L, PLA-MARTIN D, ZENKER J, CUEVAS-MARTÍN C, ESTELA A, SÁNCHEZ-ARAGÓ M, FORTEZA-VILA J, CUEZVA JM, CHRAST R, PALAU F. Lack of GDAP1 induces neuronal calcium and mitochondrial defects in a knockout mouse model of Charcot-Marie-Tooth neuropathy. PLoS Genet 2015; 11: e1005115.

OLIVARES M, NEEF A, CASTILLEJO G, PALMA GD, VAREA V, CAPILLA A, PALAU F, NOVA E, MARCOS A, POLANCO I, RIBES-KONINCKX C, ORTIGOSA L, IZQUIERDO L, SANZ Y. The HLA-DQ2 genotype selects for early intestinal microbiota composition in infants at high risk of developing coeliac disease. Gut 2015; 64:406-417

HOENICKA J, GARCÍA-RUIZ P, PONCE G, HERRANZ A, MARTÍNEZ-RUBIO D, PÉREZ-SANTAMARINA E, PALAU F. The addiction-related gene ANKK1 in parkinsonian patients with impulse control disorder. Neurotox Res 2015; 7:205-208

SEVILLA T, SIVERA R, MARTÍNEZ-RUBIO D, LUPO V, CHUMILLAS MJ, CALPENA E, DOPAZO J, VÍLCHEZ JJ, PALAU F, ESPINÓS C. The EGR2 gene is involved in axonal Charcot-Marie-Tooth disease. Eur J Neurol 2015, 22: 1548–1555

Highlights

CURRENT RESEARCH GRANTS

Translational Research, Experimental Medicine And Therapeutics on Charcot-Marie-Tooth Disease – Spanish CMT Consortium TREAT-CMT. IR11, funded by the Instituto de Salud Carlos III and the International Rare Diseases Research Consortium (IRDiRC), 2012 – 2015. PI: Francesc Palau (coordinator), Centro de Investigación Príncipe Felipe (CIPF), Valencia.

Dissecting mitocondrial pathophysiology Charcot-Marie-Tooth neuropathy. SAF2012-32425, funding by the Ministry of Economy and Competitiveness, R+D National Plan, 2013-2015. PI: Francesc Palau, Centro de Investigación Príncipe Felipe (CIPF), Valencia.

Genes, proteins and signalling pathways in rare diseasess (BioMeder). PROMETEOII/2014/029 (research groups of excellence), funded by the Generalitat Valenciana, 2014-15. PI: Francesc Palau, Centro de Investigación Príncipe Felipe (CIPF), Valencia.

The landscape between phenotype and genotype in neurological diseases development: validation of a clinical model of functional biology. Cooperative and Complementary Intramural Actions (ACCI), funded by the CIBER on Rare Diseases (CIBERER), 2015-2016. PI: Francesc Palau, Institut de Recerca Pediàtrica-HSJD/CIBERER, Barcelona.

The landscape of axonal biology and mitochondrial-associated membranes in neurogenetic diseases. SAF2015-66625-R, applied and funded the Ministry of Economy and Competitiveness, R+D National Plan, 2016-2019. IP1: Francesc Palau; IP2: Pilar González Cabo, Institut de Recerca Pediàtrica-HSJD, /CIBERER, Barcelona y Valencia.

SCIENTIFIC HALLMARKS

1. Demonstration that the GDAP1 deficiency produces axonal neuropathy and defects in the mitochondria-endoplasmic reticulum interaction and cellular calcium homeostasis in the knockout mouse model.

2. Demonstration that juntophilin-1 (JPH1) is a genetic modifier of the clinical expression of the Charcot-Marie-Tooth disease caused by mutations in GDAP1.

TEACHING

F. Palau, Adjunct Profesor of Human Genetics, Faculty of Medicine at Ciudad Real, University of Castilla-La Mancha, and Visiting Professor of Pediatrics, Faculty of Medicine, University of Barcelona.

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Group U733

Programme: Inherited Cancer, Haematological & Dermatological Diseases
Lead Researcher: Pallardó Calatayud, Federico

Group members

STAFF MEMBERS: García Giménez, José Luis.

ASSOCIATED MEMBERS: Markovic, Jelena | Romá Mateo, Carlos | Seco Cervera, Marta.

Main lines of research

- Physiopathology of oxidative stress in Fanconi anemia and Friedreich ataxia.
- Kindler's syndrome fibroblast oxidative profile.
- Cell cycle regulation in Down syndrome.
- Epigenetics in rare diseases.

Most relevant scientific articles

ROMÁ-MATEO C, AGUADO C, GARCÍA-GIMÉNEZ JL, KENCHT E, SANZ P, PALLARDO FV. Oxidative stress, a new hallmark in the pathophysiology of Lafora progressive myoclonus epilepsy. Free Radical Bio Med. 2015; 88: 33-41.

PAGANO G, D´ISCHIA M, PALLARDO F. Fanconi anemia (FA) and crosslinker sensitivity: re-appraising the origins of FA definition. Pediatr Blood Cancer. 2015; 62:1137-43.

GARCÍA-GIMÉNEZ JL (ed). Epigenetic biomarkers and diagnostics. Nueva York: Academic Press; 2015.

LÓPEZ DEL AMO V; SECO-CERVERA M, GARCÍA-GIMÉNEZ JL, WHITWORTH AJ, PALLARDÓ FV, GALINDO MI. Mitochondrial defects and neuromuscular degeneration caused by altered expression of Drosophila Gdap1: implications for the Charcot-Marie-Tooth neuropathy. Hum Mol Genet. 2015; 24(1):21-36.

GARCÍA-GIMÉNEZ JL, ROMÁ-MATEO C, SECO-CERVERA M, IBAÑEZ-CABELLOS S, PALLARDÓ FV. Circulating histones and nucleosomes as biomarkers in sepsis and septic shock. En. García-Giménez JL (ed). Epigenetic biomarkers and diagnostics. Nueva York: Academic Press; 2015: 498-519.

Highlights

Among the scientific activities of the research group emphasizes the European patent for the method and kit of diagnosis for idiopathic scoliosis by miRNAs (EP15382319.0). New funded research projects are the following: "Identifying circulating histones by mass spectrometry methods in plasma of patients with severe sepsis and septic shock" by INCLIVA, and "Analysis of microRNAs as biomarkers of drug monitoring for Lafora disease models", by the micro-cluster of ER (MCI-FER) of VLC / Campus and CIBERER´s spin-off (EpiDisease), together with the development of other projects initiated in 2013 and 2014, as the "HIST-BIRTH innovative project and rapid point-of-care histone test strips for early diagnosis of sepsis in pregnancy and childbirth " project.

Regarding teaching activities we highlight the inclusion of the optional teaching subject "Rare Diseases" (RD) in the curricula of the medical degree (course 2015-2016) taught at the University of Valencia, being the first course in this area that it´s taught at medical schools at national level, and it has been awarded with FEDER recognition to the best initiative to increase the quality of life of people with rare diseases. Additionally, our team participates as teaching staff at the Master of Rare Diseases organized at the UV and directed by Dr. Pallardó.

On 20th, May 2015 an oficial agreement for the establishment of the Alliance in translational research in Rare Diseases of the Valencian Community (DOCV 7654, 10/11/15) was signed between the Generalitat Valenciana, CIBERER, FEDER and other valencian entities to develope a common research strategy in Rare Diseases. Dr. Pallardó was appointed as president of the scientific committee of the Alliance. Currently, Alliance members are working on a coordinated strategy for a joint request of FEDER funds (European Union) for the acquisition of research infrastructure in RD, the development of training and dissemination of RD and development of informatics databases to be used by patients and health professionals.

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Group U734

Programme: Genetic Medicine

Lead Researcher: González Manchón, Consuelo

Group members

STAFF MEMBERS: Porras Franco, María de Gracia.

ASSOCIATED MEMBERS: Martín Requero, Ángeles | Sánchez Ayuso, Matilde.

Main lines of research

- Development and characterization of conditional knockout mice for Cd40lg with specific gen ablation at different steps of hematopoietic development, animal models of X-linked hyper IgM.
- Production of mice with conditional ablation of podocalyxin (Podxl) in vascular endothelial cells as a model for the study of human vasculitis.
- Molecular basis of hemorrhagic syndromes (Glanzmann thrombasthenia, Bernard-Soulier syndrome, FXIII deficiency, among others).
- Establishment of lymphoblastoid cell lines from patiens with Amyotrophic Lateral Sclerosis (ALS), Frontotemporal Dementia (associated with mutations in progranulin), and Alzheimer Disease for systemic study of the mechanisms controlling cell survival/death associated with neurodegeneration.

Most relevant scientific articles

ESTERAS N, ALQUÉZAR C, BARTOLOMÉ F, DE LA ENCARNACIÓN A, BERMEJO-PAREJA F, MOLINA JA, MARTÍN-REQUERO A. G1/S Cell cycle checkpoint dysfunction in lymphoblasts from sporadic Parkinson's disease patients. Mol Neurobiol. 2015; 52 (1): 386-98.

DE LA ENCARNACIÓN A, ALQUÉZAR C, MARTÍN-REQUERO Á. Increased Wnt signaling and reduced viability in a neuronal model of progranulin-deficient frontotemporal lobar degeneration. Mol Neurobiol. 2015 Dec 17. [Epub ahead of print] PMID: 26676574.

DE LA ENCARNACIÓN A, ALQUÉZAR C, ESTERAS N, MARTÍN-REQUERO A. Progranulin deficiency reduces CDK4/6/pRb activation and survival of human neuroblastoma SH-SY5Y cells. Mol Neurobiol. 2015; 52 (3): 1714-25.

ALQUÉZAR C, DE LA ENCARNACIÓN A, MORENO F, LÓPEZ DE MUNAIN A, MARTÍN-REQUERO A. Progranulin deficiency induces overactivation of WNT5A expression via TNF-α/NF-κB pathway in peripheral cells from frontotemporal dementia-linked granulin mutation carriers. J Psychiatry Neurosci. 2015; 41 (1): 150131.

ALQUÉZAR C, ESTERAS N, DE LA ENCARNACIÓN A, MORENO F, LÓPEZ DE MUNAIN A, MARTÍN-REQUERO A. Increasing progranulin levels and blockade of the ERK1/2 pathway: upstream and downstream strategies for the treatment of progranulin deficient frontotemporal dementia. Eur Neuropsychopharmacol. 2015; 25 (3): 386-403.

Highlights

RESULTS

• We have completed the phenotypic characterization of a mouse model with ablation of podocalicina (Podxl) in the vascular endothelium, which represents an excellent tool for studying diseases involving increased vascular permeability, including systemic vasculitis (ORPHA52759). We are investigating the possibility that Podxl is an essential component of the glycocalyx in maintaining the integrity of the endothelial barrier.

• We continued to study the mechanisms that cause cell death in Alzheimer's disease, frontotemporal dementia (FTLD-TDP), and other neurodegenerative disorders. The work focuses on cell cycle dysfunction, apoptosis, mitochondrial impairment, oxidative damage, and protein degradation using in vivo models of neurodegeneration and in vitro culture of cells, including peripheral cells from patients. In particular, we have evaluated the pathogenic influence of mutations on the GRN gene, leading to haploinsufficiency of the protein, in neurodegeneration associated to FTLD-TDP. Our work allowed us to unveil an important role of the Wnt5a/ERK1/2CDK6/pRb cascade in FTLD-TDP pathogenesis. In addition, we have used lymphoblatoid cell lines from FTLD or Parkinson (PD) patients as a platform to test the therapeutic potential of certain drugs impacting this signaling cascade and/or the cell cycle.

PATENTS

Patent Application Ref # ES 1641.1194

Title of the invention: A new family of indazol carbonyl derivatives with properties of cannabinoids and/or cholinergic and/or regulator of peptide beta-amyloid.

Inventors: JA Paez Prosper, NE Campillo Martin, C Perez Martin, PJ González Naranjo, M Perez Macias, M López de Ceballos, A Martin Requero, C Alquézar Burillo, MI Martin Fontelles, MR Garcia Moreno, EM Sánchez Robles, J Romero Paredes.

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Group U735

Programme: Paediatric and Developmental Medicine
Lead Researcher: Pérez Jurado, Luis

Group members

STAFF MEMBERS: Cusco Martí, Ivón | Serra Juhe, Clara.

ASSOCIATED MEMBERS: Borralleras Fumaña, Cristina | Campuzano Uceda, Victoria | Codina Solà, Marta | Del Campo Casanelles, Miguel | Flores Peirats, Raquel | Palacios Verdú, María Gabriela | Pérez García, Débora | Reina Castillón, Judith | Rodríguez Santiago, Benjamín.

Main lines of research

- Williams-Beuren syndrome. Molecular basis and pathogenic mechanisms.
- Williams-Beuren syndrome. Mouse model generation and analysis.
- Study of the genetic basis of autism spectrum disorders (ASD) and language specific impairment. Study of the microduplication 7q11.23 syndrome.
- Clinical and therapeutic research into medical genetics: Williams-Beuren syndrome, novel genomic syndromes, autism and intelectual disability.
- Human genome plasticity and disease susceptibility.
- Somatic mosaicism and chromosomal inversions. Mutational mechanisms and relationship with germline and somatic disease.
- Development and validation of high-throughput technology for diagnostic applications in medical genetics.

Institution: Universidad Pompeu Fabra · **Contact:** Facultad de Ciencias Experimentales y de la Salud
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Group U737

Programme: Inherited Metabolic Medicine
Lead Researcher: Ribes, Antonia

Group members

STAFF MEMBERS: Matalonga Borrel, Lesley | Texidó Viyuela, Laura | Tort Escalé, Frederic.

ASSOCIATED MEMBERS: Briones Godino, María Paz | Coll Rosell, María José | Ferrer Cortés, Xènia | Girós Blasco, María Luisa | Gort Mas, Laura | Macías Vidal, Judit | Pampols Ros, Teresa.

Main lines of research

- Lysosomal and peroxisomal diseases.
- Intermediary metabolism and mitochondrial energy metabolism diseases.
- Protein glycosilation defects.
- Search for new disease-causing genes.

Most relevant scientific articles

ORTIGOZA-ESCOBAR JD, MOLERO-LUIS M, ARIAS A, OYARZABAL A, DARÍN N, SERRANO M, GARCÍA-CAZORLA A, TONDO M, HERNÁNDEZ M, GARCÍA-VILLORIA J, CASADO M, GORT L, MAYR JA, RODRÍGUEZ-POMBO P, RIBES A, ARTUCH R, PÉREZ-DUEÑAS B. Free-thiamine is a potential biomarker of thiamine transporter-2 deficiency: a treatable cause of Leigh syndrome. Brain. 2016; 139:31-38. (D1 IF:9.19).

PAJARES S, ARIAS A, GARCÍA-VILLORIA J, MACÍAS-VIDAL J, ROS E, DE LAS HERAS J,GIRÓS M, COLL MJ, RIBES A. Cholestane-3β,5α,6β-triol: high levels in Niemann-Pick type C, cerebrotendinous xanthomatosis, and lysosomal acid lipase deficiency. J Lipid Res. 2015 ;56:1926-1935. (Q1; IF:4.42).

MATALONGA L, ARIAS Á, TORT F, FERRER-CORTÉS X, GARCÍA-VILLORIA J, COLL MJ, GORT L, RIBES A. Effect of Readthrough Treatment in Fibroblasts of Patients Affected by Lysosomal Diseases Caused by Premature Termination Codons. Neurotherapeutics. 2015 ;12: 874-886. (D1; IF:5.05).

ZAMPIERI S, FILOCAMO M, PIANTA A, LUALDI S, GORT L, COLL MJ, SINNOTT R,GEBERHIWOT T, BEMBI B, DARDIS A. SMPD1 Mutation Update: Database and Comprehensive Analysis of Published and Novel Variants. Hum Mutat. 2016; 37:139-147. (Q1; IF: 5.34).

FERRER-CORTÈS X, NARBONA J, BUJAN N, MATALONGA L, DEL TORO M, ARRANZ JA,RIUDOR E, GARCÍA-CAZORLA A, JOU C, O'CALLAGHAN M, PINEDA M, MONTERO R, ARIAS A, GARCÍA-VILLORIA J, ALSTON CL, TAYLOR RW, BRIONES P, RIBES A, TORT F. A leaky splicing mutation in NFU1 is associated with a particular biochemical phenotype. Consequences for the diagnosis. Mitochondrion. 2015; 26:72-80. (Q2, IF:3.3).

Highlights

We have identified two new genes associated to disease through exome sequencing. These genes are MRP63 associated to complex V of the mitocondrial respiratory chain and, TRAPPC11associated to a glycosilation defect . We are now finishing the expression studies.

Concerning the search for therapies, we have patented and licensed a compound capable of inducing lysosomal exocytosis (WO 2015 / 097088A19).

We have found a biomarker (cholestane-3ß, 5a, 6ß-triol) for Niemann-Pick type C, Cerebrotendinous xanthomatosis and lysosomal acid lipase deficiency.

We have continued to make progress in the knowledge of the metabolic pathway of lipoic acid and other cofactors of mitochondrial energy metabolism (see publications 2015).

We have participated in the development of two clinical guidelines (mitochondrial beta-oxidation deficiencies and glutaric aciduria type I) promoted by the Spanish Association of Inborn Errors of Metabolism.

We participate in two FIS projects and in a project of excellence INTERCIBER and two intramural projects CIBERER and two European DG-SANCO projects, one for the study of Niemann Pick disease type C, type A and type B and another for the study of homocistinurias. We also have an autonomous project (AGAUR).

At the level of collaboration with industry we have developed a project with Laboratorios Esteve SA, for the valuation of heparan sulfate in plasma, CSF and urine, as well as for the assessment of heparan sulfatase CSF and leukocytes. At the end of 2015 we obtained the 15,189 accreditation for these determinations. That would be of great help to evaluate the efficay of gene therapy for Sanfilippo A disease.

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Group U738

Programme: Genetic Medicine

Lead Researcher: Rodríguez de Córdoba, Santiago

Group members

STAFF MEMBERS: Pinto García, Sheila | Ruiz Sánchez, Ángela Olimpia.

ASSOCIATED MEMBERS: Durán Trío, Lara | García Fernández, Jesús María | Navarro Fernández-Balbuena, Carmen | Subías Hidalgo, Marta | Tortajada Alonso, Agustín.

Main lines of research

- Molecular diagnostics and characterization of pathogenic mechanisms in pathologies associated with deregulation of the complement system.
- Molecular basis for Lafora disease.
- Animal models of disease and development of therapeutic strategies.

Most relevant scientific articles

CAMPISTOL JM., ARIAS M., ARICETA G., BLASCO M., ESPINOSA L., ESPINOSA M., GRINYÓ JM., MACÍA M., MENDIZÁBAL S., PRAGA M., ROMÁN E., TORRA R., VALDÉS F., VILALTA R. AND RODRÍGUEZ DE CÓRDOBA S. An update for atypical haemolytic uraemic syndrome: diagnosis and treatment. A consensus document (Actualización en síndrome hemolítico urémico atípico: diagnóstico y tratamiento. Documento de consenso) Nefrología. 35:421-447 (2015).

RECALDE S., TORTAJADA A., SUBIAS M., ANTER J., BLASCO M., MARANTA R., COCO R., PINTO S., NORIS M., GARCÍA-LAYANA A. AND RODRÍGUEZ DE CÓRDOBA S. Molecular basis of Factor H R1210C association with ocular and renal diseases. J. Am. Soc. Nephrol. doi: 10.1681/ASN.2015050580 (2015).

JÓZSI M., TORTAJADA A., UZONYI B., GOICOECHEA DE JORGE E. AND RODRÍGUEZ DE CÓRDOBA S. Factor H-related proteins determine complement-activating surfaces. Trends Immunol 36:374-384 (2015).

MARTÍNEZ-BARRICARTE R., HEURICH M., LÓPEZ-PERROTE A., TORTAJADA A., PINTO S., LÓPEZ-TRASCASA M., SÁNCHEZ-CORRAL P., MORGAN BP., LLORCA O., HARRIS CL. AND RODRÍGUEZ DE CÓRDOBA S. The molecular and structural bases for the association of complement C3 mutations with atypical hemolytic uremic syndrome. Mol. Immunol. 66:263-273 (2015).

VALOTI E.*, ALBERTI M.*, TORTAJADA A.*, GARCÍA-FERNÁNDEZ JM., GASTOLDI S., BESSO L., BRESIN E., REMUZZI G., RODRÍGUEZ DE CÓRDOBA S. AND NORIS M. A novel atypical Hemolytic Uremic Syndrome – associated hybrid CFHR1/CFH gene encoding a fusion protein that antagonizes factor H-dependent complement regulation. J Am Soc Nephrol 26:209-219 (2015) (* Equally contributed as first Author).

Highlights

Our research and translational activity focus in the study of rare diseases associated with complement dysregulation like atypical Hemolytic Uremic Syndrome (aHUS), C3-glomerulopathy (C3G) or Paroxysmal Nocturnal hemoglobinuria (PNH). During 2015 we have contributed further to understand their pathogenic mechanisms through the functional characterization of pathogenic genetic variants and the development of animal. We have also contributed to educational programs generating reviews and consensus reports where we have emphasized our views regarding molecular diagnostics in this area, highlighted the important contribution that complement dysregulation plays in these diseases and how the improved knowledge of rare diseases have also important consequences in prevalent diseases like Age-related Macular Degeneration and IgA Nephropathy. During 2015 our laboratory lectured several educational talks or seminars to different clinical groups (national and international), where we emphasized the important advances in the complement field and the usefulness of this knowledge in the clinical practice. During 2015 we have continue developing diagnostics strategies, including new methods for the detection of CNVs and new NGS platforms for the screening of the complement genes.

Also, we began new research projects to evaluate biological markers associated with the progression of the disease and to develop complement inhibitors with therapeutic interest having as target the C5a molecule. Our group is an international reference in the physiopathology of the complement system and a very important asset for the Spanish's health public system. We develop a very strong translational activity in different medical specialties like nephrology, ophthalmology and hematology, providing to many patients (more than 120 during 2015) with a genetic and molecular analysis of the complement system and specific suggestions related to their treatments. Also of strategic interest is the registry of patients with renal pathology that we have developed with the supervision and support of CIBERER.

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Group U739

Programme: Inherited Metabolic Medicine

Lead Researcher: Rubio Zamora, Vicente

Group members

STAFF MEMBERS: Gougeard, Nadine | Marco Marín, Clara.

ASSOCIATED MEMBERS: Barcelona Andrés, Belén | Cervera Miralles, Francisco Javier | Fernández Murga, María Leonor | Llacer Guerri, José Luis | Marina Moreno, Alberto | Polo Ilacqua, Luis Mariano | Sancho Vaello, Enea.

Main lines of research

- Urea cycle related enzymopathologies.
- Structural biology of congenital hyperammonemias.
- Structural biology of rare diseases.

Most relevant scientific articles

DE CIMA S, POLO LM, DÍEZ-FERNÁNDEZ C, MARTÍNEZ AI, CERVERA J, FITA I, RUBIO V. Structure of human carbamoyl phosphate synthetase: deciphering the on/off switch of human ureagenesis. Sci Rep. 2015 Nov 23;5:16950. doi: 10.1038/srep16950.

PANZA E, ESCAMILLA-HONRUBIA JM, MARCO-MARÍN C, GOUGEARD N, DE MICHELE G, MORRA VB, LIGUORI R, SALVIATI L, DONATI MA, CUSANO R, PIPPUCCI T, RAVAZZOLO R, NÉMETH AH, SMITHSON S, DAVIES S, HURST JA, BORDO D, RUBIO V*, Seri M* (senior co-authors; equal leadership). ALDH18A1 gene mutations cause dominant spastic paraplegia SPG9: loss of function effect and plausibility of a dominant negative mechanism. Brain. 2016 Jan;139(Pt 1):e3. doi:10.1093/brain/awv247. Epub 2015 Aug 21.

Díez-Fernández C, Gallego J, Häberle J, Cervera J, Rubio V. The Study of Carbamoyl Phosphate Synthetase 1 Deficiency Sheds Light on the Mechanism for Switching On/Off the Urea Cycle. J Genet Genomics. 2015 May 20;42(5):249-60. doi: 10.1016/j.jgg.2015.03.009. Epub 2015 Apr 1. PubMed PMID: 26059772.

NGUYEN LE MINH P, DE CIMA S, BERVOETS I, MAES D, RUBIO V, CHARLIER D. Ligand binding specificity of RutR, a member of the TetR family of transcription regulators in Escherichia coli. FEBS Open Bio. 2015 Jan 28;5:76-84. doi: 10.1016/j.fob.2015.01.002. eCollection 2015. PubMed PMID: 25685666; PubMed Central PMCID: PMC4325133.

BEM AE, VELIKOVA N, PELLICER MT, BAARLEN PV, MARINA A, WELLS JM. Bacterial histidine kinases as novel antibacterial drug targets. ACS Chem Biol. 2015 Jan 16;10(1):213-24. doi: 10.1021/cb5007135.

Highlights

PROJECTS:

- MICIN BFU2011-30407, Plan Nacional I+D+I, "Luz estructural sobre señalizacion y regulacion por nitrogeno y sobre biosintesis de arginina/urea, sus errores congenitos, y su conexion con biologia del envejecimiento" (PI, Vicente Rubio), extended till 30/06/2015.

- PrometeoII2014/029 (Generalitat Valenciana) "Genes, Proteínas y Rutas de señalización en Enfermedades Raras" (V. Rubio), extended till 31/12/2015.

- MINECO BFU2014-58229-P, Plan Nacional I+D+I "Una mirada molecular al control de la detoxificación de amonio y a sus patologías y errores congénitos, y a la señalización por nitrógeno. En busca del papel de la proteína CutA" (01/01/2015-31/12/2017; PI V. Rubio), has been awarded.

- MECD, PRX 14/00433 "Bases moleculares de la señalización por dUTPasas: estructura tridimensional a resolución atómica de macrocomplejos señalizadores mediante crio-microscopía electrónica de alta resolución" (1/4/2015-30/09/2015; PI, A. Marina) was awarded.

- AORG/2015/112 (Generalitat Valenciana; PI: Vicente Rubio; 12.000 €), to organize the XXXVIII Congress of the Sociedad Española de Bioquímica y Biología Molecular (Valencia, 7-10/09/2015, presided by V. Rubio), including one Symposium on Rare Deseases (together with CIBERER), a group meeting on "Molecular Bases of Pathology", and a satelite meeting with patients on "Retinal distrophies: knowing them for curing them)" (together with FUNDALUCE).

CONTRACT: To improve biosynthesis of gaxilose for hipolactasia diagnosis. With Interquim S.A.: Improving biocatalysts to synthesize pharmaceutically intersting oligosacharides (1/11/2015-30/10/2016; PI A.Marina).

RESULTS: that stand out include the determination of the structure of human CPS1, whose inborn errors cause hyperammonemia, the characterization of the effects of patient's mutations mapping in the regulatory domain of CPS1, and the identification of mutations in the gene encoding P5CS that cause dominant spastic paraplegia and the propodsal of a plausible structure-based disease mechanism for negative dominance.

OTHER ACHIEVEMENTS: The XXXVIII SEBBM Congress took place under V. Rubio's presidency, with 800 delegates, 500 posters,13 plenary lectures, 150 oral comunications and 7 satelites.

Chapter on Hyperammonemia of the Saudubray book on Inherited Metabolic disorders was written by J Häberle & V. Rubio.

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Group U740

Programme: Inherited Metabolic Medicine

Lead Researcher: Salido, Eduardo

Group members

STAFF MEMBERS: Rodríguez Rodríguez, Bárbara.

ASSOCIATED MEMBERS: Arnau Díaz Llanos, María Rosa | Lorenzo Sellares, Víctor | Santana Rodríguez, Alfredo.

Main lines of research

- Inherited metabolic disease
- Inherited renal diseases.

Most relevant scientific articles

MARTIN-HIGUERAS C, LUIS-LIMA S, SALIDO E. Glycolate oxidase is a safe and efficient target for substrate reduction therapy in a mouse model of Primary Hyperoxaluria Type I. Mol Ther. 2015 Dec 22. PMID: 26689264.

LUIS-LIMA S, MARRERO-MIRANDA D, GONZÁLEZ-RINNE A, TORRES A, GONZÁLEZ-POSADA JM, RODRÍGUEZ A, SALIDO E, ALDEA-PERONA A, GASPARI F, CARRARA F, GÓMEZ-GERIQUE JA, NEGRÍN-MENA N, PÉREZ-TAMAJÓN L, GONZÁLEZ-RINNE F, JIMÉNEZ-HERNÁNDEZ H, JIMÉNEZ-SOSA A, PORRINI E. Estimated Glomerular Filtration Rate in Renal Transplantation: The Nephrologist in the Mist. Transplantation. 2015 Dec;99(12):2625-33. PMID: 26247554.

MESA-TORRES N, TOMIC N, ALBERT A, SALIDO E, PEY AL. Molecular recognition of PTS-1 cargo proteins by Pex5p: implications for protein mistargeting in primary hyperoxaluria. Biomolecules. 2015 Feb 13;5(1):121-41. PMID: 25689234

HERNÁNDEZ D, TRIÑANES J, SALIDO E, PITTI S, RUFINO M, GONZÁLEZ-POSADA JM, TORRES A. Artery Wall Assessment Helps Predict Kidney Transplant Outcome. PLoS One. 2015 Jun 12;10(6):e0129083. PMID: 26066045

ESPINO M, FONT-LLITJÓS M, VILCHES C, SALIDO E, PRAT E, LÓPEZ DE HEREDIA M, PALACÍN M, NUNES V. Digenic Inheritance in Cystinuria Mouse Model. PLoS One. 2015 Sep 11;10(9):e0137277. PMID: 26359869

Highlights

TWO EUROPEAN GRANT APPLICATIONS (H2020):

One as leader (Glycolate oxidase inhibitors for the treatment of Primary Hyperoxaluria) and another as partner (OxyGene: Gene therapy for the treatment of Primary Hyperoxaluria); one made it to the second round of evaluation, but none was funded.

ERARE PROJECT: ERAdicatPH (proposal-196): Understanding primary hyperoxaluria type 1 towards the development of innovative therapeutic strategies. Financed: 679124 euros; partner #2: 39930 euros. 2016-2018.

MOST RELEVANT RESEARCH RESULTS:

Preclinical studies (genetically modified mouse) on the safety and efficacy of a substrate reduction therapy approach to treat primary hyperoxalurias by inhibiting glycolate oxidase in one of two ways: siRNA and small molecules. Collaboration with Dicerna Pharmaceuticals to launch a clinical trial based on Glycolate Oxidase siRNA nanoparticles.

Institution: Fundación Canaria de Investigación Sanitaria (FUNCANIS)
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Group U741

Programme: Inherited Metabolic Medicine

Lead Researcher: Sánchez Jiménez, Francisca

Group members

STAFF MEMBERS: Montañez Martínez, Raul.

ASSOCIATED MEMBERS: Abrighach, Hicham | Falardo Paredes , Ignacio José | García Ranea, Juan Antonio | García Vilas García, Javier Alejandro | Medina Torres, Miguel Ángel | Rodríguez Quesada, Ana | Urdiales Ruiz, José Luis.

Main lines of research

- Development of bioinformatics tools for automated capture of biological information.
- From biogenic amine-related pathophysiological knowledge to applications on rare diseases.
- Search and characterization of angiogenesis modulators.

Most relevant scientific articles

RUIZ-PÉREZ MV, MEDINA MA, URDIALES JL, KEINÄNEN TA, SÁNCHEZ-JIMÉNEZ F. Polyamine metabolism is sensitive to glycolysis inhibition in human neuroblastoma cells. J Biol Chem. 2015;290:6106-19. doi: 10.1074/jbc.M114.619197. PMID: 2559331.

GARCÍA-VILAS JA, MEDINA MA, MELO FR, PEJLER G, GARCÍA-FAROLDI G. Damnacanthal inhibits IgE receptor-mediated activation of mast cells. Mol Immunol. 2015;65:86-93. doi: 10.1016/j.molimm.2015.01.008. PMID: 25656801.

GARCÍA-VILAS JA, QUESADA AR, MEDINA MA. Damnacanthal, a noni anthraquinone, inhibits c-Met and is a potent antitumor compound against Hep G2 human hepatocellular carcinoma cells. Sci Rep. 2015;5:8021. doi: 10.1038/srep08021. PMID: 25620570.

LEES JG, RANEA JA, ORENGO CA. Identifying and characterising key alternative splicing events in Drosophila development. BMC Genomics. 2015 Aug 16;16:608. doi: 10.1186/s12864-015-1674-2. PMID: 26275604.

LEES JG, HÉRICHÉ JK, MORILLA I, FERNÁNDEZ JM, ADLER P, KRALLINGER M, VILO J, VALENCIA A, ELLENBERG J, RANEA JA, ORENGO C. FUN-L: gene prioritization for RNAi screens. Bioinformatics. 2015 Jun 15;31(12):2052-3. doi: 10.1093/bioinformatics/btv073. PMID: 25667547.

Highlights

As members of the Inherited Metabolic Medicine area and the platform BIER we have revealed a metabolic relationship among the degree of NMYC amplification, aerobic glicolysis and polyamine biosynthesis in pediatric neuroblastoma (ORPHA635), which open new perspectives for combined therapies (PMID:2559331), in accordance with results from a USA clinical phase trial (i.e.: PMID:25415050). Our results on the roles of biogenic amines in the field of rare diseases deserved to be invited papers in international specialized meetings (ie: 44th annual meeting of EHRS and Gordon Conference on Polyamine 2015).

We continue working on the characterization of compounds acting as angiogenesis modulators, a subject relevant in many rare diseases (RD) (PMID22882737); for instance, mastocytosis (ORPHA98292) and other immune RD and hepatocellular carcinoma (ORPHA88673)(PMIDs:25656801; 25620570 y 26703630).

We have developed a method to enhance proteomic analysis of proteins expressed at low levels as well as their post-translational modifications (ie: phosphorilation) (PMID:26620529). This method will be very usefull to understand metabolic/signal transduction changes underlying many RD.

In the Biocomputational field, we have participated in development of Kpath (PMID:26055101), a database able to integrate metabolic information. It also enables not only the browsing but also a deep use of the integrated data to build metabolic networks. In addition, we continue our collaborations with several other CIBERER groups to apply our previous developed tools, as well as with other international groups to develop new biocomputational predictive tools to be applied on RD (PMIDs:26275604 y 25667547).

We also participated in several RD information divulgative events.

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Website: http://www.bmbq.uma.es/procel/index.html

Group U742

Programme: Genetic Medicine
Lead Researcher: Sanz, Pascual

Group members

STAFF MEMBERS: Heredia Pérez, Miguel | García Gimeno, Mª Adelaida
ASSOCIATED MEMBERS: Muñoz Ballester, Carmen | Rubio Villena, Carla | Sánchez Martín, Pablo.

Main lines of research

- Lafora disease molecular basis.
- Molecular mechanisms of laforin and maline actions.
- Implication of AMP-activated kinase (AMPK) in metabolic regulation.
- Implication of type PP1 phosphatase in metabolic regulation.
- Structure and function of glucokinase and its repercussion on metabolic regulation.

Most relevant scientific articles

RATHTHAGALA M, BREWER K.M., PARKER M.W., SHERWOOD A.R., WONG B.K., HSU S., BRIDGES T.M., PAASCH B.C, HELLMAN L.M, HUSODO S., MEEKINS D.A., TAYLOR A.O., TURNER B.D., AUGER K.D., DUKHANDE V.V., CHAKRAVARTHY S., SANZ P., WOODS V.V., LI S., VANDER KOOI C.W. AND GENTRY M.S. "Structural Mechanism of Laforin Function in Glycogen Dephosphorylation and Lafora Disease". Molecular Cell. 2015, 57: 261-272.

ROMÁ-MATEO, C., AGUADO, C., GARCÍA-GIMÉNEZ, J.L., IBAÑEZ-CABELLOS, S., SECO-CERVERA, M. PALLARDO, F.V., KNECHT, E., SANZ, P. "Increased oxidative stress and impairment of antioxidant systems in Lafora disease models". Mol. Neurobiol. 2015, 51: 932-946.

BERTHIER, A., PAYÁ, M., GARCÍA-CABRERO, A.M., BALLESTER, M.I., HEREDIA, M., SERRATOSA, J.M., SÁNCHEZ, M.P., SANZ, P. "Pharmacológical interventions to ameliorate neuropathológical symptoms in a mouse model of Lafora disease". Mol. Neurobiol, 2015, PMID: 25627694.

Romá-Mateo, C., Aguado, C., García-Giménez, J.L., Knecht, E., Sanz, P., Pallardó, F.V. "Oxidative stress, a new hallmark in the pathophysiology of Lafora progressive myoclonus epilepsy". Free Rad. Biol. Med. 2015, 88: 30-41.

SÁNCHEZ-MARTIN, P., ROMÁ-MATEO, C., VIANA, R. AND SANZ, P. "Ubiquitin conjugating enzyme E2-N and sequestosome 1 (p62) are components of the ubiquitination process mediated by the malin-laforin E3-ubiquitin ligase complex". Int. J. Biochem Cell Biol 2015, 69: 204-214.

Highlights

During 2015 we have contributed to the understanding of the pathophysiological basis of Lafora disease. First, we have collaborated in the description of the molecular structure of the protein phosphatase laforin. These results will allow the understanding of the pathological defects of the mutations in the corresponding gene found in Lafora disease patients and in the design of personalized medicine. We have also described that Lafora disease is characterized by the presence of conditions of oxidative stress that are produced by a mitochondrial dysfunction. Finally, we have described that the treatment of murine models of disease with 4-phenylbutirate (a chemical chaperone) and metformin (an activator of protein kinase AMPK) decreases the accumulation of Lafora bodies in the brain of treated animals, diminishes neurodegeneration and alleviates the neuropathological symptoms of the disease. These results open the possibility for establishing a clinical trial in human patients, since these compounds have good safety records and are currently being used in the treatment of other pathologies. These results appeared published in the outstanding news of the CIBERER web page in May and June 2015.

The group has been co-author of two patents in 2015 (PCT/ES2015/070677 y P201531786) on new activators of protein kinase AMPK and its use in the treatment of diabetes and related diseases. One of them was chosen to be presented in the FarmaIndustria meeting in November 2015 to check the interest of the Pharma companies that participated in the event.

Finally, the group has participated in the organization of information events on rare diseases, such as the VII Meeting "Investigar es Avanzar" (Rare diseases world day, Valencia 25th February) and the "Asociación Valenciana de Enfermedad de Huntington, AVAEH" (Valencia, 21st November 2015).

Institution: Agencia Estatal Consejo Superior de Investigaciones Científicas
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Group U743

Programme: Mitochondrial and Neuromuscular Medicine
Lead Researcher: Satrústegui Gil-Delgado, Jorgina

Group members

STAFF MEMBERS: Contreras Balsa, Laura
AT THE EXPENSE OF THE PROJECT: Martínez Valero, Paula.
ASSOCIATED MEMBERS: De Arco Martínez, Araceli.

Main lines of research

- Global Cerebral Hipomyelination. Pathogenic mechanisms of the disease caused by mutations in aralar/AGC1 studied with the use of AGC1 KO mice. Effects on myelination, formation of brain N-acetyl-aspartate, glial glutamate and glutamine synthesis. Possible implication of aralar/AGC1 inl diseases characterized by low levels of brain N-acetylaspartate.
- Charcot-Marie-Tooth disease. Alterations in calcium signaling mechanisms, particularly calcium signaling to mitochondria in forms of CMT caused by mutations in GDAP1 and MFN2.
- Mitochondrial pathology: 1. Possible implication of SCaMCs in mitochondrial diseases characterized by deletions in DNAmit deletions and ophthalmoplegia, 2) Possible implication of mutations in SCaMC-3 in human disease associated with deletions or depletion of liver, but not muscle, DNAmit.
- Regulation of calcium signaling to mitochondria and calcium handling by mitochondria. Role of the calcium uniporter and calcium regulated mitochondrial carriers Aralar/AGC1 and SCaMCs. Role of these carriers in deregulation of mitochondrial calcium. Involvement in human pathology.
- Tissue-specific mechanisms of oxidative phosphorylation regulation.
- Mitochondrial retrograde signaling to nuclei as a possible target in mitochondrial pathologies.

Most relevant scientific articles

RUEDA CB, TRABA J, AMIGO I, LLORENTE-FOLCH I, GONZÁLEZ-SÁNCHEZ P, PARDO B, ESTEBAN JA, DEL ARCO A, SATRÚSTEGUI J. Mitochondrial ATP-Mg/Pi carrier SCaMC-3/Slc25a23 counteracts PARP-1-dependent fall in mitochondrial ATP caused by excitotoxic insults in neurons. J Neurosci. 2015 35(8):3566-81.

LLORENTE-FOLCH I, RUEDA CB, PARDO B, SZABADKAI G, DUCHEN MR, SATRUSTEGUI J. The regulation of neuronal mitochondrial metabolism by calcium. J Physiol. 2015; 593(16):3447-62.

DU J, ROUNTREE A, CLEGHORN WM, CONTRERAS L, LINDSAY KJ, SADILEK M, GU H, DJUKOVIC D, RAFTERY D, SATRUSTEGUI J, KANOW M, CHAN L, TSANG SH, SWEET IR, HURLEY JB. Phototransduction influences metabolic flux and nucleotide metabolism in mouse retina. J Biol Chem. 2015 pii: jbc. M115.698985.

CASCÓN A, COMINO-MÉNDEZ I, CURRÁS-FREIXES M, DE CUBAS AA, CONTRERAS L, RICHTER S, PEITZSCH M, MANCIKOVA V, INGLADA-PÉREZ L, PÉREZ-BARRIOS A, CALATAYUD M, AZRIEL S, VILLAR-VICENTE R, ALLER J, SETIÉN F, MORAN S, GARCÍA JF, RÍO-MACHÍN A, LETÓN R, GÓMEZ-GRAÑA Á, APELLÁNIZ-RUIZ M, RONCADOR G, ESTELLER M, RODRÍGUEZ-ANTONA C, SATRÚSTEGUI J, EISENHOFER G, URIOSTE M, ROBLEDO M. Whole-exome sequencing identifies MDH2 as a new familial paraganglioma gene. J Natl Cancer Inst. 2015; 107(5). pii: djv053.

GARCÍA-BERMÚDEZ J, SÁNCHEZ-ARAGÓ M, SOLDEVILLA B, DEL ARCO A, NUEVO-TAPIOLES C, CUEZVA JM. PKA Phosphorylates the ATPase Inhibitory Factor 1 and Inactivates Its Capacity to Bind and Inhibit the Mitochondrial H(+)-ATP Synthase. Cell Rep. 2015; 12(12):2143-55.

Highlights

We have advanced in the knowledge of the role of Ca2+-dependent mitochondrial metabolite carriers and the calcium uniporter complex in mitochondrial Ca2+ signalling and regulation of respiration in neurons (Llorente-Folch et al., JPhysiol).

We have determined the consequences of the deficiency of the ATP-Mg/Pi transporter SCaMC-3/Slc25a23 in neurons, by both in vitro and in vivo models of glutamate excitotoxicity. The transport of adenine nucleotides in mitochondria through SCaMC-3 was found to be essential to counteract the drop in mitochondrial ATP levels caused by PARP1 activation, an early event in glutamate excitotoxicity (Rueda et al., JNeurosci).

In collaboration with JB. Hurley (Univ. Washington) we have continued studying the function of Aralar/AGC1 in the metabolism of the retina. It was found that light slows metabolic flow through glycolysis and the TCA cycle due to opposing effects mediated by Ca2+ on metabolic fate of α-KG, oxidation vs export, findings revealed using Aralar/AGC1 KO mice (Du et al., JBC).

We have collaborated with CIBERER U713 (JMCuezva) and U706 (AGascón) units in the functional analysis of mitochondrial proteins involved in tumor development and OXPHOS regulation. In the first case, the analysis of PKA-mediated phosphorylation of the ATP synthase inhibitor IF1 revealed a role of IF1 phosphorylation status in regulating aerobic glycolysis and OXPHOs. (García-Bermúdez et al., CellReports). In the second case, mutations in MDH2 have been identified as cause of familial paragangliomas, revealing the existence of a novel tumor susceptibility gene (Cascón et al., JNatlCancerInst.).

We have established a protocol to detect "PTP-prone" mitochondria in MEFS and fibroblasts as a way to detect the possible involvement of the PTP in Rare and common diseases. At present, treatments against myopathies involving the PTP are being developed and the protocols prepared may be used to evaluate these treatments in ER patients' fibroblasts (ACCI2014 Project in collaboration with CIBERER units U729 U723).

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Group U744

Programme: Genetic Medicine

Lead Researcher: Serratosa, José

Group members

STAFF MEMBERS: Guerrero López, Rosa.

ASSOCIATED MEMBERS: Álvarez Linera Prado, Juan | González Giráldez, Beatriz | Marinas Alejo, Ainhoa | Ortega Moreno, Laura | Sánchez Elexpuru, Gentzane | Sánchez García, Marina.

Main lines of research

- Clinical and molecular study of rare genetic epilepsias. Molecular basis of progressive myoclonus epilepsy of Lafora.

Most relevant scientific articles

GIRÁLDEZ BG, SERRATOSA JM. Jeavons syndrome as an occipital cortex initiated generalized epilepsy: Further evidence from a patient with a photic-induced occipital seizure. Seizure 2015;32:72-4.

BERTHIER A, PAYA P, GARCÍA-CABRERO AM, BALLESTER MI, HEREDIA M, SERRATOSA JM, SÁNCHEZ MP, SANZ P. Pharmacológicalinterventions to ameliorateneuropathológicalsymptoms in a mouse model of Lafora disease. Mol Neurobiol 2016;53:1296-309.

SYRBE S, HEDRICH UB, RIESCH E, DJÉMIÉ T, MÜLLER S, MØLLER RS, MAHER B, HERNÁNDEZ HERNÁNDEZ L, SYNOFZIK M, CAGLAYAN HS, ARSLAN M, SERRATOSA JM, NOTHNAGEL M, MAY P, KRAUSE R, LÖFFLER H, DETERT K, DORN T, VOGT H, KRÄMER G, SCHÖLS L, MULLIS PE, LINNANKIVI T, LEHESJOKI AE, STERBOVA K, CRAIU DC, HOFFMAN-ZACHARSKA D, KORFF CM, WEBER YG, STEINLIN M, GALLATI S, BERTSCHE A, BERNHARD MK, MERKENSCHLAGER A, KIESS W; EUROEPINOMICS RES, GONZÁLEZ M, ZÜCHNER S, PALOTIE A, SULS A, DE JONGHE P, HELBIG I, BISKUP S, WOLFF M, MALJEVIC S, SCHÜLE R, SISODIYA SM, WECKHUYSEN S, LERCHE H, LEMKE JR. De novo loss- or gain-of-function mutations in KCNA2 cause epileptic encephalopathy. Nat Genet 2015;47:393-9.

ORTEGA-MORENO L, GIRÁLDEZ BG, VERDÚ A, GARCÍA-CAMPOS O, SÁNCHEZ-MARTÍN G, SERRATOSA JM, GUERRERO-LÓPEZ R. Novel mutation in STXBP1 gene in a patient with non-lesional Ohtahara syndrome. Neurología 2015;24. pii: S0213-4853(14)00243-6.

GIRÁLDEZ BG, GUERRERO-LÓPEZ R, ORTEGA-MORENO L, VERDÚ A, CARRASCOSA-ROMERO MC, GARCÍA-CAMPOS Ó, GARCÍA-MUÑOZGUREN S, PARDAL-FERNÁNDEZ JM, SERRATOSA JM. Uniparental disomy as a cause of spinal muscular atrophy and progressive myoclonic epilepsy: phenotypic homogeneity due to the homozygous c.125C>T mutation in ASAH1. Neuromuscul Disord 2015;25:222-4.

Highlights

UNIT 744 aims to: a) The identification and characterization of genes involved in familial and sporadic genetic epilepsies (mainly epileptic encephalopathies of childhood), b) The generation of diagnostic and therapeutic tools that improve the quality of life of patients and families affected by these diseases, c) The understanding and treatment of Lafora disease by studying animal models in order to translate findings to clinical practice.

During 2015 we have initiated the study of full exomes in familial genetic epilepsies and in epileptic encephalopathies of childhood. In addition, we have described a new mutation in the STXBP1 gene responsible for an epileptic encephalopathy starting in the first months of life.

Unit 744 has continued leading of the Spanish Group of Genetics of Childhood Epilepsies GEGEI (www.gegei.es).

During this year we continued with pharmacological studies in animal models of Lafora disease in order to prepare a clinical trial in patients. We have also continued with a clinical trial studying the efficacy of Lacosamide in nocturnal seizures and developed devices to measure the frequency of nocturnal seizure in the patient's home.

At ian nternational level we have represented Spain in the "Collaborative Research Project (CRP) on Rare Epilepsy Syndromes" of EUROEPINOMICS (European Science Foundation) participating in the identification of new genes in different types of rare epilepsy syndromes. We have also participated in preparing and submitting the grant "Lafora Epilepsy - Basic Mechanisms to therapy" to the American NINDS (Program Project or PO1, under evaluation).

Unit 744 offers the possibility of clinical and genetic studies to patients with rare epilepsies.

Projects:

SAF2014-59594-R: Genetics of human epilepsies: identification of new genes, early diagnosis and clinical utility.

SAF2013-48960-P: Genetics of human epilepsies: towards early diagnosis and personalized therapy.

Institution: Fundación Instituto de Investigación Sanitaria Fundación Jiménez Díaz
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Group U745

Programme: Inherited Cancer, Haematological & Dermatological Diseases
Lead Researcher: Surrallés, Jordi

Group members

STAFF MEMBERS: Bogliolo, Massimo | Pujol Calvet, Mª Roser | Ramírez de Haro, María José.

ASSOCIATED MEMBERS: Cabré Fabré, Oriol | Hernández Viedma, Gonzalo | Marín Vilar, María | Mina, Leonardo | Minguillón Pedreño, Jordi | Montanuy Escribano, Helena | Umbert Mestres, Gloria.

Main lines of research

- Genetics and molecular biology of Fanconi Anemia. Genetic characterization of Fanconi patients and identification of new genes involved in the disease and into hereditary breast cancer syndrome and its functions.
- Development of new diagnostic and therapeutic tools on Fanconi anemia, including gene therapy, regenerative medicine and drug reporsuping.
- Mechanism of genomic instability and predisposition to cancer. Study of DNA lesions repair and biological and clinical consequences of repair mechanisms failure.
- Fanconi/BRCA pathway in cancer. Implication of Fanconi genes in cancer and use of them as a therapeutic target against cancer.

Most relevant scientific articles

TRUJILLO JP AND J SURRALLES (2015) Savior siblings and Fanconi anemia: analysis of success rates from the family's perspective. Genetics in Medicine. Nov;17(11):935-8.

SEGUÍ N, MINA LB, LÁZARO C, SANZ-PAMPLONA R, PONS T, NAVARRO M, BELLIDO F, LÓPEZ-DORIGA A, VALDÉS-MAS R, PINEDA M, GUINÓ E, VIDAL A, SOTO JL, CALDÉS T, DURÁN M, URIOSTE M, RUEDA D, BRUNET J, BALBÍN M, BLAY P, IGLESIAS S, GARRÉ P, LASTRA E, SÁNCHEZ-HERAS AB, VALENCIAA, MORENO V, PUJANA MÁ, VILLANUEVA A, BLANCO I, CAPELLÁ G, SURRALLÉS J, PUENTE XS, VALLE L.(2015) Germline Mutations in FAN1 Cause Hereditary Colorectal Cancer by Impairing DNA Repair, Gastroenterology. Sep;149(3):563-6.

CASTILLO P, M BOGLIOLO AND J SURRALLES.(2015) Activation of the Fanconi anemia/BRCA pathway at low doses of ionization radiation.Mutation Research - Genetic Toxicology and Environmental Mutagenesis.Nov;793:9-13.

PETERLONGO P, IRENE CATUCCI, MARA COLOMBO, LAURA CALECA, ELISEOS MUCAKI, MASSIMO BOGLIOLO et al. (2015) FANCM c.5791C>T nonsense mutation (rs144567652) induces exon skipping, affects DNA repair activity and is a familial breast cancer risk factor. Hum Mol Genet. Sep 15;24(18):5345-55.

BOGLIOLO M AND SURRALLES J (2015) Fanconi anemia: A model disease for studies on human genetics and advanced therapeutics. Current Opinion in Genetics & Development. Aug 6;33:32-40.

Highlights

During 2015 we published the involvement of the Fanconi / BRCA pathway in breast cancer and hereditary colon cancer. Specifically, we have investigated the involvement of mutations in FANCM and FAN1 from population studies and have made the appropriate functional studies of pathogenicity by lentivirus-mediated complementation. In parallel, we have published the follow-up of 38 cycles of preimplantational genetic diagnosis to select embryos to generate HLA compatible sibling donor to cure a patient with Fanconi anemia. We have also demonstrated that the FA pathway is activated at very low doses of ionizing radiation which could be related to the reported radiosensitivity of Fanconi patients. We have also investigated the role of telomere shortening in Cushing syndrome. Finally we have published an invited review article in Curr Opinion Genet and Dev on Fanconi anemia, focused on advanced genetic and therapeutic research in the last five years.

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Group U746

Programme: Inherited Metabolic Medicine

Lead Researcher: Pérez González, María Belén

Group members

STAFF MEMBERS: Ecay Crespo, María Jesús | Leal Pérez, Fátima | Navarrete López de Soria, Rosa.

ASSOCIATED MEMBERS: Alcaide Alonso, Patricia | Belanguer Quintana, Amaya | Castro Reguera, Margarita | Ferrer López, Isaac | Gallego Villar, Lorena | Gámez Abascal, Alejandra | Martínez-Pardo Casanova, Mercedes | Medrano Rodríguez, Celia | Merinero Cortés, Begoña | Oyarzaval Sanz, Alfonso | Pérez-Cerdá Silvestre, Celia | Richard Rodríguez, Eva María | Rodríguez Pombo, Pilar | Ruiz Desviat, Lourdes | Ruiz Sala, Pedro | Yuste Checa, Patricia.

Main lines of research

- Biochemical, genetic and proteomic analysis of glycosylation congenital disorders.
- Application of next generation sequencing and metabolomic techniques for identification of genetic basis of unsolved patients.
- Development of antisense and pharmacological chaperone therapies in neurometabolic disorders.
- Study of mitochondrial dysfunction and oxidative stress in meatabolic hereditary diseases. Antioxidant treatment.
- Molecular basis of cofactors involved in mitocondrial metabolism.

Most relevant scientific articles

ANA RIVERA-BARAHONA EQUAL CONTRIBUTOR, ROCÍO SÁNCHEZ-ALCUDIA EQUAL CONTRIBUTOR, HIU MAN VIECELLI, VERONIQUE RÜFENACHT, BELÉN PÉREZ, MAGDALENA UGARTE, JOHANNES HÄBERLE, BEAT THÖNY, LOURDES RUIZ DESVIAT. Functional Characterization of the spf/ash Splicing Variation in OTC Deficiency of Mice and Man. PLOS ONE(2015) 10(4).

YUSTE-CHECA P, GÁMEZ A, BRASIL S, DESVIAT LR, UGARTE M, PÉREZ-CERDÁ C, PÉREZ B. The Effects of PMM2-CDG-Causing Mutations on the Folding, Activity, and Stability of the PMM2 Protein. Human Mutation(2015) 36(9):851-860.

ILIANA MATOS, VÂNIA GONÇALVES, EUGÉNIA PINTO, FRANCISCO LARANJEIRA, MARIA JOÃO PRATA, PETER JORDAN, LOURDES R.DESVIAT, BELÉN PÉREZ, SANDRA ALVES. Functional analysis of splicing mutations in the IDS gene and the use of antisense oligonucleotides to exploit an alternative therapy for MPS II. Biochimica et Biophysica Acta(2015) 1852(12):2712-2721.

MERCEDES SERRANO, VÍCTOR DE DIEGO, JORDI MUCHART, DANIEL CUADRAS, ANA FELIPE, ALFONS MACAYA RAMÓN VELÁZQUEZ, M. PILAR POO1, CARMEN FONS, M. MAR O'CALLAGHAN, ANGELS GARCÍA-CAZORLA, CRISTINA BOIX, BERNABÉ ROBLES, FRANCISCO CARRATALÁ, MARISA GIRÓS, PAZ BRIONES, LAURA GORT, RAFAEL ARTUCH, CELIA PÉREZ-CERDÁ, JAAK JAEKEN, BELÉN PÉREZ, BELÉN PÉREZ-DUEÑAS. Phosphomannomutase deficiency (PMM2-CDG): ataxia and cerebellar assessment. Orphanet J Rare Dis. 2015 Oct 26;10:138.

YUSTE-CHECA P, MEDRANO C, GÁMEZ A, DESVIAT LR, MATTHIJS G, UGARTE M, PÉREZ-CERDÁ C, PÉREZ B. Antisense-Mediated Therapeutic Pseudoexon Skipping In TMEM165-CDG. Clin Genet. 2015 Jan;87(1):42-8.

Highlights

The Centre for Diagnosis and Research of inherited metabolic diseases is focused on two challenges in the context of Precision Medicine in rare diseases: improve the diagnosis of inherited metabolic disorders and development of new mutation-specific therapies. Regarding the biochemical diagnosis we have implemented the detection of new biomarkers in physiological fluids and a number of enzymatic activities in plasma and patient-derived fibroblasts. At the genetic level we have continued with the implementation of massive parallel sequencing as a tool for confirmation of metabolic disorders detected in newborn screening and for differential diagnosis of genetic heterogeneous diseases, such as peroxisomal disorders, glycogen storage disease, mitochondrial disorders or congenital defects of glycosylation. The group has also participated, at national and international level, in the development of guidelines and recommendations for improving neonatal screening program for homocistinurias and methylmalonic aciduria in the context of the "Newborn screening working group" belonging to the European project E-HOD: European Network and Registry for Homocystinurias and Methylation Disorders (Head leader Prof H Blom). The group has participated in the evaluation of effectiveness of screening for biotinidase and has participated making a clinical, biochemical and genetic diagnostic protocol for congenital disorders of glycosylation. Concerning the research on mutation specific therapies, we highlight the successful functional analysis by cell-based assays to study exonic and intronic splicing and missense mutations in several inherited metabolic disorders. Two new projects have been granted: "Understanding, prediction and validation of the phenotype of pathological mutations: transforming the basic results in diagnostic tools" (BIO2014-57314-REDT) and "Genomic and transcriptomic analysis to identify splicing defects and in vivo evaluation of antisense therapy" (Fundación Ramón Areces). We have also signed an agreement entitled "The genotypic spectrum of classic nonketotic hyperglycinemia" with the Children's Hospital Colorado, University of Colorado.

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Group U747

Programme: Endocrine Medicine
Lead Researcher: Webb, Susan

Group members

STAFF MEMBERS: Resmini, Eugenia.

ASSOCIATED MEMBERS: Aulinas Maso, Anna | Badia Llach, Xavier | Barahona Costanzo, María José | Crespo Martín, Iris | Martínez Momblan, María Antonia | Santos Vives, Alicia | Sucunza Alfonso, Nuria | Valassi, Elena

Main lines of research

- Morbidity and mortality, low grade inflammation and cardiovascular disease risk of patients suffering from acromegaly and Cushing's syndrome.
- Neuroradiological, neuropsychiatric and hormonal correlation in patients with endogenous hypercortisolism.
- Spanish Acromegaly Registry.
- Etiology of cardiopathy in acromegaly and its relation to body composition.
- ERCUSYN: European Registry on Cushing's Syndrome. Maintenance and exploitation of this database which contains data on over 1200 patients and is the largest one ever on patients with this diagnosis.
- Role of telomeres in endocrine diseases. In collaboracton with the group of J Surrallés U745.
- International consortium collaboration to identify genes and pathogenetic mechanisms involved in the development of craniopharyngiomas and pituitary adenomas.
- Study of bone microarchitecture and resistance and their determining factors in Cushing syndrome or acromegaly in remission. Model to investigate the interaction bone- body fat.

Most relevant scientific articles

SANTOS A, RESMINI E, GÓMEZ-ANSÓN B, CRESPO I, GRANELL E, VALASSI E, PIRES P, VIVES-GILABERT Y, MARTÍNEZ-MOMBLÁN MA, DE JUAN M, MATARÓ M, WEBB SM. Cardiovascular risk and white matter lesions after endocrine control of Cushing's syndrome. Eur J Endocrinol. 2015 Dec;173(6):765-75. doi: 10.1530/EJE-15-0600. PMID: 26497546

CRESPO I, SANTOS A, VALASSI E, PIRES P, WEBB SM, RESMINI E. Impaired decision making and delayed memory are related with anxiety and depressive symptoms in acromegaly. Endocrine. 2015 Dec;50(3):756-63. doi: 10.1007/s12020-015-0634-6. PMID: 26018738

AULINAS A, RAMÍREZ MJ, BARAHONA MJ, VALASSI E, RESMINI E, MATO E, SANTOS A, CRESPO I, BELL O, SURRALLÉS J, WEBB SM. Dyslipidemia and chronic inflammation markers are correlated with telomere length shortening in Cushing's syndrome. PLoS One. 2015 Mar 23;10(3):e0120185. doi: 10.1371/journal.pone.0120185. eCollection 2015. PMID: 25799396

ANDELA CD, VAN HAALEN FM, RAGNARSSON O, PAPAKOKKINOU E, JOHANNSSON G, SANTOS A, WEBB SM, BIERMASZ NR, VAN DER WEE NJ, PEREIRA AM. MECHANISMS IN ENDOCRINOLOGY: Cushing's syndrome causes irreversible effects on the human brain: a systematic review of structural and functional magnetic resonance imaging studies. Eur J Endocrinol. 2015 Jul;173(1):R1-14. doi: 10.1530/EJE-14-1101. PMID: 25650405

DÉNES J, SWORDS F, RATTENBERRY E, STALS K, OWENS M, CRANSTON T, ET AL. Heterogeneous genetic background of the association of pheochromocytoma/ paraganglioma and pituitary adenoma: results from a large patient cohort. J Clin Endocrinol Metab. 2015 Mar;100(3):E531-41. doi: 10.1210/jc.2014-3399. PMID: 25494863

Highlights

The U747 performs clinical research oriented to Rare Pituitary Diseases, with translation to the NHS, registries and collaborations with patient associations. In translation we have continued to collaborate with EPIRARE, Orphanet-Spain and the PI is the coordinator of the CIBERER program "Endocrine Medicine"; in 2015 with the 5 linked clinical groups, a translational research project has been funded by CIBERER as well as a Personalized Medicine ISCIII project. Since 1982, the PI is responsible of specialized clinics for Rare Pituitary Diseases, and is a recognized reference centre due to its professional excellence. We have obtained a new publically funded research project PI 14/000194, ISCIII: "Study of bone microarchitecture and resistance and their determining factors in Cushing syndrome or acromegaly in remission. Model to investigate the interaction bone- body fat".

We have continued to collaborate in patients meetings collaborating with the associations of acromegaly and Addison's disease patients.

In transference to the productive market, we have been involved in clinical trials (in phase 2, 3 and 4), epidemiological Studies, R&D&I and several advisory boards on Rare Pituitary Diseases, and have thus funded the salary of a research nurse.

The copyright fees of the PI and the ascribed researcher X Badia of the specific quality of life questionnaires for acromegaly, Cushing's sd (and recently also for primary hyperparathyroidism), are also fed back into the Group to hire a predoctoral research fellow.

The Agencia de Gestió d'Ajuts Universitaris i de Recerca (AGAUR) has recognized the Group (355) in the call for Support for Research Groups, and classified it as the 4th (the first clinical group) of the 60 groups of the IIB-S Pau, demonstrating its internal and external value.

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Group U749

Programme: Inherited Cancer, Haematological & Dermatological Diseases
Lead Researcher: Fernández Piqueras, José

Group members

STAFF MEMBERS: Cobos Fernández, María de los Ángeles | González Sánchez, Laura.
ASSOCIATED MEMBERS: Santos Hernández, Javier | Villa Morales, María.

Main lines of research

An integrated genomic and epigenomic view of intratumor heterogeneity during the evolution of precursor T-cell lymphoblastic neoplasms in the context of a precision and individualized medicine

Precursor T-cell lymphoblastic neoplasms are aggressive haematological malignancies, which mainly develop in children but can also affect adults. Most often they manifest with extensive marrow and blood affectation (acute T-cell lymphoblastic leukaemia, T-ALL), and less commonly as a mass lesion in the thymus/anterior mediastinum or in lymph nodes, with less than 25% marrow blasts (T-cell lymphoblastic lymphoma, T-LBL). As any type of cancer, T-cell lymphoblastic neoplasms consist of a very heterogeneous group of diseases characterized by the joint occurrence of genetic and epigenetic alterations, which evolve from the time of diagnosis in the context of intratumoral heterogeneity as an unavoidable consequence of genetic instability, and may be deeply modified in relapses. In view of this background, our first aim is to assess for intratumoral heterogeneity in selected series of human T-cell lymphoblastic neoplasms using next generation sequencing (tailored genomic and transcriptomic analyses) and epigenomic approaches in paired samples at diagnosis and relapse. Since preliminary results evidenced overexpression of several deaminases of the ADAR and APOBEC families, we are comparing genomic and transcriptomic sequences to assess for DNA and/or RNA editing. Another goal is to explain aberrant expression of critical genes. Epigenetic changes at critical regulatory regions and deregulation of specific microRNAs may be instrumental in resolving this complex puzzle. Finally, we are performing in vitro and in vivo (with xenotransplanted mice) preclinical assays in order to reappraise clinical therapeutic strategies.

KEY WORDS: Precursor T-cell lymphoblastic neoplasms (T-ALL/TLBL). Individualized precision medicine. Next-generation sequencing. Intratumoral heterogeneity. RNA editing. MicroRNAs. Cancer exosomes. Epigenomic analyses. Signaling pathways. Critical mutations. Aberrant expression.

Most relevant scientific articles

PEREZ-GOMEZ E, ANDRADAS C, BLASCO-BENITO S, CAFFAREL MM, GARCÍA-TABOADA E, VILLA-MORALES M, ET AL. Role of cannabinoid receptor CB2 in HER2 pro-oncogenic signaling in breast cancer. J Natl Cancer Inst. 2015;107(6):djv077.

RONCERO AM, LÓPEZ-NIEVA P, COBOS-FERNÁNDEZ MA, VILLA-MORALES M, GONZÁLEZ-SÁNCHEZ L, LÓPEZ-LORENZO JL, ET AL. Contribution of JAK2 mutations to T-cell lymphoblastic lymphoma development. Leukemia. 2016;30(1):94-103.

Highlights

Our work has made possible the publication of two articles in high impact journals. The most significant outcomes were: (1) the demonstration of the functional consequences of multiple mutations at the JAK2 gene involved in the development of T-cell lymphoblastic lymphomas, which are able to activate the canonical via (activation of JAK/STAT signalling pathway) and another non-canonical-epigenetic via that operates through the induction of the LMO2 oncogene. These results call for the use of JAK-pan-inhibitors in conventional protocols for the treatment of these diseases (Leukemia; IF. 10,431); and (2) our collaboration to demonstrate that a cannabinoid receptor plays an important role in the development of breast cancer (J Natl Cancer Inst; IF: 15,161).

As to investigation projects, it has to be emphasized our involvement in an European project (OPERRA-604984), the direction of an ACCI-CIBERER-16 (which bring together tree different groups of the CIBERER), our participation in another ACCI project directed by Dr. Rosario Perona, and our continued engagement in the development of a SAF-2012 project and a Grant-Agreement covered by the IIS-FJD.

It should be also noted that we have presented two doctoral theses, we have organized an advanced training course for science teachers from the Community of Madrid, we have lectured at multiple Specialisation Courses and Masters organized by different institutions (UAM, UCM, UAH, CNIO, Escuela de Salud-ISCIII etc., including a Course about the Management in Biomedical Research by the Hospital La Paz). Additionally, we have participated in various training courses and meetings organized by the CIBERER and other institutions belonging to the ISCIII, including a joint meeting with the CIBERER, CIBERBBN, the Cluster4eyE, patients associations and OftaRed. Finally, we would like to comment on our work in the Experts Committee on Human Genetics (Community of Madrid), and the Chairmanship of the Scientific Advisory Board of the FARPE/FUNDALUCE Foundation.

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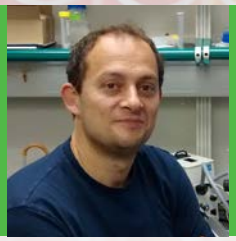
Group U750

Programme: Inherited Metabolic Medicine

Lead Researcher: Estévez Povedano, Raúl



Group members

STAFF MEMBERS: Gaitán Peñas, Héctor

ASSOCIATED MEMBERS: Arnedo Llena, Tanit / Barrallo Gimeno, Alejandro / Elorza Vidal, Xavier / López Hernández, Tania

Main lines of research

- Neurogenetics.
- Myelin.
- Neurodegeneration.
- Ion channels.
- Glial regulation.
- Myotonia.
- Bartter syndrome.

Most relevant scientific articles

PÉREZ-RIUS C, GAITÁN-PEÑAS H, ESTÉVEZ R, BARRALLO-GIMENO A. Identification and characterization of the zebrafish ClC-2 chloride channel orthologs. Pflugers Arch. 2015 Aug;467(8):1769-81. doi: 10.1007/s00424-014-1614-z. Epub 2014 Sep 20. PubMed PMID: 25236920.

BARRALLO-GIMENO A, GRADOGNA A, ZANARDI I, PUSCH M, ESTÉVEZ R. Regulatory-auxiliary subunits of CLC chloride channel-transport proteins. J Physiol. 2015 Sep 15;593(18):4111-27. doi: 10.1113/JP270057. PubMed PMID:25762128; PubMed Central PMCID: PMC4594287.

CAPDEVILA-NORTES X, JEWORUTZKI E, ELORZA-VIDAL X, BARRALLO-GIMENO A, PUSCH M, ESTÉVEZ R. Structural determinants of interaction, trafficking and function in the ClC-2/MLC1 subunit GlialCAM involved in leukodystrophy. J Physiol. 2015 Sep15;593(18):4165-80. doi: 10.1113/JP270467. Epub 2015 Jun 23. PubMed PMID:26033718; PubMed Central PMCID: PMC4594291.

VINDAS-SMITH R, FIORE M, VÁSQUEZ M, CUENCA P, DEL VALLE G, LAGOSTENA L,GAITÁN-PEÑAS H, ESTEVEZ R, PUSCH M, MORALES F. Identification and Functional Characterization of CLCN1 Mutations Found in Nondystrophic Myotonia Patients. HumMutat. 2016 Jan;37(1):74-83. doi: 10.1002/humu.22916. Epub 2015 Oct 28. PubMed PMID: 26510092.

Highlights

During this year (2015) we have obtained funding from the present projects:

- E-Rare european project: CLC chloride channels & megalencephalic leukoencephalopathy.
- ELA Research Foundation: MLC disease: identification of proteins which could modulate the disease phenotype.
- AFM: Development and characterization of zebrafish models of myotonia congenita.
- ICREA Academia prize for Raúl Estévez.
- Grupo consolidado de la Generalitat (SGR).
- Project SAF 2012-31486 del MICINN.
- Donation from a spanish famioly affected by megalencephalic leukoencephalopathy.
- Research contract with the company Medday to test a compound in a mice model of Megalencephalic leukoencephalopathy.

During this year, in the context of MLC disease we have gained new insights about the structure-function relationship of the GlialCAM molecular and the modulation of the functional properties of the chloride channel ClC-2. This work resulted in a publication in Journal of Physiology, where we also contributed ClC-2 chloride channels in zebrafish, which allowed us to choose what was the better isoform to perform a knockout model in the fish. In this year, we have obtained new information about the molecular basis of mutations in the genes ClC.1 and ClC-2. The mutations in ClC-1 have been published in Human Mutation and we are rewriting an article about mutations in ClC-2 for Human Mutation. Finally, in this year 2015, we have been working with the volume-regulated chloride channels LRRC8, and we submitted an article to Nature Communications at the end of January 2016.

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Group U752

Programme: Inherited Metabolic Medicine
Lead Researcher: Giraldo Castellano, Pilar

Group members

STAFF MEMBERS: Alfonso Palacín, María Pilar.

AT THE EXPENSE OF THE PROJECT: Irún Irún, María Pilar.

ASSOCIATED MEMBERS: Andrade Campos, Marcio | Capablo Liesa, José Luis | Latre Martínez, Paz | Pocoví Mieras, Miguel | Roca Espiau, Mercedes | Sáenz de Cabezón Álvarez, Alicia.

Main lines of research

- Gaucher disease epidemiology, in Spain: National Registry acredited by ISO 9001 (Num EC2751/07).
- Genetic analysis and search of genes related to clinical heterogeneity. Directed mutagenesis. DNA, serum, plasma and leukocyte patient samples biobank.
- Study of biomarkers and inflammatory cytokines and its relationship with response to treatment.
- Study of bone disease by imaging techniques and its relationship with plasma biomarkers.
- Neurological disease evaluation by clinical, neurophysiological and imaging methods.
- Clinical research of new drugs on clinical trials (OGT-011, TKT034, TKT039, Protalix). Independent clinical trial.
- Epidemiology of hematological neoplasias. Gene expression marker study and search of polymorphisms accounting for familial aggregations.
- Approach to study of internalization of nanoparticles containing small drug molecules on monocytes and macrophages and application to treat deposit diseases.
- Analysis of the effect of pharmacological chaperones on protein mutants in Gaucher Disease.
- Plasma miRNAs profile in Haematological malignancies and predictor use to developed acute leukaemia.

Most relevant scientific articles

FERRAZ MJ, MARQUES AR, GASPAR P, MIRZAIAN M, VAN ROOMEN C, OTTENHOFF R, ET AL Lyso-glycosphingolipid abnormalities in different murine models of lysosomal storage disorders. Mol Genet Metab. 2015 Dec 23.

GERVAS-ARRUGA J, CEBOLLA JJ, IRUN P, PEREZ-LÓPEZ J, PLAZA L, ROCHE JC, ET AL. Increased glycolipid storage produced by the inheritance of a complex intronic haplotype in the α-galactosidase A (GLA) gene. BMC Genet. 2015 Sep 3;16:109.

GERVAS-ARRUGA J, CEBOLLA JJ, DE BLAS I, ROCA M, POCOVI M, GIRALDO P. The influence of genetic variability and proinflammatory status on the development of bone disease in patients with Gaucher disease. PLoS One. 2015 May 15;10(5).

ANDRADE-CAMPOS MM, MONTES-LIMÓN AE, SORO-ALCUBIERRE G, LIEVANO P, LÓPEZ-GÓMEZ L, BARINGO T ET AL. Patients Older Than 65 Years With Non-Hodgkin Lymphoma Are Suitable for Treatment With (90)Yttrium-Ibritumumab Tiuxetan: A Single-Institution Experience. Clin Lymphoma Myeloma Leuk. 2015 Aug;15(8):464-71.

LEDESMA M, HURTADO-ROCA Y, LEON M, GIRALDO P, POCOVI M, CIVEIRA F, ET AL. Association of Ferritin Elevation and Metabolic Syndrome in Males. Results from the Aragon Workers' Health Study(AWHS). J Clin Endocrinol Metab. 2015 May;100(5):2081-9.

Highlights

Appointment of the IP Group Pilar Giraldo Castellano as Program Director of the PhD in Health Sciences from the University of San Jorge Zaragoza (25 May 2015).

Two members of the group, the Rio Hortega predoctoral researcher Marcio Andrade Campos and the predoctoral researcher Jorge Cebolla Sanz. presented two oral talks at the 2015 Lysosomal Disease Network (LDN) WORLD 11th Annual Symposium held in Orlando (USA) 11 - 14 February 2015.

The CIBERER contracted researcher Pilar Irun Irun and the predoctoral researcher Jorge Cebolla Sanz have succeeded in establishing the enzymatic determination in dried blood spot for the screening of lysosomal acid lipase deficiency and the biomarker chitotriosidase, also has joined the determine of enzymatic activity lysosomal acid lipase (LAL) in leukocytes and gene sequencing LIPA allowing make a prospective study in patients with clinical suspicion of LAL deficit, the results will be presented at the next SEGHNP congress in 2016.

The predoctoral researcher Marcio Andrade Campos has achieved at the Annual Meeting of the American Society of Hematology 2015, an "ASH Abstract Achievement Award" for the work presented in this prestigious Congress with "miR-140-3p and miR-99B-5p can Improve the study risk assessment in Patients with MDS Independently of the normal karyotype and IPSS-R category " as part of the work carried out to obtain the degree of doctor.

The group has contributed to the edition of "Manual for the Control and Management of Patients with Chronic Myelogenous Leukemia", available at the website of the AEHH (http://www.sehh.es/es/documentos/manuales.html) Guide.

The group has obtained the FIS PI15 / 00616 with the project: Evaluation of the role of channels in inflammatory KCa3.1 complex induced Gaucher cells and development of bone complications in EG. Possibility of therapeutic actions.

The group has get to host in Zaragoza of next International Congress of European Working Group on Gaucher Disease 12th EWGGD 2016, attended by over 300 world experts on Gaucher Disease and European patient, to be held on June 29- July 2, 2016. http://www.ewggd2016zaragoza.com

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Group U753

Programme: Paediatric and Developmental Medicine
Lead Researcher: Lapunzina Badía, Pablo Daniel

Group members

STAFF MEMBERS: Benito Sanz, Sara | Martínez González, Víctor Manuel.

ASSOCIATED MEMBERS: Aza Carmona, Miriam | Barroso Ramos, Eva | Belinchón Martínez, Alberta | Campos Barros, Angel | De Torres Pérez Hidalgo, Mª Luisa | Del Pozo Maté, Ángela | Ezquieta Zubicaray, Begoña | Fernández García Moya, Luis | García Miñaur Rica, Sixto | García Santiago, Fe Amalia | Heath, Karen Elise | Mansilla Aparicio, Elena | Martínez Fernández, Pilar | Martínez Montero, Paloma | Molano Mateos, Jesús | Mori Álvarez, Mª de los Ángeles | Nevado Blanco, Julián | Palomares Bralo, María | Rodríguez Laguna, Lara | Santos Simarro, Fernando | Solera García, Jesús | Torres Jiménez, Rosa | Vallespín García, Elena.

Main lines of research

- Subtelomeric rearrangements in patients with idiopathic mental retardation.
- Genetic and functional analysis of genes SHOX and SHOX2 in human growth.
- Genetic and functional analysis of skeletal dysplasias. Multidisciplinary Skeletal Dysplasia Unit (UMDE).
- Overgrowth syndromes. Epidemiology. Clinical presentations and molecular analysis.
- Genetic aspects of harmonious growth.
- Determinants and genetic modifiers of monogenic diabetes.
- Genetic analysis of the ghrelin axis in childhood obesity.
- Congenital alterations of purine metabolism.
- Study of the physiopathology of neurological manifestations in HPRT deficiency. Implication of purines as neuromodulators.
- Design and optimization of a SNPs microarray for the evaluation of the therapeutic response and toxicity of a series of HIV patients.
- Rearrangements and complex genetic anomalies detected by a CGH array in patients with birth defects, mental retardation or tumours.
- Molecular genetics of hypertrophic myocardiopathy.
- Functional characterization of CLCN1 mutations causing congenital myotonia.

- Molecular characterization of the 22q11.2 region by MLPA techniques and its correlation with microsatellite genotyping and FISH.
- Pharmacogenetics and pharmacogenomics.
- Autosomal recessive osteogenesis imperfecta.
- Genomic diagnostic tools. Oligo-based microarrays, BCAs and SNPs.
- Genomic, epigenetic and transcriptional study of tumours in polymalformative genetic syndromes. Macrocephaly-Capillary Malformation.
- Next Generation Sequencing as a new diagnostic tool in genetic disorders.
- Dravet Syndrome.

Most relevant scientific articles

LUPIÁÑEZ DG, KRAFT K, HEINRICH V, KRAWITZ P, BRANCATI F, KLOPOCKI E ET AL. Disruptions of topológical chromatin domains cause pathogenic rewiring of gene-enhancer interations. Cell. 2015;161(5):1012-25.

GORDO-GILART R, ANDUEZA S, HIERRO L, MARTÍNEZ-FERNÁNDEZ P, D´AGOSTINO D, JARA P, ALVAREZ L. Functional analysis of ABCB4 mutations relates clinical outcomes of progressive familial intrahepatic cholestasis type 3 to the degree of MDR3 floppase activity. Gut. 2015;64(1):147-55.

CAPARRÓS-MARTÍN JA, DE LUCA A, CARTAULT F, AGLAN M, TEMTAMY S, OTAIFY GA ET AL. Specific variants in WDR35 cause a distinctive form of Ellis-van Creveld syndrome by disrupting the recruitment of the EvC complex and SMO into the cilium. Hum Mol Genet. 2015;24(14):4126-37.

HISADO-OLIVA A, GARRE-VÁZQUEZ AI, SANTAOLALLA-CABALLERO F, BELINCHÓN A, BARREDA-BONIS AC, VASQUES GA ET AL. Heterozygous NPR2mutations cause disproportionate short stature, similar to Léri-Weill Dyschondrosteosis. J Clin Endocrinol Metab. 2015;100(8):E1133-42.

VERDIN H, FERNÁNDEZ MIÑÁN A, BENITO-SANZ S, JANSSENS S, CALLEWAERT B, WAELE KD ET AL. Profiling of conserved non-coding elements upstream of SHOX and functional characterisation of the SHOX cis-regulatory landscape. Sci Rep. 2015;5:17667.

Highlights

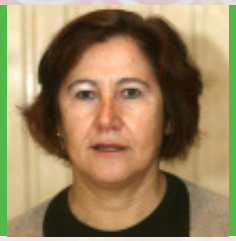
During 2015 we have contributed with 38 publications, with an average impact factor of 4.1. Among them we can highlight articles in journals such as Cell, Gut, J Clin End Metabol, Hum Mol Genet, etc. As achieved technological milestones, we have developed genomic technologies such as arrays and NGS platforms at the clinical setting, being a pioneer initiative in Spanish hospitals. We have also supported the first section of bionformatics located in a public hospital in Madrid, with three bioinformaticians. During this period 14 competitive research projects were active, especially from public agencies (Ministries/FIS) and some European and American (2 of them managed by the CIBERER). We have initiated new interdisciplinary consultations and increased our genetic service portfolio. We increased our participation in cooperative activities. The contribution of the 2 hired CIBERER (one in aspects of clinical and translational research and the other in aspects of basic research and mechanisms and biology of rare diseases) is excellent. A large number of joint activities within the PdI such as organizing confer-ences, national and international workshops, the CIBERER-DNA-DAY, and organization of conferences and meetings with patients associations were per-formed. The position and contribution of the group within the CIBERER is excellent. Our principal value are multidisciplinary and hospital integration and gender balance (clinical basic, clinical, molecular re-search and the biological basis of disease, and in the last two years, especially bioinformatics, genomics and systems biology). The INGEMM consists of 19 sections and has a large number of patients and samples from patients with rare genetic diseases.

Institution: Servicio Madrileño de Salud
Contact: Hospital La Paz. Paseo de la Castellana, 261. 28046 Madrid · Tel.: 91 727 72 17

Group U754

Programme: Genetic Medicine

Lead Researcher: López Trascasa, Margarita



Group members

STAFF MEMBERS: López Lera, Alberto.

ASSOCIATED MEMBERS: Bernabeu Herrero, Elvira | Caballero Molina, María Teresa | Garrido Herrero, Sofía | Mena de la Cruz, Rocío | Nozal Aranda, Pilar | Sánchez-Corral Gómez, Pilar.

Main lines of research

- Diagnosis and characterization of pathologies associated with congenital or acquired deficiencies of the complement.
- Dysregulation of the Complement system in renal pathology.
- Hereditary angioedema:

  a) Identification of modifying genes in clinical manifestations.

  b) Assessment of clinical eficacy of novel treatments and evaluation of quality of life in patients.

Most relevant scientific articles

CORVILLO F, GARCÍA-MORATO MB, NOZAL P, GARRIDO S, TORTAJADA A, DE CÓRDOBA SR, ET AL. Serum properdin consumption as a biomarker of C5 convertase dysregulation in C3 glomerulopathy. Clin Exp Immunol. 2015 Dec 13. [Epub ahead of print] PubMed PMID: 26660535.

BERNABÉU-HERRERO ME, JIMÉNEZ-ALCÁZAR M, ANTER J, PINTO S, SÁNCHEZ CHINCHILLA D, GARRIDO S, ET AL. Complement factor H, FHR-3 and FHR-1 variants associate in an extended haplotype conferring increased risk of atypical hemolytic uremic syndrome. Mol Immunol. 2015 Oct;67(2 Pt B):276-86.

GHANNAM A, SELLIER P, DEFENDI F, FAVIER B, CHARIGNON D, LÓPEZ-LERA A, ET AL. C1 inhibitor function using contact-phase proteases as target: evaluation of an innovative assay. Allergy. 2015 Sep;70(9):1103-11.

MARTÍNEZ-BARRICARTE R, HEURICH M, LÓPEZ-PERROTE A, TORTAJADA A, PINTO S, LÓPEZ-TRASCASA M, ET AL. The molecular and structural bases for the association of complement C3 mutations with atypical hemolytic uremic syndrome. Mol Immunol. 2015 Aug;66(2):263-73.

BYGUM A, AYGÖREN-PÜRSÜN E, BEUSTERIEN K, HAUTAMAKI E, SISIC Z, WAIT S, ET AL. Burden of illness in hereditary angioedema: a conceptual model. Acta Derm Venereol. 2015 Jun 24;95(6):706-10.

Highlights

The Group has a sustained research activity in the rare diseases atypical Haemolytic Uremic Syndrome (aHUS), C3 glomerulopathy (C3G) and Hereditary Angioedema (HAE) while maintaining its translational actions by generating clinical data and diagnostic reports on patients affected of these pathologies. During 2015, the group has been fund by 3 MINECO projects headed by the group's PIs: Margarita López Trascasa (SAF2012-386360), Pilar Sánchez-Corral Gómez (PI12/00597) and Teresa Caballero Molina (PI13/01758). Additionally, the group director has obtained funding for a new project entitled: Novel biomarkers in complement-mediated diseases (PI15/00255). Regarding intramural actions, during 2015 the group has collaborated with CIBERER units U738 and U709 in a Common-Rare ACCI entitled "Pathogenic mechanisms in rare and common diseases associated to complement dysregulation" which has been renewed for 2016 (Complement and Disease. Search for pathogenic mechanisms shared by rare and common diseases). These actions allowed us for generating novel patient cohorts and developing novel tools for molecular diagnosis which are now being evaluated.

Besides several International scientific publications, the main results of the group along 2015 have been presented in International conferences and the annual CIBERER meeting.

Moreover, in the present year, Pilar Sánchez Corral quit the European Complement Network' scientific board after 4 years in the position, being replaced by Margarita López Trascasa.

As part of the group's translational activities, we have participated in patients associations meetings on HAE (AEDAF) and aHUS (ASHUa).

Among the formative activities during the evaluated period, it is worth noting the PhD thesis presented by Nieves Prior Gómez: Development and validation of HAE-QoL (a specific health-related quality-of-life questionnaire for adult patients with Hereditary Angioedema due to C1-Inhibitor deficiency) (directed by Dr. Teresa Caballero Molina) at Universidad Autónoma de Madrid with cum laude distinction.

Institution: Servicio Madrileño de Salud · **Contact:** Hospital La Paz
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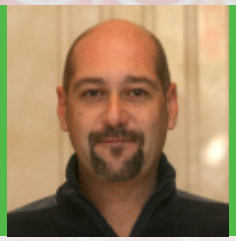
Group U755

Programme: Sensorineural Pathology

Lead Researcher: Millán Salvador, José María



Group members

STAFF MEMBERS: Aller Mañas, Elena | Olivares González, Lorena.

ASSOCIATED MEMBERS: Aparisi Navarro, María José | Jaijo Sanchís, Teresa | Morera Pérez, Constantino | Pérez Garrigues, Herminio | Rodrigo Nicolás, Regina | Sequedo Pérez, María Dolores | Vázquez Manrique, Rafael.

Main lines of research

- Usher (USH) syndrome: molecular analysis of the genes involved in Usher syndrome by means of NGS, translation to diagnosis and therapeutic approaches based on gene therapy.
- Experimental models of retinal degeneration: role of oxidative stress and inflammation in neurodegeneration. Pharmacological therapy testing before translational application.
- Translational genomics and identification of biomarkers for the diagnosis of Charcot Marie Tooth neuropathy.
- Identification of prognostic biomarkers for spinal muscular atrophy.
- Search for Huntington's disease modifying genes in a model of the disease in C. elegans.
- Editing the huntingtin gene in patients' cells by means of CRISPR/Cas9.

Most relevant scientific articles

NAGY AI*, VÁZQUEZ-MANRIQUE RP*, LÓPEZ M, CHRISTOV CP, SEQUEDO MD, HERZOG M, HERLIHY AE, BODAK M, GATSI R, BAYLIS HA.. IP3 signalling regulates exogenous RNAi in Caenorhabditis elegans. EMBO Rep. 2015; 16(3): 341-50. * Ambos autores han contribuido igualmente

AYUSO C, MILLÁN JM, DAL-RÉ R. Management and return of incidental genomic findings in clinical trials. The Pharmacogenomics Journal. 2015; 15 (1): 1-5

BLANCO-KELLY F, JAIJO T, ALLER E, ÁVILA-FERNÁNDEZ A, LÓPEZ MOLINA MI, JIMÉNEZ A, GARCÍA SANDOVAL B, MILLÁN JM*, AYUSO C*. Clinical aspects of Usher syndrome and the USH2A gene in a cohort of 433 patients. JAMA Ophthalmol. 2015; 133 (2): 157-64. *Ambos autores han contribuido igualmente

GONZÁLEZ-DEL POZO M, BRAVO-GIL N, MÉNDEZ-VIDAL C, MONTERO-DE-ESPINOSA I, MILLÁN JM, DOPAZO J, BORREGO S, ANTIÑOLO G. Re-evaluation casts doubt on the pathogenicity of homozygous USH2A p.C759F. Am J Med Genet A. 2015; 167 (7): 1597-1600

MARTÍNEZ-FERNÁNDEZ DE LA CÁMARA C, HERNÁNDEZ-PINTO AM, OLIVARES-GONZÁLEZ L, CUEVAS-MARTÍN C, SÁNCHEZ-ARAGÓ M, HERVÁS D, SALOM D, CUEZVA JM, DE LA ROSA EJ, MILLÁN JM, RODRIGO R. Adalimumab reduces photoreceptor cell death in a mouse model of retinal degeneration. Scientific Reports. 2015; 5:11764

Highlights

We have been granted with five projects to continue our research in retinal dystrophies, both in terms of diagnosis, identification of new genes and therapeutic approaches.

Therapeutic Approaches for retinitis pigmentosa and Usher syndrome based on Genome-Editing by CRISP/Cas9. Telemarathon "Todos somos raros."

molecular genetic diagnosis of hereditary retinal dystrophies by massive next-generation sequencing (NGS). ONCE Foundation.

Application of nanotechnology to the treatment of retinitis pigmentosa with anti-TNFa antibodies. synergy with antioxidants. ISCIII.

molecular genetic diagnosis of Leber congenital amaurosis by massive next-generation sequencing (NGS). Mutua Madrileña.

Identification of new genes and molecular mechanisms Usher syndrome and their translation to the diagnosis. Valencian Council of Health.

We have initiated several projects closely related to the translation to the clinic (clinical trials) and R + D + i Technology applied to rare diseases:

"Development of a new biomarker in Huntington's disease by analysis of the morphology of the retina."

Effect of the AMPK activator effect, metformin, on motor and cognitive ability of patients Huntington's disease.

Baculovirus encoding guided-RNA nucleases as a versatile tool to edit genes of biomedical interest funded by the University of Valencia and IIS-La Fe nucleases.

Polymer systems as support of monoclonal antibodies for the treatment of retinitis pigmentosa. IIS-La Fe-RETIC.

Cristina Martínez Fernández defended her doctoral thesis "Role of oxidative stress and inflammation in retinitis pigmentosa. Effect of inhibition of TNF-alpha in the progression of retinal degeneration "supervised by Rodrigo Regina and presented at the Polytechnic University of Valencia.

Institution: Fundación para la Investigación del Hospital la Fe · **Contact:** Hospital Universitario de La Fe Avda Fernando Abril Martorell, 106. 46009 Valencia. · Tel.: 96 197 31 53 · E.mail: millan_jos@gva.es
Website: http://www.iislafe.es

Group U756

Programme: Sensorineural Pathology
Lead Researcher: Montoliú José, Lluis

Group members

STAFF MEMBERS: Fernández López, Almudena.

ASSOCIATED MEMBERS: Cantero González, Marta María | Fernández Punzano, Juliana | Josa de Ramos, Santiago | Montalban Iglesias, Soledad | Sánchez Sánchez, Óscar Javier | Seruggia, Davide.

Main lines of research

- Animal models of congenital hypopigmentation diseases: oculocutaneous albinism type I and ocular albinism.
- ALBINOCHIP: Design and validation of a new system for the genetic diagnosis of all the mutations known associated with any type of albinism.
- New animal model of achromatopsia involved in the cone deficit phenotype observed in the commercial albino mice with no blood relations.
- Optimization of methodologies in animal transgenesis: new methods CRISPR-Cas9, protocols and techniques for more efficient generation, analysis and cryopreservation of animal models.
- Pre-clinical therapeutic proposals for albinism, use of L-DOPA and nitisinone in mouse models.
- Mechanism of action of L-DOPA in retinal development in mammals.

Most relevant scientific articles

WANG J, VICENTE-GARCÍA C, SERUGGIA D, MOLTÓ E, FERNÁNDEZ-MIÑÁN A, NETO A, LEE E, GÓMEZ-SKARMETA JL, MONTOLIU L, LUNYAK VV, JORDAN IK. MIR retrotransposon sequences provide insulators to the human genome. Proc Natl Acad Sci U S A. 2015 Aug 11;112(32):E4428-37.

SCAVIZZI F, RYDER E, NEWMAN S, RASPA M, GLEESON D, WARDLE-JONES H, MONTOLIU L, FERNÁNDEZ A, DESSAIN ML, LARRIGALDIE V, KHORSHIDI Z, VUOLTEENAHO R, SOININEN R, ANDRÉ P, JACQUOT S, HONG Y, DE ANGELIS MH, RAMIREZ-SOLIS R, DOE B. Blastocyst genotyping for quality control of mouse mutant archives: an ethical and economical approach. Transgenic Res. 2015 Oct;24(5):921-7.

SERUGGIA D, FERNÁNDEZ A, CANTERO M, PELCZAR P, MONTOLIU L. Functional validation of mouse tyrosinase non-coding regulatory DNA elements by CRISPR-Cas9-mediated mutagenesis. Nucleic Acids Res. 2015 May 26;43(10):4855-67.

INFRAFRONTIER Consortium. INFRAFRONTIER--providing mutant mouse resources as research tools for the international scientific community. Nucleic Acids Res. 2015 Jan;43(Database issue):D1171-5.

Highlights

Experimental demonstration that endogenous non-coding DNA sequences of mouse tyrosinase locus, whose mutations are associated with oculocutaneous albinism type I (OCA1), also correlate with the appearance of phenotypes compatible with OCA1B.

Coordination, funding granted and start of activities of project ACCI “New animal models of neursensorial rare diseases generated with CRISPR-Cas9 technology”, with all groups from Neurosensorial Pathology Area.

Funding granted and start of activities of project ACCI “Genetic diagnose and possible treatment of albinism” in collaboration with U711 Angel Carracedo de USC.

Funding granted, participation and start of activities of EU-H2020 project “IPAD-MD: Research Infrastructures for Phenotyping, Archiving and Distribution of Mouse Disease Models – Promoting International Cooperation and User Engagement to Enhance Biomedical Innovation” H2020-INFRASUPP-2014-2, Ref. 653961 (2015-2018).

Organization and participation in the meeting 1st International Workshop on Oculocutaneous Albinism in Subsaharian Africa, Douala, Cameroon, 24-25 July 2015.

Organization and participation in the Frist Clinical Day of Albinism in Spain, Fundación Jiménez Díaz, Madrid, Friday 2 October 2015.

Organization and participation in the IX Annual Meeting of ALBA, La Cristalera, Miraflores de la Sierra, Madrid, 3-4 October 2015.

Updating web devoted to albinism: http://wwwuser.cnb.csic.es/~albino/

Genetic diagnose and preparation and distribution of genetic reports to patients and relatives with albinism, in collaboration with U711 Angel Carracedo de USC.

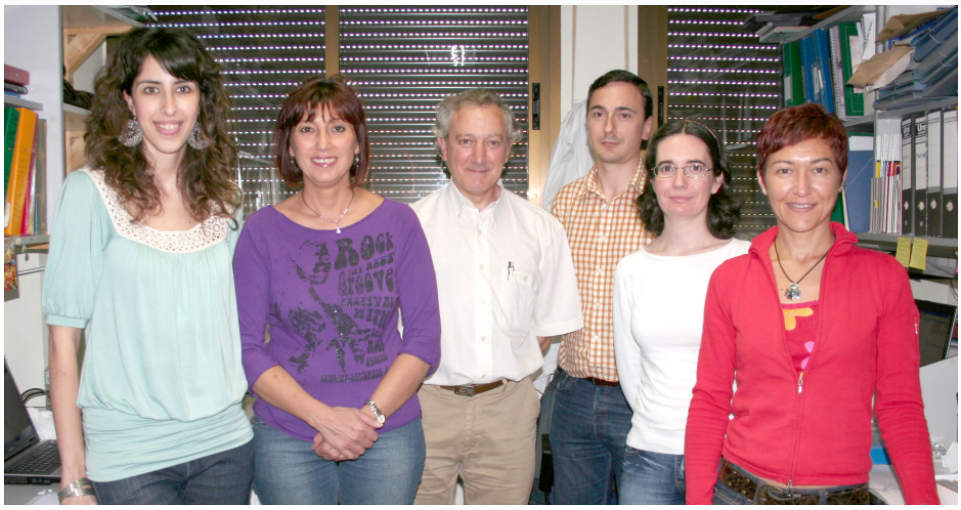
Preclinical evaluatio, in different mouse mutant models of OCA1B, of the use of nitisinone as potential treatment of certain types of OCA1B.

Institution: Agencia Estatal Consejo Superior de Investigaciones Científicas
Contact: Centro Nacional De Biotecnología. c/ Darwin, 3. Universidad Autónoma de Madrid. Cantoblanco. Dpto de Biología Molecular y Celular. 28049 Madrid · Tel.: 91 585 48 44 · E.mail: montoliu@cnb.csic.es
Website: http://www.cnb.csic.es/~montoliu/

Group U757

Programme: Inherited Cancer, Haematological & Dermatological Diseases
Lead Researcher: Perona Abellón, Rosario

Group members



STAFF MEMBERS: Manguán García, Cristina.
ASSOCIATED MEMBERS: Carrillo García, Jaime | Sánchez Pérez, Isabel | Sastre Garzón, Leandro.

Main lines of research

- Application of a rescue therapy in diseases associated with telomerase activity deficiency. Signalling pathways active in dyskeratosis congenita in response to DNA damage. Improve the activity of nanoparticles and lentiviral vectors for gene therapy.
- Development of a therapy base in the GSE24.2 peptide fro the treatment of short telomeres associated diseases, increase oxidative stress and geentic instability.
- Genetic diagnosis of DC y study of telomere lenght in patients of DC and idiophatic pulmonary fibrosis. Study of models of idiopathic pulmonary fibrosis using stem cells and KO mouse models for DUSP1.
- Investigation about the activity of GSE4 for the treatment of idiophatic pulmonary fibrosis.
- Use of GSE4 for the treatment of ataxia telangiectasia.

Most relevant scientific articles

EGUSQUIAGUIRRE SP, MANGUÁN-GARCÍA C, PINTADO-BERNINCHES L, IARRICCIO L, CARBAJO D, ALBERICIO F, ROYO M, PEDRAZ JL, HERNÁNDEZ RM, PERONA R, IGARTUA M. Development of surface modified biodegradable polymeric nanoparticles to deliver GSE24.2 peptide to cells: a promising approach for the treatment of defective telomerase disorders. . Eur J Pharm Biopharm. 2015 Apr;91:91-102. doi: 10.1016/j.ejpb.2015.01.028. Epub 2015 Feb 7. PMID:25660910.

CALVETE O, MARTÍNEZ P, GARCÍA-PAVIA P, BENITEZ-BUELGA C, PAUMARD-HERNÁNDEZ B, FERNÁNDEZ V, ET AL. A mutation in the POT1 gene is responsible for cardiac angiosarcoma in TP53-negative Li-Fraumeni-like families.Nat Commun. 2015 Sep 25;6:8383. doi: 10.1038/ncomms9383. PMID: 26403419.

IARRICCIO L, MANGUÁN-GARCÍA C, PINTADO-BERNINCHES L, MANCHEÑO JM, MOLINA A, PERONA R, SASTRE L. GSE4, a Small Dyskerin- and GSE24.2-Related Peptide, Induces Telomerase Activity, Cell Proliferation and Reduces DNA Damage, Oxidative Stress and Cell Senescence in Dyskerin Mutant Cells. PLoS One. 2015 Nov 16;10(11):e0142980. doi: 10.1371/journal.pone.0142980. eCollection 2015. PMID: 2657138.

BENITEZ-BUELGA C, SÁNCHEZ-BARROSO L, GALLARDO M, APELLÁNIZ-RUIZ M, INGLADA-PÉREZ L, ET AL. Impact of chemotherapy on telomere length in sporadic and familial breast cancer patients. Breast Cancer Res Treat. 2015 Jan;149(2):385-94. doi: 10.1007/s10549-014-3246-6. Epub 2014 Dec 21. PMID: 25528024.

LÓPEZ-AYLLÓN BD, DE CASTRO-CARPEÑO J, RODRÍGUEZ C, PERNÍA O, IBAÑEZ DE CÁCERES I, BELDA-INIESTA C, PERONA R, SASTRE L. Biomarkers of erlotinib response in non-small cell lung cancer tumors that do not harbor the more common epidermal growth factor receptor mutations. Int J Clin Exp Pathol. 2015 Mar 1;8(3):2888-98. eCollection 2015. PMID: 2604.

Highlights

PATENTS:

Método para predecir la respuesta al tratamiento con radioterapia combinada con quimioterapia basada en cisplatino. Application No. P2011330783. Inventors: Inmaculada Ibañez de Cáceres, Rosario Perona, Cristobal Belda-Iniesta, Olga Pernía y María Cortes Sempere. Presentation date: May 9, 2013. International Phase, USA (2015).

Péptidos Derivados de GSE24.2 para Tratar Enfermedades Producidas por Estrés Oxidativo y Daño al ADN. P201331573, Presentation date: October 25, 2013. Inventors: Rosario Perona, Leandro Sastre, Laura Pintado Berninches, Jaime Carrillo García, Antonio Molina Pachón, Laura Iarriccio Silva y Cristina Manguan García. PCT presented. International phase. Licence to Advanced Medical Projects.

THESIS

Mecanismos reguladores de las células madre neuronales: implicación en los procesos de envejecimiento y cáncer. Olatz Arrizabalaga Garde. Apto Cum laude, 2015).

PROJECTS

1-Estudio Molecular integrado en CNMP. Búsqueda de marcadores moleculares pronósticos, heterogeneidad de células circulantes tumorales y sensibilidad extrema a tratamiento. Inv. Principal. R. Perona. FIS PI14/01495. Duration 2015-2018.

RESULTS

In collaboration with Advanced Medical Projects and a US Pharma dedicated to rare diseases we are performing the preclinical assays (efficiency, biodistribution, toxicity, efficacy in animal models and cells derived from patients) for the therapeutic application and clinical trials of PLGA/PEI nanoparticles loaded with the peptide GSE4 for the treatment of dyskeratosis congenita and idiopathic pulmonary fibrosis.

Institution: Agencia Estatal Consejo Superior de Investigaciones Científicas
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Tel.: 91 585 44 63 · E.mail: rperona@iib.uam.es

Group U758

Programme: Paediatric and Developmental Medicine
Lead Researcher: Posada de La Paz, Manuel

Group members

STAFF MEMBERS: Monzón Fernández, Sara.

ASSOCIATED MEMBERS: Abaitua Borda, Ignacio | Alonso Ferreira, Verónica | Hens Pérez, Manuel | Morales Piga, Antonio | Villaverde Hueso, Ana.

Main lines of research

- Epidemiology and risk factors in autism: Early diagnosis (screening); case-cohort studies; case-control studies.
- Epidemiology and risk factors in connective tissue diseases and autoimmune diseases: Risk factor analysis; search for drugs; quality of life; registry; costs.
- General epidemiology of rare diseases: Rare disease registry; health costs; quality of life.
- National Rare Disease Registry (SpainRDR).
- Undiagnosed rare diseases program
- National Rare Disease Biobank (BioNER).
- National germ line mutations database (Spain-MDB).
- Development of computer workflows for the analysis and interpretation of data generated by massive sequencing.
- Identification of microRNAs involved in regulating genes causing rare diseases by means of high-throughput assays with microRNA libraries.
- Genetics of retinoblastoma.
- Molecular and cellular biology of rare childhood tumors (sarcomas).

Most relevant scientific articles

CASTAÑO A, CUTANDA F, ESTEBAN M, PÄRT P, NAVARRO C, GÓMEZ S, ET AL. Fish consumption patterns and hair mercury levels in children and their mothers in 17 EU countries. Environ Res. 2015;141:58-68.

PAZ S, TORRENT J, POVEDA JL, PEREZ J, MORENO JL, MARTIN A, GONZÁLEZ L, CRUZ J, COMELLAS M, ABAITUA I, URCELAY J. Experts Consensus on The Future of Rare Diseases Care and Orphan Drugs Access In Spain: A Delphi Study. Value Health. 2015;18(7):A679.

GARCÍA-PÉREZ J, LÓPEZ-ABENTE G, GÓMEZ-BARROSO D, MORALES-PIGA A, ROMAGUERA EP, TAMAYO I, FERNÁNDEZ-NAVARRO P, RAMIS R. Childhood leukemia and residential proximity to industrial and urban sites. Environ Res. 2015;140:542-53.

BLADEN CL, SALGADO D, MONGES S, FONCUBERTA ME, KEKOU K, KOSMA K ET AL. The TREAT-NMD DMD Global Database: analysis of more than 7,000 Duchenne muscular dystrophy mutations. Hum Mutat. 2015 Apr;36(4):395-402.

RAMIS R, GÓMEZ-BARROSO D, TAMAYO I, GARCÍA-PÉREZ J, MORALES A, PARDO ROMAGUERA E, LÓPEZ-ABENTE G. Spatial analysis of childhood cancer: a case/control study. PLoS One. 2015;10(5):e0127273.

Highlights

In 2015, U758 group participated in 9 projects (3 funded by the European Commission and 6 by national agencies) and lead three of them. Projects to highlight:

- "Autism Spectrum Disorders in the European Union" (DG-SANTÉ) lead by the head of U758.
- "SpainRDR" (ISCIII, IRDiRC) lead by the head of U758. The creation of a legal framework for RD registries at national and Autonomous Community level has been one of this project's major achievements.

National Platforms supporting RD research developed and sustained by U758:

- National Rare Diseases Biobank, full partner of the ISCIII Biobank Platform. RD working group is coordinate by both our biobank and Val d'Hebron Hospital biobank.
- National Rare Diseases Registry. Spanish Royal Decree where the official creation of the National RD Registry was published in the official gazette at the end of 2015. This law gathers the last 3 years' experience of the SpainRDR project.

New programs:

- Germinal line mutations database "SpainMDB".
- Undiagnosed RD cases "SpainUDP" in collaboration with the International Undiagnosed Diseases Program launched by the NIH.

Manuel Posada is independent expert of the Commission Expert Group on RD, and collaborating partner of the new Joint Action namely RD-ACTION. He is a member of the Steering Committee of the "Global Rare Diseases Registries" (NIH) and the Advisory Board from the ERARE3 consortium. He is also member of the IRDiRC Task Force "Patient Centred Outcome Measurements" launched in 2015. He is the ICORD President Elect and President of the Scientific Committee. Finally he is responsible of the epidemiological module of the RD Master organized by José Antonio Alcazar (U729).

IntraCIBERER collaboration is mainly related to the National RD Registry and the Biobank Platform. International projection of U758 group is showing through their projects, participation in international actions, high level committees and RD decision making.

Institution: Instituto de Salud Carlos III · **Contact:** Instituto de Investigación en Enfermedades Raras
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Website: http://www.isciii.es/ISCIII/es/contenidos/fd-el-instituto/fd-organizacion/fd-estructura-directiva/fd-subdireccion-general-servicios-aplicados-formacion-investigacion/fd-centros-unidades/instituto-investigacion-enfermedades-raras.shtml

Group U759

Programme: Inherited Metabolic Medicine

Lead Researcher: Pujol Onofre, Aurora

Group members

STAFF MEMBERS: Launay, Nathalie | Ruiz Sales, Montserrat.

ASSOCIATED MEMBERS: Fourcade Guillou, Stephane | Grau Guijarro, Laia | Guilera Zapater, Cristina | Martínez García, Juan José | Ranea Robles, Pablo | Schluter Martin, Ágatha.

Main lines of research

- Physiopathology of adrenoleukodystrophy: impact of oxidative stress in mitochondrial function, energetic homeostasis and proteolytic processes, using the mouse model developed and characterized in our laboratory and tissues of X-ALD patients.
- Treatment of adrenoleukodystrophy: preclinical tests in the mouse model and clinical trials in patients with X-ALD.
- Peroxisomal integrative genomics. Peroxisomal metabolome characterization and the organelle's evolutive origin.
- Physiopathology of Pelizaeus Merzbacher disease, metachromatic leukodystrophy and other leukodystrophies.
- Disease model of adrenoleukodystrophy in C.elegans: role of fatty acids in oxidative stress, neurodegeneration and aging.
- Systems biomedicine for unravelling the molecular basis and modelling leukodystrophies and inherited spastic paraplegias.

Most relevant scientific articles

MORATÓ L, RUIZ M, BOADA J, CALINGASAN NY, GALINO J, GUILERA C ET AL. Redox regulation of SIRT1 controls mitochondrial function and underlies axonal degeneration. Cell Death Differ. 2015; 22:1742-1753.

LAUNAY N, AGUADO C, FOURCADE S, RUIZ M, GRAU L, RIERA J ET AL. Autophagy induction halts axonal degeneration in a mouse model of X-adrenoleukodystrophy. Acta Neuropathol. 2015; 129:399-415.

RUIZ M, JOVE M, SCHLUTER A, CASASNOVAS C, VILLARROYA F, GUILERA C ET AL. Altered glycolipid and glycerophospholipid signaling drive inflammatory cascades in adrenomyeloneuropathy. Hum Mol Genet. 2015; 24(24):6861-76.

FOURCADE S, FERRER I, AND PUJOL A. Oxidative stress, mitochondrial and proteostasis malfunction in adrenoleukodystrophy: A paradigm for axonal degeneration. Free Radic Biol Med. 2015; 88(Pt A):18-29.

KRUSKA N, SCHÖNFELD P, PUJOL A AND REISER G. Astrocytes and mitochondria from adrenoleukodystrophy protein (ABCD1)-deficient mice reveal that the adrenoleukodystrophy-associated very long-chain fatty acids target several cellular energy-dependent functions. Biochim Biophys Acta. 2015; May;1852(5):925-36.

Highlights

In 2015 we achieved to:

i) increase the knowledge of molecular basis and pathophysiology in X-ALD;

ii) identify new therapeutic targets as the mitochondrial biogenesis drivers (Sirt1/PGC-1/PPARy axis) and autophagic flux (via mTOR);

iii) demonstrate, through integrated analysis systems, that the AMN patients also exhibit alterations in pro-inflammatory cascades;

and iv) identify drugs like resveratrol or temsirolimus, able to reverse the axonal degeneration in the mouse model.

We also finished the first year of treatment of AMN patients included in a multicenter international phase II clinical trial with biotin and started a new phase II clinical trial with pioglitazone, promoted by our unit. We have also initiated the proceedings to obtain the orphan drug designation for temsirolimus in ALD (with U721).

Within the PDI structure, we started the intramural project achieved in the ACCI 2014 call, together with U703 and U711 units for the identification and functional and metabolic characterization of new variants/genes involved in leukodystrophies and spastic paraplegia. We have already identified some new variants, being currently validated in the zebrafish model.

At international level, we started in 2013 to collaborate with Dr. G. Reiser from Magdeburg, Germany, with a first publication in Biochim Biophys Acta in 2015. In addition, we have been included in the MSeqDR Consortium, which aims to facilitate deposition, curation, annotation, and integrated systems biology approach analysis of genomic data for the mitochondrial disease clinical and research communities.

Finally, as members of the SEFALer platform, we continue to perform phenotyping services of locomotor disorders and neuromuscular coordination for the interested groups.

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Group U760

Programme: Paediatric and Developmental Medicine

Lead Researcher: Ruiz Pérez, Víctor Luis

Group members

STAFF MEMBERS: Calatrava Ferreras, Lucía.

Main lines of research

- Molecular analysis and physiopathological mechanisms of Ellis-van Creveld syndrome and Weyer's acrodental dysostosis.
- Molecular analysis of cases with autosomal recessive and autosomal dominant osteogenesis imperfecta.
- Identification and characterization of new genes responsible for pediatric disorders.

Most relevant scientific articles

CAPARRÓS-MARTÍN JA, DE LUCA A, CARTAULT F, AGLAN M, TEMTAMY S, OTAIFY GA, MEHREZ M, VALENCIA M, VÁZQUEZ L, ALESSANDRI JL, NEVADO J, RUEDA-ARENAS I, HEATH KE, DIGILIO MC, DALLAPICCOLA B, GOODSHIP JA, MILL P, LAPUNZINA P, RUIZ-PEREZ VL. Specific variants in WDR35 cause a distinctive form of Ellis-van Creveld syndrome by disrupting the recruitment of the EvC complex and SMO into the cilium. Hum Mol Genet. 2015 Jul; 24(14):4126-37.

MATTOS EP, SILVA AA, MAGALHÃES JA, LEITE JC, LEISTNER-SEGAL S, GUS-KESSLER R, PEREZ JA, VEDOLIN LM, TORREBLANCA-ZANCA A, LAPUNZINA P, RUIZ-PEREZ VL, SANSEVERINO MT. Identification of a premature stop codon mutation in the PHGDH gene in severe Neu-Laxova syndrome-evidence for phenotypic variability. Am J Med Genet A. 2015 Jun;167(6):1323-9.

VALENCIA M, TABET L, YAZBECK N, ARAJ A, RUIZ-PEREZ VL, CHARAFFEDINE K, FARES F, BADRA R, FARRA C. Ellis-van Creveld Syndrome: Mutations Uncovered in Lebanese Families. Case Rep Genet. 2015; 2015:528481. doi: 10.1155/2015/528481.

Highlights

Ellis-van Creveld syndrome (MIM: 225500; EvC) is a developmental disorder characterized by short ribs and limbs, ectodermal defects in teeth and nails and congenital heart disease. Until now all patients with EvC had been reported with mutations in EVC or EVC2, however studies from different labs had suggested wider genetic heterogeneity. In 2015 our group in collaboration with the U753 and other international labs from United Kingdom, Italy, France and Egypt described splicing mutations in WDR35 in patients diagnosed with EvC. In addition to the classical findings of EvC, these patients also had some features present in Sensenbrenner syndrome (MIM:613610). On the other hand, we revealed that Wdr35 is required for the localization of EVC, EVC2 and SMO to primary cilia, an organelle which is essential for Hedgehog (Hh) signal transduction. The analysis of this pathway showed that the WDR35 mutations identified in EvC patients, like the mutations in EVC or EVC2, all result in partial inhibition of Hh signaling, hence providing a molecular explanation for the convergence of phenotypes associated with mutations in WDR35 and EVC-EVC2.

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Group U761

Programme: Sensorineural Pathology
Lead Researcher: Varela Nieto, Isabel

Group members

STAFF MEMBERS: Murillo Cuesta, Silvia | Rodríguez de la Rosa, Lourdes.

AT THE EXPENSE OF THE PROJECT: Jareño Flores, Tania.

ASSOCIATED MEMBERS: Baeza Ochoa de Ocariz, María Luisa | Cediel Algovia, Rafael | Celaya Puértolas, Adelaida | Contreras Rodríguez, Julio | García Alcántara, Fernando | Magariños Sánchez, Marta | Rivera Rodríguez, Teresa | Zubeldia Ortuño, José Manuel.

Main lines of research

- Characterization of animal and cellular models of syndromic sensorineural deafness.
  - Physiopathology of the deficit and the haploinsuficiencia in IGF-1 using animal and cellular models. Exploring the role of IGF-1 intracellular networks in hearing loss. Signature neuroinflammation and redox balance.
  - Interaction genome-environment in animal models of hereditary hearing loss under environmental stress: ototoxic, noise and nutritional deficit.
  - Genetic predisposition, cellular senescence and presbycusis.
- Identification of potential therapeutic targets and biomarkers for progression of hearing loss.
  - Role of regulating the activity of inflammatory kinases p38 MAPKJNK in hearing damage.
  - Role of the loss of function of the RAF (rasopathies) family and autophagy genes.
  - Participation of micronutrients and the metabolism of methionine and homocysteine (hyperhomocysteinemia).
- Testing of new therapies with small molecules and stem cells in animal models of sensorineural deafness.
  - Inhibitors of apoptosis.
  - Facilitators of cell survival.
  - Developers of neuritogenesis.
- Animal and cellular models of retinal degeneration associated with deficits in IGF-1 and their intracellular targets.

Most relevant scientific articles

RODRÍGUEZ-DE LA ROSA L, SÁNCHEZ-CALDERÓN H, CONTRERAS J, MURILLO-CUESTA S, FALAGAN S, AVENDAÑO C, DOPAZO J, VARELA-NIETO I, MILO M. Comparative gene expression study of the vestibular organ of the Igf1 deficient mouse using whole-transcript arrays. Coautor senior. Hear Res. 2015 Dec;330(Pt A):62-77. doi: 10.1016/j.heares.2015.08.016. Epub 2015 Sep 1.PMID: 26341476.

DE IRIARTE RODRÍGUEZ R, MAGARIÑOS M, PFEIFFER V, RAPP UR, VARELA-NIETO I. C-Raf deficiency leads to hearing loss and increased noise susceptibility. Cell Mol Life Sci. 2015 Oct;72(20):3983-98. doi: 10.1007/s00018-015-1919-x. Epub 2015 May 15. PMID: 25975225.

DE IRIARTE RODRÍGUEZ R, PULIDO S, RODRÍGUEZ-DE LA ROSA L, MAGARIÑOS M, VARELA-NIETO I. Age-regulated function of autophagy in the mouse inner ear. Hear Res. 2015 Dec;330(Pt A):39-50. doi: 10.1016/j.heares.2015.07.020. Epub 2015 Jul 31. PMID: 26235979

MURILLO-CUESTA S, RODRÍGUEZ-DE LA ROSA L, CONTRERAS J, CELAYA AM, CAMARERO G, RIVERA T, VARELA-NIETO I. Transforming growth factor β1 inhibition protects from noise-induced hearing loss. Front Aging Neurosci. 2015 Mar 20;7:32. doi: 10.3389/fnagi.2015.00032. eCollection 2015. PMID: 25852546.

MARTÍNEZ-VEGA R, GARRIDO F, PARTEARROYO T, CEDIEL R, ZEISEL SH, MARTÍNEZ-ÁLVAREZ C, VARELA-MOREIRAS G, VARELA-NIETO I, PAJARES MA. Folic acid deficiency induces premature hearing loss through mechanisms involving cochlear oxidative stress and impairment of homocysteine metabolism. Coautor senior. FASEB J. 2015 Feb;29(2):418-32. doi: 10.1096/fj.14-259283. PMID: 25384423.

Highlights

In 2015, the Neurobiology of hearing group has continued to work on projects and European partnership initiatives for the study of the genetic and molecular bases of hearing loss (FP7-HEALTH-AFHELO, EIP-A3 and FP7-PEOPLE-TARGEAR), with a strong orientation towards the development of new therapies for the prevention and repair of hearing loss and aging. In the context of the Marie Curie TARGEAR action we have carried out numerous training activities (Master of Neuroscience, UAM) and participation in the Researcher´s Night and Science Week. These outreach activities have counted with the support of associations "Fundación Oír es Clave" and FIAPAS. Participation in the Researcher´s Night of Madrid is supported by the project H2020-PEOPLE-2014-2015-NIGHT. At the international level it can be mentioned the participation in the Organization of the Inner Ear Biology Workshop in Rome and in the Committee of the Spoendlin Award, as well as the nomination of Dr. Varela-Nieto to the International Committee of ARO (USA). As coordinators of the SEFALer platform, networking, information and training activities have been carried out, and CIBERER has joined the COST Action BM1402 MouseAGE. At the national level it has been renewed the SAF-challenges project focused on the study of the mechanisms of aging and neuropathogenesis of hearing loss, study of factors of protection and repair. This project has a strong translational focus as does the research and development project of the CDTI coordinated by the Salvat company. Finally, we have strengthened the participation in the IdiPAZ and the collaboration with the services of ORL of the University Hospital de la Paz and Alcalá de Henares.

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Group U762

Programme: Mitochondrial and Neuromuscular Medicine

Lead Researcher: Illa Sendra, Isabel

Group members

STAFF MEMBERS: Araque Palacios, Josefa | De Luna Salva, Noemí.

ASSOCIATED MEMBERS: Alejaldre Monforte, Aida | Díaz Manera, Jorge Alberto | Gallardo Vigo, Eduardo | Navas Madroñal, Miquel | Nogales Gadez, Gisela | Ortiz Losada, Esther | Querol Gutiérrez, Luis Antonio | Ramos Fransi, Alba | Rojas García, Ricardo | Suárez Calvet, Xavier.

Main lines of research

- Search for biomarkers in neuromuscular disorders: A) Search for new autoantibodies in immune-mediated NMD (Myasthenia, CIDP, NMM,..) and its correlation with specific phenotypes and new treatments. B) Analysis of miRNA profile in plasma/serum of patients with muscular dystrophies, Pompe's disease and myasthenia as biomarkers of the progresión of the different diseases C) Study of the secretome in human primary cultures of skeletal muscle from patients with well- characterized to determine its utility as a biomarker of clinical progression and to gain knowledge of the pathogenesis of these diseases D) Serial studies of muscle MRI in patients with muscular dystrophies to establish patterns of involvement that may be useful for the differential diagnosis and etiology of these diseases. In addition, quantitative studies of changes in muscle involvement to determine its utility as a non-invasive follow up test to monitor the efficacy of future treatments.
- Research of pathogenic mechanisms of NMD. : A) Study of pericytes from skeletal muscle as a source of cells for physiological muscle regeneration and as a source of cells for cell therapy in patients with muscular dystrophies. B) To study factors involved in muscle regeneration and fibrosis.C) To study the role of innate immunity in inflammatory myopathies. D) Analysis of subpopulations of B cells in patients with autoimmune NMD. E) Estudios epidemiológicos y genéticos en ELA.
- Spanish registry of NMD. A nationwide registry of patients with NMD in Spain is in progress with epidemiological and research purposes (e.g search for new genes, clinical guidelines,...) At present, 4.500 patients have been registered. Twenty-seven hospitals in Spain participate in the registry and curator is in charge of the quality control of all data included in it (as part of CIBERER facilities).

Most relevant scientific articles

QUEROL L, ILLA I. Paranodal and other autoantibodies in chronic inflammatory neuropathies. Curr Opin Neurol. 2015 Oct;28(5):474-9.

QUEROL L, ROJAS-GARCÍA R, DÍAZ-MANERA J, BARCENA J, PARDO J, ORTEGA-MORENO A, SEDANO MJ, SERÓ-BALLESTEROS L, CARVAJAL A, ORTIZ N, GALLARDO E, ILLA I. Rituximab in treatment-resistant CIDP with antibodies against paranodal proteins. Neurol Neuroimmunol Neuroinflamm. 2015 Sep 3;2(5):e149.

DÍAZ-MANERA J, ALEJALDRE A, GONZÁLEZ L, OLIVÉ M, GÓMEZ-ANDRÉS D, MUELAS N, VÍLCHEZ JJ, LLAUGER J, CARBONELL P, MÁRQUEZ-INFANTE C, FERNÁNDEZ-TORRÓN R, POZA JJ, LÓPEZ DE MUNÁIN A, GONZÁLEZ-QUEREDA L, MIRABET S, CLARIMON J, GALLANO P, ROJAS-GARCÍA R, GALLARDO E, ILLA I. Muscle imaging in muscle dystrophies produced by mutations in the EMD and LMNA genes. Neuromuscul Disord. 2016 Jan;26(1):33-40.

RAMOS-FRANSI A, ROJAS-GARCÍA R, SEGOVIA S, MÁRQUEZ-INFANTE C, PARDO J, COLL-CANTÍ J, JERICÓ I, ILLA I. Myasthenia gravis: descriptive analysis of life-threatening events in a recent nationwide registry. Myasthenia NMD-ES Study Group. Eur J Neurol. 2015 Jul;22(7):1056-61.

HUIJBERS MG, QUEROL LA, NIKS EH, PLOMP JJ, VAN DER MAAREL SM, GRAUS F, DALMAU J, ILLA I, VERSCHUUREN JJ. The expanding field of IgG4-mediated neurológical autoimmune disorders. Eur J Neurol. 2015 Aug;22(8):1151-61.

Highlights

The group is composed of clinical and basic researchers. Our clinical work is mainly focused on rare genetically determined neuromuscular diseases (muscular dystrophies), neurodegenerative diseases (ALS), and immune-mediated (gravis, CIDP, inflammatory myopathies). In October 2015, following an audit (clinical care, teaching, research) we obtained the approval of the Ministry of Health as a CSUR center in neuromuscular diseases.

In Europe there is an initiative similar to CSUR, the ERN (European Reference Networks). We participate in designing criteria for the ERN- Neuromuscular network.

Research activity has a significant translational component. Part of the results of the investigation of biomarkers, result in diagnostic tests that are performed in our laboratory (samples national / international), which in 2015 received the ISO9001 accreditation.

Research areas: 1) muscular dystrophies, FISPI12 / 02291 (secretome, muscular microRNAs RMN). Studies continue in FISPI15 / 01822 (PDGF as a biomarker and therapeutic target). 2) ELA (neurodegenerative disease), the group has research experience in genetics and epidemiology. Current projects (MaratóTV3 and FISPI15 / 01618) to develop neuroradiological studies and biomarkers in CSF of patients with ALS and ALS with dementia. 3) autoimmune diseases. CIDP, gravis. Search for new autoantibodies, basic immune response mechanisms in the IgG4; efficacy of a Mab in patients with autoantibodies described by us. European funds (E-rares, AFM (17215 and 18476), private foundations (GBS-CIDP Foundation and Myositis Association), FISPI13 / 0937. Dermatomyositis and innate immunity. FISPI15 / 01597.

We lead the National Registry of ENM-ES. This database, currently included in CIBERER, has more than 5000 patients included and the work of the last two years has been the connection of this registry with RD-CONNECT and TREAT-NMD.

We participate in European committees, at present 6 doctoral thesis are in progress, we conducted an annual training course on neuromuscular diseases, in 2015 participated as speakers in 8 international and national meetings and have contributed as experts in five patient's associations meetings.

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Group U763

Programme: Mitochondrial and Neuromuscular Medicine

Lead Researcher: Vílchez Padilla, Juan Jesús

Group members

STAFF MEMBERS: Azorín Villena, Inmaculada Concepción | Gómez Perpiñá, Lorena.

ASSOCIATED MEMBERS: Bataller Alberola, Luis | Chumillas Luján, Josefina | Martí Martínez, María Pilar | Mayordomo Fernández, Fernando | Muelas Gómez, Nuria | Sevilla Mantecón, María Teresa.

Main lines of research

- Clinical and genetic characterization of herreditary motor and sensory neuropathies.
- Clinical, Genetic and neuroimaging characterization of Motor neuron disorders.
- Clinical studies, trial and experimental therapies in muscular dystrophies.
- Immunopathogenesis of hereditary and adquired ataxias.
- Clinical and genetic characterization of congenital myastehnia.

Most relevant scientific articles

SEVILLA, T; SIVERA, R; MARTÍNEZ-RUBIO, D; LUPO, V; CHUMILLAS, M J; CALPENA, E; DOPAZO, J; VILCHEZ, J J; PALAU, F; ESPINOS, C The EGR2 gene is involved in axonal Charcot-Marie-Tooth disease. European journal of neurology. 2015;22(12):1548-55.

PLA-MARTIN, D; CALPENA, E; LUPO, V; MARQUEZ, C; RIVAS, E; SIVERA, RA; SEVILLA, T; PALAU, F; ESPINOS, C.Junctophilin-1 is a modifier gene of GDAP1-related Charcot-Marie-Tooth disease Human Molecular Genetics. 2015; ;24(1):213-29.

BARGIELA A; CERRO-HERREROS E; FERNÁNDEZ-COSTA, J M.; VILCHEZ, J J.; LLAMUSI, B; ARTERO, R. Increased autophagy and apoptosis contribute to muscle atrophy in a myotonic dystrophy type 1 Drosophila model. Disease Models & Mechanisms. 2015; 8(7):679-90.

GUTIÉRREZ-RIVAS E, BAUTISTA J, VÍLCHEZ JJ, MUELAS N, DÍAZ-MANERA J, ILLA I, MARTÍNEZ-ARROYO A, OLIVÉ M, SANZ I, ARPA J, FERNÁNDEZ-TORRÓN R, LÓPEZ DE MUNÁIN A, JIMÉNEZ L, SOLERA J, LUKACS Z.Targeted screening for the detection

of Pompe disease in patients with unclassified limb-girdle muscular dystrophy or asymptomatic hyperCKemia using dried blood: A Spanis3h cohort. Neuromuscul Disord. 2015; 25(7):548-53.

ARINO, H; HOEFTBERGER, R; GRESA-ARRIBAS, N; MARTÍNEZ-HERNÁNDEZ, E; ARMANGUE, T; KRUER, M C.; ARPA, J; DOMINGO, J; ROJC, B; BATALLER, L; SAIZ, A; DALMAU, J; GRAUS, F. Paraneoplastic Neurológical Syndromes and Glutamic Acid Decarboxylase Antibodies. JAMA Neurology. 2015 ;72(8):874-81.

Highlights

In the annuity 2015 two have been the most important contributions in our line of work of genetic neuropathies: the discovery of an axonal CMT form associated with a gene mutation EGR2 (Sevilla T et al), gene transcription myelination whose alteration so far only it was associated with demyelinating neuropathies, opening new questions for explaining the pathogenesis of these diseases; the other contribution, also in collaboration with the group of genetics CIB Principe Felipe (Drs Palau and Espinós) is the discovery that the gene Junctophilin-1 can act as a modulator of the clinical expression of CMT neuropathies caused by GDAP1 gene mutations (Pla-Martin eta al), resulting in a tremendous clinical variability has hitherto been inexplicable. Other activities that have been made in this area is the maintenance and operation of the database of Spanish patients CMT who is serving as the basis for an epidemiological study of prevalence in Valencia and to identify families and cases that do not have a genetic characterization and have given way to the discovery of two new genes whose publication is pending. We must also point out our cooperation in the development of a Spanish clinic guide amyloid polyneuropathy associated with mutations in the transthyretin.

In the field of motor neuron diseases, we have started a new line of research with the addition of Dr. Vazquez with a research contract Post-MIR-oriented clinical, genetic and neuroimaging of patients with ALS characterization.

In the field of the muscular dystrophies and myopathies the two most relevant publications of 2015 dealing show that autophagy and apoptosis are activated in myotonic dystrophy 1 (Barguiela A et al), with the mechanisms responsible for muscle atrophy that is one of the most debilitating signs of this disease; The study has an experimental side in a Drosophila model, made by the team of genetics prof. Artero (University of Valencia), and a clinical experimental side which has been performed in our laboratory using muscle biopsies from patients. The other work is a Spanish metacentric study including a large number of patients, of which our center has been a leader of inclusion, in which a screening for Pompe disease late by the enzymatic method of dry drop of blood is performed. The result has been a prevalence of such glucogenosis at 5 and 2% of patients with myopathy and waists or unexplained hiperCkemia maintained, respectively. Moreover, we continued with the development of clinical trials of advanced therapies in Duchenne Muscular Dystrophy, highlighting the closure of two mega clinical phase III trials using a drug that corrects the nonsense mutations (Atalureno) and another that acts by activating the NO by tadalafil. Finally note that we have participated in the development of a clinical guideline for monitoring patients with Pompe disease late.

Finally, in the field of autoimmune encephalopathies ataxias and whose activity leads in our group Dr. Bataller, highlights a multicenter study coordinated by Dr. Graus of H Clinic of Barcelona on neurological syndromes associated with GAD antibodies which are also the expression a paraneoplastic syndrome. This field should be noted in our Biobank availability of a serum containing large-sized samples of numerous valuable encephalopathies, autoimmune ataxias and neuromuscular diseases.

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- **Jordi Rosell** (Hospital Son Espases, Palma de Mallorca)
- **Isabel Tejada** (Hospital Cruces, Bilbao)

INHERITED METABOLIC MEDICINE RESEARCH PROGRAMME

- **Luis Aldámiz-Echevarría Azuara** (Hospital Cruces, Bilbao)
- **Mª Luz Couce** (Hospital Clínico de Santiago de Compostela, La Coruña)
- **Luis González Gutiérrez-Solana** (Hospital Infantil Niño Jesús, Madrid)
- **Eduardo López Laso** (Hospital Reina Sofía, Córdoba)
- **Guillem Pintos** (Hospital Germans Trías i Pujol, Barcelona)
- **Mireia del Toro** (Hospital Vall d´Hebrón, Barcelona)

ENDOCRINE MEDICINE RESEARCH PROGRAMME

- **Irene Halperin** (Hospital Clínic, Barcelona)
- **Mónica Marazuela** (Hospital La Princesa, Madrid)
- **Antonio Picó** (Hospital General de Alicante, Alicante)
- **Manuel Puig Domingo** (Hospital Germans Trías i Pujol)
- **Alfonso Soto** (Hospital Virgen del Rocío, Sevilla)

INHERITED CANCER, HAEMATOLOGICAL & DERMATOLOGICAL DISEASES RESEARCH PROGRAMME

- **Isabel Badell** (Hospital de la Santa Creu i Sant Pau, Barcelona)
- **Cristina Beléndez** (Hospital Gregorio Marañón, Madrid)
- **Albert Català** (Hospital San Joan de Déu, Barcelona)
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