



IFIR

Annual Report

2016

ciberer

Centro de Investigación Biomédica en Red
Enfermedades Raras

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Pablo Lapunzina, Scientific Director

Scientific Director's Presentation

CIBERER is celebrating the 10th anniversary of its creation in November 2006. The CIBER model is a vital pillar for this country's biomedical research. Having an identity as a centre is a major step forward with regard to the networks; having a management structure and the ability to apply our own scientific strategy is a key matter for undertaking cooperative research and its coordination.

CIBERER is the national benchmark network for research into rare diseases (RD) and because of our multidisciplinary nature, we obtain results in a large number of groups of rare pathologies. Our advantage is being the only state centre that is capable of connecting the generation of basic knowledge with its clinical application. Because of their complexity and diversity, RD require diversified and network research, the accumulation of all the new technologies available and specific knowledge in each pathology, in order to obtain the best research results. CIBERER is now under the obligation to give a response to the needs meant by being an excellence centre of this kind and to the challenges in the field of RD for the coming years, developing new treatments and improving access to the diagnosis of RD, in line with national and international policies.

The greatest step forward made in the diagnosis of RD over the last few years has been the incorporation of massive sequencing technology. This technology enables us to read millions of sequences of DNA at a hitherto unimaginable speed and at an increasingly low cost. This has enabled us to find the genes that cause a large number of RD. Its potential has enabled developing new applications and biological tests which are finding widespread application in the postnatal and prenatal diagnosis of genetic diseases. We should stress our Programme of Undiagnosed Rare Diseases, ENoD, whose aim is to contribute to a precise molecular diagnosis of clinical cases still unsolved after "all" the (suitable) protocols available in the Health System service portfolio have been applied.

CIBERER also continues to further therapeutic strategies and thus takes a direct part as promoter of orphan drugs. It is currently the sponsor of a total number of 6 medications classified as orphan drugs by the European Medicines Agency (EMA), 3 of which have also been designated as such by the American Agency (FDA). (3 are for gene therapy and 3 for repurposing drugs).

Lastly, CIBERER renewed the members of its Management Committee and its External Advisory Scientific Committee in 2016. We should stress that representatives of affected people have been included in the second of these bodies, which will unquestionably strengthen our structure and our commitment to patients. I would like to take this opportunity to thank all the members of the previous Management Committee for their great commitment to the centre and in particular thank Professor Francesc Palau, "our" Scientific Director for the last 10 years, for his commitment and work done for the CIBERER.



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Organisation

Organisational Structure

The CIBERER is one of the eight thematic areas in the Centro de Investigación Biomédica en Red (CIBER), a Spanish research consortium in the field of biomedical research with enormous scientific potential, under the Instituto de Salud Carlos III (ISCIII) – Ministry of the Economy and Competitiveness. In 2016 this consisted of 8 thematic areas, which were extended to 11 in 2017.

The CIBERER is made up of 62 research groups, belonging to institutions of different types: University Hospitals, Universities, Public Research Bodies, such as the Instituto de Salud Carlos III (ISCIII) itself, the Consejo Superior de Investigaciones Científicas (CSIC) and the Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas (CIEMAT), as well as the Research Centres of Spain's regional 'Autonomous Communities'. Each of these groups constitutes a CIBERER Unit.

The CIBERER has a large team of human resources consisting of over 700 people, including a substantial staff of its own researchers and members of groups as personnel attached to the CIBERER. This extensive team is made up of basic and clinical biomedical researchers, research technicians and management staff.

As a public consortium, the CIBERER is thus governed by a Governing Body and a Permanent Committee (its governing and management bodies) in which the institutions in the consortium take part. The organisational structure is made up of the Scientific Management, under Dr. Lapunzina, which along with the Management Committee coordinates the work done by the 7 Scientific Programmes into which CIBERER groups are split. The CIBER Technical Unit and the Scientific Management Team provide the administrative support required for the Institution to run.

Members of the Management Committee

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

Name	Post
Pablo Lapunzina	Scientific Director
Susan Webb	Scientific Assistant Director
Ángel Carracedo	Coordinator of the Genetic Medicine Programme
Rafael Artuch	Coordinator of the Inherited Metabolic Medicine Programme
Francesc Palau	Coordinator of the Mitochondrial and Neuromuscular Programme
Montserrat Milà	Coordinator of the Paediatric and Developmental Medicine Programme
Lluís Montoliu	Coordinator of the Sensorineural Pathology Programme
Susan Webb	Coordinator of the Endocrine Medicine Programme
Juan Antonio Bueren	Coordinator of the Inherited Cancer, Haematological and Dermatological Diseases Programme
Luis Pérez Jurado	Coordinator of the Training Programme
Manuel Sánchez	Manager

External Advisory Scientific Committee

The External Advisory Scientific Committee is a body providing scientific assessment and support, made up of relevant personalities in the field of health sciences who are well-known for their professional or scientific careers compatible with the objectives of the centre. This is the body which carries out the annual appraisal of the work done by CIBERER and its research groups.

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

Scientific Management

Name	Post
Ingrid Mendes	Attached to Scientific Director
Beatriz Gómez	Scientific Activity Manager
Juan Luque	Scientific Activity Manager
Andrés Medrano	Head of Training and Management Activity

Contact: <http://www.ciberer.es/en/about-us/contact>

Technical Unit

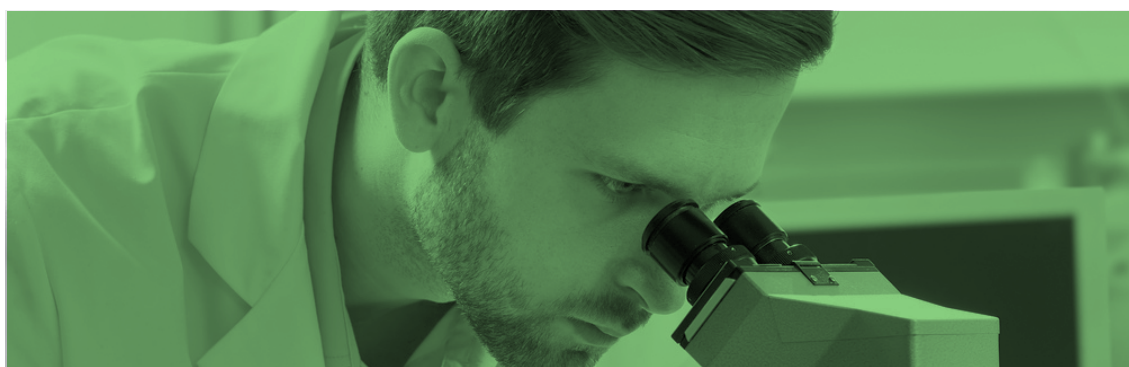
See list of personnel: <http://www.ciberer.es/en/about-us/structure/head-office>

Directory of Groups and Institutions

Group Leader	Institution	Centre	Centre Prov.
Antíñolo, Guillermo	Fund. Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla	Hospital Virgen del Rocío	Sevilla
Artuch Iriberrí, Rafael	Fundación para la Investigación y Docencia Sant Joan de Deu	Hospital Sant Joan de Déu	Barcelona
Ayuso, Carmen	Fundación Instituto de Investigación Sanitaria Fundación Jiménez Díaz	Instituto de Investigación Sanitaria. Fundación Jiménez Díaz	Madrid
Benítez, Javier	Fundación Centro Nacional de Investigaciones Oncológicas	Fundación Centro Nacional de Investigaciones Oncológicas	Madrid
Bermejo Sánchez, María Eva	Instituto de Salud Carlos III	Centro de Investigación de Anomalías Congénitas	Madrid
Bernal, Juan	Agencia Estatal Consejo Superior de Investigaciones Científicas	Instituto de Investigaciones Biomédicas Alberto Sols	Madrid
Botella Cubells, Luisa María	Agencia Estatal Consejo Superior de Investigaciones Científicas	Centro de Instituciones Biológicas	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 (CIEMAT)	Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas (CIEMAT)	Madrid
Cardellach López, Francesc	Hospital Clínico y Provincial de Barcelona	Hospital Clínico y Provincial de Barcelona	Barcelona
Carracedo, Ángel	Universidad de Santiago de Compostela	Facultad de Medicina	A Coruña

Group Leader	Institution	Centre	Centre Prov.
Carrascosa, Antonio	Fundación Hospital Universitario Vall d' Hebron - Institut de Recerca (VHIR)	Hospital Universitario Vall d' Hebron	Barcelona
Castaño González, Luis	Asociación Instituto de Investigación Sanitaria de Biocruces	Hospital Universitario Cruces	Vizcaya
Cuezva, José Manuel	Universidad Autónoma de Madrid	Centro de Biología Molecular Severo Ochoa	Madrid
Dalmau Obrador, Josep	Instituto de Investigaciones Biomédicas August Pi i Sunyer	Instituto de Investigaciones Biomédicas August Pi i Sunyer	Barcelona
Del Río Nechaevsky, Marcela	Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas (CIEMAT)	Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas (CIEMAT)	Madrid
Dopazo Blazquez, Joaquin	Fundación Centro de Investigación Príncipe Felipe	Fundación Centro de Investigación Príncipe Felipe	Valencia
Estévez Povedano, Raúl	Universidad de Barcelona	Facultad de Medicina	Barcelona
Fernández Piqueras, José	Universidad Autónoma de Madrid	Centro de Biología Molecular Severo Ochoa	Madrid
Fillat, Cristina	Instituto de Investigaciones Biomédicas August Pi i Sunyer	Instituto de Investigaciones Biomédicas August Pi i Sunyer	Barcelona
Gallano Petit, María Pía	Instituto de Investigación del Hospital de la Santa Creu i Sant Pau	Instituto de Investigación del Hospital de la Santa Creu i Sant Pau	Barcelona
Garesse, Rafael	Universidad Autónoma de Madrid	Universidad Autónoma de Madrid	Madrid
Giraldo Castellano, Pilar	Instituto Aragonés de Ciencias de la Salud	Hospital Miguel Servet	Zaragoza
González Manchón, Consuelo	Agencia Estatal Consejo Superior de Investigaciones Científicas	Centro de Investigaciones Biológicas	MADRID
Gratacos, Eduard	Hospital Clínico y Provincial de Barcelona	Instituto de Investigaciones Biomédicas August Pi i Sunyer	Barcelona
Grinberg, Daniel	Universidad de Barcelona	Facultad de Biología. Universidad de Barcelona	Barcelona
Illa Sendra, Isabel	Instituto de Investigación del Hospital de Santa Creu i Sant Pau	Instituto de Investigación del Hospital de Santa Creu i Sant Pau	Barcelona
Knecht, Erwin	Fundación Centro de Investigación Príncipe Felipe	Centro de Investigación Príncipe Felipe	Valencia
Lapunzina Badía, Pablo Daniel	Servicio Madrileño de Salud	Hospital La Paz	Madrid
López Trascasa, Margarita	Servicio Madrileño de Salud	Hospital La Paz	Madrid
Marfany Nadal, Gemma	Universidad de Barcelona	Departamento de Genética. Facultad de Biología	Barcelona
Martí Seves, Ramón	Fundación Hospital Universitario Vall d' Hebron - Institut de Recerca (VHIR)	Hospital Universitario Vall d' Hebron	Barcelona
Martín Casanueva, Miguel Ángel	Servicio Madrileño de Salud	Hospital Universitario 12 de Octubre	Madrid
Medina Torres, Miguel Ángel	Universidad de Málaga	Facultad de Ciencias Experimentales y de la Salud	Málaga
Milà, Montserrat	Hospital Clínico y Provincial de Barcelona	Hospital Clínico y Provincial de Barcelona	Barcelona
Millán Salvador, José María	Fundación para la Investigación del Hospital la Fe	Hospital Universitario La Fe	Valencia
Montoliu Jose, Lluís	Agencia Estatal Consejo Superior de Investigaciones Científicas	Centro Nacional de Biotecnología	Madrid
Montoya Villarroya, Julio	Universidad de Zaragoza	Facultad de Veterinaria	Zaragoza
Moreno Pelayo, Miguel Ángel	Servicio Madrileño de Salud	Hospital Ramón y Cajal	Madrid
Navas, Plácido	Universidad Pablo de Olavide	Centro Andaluz de Biología Molecular y Medicina Regenerativa	Sevilla
Nunes, Virginia	Fundación IDIBELL	Hospital Durán y Reynals	Barcelona

Group Leader	Institution	Centre	Centre Prov.
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 Déu	Barcelona
Pallardo Calatayud, Federico	Universidad de Valencia	Facultad de Medicina de Valencia	Valencia
Pérez González, María Belén	Universidad Autónoma de Madrid	Centro de Biología Molecular Severo Ochoa	Madrid
Pérez Jurado, Luis	Universidad Pompeu Fabra	Facultad de Ciencias Experimentales y de la Salud	Barcelona
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 Durán y Reynals	Barcelona
Ribes, Antonia	Hospital Clínico y Provincial de Barcelona	Instituto de Bioquímica Clínica	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
Ruiz Pérez, Víctor Luis	Agencia Estatal Consejo Superior de Investigaciones Científicas	Instituto de Investigaciones Biomédicas Alberto Sols	Madrid
Salido, Eduardo	Fundación Canaria de Investigación Sanitaria (FUNCANIS)	Hospital Universitario de Canarias	Santa Cruz de Tenerife
Sanz, Pascual	Agencia Estatal Consejo Superior de Investigaciones Científicas	Instituto de Biomedicina de Valencia	Valencia
Satrústegui Gil Delgado, Jorgina	Universidad Autónoma de Madrid	Centro de Biología Molecular Severo Ochoa	Madrid
Serratos, José	Fundación Instituto de Investigación Sanitaria Fundación Jiménez Díaz	Instituto de Investigación Sanitaria. Fundación Jiménez Díaz	Madrid
Surrallés, Jordi	Universidad Autónoma de Barcelona	Facultad de Biociencias	Barcelona
Varela Nieto, Isabel	Agencia Estatal Consejo Superior de Investigaciones Científicas	Instituto de Investigaciones Biomédicas Alberto Sols	Madrid
Vicente García, Vicente	Fundación para la Formación e Investigación Sanitarias de la Región de Murcia (FFIS)	Hospital José María Morales	Murcia
Vilchez Padilla, Juan Jesús	Fundación para la Investigación del Hospital la Fe	Hospital Universitario de La Fe	Valencia
Webb, Susan	Instituto de Investigación del Hospital de la Santa Creu i Sant Pau	Instituto de Investigación del Hospital de la Santa Creu i Sant Pau	Barcelona



Budget

INCOME				
ISCI III TRANSFER	GRANTS PROJECTS	SERVICES RENDERED	OTHER INCOME	TOTAL
4.905.860,00	368.533,19	693.631,01	58.849,51	6.026.873,71

EXPENDITURE				
Project	Inventoriable	Provisions and other activity expenses	Personnel	TOTAL
Scientific Management, Scientific Secretariat, Communication	0,00	178.234,14	39.678,90	217.913,04
Groups	0,00	13.367,16	3.334.989,76	3.348.356,99
Training	0,00	23.576,06	61.961,25	85.537,32
Programmes	861,52	63.999,75	104.685,43	169.546,71
Platforms	1.097,39	88.588,31	214.070,58	303.756,37
Transfer- translation	0,00	83.229,67	0,00	83.229,67
Intramural projects	24.744,61	369.490,57	1.579,82	395.815,00
External projects	18.469,39	662.917,92	311.604,93	992.992,25
TOTAL	45.172,91	1.483.403,58	4.068.570,67	5.597.147,35

Personnel

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

	MEN	WOMEN	Total general
Diploma holders	-	1	1
Doctors	17	55	72
Graduates	11	33	44
Technical staff	1	20	21
TOTAL	29	109	138

Significant Activities

Projects

NATIONAL

Financing Agency: Instituto de Salud Carlos III

Study of the pathways 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 diagnosis in patients.

Identification and characterisation of the molecular mechanisms involved in Sexual Differentiation Alterations (SDA) by applying massive sequencing techniques and aCGH.

Muscular atrophy in ageing and inherited neurometabolic pathologies: an approach to diagnosis and intervention. Part 2: Approaches to therapies based on the use of iPSCs.

The Landscape of Axonal Biology and Membranes Associated with Mitochondria in Neurogenetic Disease.

COHORTE project: Characterisation and contribution to genetic diagnosis in a cohort of patients with intellectual disability, autism and/or epilepsy.

Financing Agency: Ministry of the Economy and Competitiveness

Regulation of mitochondrial DNA in human pathology: importance of homeostasis of the dNTPs pool.

Platform for support for internationalisation of the CIBER_BBN/ER/RES.

Others

Fundación Todos Somos Raros.

PIK3CA Overgrowth Syndromes: Diagnosis, Phenotype and Clinical Guidelines.

INTERNATIONAL PROJECTS EU

European network and registry for homocystinurias and methylation defects (E-HOD).

Promoting Implementation of Recommendations on Policy, Information and Data for Rare Diseases (RD-ACTION).

Novel therapeutic perspectives for mitochondrial DNA depletion and deletion syndrome due to defective dNTP homeostasis: The specific case of TK2 deficiency.

Project financed by AFM- TELETHON private foundation.

Transfer

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

- Continuous contact with our researchers to monitor their results and train them in managing innovation.

A Technology Transfer Session was arranged for this purpose on 29 and 30 November 2016 as part of the 30th anniversary of ISCIII. Experts in different areas attending this event shared their knowledge on industrial property, company creation, licencing processes, venture capital, grants for internationalisation, etc..

- Protection of the results of research and management of cooperation with other agents, as is accredited by the application for patents and signing licence contracts, amongst other agreements. In 2016 eleven new patent applications and a registration of software were submitted at the CIBER. Seven inventions are also in the patentability study stage and one in the drafting stage, and these are expected to be submitted in early 2017. Eight licence contracts have also been signed and in 2016 different negotiations that are expected to end successfully in the first quarter of 2017 were also got under way. Three new patents were applied for by the RD in 2016 and two licence contracts were signed with companies, a further two being in the negotiation process. Two of the licences signed and one being negotiated specifically belong to agreements with the company Rocket Pharmaceuticals. These are associated with an RCA (Research Cooperation Agreement, and an MRA (Master Research Agreement) for financing several preclinical and clinical projects. The whole action is valued at over 10 million euros.
- Presentation of the results of research and technological capacities of our groups in technology transfer sessions. Amongst many other measures and only as an example of this, CIBER had a stand at BIOSPAIN 2016 (28-30 September, Bilbao) which was visited by members of institutions.
- Support for creating technology-based companies resulting from CIBER groups. Through its Rare Disease area, the CIBER has since 2014 been participating in Epidisease (<http://www.epidisease.com/es/>), which it has continued to support over these years, with the following specific actions in 2016:
 - Presentation to the “Mind the Gap” Programme of the Fundación Botín (in the final stage, pending their decision).
 - “Neotec” project applied for at CDTI (pending resolution).
 - Finalist in the FIPSE-MIT- IDEA2 Global programme.
 - Selected by DCN to be joined by several investors (presentation of the project in February 2017 at the Scientific Committee).
- Other activities involving innovation, public-private cooperation and industrial and intellectual property.

Dissemination

In 2016 the CIBER’S Communication Department carried out different dissemination and diffusion measures in order to raise awareness about the Centre, as well as to spread knowledge about the research work done by the groups in its eight thematic areas.

The main highlights of the Communication work done by CIBERER in 2016 are as follows:

- **The CIBERER in the media:** 67 CIBER press releases were issued in this period, 6 of these from the CIBERER and 2 in cooperation between several CIBER areas.

Date	Thematic area	Title
19/01/2016	CIBERER	La primera Jornada Nacional de la Enfermedad de Menkes acogerá la presentación de un proyecto de investigación sobre este trastorno ultra-raro
08/02/2016	CIBERER	Expertos internacionales explican sus avances en terapia génica para tratar enfermedades hematológicas
25/02/2016	CIBERER	La Región de Murcia cuenta con un grupo de referencia en enfermedades raras hematológicas que se ha incorporado al CIBERER
03/03/2016	CIBERER	Un grupo multidisciplinar de autores lanza el primer libro en español sobre la ética en la investigación de las enfermedades raras
07/03/2016	CIBERER	Investigadores del CIBERER utilizan la tecnología de edición genética CRISPR-Cas9 en diversos proyectos sobre enfermedades raras

Date	Thematic area	Title
05/04/2016	CIBERER	Un vector de terapia génica para tratar la deficiencia en piruvato quinasa es declarado medicamento huérfano en Estados Unidos
17/05/2016	CIBERER	Un vector lentiviral para tratar la anemia de Fanconi es declarado medicamento huérfano en Estados Unidos
15/06/2016	CIBERER	Temsirolimus, designado medicamento huérfano para el tratamiento de la adrenoleucodistrofia
14/07/2016	CIBER/CIBERER	Patentado un nuevo kit para el diagnóstico y seguimiento de la Escoliosis Idiopática del Adolescente
21/07/2016	CIBERER	FEDER y CIBERER intensifican su colaboración en la investigación de las enfermedades raras
31/10/2016	CIBERER	Una investigación pionera contribuirá a mejorar el conocimiento de las enfermedades minoritarias mitocondriales
02/11/2016	CIBERER	Ubiquinol, designado medicamento huérfano para el tratamiento de la deficiencia primaria de coenzima Q10
16/11/2016	VARIOS CIBER	El CIBER acerca su investigación a la sociedad de la mano de la improvisación teatral en #ImproCiencia

1121 appearances in the media were also recorded:

2016	News items	Audience
CIBERER	1.121	134.431.600

- **CIBER Newsletter**

This year 5 CIBER newsletters were published and circulated, including relevant content about the CIBERER and other thematic areas. Digital newsletters were sent to nearly 4000 subscribers.

<http://www.ciberisciii.es/en/press/newsletter>

- **CIBERER web site**

In 2016 the CIBERER web page published 161 news items and 129 events on the agenda.

Statistics on visits to the web page 2016							
	No. of visits to page	Sessions*	Users	Pages / session	Average duration of session	% rebound**	% new sessions
CIBERER	161.248	60.158	34.141	2,68	2:19	57,86	55,05

(*) Sessions: a session is a set of interactions taking place on this website in a certain period. For example, a single session may involve several pages being viewed.

(**) Rebound: the rebound percentage is the percentage of sessions of a single page, i.e. the sessions in which the user has left the site on the entry page without interacting with this.

- **Social Networks**

Main indicators of the presence of CIBERER in Twitter:

	Followers		Updates		Klout (Influence)	
	January	December	January	December	January	December
CIBERER	3078	3610	3883	5049	55	54

- **CIBERER Annual Report**

The CIBERER Communication area coordinated the content of the CIBERER Report 2015 in Spanish/ English in cooperation with the CIBERER, drawing up and circulating 2 reports in interactive (flipbook) and PDF format. These reports have been distributed over the web page and through the Twitter account: <http://www.ciberisciii.es/en/press/annual-report>

- **CIBER #ImproCiencia Science Week**

The #ImproCiencia dissemination event, held on 16 November in Madrid, combined science and theatre improvisation in an entertaining exposition of the biomedical research work done by the CIBER in its eight thematic areas. The CIBERER presented the clinical trial for application to gene therapy in Fanconi Anaemia, coordinated by Dr. Juan Antonio Bueren.

Scientific Production

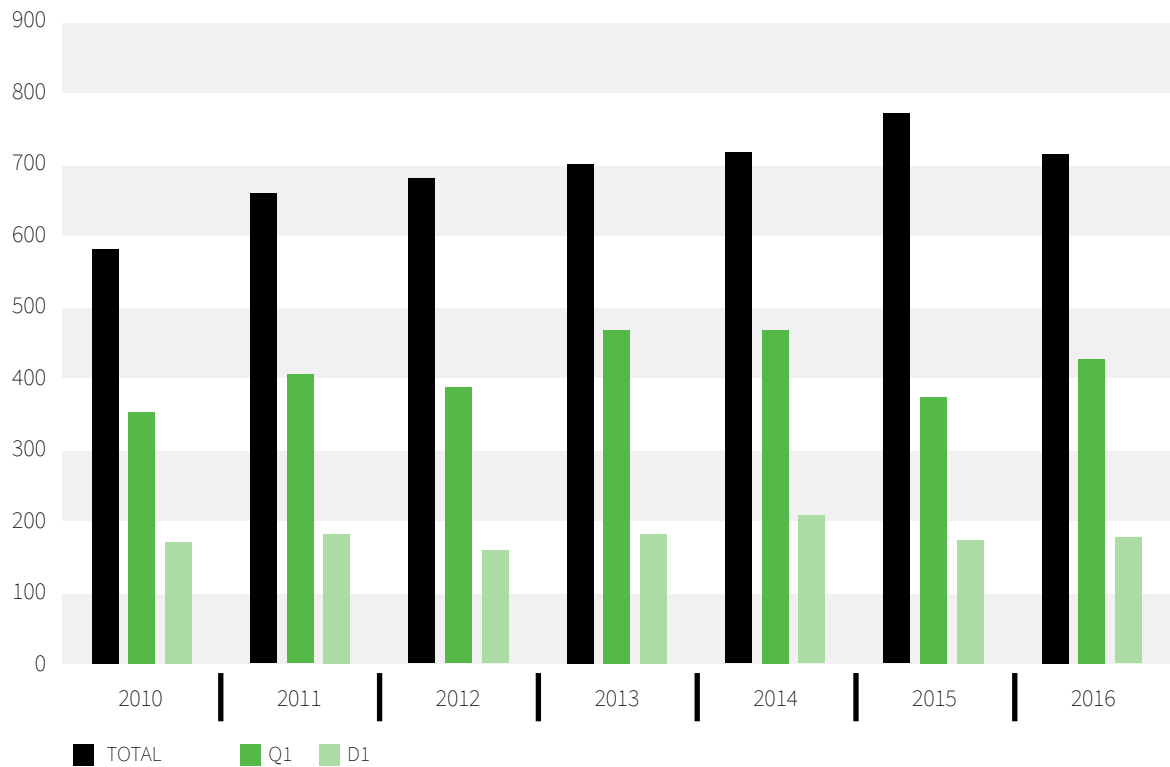
The graphic evolution of CIBERER publications can be seen from the following tables, in which the data for 2010 to 2016 is analysed. Details are also given of publications per group for this year, as well as interCIBER and intraCIBER cooperation work.

Publications

Publications per year							
CIBERER	2010	2011	2012	2013	2014	2015	2016
Total No.	584	662	683	704	720	775	718
Q1	354	407	389	470	470	375	429
D1	171	182	159	182	208	174	177



EVOLUTION OF CIBERER PUBLICATIONS 2010-2016



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

Publication	Impact factor
Latorre-Pellicer A., Moreno-Loshuertos R., Lechuga-Vieco A.V., Sanchez-Cabo F., Torroja C., Acin-Perez R. et al. Mitochondrial and nuclear DNA matching shapes metabolism and healthy ageing. <i>Nature</i> . 2016;535(7613):561-565.	38,891
Dunning A.M., Michailidou K., Kuchenbaecker K.B., Thompson D., French J.D., Beesley J. et al. Breast cancer risk variants at 6q25 display different phenotype associations and regulate ESR1, RMND1 and CCDC170. <i>Nature Genetics</i> . 2016;48(4):374-38.	38,138
Zhou W., Machiela M.J., Freedman N.D., Rothman N., Malats N., Dagnall C. et al. Mosaic loss of chromosome Y is associated with common variation near TCL1A. <i>Nature Genetics</i> . 2016;48(5):563-568.	37,369
Kenna K.P., Van Doormaal P.T.C., Dekker A.M., Ticozzi N., Kenna B.J., Diekstra F.P. et al. NEK1 variants confer susceptibility to amyotrophic lateral sclerosis. <i>Nature Genetics</i> . 2016;48(9):1037-1042.	34,661
Van Rheenen W., Shatunov A., Dekker A.M., McLaughlin R.L., Diekstra F.P., Pulit S.L. et al. Genome-wide association analyses identify new risk variants and the genetic architecture of amyotrophic lateral sclerosis. <i>Nature Genetics</i> . 2016;48(9):1043-1048.	34,090
de la Torre R., de Sola S., Hernandez G., Farre M., Pujol J., Rodriguez J. et al. Safety and efficacy of cognitive training plus epigallocatechin-3-gallate in young adults with Down's syndrome (TESDAD): A double-blind, randomised, placebo-controlled, phase 2 trial. <i>The Lancet Neurology</i> . 2016;15(8):801-810.	34,090

Publication	Impact factor
Scialo F., Sriram A., Fernandez-Ayala D., Gubina N., Lohmus M., Nelson G. et al. Mitochondrial ROS Produced via Reverse Electron Transport Extend Animal Lifespan. Cell Metabolism. 2016;23(4):725-734.	27,184
Mitchell S.J., Madrigal-Matute J., Scheibye-Knudsen M., Fang E., Aon M., Gonzalez-Reyes J.A. et al. Effects of Sex, Strain, and Energy Intake on Hallmarks of Aging in Mice. Cell Metabolism. 2016;23(6):1093-1112.	22,003
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Publications per group 2016

Group leader	Publications total	Q 1	D 1
U701 Martí Seves, Ramón	13	9	6
U702 Antiñolo, Guillermo	12	5	1
U703 Artuch Iriberrí, Rafael	37	14	6
U704 Ayuso, Carmen	20	13	1
U705 Gallano Petit, María Pía	6	2	1
U706 Benítez, Javier	47	35	13
U707 Botella Cubells, Luisa María	8	5	1
U708 Bernal, Juan	4	2	1
U709 Bovolenta, Paola	4	1	1
U710 Bueren, Juan Antonio	15	10	3
U711 Carracedo, Ángel	14	7	3
U712 Carrascosa, Antonio	5	3	-
U713 Cuezva, José Manuel	8	5	-
U714 Del Río Nechaevsky, Marcela	16	11	3
U715 Dopazo Blázquez, Joaquín	24	19	11
U716 Fillat, Cristina	7	6	2
U717 Garesse, Rafael	15	13	2
U718 Marfany Nadal, Gemma	4	2	-
U719 Gratacos, Eduard	48	36	18
U720 Grinberg, Daniel	14	10	3
U721 Knecht, Erwin	4	2	-
U722 Cardellach López, Francesc	14	8	5
U723 Martín Casanueva, Miguel Ángel	32	17	7
U724 Bermejo Sánchez, María Eva	5	2	-
U725A Castaño González, Luis	17	6	1
U726 Milà, Montserrat	55	27	17
U727 Montoya Villarroya, Julio	10	7	2

Group leader		Publications total	Q 1	D 1
U728	Moreno Pelayo, Miguel Ángel	1	1	1
U729	Navas, Plácido	26	14	7
U730	Nunes, Virginia	1	1	1
U731	Palacín, Manuel	6	4	3
U732	Palau Martínez, Francesc	6	4	2
U733	Pallardo Calatayud, Federico	3	2	-
U734	González Manchón, Consuelo	5	4	1
U735	Pérez Jurado, Luis	17	11	7
U737	Ribes, Antonia	20	8	2
U738	Rodríguez de Córdoba, Santiago	9	3	1
U739	Rubio Zamora, Vicente	7	7	3
U740	Salido, Eduardo	10	8	3
U741	Medina Torres, Miguel Ángel	8	5	1
U742	Sanz, Pascual	7	5	-
U743	Satrústegui Gil Delgado, Jorgina	8	7	2
U744	Serratos, José	8	4	2
U745	Surallés, Jordi	1	-	-
U746	Pérez González, María Belén	12	5	3
U747	Webb, Susan	15	5	-
U749	Fernández Piqueras, José	5	5	3
U750	Estévez Povedano, Raúl	2	1	-
U752	Giraldo Castellano, Pilar	20	8	4
U753	Lapunzina Badia, Pablo Daniel	25	8	2
U754	López Trascasa, Margarita	14	-	-
U755	Millán Salvador, José María	13	8	-
U756	Montoliu Jose, Lluís	4	3	3
U757	Perona Abellón, Rosario	5	4	-
U758	Posada de la Paz, Manuel	20	17	1
U759	Pujol Onofre, Aurora	8	5	5
U760	Ruiz Pérez, Víctor Luis	2	1	-
U761	Varela Nieto, Isabel	14	6	3
U762	Illa Sendra, Isabel	15	9	5
U763	Vilchez Padilla, Juan Jesús	16	8	6
U764	Dalmau Obrador, Josep	20	15	13
U765	Vicente García, Vicente	20	15	4

COLLABORATIVE WORK

Collaborative Work	2015	2016
IntraCIBER publications	88	87
InterCIBER publications	87	99



3

Scientific Programmes

Genetic Medicine

Coordinator: **Ángel Carracedo**

The Genetic Medicine Programme continues to lead the process for implementation of NGS and other omic applications for diagnostic practice at hospitals.

The most strategic action in this respect was the cooperative CIBERER project, led by Dr. Dopazo's group (U715), to develop a pilot system for storage and management of genomic data (exomes or large panels). Seven hospitals from four of Spain's regional "Autonomous Communities" took part in the project: La Paz, Fundación Jiménez Díaz, Ramón y Cajal, CBM (Madrid), Virgen del Rocío (Seville), Hospital del Mar (Barcelona), HU La Fe (Valencia). This and other initiatives continue to enable us to discover new genes involved in RD and as examples of this there are such discoveries as:

- In the field of inherited thrombophilia, we should stress the identification of the molecular basis of a very relevant proportion of cases with antithrombin deficiency without mutations in the encoding gene (SERPINC1) by Dr. Vicente's Group (U765).
- Apart from this, the first catalogue of the healthy Spanish population's genetic variation was published. This work was jointly performed by Dr. Dopazo's group (U715) and that of Dr. Antiñolo (U702). Dopazo et al, Mol Biol Evol. 2016 Jan 13.

A lot of work was done this year in the lines of research into therapies.

Dr. Sanz's group (U742) along with that of Dr. Serratosa (U744) have treated malin-deficient mice models of Lafora disease in order to find out whether they improved their neurological symptoms. The results indicate the possible utility of these compounds to slow down the development of the disease (Berthier et al., 2016, Mol. Neurobiol, 53: 1296-1309). As a result of these findings the designation of orphan drug was obtained from the European Medicines Agency (EMA) for metformin in treatment of Lafora disease.

In 2016, the EMA also accepted the denomination of tamsulosin as orphan drug for treatment of X-adrenoleukodystrophy, based on a publication and a European patent (EP14382353.2) of the CIBERER. A cooperative work between Dr. Knetch's group U721 and Dr. Pujol's group (U759).

Lastly a dossier has been sent to the EMA for designation of propranolol as an orphan drug for Von Hippel-Lindau, which was approved in January 2017. A protocol for a clinical trial for HHT was also drawn up, and presented to the AEMPs for a clinical trial at the Ramón y Cajal hospital with an antiangiogenic component.

As far as training is concerned we should stress the organisation of the second edition of the course on "Complement and renal pathology" at the Hospital Universitario La Paz, coordinated by CIBERER unit U754 (Dr. Margarita López), which was financed by the CIBERER and at which a total number of 140 professionals from the national healthcare field took part.



Inherited Metabolic Medicine

Coordinator: **Rafael Artuch**

In 2016 the 12 groups and 6 linked clinical groups in the Programme obtained relevant scientific results and got under way a large number of strategic actions to tackle RD with the basic feature of alteration of the homeostasis caused by mutations in genes connected with intermediary metabolism. We should stress some milestones and activities:

PARTICIPATION OF GROUPS IN THE FOLLOWING EUROPEAN REFERENCE NETWORKS:

- Rare Neuromuscular Diseases (EURO-NMD): Mireia del Toro, from the Hospital Vall d' Hebron-GCV 9.
- Rare Hereditary Metabolic Disorders (METAB-ERN): M^a Luz Couce from the Hospital de Santiago de Compostela-GCV 5, Luis Aldámiz Echevarría from the Hospital de Cruces-GCV 10, Mireia del Toro from the Hospital Vall d' Hebron-GCV 9 and Rafael Artuch from the Hospital San Joan de Déu-U703.
- Rare Neurological Diseases (ERN-RND): Rafael Artuch from the Hospital San Joan de Deu-U703 and Mireia del Toro. Hospital Vall d' Hebron-GCV 9.

ACHIEVEMENTS IN THERAPEUTIC AND CLINICAL ASPECTS OF THESE DISEASES:

- Designation of 2 orphan medicines by the European Medicines Agency (EMA):
 - Temsirolimus, as an orphan drug for treatment of adrenoleukodystrophy. The studies on the possible application of this orphan medicine for treatment of X-adrenoleukodystrophy, which were until now limited to animal models of the disease, have been developed by U759 (Dr. Pujol) and U721 (Dr. Knecht).
 - Ubiquinol as an orphan drug for treatment of primary coenzyme Q10 deficiency. The studies on the possible application of this orphan drug for treatment of primary coenzyme Q10 deficiency were directed by U729 (Dr. Navas), with the cooperation of U703 (Dr. Artruch).
- Therapeutic strategies in different diseases studied at the Pdl such as hyperoxaluria, MLC, or the first proof of concept of a possible treatment for glycosylation disorder PMM2- CDG.

MEETINGS, EVENTS OF INTEREST:

- About 150 persons attended the 6th edition of the Jornada del Grupo de Enfermedades Minoritarias del Adulto at the Hospital Clínic in May, co-organised by group U737 (Dr. Ribes).
- 12 Congreso del Grupo Europeo de Enfermedad de Gaucher (EWGGD) held in Saragossa in June with the attendance of 278 researchers, healthcare professionals and patients of the European Gaucher Alliance, from 42 countries, and at which over 80 pieces of work were presented. Several CIBERER researchers from different groups attended. Arranged by the U752 (Dr. Giraldo).
- Specialist and families took part in the first Jornada de la Asociación de familias con deficiencia de GLUT-1. Different CIBERER researchers took part, from Units 703 (Dr. Artuch), 729 (Dr. Navas), 746 (Dr. González), GCV6 (Dr. Pérez González) and GCV5 (Dr. Couce).

CLOSE COOPERATION WITH PATIENTS

- Donation of 32,400 euros thanks to the Asociación Síndrome del Opitz C for research into identification of the genes causing this pathology, done by U720 (Dr. Grinberg).
- Micro-sponsorship campaign collecting 20,000 euros promoted by affected families assigned to research into this disease, x-linked adrenoleukodystrophy (X-ALD) carried out by U759 (Dr. Pujol).

Mitochondrial and Neuromuscular Medicine

Coordinator: **Francesc Palau**

The 12 groups in the Programme have obtained some important results in the scientific field, in dissemination and cooperation with patients' associations, both on their own and in cooperation with other CIBERER groups.

In the scientific domain we should stress the progress made with regard to tackling diseases with mitochondria as their physiopathological target and which affect the individual's bioenergy balance, through a study of the genome-mitochondrial communication and of physiopathology and disease mechanisms in cell models and iPSC, on the promotion of translational research and of therapeutic research from the development of animal models to the preclinical stage, biomarkers, especially in neuromuscular pathologies.

Some of the accomplishments in the therapeutic field to be emphasised could be the designation as orphan drug by the European Medicines Agency (EMA) of Ubiquinol for treatment of primary Q10 enzyme deficiency. We should also stress the search for therapeutic strategies for mitochondrial diseases with nucleosides or the approaches with gene therapy.

From the translation standpoint we could highlight the implication of groups in the Pdl in the following Reference European networks: Rare Neuromuscular Diseases, Rare Hereditary Metabolic Disorders and Rare Neurological Diseases.

The groups in the Pdl are also doing a lot of work in Registries: Registro Español de Enfermedades Neuromusculares NMD-ES, Registro de Enfermedades Mitocondriales (in cooperation with AEPMI- Asociación de Enfermos de Patologías Mitocondriales and the Fundación Ana Carolina Díaz Mahou) and McArdle Registry (EUROMAC).

As regards the transversal contribution to the CIBERER as a whole we should mention the coordination of the energy metabolism phenotyping platform PROTEOmAB.

The groups in the programme have also cooperated with patients' associations, such as AEPMI, whose president spoke at the Programme's Annual Meeting in representation of the Association and ASEM (Federación Española de Enfermedades Neuromusculares), with which a cooperation agreement was signed this year.

We should also stress the cooperation agreement signed by the CIBERER, the Obra Social "la Caixa" and the Fundación Mencía to carry out a preclinical research project on a mitochondrial disease led by the U701 (Dr. Martí).

The groups in the Programme arranged different meetings or events of interest, some of the more noteworthy of these being as follows:

- *4ª Reunión Científica Anual del Programa de Investigación*, held on 12 December at the Hospital 12 de Octubre in Madrid.
- *I Jornada Nacional de la Enfermedad de Menkes*, organised by the CIBERER, the Hospital Sant Joan de Déu de Barcelona and the Asociación Amigos de Nono, on 29 and 30 January in Barcelona.
- *II Jornadas de Investigación Traslacional en Enfermedades Raras: Últimos Avances en Enfermedades Neuromusculares*, arranged by the Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC) along with the Asociación de Enfermedades Neuromusculares de Córdoba (ASENCO) in cooperation with the CIBERER, on 11 and 12 November in Cordova.
- *Jornada TREAT CMT sobre investigación traslacional, medicina experimental y terapéutica de la enfermedad de Charcot-Marie-Tooth (CMT)*, on 23 November at the ISCIII.

Paediatric and Developmental Medicine

Coordinator: **Montserrat Milà**

We will now sum up the main activities and results connected with the objectives defined in the Action Plan 2016:

- **Furthering the development of genomic diagnosis tools for the diseases of interest in the programme:**

The most outstanding point as regards transversal work was getting under way the transversal project: “Characterisation and contribution to genetic diagnosis in a cohort of patients with intellectual disability, autism and/or epilepsy”. Three full member groups took part in this project –U726 (Dr. Milà), U735 (Dr. Jurado) and U753 (Dr. Lapunzina)– from this Pdl, along with a group from the Genetic Medicine Pdl (U715, Dr. Dopazo) and the four clinical groups associated with the Paediatric and Developmental Medicine Programme (GCV01, 02, 03 and 04). An online tool has been developed for collecting the clinical information on the cases and this compilation has started with over 70 cases included and intending to reach at least 200.

Apart from this there have been a large number of individual publications of the groups in this approach, described in greater detail when we go into the work done by each group.

- **Developing tools for epidemiological research into rare diseases.**

We should highlight the Registro Nacional de Enfermedades Raras 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 that of the Telephone Information Services SITTE and SITE (both concerning risks for prenatal development), led by Dr. Bermejo (U724).

- **Contributing to training healthcare professionals and the general public.**

A Dysmorphology Session was held at the Hospital de la Paz (U753, Dr. Lapunzina) for doctors; a session on XGFRIL premutation in the framework of the AEGH (GCV04 and U726, Dr. Milà); a session for patients and families affected by Williams Syndrome (U735, Dr. Jurado) and the Annual Meeting and Refresher Course on Congenital Defects, intended for doctors all over Spain (U724, Dr. Bermejo).

Sensorineural Pathology

Coordinator: **Lluís Montoliu**

In 2016 the 7 groups forming the Programme obtained some significant results in the scientific, dissemination fields and in cooperation with patients’ associations, both independently and in cooperation with other CIBERER groups.

On the scientific level we should underline the development of new cell and animal models of RD, intended above all for leadership in preclinical research into sensorineural RD, as well as the development of genomic diagnosis tools and the discovery of new genes.

As regards cooperation we could highlight the fact that at the ACCI call in 2016 all the groups in the programme have at least one project granted and 2 groups are even involved in 3 proposals.

Special mention should be given to the fact that 6 groups from the Programme are taking part in an intramural project: “Phenotyping and analysis of the new animal and cell models of sensorineural diseases generated by means of CRISPR-Cas9 technology”, which consolidates the continuity of the intramural project previously granted and reinforces the strategic positioning and the cooperation found between the groups.

The Programme held its 6th Annual Scientific Meeting on 1 December at the Hospital Ramón y Cajal in Madrid, as well as the one that took place as part of the CIBERER'S annual general meeting.

The groups in the programme organised different **scientific events** with CIBERER financing, among which we could stress the International Symposium "Plataformas Internacionales de investigación biomédica y su valor en el estudio de las enfermedades raras" (Fundación Ramón Areces, 3 and 4 November, Madrid "Avanzando hacia las nueva terapias: Retos actuales de los pacientes" along with the Asociación ES Retina Asturias (Universitat de Barcelona, 8 October) and "V Jornada de Lengua de Signos Española aplicada a la Consulta de Genética", (Hospital Clínico San Carlos, 11 March). There were also other scientific events with our own financing in which it was clearly visible that these belonged to the CIBERER.

As regards the **training field**, several CIBERER courses have been arranged by groups in the programme, one on the phenotyping of animals (organised by the SEFALER platform, whose coordination is handled by unit U761, Dr. Varela, and which U756, Dr. Montoliu, also forms part of), another on models alternative to mice by unit U728 (Dr. Moreno) and another on tools for gene edition by unit U756, Dr. Montoliu (along with U710, Dr. Bueren and VIVEbioTECH).

The groups in the programme have also cooperated with patients' associations, this year stressing the cooperation with such organisations 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).

The Programme has also supported the production of a short documentary "¿Lo ves?" which also received financing from the ONCE and was sponsored by the Fundación Divina Pastora

and the Asociación de Ayuda a personas con Albinismo (ALBA). Written and directed by Patty Bonet, who has the genetic condition of albinism, it displays the visual limitations which its author has to face in everyday situations.

Endocrine Medicine

Coordinator: **Susan Webb**

In 2016 the Endocrine Medicine programme carried out the main phase of the project entitled: "*Silent corticotroph adenomas: Do these constitute a subtype of the non-functioning pituitary adenoma with a more aggressive clinical behaviour?*", financed by the CIBERER to combine the Linked Clinical Groups in the Programme with the full-member groups led by Dr. Webb and Dr. Castaño. This project enabled the joint study of the collections of clinical cases of the groups which were disperse until now, in order to review the classification of this type of adenomas.

Quite apart from the major contribution made by the Linked Clinical Groups one should bear in mind that this Research Programme is made up of only three full-member research groups and a fourth associated group.

The Endocrine Medicine Programme worked with the CIBER'S own funds on dissemination of the research and contact with the patient by taking different measures in 2016: organising the Session on "*Las hormonas tiroideas y su música. Hormonas tiroideas y desarrollo del sistema nervioso central Patologías asociadas: de lo común a lo raro*" led by Dr. Morte (U708), in which an innovative perspective on the causes and physiology of these disorders was disclosed. Action was also taken on the adaptation and translation of online content in the form of informative videos intended for persons affected by adrenal failure by attached researcher I. Crespo (U747).

As regards significant scientific progress, we could mention the description of epigenetic bases of the Cushing syndrome, new tools for its assessment and clinical handling; also for acromegaly, with the publication of a study concerning the quality of life in cooperation with the affected persons, along with others with regard to treatments for Mct8 deficiency.

Inherited Cancer, Haematological and Dermatological Diseases

Coordinator: **Juan Antonio Bueren**

A number of relevant results were accomplished in 2016 by the groups in this programme.

In the aspect of new therapies we could highlight the start of the first clinical test on patients with Fanconi anaemia subtype A by correction with lentiviral vectors of mobilised peripheral blood stem cells and obtaining the designation of two orphan drugs in both Europe and the U.S.A. for treatment of erythrocyte pyruvate kinase deficiency and of leukocyte adhesion deficiency type –I led by Dr. Bueren’s group (U710).

Some important steps have also been taken for developing therapeutic strategies by gene edition for Fanconi anaemia, erythrocyte pyruvate kinase deficiency and recessive dystrophic Epidermolysis Bullosa (RDEB), the latter led by Dr. Marcela del Río’s team (U714).

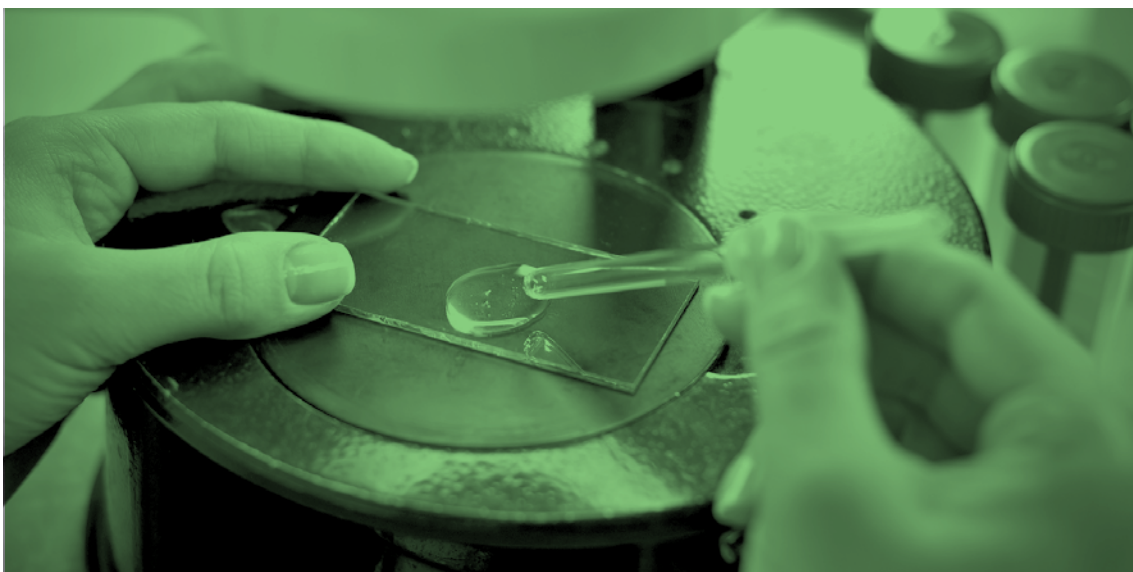
Dr. Perona’s group (U757) has established an animal model in which idiopathic pulmonary fibrosis has successfully been reverted in preventive and curative protocols, with treatment of nanoparticles charged with GSE4.

In the area more specifically covering biomarkers and diagnosis we should stress the work done by Dr. Fernández-Piqueras’ group (U749) on the demonstration of the functional effect of different mutations in the JAK2 gene contributing to the development of T-cell lymphoblastic lymphoma, indicating the advisability of using NGS and new treatment protocols (Roncero et al. Leukaemia. 2016).

The group headed by Dr. Surrallés (U745) has identified two new components of the Fanconi/BRCA pathway whose mutations cause Fanconi anaemia and a new Fanconi-like syndrome of tumour predisposition. The group led by Dr. Benítez (U706) has identified new variants in the OGG1 gene which affect the risk of cancer in persons carrying mutations in

BRCA1 and BRCA2 (Benitez-Buelga et al Oncotarget. 2016 May 3;7(18)).

Dr. Pallardó’s group developed the patent “*Mass spectrometry-based methods for the detection of circulating histones H3 and H2B in plasma from sepsis or septic shock (SS) patients (European patent EP 16 382 509.4)*”, as a new diagnosis and prognosis method.



Training Programme

The CIBERER Training Programme's main work in 2016 took the form of three overall approaches:

- Courses: Organisation and calls for grants for attendance.
- Mobility grants.
- Predoctoral grants 2016.

Courses: Organisation and calls for attendance grants

- CIBERER *Course on Genomic Data Analysis*, 28 to 30 September 2016, at the Centro de Investigación Príncipe Felipe, Valencia: a CIBERER course arranged by the BIER platform (U715). This gave training in methods for filtration of genetic variants and interpretation of their meaning as regards potential causes of pathology for 20 researchers, 11 of whom obtained grants for CIBERER training for travel and accommodation.
- Introduction to Research into Genetically Modified Animals (4th Edition) 23, 24 and 25 November 2016. Veterinary Faculty, UCM-Hospital Clínico Veterinario UCM, Madrid. Organised by CIBERER'S SEFALER platform and coordinated by Doctors Varela and Murillo (U761). Practical training was given with different models, mainly murine, in basic knowledge for characterisation of physiopathology of RD and assessment of therapies in models of disease.
- 2nd Edition of the Course on functional tests in models alternative to the mouse in Biomedical Research. 25 to 28 October 2016. Hospital Ramón y Cajal-IRYCIS, Madrid. The second edition of this course arranged by the CIBERER from U728 group of 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 becoming increasingly necessary to learn how to handle alternative models for this process.

Calls for aid for attending courses and training activities organised by CIBERER groups:

- “*Auditory Neuroscience. Summer School 2016*” UAM, Madrid, 6 to 8 July 2016. 2 grants awarded
- “*ESO, CNIO and NRCO Conference on Familial Cancer*”, Madrid, 19 and 20 May 2016. 3 grants awarded.

Mobility grants

In 2016 CIBERER continued with its mobility programme to further its researchers' training and cooperation between the groups in the network. More specifically, 12 mobility grants were awarded over the year, 8 of these intramural, two to CIBERSAM groups and two international mobility grants.

Predoctoral grants 2016

CIBERER predoctoral grants are a specific tool for attracting new graduates to CIBERER groups. After a year without any in 2015, in 2016 a new call was launched with 10 beneficiaries granted from a total number of 18 valid applications. This year, apart from keeping up the high minimum entry mark, a further requisite added was for them to have the master completed during the year.

Knowledge Application Programme

Translation

Quite unquestionably one of the CIBERER'S achievements in translation in 2016 was the work done in promoting orphan drugs.

In 2016 CIBERER obtained as sponsor the designation of 4 orphan drugs by the European Medicines Agency (EMA) and 3 by the American agency (FDA). This means a total number of 6 orphan drugs by the EMA, 3 of which are also classified as such by the FDA.

Three of these drugs are for gene therapy and the other three involve repurposing, i.e. drugs which are used for other pathologies which are being appraised for use in some rare disease.

The 6 orphan drugs promoted by the CIBERER are:

- Lentiviral vector containing the gene of Fanconi A anaemia (FANCA) for treatment of this disease. This is led by Juan A. Bueren U710 (designated by the EMA and the FDA).
- Lentiviral vector containing the liver and erythroid pyruvate kinase gene (PKLR) for treatment of pyruvate kinase deficiency. Led by José Carlos Segovia U710 (designated by the EMA and the FDA).
- Haematopoietic stem cells modified with a lentiviral vector containing the CD18 (ITGB2) gene for treating leukocyte adhesion deficiency type 1. Led by Juan A. Bueren U710 (EMA and FDA).
- Temsirolimus for adrenoleukodystrophy. Led by Aurora Pujol U759 and Erwin Knecht U721 (designated by the EMA).
- Ubiquinol for the primary coenzyme Q10 deficiency. Led by Plácido Navas U720 and Rafael Artuch U703 (designated by the EMA).
- Metformin for Lafora disease. Led by Pascual Sanz U742 and José Serratosa U733 (designated by the EMA).

A Protocol Assistance has also been requested for the Lentiviral vector containing liver and erythroid pyruvate kinase gene (PKLR) for treatment of pyruvate kinase deficiency by José Carlos Segovia U710.

After completing the designation process, a lengthy process of seeking financing sources and undertaking clinical trials begins, until marketing authorisation is obtained by regulatory agencies. It is vital to support researchers during this process in order to valorise their projects.

Transfer

3 patents were applied for in 2016, 2 of these European and 1 American:

- Mass spectrometry-based methods for the detection of circulating histones H3 and H2b in plasma from sepsis or Septic Shock (SS) patients by Federico Pallardó's group U733 (EP 16 382 509).
- New therapeutic uses of TUDCA for adrenoleukodystrophy, carried out by Aurora Pujol's group - U759 (EP16382602).
- "Gene therapy for patients with Fanconi anemia" carried out by Juan Antonio Bueren's group - U710 (EP15382545 5).

2 licence agreements for CIBER technology were signed in 2016. The first in gene therapy with lentivirus for pyruvate kinase deficiency and Fanconi anaemia and the second in leukocyte adhesion deficiency type-1 syndrome.

Programme for Cooperative and Complementary Intramural Action

Cooperative and complementary intramural actions (ACCI) are competitive collaborative intramural projects financed with the CIBERER's own funds. These are intended to further cooperative research into RD and thus be able to increase knowledge, technical capacity, diagnostic development or therapeutic progress. These are the ones that started in 2016:

Title	IP	Coord. Unit	Participating Units	Programme
New animal models of sensorineural rare diseases generated by CRISPR-Cas9 technology.	Montoliu Jose, Lluís	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 Disorders: Validation of a Model of Clinical Functional Biology [Neuro Landscape].	Palau Francesc, Martínez	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 anaemia.	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 Myasthenic Syndromes: a model of translational research in rare diseases.	Gallano Petit, Pia	705	711, 732, GCV01, GCV02, GCV03, GCV04	Mitochondrial and Neuromuscular Medicine

Internationalisation Programme

Last 11 May 2015 the CIBER Platform for Support for Internationalisation was set up. The Platform for Support for Internationalisation (PAI) emerged 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), with the aim of reinforcing and coordinating the efforts made to promote its researchers' participation in European Programmes and of creating a common structure for promoting internationalisation and leadership of research and innovation in these three thematic areas.

In 2016 the platform concentrated its efforts on two main areas: encouraging participation of all the CIBER groups in international projects and improving the visibility of the CIBER on an international scale.

As regards promoting the participation of CIBER groups in international projects and improving the quality of the proposals presented, the PAI held 4 specific sessions for dissemination of the advantages of internationalisation and gave 3 specific courses on drafting and managing European Projects intended for researchers and managers in the CIBER environment: "Relevant aspects in presenting and justifying European proposals in the CIBER environment" (April 2016, with 70 persons attending) and "Drafting successful collaborative proposals in the H2020 setting" (Madrid edition, June 2016, with 40 attending and Barcelona Edition, September 2016, with 44 attending) which were a great success with the participants.

In order to raise the quality of the proposals and improve returns the PAI got under way a Service for editing proposals which carried out the following activities: 1) Solving doubts and positioning proposals (contrasting the scientific idea with that of the call and issuing a grounded report with recommendations on how to adapt the idea, need for strategic partners, etc...) in which the PAI has received over 27 consultations in this respect; 2) Editing proposals (PAI has edited over 20 proposals); 3) Evaluation of results (in previous proposals or those not sent through the PAI), giving a grounded criticism of the result and proposing where there is room for improvement (12 requests in the period); 3) Seeking strategic partners (6 requests in this period, plus 6 external partners who got in touch with CIBER to propose joint cooperation).

Thanks to this work, CIBER put forward 36 new proposals in 2016, 4 new projects being granted. Interest was expressed in the presentation of 10 new proposals. In this field it should be stressed that CIBER has received 5 new contacts from research groups or companies in order to establish agreements for joint presentation of proposals in the H2020 environment, and 2 of these contacts have now materialised in the real presentation of two H2020 proposals.

In the field of the CIBER'S international visibility, the CIBER has done some intensive work by attending over 18 events (including informative sessions, infodays and events for seeking partners). The platform also placed special emphasis on establishing a smooth relationship with different national representatives and national points of contact, by means of specific meetings, acting as a liaison on the institutional level. In order to improve international presence, specific meetings were held with NCPs and with the head of the H2020 programme for the purpose of establishing easier relations. Thanks to this improvement in communication the CIBER was invited to the Forum for strategic definition of the Wp2018-2020 and took an active part in defining the 2017 work programmes and IMI calls as scientific experts. It was also decided to include postulating CIBER for participation in joint actions JA-01, 02, 03, 04, 05-2016 in which the possibility of taking part in measures as associated centres was put forward. We should point out that the campaign for recruiting experts promoted by the PAI has led to the CIBER including over 15 new profiles in the Cordis database and it has also promoted updating the existing ones. As a result of this work CIBERER researcher Carmen Ayuso was selected to form part of the group of experts in Ethics and Scientific Integrity, in the framework of the Science with and for Society of the 2020 Horizon (SwafS-ethics) programme, while researchers Mercedes Serrano and Isabel Varela, recently created profiles, were contacted to take part as assessors.

Scientific-Social Dissemination Programme

CIBERER constantly presents society with the work done by its research groups, its projects, the diseases which are being worked on and the new knowledge generated, through its scientific-social dissemination programme.

CIBERER has worked hard to make its web page (www.ciberer.es) an effective instrument. This is accredited by the Scopus ranking, which considers it one of the most important scientific web pages. More than 160 news items and 120 records on the centre's work and of interest in the field of RD have been published through this portal. In 2016 its new version in English also came out. CIBERER has furthermore published 11 press releases over the year, with a large number of appearances in the media.

We should also stress the issue of CIBERER's newsletter, a very effective publication which 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 2016, knowledge of the different parties involved was improved and cooperation has been enhanced by means of the 10 scientific and 5 social newsletters issued

Along with the Fundación Genzyme, CIBERER sponsored the book entitled "*Ética en la investigación de las enfermedades raras*" (Ethics in research into rare diseases) directed by Doctors Carmen Ayuso (U704), Rafael Dal-Ré (Universidad Autónoma de Madrid) and Francesc Palau (U732), which is intended to generate reflection and provide information to come to terms with the ethical concerns currently arising through research into rare diseases.

Lastly, CIBERER organised several scientific encounters for outreach to those affected over the year. Here are some examples of these events:

- In February CIBERER celebrated the World Rare Disease day as a network, by joining the FEDER campaign "Creando REDES de esperanza".
- The 9th Annual Meeting of the CIBERER, at which over 240 members of the thematic area presented the progress made in translational research into RD in Castelldefels in March.
- The CIBERER co-organised 2 international symposia with the Fundación Ramón Areces: one Symposium on international platforms of biomedical research and their value in the study of rare diseases and others on rare skin diseases, both in Madrid in November and October.



5

Platforms

CIBERER BIOBANK

Objective 1: To supply the Biobank with biological samples

The total number of samples of RD collected at the end of 2016 was over 600, of more than 70 different pathologies (<http://www.ciberer-biobank.es>).

Objective 2: To further the Plan for Strategic Alliances and Dissemination

COLLABORATION:

- Member of the Red Valenciana de Biobancos (RVB) since 2010, taking an active part in the different work groups.
- Cooperation Agreement with the Biobanco de Investigación Biomédica y Salud Pública de FISABIO.
- Framework agreement with the National DNA Bank.
- Biobank cooperating with the Red Nacional de Biobancos (RNB) of the ISCIII since 2010, and a member of the Haematic Derivatives Work Group.
- Agreement with the Fundación FEDER for contracting technical staff for supporting the development of the technique for generating human iPS.
- Cooperation agreement between the Institut d'Investigació Biomèdica de Bellvitge, the Universidade de Vigo and the CIBERER for implementing the REWBA Registry.
- Contract with ABF Pharmaceutical Services GmbH for taking part in a clinical trial promoted by Boehringer Ingelheim Pharma GmbH & Co.
- Cooperation with the RNB and the Universidad Católica de Valencia in the University Master course on Biobanks.

MEASURES FOR DISSEMINATION OF THE WORK DONE BY THE BIOBANK

I Congreso de Investigación Traslacional de ER de la Comunidad Valenciana (oral presentation, OP), 9th Annual CIBERER Meeting (OP); OP of the biobank for medicine students, FISABIO; VII Congreso de la Red Nacional de Biobancos; Simposium Internacional de Plataformas de ER de la Fundación Ramón Areces-CIBERER.

Objective 3: To generate added value for CIBERER groups

SERVICES RENDERED

- Preparing and offering new services: keeping samples, establishing cell cultures and generation of lymphoblastoid lines, techniques for quality control of the samples.
- Work has continued to be done in the development of other services (culture of myoblasts, technique for immortalising fibroblasts at the request of several CIBERER groups and generation of iPS cells).
- In 2016 there were 12 assignments and 21 services provided for processing and safekeeping samples, establishment of cell cultures, cell immortalisation and advice for CIBERER groups.

Objective 4: To foster and support 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.
- Participation, along with the U730 CIBERER group, in an international project for studying the *Wolfram Syndrome*, assuming responsibility for management of samples and immortalisation of lymphoblastoid lines.
- *Spanish Exomes Project, SPANEX*. A project financed with CIBERER funds in which it takes part along with 9 CIBERER groups by giving logistics support for collecting and storing samples, as well as advice on ethical/legal aspects.
- *New diagnostic approaches for hereditary syndromes with bone medulla failure for treatment with innovative therapies (SHIMO)* PI: Julián Sevilla (GCV19). Groups taking part: U710 (Dr. Bueren), U745 (Dr. Surallés); U753 (Dr. Lapunzina), U757 (Dr. Perona); GCV16-19.
- *Induced pluripotent stem cells for modelling Charcot-Marie-Tooth disease*. PI: Dr. Torres (U. Valencia). IP: Dr. Torres (U. Valencia).

ORPHANET

Collecting and updating information

At the end of 2016, the total number of Spanish activities reflected in the Orphanet database was as shown below:

Total Spanish activities in 2016	
Expert centres	303
Patients associations	216
Diagnostic tests	8,520
Clinical trials	981
Research projects	480
Registries / Biobanks	73

Translations

A total number of 260 abstracts of diseases and 644 names of new RD were translated into Spanish along with the modification of 2777 names of RD.

In 2016 the translation of the “Disability datasheets” started, describing the functional consequences of RD and their handling, and 4 of these datasheets were translated.

A guide intended for emergency service personnel was also translated.

Furthering the active participation of the Scientific Committee (CC)

In 2016 the members of the CC were involved in different tasks such as the review of summaries of diseases and of clinical guides produced by the Orphanet, the validation of external guides to be included in the database and the directories of expert centres, as well as in replies to patients’ enquiries.

Furthering the communication and dissemination plan

- Contributions to the Orphanews Europe newsletter.
- Maintenance of the Orphanet España web site:
The Orphanet-España web site, which published roughly 64 news items in 2016. In cooperation with patients associations, publicised events on RD and gave access to documents in Spanish on these diseases compiled in the Orphanet in “The Orphanet-Spain Encyclopaedia” section.
In cooperation with the CIBERER communication department, the news items published further its visibility through its Twitter service. The most prominent ones are published on the CIBERER web site and in its institutional newsletter.
- Meeting with the Scientific Committee of Orphanet-España, at the Hospital 12 de Octubre in Madrid.
- Seminar: *Information portal of reference in RD and orphan drugs*, as part of the “Rare Diseases” course in the Medicine Degree at the Universitat de València.
- Informative desk on the Orphanet at the “I Congreso de Investigación Traslacional en ER de la Comunidad Valenciana” held at the Universitat de València.
- Presentation: *Orphanet as a platform for raising awareness on the clinical work done by the CIBERER and its Linked Clinical Groups*, 9th Annual Meeting of the CIBERER in Castelldefels, Barcelona.

- Informative tools on RD (Orphanet, Eurodis...), in the course on “Introduction to rare diseases: research and clinical care” organised by the Escuela Valenciana de Estudios de la Salud, Valencia.
- Presentation of the Orphanet portal at the Hospital Sant Joan de Déu, Barcelona.

Furthering the resources shared by CIBERER-ORPHANET, working to ensure that the relationship between these two institutions represents added value for their respective projects

- Cooperation with the Service for Patient Care.
- Reviewing the list of diseases assigned to the projects included in the MAPER.
- Cooperation with the different Pdl of the CIBERER in updating the CIBERER activities which have been included in the Orphanet.

BIER

Last year 2016, 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.

The platform led the intramural project entitled: “Development of a platform for new generation sequencing diagnosis” which will be continued in the new project to be started in 2017: “Development of a platform for prioritising the variants of disease using data”. Both are linked developments which will generate useful applications for filtering and construing results of massive sequencing.

BiER took in mobility visits from 3 researchers from other groups in the network, with the training and cooperation implications meant by these.

It gave technological-bioinformatic advice and support services in 26 projects from 16 CIBERER groups. The analysis strategies developed were applied to data from high-performance technologies, tackling transcriptomic and genomic studies (exomes and gene panels). We worked on developing new transcriptomic analysis methods in the setting of signalling pathways and analysis of functional enrichment of microRNAs.

We took an active part in inter-group cooperation, with the reception of 11 researchers and performed the training activity “CIBERER Course on Genomic Data Analysis” organised from 28 to 30 September 2016 at the Centro de Investigación Príncipe Felipe, Valencia, which was attended by 28 pupils, 17 from CIBERER groups and 11 external.

The results of these bioinformatic developments and analyses generated 11 collaborative scientific publications.

The impact of the different online applications of the BIER web site was monitored:

The BiERapp (<http://bierapp.babelomics.org>) is a tool for analysing genomic or exomic sequences, either individual or of families or cases/controls. It had 5967 usage sessions (over double the number in 2015).

The TEAM (<http://team.babelomics.org>), a specific software for designing gene panels for NGS diagnosis which reports on diagnostic findings and optionally also unexpected findings and variants of uncertain effect. 980 usage sessions.

In 2016 two new hiPathia applications were got under way (March 2016, with 1969 usage sessions that year) and PathAct (March 2016, with 1321 usage sessions).

MAPER

In 2016 information continued to be compiled for the MAPER database, which is the interactive map drawn up by the CIBERER with information on the biomedical research projects which are under way 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 Rare Disease Strategy Committee 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 2016 is as follows:

- 647 biomedical research projects included. 96 of these included in 2016.
- 62 financing agencies participate in financing research into RD.
- 480 Principal Investigators included in the database.
- 513 RD included in the registry.
- 15 Spanish 'autonomous communities' or regions (29 provinces) where these projects are active.
- Presentation of results of the Congreso de Investigación Traslacional en Enfermedades Raras de la Comunidad Valenciana. Valencia 24-25 February 2016.



The screenshot shows the MAPER website interface. At the top, there is a navigation menu with links: Inicio, ¿Qué es MAPER?, Enfermedades Raras, Información incluida, Contacto, and Enlaces. Below the menu, there are two search boxes: 'Buscador por Enfermedad' and 'Buscador Geográfico'. The 'Buscador por Enfermedad' is active, showing a search for 'Síndrome de X frágil'. Below the search box, there is a table with the following data:

Nombre Enfermedad	Nº Orphanet	Nº Proyectos
Síndrome de X frágil	908	3

Below the table, there are filters for 'Sin filtro', 'Provincias', and 'C. Autónomas'. At the bottom, there is a map of Spain with several green triangle markers indicating the locations of research projects.



SEFALer

The “Service for Laboratory Animals Phenotyping” came about as a result of cooperation with the Consejo Superior de Investigaciones Científicas (CSIC) and is open to participation by other public-private institutions.

This service has the following objectives: I) Functional and histological phenotyping of animal models of human diseases; II) The archive of genetically modified mice; III) Continued training; IV) Specialised and expert advice in phenotyping; and V) Scientific dissemination and disclosure.

- 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. Over 15 publications have been issued as a result of this work as well as participation in research projects, stressing the COST-BM1402 MouseAGE action. The groups in the SEFALer have also participated in 3 ACCIs during the year.
- Archiving and revitalisation of mutants in the Spanish node of EMMA/Infrafrontier (www.infrafrontier.eu).
- Organising the 7th SEFALer training course “Introduction to research on genetically modified animals” in cooperation with the Colegio de Veterinarios de Madrid and with the participation of CIBERER researchers. This course is accredited by Madrid Community’s Continued Training for Healthcare Professions Commission (3.1 credits). The education resources generated are available online for pupils on the course and teaching staff.
- Sefaler took part in scientific dissemination activities (Researchers’ Night, Science Week, Brain Awareness Week...) and in sessions with patients associations (FIAPAS, ALBA, etc.).

The following achievements of SEFALer units are worthy of mention:

- I) Organising and participating in the 7th Edition of SEFALer Courses, at the Auditory Neuroscience Summer School and at the Symposium Ramón Areces “International Platforms for biomedical research: A focus on rare diseases”; II) Participation in projects (FP7-AFHELO, FP7-TARGEAR and CDTI) for preclinical assessment of new medications and development of cochlear implants for treatment of hearing loss.
- I) Giving services for pathological anatomy and phenotyping of the renal function. Cooperation with the F1 for histological diagnosis of cochlea samples; II) Speaker at the 7th Edition of SEFALer Courses.
- I) Development of behavioural phenotyping techniques with predictive value for translational studies and on latest generation videoanalysis techniques; II) Development of a system for analysis and display of Behavioural Big Data). III) Speaker at the 7th Edition of SEFALer Courses.
- I) Implementation of new protocols for the study of platelet function in flow conditions.
- I) Assessment of the locomotor phenotype and of (immunohistochemical) axonal degeneration in the model of X- linked adrenoleukodystrophy (doble knockout mice *Abcd1* and *Abcd2 Abcd1-/-Abcd2-/-*) 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 achieved a fivefold increase in 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. III) Speaker at the 7th Edition of SEFALer Courses.

PROTEOmAb

PROTEOmAb provides a service for quantitative analysis of energy metabolism proteins and oxidative stress in biological samples in a simple and repeatable manner, using high-affinity and high-specificity monoclonal antibodies (mAbs) developed by the service itself. This service is provided through the Centro de Biología Molecular Severo Ochoa.

The most noteworthy achievements of 2016 involve the following activities:

Identification of new diagnostic biomarkers and progression of pathology in biopsies of patients affected by rare diseases.

- Peripheral neuropathies: In the framework of the TREAT-CMT project and in cooperation with U732 (Dr. Palau) and U763 (Dr. Vilchez) it has been identified in skin biopsies of patients with Charcot-Marie-Tooth (CMT) 1A that proteins of the OXPHOS system and of the antioxidant system provide new early biomarkers of the progression of the disease. We have also developed a non-oriented and high-performance metabolomic approach which has enabled identifying non-invasive plasma biomarkers which are correlated with the stages in the progression of the disease and which can thus facilitate diagnosis and prognosis of patients with Charcot-Marie-Tooth 1A.
- Inflammatory myopathies: in cooperation with group U722 (Dr. Cardellach) new biomarkers for differential diagnosis of DM and sIBM have been identified in biopsies of patients affected by Polymyositis (PM), Dermatomyositis (DM) and Sporadic Inclusion Body Myositis (sIBM). We should stress PKM2 and IF1 as potential markers of development of cancer in DM.
- Pathologies with effect on the OXPHOS system: in cooperation with units U723 (Dr. Martín) and U701 (Dr. Martí) we are proceeding to analyse the markers of metabolism in biopsies of muscle of patients with progressive external ophthalmoplegia (PEO) with single or multiple deletion of the mitochondrial DNA (mtDNA). A cohort of patients with mitochondrial encephalomyopathy with lactic acidosis (MELAS) is also being studied, with healthy individuals to identify markers of differential diagnosis of these diseases using the reverse phase protein array platform (ProteomAb). The project is in the implementation phase.

Phenotyping of animal models of rare diseases.

- Phenotyping of the model of Propionic Acidemia (2015-2016): In cooperation with group U746 (Dr. Pérez) an analysis has been made of the metabolic phenotype of different tissues of hypomorphic model of mouse *Pcca*^{-/(A138T)} of Propionic Acidemia disease at different ages. The analysis of the experimental model has enabled identifying alterations in the expression of specific proteins of energy metabolism of the tissue. The metabolic changes identified are maintained in each tissue regardless of the age, except for the brain, whose alterations proved to be less pronounced in older mice. The study led to the following publication:

In vivo evidence of mitochondrial dysfunction and altered redox homeostasis in a genetic mouse model of propionic acidemia: Implications for the pathophysiology of this disorder. L. Gallego-Villar, A. Rivera-Barahona, C. Cuevas-Martín, A. Guenzel, B. Pérez, M.A. Barry, M.P. Murphy, A. Logan, A. Gonzalez-Quintana, M.A. Martín, S. Medina, A. Gil-Izquierdo, J.M. Cuezva, E. Richard, L.R. Desviat. *Free Radical Biology and Medicine*, 2016 Jul;96:1-12.

- Metabolic phenotyping of Mouse Embryonic Fibroblasts. In cooperation with Dr. José M Torres' group of the Universitat de València an analysis was made of the metabolic phenotype of mouse embryonic fibroblasts (MEFs), embryonic stem cells (ESCs) and of induced pluripotent stem cells (iPSCs) during reprogramming induced by different cell reprogramming factors.



6


Research
Groups




LEAD RESEARCHER

Antiñolo, Guillermo

 Fund. Pública Andaluza para la
Gestión de la Investigación en
Salud de Sevilla
Hospital Virgen del Rocío
Avda. Manuel Siurot, s/n
41013 Sevilla

 (+34) 671 563 132

 guillermo.antinolo.sspa@
juntadeandalucia.es

 [Group website](#)

PROGRAMMES

Genetic Medicine



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

- DOPAZO J., AMADOZ A., BLEDA M., GARCIA-ALONSO L., ALEMAN A., GARCIA-GARCIA F. ET AL. 267 Spanish Exomes Reveal Population-Specific Differences in Disease-Related Genetic Variation. *Molecular Biology and Evolution*. 2016;33(5):1205-1218.
- ENGUIX-RIEGO M.V., TORROGLOSA A., FERNANDEZ R.M., MOYA-JIMENEZ M.J., DE AGUSTIN J.C., ANTINOLO G. ET AL. Identification of different mechanisms leading to PAX6 down-regulation as potential events contributing to the onset of Hirschsprung disease. *Scientific Reports*. 2016;6.
- BRAVO-GIL N., MENDEZ-VIDAL C., ROMERO-PEREZ L., GONZALEZ-DEL POZO M., RODRIGUEZ-DE LA RUA E., DOPAZO J. ET AL. Improving the management of Inherited Retinal Dystrophies by targeted sequencing of a population-specific gene panel. *Scientific Reports*. 2016;6.
- TANG CS, GUI H, KAPOOR A, KIM JH, LUZÓN-TORO B, PELET A ET AL. Trans-ethnic meta-analysis of genome-wide association studies for Hirschsprung disease. *Human molecular genetics*. 2016.
- MANCIKOVA V, MONTERO-CONDE C, PERALES-PATON J, FERNANDEZ A, SANTACANA M, JODKOWSKA K ET AL. Multilayer OMIC Data in Medullary Thyroid Carcinoma Identifies the STAT3 Pathway as a Potential Therapeutic Target in RET M918T Tumors. *Clinical cancer research: an official journal of the American Association for Cancer Research*. 2016.

Highlights

The group has received funding from external agencies in national projects (ISCIII: PI13/01560 and the Intralud project PI11/02923), and autonomic projects (Junta de Andalucía: PI-0105–2011, PI-0445-2013 and projects of excellence, CTS-7447 and CTS-1664).

Several results of these projects during 2016 are worth mentioning:


- Implementation of a NGS panel of 68 retinal dystrophies genes in the Spanish population. These results have contributed to develop a personalized medicine tool comprising bioinformatics and the automatic generation of diagnostic report that links with the electronic health record.
- Generation of a catalogue of genetic variability in the Spanish population through exome sequencing of 267 healthy, control individuals. This study constitutes a valuable tool for the identification of genes associated with rare diseases.
- A study of the mechanisms involved in the reduced expression of PAX6, previously observed by our group in a cohort of Hirschsprung (HSCR) patients, has led to the identification of a highly repetitive region in its promoter that could alter the binding of EP300 and, consequently, the signaling pathways involved in the etiology of HSCR.
- GWAS studies of 507 cases HSCR and 1191 controls, led to the identification of three common susceptibility variants in RET, SEMA3 and NRG1 loci in European and Asian populations. Two variants of low frequency were detected, including SEMA3 rs80227144 (Europe-specific), and RET rs9282834 (Asia-specific), that in association with the enhancer of the intron 1 of RET, significantly increase the risk to develop HSCR.
- Analysis of the DNA methylation profile of more than 27,000 CpG islands in 48 cases of medullary thyroid cancer, a rare disease of quite unknown etiology, led us to conclude that STAT3 can be a therapeutic target for the treatment of tumors with RET M918T.

In the context of cooperative activity, the group has published five articles, two of them within the collaboration with the International Consortium of Hirschsprung disease, two other with the CIBERER Unit U715 and finally, one with a CIBERDEM group.



LEAD RESEARCHER

Artuch Iriberry, Rafael

 **Fundación para la Investigación y Docencia Sant Joan de Déu**
Hospital Sant Joan de Déu
C/ Santa Rosa, 39-57
08950 Esplugues de Llobregat

 (+34) 932 806 169

 artuch@hsjdbcn.org

 [Group website](#)

PROGRAMMES

Inherited Metabolic Medicine
Mitochondrial and Neuromuscular Medicine



GROUP MEMBERS

Staff members: Molero Luis, Marta | Montero Sánchez, Raquel

Contratados a cargo de proyecto: Pias Peleteiro, Leticia

Associated members: Armstrong Morón, Judith | Campistol Plana, Jaume | Fons Estupiña, María del Carmen | García Cazorla, María Ángeles | Jiménez Mallebrera, Cecilia | Jou Muñoz, Cristina | Martorell Sampol, Loreto | Nascimento Osorio, Andrés | Ormazábal Herrero, Aída | Pérez Dueñas, Belén | Serrano Gimaré, Mercedes

Main lines of research

Sus líneas de investigación consolidadas son:

- 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, Turkey and other countries.
- Muscular dystrophies in childhood.
- Congenital disorders of glycosylation.
- Movement disorders in childhood.

Most relevant scientific articles

- YUBERO D., BRANDI N., ORMAZABAL A., GARCIA-CAZORLA A., PEREZ-DUENAS B., CAMPISTOL J. ET AL. Targeted next generation sequencing in patients with inborn errors of metabolism. PLoS ONE. 2016;11(5).
- ORTIGOZA-ESCOBAR J.D., MOLERO-LUIS M., ARIAS A., OYARZABAL A., DARIN N., SERRANO M. ET AL. Free-thiamine is a potential biomarker of Thiamine transporter-2 deficiency: A treatable cause of Leigh syndrome. Brain. 2016;139(1):31-38.
- CAMPISTOL J., DIEZ-JUAN M., CALLEJON L., FERNANDEZ-DE MIGUEL A., CASADO M., GARCIA CAZORLA A. ET AL. Inborn error metabolic screening in individuals with nonsyndromic autism spectrum disorders. Developmental Medicine and Child Neurology. 2016.
- YUBERO D, ADIN A, MONTERO R, JOU C, JIMÉNEZ-MALLEBRERA C, GARCÍA-CAZORLA A ET AL. A statistical algorithm showing coenzyme Q10 and citrate synthase as biomarkers for mitochondrial respiratory chain enzyme activities. Scientific reports. 2016;6(1):15.
- MONTERO R., YUBERO D., VILLARROYA J., HENARES D., JOU C., RODRIGUEZ M.A. ET AL. GDF-15 is elevated in children with mitochondrial diseases and is induced by mitochondrial dysfunction. PLoS ONE. 2016;11(2).

Highlights

We have consolidated our research lines by the funding of different research projects by public or private organisms, such as 2 projects about neurotransmitters and vitamin defects in neuropediatric patients funded by the ISCIII. As more relevant research results, we have described 2 new biomarkers for the diagnosis of mitochondria disorders: GDF-15 and thiamine.

Due to our intensive clinical activity, we got the designation as CSUR for inborn errors of metabolism, for movement disorders and for neuromuscular diseases. These designations opened us the possibility of participations in different European reference networks (metabERN) related with the above-mentioned topics.


We have also participated in the development of 3 international clinical guidelines about inborn errors of metabolism and about aromatic amino acid decarboxylase deficiency, both of the published in international journals during 2016-2017 period.


Our lab has experimented a deep transformation during 2016, thanks to a relevant funding that was got this year. We have purchased an UPLC/MS-MS platform which will give us the possibility to improve our capacities about metabolomic studies. Moreover, the medical genetics laboratory, headed by Dr. Palau, will move close to our Laboratory, creating a new department of medical and biochemical genetics, with the main objective of giving a rapid response to the biological questions raised in the investigation of rare disease patients in the NGS era (this laboratory has 2 NGS systems). Finally, the hystopathological department will support all this activity since they also got a confocal microscopy system to confirm the pathogenicity of mutations, and this laboratory is also allocated in the same area.




LEAD RESEARCHER

Ayuso, Carmen

 Instituto de Investigación Sanitaria Fund. Jiménez Díaz
Instituto de Investigación Sanitaria - Fund. Jiménez Díaz
Avda. Reyes Católicos, 2
28040 Madrid

 (+34) 91 550 48 72 / 73

 cayuso@fjd.es

 [Group website](#)

PROGRAMMES

**Sensorineural Pathology
Genetic Medicine**



GROUP MEMBERS

Staff members: Gómez Sánchez, Clara Isabel | Zurita Muñoz, Olga

Associated members: Ávila Fernández, Almudena | Blanco Kelly, Fiona | Bustamante Aragonés, Ana | Cardero Merlo, Rocío de la Libertad | Corton Pérez, Marta | Díaz Recasens, Joaquín | Fernández Moya, Jose María | Gallego Merlo, Jesús | García Sandoval, Blanca | Giménez Pardo, Ascensión | Infantes Barbero, Fernando | Lorda Sánchez, Isabel | Martín Mérida, Inmaculada | Pérez Carro, Raquel | Plaza Arranz, Francisco Javier | Ramos Corrales, Carmen | Riveiro Álvarez, Rosa | Rodríguez del Alba Freiria, Marta | Sanchez Jimeno, Carolina | Sánchez Navarro, Iker | Trujillo Tierras, 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, cardiomyopathy and malformations.
- 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

- PEREZ-CARRO R., CORTON M., SANCHEZ-NAVARRO I., ZURITA O., SANCHEZ-BOLIVAR N., SANCHEZ-ALCUDIA R. ET AL. Panel-based NGS Reveals Novel Pathogenic Mutations in Autosomal Recessive Retinitis Pigmentosa. *Scientific Reports*. 2016;6.
- BLANCO-KELLY F., GARCIA HOYOS M., LOPEZ MARTINEZ M.A., LOPEZ-MOLINA M.I., RIVEIRO-ALVAREZ R., FERNANDEZ-SAN JOSE P. ET AL. Dominant retinitis pigmentosa, p.Gly56Arg mutation in NR2E3: Phenotype in a large cohort of 24 cases. *PLoS ONE*. 2016;11(2).
- SANCHEZ-ALCUDIA R., GARCIA-HOYOS M., LOPEZ-MARTINEZ M.A., SANCHEZ-BOLIVAR N., ZURITA O., GIMENEZ A. ET AL. A comprehensive analysis of choroideremia: From genetic characterization to clinical practice. *PLoS ONE*. 2016;11(4).
- CORTON M., AVILA-FERNANDEZ A., CAMPELLO L., SANCHEZ M., BENAVIDES B., LOPEZ-MOLINA M.I. ET AL. Identification of the photoreceptor transcriptional Co-Repressor SAMD11 as novel cause of autosomal recessive retinitis pigmentosa. *Scientific Reports*. 2016;6.
- RONCERO A.M., LOPEZ-NIEVA P., COBOS-FERNANDEZ M.A., VILLA-MORALES M., GONZALEZ-SANCHEZ L., LOPEZ-LORENZO J.L. ET AL. Contribution of JAK2 mutations to T-cell lymphoblastic lymphoma development. *Leukemia*. 2016;30(1):94-103.

Highlights

PROJECTS:

- C. AYUSO. "Identificación de nuevos mecanismos moleculares en DR, traslación al diagnóstico y al desarrollo de nuevas terapias génicas y celulares" (PI13/00226). / "Desarrollo de una plataforma para el diagnóstico por secuenciación de nueva generación" (ER16-PR05-ACCI-704-2). / "Eye Rare WES" CNAG-BBMRI-LPC. / "Secuenciación del exoma clínico como aproximación para la caracterización clínica y genética de familias españolas afectadas de DRS" (ONCE2015). / "Aplicación de algoritmos bioinformáticos y secuenciación genómica para el descubrimiento de nuevos mecanismos causales" (ONCE2016). / "Implicación del gen USH2A en la patogénesis de la ARRP y el USH2. Papel de la mutación p.C759F" (Fundaluce2015). / "Beyond the Genome; training the next generation of ophthalmic researchers" EyeTN-Marie-Curie-International-Training-Network). / "Diabetes Cancer Connect: Targeting common inflammatory markers and signaling pathways in diabetes mellitus and cancer" (PIE13/00051-WP3). / "mRNA engineered mesenchymal stromal cells: a second generation of cell therapy for inflammatory diseases" (PIE15/00048-WP7).
- EEOO. adRP with misfolded Rod Opsin Mutations (Shire-SHP630-001). / Stargardt de Inicio Temprano (Sanofi-Aventis-EO43/2016).
- M. CORTÓN. "Diagnóstico genético y posible tratamiento del albinismo" (ER16-PR05-ACCI-704-3). / "Towards a better understanding of the genetic basis of congenital ocular malformations using high-throughput genomic technologies" (MiguelServet2013). / "Aniridia y otras Malformaciones Oculares Congénitas: Búsqueda de nuevos mecanismos genéticos mediante NGS" (SAF2013-46943-R). / "Aplicación de nuevas técnicas de secuenciación masiva al estudio genético de la Aniridia y otras disgenesias del segmento anterior" (FMM).
- A. BUSTAMANTE. "Diagnóstico genético prenatal no invasivo, en sangre materna, de EERR" (FMM).

BOOKS / CLINICAL GUIDES "Ethics in the investigation of the ERs". Ed.Ergon ISBN:978-84-16270-85-9 DL:M-2688-2016 / "Genetics implications of aniridia". Spanish guidelines for the management of congenital aniridia, Chapter3 Section I. EneEdiciones, p.31-42.ISBN:978-84-85395-73-6.

WORKING GROUPS: "Update of the Guide for decision making on the incorporation of new genetic tests in the National Health System (GEN Guide)". MSSSI-AETSA-ISBN:978-84-15600-86-2/NIPO:680-15-194-X / "Usefulness of exome sequencing in the diagnosis of dysmorphia with or without intellectual disability". MSSSI-AETSA. / "Clinical Practice Guideline for Hereditary Retinal Dystrophies". MSSSI-AETSA.


ORGANIZATION OF COURSES / DAYS: Pharmacogenetics-DNAday-Research of the EERR-Translational Investigation-XVII Atheneum of bioethics-Discovering Rare Disease Research".


ORGANIZATION OF 2 MEETINGS: "ERDC-ERTC", "Alstrom Europe Meeting".



LEAD RESEARCHER

Benítez, Javier

 Fundación Centro
Nacional de Investigaciones
Oncológicas
Melchor Fernández Almagro, 3
28029 Madrid

 (+34) 912246965 / 917328000

 jbenitez@cniio.es

 [Group website](#)

PROGRAMMES

**Inherited Cancer, Haematological
and Dermatological Diseases**



GROUP MEMBERS

Staff members: Inglada Pérez, Lucía | Martín Gimeno, Paloma

Associated members: Calvete Torres, Oriol | Cascón Soriano, Alberto | Fernández de Gabriel, Victoria | García Pérez, María José | Osorio Cabrero, Ana Laura | Robledo Batanero, Mercedes | Rodríguez González de Antona, Cristina | Urioste Azcorra, Miguel

Main lines of research

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

Most relevant scientific articles

- APELLÁNIZ-RUIZ M, TEJERO H, INGLADA-PÉREZ L, SÁNCHEZ-BARROSO L, GUTIÉRREZ-GUTIÉRREZ G, CALVO I ET AL. Targeted Sequencing Reveals Low-Frequency Variants in EPHA Genes as Markers of Paclitaxel-Induced Peripheral Neuropathy. *Clinical cancer research: an official journal of the American Association for Cancer Research*. 2016.
- MANCIKOVA V, MONTERO-CONDE C, PERALES-PATON J, FERNANDEZ A, SANTACANA M, JODKOWSKA K ET AL. Multilayer OMIC Data in Medullary Thyroid Carcinoma Identifies the STAT3 Pathway as a Potential Therapeutic Target in RET M918T Tumors. *Clinical cancer research: an official journal of the American Association for Cancer Research*. 2016.
- VACLOVÁ T, WOODS NT, MEGÍAS D, GOMEZ-LOPEZ S, SETIÉN F, GARCÍA BUENO JM ET AL. Germline missense pathogenic variants in the BRCA1 BRCT domain, p.Gly1706Glu and p.Ala1708Glu, increase cellular sensitivity to PARP inhibitor olaparib by a dominant negative effect. *Human molecular genetics*. 2016.
- PEREA J., ARRIBA M., RUEDA D., SANCHEZ R., GARCIA J.L., PEREZ J. ET AL. Comment on 'Wild-type APC prediction of poor prognosis in microsatellite-stable proximal colorectal cancer differs according to the age of onset'. *British Journal of Cancer*. 2016;114(10):e7.
- BENITEZ-BUELGA C., VACLOVA T., FERREIRA S., URIOSTE M., INGLADA-PEREZ L., SOBERON N. ET AL. Molecular insights into the OGG1 gene, a cancer risk modifier in BRCA1 and BRCA2 mutations carriers. *Oncotarget*. 2016;7(18):25815-25825.

Highlights

One of the most relevant aspects of the group is the participation in international projects.

The European project BRIDGES (call 2015 Horizon 2020), aims to uncover which high susceptibility genes could be applied to the study of families with breast and ovarian cancer. The project consists of three stages. The first stage will study a set of 31 genes (panel 1) by massive sequencing in 40,000 women with cancer breast BRCA negative and 40,000 controls. These genes have been published as candidates to be medium/high risk genes, and the aim is to clarify which can be really high risk genes. A second stage will analyze the same cases and controls for a second set of 30 genes (panel 2) selected through the COMPLEXO Consortia. In a third stage the most interesting genes (panel 1 and 2) will be selected to build a new panel of clinical application. The project consists of six WP and our group is responsible of the coordination of the WP2, which includes the selection of genes from the two panels, organization of samples, preparation of libraries, sequencing and variant calling.


The first stage has been finished in 2016 and we are currently analyzing data (WP3) and selecting the second set of genes.

Another international project beginning in 2016 is focused on the search for new treatments for metastatic pheochromocytoma. It involves seven groups (5 Europeans and two Americans). Our group leads the WP centered in the construction of a database that contains all genomic data published until so far on this disease, and the analysis of exomes from primary tumors and matched metastasis, looking for secondary mutations potentially related with the progression of the disease. Our group defines genomic profiles of cellular and animals models generated by the other groups, to identify the most representative in order to apply different treatments.



LEAD RESEARCHER

**Bermejo Sánchez,
María Eva**

 Instituto de Salud Carlos III
Instituto de Investigación en
Enfermedades Raras
Monforte de Lemos, 5
28029 Madrid

 (+34) 918222434

 eva.bermejo@isciii.es

 [Group website](#)

PROGRAMMES

Pediatric and Developmental Medicine



GROUP MEMBERS

Staff members: Martínez Fernández, María Luisa

Associated members: Arroyo Carrera, Ignacio | Barcia Ruiz, José María | Beseler Soto, Beatriz | Calvo Aguilar, María José | Canduela Martínez, Víctor Manuel | Centeno Malfaz, Fernando | Colli Lista, Gloria | Cuevas Catalina, Lourdes | Esteban Marfil, María Victoria | Félix Rodríguez, Valentín José | Foguet Vidal, Antoni | Galán Gómez, Enrique | Gallardo Hernández, Francisca Luisa | García Alix Pérez, Alfredo | García García, Ángel | García González, María del Mar | García Martínez, María José | García Vicent, Consuelo | Gómez Martín, Hilario | González de Dios, Javier | Marugán Isabel, Víctor Manuel | Mayoral González, Begoña | Ochoa Sangrador, Carlos | Pi Castán, Graciela | Rodríguez Pando, María del Carmen | Rosal Roig, Jaime | Rota Zapata, Lucía | Sánchez Estévez, Carlos | Sanchís Calvo, María Desamparados | Silveira Cancela, Manuel | Zuazo Zamalloa, Ester

Main lines of research

- Research on the descriptive and analytical epidemiological aspects of infants born with malformations and other congenital defects.
- 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.

Most relevant scientific articles

- PEREZ-CERDA C., GIROS M.L., SERRANO M., ECAY M.J., GORT L., PEREZ DUENAS B. ET AL. A Population-Based Study on Congenital Disorders of Protein N- and Combined with O-Glycosylation Experience in Clinical and Genetic Diagnosis. *Journal of Pediatrics*. 2016.
- YUBERO D., BRANDI N., ORMAZABAL A., GARCIA-CAZORLA A., PEREZ-DUENAS B., CAMPISTOL J. ET AL. Targeted next generation sequencing in patients with inborn errors of metabolism. *PLoS ONE*. 2016;11(5).
- SANCHEZ-DIAZ G., ARIAS-MERINO G., VILLAVERDE-HUESO A., MORALES-PIGA A., ABAITUA-BORDA I., HENS M. ET AL. Monitoring Huntington's Disease Mortality across a 30-Year Period: Geographic and Temporal Patterns. *Neuroepidemiology*. 2016;155-163.
- GARCIA TERESA M.A., PORTO ABAL R., RODRIGUEZ TORRES S., GARCIA URABAYEN D., GARCIA MARTINEZ S., TRANG H. ET AL. Spanish patients with central hypoventilation syndrome included in the European Registry. The 2015 data. *Anales de Pediatría*. 2016.
- ARROYO-CARRERA I., DE ZALDIVAR-TRISTANCHO M.S., MARTIN-FERNANDEZ R., VERA-TORRES M., DE BUITRAGO-AMIGO J.F.G., BOTET-RODRIGUEZ J. RIT1: A novel gene associated with Noonan syndrome. *Revista de Neurología*. 2016;63(8):358-362.

Highlights

- Maintenance of ECEMC's Clinical Network (Spanish Collaborative Study of Congenital Malformations - more than 400 physicians).
- Clinical-dysmorphological assessment: 932 newborns or fetuses with birth defects (BD).
- Epidemiological surveillance of BD: Spain (in ECEMC), Worldwide (with ICBDSR www.icbdsr.org), Europe (with EUROCAT www.eurocat-network.eu), and Establishment in ICBDSR of guidelines for worldwide surveillance of BD related to Zika virus.
- Cytogenetics laboratory: 194 studies (ECEMC's setting).
- SITTE (Spanish Teratology Information Service): 692 physician's consultations.
- SITE (Telephon Information Service for Pregnant Women): 2,527 consultations.
- Confirmation as Chair of ICBDSR's Executive Committee (Eva Bermejo-Sánchez).
- Doctoral Thesis of the CIBERER's hired personnel.
- Project: "Research on the clinica and etiological aspects of congenital atypical cranio-facial clefts". PI: E. Bermejo-Sánchez. PI12/00759.
- Participation in 17 subprojects of the "Collaborative project on the mortality/survival of selected non-cardiac defects" of ICBDSR.
- Participation in the international Project "ICBDSR-Global Epidemiology of Gastroschisis Project".
- Co-authorship of the book "Enfermedades Raras" (M. Posada, V. Alonso, E Bermejo. Ed. Catarata-ISCIII. ISBN 978-84-9097-224-3).
- Teaching: Official Magisters "Conocimiento actual de las Enfermedades Raras" (UNIA), "Máster de Farmacoepidemiología y Farmacovigilancia" (Fac. Medicina. UAH), and "IX Curso de Especialista en Discapacidad Infantil, Diagnóstico y Rehabilitación" (Título Propio UCM).
- Invited speaker: 3 international congresses, 2 national.
- 15 teaching activities. Several national and international congresses on BD.
- Eva Bermejo participated as Invited Expert designated by MSSSI, in the "Meeting on RD Research". Brussels.
- Organization of: "XXXIX Reunión Anual del ECEMC" and "Curso de Actualización sobre la Investigación de los DC" (2.2 credits); "43 Annual Meeting of the International Clearinghouse for Birth Defects Surveillance and Research", Germany; Second "World Birth Defects Day", together with worldwide health organizations, on March 3, 2016; Two editions of the "Jornada sobre Teratología Clínica". Consejería de Sanidad de Castilla y León, Avila and Zamora.
- Publication of 1 "Propositus: Hoja Informativa del ECEMC" (<http://www.fundacion1000.es/boletines-ecemc>)



LEAD RESEARCHER
Bernal, Juan

📍 Agencia E. Consejo Superior de Investigaciones Científicas
Instituto de Investigaciones Biomédicas Alberto Sols
C/ Arturo Duperier 4
28029 Madrid

☎ (+34)91 5854447 / 600 763276

✉ jbernal@iib.uam.es

🌐 [Group website](#)

PROGRAMMES
Endocrine Medicine



GROUP MEMBERS

Staff members: Morte Molina, Beatriz

Associated members: Báñez López, Soledad | Gil Ibáñez, Pilar | Guadaño Ferráz, Ana Cristina | Martín Belinchón, Mónica

Main lines of research

- **CONGENITAL HYPOTHYROIDISM:** 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

- BÁREZ-LÓPEZ S, OBREGON MJ, MARTÍNEZ-DE-MENA R, BERNAL J, GUADAÑO-FERRAZ A, MORTE B. Effect of Triiodothyroacetic Acid Treatment in Mct8 Deficiency: A Word of Caution. *Thyroid: official journal of the American Thyroid Association*. 2016.
- IWAYAMA H., LIAO X.-H., BRAUN L., BAREZ-LOPEZ S., KASPAR B., WEISS R.E. ET AL. Adeno Associated Virus 9-Based Gene Therapy Delivers a Functional Monocarboxylate Transporter 8, Improving Thyroid Hormone Availability to the Brain of Mct8-Deficient Mice. *Thyroid*. 2016;26(9):1311-1319.
- PATRIZIA STOHN J, ELENA MARTINEZ M, MATOIN K, MORTE B, BERNAL J, ANNE GALTON V ET AL. MCT8 Deficiency in Male Mice Mitigates the Phenotypic Abnormalities Associated with the Absence of a Functional Type 3 Deiodinase. *Endocrinology*. 2016; en20161162.
- ESPAÑA-SERRANO L, GUERRA MARTÍN-PALANCO N, MONTERO-PEDRAZUELA A, PÉREZ-SANTAMARINA E, VIDAL R, GARCÍA-CONSUEGRA I ET AL. The Addiction-Related Protein ANKK1 is Differentially Expressed During the Cell Cycle in Neural Precursors. *Cerebral cortex (New York, N.Y.: 1991)*. 2016.

Highlights

Project: “Therapeutics for the Allan-Herndon-Dudley: Assessing new treatment delivery pathways”
Sherman Foundation OTR02211, 2016-2017. 39.616 €. IP: Ana Guadaño Ferraz.

Invited participation in scientific meeting, organized by patient’s association: MCT8 Symposium 2016, Current Knowledge, Future Research on Treatment. Sherman Foundation. (Síndrome de Allan-Herndon-Dudley). Los Angeles, California, January 2016.

Organization of scientific meetings:


1. Symposium: “Hormonas tiroideas y sistema nervioso central: De lo común a lo raro”. Organizer: Beatriz Morte Molina. 16 de junio de 2016.
2. Ana Guadaño Ferraz organizing committee for the 3rd Symposium on Biomedical Research on “Advances and Perspectives in Neuroscience” Instituto de Investigaciones Biomédicas “Alberto Sols” (CSIC-UAM) and Facultad de Medicina (UAM).
3. Juan Bernal is a member of the program committee for the Congreso de la Sociedad Española de Endocrinología, Barcelona, October 2017.


Diagnosis: We have performed genetic diagnosis of rare diseases of the thyroid. Specifically for the diagnosis of Familial Dysalbuminemic Hyperthyroxinemia, Resistance to thyroid hormones, Resistance to TSH, and MCT8 defects.



LEAD RESEARCHER

**Botella Cubells,
Luisa María**

 Agencia E. Consejo Superior
de Investigaciones Científicas
Centro de Investigaciones
Biológicas
Ramiro de Maeztu, 9
28040 Madrid

 (+34) 918373112

 [Group website](#)

PROGRAMMES

Genetic Medicine

GROUP MEMBERS

Staff members: Albiñana Díaz, Virginia | Ruiz Llorente, Lidia

Associated members: Bernabéu, Carmelo | 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

- GALLARDO-VARA E., BLANCO F.J., ROQUE M., FRIEDMAN S.L., SUZUKI T., BOTELLA L.M. ET AL. Transcription factor KLF6 upregulates expression of metalloprotease MMP14 and subsequent release of soluble endoglin during vascular injury. *Angiogenesis*. 2016;1-17.
- OJEDA-FERNANDEZ L., RECIO-POVEDA L., ARISTORENA M., LASTRES P., BLANCO F.J., SANZ-RODRIGUEZ F. ET AL. Mice Lacking Endoglin in Macrophages Show an Impaired Immune Response. *PLoS Genetics*. 2016;12(3).
- PARRA J.A., CUESTA J.M., ZARRABEITIA R., FARINAS-ALVAREZ C., BUENO J., MARQUES S. ET AL. Screening pulmonary arteriovenous malformations in a large cohort of Spanish patients with hemorrhagic hereditary telangiectasia. *International Journal of Cardiology*. 2016; 218:240-245.
- ZARRABEITIA R., OJEDA-FERNANDEZ L., RECIO L., BERNABEU C., PARRA J.A., ALBINANA V. ET AL. Bazedoxifene, a new orphan drug for the treatment of bleeding in hereditary haemorrhagic telangiectasia. *Thrombosis and Haemostasis*. 2016;115(6):1167-1177.
- NUNEZ-GOMEZ E., PERICACHO M., OLLAURI-IBANEZ C., BERNABEU C., LOPEZ-NOVOA J.M. The role of endoglin in post-ischemic revascularization. *Angiogenesis*. 2016;1-24.

Highlights

Immune system response is affected in HHT patients. This is a new clinical aspect of this multisystemic vascular dysplasia. These results have been reported in a myeloid-lineage specific eng KO murine model, developed in our group. Clinical consequences derived of these results are directly in line with the prevention/treatment of rare infections, nosocomial infections, brain abscesses and sepsis developed by HHT patients. The molecular basis of bazedoxifene action as therapeutic drug in HHT, together with a pilot study with 5 HHT patients, has been described in a comprehensive manner. The content of this work is the support for the 2nd orphan designation for HHT obtained from EMA by the end of 2014. The direct cooperation with clinicians from Sierrallana/Valdecilla clinicians has led to a papers in a large cohort of HHT Spanish patients, from which we get samples to study biomarkers: miRNAs, growth factors and cytokines.

The wound healing molecular basis are studied in vessels and endothelial cells. Actors of the process are membrane endoglin, MMP14 and the endoglin soluble form release, and the role played in angiogenesis and vascular repair. All this process is orchestrated by KLF6 as a master transcription factor and in relation to HHT situations.

Endoglin is being studied in other pathologies related with hemostasis and kidney fibrosis.

A new designation of orphan drug has been applied for propranolol in Von Hippel Lindau disease, to EMA. The answer was positive at the COMP meeting of January 19th 2017. A protocol for a pilot clinical trial in HHT, was presented to AEMPs to start presumably this year 2017, after approval.



LEAD RESEARCHER

Bovolenta, Paola

📍 Agencia E. Consejo Superior de Investigaciones Científicas
Centro de Biología Molecular Severo Ochoa.
Campus Cantoblanco
Nicolás Cabrera
28049 Madrid

☎ (+34) 91 196 4718

✉ pbovolenta@cbm.csic.es

🌐 [Group website](#)

PROGRAMMES

Sensorineural Pathology



GROUP MEMBERS

Staff members: Sandonís Consuegra, África

Associated members: Cardozo Ruiz, Marcos Julián | Cavodeassi Madarro, Florencia | Esteve Pastor, Pilar

Main lines of research

Our group investigates the genetic and dynamic events that coordinate early development of the anterior vertebrate neural plate, from which the telencephalon, retina and hypothalamus arise, focusing on aspects that may represent causes of congenital developmental disorders. Driven by unexpected findings, we have also expanded our interests to explore specific aspects of brain and retinal neurodegeneration, with particular interest in retinal dystrophies and Alzheimer's disease-like disorders. To address these issues we use multidisciplinary approaches applied to zebrafish, chick and mouse as experimental models and human brain samples provided by clinical collaborators where necessary.

In the reporting year, we have followed our long-standing interest in retina pigment epithelium (RPE) specification and generated genetic tools in zebrafish to study RPE morphogenesis and how this tissue as whole contributes to optic cup folding. In collaboration with the lab of JR. Martinez-Morales (CABD), we have also exploited these tools and massive genomic approaches to define the gene regulatory network that drives RPE differentiation. Still related to eye patterning and according to our demonstration that the transmembrane proteins Cdon and Boc can act as Shh decoy receptors, we have applied CRISPR/cas9 technology in zebrafish and generate tools to follow Cdon/Boc/Hh interaction in eye and kidney development, thus modelling developmental disease linked to the dysfunction of these proteins. In the frame of an EraNet funded grant and in collaboration with two of the participating groups (M. Nieto, CNB-CSIC, Madrid and S. Nicolis, Bicocca University, Milan), we are addressing how defects in one visual

structure (i.e. eye or dLGN, caused by mutations in specific transcription factors) affect the entire system. On the other hand, we have followed our interest in Secreted Frizzled Related Proteins (Sfrps) that are multifunctional regulator of Wnt and metalloproteases activity. We are actively working on the idea that Sfrp1 might be one of the multiple and yet unclear triggers of Alzheimer's disease. We are using multiple genetic approaches in mice and human tissue to test this hypothesis.

Most relevant scientific articles

- MORALES A.V., ESPESO-GIL S., OCANA I., NIETO-LOPEZ F., CALLEJA E., BOVOLENTA P. ET AL. FGF signaling enhances a sonic hedgehog negative feedback loop at the initiation of spinal cord ventral patterning. *Developmental Neurobiology*. 2016.

Highlights

PROJECTS

- Control of cell-cell communication: from neural development to neurodegeneration. MINECO (BFU2013-43213-P), 2014-2016, 508.200 €. PRINCIPAL INVESTIGATOR: Paola Bovolenta y Pilar Esteve.
- Generating neuronal diversity. (RedDevNeural), MINECO (BFU2014-55738-REDT), 01/12/2014 a 30/11/2016, 32.000 €. INVESTIGADOR PRINCIPAL: Paola Bovolenta (10 groups).
- Understanding and reprogramming developmental visual disorders: from anophthalmia to cortical impairments (Improvision), ERA-NET Neuron II, 2015-2018, 149.000 € por el grupo. Coordinator: Paola Bovolenta (5 groups).
- Understanding Sfrp1 activity as a novel component implicated in the pathogenesis of alzheimer's disease. Fundación Tatiana Pérez de Guzmán el Bueno, 2015-2017, 108.900 €. PRINCIPAL INVESTIGATOR: Paola Bovolenta.

COEDITOR OF THE FOLLOWING BOOK

- Organogenetic gene networks. Castelli-Gair Hombria, J and Bovolenta P. editors, Springer.

BOOK CHAPTERS

- Castelli-Gair Hombria, J and Bovolenta P (2016) Models for studying Organogenetic gene networks in the 21st century. In: Organogenetic gene networks. Castelli-Gair Hombria, J and Bovolenta P. editors, Springer. pp 1-7.
- Cavodeassi, F., Moreno-Marmol, T., Henandez-Bejarano, M and Bovolenta, P. (2016) Principles of early vertebrate forebrain formation. In: Organogenetic gene networks. Castelli-Gair Hombria, J and Bovolenta P. editors, Springer. pp 299-317.



LEAD RESEARCHER

Bueren, Juan Antonio

📍 Centro de Investigaciones
Energéticas, Medioambientales
y Tecnológicas (CIEMAT)
Avda. Complutense, 40
Edificio, 70a
28040 Madrid

☎ (+34) 91 346 65 18

✉ juan.bueren@ciemat.es

🌐 [Group website](#)

PROGRAMMES

**Inherited Cancer, Haematological
and Dermatological Diseases**



GROUP MEMBERS

Staff members: Damian Burgoa, Carlos | Hernando Rodríguez, Miriam | Sánchez Domínguez, Rebeca

Associated members: Aldea García, Montserrat | Almarza Novoa, Elena | Álvarez Ramos, Lara | Casado Olea, José Antonio | Cerrato Carrasco, Laura | Fernández García, Raquel María | García Bravo, María | Garín Ferreira, Marina Inmaculada | Güenechea Amurrio, Guillermo | Lamana Luzuriaga, María Luisa | López Santalla, Mercedes | Lozano Vinagre, María de la Luz | Navarro Ordoñez, Susana | Orman Bernal, Israel | Quintana Bustamante, Oscar | Río Galdo, Paula | Rodríguez Fornes, Fátima | Román Rodríguez, Francisco José | Segovia Sanz, José Carlos | Yañez González, Rosa María

Main lines of research

The main research lines of our group are summarized as follows:

1. Investigation of the molecular and genetic basis of rare diseases affecting the hematopoietic system.
2. Gene Therapy of rare diseases affecting blood cells.
3. Therapy with mesenchymal stromal cells (MSCs) for the treatment of autoimmune and inflammatory pathologies.

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 2016 we have worked in the following research areas:

- **Gene therapy in congenital blood cell syndromes**
 - Lentiviral gene therapy of patients with Fanconi anemia (FA).
 - Lentiviral gene therapy in erythrocyte pyruvate kinase deficiency anemia (PKD).
 - Gene therapy in immunodeficiency by leukocyte adhesion deficiency type 1 (LAD-I).
 - Gene therapy by homologous recombination in Fanconi anemia.
 - Gene therapy by homologous recombination of the erythrocyte pyruvate kinase gene.
 - Gene therapy in dyskeratosis congenital.
 - Advanced therapies in Blackfan Diamond Anemia.
 - Reprogramming and gene therapy of cells from patients with primary hyperoxaluria type 1 (HP1).
- **Therapy with stromal mesenchymal cells (MSC) in inflammatory and autoimmune pathologies**
 - Cell therapy for rheumatoid arthritis.
 - Cell therapy of inflammatory bowel disease and acute inflammation.

- Cell therapy aimed at enhancing the therapeutic effect of mesenchymal stem cells through its phenotypic modification.
- Manufacture of clinical grade stromal mesenchymal cells.

During 2016 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 (FAMOCURE, EPISEVI 2.0, PKRESET and EUROFANCOLEN Project). The work is done in collaboration with other groups from the CIBER, including Associated Clinical Groups (i.e. H. Niño Jesús GCV19 y H San Joan de Deu GCV18) and the Hospital Fundación Jimenez Diaz (with whom we form a Joint Unit for Advanced Therapies). Additionally, we offer collaboration with other researchers from the CIBER to develop new advanced therapies for rare diseases.

Most relevant scientific articles

- LOPEZ-SANTALLA M., MANCHENO-CORVO P., MENTA R., LOPEZ-BELMONTE J., DELAROSA O., BUEREN J.A. ET AL. Human Adipose-Derived Mesenchymal Stem Cells Modulate Experimental Autoimmune Arthritis by Modifying Early Adaptive T Cell Responses. *Stem Cells*. 2016;33(12):3493-3503.
- PULECIO J., ALEJO-VALLE O., CAPELLERA-GARCIA S., VITALONI M., RIO P., MEJIA-RAMIREZ E. ET AL. Direct Conversion of Fibroblasts to Megakaryocyte Progenitors. *Cell Reports*. 2016;17(3):671-683.
- LEON-RICO D., ALDEA M., SANCHEZ-BALTASAR R., MESA-NUNEZ C., RECORD J., BURNS S.O. ET AL. Lentiviral Vector-Mediated Correction of a Mouse Model of Leukocyte Adhesion Deficiency Type i. *Human Gene Therapy*. 2016;27(9):668-678.
- GARCIA-GOMEZ M., CALABRIA A., GARCIA-BRAVO M., BENEDICENTI F., KOSINSKI P., LOPEZ-MANZANEDA S. ET AL. Safe and efficient gene therapy for pyruvate kinase deficiency. *Molecular Therapy*. 2016;24(7):1187-1198.
- LOPEZ-LUQUE J., CABALLERO-DIAZ D., MARTINEZ-PALACIAN A., RONCERO C., MORENO-CACERES J., GARCIA-BRAVO M. ET AL. Dissecting the role of epidermal growth factor receptor catalytic activity during liver regeneration and hepatocarcinogenesis. *Hepatology*. 2016;63(2):604-619.

Highlights

As a complement to the National Programs and programs of the European Commission, during 2016 three lentiviral vectors developed by our laboratory have been licensed to a US company, Rocket-Pharma. Additionally, a contract has been signed for the development with Rocket Pharma for the development of a clinical trial in patients with erythrocyte pyruvate kinase deficiency, and also a Framework Agreement between this company and the CIEMAT, CIBER and Fundación Jiménez Díaz.

In the field of gene therapy, our work continues focused on the research and gene therapy of rare diseases that affect blood cells. These include congenital bone marrow failures, as well as congenital anemias and primary immunodeficiencies. Particularly throughout 2016 we have made significant progresses in the following fields.

- Implementation of the first clinical trial of patients with Fanconi anemia of subtype A by correction with lentiviral vectors of mobilized peripheral blood cells.
- Designation of two orphan drugs in the European Commission and the Food and Drug Agency in the USA for the treatment of erythrocyte pyruvate kinase deficiency and type I leukocyte adhesion deficiency.
- Development of gene editing strategies in hematopoietic stem cells for Fanconi anemia and deficiency in erythrocyte pyruvate kinase.
- Reprogramming and gene therapy of cells from patients with primary hyperoxaluria type 1.


In the field of the studies with mesenchymal stromal cells (MSC), we have worked on the following research lines:

- Characterization of a new application of MSCs to facilitate the engraftment of genetically corrected hematopoietic stem cells.
- Preclinical demonstration of the therapeutic effect of MSCs in rheumatoid arthritis and inflammatory bowel disease.
- Phenotypic modification of MSCs to enhance their therapeutic effect.



LEAD RESEARCHER

**Cardellach López,
Francesc**

 **Hospital Clínico y Provincial
de Barcelona**
Facultad de Medicina
Planta 4, Dep. 4B Cellex
(IDIBAPS)
C/ Villarroel 170
08036 Barcelona

 (+34) 93 227 54 00- Ext 2907

 fcardell@clinic.ub.es

 [Group website](#)

PROGRAMMES

Mitochondrial and Neuromuscular Medicine



GROUP MEMBERS

Staff members: Garrabou Tornos, Gloria | Morén Núñez, Constanza

Contratados a cargo de proyecto: Catalán García, Marc

Associated members: Grau Junyent, José María | Guitart Mampel, Mariona | Tobías Baraja, Ester

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 multidisciplinary 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.

Main research lines:

- Creation of the Group for Medical Assistance of Adult Patients with RD (basically of metabolic, mitochondrial and muscular origin): diagnosis and management of patients, training of specialized staff, clinical and experimental data base recruitment and biobank management. High efforts on updating the emergency clinical protocols to attend patients with metabolic diseases.
- Establishment of etiological bases, putative diagnostic/prognostic biomarkers and potential therapeutic targets in:
 1. Muscular Pathology: mitochondrial, inflammatory, autoimmune and toxic with special focus in inclusion body myositis and myopathy secondary to statin treatment.
 2. Neurodegenerative and psychiatric diseases: Parkinson disease (idiopathic or inherited), X-Fragile syndrome and schizophrenia.
 3. Obstetric problems, especially intrauterine growth restriction and cardiovascular fetal remodeling.
 4. Cardiac disease.
 5. 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).
 6. Gene therapy in MNGIE and clinical and molecular comorbidity between neuromuscular/ neurodegenerative disorders and diabetes mellitus.

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

- BOSCH M., FAJARDO A., ALCALA-VIDA R., FERNANDEZ-VIDAL A., TEBAR F., ENRICH C. ET AL. Hepatic primary and secondary cholesterol deposition and damage in Niemann-Pick disease. *American Journal of Pathology*. 2016;186(3):517-523.
- ALVAREZ-MORA M.I., RODRIGUEZ-REVENGA L., MADRIGAL I., GUITART-MAMPEL M., GARRABOU G., MILA M. Impaired Mitochondrial Function and Dynamics in the Pathogenesis of FXTAS. *Molecular Neurobiology*. 2016:1-7.
- MILISENDA J.C., PUJOL T., GRAU J.M.. Not only bright tongue sign in Pompe disease. *Neurology*. 2016;87(15):1629-1630.
- CATALÁN-GARCÍA M, GARRABOU G, MORÉN C, GUITART-MAMPEL M, HERNANDO A, DÍAZ-RAMOS À ET AL. Mitochondrial DNA disturbances and deregulated expression of oxidative phosphorylation and mitochondrial fusion proteins in sporadic inclusion body myositis. *Clinical science (London, England : 1979)*. 2016;130(19):1741-51.
- HERNANDEZ-RODRIGUEZ J., RUIZ-ORTIZ E., TOME A., ESPINOSA G., GONZALEZ-ROCA E., MENSA-VILARO A. ET AL. Clinical and genetic characterization of the autoinflammatory diseases diagnosed in an adult reference center. *Autoimmunity Reviews*. 2016;15(1):9-15.

Highlights

Our efforts in 2016 have been focused in:

Clinically:

- Updating the emergency protocols to attend patients with metabolic diseases through the Working group of adult patients with RD.
- Diagnose and follow-up patients with muscle disease.

Experimentally:

- Muscular Pathology: Describe and publish the mitochondrial lesion in patients with inclusion body myositis and understanding mitochondrial involvement in myopathy secondary to statin treatment.
- Neurodegenerative and psychiatric diseases: Describe and publish the mitochondrial lesion in patients with FXTAS (in collaboration with the CIBERER team of Dra Montse Milà) and schizophrenia (in collaboration with the CIBERSAM team of Dra Lourdes Martorell). Deep in the knowledge of mitochondrial and autophagic involvement in Parkinson disease (idiopathic or inherited) with the collaboration from the CIBERNED team of Drs. Eduard Tolosa and Maria Josefa Martí.
- Obstetric problems: Deepen in mitochondrial lesion of intrauterine growth restriction in human pregnancies and in a rabbit model in collaboration with the CIBERER team of Dr. Edauid Gratacós.
- Cardiac disease: Start the research line in mitochondrial involvement in cardiac disease in collaboration with the CIBEROBN team of Dr. Francesc Villarroya.
- Mitochondrial toxicity: Describe and publish the mitochondrial toxicity secondary to HIV and its treatment, related to mitochondrial dynamics, in human pregnancies, in collaboration with the CIBERER team of Eduard Gratacós.
- Deepen in the knowledge of therapeutic approaches using gene therapy in MNGIE with the CIBERER team of Dr. Ramón Martí and in assessing the clinical and molecular comorbidity between neuromuscular/ neurodegenerative disorders and diabetes mellitus through an InterCIBER grant with 12 groups belonging to the CIBERNED, CIBERER, CIBERDEM and CIBERBBN.

Finally, we have contributed to attend questions of RD directed to the CIBERER/Orphanet and we have organized the “Annual meeting on rare diseases in adulthood”.



LEAD RESEARCHER

Carracedo, Ángel

📍 Universidad de Santiago de Compostela
Facultad de Medicina
San Francisco, s/n
15782 Santiago de Compostela

☎ (+34) 98 195 14 91

🌐 [Group website](#)

PROGRAMMES

Genetic Medicine



GROUP MEMBERS

Staff members: Brea Fernández, Alejandro José | Cruz Guerrero, Raquel | Pischedda, Sara (sustitución por baja) | Santamariña Peña, 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 | Ruíz 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

- LATORRE-PELLICER A., MORENO-LOSHUERTOS R., LECHUGA-VIECO A.V., SANCHEZ-CABO F., TORROJA C., ACIN-PEREZ R. ET AL. Mitochondrial and nuclear DNA matching shapes metabolism and healthy ageing. *Nature*. 2016;535(7613):561-565.
- AGUIAR P., PARDO J., ARIAS M., QUINTANS B., FERNANDEZ-PRIETO M., MARTINEZ-REGUEIRO R. ET AL. PET and MRI detection of early and progressive neurodegeneration in spinocerebellar ataxia type 36. *Movement Disorders*. 2016.
- DE LA HOYA M., SOUKARIEH O., LOPEZ-PEROLIO I., VEGA A., WALKER L.C., VAN IERLAND Y. ET AL. Combined genetic and splicing analysis of BRCA1 c.[594-2A>C; 641A>G] highlights the relevance of naturally occurring in-frame transcripts for developing disease gene variant classification algorithms. *Human Molecular Genetics*. 2016;25(11):2256-2268.
- FACKENTHAL J.D., YOSHIMATSU T., ZHANG B., DE GARIBAY G.R., COLOMBO M., VECCHI G.D. ET AL. Naturally occurring BRCA2 alternative mRNA splicing events in clinically relevant samples. *Journal of Medical Genetics*. 2016.
- MARTINON-TORRES F., PNG E., KHOR C.C., DAVILA S., WRIGHT V.J., SIM K.S. ET AL. Natural resistance to Meningococcal Disease related to CFH loci: Meta-analysis of genome-wide association studies. *Scientific Reports*. 2016;6.

Highlights

In 2016 the U711 maintained an intense activity in all the lines of investigation in which we work in rare diseases. In this period, we completed the neuropsychological assessments of the participants in the ISCII-funded study on SCA36, which lead to a better understanding of clinical, neurological and cognitive characteristics of SCA36 at different stages of the disease using standardized scales. On the other hand, through the call BBMRI-LPC Whole Exome Sequencing we have sequenced the exome of several patients with albinism, which will undoubtedly contribute to improve its molecular diagnosis. In addition, one of our cancer initiatives won the GlaxoSmithKline Discovery Fast Track program. Finally, within the Innopharma Program, we gave priority to the discovery of candidate drugs for rare diseases. During this period, we have obtained funding for various studies on adverse drug reactions, rare cancers, characterization of variants in new diagnostic genes in the hereditary breast / ovarian cancer syndrome and for the development of a platform for the prioritization of variants of disease using exogenous sequencing data. Several members of the group collaborated in the elaboration of didactic material used in 2 courses aimed to health professionals in Primary Care focused on colorectal cancer and participated in the conference on Rare Diseases organized by the Department of Health of the Xunta de Galicia. In this translational field, it is also important to point out our role in the creation of the Kertor Foundation and the close collaboration with the INGADA and ANASBABI Foundations (Ciliopatías). The coordinator of the group was named head of the Genomic Medicine program in the Steering Committee of the CIBERER, continues being a member of the Interdisciplinary Committee of the IRDiRC and received awards as IV Prize for Excellence, ONCE Galicia 2016 and so on.



LEAD RESEARCHER

Carrascosa, Antonio

📍 Fundació Hospital
Universitari Vall d'Hebron -
Institut de Recerca (VHIR)
Hospital Vall d'Hebron
Passeig Vall d'Hebron, 119-129
08035 Barcelona

☎ (+34) 93 489 30 63
(+34) 93 489 40 30

✉ ancarrascosa@vhebron.net

🌐 [Group website](#)

PROGRAMMES
Endocrine Medicine



GROUP MEMBERS

Staff members: Camats Tarruella, Nuria | Fernández Cancio, Mónica

Associated members: Audi Parera, Laura | Clemente León, María | Yeste Fernández, Diego

Main lines of research

- Growth patterns and body mass index (BMI) from birth to adult height in a non-obese healthy population from Barcelona (743 women and 710 men, more than 25000 anthropometric measurements). Longitudinal study of growth 1995-2017. Preparation of apps, a webpage and an auxological programme.
- Optimization of the patients' treatment with growth hormone.
- Genetic regulation of growth in control and delayed growth populations: genes GH1, GHR, GHRHR, IGF-1, IGF1R, IGF2, NPR2, IGFALS, STAT5B, CCDC8, GHSR, SHOX.
- Genes involved in human sex differentiation: AR, SRD5A2, HSD17B3, CYP17A1, CYP19A1, StAR, NR5A1, MAMLD1, GATA4, LHCGR, CYP11A1, WT1, NR0B1, SRY. Search of new genes.
- Genes involved in congenital isolated glucocorticoid deficiency: genes MC2R, MRAP, StAR, CYP11A1, MCM4, NR0B1, CYP17A1, NR5A1, NNT, TXNRD2.
- Epidemiological and genetic factors involved in rickets. Genes VDR, MC1R, TYR1, TYRP1-1, TYRP1-2, OCA2-1, OCA2-2, SLC45A2-1, SLC45A2-2, SLC24A5-1, KITLG-1.
- Genes involved in thyroid disorders: genes TG, TSHR, PAX8, SLC26A4, SLC5A5, TPO, DUOX2, DUOX2A2, IYD, NKX2-5, NKX2-1, FOXE1, ANO1, GNAS.
- Genes involved in congenital hyperinsulinism: genes HADH, KCNJ11, SLC16A1, GCK, HNF4A, GLUD1, HNF1A, ABCC8, UCP2.

Most relevant scientific articles

- HORNIG N.C., UKAT M., SCHWEIKERT H.U., HIORT O., WERNER R., DROP S.L.S. ET AL. Identification of an AR mutation-negative class of androgen insensitivity by determining endogenous AR activity. *Journal of Clinical Endocrinology and Metabolism*. 2016;101(11):4468-4477.
- HORNIG N.C., DE BEAUFORT C., DENZER F., COOLS M., WABITSCH M., UKAT M. ET AL. A recurrent germline mutation in the 5'UTR of the androgen receptor causes complete androgen insensitivity by activating aberrant uORF translation. *PLoS ONE*. 2016;11(4):-.
- ESPIAU M., YESTE D., NOGUERA-JULIAN A., GONZALEZ-TOME M.I., FALCON-NEYRA L., GAVILAN C. ET AL. Metabolic Syndrome in Children and Adolescents Living with HIV. *Pediatric Infectious Disease Journal*. 2016;:-.
- ESPIAU M., YESTE D., NOGUERA-JULIAN A., SOLER-PALACIN P., FORTUNYC C., FERRER R. ET AL. Adiponectin, Leptin and Inflammatory Markers in HIV-Associated Metabolic Syndrome in Children and Adolescents. *Pediatric Infectious Disease Journal*. 2016;:-.
- TIOSANO D., AUDI L., CLIMER S., ZHANG W., TEMPLETON A.R., FERNANDEZ-CANCIO M. ET AL. Latitudinal clines of the human vitamin D receptor and skin color genes. *G3: Genes, Genomes, Genetics*. 2016;6(5):1251-1266.

Highlights

We continue our activity related to the translational care, diagnostic and specialised consultations in rare diseases (RDs) in Paediatric Endocrinology: growth, disorders of sex development, thyroid dysmorphogenesis, hiperinsulinism, familial glucocorticoid deficiency, raquitism and SHOX.

We also continue our collaboration with Scientific Societies (SEEP, SEEN, SEQC and ESPE) by elaborating protocols, guides for biochemical, clinical and genetic diagnosis and databases [I-DSD, COST BM1303 Project and European Reference Network for Rare Endocrine Conditions (Endo-ERN)]. We are Reference Center of the Programme for early-detection of congenital hypothyroidism in Catalonia. L. Audi is a member of the Scientific Committee of Orphanet.

We exclusively dedicate to CIBERER thanks to our diagnosis, treatment and applied Research in RDs related to Paediatric Endocrinology. Diagnosis and treatment is done in our Consultation in Hospital Vall d'Hebron (Barcelona, Spain).

Throughout 2016, thanks to the use of next-generation sequencing techniques, we were able to molecularly diagnose paediatric patients with endocrinological and pneumological disorders, which had been undiagnosed for a long time.

Besides, this year we ended our longitudinal growth study in a non-obese healthy population (743 women and 710 men, more than 25000 measurements) from Barcelona, Spain. These novel data should allow a correct evaluation of growth and obesity during infancy and adolescence. We also started to design apps, a webpage and an auxological programme.

In 2016, we have consolidated Clinical and Research collaborations with other Paediatric Groups of our Hospital, which are also working in RDs (Paediatric Pneumology, Neurology, Metabolic Diseases, Genetics, Immunodeficiencies and Neonatology). Also, our Research Group has expanded with the inclusion of Paediatric Pneumology and Neonatology Groups and is now called Growth and Development Group (Vall d'Hebron Research Institute, VHIR). Dr. Antonio Moreno is now co-director together with Dr. Antonio Carrascosa.



LEAD RESEARCHER

Castaño González, Luis

📍 Asociación Instituto de
Investigación Sanitaria de
Biocruces
Hospital Universitario Cruces
Pza. de Cruces, S/N
48903 Cruces (Barakaldo)

☎ (+34) 946006473

✉ lcastano@osakidetza.eus

🌐 Group website

PROGRAMMES

Endocrine Medicine



GROUP MEMBERS

Associated members: Bilbao Catalá, José Ramón | Cortázar Galarza, Alicia | Gaztembide Sáenz, Sonia | Rica Exterbarría, Itxaso | 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 Hirschsprung disease.

Most relevant scientific articles

- AGUAYO A, URRUTIA I, GONZALEZ-FRUTOS T, MARTINEZ R, MARTINEZ-INDART L, CASTANO L, GAZTAMBIDE S, Diabetes Epidemiology Basque Study Group. Prevalence of diabetes mellitus and impaired glucose metabolism in the adult population of the Basque Country, Spain. *Diabet Med* 2016 Jun 29 (epub ahead of print) . IF: 3.152.
- BELLIDO V, LARRANAGA I, GUIMON M, MARTINEZ-CONDE R, EGUIA A, DE NANCLARES, GP, CASTANO L, GAZTAMBIDE, S. A Novel Mutation in a Patient with Hyperparathyroidism-Jaw Tumour Syndrome. *Endocrine Pathology* June 2016 27(2): 142-146.DOI: 10.1007/s12022-016-9427-6. IF: 1.817.
- JIMÉNEZ-FONSECA P, GÓMEZ SAEZ JM, SANTAMARIA SANDI J, CAPDEVILA J, NAVARRO GONZALEZ E, ZAFON LLOPIS C, RAMÓN Y CAJAL ASENSIO T, RIESCO-EIZAGUIRRE G, GRANDE E, GALOFRÉ JC. Spanish consensus for the management of patients with anaplastic cell thyroid carcinoma.*Clin Transl Oncol* DOI 10.1007/s12094-016-1506-0. FI: 2,075.
- MARTÍNEZ R, FERNÁNDEZ-RAMOS C, VELA A, VELAYOS T, AGUAYO A, URRUTIA I, RICA I, CASTANO L. Clinical and genetic characterization of congenital hyperinsulinism in Spain. *European Journal of Endocrinology* June 2016 174: 717-726. DOI: 10.1530/EJE-16-0027. IF:3.892.
- GRANDE E, SANTAMARIA SANDI J, CAPDEVILA J, NAVARRO GONZÁLEZ E, ZAFÓN LLOPIS C, RAMÓN Y CAJAL ASENSIO T, GÓMEZ SÁEZ JM, JIMÉNEZ-FONSECA P, RIESCO-EIZAGUIRRE G, GALOFRÉ JC.Consensus on management of advanced medullary thyroid carcinoma on behalf of the Working Group of Thyroid Cancer of the Spanish Society of Endocrinology (SEEN) and the Spanish Task Force Group for Orphan and Infrequent Tumours (GETHI).*Clin Transl Oncol* 2016; Agosto. DOI 10.1007/s12094-015-1465-x IF: 2.075.

Highlights

Study of the global prevalence of vitamin D levels in healthy pediatric population of the Goierri-Urola-Gipuzkoa region” Basque Government (2011111107). 2012-2016. 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. 2013-2016.

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. 2016 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. 2009-2016.

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. 2016.



LEAD RESEARCHER

Cuezva, José Manuel

📍 Universidad Autónoma de Madrid
Centro de Biología Molecular Severo Ochoa.
Nicolás Cabrera, 1.
Campus de Cantoblanco UAM
28049 Madrid

☎ (+34) 91 196 46 18

(+34) 91 196 46 48

✉ jmcuezva@cbm.csic.es

🌐 [Group website](#)

PROGRAMMES

Mitochondrial and Neuromuscular Medicine



GROUP MEMBERS

Staff members: Núñez de Arenas Flores, Cristina | Santacatterina, Fulvio

Associated members: Formentini, Laura | Nuevo Tapioles, Cristina

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-ATPase 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

- SANTACATTERINA F, SÁNCHEZ-CENIZO L, FORMENTINI L, MOBASHER MA, CASAS E, RUEDA CB ET AL. Down-regulation of oxidative phosphorylation in the liver by expression of the ATPase inhibitory factor 1 induces a tumor-promoter metabolic state. *Oncotarget*. 2016;7(1):490-508.
- GARCIA-BERMEDEZ J., CUEZVA J.M. The ATPase Inhibitory Factor 1 (IF1): A master regulator of energy metabolism and of cell survival. *Biochimica et Biophysica Acta - Bioenergetics*. 2016;1857(8):1167-1182.
- GALLEGO-VILLAR L., RIVERA-BARAHONA A., CUEVAS-MARTIN C., GUENZEL A., PEREZ B., BARRY M.A. ET AL. In vivo evidence of mitochondrial dysfunction and altered redox homeostasis in a genetic mouse model of propionic acidemia: Implications for the pathophysiology of this disorder. *Free Radical Biology and Medicine*. 2016; 96:1-12.
- OYARZABAL A., BRAVO-ALONSO I., SANCHEZ-ARAGO M., REJAS M.T., MERINERO B., GARCIA-CAZORLA A. ET AL. Mitochondrial response to the BCKDK-deficiency: Some clues to understand the positive dietary response in this form of autism. *Biochimica et Biophysica Acta - Molecular Basis of Disease*. 2016;1862(4):592-600.
- KLIONSKY DJ, ABDELMOHSEN K, ABE A, ABEDIN MJ, ABELIOVICH H, ACEVEDO AROZENA A ET AL. Guidelines for the use and interpretation of assays for monitoring autophagy (3rd edition). *Autophagy*. 2016;12(1):1-222.

Highlights


The more relevant activities developed by our group in the field of Rare Diseases have been focused in peripheral neuropathies within the TREAT-CMT project in collaboration with U-732 and U-763. In this project we have identified proteins and metabolites in skin biopsies and in plasma samples respectively, of Charcot-Marie-Tooth 1A patients that could provide early biomarkers of the disease (*Plos One*, 2017, under revision). In the same arena, we have contributed in phenotyping the GDAP1 ^{-/-} mouse model of CMT disease (*Plos Biology*, 2015). In inflammatory myopathies, in collaboration with U-722, we have identified new biomarkers for the differential diagnosis of dermatomyositis and sporadic inclusion bodies myositis in muscle biopsies of these patients (*J. Trans. Med.* 2017). In collaboration with U-746 we have characterized the metabolic phenotype of different tissues of the genetic mouse model of propionic acidemia at different ages (*Free Rad. Biol. Med.*, 2016). In pathologies affecting the OXPHOS system, in collaboration with U-723 and U-701, we are pursuing the identification of novel biomarkers in muscle biopsies of patients affected by progressive external ophthalmoplegia (PEO) with single or multiple deletion of mitochondrial DNA. In addition, we have demonstrated the importance of the regulation of the phosphorylation of the mitochondrial ATP synthase inhibitor IF1 in mitochondrial pathophysiology (*Cell Rep.* 2015, *Biochim. Biophys. Acta* 2016 y *Cell. Mol. Life Sci.* 2017). In this regard, we have developed and characterized the transgenic mouse models that overexpress in a regulated and tissue-specific way IF1 in liver (*Oncotarget* 2016) and in colon (*Cell Rep.* 2017 under revision). Moreover, we have initiated the development of the conditional knock-out mouse model of IF1 in neurons.




LEAD RESEARCHER

Dalmau Obrador, Josep

 Instituto de Investigaciones
Biomédicas August Pi i Sunyer
C/ Rosellón, 153, Planta 2
28036 Barcelona

 (+34) 93 227 17 38

 informacion@
neuroimmunologybcn.org

 [Group website](#)

PROGRAMMES

Mitochondrial and Neuromuscular Medicine

GROUP MEMBERS

Staff members: Ariño Rodríguez, Helena

Associated members: Armangue Salvador, Thais | Mannara, Francesco | Martínez Hernández, Eugenia | Petit Pedrol, María del Mar | Planaguma Valls, Jesús | Rosenfeld, Myrna | Sabater Baudet, Lidia

Main lines of research

The principal lines of investigation are in the area of translational neuroscience. We aim to identify new disorders, develop biomarkers, and uncover mechanisms of disease in a novel group of neuroinflammatory disorders characterized by highly specific immune responses against neuronal cell surface and synaptic proteins (autoimmune encephalitis).

In addition to the clinical characterization of these disorders, we identify the associated antibody immune responses, develop diagnostic tests, and determine optimal treatment strategies. We are also investigating what leads to the development of the autoimmune response and how the antibodies interfere with neuronal function and cause the disease. These studies include basic laboratory techniques such as immunohistochemistry, immunoblotting and the development of primary neuronal cell culture as well as tissue electrophysiology studies and investigations using advanced microscopy.

Most relevant scientific articles

- TORRES-VEGA E., DURAN-MORENO M., SANCHEZ DEL PINO M., YANEZ Y., CANETE A., CASTEL V. ET AL. Immunoproteomic studies on paediatric opsoclonus-myoclonus associated with neuroblastoma. *Journal of Neuroimmunology*. 2016; 297:98-102.
- PLANAGUMA J., HASELMANN H., MANNARA F., PETIT-PEDROL M., GRUNEWALD B., AGUILAR E. ET AL. Ephrin-B2 prevents N-methyl-D-aspartate receptor antibody effects on memory and neuroplasticity. *Annals of Neurology*. 2016;80(3):388-400.
- GUASP M., SOLA-VALLS N., MARTINEZ-HERNANDEZ E., GIL M.P., GONZALEZ C., BRIEVA L. ET AL. Cerebellar ataxia and autoantibodies restricted to glutamic acid decarboxylase 67 (GAD67). *Journal of Neuroimmunology*. 2016; 300:15-17.

Highlights

- **Findings for anti-NMDA receptor encephalitis**
We used a mouse model of chronic cerebroventricular infusion of patients' NMDA receptor antibodies to demonstrate the antibody pathogenicity at multiple levels and that all antibody mediated effects can be at least partially prevented by administration of ephrin-B2, suggesting a novel molecular intervention with potential therapeutic implications for how to treat patients with this disorder.
- **Findings related to disorders associated with antibodies to GAD67**
Adult onset cerebellar ataxia is one of the most frequent syndromes associated with autoantibodies against GAD65. We demonstrated that there are patients with this disorder who are negative for GAD65 antibodies but who have antibodies to GAD67. This work demonstrates that GAD67 antibodies are biomarkers of autoimmune cerebellar ataxia and screening for these antibodies should be considered in adults with subacute onset of cerebellar ataxia when GAD65 antibodies are absent.
- **Findings related to neuroblastoma associated opsoclonus-myoclonus.**
To date a variety of autoimmune biomarkers have been found in patients with neuroblastoma associated opsoclonus-myoclonus but the predominant marker remain unknown. In this study we identified the Shaw-potassium channel Kv3.3 (KCNC3) as a potential antigenic target. Studies are now on-going to confirm this association and determine the clinical utility of finding these antibodies in children with the disorder.



LEAD RESEARCHER

**Del Río Nechaevsky,
Marcela**

📍 Centro de Investigaciones
Energéticas,
Medioambientales y
Tecnológicas (CIEMAT)
Avda. Complutense, 40
Edificio 70A. 28040 Madrid

☎ (+34) 916248210

🌐 [Group website](#)

PROGRAMMES

**Inherited Metabolic Medicine
Inherited Cancer, Haematological
and Dermatological Diseases**



GROUP MEMBERS

Staff members: Escámez 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, Núria | Larcher Laguzzi, Fernando | Meana Infiesta, Álvaro | 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: Epidermolysis Bullosa and Kindler síndrome.
- Development of humanized animal models of rare skin diseases.
- Bone regeneration through tissue engineering.

Most relevant scientific articles

- CHAMORRO C., MENCIA A., ALMARZA D., DUARTE B., BUNING H., SALLACH J. ET AL. Gene Editing for the Efficient Correction of a Recurrent COL7A1 Mutation in Recessive Dystrophic Epidermolysis Bullosa Keratinocytes. *Molecular Therapy - Nucleic Acids*. 2016;5.
- LUCHETTI M.M., MORONCINI G., JOSE ESCAMEZ M., SVEGLIATI BARONI S., SPADONI T., GRIECO A. ET AL. Induction of Scleroderma Fibrosis in Skin-Humanized Mice by Administration of Anti-Platelet-Derived Growth Factor Receptor Agonistic Autoantibodies. *Arthritis and Rheumatology*. 2016;68(9):2263-2273.
- CARRETERO M., GUERRERO-ASPIZUA S., ILLERA N., GALVEZ V., NAVARRO M., GARCIA-GARCIA F. ET AL. Differential features between chronic skin inflammatory diseases revealed in skin-humanized psoriasis and atopic dermatitis mouse models. *Journal of Investigative Dermatology*. 2016;136(1):136-145.
- MENCIA A., GARCIA M., GARCIA E., LLAMES S., CHARLESWORTH A., DE LUCAS R. ET AL. Identification of two rare and novel large deletions in ITGB4 gene causing epidermolysis bullosa with pyloric atresia. *Experimental Dermatology*. 2016;25(4):269-274.
- ALAMEDA J.P., NAVARRO M., RAMIREZ A., PAGE A., SUAREZ-CABRERA C., MORENO-MALDONADO R. ET AL. IKK α regulates the stratification and differentiation of the epidermis: Implications for skin cancer development. *Oncotarget*. 2016;7(47):76779-76792.

Highlights

During 2016 we continued our studies on the pathogenic mechanisms of various rare skin diseases and the development of therapeutical approaches translatable to the clinic. Noteworthy are the results on correction of recessive dystrophic epidermolysis bullosa (EBDR) using an ex vivo personalized gene-editing strategy (PMID 27045209). Also noteworthy are the results regarding the pathogenic mechanism of Cutaneous Scleroderma (PMID 27111463) and Familial Melanoma (PMID 28030792, intra-CIBER collaboration) published in high-impact journals. Our work on gene editing allowed us to obtain funding (competitive concurrence) from DEBRA International, the Patient Association of Epidermolysis Bullosa (EB). We also obtained DEBRA España support to continue the research and genetic diagnosis of EB in our unit, through donations made to CIBERER for the co-financing of the clinical trial of cell therapy (Eudra CT 2015-001272-21) and the hiring of a molecular geneticist during 2017. We participated in 3 European projects, one of them funded in 2016 by the European Academy of Dermatology and Venereology: "Novel serological biomarkers for early non-invasive diagnosis and monitoring of squamous cell carcinoma (SCC) in inherited epidermolysis bullosa: a multicenter European study". In the area of translation, we are also involved in the implementation of two other international trials (EBGEN and GENEGRAFT) and in the treatment of patients with EBDr. in Vall D'hebron Hospital through compassionate uses approved by the AEMPS using tissue engineering products.

We have prepared a guide of recommendations for the molecular diagnosis of EB in Spain (intra CIBERER collaboration) that will be published in the official journal of the Academy of Dermatology. We also participated in the panel of experts for the development of the guide "Clinical practice guidelines for laboratory diagnosis of Epidermolysis bullosa" funded by DEBRA International. In addition, within the dissemination activities, we have organized the International Symposium "Rare Diseases of the Skin: From Clinic to Gene and vice versa" sponsored by CIBERER and the Ramón Areces Foundation in which renowned researchers presented the most recent advances in Diagnosis and treatment of genodermatoses.



LEAD RESEARCHER

Dopazo Blázquez, Joaquín

📍 Fundación Centro de
Investigación Príncipe Felipe
C/ Eduardo Primo Yúfera 3
46013 Valencia

☎ (+34) 963289680

✉ jdopazo@cipf.es

🌐 Group website

PROGRAMMES

Genetic Medicine



GROUP MEMBERS

Staff members: Gallego Ortega, Asunción | Marín Falcó, Matías | Salavert Torres, Francisco

Associated members: García García, Francisco

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

- DOPAZO J., AMADOZ A., BLEDA M., GARCIA-ALONSO L., ALEMAN A., GARCIA-GARCIA F. ET AL. 267 Spanish Exomes Reveal Population-Specific Differences in Disease-Related Genetic Variation. *Molecular Biology and Evolution*. 2016;33(5):1205-1218.
- SALAVERT F, HIDAGO MR, AMADOZ A, ÇUBUK C, MEDINA I, CRESPO D ET AL. Actionable pathways: interactive discovery of therapeutic targets using signaling pathway models. *Nucleic acids research*. 2016;44(W1): W212-6.
- FALCO M.M., BLEDA M., CARBONELL-CABALLERO J., DOPAZO J. The pan-cancer pathological regulatory landscape. *Scientific Reports*. 2016;6.
- CORTON M., AVILA-FERNANDEZ A., CAMPELLO L., SANCHEZ M., BENAVIDES B., LOPEZ-MOLINA M.I. ET AL. Identification of the photoreceptor transcriptional Co-Repressor SAMD11 as novel cause of autosomal recessive retinitis pigmentosa. *Scientific Reports*. 2016;6.
- SALAVERT F., GARCIA-ALONSO L., SANCHEZ R., ALONSO R., BLEDA M., MEDINA I. ET AL. Web-based network analysis and visualization using CellMaps. *Bioinformatics*. 2016;32(19):3041-3043.

Highlights

During 2016 an ACCI collaborative Project was carried out to develop a pilot system for the storage and management of genomic data (exomes or large panels). The project was successfully completed and allowed to experience what were the problems produced by the management of this type of data as well as to test solutions for them. Seven hospitals from four autonomous communities across Spain were participating in this project: La Paz, Fundación Jiménez Díaz, Ramón y Cajal, CBM (Madrid), Virgen del Rocío (Sevilla), Hospital del Mar (Barcelona), HU La Fe (Valencia). We can consider this project as the largest attempt to manage genomic data in the country.


On the other hand, the BiER proposal for the analysis of genomic data from the NaGen project to sequence 1000 genomes of rare disease patients in the Navarra community was selected successful and the BiER will participate in the project.


In addition, the official version of the server of genetic variation of the Spanish population (CSVS: <http://www.ciberer.es/bier/csvs>) with data of allele frequencies of variants obtained from 790 exomes, is now running. In brief, an update with 200 more exomes will raise to about 1000 the number of individuals used to construct the database. This is one of the most comprehensive databases of local genetic variation available.




LEAD RESEARCHER

Estévez Povedano, Raül

 **Universidad de Barcelona**
Facultad de Medicina
Campus de Bellvitge
Pavelló de Govern
C/ Feixa Llarga s/n
08907 L'Hospitalet de Llobregat

 (+34) 93 403 97 81

 restevez@ub.edu

 [Group website](#)

PROGRAMMES

Inherited Metabolic Medicine

GROUP MEMBERS

Staff members: Gaitán Peñas, Héctor

Associated members: Arnedo Llana, Tanit | Barrallo Gimeno, Alejandro | Elorza Vidal, Xabier | López Hernández, Tania

Main lines of research

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

Most relevant scientific articles

- GAITAN-PENAS H., GRADOGNA A., LAPARRA-CUERVO L., SOLSONA C., FERNANDEZ-DUENAS V., BARRALLO-GIMENO A. ET AL. Investigation of LRRC8-Mediated Volume-Regulated Anion Currents in Xenopus Oocytes. *Biophysical Journal*. 2016;111(7):1429-1443.


Hightlights


In 2016, we have been studying the relationship between the GlialCAM/MLC1 proteins and the chloride channels CIC-2 and LRRC8/VRAC. We have observed that there is a direct interaction between GlialCAM/MLC1 and CIC-2 which depends on the depolarization potential of astrocytes. These results are in revision in *Human Molecular Genetics*. On the other hand we wanted to study the new chloride channel LRRC8 and its relationship with MLC1. To this end, we setup the characterization of the channel in *Xenopus* oocytes, which have been published in *Biophysical Journal*. When analyzing its functional relationship with MLC1, we have seen that they interact in an indirect manner. We hypothesize that MLC1 regulates different transduction signal events that influence on this channel. We have also participated (articles are now being written) in the characterization of mutants found in CIC-2 in patients with the leukodystrophy CC2L, in finding the degradation mechanisms of MLC1 at the plasma membrane, in the generation and characterization of a knockout of the CIC-a channel in *Drosophila*, in an structural characterization of mutations in GlialCAM and in the generation and characterization of knockout of GlialCAM in the zebrafish. On the other hand, we have characterized novel mutations in the CIC-1 chloride channel found in myotonia (results published in 2016 in *Human Mutation*) and other mutations (article in progress). We have also generated knockout models in zebrafish of the chloride channels CIC-k and CIC-1, which characterization is in progress.




LEAD RESEARCHER

Fernández Piqueras, José

 Universidad Autónoma de Madrid
Centro de Biología Molecular Severo Ochoa.
Campus de Cantoblanco UAM
Nicolás Cabrera, 1
28049 Madrid

 (+34) 911964653

 jfpiqueras@cbm.csic.es

 [Group website](#)

PROGRAMMES

Inherited Cancer, Haematological and Dermatological Diseases



GROUP MEMBERS

Staff members: González Sánchez, Laura | Lopez Nieva, María del Pilar

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 affection (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

- RONCERO A.M., LOPEZ-NIEVA P., COBOS-FERNANDEZ M.A., VILLA-MORALES M., GONZALEZ-SANCHEZ L., LOPEZ-LORENZO J.L. ET AL. Contribution of JAK2 mutations to T-cell lymphoblastic lymphoma development. *Leukemia*. 2016;30(1):94-103.
- FERNANDEZ-PIQUERAS J. New mutations for nodal lymphomas of TFH origin. *Blood*. 2016;128(11):1446-1447.
- MARIN-RUBIO J.L., DE ARRIBA M.C., COBOS-FERNANDEZ M.A., GONZALEZ-SANCHEZ L., ORS I., SASTRE I. ET AL. Deregulated FADD expression and phosphorylation in T-cell lymphoblastic lymphoma. *Oncotarget*. 2016;7(38):61485-61499.
- LOPEZ-NIEVA P., MALAVE M., GONZALEZ-SANCHEZ L., FERNANDEZ-PIQUERAS J., FERNANDEZ-NAVARRO P., SANTOS J. Transcriptomic analysis reveals sex-specific differences in the expression of Dcl1 and Fis1 genes in the radio-adaptive response of thymocytes to TRP53-mediated apoptosis. *BMC Genomics*. 2016;17(1).

Highlights

During the year 2016 we have published four 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, indicating the advisability of using NGS and new treatments (*Leukemia*; IF: 12,104); (2) a review article published in the journal *Blood* about the importance of new mutations for nodal lymphomas of TFH origin (*Blood*; IF: 11,847), and (3) the proposal of an operational model to classify T-cell lymphoblastic lymphoma according to their aggressiveness (*Oncotarget*; 5,008). As to investigation projects, it has to be emphasized our involvement in an European project, the direction of an ACCI-CIBERER-16, the direction of a SAF-2015 project, and our engagement in a Grant-Agreement covered by the IIS-FJD to the study of T-cell lymphoblastic lymphoma and the preparation of reports about patient admitted in the Hospital. It should be also noted the direction of several end-of-degree and end-of-master projects; the organization of a *Sesión Científica Extraordinaria in the Real Academia Nacional Española de Medicina*; our participation in lectures at multiple Specialisation Courses and Masters organized by different institutions (UAM, UCM, UAH, CNIO, CIB/CSIC etc.). Additionally, we have participated in various training courses and meetings organized by the CIBERER and other institutions belonging to the ISCIII. 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, given scientific advise and contributing to the evaluation of their annual Research prize; my incorporation as a member of the External Scientific Committee of the Institute for Health Research of Hospital 12 de Octubre (i+12); y my work as a member of the Executive Committee of the *Lección Conmemorativa Jiménez Díaz*.



LEAD RESEARCHER

Fillat, Cristina

 Instituto de Investigaciones
Biomédicas August Pi i Sunyer
C/Rosellón 153, Planta 2
28036 Barcelona

 (+34) 93 227 54 00 Ext. 4579

 [Group website](#)

PROGRAMMES

Pediatric and Developmental Medicine



GROUP MEMBERS

Staff members: Barallobre Filgueira, María José | Luna Cornado, Jerónimo

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 Lagrán 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

- DE LA TORRE R., DE SOLA S., HERNANDEZ G., FARRE M., PUJOL J., RODRIGUEZ J. ET AL. Safety and efficacy of cognitive training plus epigallocatechin-3-gallate in young adults with Down's syndrome (TESDAD): A double-blind, randomised, placebo-controlled, phase 2 trial. *The Lancet Neurology*. 2016;15(8):801-810.
- RUIZ-MEJIAS M., DE LAGRAN M.M., MATTIA M., CASTANO-PRAT P., PEREZ-MENDEZ L., CIRIA-SUAREZ L. ET AL. Overexpression of Dyrk1A, a down syndrome candidate, decreases excitability and impairs gamma oscillations in the prefrontal cortex. *Journal of Neuroscience*. 2016;36(13):3648-3659.
- VILLANUEVA E., MARTI-SOLANO M., FILLAT C. Codon optimization of the adenoviral fiber negatively impacts structural protein expression and viral fitness. *Scientific Reports*. 2016;6.
- MARTINEZ-BOSCH N., GUERRERO P.E., MORENO M., JOSE A., IGLESIAS M., MUNNE-COLLADO J. ET AL. The pancreatic niche inhibits the effectiveness of sunitinib treatment of pancreatic cancer. *Oncotarget*. 2016;7(30):48265-48279.
- DEL HOYO L., XICOTA L., LANGOHR K., SANCHEZ-BENAVIDES G., DE SOLA S., CUENCA-ROYO A. ET AL. VNTR-DAT1 and COMTVal158Met genotypes modulate mental flexibility and adaptive behavior skills in down syndrome. *Frontiers in Behavioral Neuroscience*. 2016;10(OCT).

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 and rare metabolic diseases, such as the glutaric aciduria.

In 2016, we have published the results of the phase 2 trial evaluating safety and efficacy of cognitive training plus epigallocatechin-3-gallate (EGCG) treatment in Down syndrome (DS) and fragile-X young adults.

An amelioration of the cognitive decline was observed after the combination treatment. To understand the mechanisms that support these effects, we evaluated the impact of a combined environmental enrichment and EGCG therapy in the Ts65Dn mouse model of DS. An amelioration of the cognitive function was detected. Such improvements were accompanied by a rescue of CA1 dendritic spine density and a normalization of the proportion of excitatory and inhibitory synaptic markers in CA1 and dentate gyrus.

Furthermore, during this year we have provided additional evidences supporting the role of DYRK1A in cognitive alterations in DS. These studies showed that an excess of DYRK1A in the prefrontal context led to functional deficits in the beta-gamma oscillations in the cortex due to alterations in the inhibitory activity.

Regarding the development of novel therapies for the treatment of rare tumors, we have identified a novel mechanism that adenoviruses use to optimize its activity in infected cells that have important consequences in the design of oncolytic adenoviruses. Moreover, we showed how tumor microenvironment interferes with the anti-neoplastic activity of receptor tyrosin kinase inhibitors.

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

LEAD RESEARCHER

Gallano Petit, María Pía

 Instituto de Investigación
del Hospital de la Santa Cruz
y San Pablo
S Antoni M^a Claret 167
08025 Barcelona

 (+34) 93 291 90 50 ext7369

 [Group website](#)

PROGRAMMES

Genetic Medicine

GROUP MEMBERS

Staff members: Alías Andreu, Laura | González Quereda, Lidia | Salazar Blanco, Juliana

Associated members: Lassa Laborde, Adriana | Páez López-Bravo, David

Main lines of research

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. Clinical/Genetic Study of familiar ALS.

Hereditary breast cancer and BRCA 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.

NEUROMUSCULAR DISORDERS:

- Duchenne and Becker muscle dystrophies: molecular pathology of DMD gene.
- Study of clinical and genetic heterogeneity of limb-girdle muscular dystrophy of autosomal recessive inheritance and autosomal dominant transmission.
- Clinical and genetic study of Congenital Myopathies and Congenital Myasthenic Syndromes.

Most relevant scientific articles

- MOYA P., SALAZAR J., ARRANZ M.J., DIAZ-TORNE C., DEL RIO E., CASADEMONT J. ET AL. Methotrexate pharmacokinetic genetic variants are associated with outcome in rheumatoid arthritis patients. *Pharmacogenomics*. 2016;17(11):11-25.
- DIAZ-MANERA J., ALEJALDRE A., GONZALEZ L., OLIVE M., GOMEZ-ANDRES D., MUELAS N. ET AL. Muscle imaging in muscle dystrophies produced by mutations in the EMD and LMNA genes. *Neuromuscular Disorders*. 2016;26(1):33-40.
- HOLLESTELLE A., VAN DER BAAN F.H., BERCHUCK A., JOHNATTY S.E., ABEN K.K., AGNARSSON B.A. ET AL. No clinical utility of KRAS variant rs61764370 for ovarian or breast cancer. *Gynecologic Oncology*. 2016;141(2):386-401.
- MEDRANO S., MONGES S., GRAVINA L.P., ALIAS L., MOZZONI J., ARAOZ H.V. ET AL. Genotype-phenotype correlation of SMN locus genes in spinal muscular atrophy children from Argentina. *European Journal of Paediatric Neurology*. 2016;20(6):910-917.

Highlights

The U705 developed its research and clinical diagnosis in rare diseases in neuromuscular and hematological diseases, Pharmacogenetics and Oncogenetics during 2016. The results of our research activity produced in this period of time have been published in international scientific journals.

The U705 members participate in several projects with funding from both the competitive agencies (FIS/ISCIII, ACCI, Ministerio de Sanidad, Servicios Sociales e Igualdad y Fundación Mutua Madrileña), and also donations from private companies (PTC-citius Pharma). Notably, many of the projects funded are being conducted in collaboration with other CIBERER Units and clinical groups.

The Unit continues to participate in activities started in previous years such as: clinical trials in spinal muscular atrophy (SMA), Duchenne muscular dystrophy (DMD) 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-.

A new interdisciplinary committee for the study of hereditary hearing loss has been created with close collaboration between Otorhinolaryngology, Ophthalmology, and Genetics (U705) Services of our Hospital. This is in addition to our continuing participation in clinical committees on genodermatoses and pediatrics, and interhospital meetings on neuromuscular diseases in which the U703 and U732 Units also collaborate.


Regarding training, a PhD thesis has been defended and two courses have been organized: “*Haciendo camino hacia la Farmacogenética*” and “*Curso avanzado en medicina personalizada: implementación de biomarcadores genéticos en la práctica clínica*”. The Unit has also continued to hold the seminar cycle in which researchers of other CIBERER Units participate.


In support of the teaching activity organized by CIBERER, a presentation was given at the conference “*II Jornadas de Investigación Traslacional en Enfermedades Raras: Últimos Avances en Enfermedades Neuromusculares*”.



LEAD RESEARCHER

Gresse, Rafael

 Universidad Autónoma de Madrid
Ctra. Colmenar Viejo,
KM 15,500
28049 Madrid

 (+34) 91 497 54 52

 rafael.gresse@uam.es

 [Group website](#)

PROGRAMMES

Mitochondrial and Neuromuscular Medicine



GROUP MEMBERS

Staff members: Gallardo Pérez, María Esther

Contratados a cargo de proyecto: Moreno Moreno, Beatriz

Associated members: 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 neurosensory 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 iPSC cells harboring mutations in structural and regulator genes of the OXPHOS function.

Most relevant scientific articles

- FERNANDEZ-MORENO M., SOTO-HERMIDA A., VAZQUEZ-MOSQUERA M.E., CORTES-PEREIRA E., RELANO S., HERMIDA-GOMEZ T. ET AL. Mitochondrial DNA haplogroups influence the risk of incident knee osteoarthritis in OAI and CHECK cohorts. A meta-analysis and functional study. *Annals of the Rheumatic Diseases*. 2016.
- GALERA T., ZURITA F., GONZALEZ-PARAMOS C., MORENO-IZQUIERDO A., FRAGA M.F., FERNANDEZ A.F. ET AL. Generation of a human iPSC line from a patient with Leigh syndrome. *Stem Cell Research*. 2016;16(1):63-66.
- ZURITA F., GALERA T., GONZALEZ-PARAMOS C., MORENO-IZQUIERDO A., SCHNEIDERAT P., FRAGA M.F. ET AL. Generation of a human iPSC line from a patient with a defect of intergenomic communication. *Stem Cell Research*. 2016;16(1):120-123.
- ZURITA-DIAZ F., GALERA-MONGE T., MORENO-IZQUIERDO A., FRAGA M.F., AYUSO C., FERNANDEZ A.F. ET AL. Generation of a human iPSC line from a patient with a mitochondrial encephalopathy due to mutations in the GFM1 gene. *Stem Cell Research*. 2016;16(1):124-127.
- GALERA-MONGE T., ZURITA-DIAZ F., MORENO-IZQUIERDO A., FRAGA M.F., FERNANDEZ A.F., AYUSO C. ET AL. Generation of a human iPSC line from a patient with an optic atrophy ‘plus’ phenotype due to a mutation in the OPA1 gene. *Stem Cell Research*. 2016;16(3):673-676.

Highlights

During 2016, our group has been focused on studying different aspects of the mitochondrial physiology. The main research lines are: 1) To search new genes involved in OXPHOS genes using the CRISPR/CAS9 genomic edition tool. 2) Generation of iPSC cells as a model to study mitochondrial disorders and as a tool of therapeutic approximation.

Our group has received funding in several competitive calls: 1) In the AES call of the ISCIII: The project PI15/00484 led by Dr. Gallardo (a permanent researcher hired by CIBER that recently has achieved a positive evaluation in the AES call 2016 from the ISCIII to be contracted as Miguel Servet I researcher). The proposal PI13/00556 led by Dr. Garesse and PI16/00789 led by Dr. Garesse (PI) and Dr. Fernández (co-PI); 2) From “Ministerio de Economía y Competitividad” the project BIO2013-50346-EXP led by Dr. Fernández and 3) ACCI call 2015 led by Dr. Plácido Navas.

From a translational point of view, the group participates in the implementation of several diagnostic platforms that include genes like POLG and sarcomeric genes for the diagnosis of cardiomyopathies (more than 30 genes).

In collaboration with other CIBERER units our group has been involved in a) the elaboration of a normalized method for mtDNA quantification and b) The development of a normalized method for the analysis of the activity of the mitochondrial respiratory chain complexes.


Finally, the group has participated in the generation of a guide: “Ethics in the research in rare diseases” and has an ongoing project in the “Mencia Foundation”. The aim of this proposal is to delve into the knowledge and therapy of the mitochondrial diseases caused by defects in the mitochondrial translation. This project is led by Dr. Gallardo and Dr. Garesse.



LEAD RESEARCHER

Giraldo Castellano, Pilar

 Instituto Aragonés de Ciencias de la Salud
Hospital Miguel Servet
Avda. de Ciba. Campus San Francisco. 50009 Zaragoza

 (+34) 670 285 339 /
976 761 283 /976 762 842

 [Group website](#)

PROGRAMMES

Inherited Metabolic Medicine



GROUP MEMBERS

Staff members: Irún Irún, María Pilar

Contratados a cargo de proyecto: Cebolla Sanz, Jorge Javier

Associated members: Andrade Campos, Marcio | Capablo Liesa, José Luis | Köhler, Ralf | Latre Martínez, Paz | Roca Espiau, Mercedes | Sáenz de Cabezón Álvarez, Alicia

Main lines of research

- Gaucher disease epidemiology, in Spain: National Registry accredited 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

- MARQUES A.R.A., GABRIEL T.L., ATEN J., VAN ROOMEN C.P.A.A., OTTENHOFF R., CLAESSEN N. ET AL. Gpnmb is a potential marker for the visceral pathology in Niemann-Pick type C disease. PLoS ONE. 2016;11(1).
- PAIVA B., MATEOS M.V., SANCHEZ-ABARCA L.I., PUIG N., VIDRIALES M.-B., LOPEZ-CORRAL L. ET AL. Immune status of high-risk smoldering multiple myeloma patients and its therapeutic modulation under lenex: A longitudinal analysis. Blood. 2016;127(9):1151-1162.
- PADRON E., DEZERN A., ANDRADE-CAMPOS M., VADDI K., SCHERLE P., ZHANG Q. ET AL. A multi-institution phase i trial of ruxolitinib in patients with chronic myelomonocytic leukemia (CMML). Clinical Cancer Research. 2016;22(15):3746-3754.
- AL-ALI H.K., GRIESSHAMMER M., LE COUTRE P., WALLER C.F., LIBERATI A.M., SCHAFHAUSEN P. ET AL. Safety and efficacy of ruxolitinib in an open-label, multicenter, single-arm phase 3b expanded-access study in patients with myelofibrosis: A snapshot of 1144 patients in the JUMP trial. Haematologica. 2016;101(9):1065-1073.
- BELMATOUG N., DI ROCCO M., FRAGA C., GIRALDO P., HUGHES D., LUKINA E. ET AL. Management and monitoring recommendations for the use of eliglustat in adults with type 1 Gaucher disease in Europe. European Journal of Internal Medicine. 2016.

Highlights

PROJECTS:

“Evaluation of the function of KCa3.1 channels in the inflammatory complex induced by Gaucher cells. Possibility of therapeutic action”. PS 15/00616. It is carried out in collaboration with the researcher Ralf Köhler. “Project screening of the lipase deficiency of Lipase Acids in Spain”, 15 new families have been identified and the work has been awarded at the Congress of Innate Errors of Metabolism (SSIEM) held in Rome 6-9 September 2016. “Gen-Epigen” project being carried out to deepen the genetic variability of NPC disease, exome study was performed in 21 patients with a single identified variant.

CONGRESSES:

We have been the organizers of the 12th Congress of the European Gaucher Disease Group (EWGGD) held in Zaragoza from 29 June to 2 July 2016. International Congress with the assistance of 278 researchers, health professionals and patients from the European Gaucher Alliance, from 42 countries and in which more than 80 works were presented. The congress was inaugurated by the Health Councilor of Aragon Sebastian Celaya, the President of the EWGGD Stephan Vom Dahl and Dra Giraldo as researcher of CIBERER. Several CIBERER researchers from different groups participated. On July 2nd, 1st GAUCHER DISEASE POST-EWGGD MEETING: “BREAKING FRONTIERS” in which Spanish and Latin American experts participated and the book “The neurological affection of Gaucher disease” was presented in collaboration with researchers Mexicans (ISBN: 9788416585236) and created the Ibero-American Working Group on Gaucher Disease. IBER @ GAUCHER.

CLINICAL TRIALS:

Participated as IP in the Gaucher E trials evaluating Eliglustat: ENCORE. (EudraCT Number: 2008-005223-28), Fabry E: phase II / III evaluating Pegunigalsidase alfa PRX-102 (EudraCT Number: 2016-001318-11, NPC E: evaluating Arimoclomol (EudraCT Number: 2015-004438-93), Myelofibrosis evaluating Momelotinib (EudraCT Number: 2013-005007-13) Chronic myeloid leukemia evaluating Bosutinib (EudraCT Number: 2013-004323-37).



LEAD RESEARCHER

**González Manchón,
Consuelo**

📍 Agencia Estatal Consejo Superior de Investigaciones Científicas
Centro de Inv. Biológicas
Ramiro de Maeztu, 9
28040 Madrid

☎ (+34) 91 837 31 12 ext 4221

✉ cgmanchon@cib.csic.es

🌐 [Group website](#)

PROGRAMMES
Genetic Medicine



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 patients 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

- ALQUEZAR C., DE LA ENCARNACION A., MORENO F., LOPEZ DE MUNAIN A., MARTIN-REQUERO A.. Progranulin deficiency induces overactivation of WNT5A expression via TNF- α /NF- κ B pathway in peripheral cells from frontotemporal dementia-linked granulin mutation carriers. *Journal of Psychiatry and Neuroscience*. 2016;41(4):225-239.
- ALQUEZAR C., SALADO I.G., DE LA ENCARNACION A., PEREZ D.I., MORENO F., GIL C. ET AL. Targeting TDP-43 phosphorylation by Casein Kinase-1 δ inhibitors: A novel strategy for the treatment of frontotemporal dementia. *Molecular Neurodegeneration*. 2016;11(1).
- HORRILLO A., PORRAS G., AYUSO M.S., GONZALEZ-MANCHON C. Loss of endothelial barrier integrity in mice with conditional ablation of podocalyxin (Podxl) in endothelial cells. *European Journal of Cell Biology*. 2016.
- WOJSIAT J., LASKOWSKA-KASZUB K., ALQUEZAR C., BIALOPIOTROWICZ E., ESTERAS N., ZDIORUK M. ET AL. Familial Alzheimer's Disease Lymphocytes Respond Differently Than Sporadic Cells to Oxidative Stress: Upregulated p53-p21 Signaling Linked with Presenilin 1 Mutants. *Molecular Neurobiology*. 2016;1-16.
- NUNEZ-GOMEZ E., PERICACHO M., OLLAURI-IBANEZ C., BERNABEU C., LOPEZ-NOVOA J.M. The role of endoglin in post-ischemic revascularization. *Angiogenesis*. 2016;1-24.

Highlights

We have continued the study of the mechanisms involved in the vasculitis of mice lacking podocalyxin (Podxl) in the vascular endothelium. In addition to regulating endothelial permeability by interacting with intracellular proteins that modulate the actin cytoskeleton, our results suggest that Podxl is an essential component of the endothelial glycocalyx by regulating leukocyte adhesion and trafficking. This is of great interest because the injury of the glycocalyx underlies many vascular diseases and the role and relevance of its components is not known.


In collaboration with unit 707 of CIBERER, we discovered a new role for endoglin in the adhesion of platelets to the endothelium mediated by the integrin α IIb β 3, whose alteration could contribute to the bleeding of patients with hereditary hemorrhagic telangiectasia (HHT) or Rendu-Osler-Weber syndrome. We continued to study the mechanisms that cause cell death in Alzheimer's disease (AD), frontotemporal dementia (FTLD-TDP), and other neurodegenerative diseases. The work focuses on cell cycle dysfunction, apoptosis, mitochondrial impairment, oxidative damage, and protein degradation using in vivo model of neurodegeneration and in vitro culture of cells, including peripheral cells from patients. We have used lymphoblastoid cell lines from patients as a platform to test the therapeutic potential of certain drugs impacting these processes for the treatment of AD and FTLD-TDP. In particular, we have studied the effects of new indazol derivatives, with activity as agonists of cannabinoid receptor of type 2, and novel selective inhibitors of Casein kinase-1 and CDC7 to decrease the phosphorylation of TDP-43.


Patent PCT / ES20167070906, 16-12-2016. Title of the invention: A new family of carboline derivatives of 1-indazolyl with properties of cannabinoids and/or cholinergic and/or regulatory peptide beta-amyloid. Inventors: JA Páez Prosper, NE Campillo Martín, C Pérez Martín, PJ González Naranjo, M Pérez Macías, M López de Ceballos, A Martín Requero, C Alquézar Burillo, MI Martín Fontelles, MR García Moreno, EM Sánchez Robles, J Romero Paredes



LEAD RESEARCHER

Gratacos, Eduard

 Hospital Clínico y Provincial
de Barcelona
Instituto de Investigaciones
Biomédicas August Pi i Sunyer
Sabino de Arana, 1
08028 Barcelona

 (+34) 93 227 99 06 / 932275600
Ext 7254/93 489 40 69

 gratacos@clinic.ub.es

 [Group website](#)

PROGRAMMES

Pediatric and Developmental Medicine



GROUP MEMBERS

Staff members: Crovetto, Francesca | Rodríguez Sureda, Víctor Manuel

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

Main lines of research

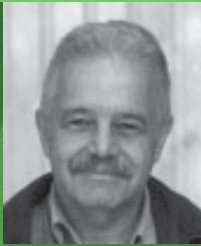
- Fetal and perinatal neurological damage.
- Diseases of placental origin and fetal programming of post-natal cardiac dysfunction.
- Highly complex fetal surgery: complications of monochorial twin pregnancy and congenital diaphragmatic hernia.
- Prenatal diagnosis of genetic and chromosomal abnormalities.
- 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

- ORTIZ J.U., EIXARCH E., PEGUERO A., LOBMAIER S.M., BENNASAR M., MARTINEZ J.M. ET AL. Chorioamniotic membrane separation after fetoscopy in monochorionic twin pregnancy: Incidence and impact on perinatal outcome. *Ultrasound in Obstetrics and Gynecology*. 2016.
- MASOLLER N., SANZ-CORTES M., CRISPI F., GOMEZ O., BENNASAR M., EGANA-UGRINOVIC G. ET AL. Severity of Fetal Brain Abnormalities in Congenital Heart Disease in Relation to the Main Expected Pattern of in utero Brain Blood Supply. *Fetal Diagnosis and Therapy*. 2016;39(4):269-278.
- EIXARCH E., MUNOZ-MORENO E., BARGALLO N., BATALLE D., GRATACOS E. Motor and cortico-striatal-thalamic connectivity alterations in intrauterine growth restriction Presented in part at the 22nd World Congress on Ultrasound in Obstetrics and Gynaecology, Copenhagen, Denmark, September 9-12, 2012. *American Journal of Obstetrics and Gynecology*. 2016;214(6): 725.e1-725.e9.
- GARCIA-OTERO L., LOPEZ M., GOMEZ O., GONCE A., BENNASAR M., MARTINEZ J.M. ET AL. Zidovudine treatment in HIV-infected pregnant women is associated with fetal cardiac remodelling. *AIDS*. 2016.
- PADILLA N, FRANSSON P, DONAIRE A, FIGUERAS F, ARRANZ A, SANZ-CORTÉS M ET AL. Intrinsic Functional Connectivity in Preterm Infants with Fetal Growth Restriction Evaluated at 12 Months Corrected Age. *Cerebral cortex* (New York, N.Y.: 1991). 2016.

Highlights

During 2016 the Fetal and Perinatal Medicine research group led by Dr. Gratacós, has contributed with several clinical algorithms for the screening and the early detection of materno-fetal pathologies, has validated a series of placental insufficiency biomarkers, has helped better define biomarkers in brain images obtained by ultrasound and magnetic resonance, has demonstrated the postnatal persistence of prenatally induced cardiac remodeling and has provided evidence in the mitochondrial toxicity associated to toxic (in collaboration con Cardellach López, Francesc - CB06/07/1002) exposure during the prenatal life. We have also launched a very ambitious project in fetal surgery (FIRST Project, in collaboration with ICFO, IQS, IBEC, UPF) that aims to develop several techniques to aid intrauterine surgery of rare diseases such as congenital diaphragmatic hernia, spina-bifida and fetal transfusion. In addition, the team has stated several clinical trials aimed to improve materno-fetal health, such as a genetic therapy trial to improve placental angiogenesis (Proyecto Europeo FP7 EVERREST), nutritional strategies and stress reduction to improve fetal growth (IMPACT), and a project to define the optimal timing of completion in fetuses with cerebral redistribution signs (RATIO37). Socially, our research group collaborates with various patients and families with rare diseases associations, such as the group called “La vida con hernia diafragmática congénita”.



LEAD RESEARCHER

Grinberg, Daniel

-  **Universidad de Barcelona**
Facultad de Biología.
Diagonal, 643
08028 Barcelona
-  (+34) 93 403 5716
-  dgrinberg@ub.edu
-  [Group website](#)

PROGRAMMES

Inherited Metabolic Medicine



GROUP MEMBERS

Staff members: Cózar Morillo, Mónica | Fernández Castillo, Noelia | Urreizti Frexedas, Roser

Associated members: Balcells Comas, Susana | Cabana Domínguez, Judit | Canals Montferrer, Isaac | Cormand Rifa, Bru | Gómez Grau, Marta | Roca Ayats, Neus | Rodríguez Pascau, Laura | Serra Vinardell, Jenny | Sintas Vives, Celia | Toma Toma, Claudio | Torrico Avlés, Bárbara | Vilageliu Arqués, Lluisa

Colaboradores: Pineda Cirera, Laura

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

- URREIZTI R., ROCA-AYATS N., TREPAT J., GARCIA-GARCIA F., ALEMAN A., ORTESCHI D. ET AL. Screening of CD96 and ASXL1 in 11 patients with Opitz C or Bohring-Opitz syndromes. American Journal of Medical Genetics, Part A. 2016;170(1):24-31.
- SINTAS C., FERNANDEZ-CASTILLO N., VILA-PUEYO M., POZO-ROSICH P., MACAYA A., CORMAND B.. Transcriptomic Changes in Rat Cortex and Brainstem After Cortical Spreading Depression With or Without Pretreatment With Migraine Prophylactic Drugs. Journal of Pain. 2016.
- DIMITRIOU E., COZAR M., MAVRIDOU I., GRINBERG D., VILAGELIU L., MICHELAKAKIS H. The Spectrum of Krabbe Disease in Greece: Biochemical and Molecular Findings. JIMD reports. 2016.
- CABANA-DOMINGUEZ J., RONCERO C., GRAU-LOPEZ L., RODRIGUEZ-CINTAS L., BARRAL C., ABAD A.C. ET AL. A Highly Polymorphic Copy Number Variant in the NSF Gene is Associated with Cocaine Dependence. Scientific Reports. 2016;6.
- FERNANDEZ-CASTILLO N., CORMAND B. Aggressive behavior in humans: Genes and pathways identified through association studies. American Journal of Medical Genetics, Part B: Neuropsychiatric Genetics. 2016.

Highlights

Within the lysosomal disease research line, we used a neuronal model of Sanfilippo C based on iPS cells to perform RNAi treatment tests. We have completed an osteoblast model of Gaucher disease, with complementary assays pending. We obtained and characterized murine models of a splicing mutation generating a pseudoexon responsible for Niemann-Pick C disease (published in 2017).

Within the line on bone diseases, we resequenced Wnt pathway genes and the FLJ42280 gene (published in 2017), and we are completing statistical and functional analyses of interesting variants identified. We generated murine ES cells with homozygous deletion of an FLJ42280 enhancer by CRISPR/Cas9, to obtain a mouse model in the future, and we are performing Hi-C studies. We also identified mutations associated with atypical femoral fractures (by WES) in patients treated with bisphosphonates (submitted).

In the field of neurological diseases, we performed large-scale studies as well as candidate gene approaches to define the genetic landscape of various disorders including autism, migraine, retinal dystrophies, ADHD, drug addiction and aggressive behaviour, including both common and rare SNV and CNV variants. We also performed transcriptomic studies of a mouse model of migraine.


Finally, we have performed WES analyses in patients with a diagnosis of Opitz C or Bohring-Opitz syndrome. We identified the putatively causal mutations in 8 different genes in 8 of 10 families studied. We have just published (2017) one case with a mutation in MAGEL2. We started functional studies of the identified mutations and have started a new round of exome sequencing on new patients of this disease.



LEAD RESEARCHER

Illa Sendra, Isabel

 Instituto de Investigación
del Hospital de la Santa Cruz
y San Pablo
S Antoni M^a Claret 167
08025 Barcelona

 (+34) 93-5565977

 iilla@santpau.cat

 [Group website](#)

PROGRAMMES

Mitochondrial and Neuromuscular Medicine



GROUP MEMBERS

Staff members: Araque Palacios, Josefa | De Luna Salva, Noemí | Segovia Simón, Sonia

Associated members: Alejandre Monforte, Aída | Díaz Manera, Jorge Alberto | Gallardo Vigo, Eduardo | Navas Madroñal, Miquel | 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, dermatomyositis..) and its correlation with specific phenotypes and new treatments. B) Analysis of miRNA profile in plasma/serum of patients with muscular dystrophies and Pompe's disease as biomarkers of the progression 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 aetiology 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:** Analysis of factors involved in muscle regeneration and fibrosis. B) Inhibition of proteasome in muscular dystrophies as a therapeutic approach, C) 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) Epidemiology and genetics of ALS. F) Role of autoantibodies in myasthenia: clinical correlations.
- **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, 5.166 patients have been registered. Twenty-eight hospitals in Spain participate in the registry and a curator is in charge of the quality control of all data included in it (as part of CIBERER facilities).

Most relevant scientific articles

- CRUZ S., CORTES-VICENTE E., ILLA I., ROJAS-GARCIA R. Transthyretin-related hereditary amyloid polyneuropathy presenting with large fibre involvement and cardiomyopathy. *Amyloid*. 2016;23(1):64-65.
- VAN RHEENEN W., SHATUNOV A., DEKKER A.M., MCLAUGHLIN R.L., DIEKSTRA F.P., PULIT S.L. ET AL. Genome-wide association analyses identify new risk variants and the genetic architecture of amyotrophic lateral sclerosis. *Nature Genetics*. 2016;48(9):1043-1048.
- SANDERS D.B., WOLFE G.I., BENATAR M., EVOLI A., GILHUS N.E., ILLA I. ET AL. International consensus guidance for management of myasthenia gravis: Executive summary. *Neurology*. 2016;87(4):419-425.
- FIGUEROA-BONAPARTE S., SEGOVIA S., LLAUGER J., BELMONTE I., PEDROSA I., ALEJALDRE A. ET AL. Muscle MRI findings in childhood/adult onset pompe disease correlate with muscle function. *PLoS ONE*. 2016;11(10).
- CORTES-VICENTE E., GALLARDO E., MARTINEZ.M.A., DIAZ-MANERA J., QUEROL L., ROJAS-GARCIA R. ET AL. Clinical characteristics of patients with double-seronegative myasthenia gravis and antibodies to cortactin. *JAMA Neurology*. 2016;73(9):1099-1104.

Highlights

ERN accreditation (European Reference Network)

After obtaining the CSUR accreditation, the Neuromuscular unit applied to the European ERN accreditation which has also been resolved favorably, forming part of the ERN: EURO-NMD.

NATIONAL REGISTRY OF NEUROMUSCULAR DISEASES.ENM-EN

Currently in CIBERER, it has 5,166 patients included. The connection is maintained with RD-CONNECT and TREAT-NMD.

ISO LABORATORY. The research activity of the group has a very important translational component. Some of the research results have resulted in diagnostic tests performed in our laboratory of Neuromuscular Diseases and we receive national and international samples. In 2015 the laboratory was audited and received ISO9001 accreditation. In May 2016, an external audit was completed favorably to renew ISO9001.

PARTICIPATION IN EUROPEAN COMMITTEES

The group participates actively in European committees related to several diseases well associated to Scientific Societies (EFNS) well connected with the European Economic Community. This is the case, for example, in the COST European Action program "MRI and MRS in neuromuscular diseases (MYO-MRI)" or ENMC workshops.

FINANCING CALL FOR FIS 2016

ILLA FIS PI16 / 01440

QUEROL FIS PI16 / 00627

DOCTORAL THESIS

Usefulness of muscle imaging studies in the diagnosis of a group of myopathies with axial weakness. Universitat Autònoma de Barcelona Aida Alejaldre Monforte 11/8/2016.

New diagnostic biomarkers and prognostic factors in myasthenia gravis. Universitat Autònoma de Barcelona Alba Ramos Fransi. 02/2016.

V COURSE NEUROMUSCULAR DISEASES. Fifth edition. Training of neurologists in clinical aspects of these diseases and in participation in research (through registry of the patients and practices in the laboratory). It has a clausus number of registrations and has a great acceptance.

RELEVANT RESULTS

Description of new muscular MRI patterns in different muscular dystrophies.

Demonstration of the benefit of thymectomy in myasthenia.

Advances in the natural history of dysferlinopathies.


Identification of new risk variants of ALS.


New methods to identify biomarkers in CIDP and Myasthenia.



LEAD RESEARCHER

Knecht, Erwin

 Fundación Centro de
Investigación Príncipe Felipe
C/ Eduardo Primo Yúfera 3
46013 Valencia

 (+34) 96 328 96 81- Ext: 2007 /
2008 (Carmen Aguado)

 eknecht@cipf.es

 [Group website](#)

PROGRAMMES
Genetic Medicine

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., RUIZ M., GRAU L., ORTEGA F.J., ILIEVA E.V., MARTINEZ J.J. ET AL. Tauroursodeoxycholic bile acid arrests axonal degeneration by inhibiting the unfolded protein response in X-linked adrenoleukodystrophy. *Acta Neuropathologica*. 2016;1-19.
- KLIONSKY DJ, ABDELMOHSEN K, ABE A, ABEDIN MJ, ABELIOVICH H, ACEVEDO AROZENA A ET AL. Guidelines for the use and interpretation of assays for monitoring autophagy (3rd edition). *Autophagy*. 2016;12(1):1-222.
- MACIAS-VIDAL J., GUERRERO-HERNANDEZ M., ESTANYOL J.M., AGUADO C., KNECHT E., COLL M.J. ET AL. Identification of lysosomal Npc1-binding proteins: Cathepsin D activity is regulated by NPC1. *Proteomics*. 2016;16(1):150-158.
- AGUADO C., PEREZ-JIMENEZ E., LAHUERTA M., KNECHT E. Isolation of lysosomes from mammalian tissues and cultured cells. *Methods in Molecular Biology*. 2016; 1449:299-311.
- LUPO V, AGUADO C, KNECHT E, ESPINÓS C. Chaperonopathies: Spotlight on Hereditary Motor Neuropathies. *Frontiers in molecular biosciences*. 2016; 3:81.

Highlights

We collaborate with other units, mainly U-742, to study Lafora disease. We found malin mainly in the nucleus, whereas only in the absence of glucose is laforin significantly located there, where it is monoubiquitinated. We have also ruled out the association of laforin/malin with cytosolic ribonucleoprotein structures and a role in mRNA transport. All these results suggest that this complex regulates the transcription of genes related to glucose metabolism. Finally, we further investigated the autophagy alteration previously described by us, demonstrating that the AKT-mTOR-ULK1 pathway is active in laforin/malin deficient cells and discarding other pathways involving GSK3beta, FOXO1, AMPK or MAPKs. That alteration prevents the phagophore formation and the elimination of damaged material, as we have confirmed with respiratory chain uncouplers with mitochondria.

In neuronal ceroid lipofuscinoses we collaborated with U-755 in a final degree project based on the application of the CRISPR/Cas9 system to study Batten's disease.

In collaboration with U-718 we have confirmed that CERKL protein, involved in retinitis pigmentosa, binds to mRNAs that encode anti-apoptotic proteins.

Also in 2016 the European Medicine Agency accepted the designation of temsirolimus as an orphan drug for the treatment of X-adrenoleukodystrophy, based on a publication and a European patent (EP14382353.2) from our collaboration with U-759.





Dr. Armengod collaborates with units U-701 and U-723 studying the role of microRNAs and mutations affecting tRNAs in mitochondrial diseases (hypertrophic cardiomyopathy and pediatric liver failure associated with mutations in tRNA modifiers, MERRF and MELAS).

Together with other groups in the Valencian Community, we participated in a Framework to establish an Alliance in Translational Research to work on Rare Diseases (DOGV, No. 7654, pp. 29208-29216) and we have been part of two Joint Units on Rare Diseases between the CIPF and two Institutes of Sanitary Research (INCLIVA and IIS La Fe).



LEAD RESEARCHER

**Lapunzina Badia,
Pablo Daniel**

-  Servicio Madrileño de Salud
Hospital La Paz
Paseo de la Castellana, 261
28046 Madrid
-  (+34) 91 727 72 17
-  plapunzina@ciberer.es
-  [Group website](#)

PROGRAMMES

Pediatric and Developmental Medicine



GROUP MEMBERS

Staff members: Benito Sanz, Sara | Martínez González, Víctor Manuel

Associated members: Aza Carmona, Miriam | Barroso Ramos, Eva | Belinchón Martínez, Alberta | Campos Barros, Ángel | De Torres Pérez Hidalgo, María Luisa | Del Pozo Mate, Ángela | Ezquieta Zubizaray, Begoña | Fernández García Moya, Luis | García Santiago, Fe Amalia | García-Miñaur Rica, Sixto | Heath, Karen Elise | Mansilla Aparicio, Elena | Martínez Fernández, Pilar | Martínez Montero, Paloma | Molano Mateos, Jesús | Mori Álvarez, María de los Ángeles | Nevado Blanco, Julián | Palomares Bralo, María | 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 cardiomyopathy.
- 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.
- Identification and characterization of molecular mechanisms involved in Disorders of Sexual Development (DSD).

Most relevant scientific articles

- EGGERMANN T., BRIOUDE F., RUSSO S., LOMBARDI M.P., BLIEK J., MAHER E.R. ET AL. Prenatal molecular testing for Beckwith-Wiedemann and Silver-Russell syndromes: A challenge for molecular analysis and genetic counseling. *European Journal of Human Genetics*. 2016;24(6):784-793.
- SANCHEZ-DELGADO M., RICCIO A., EGGERMANN T., MAHER E.R., LAPUNZINA P., MACKAY D. ET AL. Causes and Consequences of Multi-Locus Imprinting Disturbances in Humans. *Trends in Genetics*. 2016;32(7):444-455.
- SZAFRANSKI P., GAMBIN T., DHARMADHIKARI A.V., AKDEMIR K.C., JHANGIANI S.N., SCHUETTE J. ET AL. Pathogenetics of alveolar capillary dysplasia with misalignment of pulmonary veins. *Human Genetics*. 2016;135(5):569-586.
- CEA L.A., PUEBLA C., CISTERNA B.A., ESCAMILLA R., VARGAS A.A., FRANK M. ET AL. Fast skeletal myofibers of mdx mouse, model of Duchenne muscular dystrophy, express connexin hemichannels that lead to apoptosis. *Cellular and Molecular Life Sciences*. 2016;:1-17.
- GRINSPON R.P., NEVADO J., MORI ALVAREZ M.D.L.A., DEL REY G., CASTERA R., VENARA M. ET AL. 46,XX ovotesticular DSD associated with a SOX3 gene duplication in a SRY-negative boy. *Clinical Endocrinology*. 2016.

Highlights


During 2016 we have contributed with 47 publications, with an average impact factor of 3.8. Among them we can highlight articles in journals such as *Hum Mol Genet*, *J Clin End Metabol*, *Trends Genet*, *Eur J Hum Genet*, *Hum Genet*, etc. As achieved technological milestones, we have developed genomic technologies such as SNP arrays and NGS platforms at the clinical setting, being a pioneer initiative in Spanish hospitals. We have also supported the first section of bioinformatics located in a public hospital in Madrid, with three bioinformaticians. During this period 17 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 Pdl such as organizing conferences, national and international workshops, the CIBERER-DNA-DAY, and organization of conferences and meetings with patients associations were performed. 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 research and the biological basis of disease, and in the last two years, especially bioinformatics, genomics and systems biology). The INGEMM consists of 21 sections and has a large number of patients and samples from patients with rare genetic diseases.




LEAD RESEARCHER

López Trascasa, Margarita

 Servicio Madrileño de Salud
Hospital La Paz
Paseo de la Castellana, 261
28046 Madrid

 (+34) 91 207 14 63

 mltrascasa@salud.madrid.org

 [Group website](#)

PROGRAMMES
Genetic Medicine



GROUP MEMBERS

Staff members: López Lera, Alberto

Associated members: Caballero Molina, María Teresa | Corvillo Rodríguez, Fernando | 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 efficacy of novel treatments and evaluation of quality of life in patients.

Most relevant scientific articles

- NOZAL P., BERNABEU-HERRERO M.E., UZONYI B., SZILAGYI A., HYVARINEN S., PROHASZKA Z. ET AL. Heterogeneity but individual constancy of epitopes, isotypes and avidity of factor H autoantibodies in atypical hemolytic uremic syndrome. *Molecular Immunology*. 2016; 70:47-55.
- BLOM A.M., CORVILLO F., MAGDA M., STASILOJC G., NOZAL P., PEREZ-VALDIVIA M.A. ET AL. Testing the Activity of Complement Convertases in Serum/Plasma for Diagnosis of C4NeF-Mediated C3 Glomerulonephritis. *Journal of Clinical Immunology*. 2016;1-11.
- 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. *Clinical and experimental immunology*. 2016.
- ZANICHELLI A., LONGHURST H.J., MAURER M., BOUILLET L., ABERER W., FABIEN V. ET AL. Misdiagnosis trends in patients with hereditary angioedema from the real-world clinical setting. *Annals of Allergy, Asthma and Immunology*. 2016;117(4):394-398.
- LONGHURST H.J., ABERER W., BOUILLET L., CABALLERO T., MAURER M., FABIEN V. ET AL. The Icatibant Outcome Survey: Treatment of laryngeal angioedema attacks. *European Journal of Emergency Medicine*. 2016;23(3):224-227.

Highlights

During 2016, our group has continued developing its main research lines, with financial support from public and private funds. The PI Margarita López Trascasa leads 2 public research projects, SAF2012-38636 (until December 31, 2016) and PI15-00255 (2016-2018), and she has received a grant from the Spanish National Society for Nephrology (SENEFRO) for a novel project on glomerulonephritis and lipodystrophia. Pilar Sánchez-Corral, moreover, is the PI of projects PI12-00597 (until June 31, 2017) and PI16-00763 (2017-2019), both of them focused on atypical Haemolytic Uraemic Syndrome.

Several group's members have taken part in scientific meetings on thrombotic microangiopathies and Hereditary Angioedema as guest speakers. Alberto López and Pilar Nozal presented their results in the Spanish Society for Immunology meeting held on May at Alicante, where Fernando Corvillo was awarded with the "Best Poster Prize".

The book "Angioedema" (ISBN: 978-84-944977-0-4), coordinated by Teresa Caballero (with Alberto López and Margarita López as authors of one chapter), was also presented on May. In September, 2 PhD theses from our group were defended, and obtained the summa cum laude ("Defects in complement Factor H-related proteins in renal pathology" by María Elvira Bernabéu; and "Antibodies against complement alternative pathway proteins in renal disease" by Pilar Nozal).

In November 28, 140 professionals from the National Health system attended the second edition of "Complement in Renal Pathology", a training course held at Hospital La Paz and funded by CIBERER. Our group has significantly contributed to the Universidad de Alcalá-specific degree "Especialista en Angiodema Hereditario", coordinated by Teresa Caballero. Dr. Caballero has also received the IdiPAZ award for her work on Hereditary Angioedema and quality of life. She is PI of several clinical trials, like CSL830-3002 related with profilaxis with subcutaneous C1-inhibitor.



LEAD RESEARCHER

Marfany Nadal, Gemma

-  [Universidad de Barcelona](#)
Facultad de Biología.
Diagonal, 643
08028 Barcelona
-  (+34) 93 402 15 02
-  gmarfany@ub.edu
-  [Group website](#)

PROGRAMMES

Sensorineural Pathology

GROUP MEMBERS

Staff members: Andrés Ventura, María Rosa

Associated members: De Castro Miró, Marta | González Duarte, Roser

Main lines of research

Unit U718

Since I am a PI, my research has been focused on the field of human molecular genetics, and I have been closely collaborated with the group of Dr. González-Duarte, with whom we have co-supervised 6 PhD Theses, and co-authored many articles. Our research group was first committed to find new human genes on chromosome 21, putatively involved in the Down syndrome. As a result, we identified USP25, a new gene on chromosome 21 that encodes a deubiquitinase enzyme. We focused on elucidating its structure, transcriptional products, protein interactions and regulation, producing several articles and two theses. Other lines of research included the genetic bases of Alzheimer's disease and diabetes. During the last decade, I have been mainly interested in searching new causative genes of retinal dystrophies. Besides generating a large number of articles, highly cited in the field of molecular genetics vision, we submitted a patent application for the design of a high-throughput chip for retinal dystrophy genetic diagnosis, which has been expanded and is currently used in genetic diagnosis of families with retinitis pigmentosa, Leber congenital amaurosis, achromatopsia, coroideremia and cone dystrophy. Currently, most of our research goals are focused on both the genetic-molecular diagnosis and the identification of retinal dystrophy genes, as well as in the functional gene analysis either in cell cultures or in generating model organisms, thus generating knockdown (zebrafish), knockout (mouse), and of late, CRISPR-edited mouse models.

Most relevant scientific articles

- DE CASTRO-MIRO M., TONDA R., ESCUDERO-FERRUZ P., ANDRES R., MAYOR-LORENZO A., CASTRO J. ET AL. Novel candidate genes and a wide spectrum of structural and point mutations responsible for inherited retinal dystrophies revealed by exome sequencing. PLoS ONE. 2016;11(12).
- ESQUERDO M., GRAU-BOVE X., GARANTO A., TOULIS V., GARCIA-MONCLUS S., MILLO E. ET AL. Expression Atlas of the Deubiquitinating Enzymes in the Adult Mouse Retina, Their Evolutionary Diversification and Phenotypic Roles. PLoS ONE. 2016;11(3).
- MASOUMI K.C., MARFANY G., WU Y., Massoumi R. Putative role of SUMOylation in controlling the activity of deubiquitinating enzymes in cancer. Future Oncology. 2016;12(4):565-574.

Highlights

During 2016, our research group U718 changed PIs. Currently, Gemma Marfany is the PI, in substitution of Professor Roser Gonzalez.

Among the most relevant scientific activities, we generated two new murine retinal dystrophy models – bearing large or small deletions– using CRISPR/Cas9. The project was initiated with Acción Intramural del CIBERER, ACCI2015- MODCELANI_CRISPR, in a joint project led by Lluís Montoliu, IP of the U756 group, and it is now ongoing with a new ACCI 2016_FENOCRISPR, which aims to phenotype CRISPR-generated models. Our extensive studies in animal models led us to the publication of a protocol that compared gene expression in mouse and zebrafish to perform functional knockdown assays by morpholino microinjection in zebrafish embryos (published in *Methods in Molecular Biology*, Toulis et al., 2016, not included in this scientific report). Moreover, new candidate RP genes were identified in a cohort analyzed by whole exome sequencing (WES), using a prioritized pipeline. We have closely worked together with patients and their associations, by organizing several workshops 2015 (with other CIBERER groups) and 2016.

In brief, during 2016 our group has: 1) produced three articles and one protocol directly associated to rare diseases; 2) contributed to international (four) and national (eight) congresses; 3) raised grants within CIBER for implementation of ACCI-2015, and the newly granted ACCI-2016; 4) raised new competitive funds in the Programa Nacional de Retos para la sociedad (2017-2019 funding); 5) organized one scientific (october 2015) and one patient-driven (october 2016) workshops on rare diseases, always considering patients, families and their associations; 6) participated in congresses and meetings organized by patient associations, e.g. FEDER (november 2016); 7) contributed to a european COST action aiming to the training and networking of young scientists across many european countries (PROTEOSTASIS BM1307).



LEAD RESEARCHER

Martí Seves, Ramón

 **Fundación Hospital
Universitario Vall d'Hebron -
Institut de Recerca (VHIR)**
Hospital Vall d'Hebron
Passeig Vall d'Hebron, 119-129
08035 Barcelona

 (+34) 934894054

 ramon.marti@vhir.org

 [Group website](#)

PROGRAMMES

Mitochondrial and Neuromuscular Medicine



GROUP MEMBERS

Staff members: Cámara Navarro, Yolanda | Pinós Figueras, Tomás

Contratados a cargo de proyecto: Blázquez Bermejo, Cora | Molina Granada, David

Associated members: Andreu Periz, Antonio Luis | Brull Cañagueral, Astrid | Carreño Gago, Lidia | García Arumí, Elena | Melía 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

- TORRES-TORRONTERAS J., CABRERA-PEREZ R., BARBA I., COSTA C., DE LUNA N., ANDREU A.L. ET AL. Long-Term Restoration of Thymidine Phosphorylase Function and Nucleoside Homeostasis Using Hematopoietic Gene Therapy in a Murine Model of Mitochondrial Neurogastrointestinal Encephalomyopathy. *Human Gene Therapy*. 2016;27(9):656-667.
- GARCIA-CONSUEGRA I., BLAZQUEZ A., RUBIO J.C., ARENAS J., BALLESTER-LOPEZ A., GONZALEZ-QUINTANA A. ET AL. Taking advantage of an old concept, “illegitimate transcription”, for a proposed novel method of genetic diagnosis of McArdle disease. *Genetics in Medicine*. 2016;18(11):1128-1135.
- DALLA ROSA I., CAMARA Y., DURIGON R., MOSS C.F., VIDONI S., AKMAN G. ET AL. MPV17 Loss Causes Deoxynucleotide Insufficiency and Slow DNA Replication in Mitochondria. *PLoS Genetics*. 2016;12(1).
- FIUZA-LUCES C., NOGALES-GADEA G., GARCIA-CONSUEGRA I., PAREJA-GALEANO H., RUFIAN-VAZQUEZ L., PEREZ L.M. ET AL. Muscle Signaling in Exercise Intolerance: Insights from the McArdle Mouse Model. *Medicine and Science in Sports and Exercise*. 2016.
- BADIA R., ANGULO G., RIVEIRA-MUNOZ E., PUJANTELL M., PUIG T., RAMIREZ C. ET AL. Inhibition of herpes simplex virus type 1 by the CDK6 inhibitor PD-0332991 (palbociclib) through the control of SAMHD1. *Journal of Antimicrobial Chemotherapy*. 2016;71(2):387-394.

Highlights

We have obtained orphan drug designation from the EMA for two potential treatments of glycogenosis type V, (McArdle disease), for valproate (EU/3/16/1734) and triheptanoin (EU/3/16/1710).

-We have issued a patent for the treatment of mtDNA depletion syndrome with nucleosides (70% VHIR; 30% CIBER). The negotiations with the company Meves Pharmaceuticals to sign a license option are ongoing. In addition, another patent managed by Columbia University (New York) for the treatment of TK2 deficiency with nucleosides, in which Ramon Martí has 20% of participation, has been recently licensed to Meves Pharmaceuticals too.

-We have been granted with a 3-year project (2017-2019), focused on combined oxidative phosphorylation deficiency 1 (COXPD1), due to mutations in the GFM1 gene encoding the mitochondrial elongation factor G1. The main aim of the project is the generation and characterization of a murine model of the disease. The project has been granted with funds from the Fundació Mencía and Fundació La Caixa and it is managed by the CIBER.

-The EUROMAC project, a European registry of McArdle disease and other muscle glycogenoses funded by CHAFAE and coordinated by this group, has been successfully closed (December 2016) with more than 250 registered patients. Funds for the continuity and extension of the EUROMAC registry have been obtained as indicated below.

-Tomàs Pinós, a member of our group contracted by the CIBER, has been granted with a project funded by the ISCIII (PI16/01492) whose main objectives are to deepen in the study of the murine model of McArdle disease and testing potential therapy approaches. The project includes as well funds for the maintenance of the EUROMAC registry. Therefore, CIBERER is sponsoring the maintenance of this European registry for at least 3 more years (2017–2019).



LEAD RESEARCHER

**Martín Casanueva,
Miguel Ángel**

📍 **Servicio Madrileño de Salud**
Hospital Univ. 12 de Octubre.
Av. de Córdoba S/N.
Centro de Actividades
Ambulatorias
6ª Pl. Bloque D, Pasillo 1.
28041 Madrid

☎ (+34) 91 779 27 85

✉ labmito@h12o.es

🌐 [Group website](#)

PROGRAMMES

Mitochondrial and Neuromuscular Medicine



GROUP MEMBERS

Staff members: Blázquez Encinar, Alberto | Jiménez García, Sara

Associated members: Arenas Barbero, Joaquín | Atencia Cibreiro, María Gabriela | Del Hoyo Gordillo, Pilar | Delmiro Magdalena, Aitor | Domínguez González, Cristina | Esteban Pérez, Jesús | Fiuza Luces, Carmen | García Redondo, Alberto | García Silva, María Teresa | García-Consuegra Galiana, Inés | 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 and respirasome by BN_PAGE and its clinical translation
- Identification and validation of biomarkers in mitochondrial disorders.
- 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 and autophagy pathway abnormalities using a graft versus host murine model t.
- Oxygen consumption as in vivo marker of mitochondrial disorders.

Most relevant scientific articles

- GARCIA-CONSUEGRA I., BLAZQUEZ A., RUBIO J.C., ARENAS J., BALLESTER-LOPEZ A., GONZALEZ-QUINTANA A. ET AL. Taking advantage of an old concept, “illegitimate transcription”, for a proposed novel method of genetic diagnosis of McArdle disease. *Genetics in Medicine*. 2016;18(11):1128-1135.
- PÉREZ-PÉREZ R, LOBO-JARNE T, MILENKOVIC D, MOURIER A, BRATIC A, GARCÍA-BARTOLOMÉ A ET AL. COX7A2L Is a Mitochondrial Complex III Binding Protein that Stabilizes the III2+IV Supercomplex without Affecting Respirasome Formation. *Cell reports*. 2016;16(9):2387-98.
- MARTIN M.A., GARCIA-SILVA M.T., BARCIA G., DELMIRO A., RODRIGUEZ-GARCIA M.E., BLAZQUEZ A. ET AL. The homozygous R504C mutation in MTO1 gene is responsible for ONCE syndrome. *Clinical Genetics*. 2016.
- FIUZA-LUCES C., NOGALES-GADEA G., GARCIA-CONSUEGRA I., PAREJA-GALEANO H., RUFIAN-VAZQUEZ L., PEREZ L.M. ET AL. Muscle Signaling in Exercise Intolerance: Insights from the McArdle Mouse Model. *Medicine and Science in Sports and Exercise*. 2016.
- FIUZA-LUCES C., SANTOS-LOZANO A., GARCIA-SILVA M.T., MARTIN-HERNANDEZ E., QUIJADA-FRAILE P., MARIN-PEIRO M. ET AL. Assessment of resting energy expenditure in pediatric mitochondrial diseases with indirect calorimetry. *Clinical Nutrition*. 2016.

Highlights


At the clinical-translational level we are National Reference Center (CSUR) mitochondrial and inherited metabolic disorders (coordinator Dr. García-Silva), and we have been included in an European reference network (ERN). The use of NGS approaches has enabled to identify novel mutations in genes related to the OXPHOS function which has been associated to complex phenotypes (e.g. ATP8A2 gene and MTO1 gene – Dr. Martínez-Azorín). We have studied the role of the COX7A2L protein in the assembly pathway of the mitochondrial supercomplexes and the respirasome structure (Dr. Ugalde). We evaluated parameters of indirect calorimetry in pediatric patients (Dr. Silva and Dr. Morán). In collaboration with the U701 (Dr. Martí), we have advanced the multicenter personalized medicine ISCIII-FIS project, identifying new patients using NGS with mutations in nuclear genes associated with maintenance of mtDNA, and specifically establishing the clinical and laboratory parameters for the evaluation of the treatment with nucleosides in patients with TK2 mutations (Dr. Domínguez). We are finishing the intramural project ACCI (with U713 and U701) on the detection of differential bioenergetic protein biomarkers of the mitochondrial PEO phenotype. With Dr. Desviat (U746), we have collaborated on the analysis of mitochondrial dysfunction in the propionic acidemia. In collaboration with Prof. Simarro (U. Valladolid) we have investigated the role of FASTKD3 protein in the mitochondrial post-transcriptional regulation.


In McArdle’s disease (GSDV) we have accomplished the EU project of European Registry of patients, and we have published several articles related to genetics, pathophysiology and intervention with physical exercise in collaboration with U701; IGTIP (Dr. Nogales-Gadea) and UEM(Prof. Lucía); and we are developing an ISCIII project (Dr. Arenas) in the field of proteomics and genomics of the GSDV as well as a recent approved ACCI. In ALS we have participated in several large international studies for discovering new genes associated with the disease (Dr. García-Redondo).




LEAD RESEARCHER

**Medina Torres,
Miguel Ángel**

 **Universidad de Málaga**
Facultad de Ciencias
Campus de Teatinos s/n
Módulo de Biología, 1ª planta
29071 Málaga

 (+34) 952 137 132

 medina@uma.es

 [Group website](#)

PROGRAMMES

Inherited Metabolic Medicine

GROUP MEMBERS

Staff members: Montáñez Martínez, Raúl | Moya García, Aurelio Ángel

Associated members: Abrighach, Hicham | Fajardo Paredes, Ignacio José | García Ranea, Juan Antonio | García-Vilas García, Javier Alejandro | Rodríguez Quesada, Ana | Sánchez Jiménez, Francisca | Urdiales Ruiz, José Luis

Main lines of research

- From biogenic amine-related pathophysiological knowledge to applications on rare diseases.
- Identification of genes and molecular mechanisms of patho-phenotypes associated to rare diseases from Systems Biology.
- Metabolic studies in tumor and angiogenic microenvironments.
- Search and characterization of angiogenesis modulators.
- Development of bioinformatics tools for automated capture of biological information.

Most relevant scientific articles

- REYES-PALOMARES A., BUENO A., RODRIGUEZ-LOPEZ R., MEDINA M., SANCHEZ-JIMENEZ F., CORPAS M. ET AL. Systematic identification of phenotypically enriched loci using a patient network of genomic disorders. BMC Genomics. 2016;17(1).
- GARCIA-CABALLERO M., BLACHER S., PAUPERT J., QUESADA A.R., MEDINA M.A., NOEL A. Novel application assigned to toluquinol: Inhibition of lymphangiogenesis by interfering with VEGF-C/VEGFR-3 signalling pathway. British Journal of Pharmacology. 2016.
- BUENO A., MORILLA I., DIEZ D., MOYA-GARCIA A.A., LOZANO J., RANEA J.A.G. Exploring the interactions of the RAS family in the human protein network and their potential implications in RAS-directed therapies. Oncotarget. 2016;7(46):75810-75826.
- SANCHEZ-JIMENEZ F., PINO-ANGELES A., RODRIGUEZ-LOPEZ R., MORALES M., URDIALES J.L. Structural and functional analogies and differences between histidine decarboxylase and aromatic L-amino acid decarboxylase molecular networks: Biomedical implications. Pharmacological Research. 2016; 114:90-102.
- ROJANO E., RANEA J.A., PERKINS J.R.. Characterisation of non-coding genetic variation in histamine receptors using AnNCR-SNP. Amino Acids. 2016;48(10):2433-2442.

Highlights

HUMAN CAPITAL

- in 2016 joined our group Dr. Aurelio Moya as a Post-Doc CIBERER Researcher. Graduates and M.D. M^a Carmen Ocaña Farfán and Paloma Carrillo Fernández joined our group with a FPU Fellowship and with a contract associated to Grant P12-CTS-1507 (Plan Andaluz de Investigación), respectively.

SCIENTIFIC PRODUCTION

- In 2016, our group has published 15 scientific articles and 1 book chapter (García-Caballero M, Martínez-Poveda B, Medina MA, Quesada AR. Targeting tumor angiogenesis for cancer prevention. In Molecular Targets and Strategies in Cancer Prevention (Chatterjee M, ed), pp 117-149, Springer 2016, ISBN 978-3-319-31252-1).
- In 2016, CIBERER post-doctoral researcher Raúl Montañez published 5 articles. The synthetic biology approaches developed in one of these articles (Nucleic Acids Res 44, 496-507, 2016) are being adapted for the study of rare diseases.
- In 2016, our group has got a Spanish invention patent (ES2545929) and the entry into the regional phase of an international patent application (PCT/EP2014/064641).



LEAD RESEARCHER

Milà, Montserrat

-  Hospital Clínico y Provincial de Barcelona
Villarroel, 170
08036 Barcelona
-  (+34) 93 227 54 00 ext 3406
-  mmila@clinic.cat
-  [Group website](#)

PROGRAMMES

Pediatric and Developmental Medicine



GROUP MEMBERS

Staff members: Giménez Xavier, Pol | Tell Martí, Gemma

Associated members: Aguilera Peiró, Paula | Badenas Orquín, Celia | Carrera Álvarez, Cristina | Jiménez Sánchez, María Dolores | Madrigal Bajo, Irene | Malvey Guilera, Josep | Margarit Torrent, Esther | Puig Sardá, Susana | Rodríguez-Revenga Bodi, Laia | Sánchez Díaz, María Aurora | Soler Casas, Anna María

Main lines of research

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

Most relevant scientific articles

- SAEZ M.A., FERNANDEZ-RODRIGUEZ J., MOUTINHO C., SANCHEZ-MUT J.V., GOMEZ A., VIDAL E. ET AL. Mutations in JMJD1C are involved in Rett syndrome and intellectual disability. *Genetics in Medicine*. 2016;18(4):378-385.
- ALVAREZ-MORA M.I., RODRIGUEZ-REVENGA L., MADRIGAL I., GUITART-MAMPEL M., GARRABOU G., MILA M. Impaired Mitochondrial Function and Dynamics in the Pathogenesis of FXTAS. *Molecular Neurobiology*. 2016;1-7.
- PUIG S., POTRONY M., CUELLAR F., PUIG-BUTILLE J.A., CARRERA C., AGUILERA P. ET AL. Characterization of individuals at high risk of developing melanoma in Latin America: Bases for genetic counseling in melanoma. *Genetics in Medicine*. 2016;18(7):727-736.
- POTRONY M., CARRERAS E., ARANDA F., ZIMMER L., PUIG-BUTILLE J.-A., TELL-MARTI G. ET AL. Inherited functional variants of the lymphocyte receptor CD5 influence melanoma survival. *International Journal of Cancer*. 2016.
- BRUGUES A., GAMBOA M., ALOS L., CARRERA C., MALVEHY J., PUIG S.. The challenging diagnosis of eccrine poromas. *Journal of the American Academy of Dermatology*. 2016;74(6):e113-e115.


Highlights

We belong to the Pediatric Medicine and Development Program and our main areas of interest are in the fields of clinical and molecular genetics. The research activity is focused on the genetic basis of rare diseases, mainly neurodevelopmental disorders, genodermatosis and familial cancer. Our group performs its research activity closely linked to daily clinical practice; we are a clinical-translational group. Throughout this year, the U726 unit has worked in 3 projects of Health Research (FIS) awarded by the ISCIII, a collaborative project financed by the Fundació La Marató de TV3 and an ACCI project in collaboration with the U714 financed by CIBERer . Within the framework of CIBERER and together with units U-735, U-753, U715 and four clinical units, a project of the Carlos III institute has been achieved, evidencing the collaboration with other CIBERER groups (publications and collaborative project) We have also participated in a collaborative project of national scope granted by the AECC. At the clinical level, our unit has led the DIAGNÓPTICS project funded by the European Commission and has given the XVIII dermatoscopy fundamental course held in Barcelona. We have actively collaborated with patient associations of Fragile Syndrome X and Melanoma. We have edited 2 books and a special issue of *The Cerebellum* journal, related to the pathologies associated to the FMR1 gene. We believe that our group in collaboration with others from CIBERER or other CIBERs can contribute to the improvement of pre-symptomatic, prenatal and postnatal genetic diagnosis, we also can be a translational platform for other more basic groups providing clinical information, patients, samples and collaborating in the identification of genetic mutations and new genes.



LEAD RESEARCHER

**Millán Salvador,
José María**

 Fund. para la Investigación
del Hospital la Fe
Avda. F. Abril Martorell, 106
46009 Valencia

 (+34) 96 197 31 53

 millan_jos@gva.es

 [Group website](#)

PROGRAMMES

Sensorineural Pathology



GROUP MEMBERS

Staff members: García García, Gema | Olivares González, Lorena

Associated members: Aller Mañas, Elena | Aparisi Navarro, María José | Jaijo Sanchís, Teresa | Morera Pérez, Constantino | Pérez Garriguez, 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

- PEREZ-CARRO R., CORTON M., SANCHEZ-NAVARRO I., ZURITA O., SANCHEZ-BOLIVAR N., SANCHEZ-ALCUDIA R. ET AL. Panel-based NGS Reveals Novel Pathogenic Mutations in Autosomal Recessive Retinitis Pigmentosa. Scientific Reports. 2016;6.
- BLANCO-KELLY F., GARCIA HOYOS M., LOPEZ MARTINEZ M.A., LOPEZ-MOLINA M.I., RIVEIRO-ALVAREZ R., FERNANDEZ-SAN JOSE P. ET AL. Dominant retinitis pigmentosa, p.Gly56Arg mutation in NR2E3: Phenotype in a large cohort of 24 cases. PLoS ONE. 2016;11(2).
- OLIVARES-GONZALEZ L., DE LA CAMARA C.M.-F., HERVAS D., MARIN M.P., LAHOZ A., MILLAN J.M. ET AL. CGMP-phosphodiesterase inhibition prevents hypoxia-induced cell death activation in porcine retinal explants. PLoS ONE. 2016;11(11).
- TELL-MARTI G., PUIG-BUTILLE J.A., GIMENEZ-XAVIER P., SEGU-ROIG A., POTRONY M., BADENAS C. ET AL. The p. R151C Polymorphism in MC1R Gene Modifies the Age of Onset in Spanish Huntington's Disease Patients. Molecular Neurobiology. 2016;1-5.
- PEREZ-CARRO R, CORTON M, SÁNCHEZ-NAVARRO I, ZURITA O, SANCHEZ-BOLIVAR N, SÁNCHEZ-ALCUDIA R ET AL. Corrigendum: Panel-based NGS Reveals Novel Pathogenic Mutations in Autosomal Recessive Retinitis Pigmentosa. Scientific reports. 2016; 6:24843.

Highlights

As relevant milestones of 2016 we have achieved a FIS project for genomic studies, preclinical and clinical studies for Usher syndrome in order to apply a precision medicine both in this syndrome and in inherited retinal dystrophies (IRD) in general. In this regard, we have developed a panel that includes all the genes associated with IRD and 96 patients, many of them pediatric, have already been analyzed. In the same way, we have developed a panel that includes all the genes related to muscular dystrophies.

We have participated in the Clinical Practice Guide for Retinal Dystrophies requested by the Ministry of Health.

We have an ongoing clinical trial on the effect of nutraceuticals in patients with retinitis pigmentosa (RP). We have tested the protective effect of DEMOG (inhibitor of hypoxia inducible factor, HIF) on retinas of a murine model of RP.

We have been able to edit fibroblasts from patients with Usher syndrome using the CRISPR technology and we have corrected the mutation c.2299delG of the USH2A gene.

We are analyzing the use of inorganic nanoparticles as a vehicle to deliver adalimumab (which we have already shown to have a protective effect) on the retina of a murine model of RP.

The patent with the title "Use of macroazapyridinophanes metal complexes in the treatment of neurodegenerative and age-related diseases" has been requested (in collaboration with an Spin-off of the Medical Research Institute La Fe).

We investigated the protective effect of metformin in Huntington's disease models of C.elegans and mice and its effect on the behavior of Huntington's disease patients recruited in the international observational study REGISTRY has been investigated.



LEAD RESEARCHER

Montoliu Jose, Lluís

📍 Agencia Est. Consejo Superior de Investigaciones Científicas
C. Nacional de Biotecnología
Universidad Aut. de Madrid
Dpto. de Biología Molecular y Celular. Cantoblanco.
c/ Darwin, 3.
28049 Madrid

☎ (+34) 91 585 48 44

✉ montoliu@cnb.csic.es

🌐 [Group website](#)

PROGRAMMES

Sensorineural Pathology



GROUP MEMBERS

Staff members: Fernández López, Almudena

Associated members: Cantero González, Marta María | Fernández Punzano, Juliana | Josa De Ramos, Santiago | Montalbán Iglesias, Soledad | Sánchez Sánchez, Oscar Javier

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

- MOJICA F.J.M., MONTOLIU L. On the Origin of CRISPR-Cas Technology: From Prokaryotes to Mammals. *Trends in Microbiology*. 2016;24(10):811-820.
- LOPEZ-LUQUE J., CABALLERO-DIAZ D., MARTINEZ-PALACIAN A., RONCERO C., MORENO-CACERES J., GARCIA-BRAVO M. ET AL. Dissecting the role of epidermal growth factor receptor catalytic activity during liver regeneration and hepatocarcinogenesis. *Hepatology*. 2016;63(2):604-619.
- OLIVEROS JC, FRANCH M, TABAS-MADRID D, SAN-LEÓN D, MONTOLIU L, CUBAS P ET AL. Breaking-Cas-interactive design of guide RNAs for CRISPR-Cas experiments for ENSEMBL genomes. *Nucleic acids research*. 2016;44(W1): W267-71.

Highlights

During 2016, our group has consolidated the CRISPR technology, which we have applied for the generation of several new mouse models that were previously validated in cells. In particular, we have generated new genome-edited mouse models for oculocutaneous albinism type 1 (OCA1), type 2 (OCA2) and other types of albinism, from the list of 20 genes whose mutations are associated with some type of albinism. In addition, we have contributed to develop a new free web tool for the optimized design of RNA guides to be used with CRISPR systems. This new bioinformatic tool, Breaking-Cas, allows the use of any sequenced genome, as long as it has been deposited and is available through the Ensembl public platform. The web tool allows, also, to select a wide variety of Cas and Cas-like proteins, as well as experimental conditions important to restrict the selection of guide RNAs. The Breaking-Cas tool has been used for the successful design of the entire list of new mouse models generated recently in the laboratory. With regard with our activities of genetic diagnose of albinism, through the strategy we devised called ALBINOCHIP, developed in collaboration with Angel Carracedo's unit, in Santiago de Compostela, we have progressed and obtained results from patients and their relatives. Regarding our activities with patient associations we should highlight the third European Days of Albinism (3EDA), held in Milano on 7-8 April, where we met with other international experts and many other European associations in support of people with albinism. Finally, with the support from ALBA and CIBERER, we have collaborated in the making of a video project, entitled "See this?", directed by Patty Bonet, whose aim is to show the world, using subjective vision, how a person with albinism can see. With ALBA we celebrated 10 years of the association in Valencia.



LEAD RESEARCHER

Montoya Villarroya, Julio

📍 **Universidad de Zaragoza**
Facultad de Veterinaria
Miguel Servet, 117
50013 Zaragoza

☎ (+34) 976 761 640

✉ jmontoya@unizar.es

🌐 [Group website](#)

PROGRAMMES

Mitochondrial and Neuromuscular Medicine



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 with 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 the study of physiopathologic 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

- BIANCO A., MARTINEZ-ROMERO I., BISCEGLIA L., D'AGRUMA L., FAVIA P., RUIZ-PESINI E. ET AL. Mitochondrial DNA copy number differentiates the leber's hereditary optic neuropathy affected individuals from the unaffected mutation carriers. *Brain*. 2016;139(1): e1-.
- LOPEZ-GALLARDO E., LLOBET L., EMPERADOR S., MONTOYA J., RUIZ-PESINI E. Effects of tributyltin chloride on cybrids with or without an ATP synthase pathologic mutation. *Environmental Health Perspectives*. 2016;124(9):1399-1405.
- EMPERADOR S., BAYONA-BAFALUY M.P., FERNANDEZ-MARMIESSE A., PINEDA M., FELGUEROSO B., LOPEZ-GALLARDO E. ET AL. Molecular-genetic characterization and rescue of a TSFM mutation causing childhood-onset ataxia and nonobstructive cardiomyopathy. *European Journal of Human Genetics*. 2016;25(1):153-156.
- YUBERO D, ADIN A, MONTERO R, JOU C, JIMÉNEZ-MALLEBRERA C, GARCÍA-CAZORLA A ET AL. A statistical algorithm showing coenzyme Q10 and citrate synthase as biomarkers for mitochondrial respiratory chain enzyme activities. *Scientific reports*. 2016;6(1):15.
- ORTIGOZA-ESCOBAR J.D., OYARZABAL A., MONTERO R., ARTUCH R., JOU C., JIMENEZ C. ET AL. Ndufs4 related Leigh syndrome: A case report and review of the literature. *Mitochondrion*. 2016; 28:73-78.

Highlights

In addition to the FIS project PI14 / 00005 (2015-2017), we got one from the Association of Patients with Mitochondrial Pathology (AEPMI) for the "Confirmation of Pathogenicity of Mutations in Nuclear DNA Associated with Mitochondrial Pathology" (€ 60,000) and a donation of "Todos con Javier" for the "Pearson Syndrome Study (40,000 euros).

It has been shown:

- that the manifestation of LHON disease, in families with presence of the mutations in all their members, depends on mtDNA levels;
- through functional studies, the pathogenicity of mutations in the EFTS gene found in a patient with early-onset ataxia and non-obstructive cardiomyopathy.
- that the GDF-15 is a good marker for mitochondrial diseases.
- that the ATP synthase inhibitor tributyltin chloride (TBTC), which contaminates human food, modifies the phenotype of pathological mutations in mtDNA causing a more serious dysfunction. In addition, treatment of wild-type cells, without the mutation, causes effects similar to those of untreated mutated cells.
- Patients with sepsis belonging to the haplogroup JT have higher complex IV specific activity and higher survival than patients with sepsis of other haplogroups.
- Patients with sporadic myositis with inclusion bodies have been shown to have multiple deletions or depletion of the mtDNA.
- a statistical algorithm relates the Coenzyme Q and citrate synthase as markers of deficiencies of the respiratory chain.

Mitochondrial Disease Adviser for Patients' Association (AEPMI) and Ana Carolina Diez Mahou Foundation.

J. Montoya is a member of the Oversee Committee of the Italian Network for Mitochondrial Disorders.

They have been studied by PCR-RFLP or complete sequencing of mtDNA 88 patients and have found 23 mutations (8 new). Three mutations in nDNA.


Congress communications: 13; Seminars and Lectures: 6; PhD Thesis: 2.


The group also is member of the Instituto de Investigación Sanitaria de Aragón through the University of Zaragoza.




LEAD RESEARCHER

**Moreno Pelayo,
Miguel Ángel**

 Servicio Madrileño de Salud
Hospital Ramón y Cajal
Carretera de Colmenar, km 9.1
28034 Madrid

 (+34) 91 336 85 41
(+34) 91 336 89 66

 mmorenop@salud.madrid.org

 [Group website](#)

PROGRAMMES

Sensorineural Pathology



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 | Gandía Ferri, Marta | Hernández Chico, Concepción | Hernández Díaz, Elisabete | Martín Santo Domingo, Yolanda | Mayo Merino, Fernando | Santos Serrao de Castro, Luciana | Villamar López, Manuel

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

- VOGL C., PANOU I., YAMANBAEVA G., WICHMANN C., MANGOSING S.J., VILARDI F. ET AL. Tryptophan-rich basic protein (WRB) mediates insertion of the tail-anchored protein otoferlin and is required for hair cell exocytosis and hearing. EMBO Journal. 2016.
- MARIN A.V., JIMENEZ-REINOSO A., BRIONES A.C., MUNOZ-RUIZ M., AYDOGMUS C., PASICK L.J. ET AL. Primary T-cell immunodeficiency with functional revertant somatic mosaicism in CD247. Journal of Allergy and Clinical Immunology. 2016.

Highlights

PROJECTS

Obtaining three ACCL in 2016:

- Title: Development of a platform for prioritization of disease variants using exogenous sequencing data. Coordinating Unit: Joaquin Dopazo (U715). Participating Units: U702-U704-U711-U715-U728-U746-U753-U755. Pdl: Medical Genetics.
- Title: Phenotyping and analysis of new animal and cellular models of neurosensory diseases generated using CRISPR-Cas9 technology. Coordinating Unit: Lluís Montoliu (U756). Participating Units: U709-U718-U728-U755-U761-U756. Pdl: Neurosensory Pathology.
- Title: Characterization of variants in new diagnostic genes in hereditary breast / ovarian cancer syndrome. Coordinating Unit: Anna Vega (U711). Participating Units: U706-U711-U728-External. Pdl: Medical Genetics.

Obtaining an ONCE project:

- Title: Genotype-phenotype correlation in patients with alterations of the cellular anterior segment (pilot study). Standardization of a non-invasive diagnostic protocol. IP: Manuela Villamar.

GROUP NETWORKS AND ALLIANCES

Creation of a multidisciplinary unit for the development of a clinical guide for the integral management of patients with tuberous sclerosis. Agreement signed with Novartis.

TECHNOLOGY TRANSFER ACTIONS TO CLINICAL PRACTICE

Implantation in clinical practice of the diagnosis of CNVs using CGH array in pathology of the anterior segment of the eye.

Obtainment of the European training certificate for non-invasive prenatal screening (NIPT) through massive sequencing.

Clinical practice implementation of genetic-molecular diagnostic based on NGS in familial (breast-ovary-colorectal) cancer.

VISITS OF RESEARCH STAFF

Rotation of five researchers from the programs / universities: Erasmus; UAM; Pablo de Olavide University of Seville; University Carlos III.


PHD THESIS / MASTER'S DISSERTATION


Two doctoral theses have been read in 2016 from doctoral students Maria Domínguez Ruiz (Director: Ignacio del Castillo) and Lucía Borreguero Escribano (Directors: Miguel Ángel Moreno / Matías Morín) and two master's dissertations in collaboration with UC3M (Marcia Asenjo and Pablo Marín, Tutor: Miguel Ángel Moreno).




LEAD RESEARCHER

Navas, Plácido

 **Universidad Pablo de Olavide**
Centro Andaluz de Biología
Molecular y Medicina
Regenerativa
Avda. Américo Vesputio s/n
41092 Sevilla

 (+34) 95 434 93 81
(+34) 95 434 93 85

 pnavas@upo.es

 [Group website](#)

PROGRAMMES

Mitochondrial and Neuromuscular Medicine



GROUP MEMBERS

Staff members: Cascajo Almenara, María Victoria | Sánchez Cuesta, Ana María

Associated members: Arroyo Luque, Antonio | Asencio Salcedo, Claudio | Ballesteros Simarro, Manuel Ángel | Brea Calvo, Gloria Teresa | García-Testón Páez, Elena | Jiménez Hidalgo, María Auxiliadora | Moreno Fernández-Ayala, Daniel José | Rodríguez Aguilera, Juan Carlos | Rodríguez Hernández, María de los Ángeles | Sánchez Alcázar, José Antonio | Santos Ocaña, Carlos | Vazquez 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

- ALCAZAR-FABRA M., NAVAS P., BREA-CALVO G. Coenzyme Q biosynthesis and its role in the respiratory chain structure. *Biochimica et Biophysica Acta - Bioenergetics*. 2016.
- CASCAJO M.V., ABDELMOHSEN K., NOH J.H., FERNANDEZ-AYALA D.J.M., WILLERS I.M., BREA G. ET AL. RNA-binding proteins regulate cell respiration and coenzyme Q biosynthesis by post-transcriptional regulation of COQ7. *RNA Biology*. 2016;1-13.
- SCIALO F., SRIRAM A., FERNANDEZ-AYALA D., GUBINA N., LOHMUS M., NELSON G. ET AL. Mitochondrial ROS Produced via Reverse Electron Transport Extend Animal Lifespan. *Cell Metabolism*. 2016;23(4):725-734.
- GUARAS A., PERALES-CLEMENTE E., CALVO E., ACIN-PEREZ R., LOUREIRO-LOPEZ M., PUJOL C. ET AL. The CoQH2/CoQ Ratio Serves as a Sensor of Respiratory Chain Efficiency. *Cell Reports*. 2016;15(1):197-209.
- MITCHELL S.J., MADRIGAL-MATUTE J., SCHEIBYE-KNUDSEN M., FANG E., AON M., GONZALEZ-REYES J.A. ET AL. Effects of Sex, Strain, and Energy Intake on Hallmarks of Aging in Mice. *Cell Metabolism*. 2016;23(6):1093-1112.

Highlights

During the year 2016 the group has maintained his activity combining the activity in translational science base on the biochemical and genetic diagnostic and the basic genetic and molecular research in mitochondrial pathologies with putative deficiency in coenzyme Q. We maintain an active consortium with the groups of Rafael Artuch and Antonia Ribes in CIBERER, including the foreign researchers: Leonardo Salviati (Padova University), Sandra Jackson (Dresden University) y Iain Hardgreaves (University College London Hosp).

The goals of the group during 2016 have been:

1. The European Medicines Agency (EMA) has accepted our proposal for the acceptance of ubiquinol as orphan medicament for the treatment of the primary deficiency in CoQ10. (EU/3/16/1765).
2. We continue working on the analysis of the phenotype of a transgenic mice model of ADCK2+/- KO that show deficiency in coenzyme Q but, for first time in this type of diseases, demonstrates an specific deficiency of CoQ in skeletal muscle without neurological affectation.
3. We continue carrying out a project to find putative therapies in CoQ deficiency based on bioactive compounds with a project financed by the Andalusian Government in collaboration with the Medina Foundation in Granada.
4. During 2016 we maintain a diagnostic service focussed on the mitochondrial pathology and the analysis of coenzyme Q in muscle biopsies and/or primary fibroblasts from patients of public and private hospitals of Andalusia. We maintain an European Consortium for the diagnostic of coenzyme Q deficiency in which we collaborate with determinations of the amount of coenzyme Q, its synthesis and functional complementation. We maintain our services with the analysis of changes in mitochondrial DNA and test for the molecular diagnostic of lysosomal diseases for public and private hospitals.
5. Our group also continues with the study of the COQ4 gene and its repercussion in the deficiency of coenzyme Q.



LEAD RESEARCHER

Nunes, Virginia

-  **Fundación IDIBELL**
Hospital Durán y Reynals
Gran Vía de l'Hospitalet, 199
08908 Hospitalet de Llobregat
-  (+34) 93 260 74 06
-  vnunes@idibell.cat
-  [Group website](#)

PROGRAMMES

Inherited Metabolic Medicine



GROUP MEMBERS

Staff members: González Simarro, Laura | López De Heredia Alonso, Miguel

Associated members: Prat Pedrola, Esther

Main lines of research

- Molecular bases of the amino acid renal reabsorption.
- Involvement of heteromeric amino acid transporters (HAT) in inherited human diseases.
- Cystinuria: Search for cystine lithiasis modulation genes and possible therapies.
- Characterization of SLC7A8 as gene for ARHL and cataracts from the ear and ocular phenotype in the knockout mouse for LAT-2 transporter.
- Generation and characterization of the double LAT-2/TAT1 knockout mouse.
- Molecular bases of the Megalencephalic Leukoencephalopathy with subcortical quists (MLC1).
- Identification of MLC1 interactome.

Most relevant scientific articles

- NAGAMORI S., WIRIYASERMKUL P., GUARCH M.E., OKUYAMA H., NAKAGOMI S., TADAGAKI K. ET AL. Novel cystine transporter in renal proximal tubule identified as a missing partner of cystinuria-related plasma membrane protein rBAT/SLC3A1. Proceedings of the National Academy of Sciences of the United States of America. 2016;113(3):775-780.

Highlights

In 2016 we have continued investigating the renal reabsorption of amino acids using KO mouse models for different heteromeric aminoacids transporters (HAT). In collaboration with Manuel Palacin (U731) we have described a new cystine transporter in kidney, AGT1, responsible of the 10-15% of its reabsorption (Nagamori et to the., 2016). As possible new gene involved in Cystinuria, we have collected and analyzed families of Cystinuria, to correlate mutations in AGT1 with levels of aminoacids excretion in urine. We described and analyzed SLC7A8 mutations in patients with deafness, from identifying the ARHL Phenotype in mouse *Slc7a8*^{-/-}-collaborating with Manuel Palacin (U731) and Isabel Varela Nieto (U761) (Espino et al., submitted). At the same time we have described SLC7A8 as gene causing cataracts, again starting from the phenotype detected in the *Slc7a8*^{-/-}-KO, phenotype favored in the model double KO *Slc7a8*^{-/-} *Slc16a10*^{-/-} in collaboration with Manuel Palacin (U731) and François Verrey in Switzerland (Vilches and cols., pending of submission).

Within the FIS project aimed at the study of a compound as a treatment for Cystinuria, we set up the determination of L-Erg in mouse urine, we carry out a treatment of *Slc7a9*^{-/-} litiasic mice with L-Erg for three months (data under analysis) and prepared the treatment for 6 months from weaning. We Performed a proteomic study from renal brush borders samples to identify possible modulators of cystine lithiasis, currently in analysis.

Within the intramural project, (ref. E17P2AC730) in collaboration with units (U731, U737), we have carried out a Transcriptomic study by using different HATs mouse models (*Slc7a9*^{-/-}, *Slc3 a1*^{-/-}, *Slc7a7*^{-/-}, *Slc7a8*^{-/-} and the double, *Slc7a8*^{-/-}/*Slc16a10*^{-/-}). Data currently under analysis.

Collaborating with Raul Estevez (U751) we carried out a pilot trial to test the therapeutic possibilities of a compound for MLC, in our *Mlc*^{-/-} mice (collaboration with MedDay). We have generated the colony for the second MLC gene the *GLialCAM*^{-/-}.




LEAD RESEARCHER

Palacín, Manuel

 Fundació privada Instituto de Recerca Biomèdica (IRB-Barcelona)
C/ Baldori Reixac 10-12
08028 Barcelona

 (+34) 93 403 71 98 / 9

 manuel.palacin
@irbbarcelona.org

 [Group website](#)

PROGRAMMES

Inherited Metabolic Medicine



GROUP MEMBERS

Staff members: Bartoccioni, Paola Chiara | Fort Baixeras, Joana

Associated members: Boday Salvans, Susana | Cano Crespo, Sara | Rosell Febres, Albert | Sotillo Rodríguez, Fernando

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 M.E., OKUYAMA H., NAKAGOMI S., TADAGAKI K. ET AL. Novel cystine transporter in renal proximal tubule identified as a missing partner of cystinuria-related plasma membrane protein rBAT/SLC3A1. Proceedings of the National Academy of Sciences of the United States of America. 2016;113(3):775-780.
- DE LA BALLINA L.R., CANO-CRESPO S., GONZALEZ-MUNOZ E., BIAL S., ESTRACH S., CAILLETEAU L. ET AL. Amino acid transport associated to cluster of differentiation 98 heavy chain (CD98HC) is at the cross-road of oxidative stress and amino acid availability. Journal of Biological Chemistry. 2016;291(18):9700-9711.
- RODRIGUEZ-BANQUERI A., ERRASTI-MURUGARREN E., BARTOCCIONI P., KOWALCZYK L., PERALVAREZ-MARIN A., PALACIN M. ET AL. Stabilization of a prokaryotic LAT transporter by random mutagenesis. Journal of General Physiology. 2016;147(4):353-368.
- SEBASTIAN D., SORIANELLO E., SEGALES J., IRAZOKI A., RUIZ-BONILLA V., SALA D. ET AL. Mfn2 deficiency links age-related sarcopenia and impaired autophagy to activation of an adaptive mitophagy pathway. EMBO Journal. 2016.
- CORMERAIS Y., GIULIANO S., LEFLOCH R., FRONT B., DURIVault J., TAMBUTTE E. ET AL. Genetic disruption of the multifunctional CD98/LAT1 complex demonstrates the key role of essential amino acid transport in the control of mTORC1 and tumor growth. Cancer Research. 2016;76(15):4481-4492.

Highlights

Our activity has been focused in four research lines. At first instance, in collaboration with Virginia Nunes (U730) we have identified the second amino acid transporter associated with the heavy subunit rBAT (AGT1) (Nagamori et al., PNAS 2016). Because AGT1 transports cysteine and is expressed in the proximal straight tubule is a candidate transporter to have a role in cystinuria.

Secondly, we have demonstrated a key role of CD98hc, the heavy subunit of amino acid transporters involved in inherited rare diseases like lysinuric protein intolerance (y+LAT1/CD98hc) and autism (LAT1/CD98hc), in oxidative stress, essential amino acid availability and harmonization of the amino acid content (basic and neutral) in the cell (De la Ballina et al., JBC; Cormerais et al., Cancer Res, 2016).

In third place, we have established a strategy based on random mutagenesis to improve the stability of membrane proteins for structural biology studies (crystallography and X ray diffraction) (Rodríguez-Banqueri et al. General Physiology 2016).


Finally, we have demonstrated that ablation of Mfn2, related to the rare inherited disease Charcot-Marie-Tooth, inhibits autophagy and causes age-related sarcopenia (Sebastian et al., PNAS 2016).


At present, we run joint projects in collaboration with Virginia Nunes U730, Isabel Varela U761 and Rafael Artuch U703 in the study of the role of amino acid transporters in hearing loss, cataracts and neurological disorders.



LEAD RESEARCHER

Palau Martínez, Francesc

 **Fundación para la Investigación y Docencia Sant Joan de Déu**
Hospital Sant Joan de Déu
C/ Santa Rosa, 39-57
08950 Esplugues de Llobregat

 fpalau@sjdhospitalbarcelona.org

 [Group website](#)

PROGRAMMES

Mitochondrial and Neuromuscular Medicine



GROUP MEMBERS

Staff members: Domínguez Berzosa, Laura | López López, Dolores | Rodríguez Rivero, Cristina

Contratados a cargo de proyecto: Civera Tregón, Azahara

Associated members: Barneo Muñoz, Manuel

Main lines of research

- Neurobiology and cellular pathophysiology of neurogenetic disorders: mitochondrial Charcot-Marie-Tooth neuropathy, Friedreich ataxia, Duchenne muscular dystrophy, Menkes disease and genetic Parkinson disease.
- 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

- SEVILLA T., LUPO V., MARTINEZ-RUBIO D., SANCHO P., SIVERA R., CHUMILLAS M.I.J. ET AL. Mutations in the MORC2 gene cause axonal Charcot-Marie-Tooth disease. *Brain*. 2016;139(1):62-72.
- MOLA B., RIVEIRO F., BOLINCHES-AMOROS A., MUNOZ-LASSO D.C., PALAU F., GONZALEZ-CABO P. Two different pathogenic mechanisms, dying-back axonal neuropathy and pancreatic senescence, are present in the YG8R mouse model of Friedreich's ataxia. *DMM Disease Models and Mechanisms*. 2016;9(6):647-657.
- YUBERO D., BRANDI N., ORMAZABAL A., GARCIA-CAZORLA A., PEREZ-DUENAS B., CAMPISTOL J. ET AL. Targeted next generation sequencing in patients with inborn errors of metabolism. *PLoS ONE*. 2016;11(5).
- LUPO V., GARCIA-GARCIA F., SANCHO P., TELLO C., GARCIA-ROMERO M., VILLARREAL L. ET AL. Assessment of Targeted Next-Generation Sequencing as a Tool for the Diagnosis of Charcot-Marie-Tooth Disease and Hereditary Motor Neuropathy. *Journal of Molecular Diagnostics*. 2016;18(2):225-234.
- PRIETO J., LEON M., PONSODA X., GARCIA-GARCIA F., BORT R., SERNA E. ET AL. Dysfunctional mitochondrial fission impairs cell reprogramming. *Cell Cycle*. 2016;15(23):3240-3250.

Highlights

Highlights of the Group in 2016:

- Discovery of a new gene, MORC2, as a cause of axonal Charcot-Marie-Tooth neuropathy with autosomal dominant inheritance, in collaboration with Group 761 of the Hospital La Fe (Dr. T. Sevilla and J. Vilchez). It is a form of onset illness in the first decade of life with progressive course and many patients require wheelchair into the half-life. Additional features include proximal and early asymmetrical limb weakness, deafness, and developmental delay.
- Description, in the murine model YG8R of Friedreich's ataxia, of the neurobiological and axonal processes of the dying-back phenomenon and cellular senescence in the pancreas as pathogenic mechanisms of the disease.
- Application of genomic techniques of NGS in the genetic diagnosis of Charcot-Marie-Tooth disease and, as a collaborator with the group 703 of R. Artuch, in hereditary metabolic diseases.

Among the competitive projects, it is worth mentioning: (1) Study of the pathophysiology of mitochondrial Charcot-Marie-Tooth disease and other genetic axonopathies funded by MINECO, SAF2012-32425 (extension 2016) and SAF2015-66625-R (1st annual). (2) Study on clinical and functional genomics of neurogenetic and neurodevelopmental disorders, including the NeuroPaisaje project, funded by CIBERER (ACCI12-2105) and the Isabel Gemio Foundation, and the GenomicInnova project for technological development in health (DTS16/00196) financed by ISCIII. (3) GenomicScientia - Center for Genomic Sciences in Medicine of the Institut de Recerca Sant Joan de Déu, funded by the 2015 FEDER/S-21 project of the Singular Installation programme of the Generalitat de Catalunya.


We have participated in the editing and writing of the book 'Ética de la Investigación en Enfermedades Raras'. Ediciones Ergon, Madrid, 2016, by C. Ayuso, R. Dal-Ré and F. Palau. ISBN: 978-84-16270-85-9.


Coordination of Orphanet-Spain team <http://www.orpha.net/national/ES-ES/index/inicio/>



LEAD RESEARCHER

**Pallardo Calatayud,
Federico**

 **Universidad de Valencia**
Facultad de Medicina
de Valencia
Avda. V. Blasco Ibañez, 15
46010 Valencia

 (+34) 963 864 646

 federico.v.pallardo@uv.es

 [Group website](#)

PROGRAMMES

**Inherited Cancer, Haematological
and Dermatological Diseases
Sensorineural Pathology**



GROUP MEMBERS

Staff members: García Giménez, José Luis | González Cabo, Pilar

Associated members: Ibañez Cabellos, José Santiago | Romá Mateo, Carlos | Seco Cervera, Marta

Main lines of research

- Pathophysiology of Friedreich ataxia.
- Study of oxidative stress and mechanisms of DNA repair in different progeroid syndromes and genodermatosis.
- Epigenetic regulation in the physiopathology of rare diseases.

Most relevant scientific articles

- MOLLA B., RIVEIRO F., BOLINCHES-AMOROS A., MUNOZ-LASSO D.C., PALAU F., GONZALEZ-CABO P. Two different pathogenic mechanisms, dying-back axonal neuropathy and pancreatic senescence, are present in the YG8R mouse model of Friedreich's ataxia. *DMM Disease Models and Mechanisms*. 2016;9(6):647-657.
- ROMA-MATEO C., RATHTHAGALA M., GENTRY M.S., SANZ P. Assessing the biological activity of the glucan phosphatase laforin. *Methods in Molecular Biology*. 2016; 1447:107-119.
- KLIONSKY DJ, ABDELMOHSEN K, ABE A, ABEDIN MJ, ABELIOVICH H, ACEVEDO AROZENA A ET AL. Guidelines for the use and interpretation of assays for monitoring autophagy (3rd edition). *Autophagy*. 2016;12(1):1-222.

Highlights

Among the scientific activity of the research group, remarkable achievements are the European patent "Mass spectrometry-based methods for the detection of circulating histones H3 and H2B in plasma from sepsis or septic shock (ss) patients (EP 16 382 509.4)", and the extension to PCT phase (PCT/EP2016/063935) and transference to the CIBER spin-off EpiDisease, S. L., of the patent "Kit and method for the diagnosis/prognosis of idiopathic scoliosis".

In reference to acquisition of budget and resources, funding from the following programs and grants has been obtained: VLC-Bioclinic (1 project, 2016), Grupo Español de Estudio del Raquis (1 project, 2016-2017), Plan Nacional I+D+i del Mineco (1 project, 2016-2019), AES 2016 (2 projects, 2017-2019), Fundación Ramón Areces (1 project, 2017-2019).

Regarding teaching and outreach activities, the group has maintained the teaching of the subject "Enfermedades raras", from the Grade on Medicine's study plan at the University of Valencia; and also in the "Máster de enfermedades raras", directed by Dr. Pallardó, at the same University. Besides, it was organized, in collaboration with the Escuela Valenciana de Estudios de la Salud and the CIBERER, the 1st edition of the on-line course "Introducción a las EE.RR: investigación y atención clínica" addressed to residents of medical specialities from the Valencian public health system. In the context of scientific outreach activities, Dr. Romá-Mateo has published the book "¿Qué sabemos de? La epigenética" (ISBN: 978-84-00-10073-5).

Within the framework of the Alliance for translational research in rare diseases of the Comunitat Valenciana, Dr. Pallardó has coordinated the joint appliance for FEDER funding for acquisition of research infrastructure. Recently, the Conselleria de Sanitat has confirmed availability of those funds (3.000.000 €) for 2017. Accordingly, the conference "I Congreso de Investigación Traslacional en EE.RR. de la CV" was held at the Faculty of Medicine and Dentistry, University of Valencia, on February 25th-26th 2016.



LEAD RESEARCHER

**Pérez González,
María Belén**

📍 Universidad Autónoma
de Madrid
Centro de Biología Molecular
Severo Ochoa
Nicolás Cabrera, 1
Campus de Cantoblanco UAM
28049 Madrid

☎ (+34) 91 497 45 89
(+34) 91 196 45 66

✉ bperez@cbm.csic.es

🌐 [Group website](#)

PROGRAMMES

Inherited Metabolic Medicine



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

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 mitochondrial metabolism.

Most relevant scientific articles

- JANSEN J.C., CIRAK S., VAN SCHERPENZEEL M., TIMAL S., REUNERT J., RUST S. ET AL. CCDC115 Deficiency Causes a Disorder of Golgi Homeostasis with Abnormal Protein Glycosylation. *American Journal of Human Genetics*. 2016;98(2):310-321.
- OYARZABAL A., BRAVO-ALONSO I., SANCHEZ-ARAGO M., REJAS M.T., MERINERO B., GARCIA-CAZORLA A. ET AL. Mitochondrial response to the BCKDK-deficiency: Some clues to understand the positive dietary response in this form of autism. *Biochimica et Biophysica Acta - Molecular Basis of Disease*. 2016;1862(4):592-600.
- GALLEGO-VILLAR L., RIVERA-BARAHONA A., CUEVAS-MARTIN C., GUENZEL A., PEREZ B., BARRY M.A. ET AL. In vivo evidence of mitochondrial dysfunction and altered redox homeostasis in a genetic mouse model of propionic acidemia: Implications for the pathophysiology of this disorder. *Free Radical Biology and Medicine*. 2016; 96:1-12.
- VEGA A.I., MEDRANO C., NAVARRETE R., DESVIAT L.R., MERINERO B., RODRIGUEZ-POMBO P. ET AL. Molecular diagnosis of glycogen storage disease and disorders with overlapping clinical symptoms by massive parallel sequencing. *Genetics in Medicine*. 2016;18(10):1037-1043.
- YUSTE-CHECA P., BRASIL S., GAMEZ A., UNDERHAUG J., DESVIAT L.R., UGARTE M. ET AL. Pharmacological Chaperoning: A Potential Treatment for PMM2-CDG. *Human Mutation*. 2016.


Highlights

The research projects of the Diagnostic and Research of Inherited Metabolic diseases (IMD) are aimed to improve the diagnosis using cutting-edge genomic technologies and to develop therapeutic strategies based on the analysis of the mechanisms of action of the mutations identified. Concerning the advances in diagnosis, the group has been able to improve the diagnosis rate by combination of comprehensive biochemical and cellular studies with functional analyzes of either exonic or intronic variants. In addition, the group participates in national and international networks of biochemical and genetic diagnosis for gathering and registry of patients sharing the same phenotype in order to gain clues for better diagnosis. At the genetic level we highlight the study, for the first time in our country, of patients diagnosed with glycogen storage disorders (GSD) by massive parallel sequencing. In addition to the diagnosis of GSD patients we highlight the detection of mutations in other genes sharing phenotypic characteristics with GSD (hepatic, cardiac and / or muscular alterations), resulting in an erroneous initial diagnostic suspicion. On the other hand we have been actively involved in the identification of a new CDG-causing gene (CCDC115). The results obtained after functional cellular, biochemical and clinical analysis suggests that this gene is involved in Golgi trafficking. Regarding the therapeutic research we highlight the studies of pathophysiology, using animal and cellular models of propionic aciduria and deficiency of BCKDK disorders. In both cases the results show that therapies aimed to avoid oxidative damage and targeted for recovering mitochondrial function and biogenesis could be beneficial in combination with current conventional therapies. Finally, after the screening of a library of 10000 compounds we have described a promising chemical structure as a starting point for the development of new therapeutic agents to treat destabilizing mutations identified on PMM2-CDG disease.



LEAD RESEARCHER

Pérez Jurado, Luis

 **Universidad Pompeu Fabra**
Facultad de Ciencias
Experimentales y de la Salud
Dr. Aiguader, 88
08003 Barcelona

 (+34) 93 3160856 / 93 3160821

 luis.perez@upf.edu

 [Group website](#)

PROGRAMMES

Pediatric and Developmental Medicine



GROUP MEMBERS

Staff members: Cusco Martí, Ivon | Serra Juhé, Clara

Contratados a cargo de proyecto: Tatu Boncota, Sorina Daniela

Associated members: Borralleras Fumaña, Cristina | Campuzano Uceda, Victoria | Corominas Castiñeira, Roser | Del Campo Casanelles, Miguel | Flores Peirats, Raquel | Palacios Verdú, María Gabriela | Pérez García, Débora | Reina Castellón, Judith | Rodríguez Santiago, Benjamin

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 intellectual 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.

Most relevant scientific articles

- HOMS A, CODINA-SOLÀ M, RODRÍGUEZ-SANTIAGO B, VILLANUEVA CM, MONK D, CUSCÓ I ET AL. Genetic and epigenetic methylation defects and implication of the ERMN gene in autism spectrum disorders. *Translational psychiatry*. 2016;6(7): e855.
- ZHOU W., MACHIELA M.J., FREEDMAN N.D., ROTHMAN N., MALATS N., DAGNALL C. ET AL. Mosaic loss of chromosome Y is associated with common variation near TCL1A. *Nature Genetics*. 2016;48(5):563-568.
- DAUBER A., MUNOZ-CALVO M.T., BARRIOS V., DOMENE H.M., KLOVERPRIS S., SERRA-JUHE C. ET AL. Mutations in pregnancy-associated plasma protein A2 cause short stature due to low IGF-I availability. *EMBO Molecular Medicine*. 2016.
- CACERES A., ESKO T., PAPPALÀ I., GUTIERREZ A., LOPEZ-ESPINOSA M.-J., LLOP S. ET AL. Ancient haplotypes at the 15q24.2 microdeletion region are linked to brain expression of MAN2C1 and children's intelligence. *PLoS ONE*. 2016;11(6).
- BORRALLERAS C., MATO S., AMEEDÉ T., MATUTE C., MULLE C., PEREZ-JURADO L.A. ET AL. Synaptic plasticity and spatial working memory are impaired in the CD mouse model of Williams-Beuren syndrome. *Molecular Brain*. 2016;9(1).

Highlights

We have coordinated and organized the CIBERER undiagnosed rare diseases program (ENoD) and obtained funding for its development in neurobehavioral phenotypes through a project entitled: Characterization and contribution to genetic diagnosis in a cohort of patients with intellectual disability, autism and / or epilepsy (ER16P08 2016-2018 / 149500 €), involving 4 CIBERER groups and 4 linked clinical groups.

We have also obtained funding through an ACCI to continue the ongoing project searching for early tumor risk markers in patients with chromosomal instability syndromes, coordinating the participation of other CIBERER groups and the clinical groups linked to the Instability and Cancer Program. The study is demonstrating clear clinical utility for patients.

Another milestone, in collaboration with CIBEROBN, has been the definition of a new syndromic condition due to deficiency of PAPP2 with secondary deficiency of bioavailability of IGF1. This rare growth disorder has been shown to respond well to recombinant IGF1. There is still an ongoing observational clinical trial that will allow the repositioning of the drug as an orphan drug.

We were the guests for the meeting of the TransNational Alliance of Genetic Advisors in Barcelona (June 2016) in which the guidelines were established to define the competencies of the Genetic Advisors and to establish methods of cross-evaluation and recognition.


During 2016, there were a total of three doctoral theses presented by members of the group at the Universitat Pompeu Fabra, all in relation to our research activity in rare diseases.


LEAD RESEARCHER


Perona Abellón, Rosario

PROGRAMMES

**Inherited Cancer, Haematological
and Dermatological Diseases**

 Agencia Estatal Consejo Superior de Investigaciones Científicas
Instituto de Investigaciones Biomédicas Alberto Sols
C/ Arturo Duperier 4
28029 Madrid

 (+34) 91 585 44 63

 rperona@iib.uam.es

 [Group website](#)

GROUP MEMBERS

Staff members: Manguan García, Cristina

Contratados a cargo de proyecto: Rodríguez Centeno, Javier

Associated members: 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 for the treatment of short telomeres associated diseases, increase oxidative stress and genetic instability.
- Genetic diagnosis of DC and study of telomere length in patients of DC and idiopathic 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 idiopathic pulmonary fibrosis.
- Use of GSE4 for the treatment of ataxia telangiectasia.

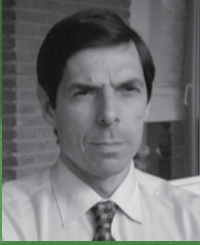
Most relevant scientific articles

- BARGIELA-IPARRAGUIRRE J., PRADO-MARCHAL L., FERNANDEZ-FUENTE M., GUTIERREZ-GONZALEZ A., MORENO-RUBIO J., MUNOZ-FERNANDEZ M. ET AL. CHK1 expression in Gastric Cancer is modulated by p53 and RB1/E2F1: Implications in chemo/radiotherapy response. Scientific Reports. 2016;6.
- RODRIGUEZ-CENTENO J., SASTRE L. Biological activity of the alternative promoters of the Dictyostelium discoideum adenylyl cyclase a gene. PLoS ONE. 2016;11(2).
- STELLA-ASCARIZ N., MONTEJANO R., PINTADO-BERNINCHES L., MONGE S., BERNARDINO J.I., PEREZ-VALERO I. ET AL. Differential effects of Tenofovir, Abacavir, Emtricitabine and Darunavir on telomerase activity in vitro. Journal of Acquired Immune Deficiency Syndromes. 2016.

Highlights


PROJECTS:

- Blood Biomarker-based Diagnostic Tools for Early Stage Alzheimer's Disease (BBDiag).
- Project ITN 721281. Marie Curie PhD fellow.
Principal Investigator: Genhua-Pan UK.
Establish in an animal model the curative effect of GSE4 loaded nanoparticles for the treatment of idiopathic pulmonary fibrosis.




LEAD RESEARCHER

Posada de la Paz, Manuel

 Instituto de Salud Carlos III
Instituto de Investigación en
Enfermedades Raras
Monforte de Lemos, 5
28029 Madrid

 (+34) 918222044 /680457649

 mposada@isciii.es

 [Group website](#)

PROGRAMMES

Pediatric and Developmental Medicine



GROUP MEMBERS

Staff members: López Martín, Estrella

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 (SpainUDP).
- National Rare Disease Biobank (BioNER).
- National germ line mutations database (SpainMDB).
- 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

- GARCIA-PEREZ J., MORALES-PIGA A., GOMEZ-BARROSO D., TAMAYO-URIA I., PARDO ROMAGUERA E., FERNANDEZ-NAVARRO P. ET AL. Risk of neuroblastoma and residential proximity to industrial and urban sites: A case-control study. *Environment International*. 2016;92-93:269-275.
- GAINOTTI S., TURNER C., WOODS S., KOLE A., MCCORMACK P., LOCHMULLER H. ET AL. Improving the informed consent process in international collaborative rare disease research: Effective consent for effective research. *European Journal of Human Genetics*. 2016;24(9):1248-1254.
- HANSSON M.G., LOCHMULLER H., RIESS O., SCHAEFER F., ORTH M., RUBINSTEIN Y. ET AL. The risk of re-identification versus the need to identify individuals in rare disease research. *European Journal of Human Genetics*. 2016;24(11):1553-1558.
- GARCIA-PEREZ J., MORALES-PIGA A., GOMEZ-BARROSO D., TAMAYO-URIA I., PARDO ROMAGUERA E., LOPEZ-ABENTE G. ET AL. Residential proximity to environmental pollution sources and risk of rare tumors in children. *Environmental Research*. 2016; 151:265-274.
- SANCHEZ-DIAZ G., ARIAS-MERINO G., VILLAVERDE-HUESO A., MORALES-PIGA A., ABAITUA-BORDA I., HENS M. ET AL. Monitoring Huntington's Disease Mortality across a 30-Year Period: Geographic and Temporal Patterns. *Neuroepidemiology*. 2016;155-163.

Highlights

The Institute of Rare Diseases Research (IIER) is involved in three national projects (FIS) and three European projects (RareBestPractices; RD-CONNECT and ASDEU, being the IP in Europe in the latter).

RareBestPractices project has finished and all its objectives are fulfilled: A repository of clinical practice guidelines (CPG); a methodology for evaluation of CPG following the GRADE method and tested on two rare diseases; a new open access journal on rare diseases and a training system on GPC evaluation and development.

The IIER is uploading exomes corresponding to undiagnosed cases into the RD-CONNECT platform, whose server is located in the CNAG. In addition, the phenotypic information corresponding to these cases are being uploaded into Phenotips and Phenome Central.

ASDEU is developing prevalence studies in the Basque Country and the Balearic Islands, as well as in 10 other European countries.

The IP of the group is the current Chairman of the International Conference on Rare Diseases and Orphan Drugs (ICORD) and also serves as an independent expert to the Commission's Rare Disease Expert Group (CEGRD) and to the Advisory Group on European JRC registration platform, EC. As an expert, he has contributed to the recommendation of the CEGRD on "supporting and incorporating rare diseases into social services and policies" and has advised the JRC on actions related to the implementation of registries in the context of the European Reference Networks.


The group has been annexed to the International Network of Non-Diagnostic Cases (UDN-I), a program related to the developed in ISCIII, SpainUDP.


Phenotips has been translated into Spanish allowing phenotypic data to be entered into this language in this platform, essential for establishing the genotype-phenotype relationship of complex cases and facilitating the data sharing.



LEAD RESEARCHER

Pujol Onofre, Aurora

 **Fundación IDIBELL**
Hospital Durán y Reynals
3a planta
Gran Vía de l'Hospitalet, 199
08908 Hospitalet de Llobregat

 (+34) 93 260 71 37

 apujol@idibell.cat

 [Group website](#)

PROGRAMMES
Inherited Metabolic Medicine



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 Martín, Agatha

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

- LAUNAY N., RUIZ M., GRAU L., ORTEGA F.J., ILIEVA E.V., MARTINEZ J.J. ET AL. Tauroursodeoxycholic bile acid arrests axonal degeneration by inhibiting the unfolded protein response in X-linked adrenoleukodystrophy. *Acta Neuropathologica*. 2016:1-19.
- SOEHN A.S., RATTAY T.W., BECK-WODL S., SCHAFERHOFF K., MONK D., DOBLER-NEUMANN M. ET AL. Uniparental disomy of chromosome 16 unmasks recessive mutations of FA2H /SPG35 in 4 families. *Neurology*. 2016;87(2):186-191.
- WEBSTER R., CHO M.T., RETTERER K., MILLAN F., NOWAK C., DOUGLAS J. ET AL. De novo loss of function mutations in KIAA2022 are associated with epilepsy and neurodevelopmental delay in females. *Clinical Genetics*. 2016.
- PÀMPOLS T, RAMOS FJ, LAPUNZINA P, GOZALO-SALELLAS I, PÉREZ-JURADO LA, PUJOL A. A view on clinical genetics and genomics in Spain: of challenges and opportunities. *Molecular genetics & genomic medicine*. 2016;4(4):376-91.
- KLIONSKY DJ, ABDELMOHSEN K, ABE A, ABEDIN MJ, ABELIOVICH H, ACEVEDO AROZENA A ET AL. Guidelines for the use and interpretation of assays for monitoring autophagy (3rd edition). *Autophagy*. 2016;12(1):1-222.

Highlights

In 2016 we achieved to:


- Translational research: i) increase the knowledge of molecular basis and pathophysiology in X-ALD; ii) identify new therapeutic targets as the UPR system; iii) identify drugs able to reverse the axonal degeneration in the mouse model as TUDCA, the repositioning of which has been patented for our group and iv) the orphan drug designation for temsirolimus, an autophagy activator, in ALD (with U721). This work, published in *Acta Neuropathologica* in 2015, was awarded with the National Research Prize of the “Colegio de Médicos” of Cordoba/CaixaBank in 2016. The importance of the autophagy in medicine has been underlined with the Nobel Prize in Medicine awarded to Dr. Ohsumi in 2016.
- Clinical trials: i) We finished the treatment with biotin in AMN patients included in a multicenter, double-blind, international phase II clinical trial (promoted by Medday Pharmaceuticals) and ii) we included new patients in our multicenter, phase II clinical trial with pioglitazone, funded by the ISCiii.
- Diagnosis: we finished the intramural project ACCI-2014 (with U703 and U711) for the identification and functional characterization of new genes involved in leukodystrophies and spastic paraplegia. Functional in vitro and zebrafish validations are ongoing. We continue analyzing new exomes in collaboration with Dr. A. Macaya (GCV9). At international level, we started a collaboration with Prof. L. Schoels (Tübingen, Germany), with a publication in the journal *Neurology*.
- CIBERER collaborations: together with other 4 Ciberer groups, we published a review article in *Molecular Genetics and Genomic Medicine* and a clinical guideline. As members of the SEFALer platform, we continue to perform phenotyping services of locomotor disorders and neuromuscular coordination for the interested groups.




LEAD RESEARCHER

Ribes, Antonia

 Hospital Clínico y Provincial
de Barcelona
Instituto de Bioquímica Clínica
Mejía Lequerica, s/n
Edificio Helios III, planta baja
08028 Barcelona

 (+34) 932279340 / 932275672

 aribes@clinic.cat

 [Group website](#)

PROGRAMMES

Inherited Metabolic Medicine



GROUP MEMBERS

Staff members: Matalonga Borrel, Lesley | Texido Viyuela, Laura | Tort Escalé, Frederic

Associated members: Briones Godino, María Paz | Coll Rosell, María José | Ferrer Cortés, Xenia | Giros Blasco, María Luisa | Gort Mas, Laura | Pampols Ros, Teresa

Main lines of research

The strategic objective of our group is to investigate the genetic and biochemical bases, as well as the physiopathological mechanisms, of inherited metabolic diseases with the ultimate aim to develop new diagnostic and therapeutic strategies.

LINE 1.- Identification of genes responsible for Mendelian disorders in patients preselected on the basis of their clinical and biochemical characteristics; within this line we have used exome sequencing and other NGS tools to identify genes in patients with mitochondrial respiratory chain deficiencies, organic acidurias and congenital disorders of glycosylation (CDG).

Recently, our group has been focused in the identification of genes involved in the biosynthesis and transport of cofactors of the mitochondrial energy metabolism (lipoic acid, thiamine, CoQ10, riboflavin and iron sulfur clusters), as well as 3-methylglutaconic aciduria. We aim to identify new defects to generate knowledge that could be implemented to the diagnosis. On the other hand, we are interested not only in the identification of new genes, but also in the physiopathological knowledge of the metabolic pathway and consequently, of the disease.

LINE 2.- In vitro therapeutic approaches. This line of research involves the testing of chemical and peptide libraries. Selection has been made of disease-causing mutations, previously identified by our group, in a wide range of diseases. We make use of fibroblasts, pluripotent induced stem (IPS) cells and neuronal cultures derived from IPS cells. When necessary, preclinical studies will be performed.

Most relevant scientific articles

- ORTIGOZA-ESCOBAR J.D., MOLERO-LUIS M., ARIAS A., OYARZABAL A., DARIN N., SERRANO M. ET AL. Free-thiamine is a potential biomarker of Thiamine transporter-2 deficiency: A treatable cause of Leigh syndrome. *Brain*. 2016;139(1):31-38.
- TORT F., UGARTEBURU O., TORRES M.A., GARCIA-VILLORIA J., GIROS M., RUIZ A. ET AL. Lysine restriction and pyridoxal phosphate administration in a NADK2 patient. *Pediatrics*. 2016;138(5).
- PEREZ-CERDA C., GIROS M.L., SERRANO M., ECAY M.J., GORT L., PEREZ DUENAS B. ET AL. A Population-Based Study on Congenital Disorders of Protein N- and Combined with O-Glycosylation Experience in Clinical and Genetic Diagnosis. *Journal of Pediatrics*. 2016.
- MACIAS-VIDAL J., GUERRERO-HERNANDEZ M., ESTANYOL J.M., AGUADO C., KNECHT E., COLL M.J. ET AL. Identification of lysosomal Npc1-binding proteins: Cathepsin D activity is regulated by NPC1. *Proteomics*. 2016;16(1):150-158.
- FERRER-CORTES X., NARBONA J., BUJAN N., MATALONGA L., DEL TORO M., ARRANZ J.A. ET AL. A leaky splicing mutation in NFU1 is associated with a particular biochemical phenotype. Consequences for the diagnosis. *Mitochondrion*. 2016; 26:72-80.

Highlights

In 2016 the most outstanding achievements of our group have been: 1) introduction of lipidomics in the study of the pathophysiology related to 3-methylglutaconic aciduria. Patients with mutations in TAZ, SERAC1, DNAJC19 and a patient with mutations in TIMM50 have been studied by UPLC-MS / MS. The results show an alteration in TIMM50 very similar to that of TAZ, SERAC1 and DNAJC19 patients, suggesting that the alteration of mitochondrial phospholipid metabolism may be a key factor in determining the pathophysiology of these diseases. 2) Cellular exome studies include the finding of a patient with protein glycosylation disorder (CDG) associated with a new gene, TRAPC11, this study was published in *Human Mutation* in 2017. Within this line, the finding of a patient with mutations in NADK2 (second patient reported in the literature) has allowed us to speculate and confirm the benefit of the treatment with pyridoxal-phosphate (*Pediatrics*, 2016, 1st decile). 3) In the treatment search line we must mention the confirmation of the chaperone action for GA-I of a repositioning compound, as well as the mechanism of action through mTOR of another compound that favors autophagy and lysosomal exocytosis. 4) Three projects were obtained: 1 FIS project to continue the research line focused on the identification and characterization of new defects of mitochondrial energy metabolism, 1 European project for exome sequencing, and 1 CIBERER intramural project within the previous lines. 5) Three doctoral theses have been read.



LEAD RESEARCHER

**Rodríguez de Córdoba,
Santiago**

📍 Estatal Consejo Superior de
Investigaciones Científicas
Centro de Investigaciones
Biológicas.
Ramiro de Maeztu, 9
28040 Madrid

☎ (+34) 91 837 31 12 x4432/3

✉ srdecordoba@cib.csic.es

🌐 [Group website](#)

PROGRAMMES
Genetic Medicine



GROUP MEMBERS

Staff members: Nogales González, Nuria (sustitución por baja) | Pinto García, Sheila | Ruiz Sánchez, Ángela
Olimpia

Associated members: García Fernández, Jesús María | Juana López, Lucía | 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

- DE CORDOBA S.R. Complement genetics and susceptibility to inflammatory disease. Lessons from genotype-phenotype correlations. *Immunobiology*. 2016.
- 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. *Journal of the American Society of Nephrology: JASN*. 2016;27(5):1305-11.
- GOODSHIP T.H.J., COOK H.T., FAKHOURI F., FERVENZA F.C., FREMEAUX-BACCHI V., KAVANAGH D. ET AL. Atypical hemolytic uremic syndrome and C3 glomerulopathy: Conclusions from a “Kidney Disease: Improving Global Outcomes” (KDIGO) Controversies Conference. *Kidney International*. 2016.
- XIAO X., GHOSSEIN C., TORTAJADA A., ZHANG Y., MEYER N., JONES M. ET AL. Familial C3 glomerulonephritis caused by a novel CFHR5-CFHR2 fusion gene. *Molecular Immunology*. 2016; 77:89-96.
- BLOM A.M., CORVILLO F., MAGDA M., STASILOJC G., NOZAL P., PEREZ-VALDIVIA M.A. ET AL. Testing the Activity of Complement Convertases in Serum/Plasma for Diagnosis of C4NeF-Mediated C3 Glomerulonephritis. *Journal of Clinical Immunology*. 2016;1-11.

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 2016 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. In this sense, 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 2016 we have continue developing diagnostics strategies, improving methods for the detection of CNVs and our NGS platforms. Also, we have developed a set of monoclonal antibodies to identify biological markers associated with the progression of the disease and as a starting point to develop complement inhibitors with therapeutic interest. 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 125 during 2016) 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.



LEAD RESEARCHER

Rubio Zamora, Vicente

📍 Agencia Estatal Consejo Superior de Investigaciones Científicas
Instituto de Biomédicina de Valencia
Jaume Roig, 11
46010 Valencia

☎ (+34) 96 339 17 74

✉ rubio@ibv.csic.es

🌐 [Group website](#)

PROGRAMMES

Inherited Metabolic Medicine



GROUP MEMBERS

Staff members: Gougéard, 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

- SANCHO-VAELLO E., MARCO-MARIN C., GOUGEARD N., FERNANDEZ-MURGA L., RUFENACHT V., MUSTEDANAGIC M. ET AL. Understanding N-Acetyl-L-Glutamate Synthase Deficiency: Mutational Spectrum, Impact of Clinical Mutations on Enzyme Functionality, and Structural Considerations. *Human Mutation*. 2016.
- PANZA E., ESCAMILLA-HONRUBIA J.M., MARCO-MARIN C., GOUGEARD N., DE MICHELE G., MORRA V.B. ET AL. ALDH18A1 gene mutations cause dominant spastic paraplegia SPG9: loss of function effect and plausibility of a dominant negative mechanism. *Brain : a journal of neurology*. 2016;139.
- MAIQUES E., QUILES-PUCHALT N., DONDERIS J., CIGES-TOMAS J.R., ALITE C., BOWRING J.Z. ET AL. Another look at the mechanism involving trimeric dUTPases in *Staphylococcus aureus* pathogenicity island induction involves novel players in the party. *Nucleic Acids Research*. 2016;44(11):5457-5469.
- VELIKOVA N., FULLE S., MANSO A.S., MECHKARSKA M., FINN P., CONLON J.M. ET AL. Putative histidine kinase inhibitors with antibacterial effect against multi-drug resistant clinical isolates identified by in vitro and in silico screens. *Scientific Reports*. 2016;6.
- PALANCA C., RUBIO V. Structure of AmtR, the global nitrogen regulator of *Corynebacterium glutamicum*, in free and DNA-bound forms. *FEBS Journal*. 2016;283(6):1039-1059.

Highlights

In 2016 we succeeded in renewing the PrometeoII2014/029 Project (Valencian Community) “Genes, Proteins and signaling cascades in Rare Diseases” (includes V.Rubio and A.Marina); in securing two continued access projects for the Diamond (UK) and ALBA (Barcelona) synchrotrons; and in getting another Plan Estatal Project awarded (PI, A.Marina) for 2017-2019. We have continued developing two Plan Estatal projects (PIs, V.Rubio and A.Marina) and work under contract for Interquim SA (Ferrer Group) for improving diagnosis of hypolactasia. Highlighted results for 2016: description of dominant inheritance for pyrroline-5-carboxylate synthetase deficiency with complicated spastic paraplegia, reflected already in OMIM *138250 and # 601162; mutational spectrum and structure-function relations for N-acetyl-L-glutamate synthase deficiency; advances on both target characterization and drug testing and improvement, towards better antibacterials with potential use in cystic fibrosis. Translational-dissemination activities include: the 2016 publication of the chapter “Disorders of the Urea Cycle and Related Enzymes” in the highly used book “Inborn Metabolic Diseases. Diagnosis and Treatment” (Saudubray et al., eds); the participation of V.Rubio in the work for updating the European Guideline on Urea Cycle Disorders (*Orphanet J Rare Dis* 2012;7:32; to be completed in 2017); the invited participation of V.Rubio in the SSIEM 2016 Congress of Rome, giving an Update on Inborn Errors of Proline Metabolism and being a speaker in the Satellite Symposium “Expert Viewpoints” on Organic Acidemias; his being a speaker in the III Reunión Post-SSIEM (Madrid) to disseminate the conclusions of the 2016 SSIEM Congress among Spanish physicians; speaker in the Congress for Rare Disorders of the Valencian Community; and giving a Seminar in Bologna University (Italy) on P5CS deficiency. Of paramount social impact, our role in establishing the “Alliance for the Research on Rare Disorders of the Valencian Community” (FEDER Award, March 2017), with V.Rubio having become a member of the Scientific Committee of this Alliance.



LEAD RESEARCHER

Ruiz Pérez, Víctor Luis

📍 Agencia Estatal Consejo Superior de Investigaciones Científicas
Instituto de Investigaciones Biomédicas Alberto Sols
C/ Arturo Duperier 4
28029 Madrid

☎ (+34) 91 585 43 87

✉ vlruiz@iib.uam.es

🌐 [Group website](#)

PROGRAMMES

Pediatric and Developmental Medicine

GROUP MEMBERS

Staff members: Estañ Omaña, María Cristina

Main lines of research

- Molecular analysis and physiopathological mechanisms of Ellis-van Creveld syndrome and Weyer's acrocentric 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

- CAPARROS-MARTIN JA, AGLAN MS, TEMTAMY S, OTAIFY GA, VALENCIA M, NEVADO J ET AL. Molecular spectrum and differential diagnosis in patients referred with sporadic or autosomal recessive osteogenesis imperfecta. *Molecular genetics & genomic medicine*. 2016;5(1):28-39.

Highlights

Osteogenesis imperfecta (OI) is one of the most frequent skeletal dysplasias with an estimated prevalence of 6-7/100,000. Although most cases have a dominant mode of inheritance and carry mutations in COL1A1/2, recently there has been an explosion in the number of genes responsible for both recessive and dominant forms of this disease. In the past years, our laboratory, collaborating with U753 and international groups, has contributed to the expansion of the molecular basis of OI, by identifying two new causative genes (SP7, BMP1). In 2016 we have tried to help in clinical diagnosis by analyzing which genes are mutated in patients born to unaffected parents. Patients were separated depending on parental consanguinity. As a result, patients from non-consanguineous parents were mostly found having de novo COL1A1/2 mutations, excepting 4 cases that had IFITM5 and WNT1 variants. Only one non-consanguineous case was identified with compound heterozygous mutations in a recessive gene (SERPINF1). Consanguineous cases predominantly had mutations in recessive genes (CRTAP, FKBP10, LEPRE1, PLOD2, PPIB, SERPINF1, TEMEN38B and WNT1). However, two consanguineous cases had de novo mutations in COL1A1 indicating that COL1A1/2 variants cannot be overlooked in patients from consanguineous relationships. Further to this, whole exome sequencing in patients negative for mutations in known OI loci identified deleterious variants in two genes associated with congenital insensitivity to pain, NTRK1 and SCN9A, and in the Fanconi-Bickel gene SLC2A2. Thus, these conditions should be considered in the differential diagnosis of OI. In 2016 we started a new project funded by MINECO to characterize molecular mechanisms implicated in skeletal diseases (SAF2016-75434-R) and are collaborating with Fundacion AHUCE (Spanish brittle bone disease association) to provide molecular diagnosis to Spanish patients with OI. Lastly, we have collaborated with U753 to study patients with hypophosphatasia which is a disorder phenotypically overlapping with OI.



LEAD RESEARCHER

Salido, Eduardo

📍 Fundación Canaria de
Investigación Sanitaria
(FUNCANIS)
Hospital Univ. de Canarias
Ofra, s/n. La Cuesta
38820 La Laguna

☎ (+34) 922 67 97 31

✉ esalido@ull.es

🌐 [Group website](#)

PROGRAMMES

Inherited Metabolic Medicine



GROUP MEMBERS

Staff members: Rodríguez Rodríguez, Bárbara

Associated members: Arnau Díaz, María Rosa | Lorenzo Sellares, Víctor | Santana Rodríguez, Alfredo

Main lines of research

- Inherited metabolic disease.
- Inherited renal diseases.

Most relevant scientific articles

- ZAPATA-LINARES N., RODRIGUEZ S., SALIDO E., ABIZANDA G., IGLESIAS E., PROSPER F. ET AL. Generation and characterization of human iPSC lines derived from a Primary Hyperoxaluria Type I patient with p. I244T mutation. *Stem Cell Research*. 2016;16(1):116-119.
- DUTTA C., AVITAH-L-CURTIS N., PURSELL N., LARSSON COHEN M., HOLMES B., DIWANJI R. ET AL. Inhibition of glycolate oxidase with dicer-substrate siRNA reduces calcium oxalate deposition in a mouse model of primary hyperoxaluria type 1. *Molecular Therapy*. 2016;24(4):770-778.
- 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. *Molecular Therapy*. 2016.
- LUIS-LIMA S., RODRIGUEZ-RODRIGUEZ A.E., MARTIN-HIGUERAS C., SIERRA-RAMOS C., CARRARA F., ARNAU M.R. ET AL. Iohexol plasma clearance, a simple and reliable method to measure renal function in conscious mice. *Pflugers Archiv European Journal of Physiology*. 2016;1-8.
- MESA-TORRES N., CALVO A.C., OPPICI E., TITELBAUM N., MONTIOLI R., MIRANDA-VIZUETE A. ET AL. *Caenorhabditis elegans* AGXT-1 is a mitochondrial and temperature-adapted ortholog of peroxisomal human AGT1: New insights into between-species divergence in glyoxylate metabolism. *Biochimica et Biophysica Acta - Proteins and Proteomics*. 2016.

Hightlights

Proof of concept on the substrate reduction therapy as a therapeutic modality in primary hyperoxaluria. We have shown that glycolate oxidase inhibition with siRNA or small molecules improves primary hyperoxaluria. Based on this preclinical research there are two clinical trials ongoing. Transeuropean project ERAdicatPH (Understanding primary hyperoxaluria type 1 towards the development of innovative therapeutic strategies). Collaboration with Glaxo on the screening of small molecules for substrate reduction therapy of primary hyperoxaluria (GSK fastrack award). Start of Orfan biotech (spin-off). Clinical activity on the diagnosis and management of primary hyperoxaluria patients.



LEAD RESEARCHER

Sanz, Pascual

📍 Agencia Estatal Consejo Superior de Investigaciones Científicas
Instituto de Biomédicina de Valencia
Jaume Roig, 11
46010 Valencia

☎ (+34) 96 339 17 60

🌐 [Group website](#)

PROGRAMMES
Genetic Medicine



GROUP MEMBERS

Staff members: Heredia Pérez, Miguel

Associated members: Muñoz Ballester, Carmen | Pérez Jiménez, Eva | 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

- BERTHIER A., PAYA M., GARCIA-CABRERO A.M., BALLESTER M.I., HEREDIA M., SERRATOSA J.M. ET AL. Pharmacological Interventions to Ameliorate Neuropathological Symptoms in a Mouse Model of Lafora Disease. *Molecular Neurobiology*. 2016;53(2):1296-1309.
- LOPEZ-GONZALEZ I., VIANA R., SANZ P., FERRER I. Inflammation in Lafora Disease: Evolution with Disease Progression in Laforin and Malin Knock-out Mouse Models. *Molecular Neurobiology*. 2016;:1-12.
- MUNOZ-BALLESTER C., BERTHIER A., VIANA R., SANZ P.. Homeostasis of the astrocytic glutamate transporter GLT-1 is altered in mouse models of Lafora disease. *Biochimica et Biophysica Acta - Molecular Basis of Disease*. 2016;1862(6):1074-1083.
- OLIGSCHLAEGER Y., MIGLIANICO M., DAHLMANS V., RUBIO-VILLENA C., CHANDA D., GARCIA-GIMENO M.A. ET AL. The interaction between AMPK β 2 and the PP1-targeting subunit R6 is dynamically regulated by intracellular glycogen content. *Biochemical Journal*. 2016;473(7):937-947.


Highlights


- We have treated malin-deficient Lafora disease mice with different compounds in order to check if they ameliorated their neuropathological symptoms. Our results indicate that the treatment with 4-phenylbutyrate (a chemical chaperone) or with metformin (an activator of the AMP-activated protein kinase) notably improve the neurological parameters of malin-KO mice. These results indicate a possible utility of these compounds to slow the progression of the disease (Berthier et al., 2016, *Mol. Neurobiol*, 53: 1296-1309). As a result of these findings, we have applied to the European Medicines Agency (EMA) the designation of metformin as an orphan drug for the treatment of Lafora disease.
- We have demonstrated that in primary cultures of astrocytes from mouse models of Lafora disease the uptake of glutamate is impaired. This defect is due to changes in the homeostasis of the main glutamate transporter named GLT-1/EAAT2. The laforin-malin complex alters the regular ubiquitination pattern of GLT-1/EAAT2 transporter, affecting its intracellular recycling. These results indicate that astrocytes for mouse models of Lafora disease have a reduced capacity to clear glutamate, what will maintain this neurotransmitter during more time at the synaptic cleft, leading to excitotoxicity (Muñoz-Ballester et al., 2016, *BBA Molecular Basis of Disease* 1862: 1074-1083).
- The group participates actively in the project from the National Institute of Neurological Disorders and Stroke (NINDS-NIH/USA), P01NS097197, entitled “Lafora Epilepsy – Basic mechanisms to therapy”, recently awarded (June2016-June2021). The coordinator of the project is Dr. Matthew Gentry, Univ. Kentucky, USA.
- The group is co-author of the patent PCT/ES2016/070868, on new activator compounds of the AMP-activated protein kinase, to be used in the treatment of neurodegenerative disorders.
- We have participated in the organization of the meeting of the Valencian Association of Huntington Disease (AVAEH) in November 2016.



LEAD RESEARCHER

Satrústegui Gil Delgado, Jorgina

 Universidad Autónoma de Madrid
Centro de Biología Molecular Severo Ochoa
Nicolás Cabrera, 1
Campus de Cantoblanco UAM
28049 Madrid

 (+34) 91 196 46 21

 jsatrustegui@cbm.csic.es

 [Group website](#)

PROGRAMMES

Mitochondrial and Neuromuscular Medicine



GROUP MEMBERS

Staff members: Contreras Balsa, Laura

Associated members: De Arco Martínez, Araceli | Pardo Merino, Beatriz

Main lines of research

- Global Cerebral Hypomyelination. 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 in 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 DNAmT deletions and ophthalmoplegia, 2) Possible implication of mutations in SCAmC-3 in human disease associated with deletions or depletion of liver, but not muscle, DNAmT.
- 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

- LLORENTE-FOLCH I., RUEDA C.B., PEREZ-LIEBANA I., SATRUSTEGUI J., PARDO B.. L-lactate-mediated neuroprotection against glutamate- induced excitotoxicity requires ARALAR/AGC1. *Journal of Neuroscience*. 2016;36(16):4443-4456.
- DEL ARCO A., CONTRERAS L., PARDO B., SATRUSTEGUI J.. Calcium regulation of mitochondrial carriers. *Biochimica et Biophysica Acta - Molecular Cell Research*. 2016.
- RUEDA CB, LLORENTE-FOLCH I, TRABA J, AMIGO I, GONZALEZ-SANCHEZ P, CONTRERAS L ET AL. Glutamate excitotoxicity and Ca(2+)-regulation of respiration: Role of the Ca(2+) activated mitochondrial transporters (CaMCs). *Biochimica et biophysica acta*. 2016;1857(8):1158-66.
- PÉREZ-CAÑAMÁS A, BENVENÙ S, RUEDA CB, RÁBANO A, SATRÚSTEGUI J, LEDESMA MD. Sphingomyelin-induced inhibition of the plasma membrane calcium ATPase causes neurodegeneration in type A Niemann-Pick disease. *Molecular psychiatry*. 2016.
- CONTRERAS L, RAMIREZ L, DU J, HURLEY JB, SATRÚSTEGUI J, DE LA VILLA P. Deficient glucose and glutamine metabolism in Aralar/AGC1/Slc25a12 knockout mice contributes to altered visual function. *Molecular vision*. 2016; 22:1198-1212.

Highlights


We have advanced in the understanding of glutamate excitotoxicity and the role played by Aralar/AGC1 and the malate aspartate shuttle (MAS) in allowing the protective effects of lactate (Llorente-Folch et al, *J Neurosci*; Rueda et al *BBA*), along with the role of other calcium-regulated mitochondrial carriers (del Arco et al, *BBA*). We have also explored the role of Aralar/AGC1 in retina finding that Aralar-deficient mice are not blind but have a 50% decrease in ERG amplitude response in the light-evoked activity of dark-adapted retinas, in spite of normal retina histology (Contreras et al, *Mol Vision*). The defective response and ERG alteration takes place primarily in photoreceptors, but the response to two flashes applied in fast succession also revealed an alteration in synaptic transmission consistent with an imbalance of glutamate and an energy deficit in the inner retina neurons consistent with previous findings (Du et al, *JBC*). In search for additional aspartate transporters in brain mitochondria, we have concluded that UCP2 does not play such a role, as there was no difference in aspartate labeling from 1-¹³C-glucose in the brain from UCP2-KO mice. However, the results obtained suggest that UCP2 may play a role in transporting a tricarboxylic acid cycle-related metabolite out of mitochondria (Contreras et al, *Neurochem Res*). We have collaborated with CIBERER-U713 (JM Cuezva) in analyzing the a possible “PTP prone” state due to the expression of the F0F1ATP synthase inhibitor IF1 (Santacatterina et al, *Oncotarget*), and with Dr. Ledesma’s lab at the CBMSO in studying the effects of rare disease, type A Niemann-Pick, on the activity of calcium regulation systems, finding that the plasma membrane Ca²⁺ pump is a target for excess sphingomyelin (Perez-Cañamas et al, *Mol Psychiatr*), and with Dr. López for the study of the effect of nitrotonic receptors on mitochondrial function (Navarro et al, *ARS*).




LEAD RESEARCHER

Serratos, José

 Instituto de Investigación
Sanitaria - Fund. Jiménez Díaz
Avda. Reyes Católicos, 2
28040 Madrid

 (+34) 91 550 48 00 Ext 3251

 joseserratos@me.com

 [Group website](#)

PROGRAMMES

Genetic Medicine



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

- JOHANNESSEN K, MARINI C, PFEFFER S, MØLLER RS, DORN T, NITURAD CE ET AL. Phenotypic spectrum of GABRA1: From generalized epilepsies to severe epileptic encephalopathies. *Neurology*. 2016;87(11):1140-51.
- BERTHIER A., PAYA M., GARCIA-CABRERO A.M., BALLESTER M.I., HEREDIA M., SERRATOSA J.M. ET AL. Pharmacological Interventions to Ameliorate Neuropathological Symptoms in a Mouse Model of Lafora Disease. *Molecular Neurobiology*. 2016;53(2):1296-1309.
- GOMEZ-TORTOSA E., PRIETO-JURCZYNSKA C., SERRANO S., FRANCO-MACIAS E., OLIVIE L., GALLEGO J. ET AL. Diversity of Cognitive Phenotypes Associated with C9ORF72 Hexanucleotide Expansion. *Journal of Alzheimer's Disease*. 2016;52(1):25-31.
- DJÉMIÉ T, WECKHUYSEN S, VON SPICZAK S, CARVILL GL, JAEHN J, ANTTONEN AK ET AL. Pitfalls in genetic testing: the story of missed SCN1A mutations. *Molecular genetics & genomic medicine*. 2016;4(4):457-64.

Highlights

The main objective of unit 744 of CIBERER is the identification and characterization of genes involved in familial epilepsy and rare forms of epilepsy in order to generate diagnostic and therapeutic tools to improve the care of affected patients. At present, we are focused on the search and testing of new treatments.

Since July 2016, our group has been integrated and funded in NIH's NINDS project P01 NS097197 (Lafora Epilepsy-Basic mechanisms to therapy). The main objective is to find a therapy for Lafora disease. In this line, we have performed pharmacological studies with different molecules in animal models of Lafora disease, demonstrating, in collaboration with Pascual Sanz's 742 unit, beneficial neurological effects of metformin and 4-PBA. In December 2016, metformin was designated as an orphan drug by the EMA through CIBERER (groups 742 and 744). In addition, we have performed exome sequencing studies in families with more than one affected and discordant phenotypes in order to study possible modulators of the phenotype. We are leading the design of an international registry of patients with Lafora disease. During 2016 we have collaborated in the identification of genes associated with epileptic encephalopathies and we have outlined phenotypes of genetic epilepsies (within the EUROEPINOMICS consortium).

Unit 744 has continued with the initiative of creating a registry of patients with epileptic encephalopathies (Spanish Group of Genetics of Childhood Epilepsy, GEGEI, www.gegei.es) and has maintained close collaboration with the Dementia Unit in our Institute.


Our unit has been actively involved in clinical trials of antiepileptic drugs (Phase II, III and IV) and led a in-house designed clinical trial that includes the development of devices and measuring instruments to monitor epileptic seizures in the patient's home.




LEAD RESEARCHER

Surrallés, Jordi

 **Universidad Autónoma de Barcelona**
Facultad de Biociencias
Campus de la UAB s/n.
Edif. C. Torre C3 senars 2ª pl.

 (+34) 93 581 18 30
(+34) 93 586 80 51

 jordi.surralles@uab.es

 [Group website](#)

PROGRAMMES

Inherited Cancer, Haematological and Dermatological Diseases



GROUP MEMBERS

Staff members: Bogliolo, Massimo | Pujol Calvet, María Roser | Ramírez de Haro, María José

Associated members: Cabre Fabre, Oriol | Hernández Viedma, Gonzalo | Marín Vilar, María | Miguillón Pedreño, Jordi | Mina, Leonardo | 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 repurposing.
- 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.

Highlights

Dr. Jordi Surrallés's team identified two novel components of the Fanconi/BRCA pathway and discovered that mutation in the coding genes cause Fanconi anemia or a new Fanconi-like cancer predisposition syndrome. To do so, the team applied interactomics and exome sequencing approaches. In collaboration with Dr. Luís A. Pérez Jurado's team, we managed to detect bone marrow cytogenetic clonal events in blood DNA by the use of SNP arrays and demonstrated that FA patients with clonal events have poor prognostic and their cancer-free survival is 5 times shorter. Dr. Surrallés's team has identified a new BRCA2 interactor and demonstrated that its expression level in breast cancer is of prognostic value. This result led to an European Patent. During 2016, the team screened all currently approved drugs in a cell-based system to find a cure for Fanconi anemia in a drug repurposing strategy. Finally, the team has collaborated in the Fanconi anemia gene therapy clinical trial led by Dr. Juan Bueren.





LEAD RESEARCHER

Varela Nieto, Isabel

📍 Agencia Estatal Consejo Superior de Investigaciones Científicas
Instituto de Investigaciones Biomédicas Alberto Sols
C/ Arturo Duperier 4
28029 Madrid

☎ (+34) 91 585 44 21

✉ ivarela@iib.uam.es

🌐 [Group website](#)

PROGRAMMES

Sensorineural Pathology



GROUP MEMBERS

Staff members: Murillo Cuesta, Silvia | Rodríguez De La Rosa, Lourdes

Contratados a cargo de proyecto: Celaya Puertolas, Adelaida | Jareño Flores, Tania

Associated members: Baeza Ochoa de Ocariz, María Luisa | Cediél Algovia, Rafael | Cervantes Sánchez, Blanca Aurora | Contreras Rodríguez, Julio | García Alcántara, Fernando | Magariños Sánchez, Marta | Pulido Sánchez, Sara | 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 MAPK/JNK 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 and cellular 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.
- Hereditary angioedema.

Most relevant scientific articles

- BUNIELLO A., INGHAM N.J., LEWIS M.A., HUMA A.C., MARTINEZ-VEGA R., VARELA-NIETO I. ET AL. Wbp2 is required for normal glutamatergic synapses in the cochlea and is crucial for hearing. *EMBO Molecular Medicine*. 2016.
- KLIONSKY DJ, ABDELMOHSEN K, ABE A, ABEDIN MJ, ABELIOVICH H, ACEVEDO AROZENA A ET AL. Guidelines for the use and interpretation of assays for monitoring autophagy (3rd edition). *Autophagy*. 2016;12(1):1-222.
- MARTINEZ-VEGA R., MURILLO-CUESTA S., PARTEARROYO T., VARELA-MOREIRAS G., VARELA-NIETO I., PAJARES M.A. Long-term dietary folate deficiency accelerates progressive hearing loss on CBA/Ca mice. *Frontiers in Aging Neuroscience*. 2016;8(AUG).
- ARROBA A.I., DE LA ROSA L.R., MURILLO-CUESTA S., VAQUERO-VILLANUEVA L., HURLE J.M., VARELA-NIETO I. ET AL. Autophagy resolves early retinal inflammation in Igf1-deficient mice. *DMM Disease Models and Mechanisms*. 2016;9(9):965-974.
- MARTINEZ-VEGA R., PARTEARROYO T., VALLECILLO N., VARELA-MOREIRAS G., PAJARES M.A., VARELA-NIETO I. Long-term omega-3 fatty acid supplementation prevents expression changes in cochlear homocysteine metabolism and ameliorates progressive hearing loss in C57BL/6J mice. *Journal of Nutritional Biochemistry*. 2016;26(12):1424-1433.

Hightlights

The group in 2016 has maintained collaborations with companies interested in the development of auditory therapies based on small molecules, in the framework of European projects (TARGEAR & AFHELO, Affichem) and national (Salvat Biotech, CIBER) CDTI and SAF2014-AGEAR. Collaboration with both companies is ongoing, so there have been applications to European calls, and we will formalize an agreement with Spiral Th. Results obtained are under study to assess their patentability. These projects and contracts are managed via CIBER by the competitive advantage of integrating into a single group pluridisciplinary experts.


Links with associations of people affected of hearing loss and hyperacusis have also increased by participation in events of science for society and presenting the social problem of hearing loss (H2020-researchers and science week) at events and through social networks (www.targear.eu and @targear). The association of patients FIAPAS has awarded us the prize Health by our work in the search of therapeutic solutions for the protection and repair of hearing loss.

The collaboration with national, primarily CIBER, and international groups of research has also grown and has begun to give fruits in terms of results published and in preparation. It can be emphasized the identification of genes (Wnt2 & Igf1) and processes (autophagy & micronutrients) involved in sensory loss and the development and analysis of cellular and animal models of deafness (with SEFALer). Equally successful is the work of members of the group interested in hereditary angioedema and its specialized care to patients from this rare disease. Collaborations have also resulted in applications to H2020 projects, E-RARE and ITN with CIBERER groups, and the intramural ACCI action granted.



LEAD RESEARCHER

Vicente García, Vicente

 Fundación para la Formación e Investigación Sanitarias de la Región de Murcia (FFIS)
Hospital José María Morales Meseguer
C/ L. Fontes Pagán nº 9 - 1ª pl.
30003Murcia

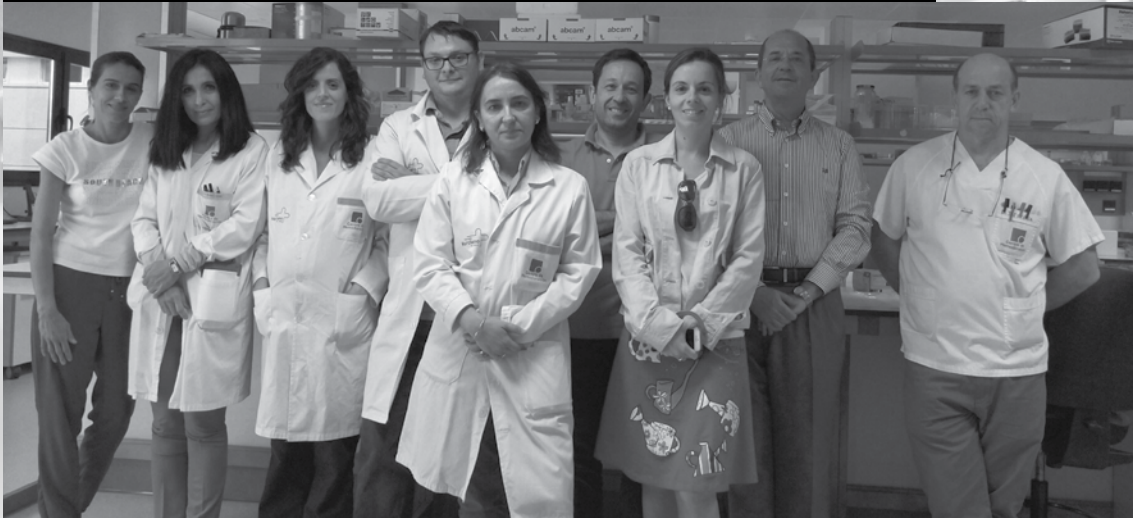
 (+34) 96 834 19 90

 vicente.vicente@carm.es

 [Group website](#)

PROGRAMMES

Genetic Medicine



GROUP MEMBERS

Staff members: Cifuentes Riquelme, Rosa | Palma Barqueros, Verónica

Associated members: Antón García, Ana Isabel | Corral de la Calle, Javier | De la Morena Barrio, María Eugenia | Ferrer Marín, Francisca | Lozano Almela, María Luisa | Martínez Martínez, Irene | Navarro Fernández, José | Rivera Pozo, José | Teruel Montoya, Raúl

Main lines of research

The main field of research of our group is the characterization of the molecular mechanisms involved in rare disorders of hematology, mainly of hemostatic disorders. During 2016, we have identified 2 novel function-disrupting mutations in RASGRP2 that account for bleeding diathesis and platelet dysfunction in 2 unrelated families. This gene encodes CalDAG-GEFI, a protein playing a role in the activation of Rap1 and subsequent activation of platelet and leukocyte integrins. Our study validates the physiological relevance of this gene in platelet function and thrombopathies (Blood). The same strategy: massive sequencing of the whole exome or a panel of candidate genes of patients with thrombopathy has also revealed a new hemizygous 1-bp deletion in WAS gene from a patient with Wiskott–Aldrich syndrome (Platelets). Also in the field of congenital bleeding diathesis, but this time impairing the coagulation cascade, we have identified a new case with combined deficiency of vitamin K dependent proteins (VKCFD). The originality of our study is the mechanism involved: an UPD of chromosome 1 that make homozygous the paternal mutation of GGX that abolished a correct splicing (JTH-1). The last article published in the field of bleeding disorders has been done in multiple myeloma. We demonstrated that the immunoglobulins of certain patients may behave as heparin-like molecules, activating antithrombin, which significantly increase the risk of bleeding and may be controlled by protamine sulphate (Haematologica). In the field of congenital thrombophilia, we point out the identification of the molecular base of a high proportion of cases with

antithrombin deficiency that is not explained by mutations in the gene encoding this anticoagulant (SERPINC1): a disorder of glycosylation. This study does not only identify a new thrombophilia, but also shows new evidences supporting that congenital disorders of glycosylation are underestimated and may be explained by new mechanisms, such as the combination of a single mutation in a gene involved in the N-glycosylation pathway and an environmental factor like alcohol consumption (JTH-2).

Most relevant scientific articles

- LOZANO M.L., COOK A., BASTIDA J.M., PAUL D.S., IRUIN G., CID A.R. ET AL. Novel mutations in RASGRP2, which encodes CalDAG-GEFI, abrogate Rap1 activation, causing platelet dysfunction. *Blood*. 2016;128(9):1282-1289.
- DE LA MORENA-BARRIO M.E., MARTINEZ-MARTINEZ I., DE COS C., WYPASEK E., ROLDAN V., UNDAS A. ET AL. Hypoglycosylation is a common finding in antithrombin deficiency in the absence of a SERPINC1 gene defect. *Journal of Thrombosis and Haemostasis*. 2016.
- BASTIDA J.M., DEL REY M., REVILLA N., BENITO R., PEREZ-ANDRES M., GONZALEZ B. ET AL. Wiskott-Aldrich syndrome in a child presenting with macrothrombocytopenia. *Platelets*. 2016;1-4.
- MARTINEZ-MARTINEZ I., GONZALEZ PORRAS J.R., JOSE CEBEIRA M., DE ARRIBA F., ESPIN S., BOHDAN N. ET AL. Identification of a new potential mechanism responsible for severe bleeding in myeloma: Immunoglobulins bind the heparin binding domain of antithrombin activating this endogenous anticoagulant. *Haematologica*. 2016;101(10): e423-e426.
- DASI M.A., GONZALEZ-CONEJERO R., IZQUIERDO S., PADILLA J., GARCIA J.L., GARCIA-BARBERA N. ET AL. Uniparental disomy causes deficiencies of vitamin K-dependent proteins. *Journal of Thrombosis and Haemostasis*. 2016.

Highlights

RESEARCH GRANTS: 1) Program of Scientific Excellence of Region de Murcia. 19873/GERM/15. Séneca Foundation. From 2016 to 2020. 2) Grants for Working groups of the Spanish Society of Thrombosis and Haemostasis. Functional and molecular characterization of patients with congenital disorders of platelets. From 2017 to 2018.

SCIENTIFIC PRIZES: 1) Price to the best scientific article of the Spanish Society of Thrombosis and Haemostasis: Novel mutations in RASGRP2, which encodes CalDAG-GEFI, abrogate Rap1 activation, causing platelet dysfunction). 2) Price of the Royan Academy of Medicine from Región de Murcia: FXI deficiency.

CIBERER COLLABORATIONS. Our recent incorporation to CIBERER has stimulated the collaboration with other groups of this network: 1) LÓPEZ TRASCASA, MARGARITA - CB06/07/1033; 2) BUEREN, JUAN ANTONIO - CB06/07/0014, 3) ARTUCH IRIBERRI, RAFAEL - CB06/07/0061; 4) GUILLÉN NAVARRO, ENCARNACIÓN - GCV14/ER/1


CONTRACTS WITH COMPANY: 1) Identifying new patients with antithrombin deficiency. Grifols SA. From 2016 to 2018



LEAD RESEARCHER

**Vilchez Padilla,
Juan Jesús**

 Fund. para la Investigación
del Hospital la Fe
Hospital Universitario de la Fe
Avda. F.Abril Martorell, 106
46009 Valencia

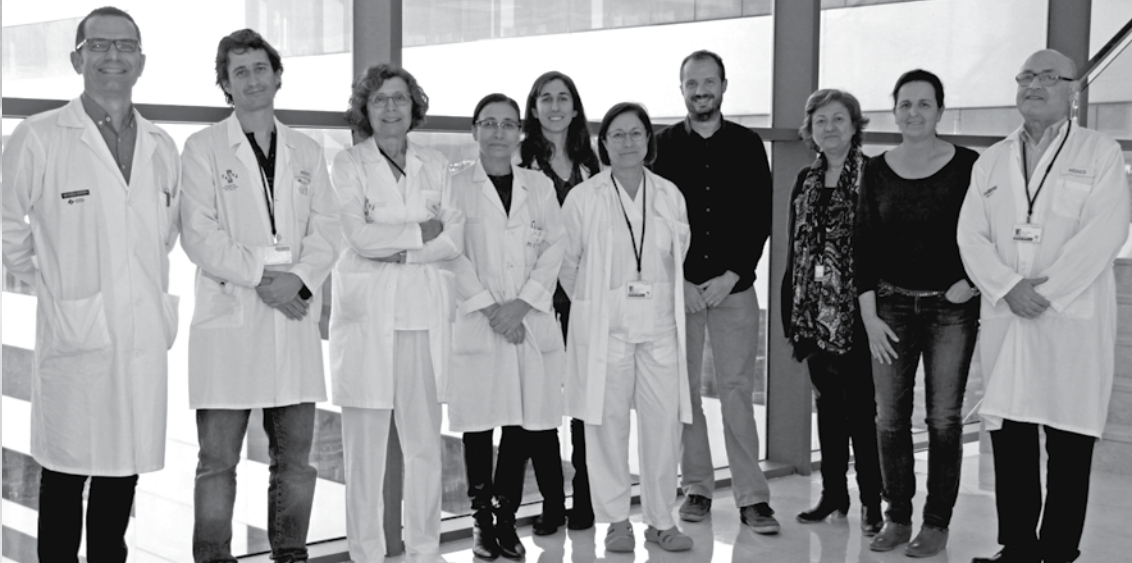
 (+34) 96 124 55 44

 vilchez_jjegva.es

 [Group website](#)

PROGRAMMES

Mitochondrial and Neuromuscular Medicine



GROUP MEMBERS

Staff members: Azorín Villena, Inmaculada Concepción | Gómez Perpiña, Lorena

Associated members: Bataller Alberola, Luis | Chumillas Luján, Josefina | Martí Martínez, María Pilar | Mayordomo Fernández, Fernando | Muelas Gómez, Núria | Sevilla Mantecón, María Teresa | Vázquez Costa, Juan Francisco

Main lines of research

- Clinical and genetic characterization of hereditary 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 acquired ataxias.
- Clinical and genetic characterization of congenital myasthenia.

Most relevant scientific articles

- SEVILLA T., LUPO V., MARTINEZ-RUBIO D., SANCHO P., SIVERA R., CHUMILLAS M.I.J. ET AL. Mutations in the MORC2 gene cause axonal Charcot-Marie-Tooth disease. *Brain*. 2016;139(1):62-72.
- VAZQUEZ-COSTA J.F., BATALLER L., VILCHEZ J.J. Primary lateral sclerosis and hereditary spastic paraplegia in sporadic patients. An important distinction in descriptive studies. *Annals of Neurology*. 2016.
- FRASQUET M, CHUMILLAS MJ, VÍLCHEZ JJ, MÁRQUEZ-INFANTE C, PALAU F, VÁZQUEZ-COSTA JF ET AL. Phenotype and natural history of inherited neuropathies caused by HSJ1 c.352+1G>A mutation. *Journal of neurology, neurosurgery, and psychiatry*. 2016;87(11):1265-1268.
- LUPO V., GARCIA-GARCIA F., SANCHO P., TELLO C., GARCIA-ROMERO M., VILLARREAL L. ET AL. Assessment of Targeted Next-Generation Sequencing as a Tool for the Diagnosis of Charcot-Marie-Tooth Disease and Hereditary Motor Neuropathy. *Journal of Molecular Diagnostics*. 2016;18(2):225-234.
- EVILA A., PALMIO J., VIHOLA A., SAVARESE M., TASCIA G., PENTTILA S. ET AL. Targeted Next-Generation Sequencing Reveals Novel TTN Mutations Causing Recessive Distal Titinopathy. *Molecular Neurobiology*. 2016;1-12.

Highlights

Among the activities in which our group has participated in the 2016 annuity, it is worth mentioning the designation as a Reference Center for the National Health System (CSUR) on rare Neuromuscular diseases and its integration within the European Network of Rare Neuromuscular Diseases. In this annuity he obtained two projects funded in a public call of the ISCIII for the study of genetic neurotoxicities CMT in childhood (Dra T Sevilla) and the genetic characterization of distal myopathies (Dres N Muelas and JJ Vilchez); Also obtained private grants from Association I. Gemio and the Association of Patients of Muscular Dystrophy LGMD1F, oriented to the development of therapies in Duchenne Dystrophy and LGMD1F dystrophy of waists. We were also selected to participate as a center in international multi-center trials on Duchenne dystrophy (gene therapy with Ataluren) and CMT Neuropathy. We proceeded to the reading of a doctoral thesis directed by our group (Dr. JJ Vilchez) on a study of the Asymptomatic HyperCKemia. We have organized or participated in various courses on neuromuscular diseases both nationally (Online course on myopathy of the SEN-JJ Vilchez) or in the Valencian Community (Training Course in myopathies of the Valencia Society of Neurology -N Muelas and JJ Vilchez). Finally, it is worth mentioning our participation in the elaboration of two guides: a national one on the management of Duchenne dystrophy (JJ Vilchez) and another one oriented to the ELA management in the network of assistance to ELA of the Valencian Community (Dr. JF Vazquez).



LEAD RESEARCHER
Webb, Susan

- Instituto de Investigación del Hospital de la Santa Cruz y San Pablo
St. Antoni M^a Claret, 167
08025 Barcelona
- (+34) 93 553 79 17
(+34) 93 556 56 61
- swebb@santpau.cat
- [Group website](#)

PROGRAMMES
Endocrine Medicine



GROUP MEMBERS

Staff members: Resmini, Eugenia | Valassi, Elena

Associated members: Aulinas Masó, Anna | Badía Llach, Xavier | Barahona Costanzo, María José | Crespo Martín, Iris | Martínez Momblán, María Antonia | Santos Vives, Alicia | Sucunza Alfonso, Núria

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

- VALASSI E., CRESPO I., MALOUF J., LLAUGER J., AULINAS A., MARIN A.M. ET AL. Reduction of trabecular and cortical volumetric bone mineral density at the proximal femur in patients with acromegaly. *European Journal of Endocrinology*. 2016;174(2):107-114.
- VALASSI E., CRESPO I., MALOUF J., VILADES D., LETA R., LLAUGER J. ET AL. Epicardial fat is a negative predictor of spine volumetric bone mineral density and trabecular bone score in acromegaly. *Endocrine*. 2016;1-5.
- CRESPO I., SANTOS A., GOMEZ-ANSON B., LOPEZ-MOURELO O., PIRES P., VIVES-GILABERT Y. ET AL. Brain metabolite abnormalities in ventromedial prefrontal cortex are related to duration of hypercortisolism and anxiety in patients with Cushing's syndrome. *Endocrine*. 2016;1-9.
- RESMINI E., SANTOS A., AULINAS A., WEBB S.M., VIVES-GILABERT Y., COX O. ET AL. Reduced DNA methylation of FKBP5 in Cushing's syndrome. *Endocrine*. 2016:1-10.
- RESMINI E., SANTOS A., WEBB S.M.. Cortisol excess and the brain. *Frontiers of Hormone Research*. 2016; 46:74-86.

Highlights

The U747 group performs clinical research oriented to Pituitary RD, with translation to the NHS, registries and collaboration with patients. In translation, it collaborates with EPIRARE and Orphanet-Spain; the PI is coordinator of Endocrine Medicine of CIBERER. There is collaboration with the 5 linked clinical groups, with a translational research project, and an ISCIII Personalized Medicine project, on pituitary tumors. Since 1982 the IP is responsible for specialized consultations on Pituitary RD.

After an ISCIII project (PI 11/0001) completed in 2014, another ISCIII competitive project, PI14 / 00194, was initiated in 2015: "Study of microarchitecture and bone resistance and their determinant factors in Cushing's sd or acromegaly in remission. Model for investigating body-bone-fat interaction".

The agreements signed with multinational pharmaceutical companies guarantee the European registry of Cushing's syndrome (ERCUSYN), that is coordinated by this group.

The group has collaborated in 2 publications of an international consortium to find new genes for endocrine RD.

It collaborates in meetings with patients with endocrine RD (acromegaly, Addison's disease).

In transfer to the productive sector, the relationship with the pharmaceutical industry participating in clinical trials (phase 2, 3 and 4), epidemiological studies, R & D + I contracts and pituitary RD consultancies should be mentioned. Likewise, the copyright of the PI and of the ascribed member X Badia of the quality of life questionnaires in acromegaly and Cushing's sd (and recently primary hyperparathyroidism), produce income that pays for salaries of members of the group.

The Gestió d'Ajuts Universitat de Recerca (AGAUR) has recognized the group (identified as 355) in the call for support to the Research Groups, and has classified it as 4th (1st clinical) of the 60 groups of IIB- S Pau.

In Training since 2013 4 doctoral theses of members of the group have been defended.

Linked Groups

Programme for Research into Paediatric and Developmental Medicine

Encarna Guillén Hospital Virgen de la Arrixaca, Murcia

Feliciano J. Ramos Hospital Lozano Blesa, Zaragoza

Jordi Rosell Hospital Son Espases, Palma de Mallorca

Isabel Tejada Hospital Cruces, Bilbao

Programme for Research into Inherited Metabolic Medicine

Luis Aldámiz-Echevarría Azuara Hospital Cruces, Bilbao

M^a 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

Programme for Research into Endocrine Medicine

Irene Halperin Hospital Clínic, Barcelona

Antonio Picó Hospital General de Alicante, Alicante

Manuel Puig Domingo Hospital Germans Trías i Pujol

Alfonso Soto Hospital Virgen del Rocío, Sevilla

Programme for Research into Inherited Cancer, Haematological and Dermatological Diseases

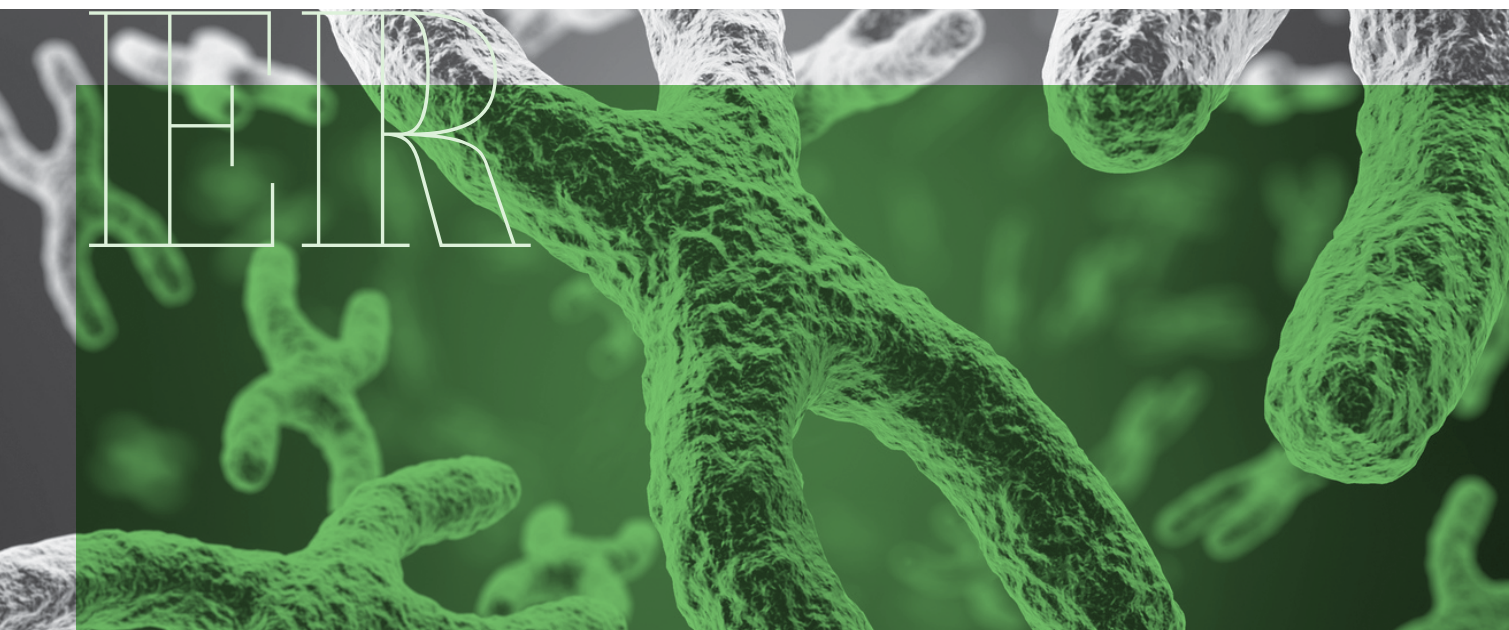
Isabel Badell Hospital de la Santa Creu i Sant Pau, Barcelona

Cristina Beléndez Hospital Gregorio Marañón, Madrid

Albert Català Hospital San Joan de Déu, Barcelona

Julián Sevilla Hospital Infantil Niño Jesús, Madrid

Joan-Lluís Vives-Corróns Hospital Clínic, Barcelona



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