ANNUAL REPORT 2014

ciberer

Centro de Investigación Biomédica en Red

Enfermedades Raras

Index

1. ORGANIZATION

Letter from the Scientific Director

Prof. Francesc Palau
Scientific Director of CIBERER

It is undeniable that in 2014, CIBERER has solidified its position as a national and international example of research on Rare Diseases (RD), undoubtedly as a result of the collaboration between the different entities in the consortium and research groups making up the Centre and the work committed to national policies (2013-2016 State Plan for Scientific, Technical and Innovative Research) and international policies (Horizon 2020 R&D&I Programme of the European Commission and International Rare Disease Research Consortium-IRDiRC) in the area of the RD, which we have been developing over the past 8 years.

Our competitive advantage has come about because we are the only state-run centre capable of bringing together all the knowledge generated by diversified networking research activity, which is inevitable when addressing problems on rare diseases.

CIBERER has contributed in the area of innovations in health care processes, health services or organisational changes, for example through the participation of some of its groups in the **Catálogo de Buenas Prácticas en el Ámbito de la Estrategia en Enfermedades Raras del Sistema Nacional de Salud**, which was published in 2014 by the Ministry of Health, Social Services and Equality (MSSSI), or the follow-up of the evaluation of the Strategy, published in 2014. This catalogue contains eight initiatives, four of which are developed by CIBERER research groups (U703, U707 and U737).

Through the creation **of the CIBERER Programme "Genes of Undiagnosed Rare Diseases (ENoD)**" in 2011, an enormous project for the application of exome sequencing to a number of RDs for the purpose of being able to diagnose patients with RDs that was not previously possible despite comprehensive clinical and genetic studies. The first results published in international journals were obtained from this work, particularly during 2013. This programme has been the basis for implementing in 2014 the **Ciberer Exome Server** and the **SPANEX Project** (database on exomes and genomic information and genetic variants of the Spanish population). A new call for proposals is expected in 2015 for the ENoD Programme in order to elucidate new genes involved on RDs.

In the translational context, it should be pointed out that the CIBERER in this period has incorporated **20 Linked Clinical Groups (LCGs)**: 4 relating to the Paediatric Medicine and Development Research Programme (RP), 6 with the Inherited Metabolic Medicine RP, 5 with the Endocrine Medicine RP and the other 5 with the Hereditary Cancer and Related Syndromes RP. These 20 groups, distributed throughout 9 Spanish Regions and 16 hospitals within the National Health System, show the CIBERER's obvious support for transferring research to clinical practice, carrying projects cooperative in specific pathologies.

In relation to the development of **new therapies for RDs**, the CIBERER has directly contributed in 2014 as a sponsor of a new **orphan drug** (OD) for anaemia due to kinase pyruvate deficiency in erythrocytes based on gene therapy. The therapy was designated as an orphan drug by the European Medicines Agency (EMA) (Reference EU/3/14/1330). So CIBERER is the sponsor of a total of 2 ODs.

The main results aimed at the **transfer of technology** to the productive sector that we would like to point out, in addition to patents application, include the energy metabolism phenotyping platform, PROTEOmAB, developed in collaboration with the Universidad Autónoma de Madrid-U713-Dr. Cuezva, and the start up from the Rare Diseases Area of the first Spin-Off with participation of the CIBER: Epidisease S.L. Epidisease is an enterprise arising from the activity of Group U733-Dr. Pallardó, of the Universitat de València, specialising in epigenetics applied to the development of new biomarkers with a diagnostic application.

On an international level, it should be pointed out that CIBERER has been nominated in 2014 by the MSSSI to participate in the future **Joint Action on Rare Diseases** (RD Action), which is the result of the union of the current Ophanet Joint Action and EUCERD Joint Action, which will be active between 2015 and 2017, and funded by the Consumers, Health, Agriculture and Food Executive Agency (CHAFEA) of the European Commission. This new participation in a Joint Action is the consequence of the work that has been performed these past few years in the EUCERD Joint Action, leading the studies in quality and improvement of practices in European Centres of Expertise on rare diseases and participation in the future European Reference Networks (ERNs). The preliminary results of this project were presented in a Workshop held in 2014 in the central office of the Ministry of Health, Social Services and Equality (MSSSI).

Technical unification of the CIBER in January 2014 will undoubtedly be a step towards the national research collaboration. The primary milestones in this first year include the grant for an integrated CIBER project of excellence entitled "Molecular links between diabetes and neurodegenerative disorders" in collaboration with CIBERDEM, CIBERBBN and CIBERNED, and the grant for a project within the National R&D&I Plan in the MINECO 2014 Networks and Managers call for proposals to develop a CIBER Internationalisation Platform, in which CIBERER, CIBER-BBN and CIBERES collaborate.

CIBERER has continued furthermore to develop and enhance the **Transversal Instrument Platforms for RDs** (PITER): the **CIBERER Biobank, the Animal Phenotyping Platform (SEFALer)** and the **Bioinformatics Platform for RDs** (BIER), thereby maintaining its significant technological support for researchers. As a Spanish **Orphanet** partner, CIBERER, continues to be part of a transnational project which plays a very relevant role as it unifies specialised knowledge and resources relating to RDs.

All this work conducted within the CIBERER groups naturally yields **scientific production** (original publications in international journals indexed in ISI-Thompson), which grows year after year in quantity and quality. Furthermore, increasingly more CIBERER work can be found among the most cited Spanish work.

Based on the foregoing, CIBERER has now more than ever the obligation to continue responding to the needs which are involved in being a centre of excellence having these characteristics and the challenges that are coming in the area of RDs on both a social and health level in the next few years.

LIST OF INSTITUTIONS AND GROUPS

In 2014, Dr. Isabel Illa Sendra's group, in the Neurology Service of the Hospital de la Santa Creu i Sant Pau de Barcelona and Dr. Juan J. Vilchez Padilla's group, in the Neurology Service of Hospital Universitario La Fe de Valencia, were moved from the Neurodegenerative Diseases CIBER to the CIBERER.

CIBERER Unit	Group Leader	Centre – Institution	Spanish Region
U701	Dr. Ramón Martí Seves	Unitat de Patologia Mitocondrial i Neuromuscular, Hospital Universitari Vall d'Hebron-Institut de Recerca, Institut Català de la Salut, Barcelona	Cataluña
U702	Dr. Guillermo Antiñolo	Unidad de Gestión Clínica de Genética, Reproducción y Medicina Fetal, Hospital Universitario Virgen del Rocío, Fundación Pública Andaluza para la Gestión de la Investigación en Salud, Sevilla	Andalucía
U703	Dr. Rafael Artuch	Laboratorio de Enfermedades Metabólicas, Hospital Sant Joan de Déu, Barcelona	Cataluña
U704	Dra. Carmen Ayuso	Servicio de Genética, ISS-Fundación Jiménez Díaz, Madrid	Madrid
U705	Dr. Eduardo Tizzano Ferrari	Servicio de Genética, Instituto de Investigación Hospital de la Santa Creu i Sant Pau, Barcelona	Cataluña
U706	Dr. Javier Benítez	Programa de Genética del Cáncer Humano, Fundación Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid	Madrid
U707	Dr. Carmelo Bernabéu	Patología vascular y receptores endoteliales, Centro de Investigaciones Biológicas, CSIC, Madrid	Madrid
U708	Dr. Juan Bernal	Hormonas tiroideas y cerebro, Instituto de Investigaciones Biomédicas "Alberto Sols", CSIC, Madrid	Madrid
U709	Dra. Paola Bovolenta	Morfogénesis y Diferenciación del Sistema Nervioso de Vertebrados, Centro de Biología Molecular "Severo Ochoa" (CBMSO). CSIC-UAM., Universidad Autónoma de Madrid, Madrid	Madrid
U710	Dr. Juan Antonio Bueren	División de Terapias Innovadoras en el Sistema hematopoyético, Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas (CIEMAT), Madrid	Madrid
U711	Dr. Ángel Carracedo	Grupo de Medicina Xenómica, Facultad de Medicina, Universidad de Santiago de Compostela, A Coruña	Galicia
U712	Dr. Antonio Carrascosa	Servicio de Pediatría, Hospital Universitari Vall d'Hebron-Institut de Recerca, Institut Català de la Salut, Barcelona	Cataluña
U713	Dr. José M. Cuezva	La mitocondria y su disfunción en patología, Centro de Biología Molecular "Severo Ochoa" (CBMSO), Universidad Autónoma de Madrid, Madrid	Madrid
U714	Dra. Marcela del Río Nechaevsky	Unidad de Medicina Regenerativa (CIEMAT) y Departamento de Bioingeniería (UC3M), Unidad Mixta de Investigación CIEMAT y Universidad Carlos III de Madrid, CIEMAT-UC3M, Madrid	Madrid
U715	Dr. Joaquín Dopazo	Departamento de Bioinformática y Genómica, Centro de Investigación Príncipe Felipe , Fundación Centro de Investigación Príncipe Felipe (CIPF), Valencia	Comunidad Valenciana
U716	Dra. Cristina Fillat	Laboratori de Teràpia Gènica, Instituto de Investigaciones Biomédicas August Pi i Sunyer (IDIBAPS), Corporació Sanitària Clínic, Barcelona	Cataluña
U717	Dr. Rafael Garesse	Departamento de Bioquímica, Laboratorio B19, Instituto de Investigaciones Biomédicas "Alberto Sols" CSIC-UAM, Facultad de Medicina UAM, Madrid	Madrid
U718	Dra. Roser González Duarte	Genètica Molecular Humana, Departament de genètica. Facultat de Biologia, Universitat de Barcelona, Barcelona	Cataluña
U719	Dr. Eduard Gratacòs	Grupo de Investigación en Medicina Fetal y Perinatal. Servicio de Medicina Materno Fetal, Instituto de Investigaciones Biomédicas August Pi i Sunyer (IDIBAPS), Corporació Sanitària Clínic, Barcelona	Cataluña

CIBERER Unit	Group Leader	Centre – Institution	Spanish Region
U720	Dr. Daniel Grinberg	Departamento de Genética, Genética Molecular Humana, Facultat de Biología, Universitat de Barcelona, Barcelona	Cataluña
U721	Dr. Erwin Knecht	Laboratorio de Degradación Intracelular de Proteínas y Enfermedades Raras, Centro de Investigación Príncipe Felipe, Fundación Centro de Investigación Príncipe Felipe (CIPF), Valencia	Comunidad Valenciana
U722	Dr. Francesc Cardellach	Patología Mitocondrial, Instituto de Investigaciones Biomédicas August Pi i Sunyer (IDIBAPS), Corporació Sanitària Clínic, Barcelona	Cataluña
U723	Dr. Miguel Ángel Martín Casanueva	Laboratorio de Enfermedades Mitocondriales y Neuromusculares, Hospital Universitario 12 de Octubre, Servicio Madrileño de Salud, Madrid	Madrid
U724	Dra. Mª Luisa Martínez-Frías	Centro de Investigación sobre Anomalías Congénitas - CIAC, Centro mixto ISCIII - ASEREMAC, Madrid	Madrid
U725A	Dr. Luis Castaño	Grupo de investigación en Endocrinología y Diabetes, Hospital de Cruces, Fundación Vasca de Innovación de Investigaciones Sanitarias, Vizcaya	País Vasco
U726	Dra. Montserrat Milà	Grupo de Investigación en Genética de Enfermedades Raras (GICER), Hospital Clinic GICER (Servicio de Bioquímica y Genética Molecular), Corporació Sanitária Clínic, Barcelona	Cataluña
U727	Dr. Julio Montoya	Departamento de Bioquímica y Biología Molecular y Celular, Facultad de Veterinaria, Universidad de Zaragoza, Zaragoza	Aragón
U728	Dr. Miguel Ángel Moreno Pelayo	Servicio de Genética, Hospital Ramón y Cajal, Servicio Madrileño de Salud, Madrid	Madrid
U729	Dr. Plácido Navas	Centro Andaluz de Biología del Desarrollo, Universidad Pablo de Olavide-CSIC, Sevilla	Andalucía
U730	Dra. Virginia Nunes	Centro de Genética Médica y Molecular CGMM, CGMM-IDIBELL Hospital Duran i Reynals, Fundació IDIBELL, Barcelona	Cataluña
U731	Dr. Manuel Palacín	Institut de Recerca Biomèdica, Fundaciò Privada Institut de Recerca Biomèdica, Barcelona	Cataluña
U732	Dr. Francesc Palau	Programa de Enfermedades Raras y Genéticas, Centro de Investigación Príncipe Felipe, Fundación Centro de Investigación Príncipe Felipe, Valencia	Comunidad Valenciana
U733	Dr. Federico Pallardó	Departamento de Fisiología, Facultat de Medicina, Universitat de València, Valencia	Comunidad Valenciana
U734	Dra. Consuelo González Manchón	Fisiopatología de trastornos hemostáticos; Bases celulares y moleculares de la enfermedad de Alzheimer y otras demencias, Centro de Investigaciones Biológicas, CSIC, Madrid	Madrid
U735	Dr. Luis Pérez Jurado	Unidad de Genética, Facultad de Ciencias Experimentales y de la Salud, Universitat Pompeu Fabra, Barcelona	Cataluña
U737	Dra. Antonia Ribes	Enfermedades Metabólicas Hereditarias, Institut de Bioquímica Clínica y Genética Molecular, Corporació Sanitària Clínic, Barcelona	Cataluña
U738	Dr. Santiago Rodríguez de Córdoba	Patología Molecular y Genética del Complemento, Centro de Investigaciones Biológicas, CSIC, Madrid	Madrid
U739	Dr. Vicente Rubio	Enzimopatología estructural, Instituto de Biomedicina de Valencia, CSIC, Valencia	Comunidad Valenciana
U740	Dr. Eduardo Salido	Departamento de Anatomía Patológica, Patología Molecular, Hospital Universitario de Canarias, Fundación Canaria Rafael Clavijo, Tenerife	Islas Canarias
U741	Dra. Francisca Sánchez Jiménez	Departamento de Biología Molecular y Bioquímica, Facultad de Ciencias, Universidad de Málaga, Málaga	Andalucía

CIBERER Unit	Group Leader	Centre – Institution	Spanish Region
U742	Dr. Pascual Sanz	Unidad de Señalización por Nutrientes, Instituto de Biomedicina de Valencia, CSIC, Valencia	Comunidad Valenciana
U743	Dra. Jorgina Satrústegui	Departamento de Biología Molecular, Centro de Biología Molecular "Severo Ochoa" (CBMSO), CSIC-UAM Universidad Autónoma de Madrid, Madrid	Madrid
U744	Dr. José Serratosa	Laboratorio de Neurología, IIS-Fundación Jiménez Díaz, Madrid	Madrid
U745	Dr. Jordi Surrallés	Departamento de Genética y Microbiología, Universitat Autònoma de Barcelona, Barcelona	Cataluña
U746	Dra. Belén Pérez González	Centro de Investigación y Diagnóstico Enfermedades Metabólicas Hereditarias, Centro de Biología Molecular "Severo Ochoa"(CBMSO), Universidad Autónoma de Madrid, Madrid	Madrid
U747	Dra. Susan Webb	Enfermedades de la hipófisis. Departamento Medicina, Servicio de Endocrinología, Instituto de Investigación Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona	Cataluña
U748	Dr. Javier Díaz Nido	Centro de Biología Molecular "Severo Ochoa" (CBMSO), Universidad Autónoma de Madrid, Madrid	Madrid
U749	Dr. José Fernández Piqueras	Centro de Biología Molecular "Severo Ochoa" (CBMSO), Universidad Autónoma de Madrid, Madrid	Madrid
U750	Dr. Raúl Estévez Povedano	Departamento de Ciencias Fisiológicas II, Facultat de Medicina, Universitat de Barcelona, Barcelona	Cataluña
U751	Dr. Cecilio Giménez Martín	Centro de Biología Molecular "Severo Ochoa" (CBMSO), Universidad Autónoma de Madrid, Madrid	Madrid
U752	Dra. Pilar Giraldo	Grupo de estudio de enfermedad de Gaucher y neoplasias hematológicas. Servicio Hematología, Hospital Universitario "Miguel Servet", Instituto Aragónés de Ciencias de la Salud, Zaragoza	Aragón
U753	Dr. Pablo D. Lapunzina Badía	INGEMM-Instituto de Genética Médica y Molecular , Hospital Universitario "La Paz", Servicio Madrileño de Salud, Madrid	Madrid
U754	Dra. Margarita López Trascasa	Diagnóstico y caracterización de alteraciones del sistema del complemento, Unidad de Inmunología y Unidad de Investigación. Hospital Universitario "La Paz", Servicio Madrileño de Salud, Madrid	Madrid
U755	Dr. José María Millán Salvador	Unidad de Genética, Hospital Universitario La Fe, IIS-Hospital La Fe, Valencia	Comunidad Valenciana
U756	Dr. Lluís Montoliu José	Modelos animales por manipulación genética, Centro Nacional de Biotecnología (CNB), CSIC, Madrid	Madrid
U757	Dra. Rosario Perona	Laboratorio de terapias de enfermedades con defectos en telomerasa, Instituto de Investigaciones Biomédicas "Alberto Sols", CSIC, Madrid	Madrid
U758	Dr. Manuel Posada de la Paz	Instituto de Investigación en Enfermedades Raras (IIER), Instituto de Salud Carlos III, Madrid	Madrid
U759	Dra. Aurora Pujol Onofre	Laboratorio de enfermedades neurometabólicas, Institut d´Investigació Biomèdica de Bellvitge IDIBELL-Hospital Duran i Reynals , IDIBELL, Barcelona	Cataluña
U760	Dr. Victor Luis Ruiz Pérez	Grupo de Genética Humana y Patología Molecular, Instituto de Investigaciones Biomédicas "Alberto Sols", CSIC, Madrid	Madrid
U761	Dra. Isabel Varela Nieto	Grupo de Neurobiología de la Audición, Instituto de Investigaciones Biomédicas "Alberto Sols", CSIC-UAM, Madrid	Madrid
U762	Dra. Isabel Illa Sendra	Servicio de Neurología, Hospital de la Santa Creu i Sant Pau, Barcelona	Cataluña
U763	Dr. Juan J. Vilchez Padilla	Servicio de Neurología, Hospital Universitario La Fe, Valencia	Comunidad Valenciana

ORGANISATIONAL STRUCTURE

The CIBERER is formed by 60 Research groups, belonging to numerous types of institutions: University Hospitals, Universities, Public Research Bodies, such as the Instituto de Salud Carlos III (ISCIII), the Consejo Superior de Investigación Científica (CSIC) and the Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas (CIEMAT), and Spanish Region Research Centres. Each of these groups is a CIBERER unit.

CIBERER comprises a large team consisting of over 700 people, many of whom are CIBERER staff researchers, and the rest are members of the groups as staff attached to the CIBERER. This team consists of basic and clinical biomedical researchers, research technicians and management staff.

As a public consortium, CIBERER is governed by a Governing Board and a Permanent Commission (administration and steering bodies) in which the 29 Institutions belonging to the CIBERER participate. The organisational structure consists of Scientific Management under Dr. Francesc Palau which, together with a Steering Committee, coordinates the activity of the 7 research programmes (RPs) into which the CIBERER groups are distributed. The CIBER Management Office offers the administrative support necessary for operation of the Institution.

Steering Committee

Scientific Director		Dr. Francesc Palau
Scientific Assistant Director		Dr. José María Millán

Research Programme Coordinators

Medical Programmes	Genetic Medicine	Dr. Guillermo Antiñolo
	Inherited Metabolic Medicine	Dra. Antonia Ribes
	Mitochondrial and Neuromuscular Medicine	Dr. Miguel A. Martín
	Paediatric and Developmental Medicine	Dr. Pablo Lapunzina
	Sensorineural Pathology	Dra. Carmen Ayuso
	Endocrine Medicine	Dra. Susan Webb
	Hereditary Cancer and Related Syndromes	Dr. Jordi Surrallés
Training Programme	Training Programme	Dr. Luis Pérez Jurado

The External Scientific Advisory Committee of each of the subject areas, in this case Rare Diseases, provides general scientific support and advice to the Board of Trustees. It consists of internationally renowned scientists in the health sciences field who stand out in their professional or scientific careers aligned with CIBERER objectives.

External Scientific Advisory Committee (ESAC)

President	Dr. Josep Torrent Farnell	Fundació Dr. Robert, Univ. Aut. de Barcelona
Member of ESAC	Dra. Ségolène Aymé	Inst. de la Santé et Recherche Médicale, Paris
	Dr. Jean-Jacques Cassiman	Catholic University of Leuven, Bélgica
	Dr. Jean-Marie Saudubray	Hôpital Pitié-Salpêtrière, Paris
	Dra. Mª Rita Passos-Bueno	C. de Estudos do Genoma Humano, São Paulo

The External Scientific Advisory Committee is responsible for advising in relation to scientific policy and institutional relations guidelines, examining and reporting on the proposal for the Strategic Plan, Annual Scientific Reports and Annual Action Plans, reporting on the suitability of programmes, resources and capabilities for consortium purposes, advising with regard to the transfer strategy, the policy for hiring scientific staff and for reporting on the creation of research programmes.

A) To be done with funding from ISCIII and balance left over from previous fiscal years

Revenues	2014 Budget
BALANCE LEFT OVER FROM PREVIOUS FISCAL YEARS	510.625,34
SURPLUS FOR A REGISTERED GRANT IN 2013 (Not implemented)	1.863.174,45
REGISTERED GRANT IN 2014	4.761.860,00
FINANCIAL REVENUES (C.I.T. NET INTEREST)	10.000,00
TOTAL FUNDING (ISCIII R.G.+ INTEREST +BALANCE LEFT OVER)	**7.145.659,79**

Expenses and Investments	2014 Budget
1.- RESEARCH PROGRAMMES: R.D. PROGRAMMES	4.460.007,20
RP I.- GENETIC MEDICINE	1.050.988,63
RP II.- INHERITED METABOLIC MEDICINE	1.091.981,09
RP III.- MITOCHONDRIAL AND NEUROMUSCULAR MEDICINE	521.243,44
RP IV.- PAEDIATRIC AND DEVELOPMENTAL MEDICINE	616.035,95
RP V.- SENSORINEURAL PATHOLOGY	394.592,84
RP VI.- ENDOCRINE MEDICINE	233.067,73
RP VII.- HEREDITARY CANCER AND RELATED SYNDROMES	552.097,53
2.- RESEARCH SUPPORT TOOLS	1.268.365,07
HAI I - PITER I.- R.D. RESEARCH SUPPORT PLATFORMS	572.096,94
HAI II - PITER II.- TRAINING IN R.D.	254.889,70
HAI III.- STRATEGIC ALLIANCES	192.000,00
HAI IV.- COMMUNICATION PLAN	123.100,00
HAI V.- INTERNATIONALISATION	5.000,00
HAI VI.- PROJECT AND PROGRAMME MANAGEMENT	121.278,43
3.- MANAGEMENT STRUCTURE	473.338,20
EG I.- SCIENTIFIC MANAGEMENT EXPENSES	96.602,00
EG II.- MANAGEMENT FEE - MANAGEMENT OFFICE	376.736,20
TOTAL EXPENSES AND INVESTMENTS BUDGET	**6.201.710,47**
a) BUDGETED SURPLUS	943.949,32

B) To be implemented with other public and private funding

Revenues	2014 Budget
OTHER PUBLIC REVENUES	1.400.323,31
PRIVATE REVENUES	285.512,54
TOTAL FUNDING FOR THESE ACTIONS (OTHER REVENUES)	**1.685.835,85**
Expenses e Investments	**Presupuesto 2014**
2.- TRANSVERSAL INSTRUMENT PLATFORMS FOR R.D.	235.387,59
PITER I.- HEALTH SERVICES AND PRODUCTS FOR R.D.	202.938,85
PITER II.- R.D. RESEARCH SUPPORT PLATFORMS	31.398,74
PITER III.- TRAINING IN R.D.	1.050,00
3.- RESEARCH SUPPORT TOOLS	262.766,28
HAI II.- COMMUNICATION PLAN	4.092,28
HAI IV.- STRATEGIC ALLIANCES	258.674,00
4.- OTHER RESEARCH PROJECTS	1.187.681,98
RP I.- GENETIC MEDICINE	483.304,41
RP II.- INHERITED METABOLIC MEDICINE	116.988,88
RP III.- MITOCHONDRIAL AND NEUROMUSCULAR MEDICINE	280.052,07
RP IV.- PAEDIATRIC AND DEVELOPMENTAL MEDICINE	135.622,55
RP V.- SENSORINEURAL PATHOLOGY	0
RP VI.- ENDOCRINE MEDICINE	63.595,98
RP VII.- HEREDITARY CANCER AND RELATED SYNDROMES	108.118,09
TOTAL EXPENSES AND INVESTMENTS BUDGET	**1.685.835,85**
b) BUDGETED SURPLUS	0

CIBERER STAFF

Number of hires in the fiscal year ending December 31 classified by categories and genders.

	MEN				Total MEN
	Indefinite	Substitute	Works & Services	Postdoctoral	
CIBERER	16		13	2	31
PhD	13		4	2	19
Degree Holder	2		9		11
Diploma Holder					
Technician	1				1
Grand total	16		13	2	31

	WOMEN				Total WOMEN
	Indefinite	Substitute	Works & Services	Postdoctoral	
CIBERER	74	1	21	4	100
PhD	40		6	4	50
Degree Holder	17	1	15		33
Diploma Holder	1				1
Technician	16				16
Grand total	74	1	21	4	100

	Indefinite	Substitute	Works & Services	Postdoctoral	Grand total
CIBERER	90	1	34	6	131
PhD	53		10	6	69
Degree Holder	19	1	24		44
Diploma Holder	1				1
Technician	17				17
Grand total	**90**	**1**	**34**	**6**	**131**

SCIENTIFIC PRODUCTION

Like in any institution scientific, the primary indicator for measuring scientific productivity is the number and quality of publications. With over 4,000 publications since is began in 2006, CIBERER is an example in scientific production on rare diseases on both a national and international level. After joining the CIBERER, research groups have experienced a significant increase in scientific productivity. From 2006 to 2014, the network went from having a total of 320 publications to having about 700 in 2014*. In relation to citable papers, the increase has been likewise substantial, going from 239 in 2006 to exceeding 500 in 2014*.

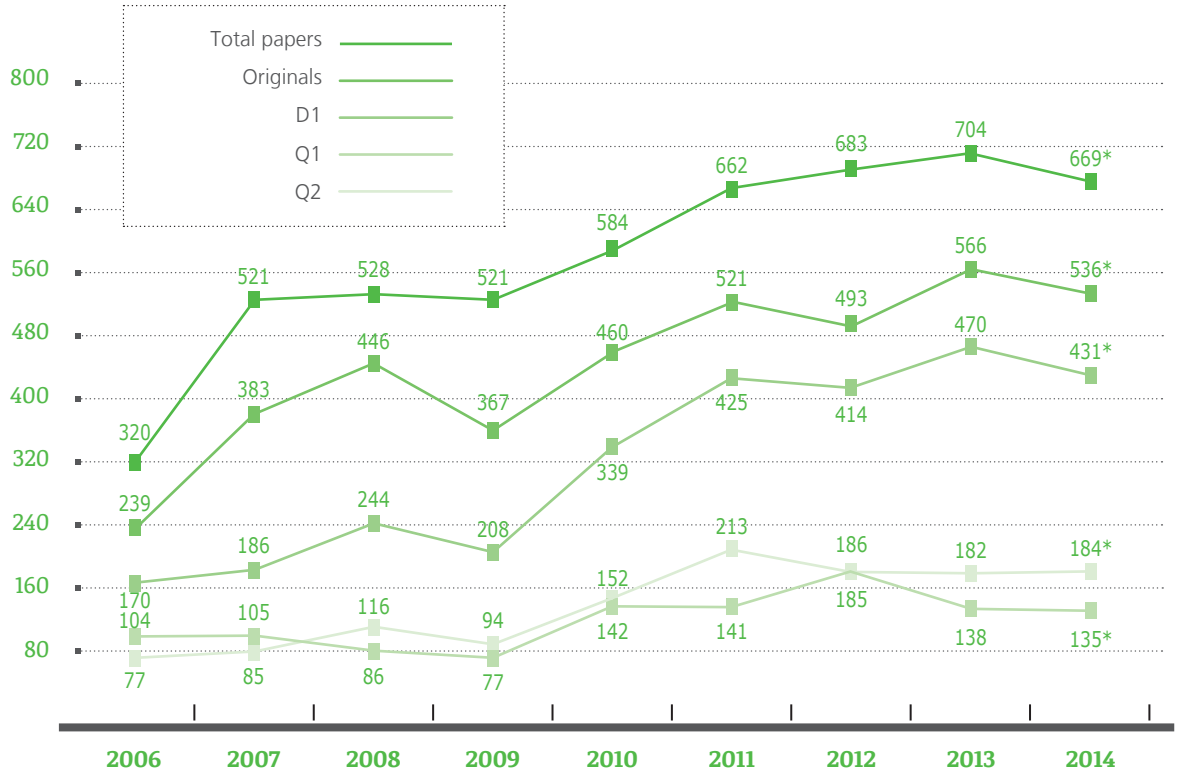
In addition, it can be seen that the rate of CIBERER's scientific production continues to surpass that of Spanish biomedical research in general and rare disease research in particular. The proportion of citable documents has never been less than 70%. CIBERER papers published in Q1 journals always represent a majority proportion. CIBERER papers are found increasingly more among the set of most frequently cited Spanish papers.

In a centre like the CIBERER, with wide-ranging subject matters of study, more than overall numbers, what is most fundamental is to determine the topic, the collaboration and the impact of the scientific publications. In this case, not only the number but also the rate of internal cooperation, the impact, the influence and the international penetration of the groups integrated in CIBERER continue to increase yet again.

The best papers written by CIBERER researchers published in 2014 can be found in the following section of this report associated with each of the units of the Centre.

PROGRESSION OF THE NUMBER OF CIBERER PAPERS (2006-1014) ACCORDING TO TYPE

*Figures not final for 2014, provisional data as of November 2014



2. SCIENTIFIC PROGRAMMES

The basic structure of CIBERER consists of **Research Programmes (RPs)** which allow grouping CIBERER units according to their areas of scientific interest. Organising into RPs allows optimizing resource allocation, strengthening research groups, promoting scientific, technical and clinical collaboration to improve scientific results and obtaining a higher degree of compliance with the proposed strategic objectives.

CIBERER programme structuring is complex, largely due to the idiosyncrasy inherent to the field of RDs, the field of medicine and the field of public health which covers over 7,000 diseases, mainstreaming all human organic systems. Conceptually speaking, 7 programmes are considered fundamentally taking into account the biological and historical aspect characterizing each RD either separately or as a group of diseases:

- **Genetic Medicine Programme**
- **Inherited Metabolic Medicine Programme**
- **Mitochondrial and Neuromuscular Medicine Programme**
- **Paediatric and Developmental Medicine Programme**
- **Sensorineural Pathology Programme**
- **Endocrine Medicine Programme**
- **Hereditary Cancer and Related Syndromes Programme**

Research groups join the different RPs according to the diseases in which they conduct their scientific work and the aspects about such diseases being investigated. The working of RPs is implemented by means of scientific, technical, translational and educational **horizontal programmes** and through **research support platforms**.

Each of the seven Research Programmes is presented below, providing a description of each one, their objectives, the rare diseases studied and the groups forming them.

Consisting of 12 research groups from different areas, including clinical genetics, molecular genetics, molecular and fundamental biology and bioinformatics.

Rare Diseases Studied

- Lafora disease and other rare genetic epilepsies.
- Neuromuscular diseases: muscular dystrophies, spinal muscular atrophy.
- Vascular diseases and diseases of the immune system: disorders affecting the vascular endothelium, causing pathologies such as HHT and complement defects.

Objectives: To incorporate Mendelian or complex diseases affecting an organ or system of the human body, using the hereditary factor as the fundamental criterion for incorporation in the programme.
The specific objectives include:

- to lead the development of innovations in genomic platforms,
- to offer support for pre-clinical research on rare epilepsies and related diseases, including Lafora disease, and
- to boost physiopathological study for therapeutic and diagnostic applications in rare vascular pathologies and in complement-mediated pathologies.

Groups forming the RPs:

- Scientific Coordinator: Dr. Guillermo Antiñolo, U702
- Dr. Eduardo Tizzano Ferrari, U705
- Dr. Carmelo Bernabéu, U707
- Dr. Ángel Carracedo, U711
- Dr. Joaquín Dopazo, U715
- Dr. Erwin Knecht, U721
- Dr. Consuelo González Manchón, U734
- Dr. Santiago Rodríguez de Córdoba, U738
- Dr. Pascual Sanz, U742
- Dr. José Serratosa, U744
- Dr. Cecilio Giménez Martín, U751
- Dr. Margarita López Trascasa, U754
- Dr. Juan Luque, RP Scientific Manager

INHERITED METABOLIC MEDICINE

Consisting of 12 research groups from different fields, including clinical genetics, molecular genetics and molecular and cell physiology.

Rare Diseases Studied

- Inherited metabolic diseases: lysosomal diseases, organic acidemias, glycosylation defects, peroxisomal diseases.

Objectives: To study RDs having the fundamental aspect of altering homeostasis caused by mutations in genes relating to intermediary metabolism.
The programme specifically seeks to define the genetic cause and the physiopathology of these pathologies affecting biomolecule synthesis, metabolism, transport and storage. They are generally serious diseases involving multiple organs and in many cases reducing the life expectancy and quality of life of patients.
Based on the definition and in depth knowledge about these clinical phenotypes, in addition to evaluating the clinical response to treatments available today, the programme is working on Innovative Therapies, such as the use of chaperones to aid in enzyme functionality.

Groups forming the RP:

- Scientific Coordinator: Dra. Antonia Ribes, U737
- Dr. Rafael Artuch, U703
- Dr. Daniel Grinberg, U720
- Dr. Virginia Nunes, U730
- Dr. Manuel Palacín, U731
- Dr. Vicente Rubio Zamora, U739
- Dr. Eduardo Salido, U740
- Dr. Francisca Sánchez Jiménez, U741
- Dr. Belén Pérez González, U746
- Dr. Raúl Estévez Povedano, U750
- Dr. Pilar Giraldo Castellano, U752
- Dr. Aurora Pujol Onofre, U759
- Mónica Bescós, RP Scientific Manager

Mitochondrial and Neuromuscular Medicine Programme: consisting of 12 research groups from different areas, specialising in the study of the physiological and functional aspects of the mitochondrion in different tissues, as well as their implication in a number of diseases (therapeutic research), particularly in neuromuscular pathologies.

Rare Diseases Studied:

- Inherited and sporadic encephalomyopathies of mitochondrial DNA (mtDNA) (it would include entities such as KSS, MELAS, MERRF, LHON, NARP/MILS, cardiomyopathies, hearing loss and mitochondrial diabetes, etc.).
- mtDNA maintenance syndromes: depletion syndromes and syndromes with multiple mtDNA deletions, such as MNGIE, PEO, SANDO, Alpers syndrome, etc.
- Diseases of the OXPHOS system associated with nuclear and assembly genes (impairments of OXPHOS subunits and assembly factors, pathologies affecting mitochondrial transcription and translation, syndromes associated with coenzyme q deficiency).
- Neuromuscular diseases: muscular dystrophies, spinal muscular atrophy, Charcot-Marie-Tooth neuropathy, ALS, myasthenia gravis and congenital myasthenias, inflammatory myopathies, hereditary and acquired ataxias, Friedreich's ataxia, myasthenias.

Objective: To address diseases with mitochondria as the physiopathological target affecting an individual's bioenergy balance.
The proposed specific objectives are:

- to study genome-mitochondrial communication,
- to study the physiopathology and mechanisms of disease in cellular models and iPSC, and
- to conduct therapeutic research, ranging from the development of animal models up to the pre-clinical stage, biomarkers, particularly in neuromuscular pathologies.

Groups forming the RP:

- Scientific Coordinator: Dr. Miguel Ángel Martín Casanueva, U723
- Dr. Ramón Martí Seves, U701
- Dr. José M. Cuezva , U713
- Dr. Rafael Garesse, U717
- Dr. Francesc Cardellach, U722
- Dr. Julio Montoya, U727
- Dr. Plácido Navas, U729
- Dr. Francesc Palau Martínez, U732
- Dra. Jorgina Satrústegui, U743
- Dr. Javier Díaz Nido, U748
- Dra. Isabel Illa Sendra, U762
- Dr. Juan J. Vilchez Padilla, U763
- Mónica Bescós, RP Scientific Manager

PAEDIATRIC AND DEVELOPMENTAL MEDICINE

Consisting of 8 research groups from different fields, including clinical genetics, molecular genetics, molecular biology, cell biology, epidemiology and fetal medicine.

Rare Diseases Studied:

- Congenital defects
- Genomic disorders (syndromes caused by genomic rearrangements).
- Disorders of the development associated with learning disability/intellectual impairment.

Objectives: To approach disorders conditioned by anomalous embryonic development, regardless of the cause, involving congenital malformation or a cognitive development disorder, particularly relevant during childhood and during the period of growth and development of the individual.
The specific objectives are:

- to encourage the development of genomic diagnostic tools for diseases of interest of the RPs,
- to lead CIBERER research in Innovative Therapies, with a particular emphasis on gene and fetal therapies,
- to boost clinical research as a result of close collaboration with national hospitals of reference, and
- to develop tools for epidemiological research on rare diseases.

Groups forming the RP:

- Scientific Coordinator: Dr. Pablo Lapunzina, U753
- Dra. Cristina Fillat, U716
- Dr. Eduard Gratacòs, U719
- Dra. Mª Luisa Martínez-Frías, U724
- Dra. Montserrat Milà, U726
- Dr. Luis Pérez Jurado, U735
- Dr. Manuel Posada, U758
- Dr. Víctor Luis Ruiz Pérez, U760
- Dr. Juan Luque, RP Scientific Manager

SENSORINEURAL PATHOLOGY

Consisting of 7 research groups from different fields, including clinical and molecular genetics, epidemiology, molecular and cell biology and animal models, for translational purposes by means of implementing new diagnostic algorithms and therapeutic orientation.

Rare Diseases Studied:

- Retinal dystrophies
- Isolated and syndromic ocular abnormalities
- Albinism
- Hereditary and congenital hypoacusis

Objectives: To approach rare diseases having an effect on sensory organs, and particularly on sight and/or hearing.
The strength of the RPs and one of their main objectives is to develop cellular and animal models of RD, particularly for the next period of leading the pre-clinical research on sensorineural RD. In addition, the RPs develop genomic diagnostic tools.

Scientific Coordinator:

Coordinadora Científica: Dra. Carmen Ayuso, U704

Dra. Paola Bovolenta, U709

Dra. Roser González Duarte, U718

Dr. Miguel Ángel Moreno, U728

Dr. José María Millán, U755

Dr. Lluís Montoliu José, U756

Dra. Isabel Varela Nieto, U761

Beatriz Gómez, RP Scientific Manager

ENDOCRINE MEDICINE

Consisting of 4 research groups from the area of endocrinology and paediatrics, ranging from basic clinical care, study of the molecular basis of a disease and the application of therapeutic solutions.

Rare Diseases Studied:

- Diseases affecting pituitary hormones and their target tissues, such as:
  - Diseases involving the growth hormone (GH): Acromegaly and GH deficiency.
  - Diseases involving steroid hormones: Cushing's syndrome, familial glucocorticoid deficiency, androgen deficiency and sexual differentiation anomalies.
  - Diseases involving thyroid hormones: Congenital hypothyroidism and resistances to thyroid hormones, including Allan-Herndon-Dudley syndrome.

Objective: To study disorders caused by hormonal dysfunction relating to the pituitary gland and target organs.

Groups forming the RP:

- Scientific Coordinator: Dra. Susan Webb, U747
- Dr. Juan Bernal, U708
- Dr. Antonio Carrascosa, U712
- Dr. Luis Castaño González, U725A
- Dr. Andrés Medrano, RP Scientific Manager

HEREDITARY CANCER AND RELATED SYNDROMES

Consisting of 7 research groups from different fields, including clinical and molecular genetics, regenerative medicine, advanced/innovative therapies, molecular biology and cell biology.

Rare Diseases Studied:

- Fanconi anemia and disorders relating to genetic instability.
- Hereditary cancer and pediatric tumors.

Objectives: To study the physiopathological mechanisms and genetic basis of hereditary cancer as well as other related syndromes, in which genetic instability is a fundamental component in disease onset or progression.
The specific objectives of this programme focus on the chromosome research, specifically on Fanconi anemia, research on rare tumors, particularly endocrine tumors, and research on advanced therapies (in collaboration with other RPs

Groups forming the RP:

- Scientific Coordinator: Dr. Jordi Surrallés, U745
- Dr. Javier Benítez, U706
- Dr. Juan A. Bueren, U710
- Dra. Marcela del Río, U714
- Dr. Federico Pallardó, U733
- Dr. José Fernández Piqueras, U749
- Dra. Rosario Perona, U757
- Dr. Andrés Medrano, RP Scientific Manager

3. TRANSVERSAL PROGRAMMES

Description

CIBERER designs and executes the start-up strategy for a series of actions intended for providing the different research groups with a critical mass of scientific and technical staff. These hiring actions have integrated new research staff into the groups of the different institutions forming CIBERER. The policy implemented by CIBERER ever since it was founded has resulted in reinforcing the research groups, consisting of personnel attached to CIBERER that comes from the same groups forming part of the Consortium Institutions and of CIBERER staff. As a result of this reinforcement of the critical mass, advancements in RD research could be consolidated.

CIBERER employees are reassigned to the groups considering the needs assessment and compliance with the objectives and strategic lines of the Centre.

Human talent is a fundamental component for implementing staff policy. Managing this talent is the key to CIBERER's success, so the primary objective of Human Resources is to appropriately consider employee training requirements.

Objectives

For CIBERER, the key to success is based on the research potential, staff professionalism and commitment to RDs. For this reason, the objectives of the Human Resources Programme are aimed at reinforcing **research excellence** of the CIBERER staff and **the high level of the specialisation of hires in RD**. To meet these objectives, for 2014 CIBERER set the following goals:

- To give added value to CIBERER staff.
- To draw up a follow-up model to track the staff's scientific activity on RDs.

Resources Used

- Economic resources: The CIBERER HR Programme has historically been the programme that absorbs the largest amount of economic resources for funding it. It involves the 62 research groups from the Consortium with the sole exception of the affiliated group (U725A) which, by definition, cannot obtain funding to hire staff.

  The funds assigned to the programme were primarily intended to fund hired staff wages. These funds are distributed among the different items of the RPs and the research support platforms.
- Staff resources: CIBERER hires, CIBERER grant holders
- Services: Scientific Management Team.

Results

CIBERER research activity means that each of the hires is assigned to one of the Research Programmes or platforms of the Centre. CIBERER brought together over 700 investigators in 2014, including personnel attached to CIBERER, grant holders and hired staff.

Diversity is an added value, because the processes to be performed can be approached from different angles. In this regard, in 2014 86% of CIBERER professional employees held a bachelor's degree, and 50% of all employees held a PhD.

The research and technical staff hired by the entity amounted to 147 employees and 23 grant holders (calls for proposals of pre-doctoral aid from 2013 and 2014) in all of 2014, and they are distributed as follows:

Category	No. of Employees	No. of Grant Holders
PHDS > 3 YEARS	73	
BACHELOR DEGREES	54	23
ASSOCIATE DEGREES	1	
VOCATIONAL TRAINING	19	
TOTAL	**147**	**23**

Cooperative and Complementary Intramural Actions (ACCI)

To encourage the development of cooperative research projects on a Rare Disease (RD) or group of related RD, a call for proposals for Cooperative and Complementary Intramural Actions was launched in 2014. Thirteen top-quality proposals were approved. The following table shows data about all the projects that were co-funded with CIBERER funds and active after January 2015.

Title	PI	Coordinator Unit	Participating units	Budget (€)
Biomedicine of systems for figuring out the molecular basis and modelling of leukodystrophies and hereditary spastic paraplegia	A Pujol	U759	U711	80.000
Complement and disease. Search for pathogenic mechanisms shared by rare and common diseases	S Rodríguez de Córdoba	U738	U709, U754	64.500
Development of a new therapeutic strategy in T-cell lymphoblastic lymphomas based on the collateral damage caused by 9p21 deletions	J Fernandez Piqueras	U749	U713, U717	48.500
Development of a cellular model to determine the pathogenicity of variants having an uncertain meaning in Fanconi anaemia and familial breast cancer	J Surralles	U745	U706, U710	76.500
Search for undiscovered telomere diseases in severe combined and variable immunodeficiency patients. Identification of new genes by exome sequencing and study of mechanisms involved in telomere shortening in cellular and animal model	R Perona	U757	U706, U749	56.500
Development of a gene therapy strategy for glutaric aciduria type I based on genetic surgery	C Fillat	U716	U737	27.500
Homologous recombination aided by CRISPR/Cas9 combined with direct reprogramming as a method for generating disease-free hepatocytes in patients with primary hyperoxaluria type 1	JC Segovia	U710	U740	38.000
Hyperexcretion of alpha-ketoglutarate in aminoacidurias, potential cellular stress response.	M Palacín	U731	U730, U737	50.000
Obtaining iPS cells for the study of progressive myoclonus epilepsy, Lafora type and Charcot-Marie-Tooth disease	P Sanz	U742	U733, U721, U732	37.500

Title	PI	Coordinator Unit	Participating units	Budget (€)
Role of oxidative stress in the development of Familial Melanoma and other common RDs with a predisposition for the development of cutaneous neoplasias.	S Puig	U726	U714	36.700
Study of the implication of the permeability transition pore (PTP) in models of diseases having a secondary affect on the mitochondrion: possible diagnostic and therapeutic use.	J Satrustegui	U743	U723, U729	26.000
Development and validation of possible biomarkers and therapeutic targets for the Friedreich's ataxia	J Díaz Nido	U748	U732, U733	33.400
Molecular and functional characterisation (cellular models) of sporadic or dominant autosomal retinal dystrophies. Combined molecular mapping and exome sequencing strategy	C Ayuso	U704	U755, U715, U702	33.400

External Projects

Research of excellence requires top-level economic, material and human resources to develop the activities and comply with objectives. Drawing in competitive and non-competitive resources is fundamental for developing far-reaching projects and actions on RDs.

In 2014, the Scientific Management Department, the CIBER Technical Office and the groups involved in the different actions continued conducting significant activity in this sense. The main actions 2014 can be accounted for as:

AID GRANTED IN 2014

The following table shows the grants and aid that were given in 2014 to competitive CIBERER projects or initiatives either by public institutions or private institutions. The type of project, the name of the principal investigator, the title or reason for the initiative and the entity/entities funding the project are provided.

PROJECTS GRANTED IN 2014 IN COMPETITIVE CALLS FOR PROPOSALS

Group	Project PI / Work Group	Title	Funding Agency - Programme	Period
National Scope, Public Entity calling for proposals				
CIBERER	Dr. Francesc Palau	CIBER_BBN/RD/RES Internationalisation Support Platform	MINECO- Networks and Managers	138.000 €
U732	Dra. Pilar González Cabo	Axonal physiopathology of Friedreich's ataxia: Axonal transport and degeneration	Generalitat Valenciana	9.600 €

U733	Dr. José Luis Gimenez	Study of the specificity and sensitivity of a method based on detection of histones circulating in plasma as serious sepsis and septic shock biomarkers	Generalitat Valenciana	7.000 €
U737, U722, U742	Dr. Ángel Raya	Molecular links between diabetes and neurodegenerative disorders	ISCIII-AES. Integrated Projects of excellence	220.000 €
Private Entity calling for proposals				
U753	Dr. Victor Martínez González	PIK3CA Overgrowth Syndromes: Diagnosis, Phenotype and Clinical Guidelines	RTVE TV Marathon	87.815 €

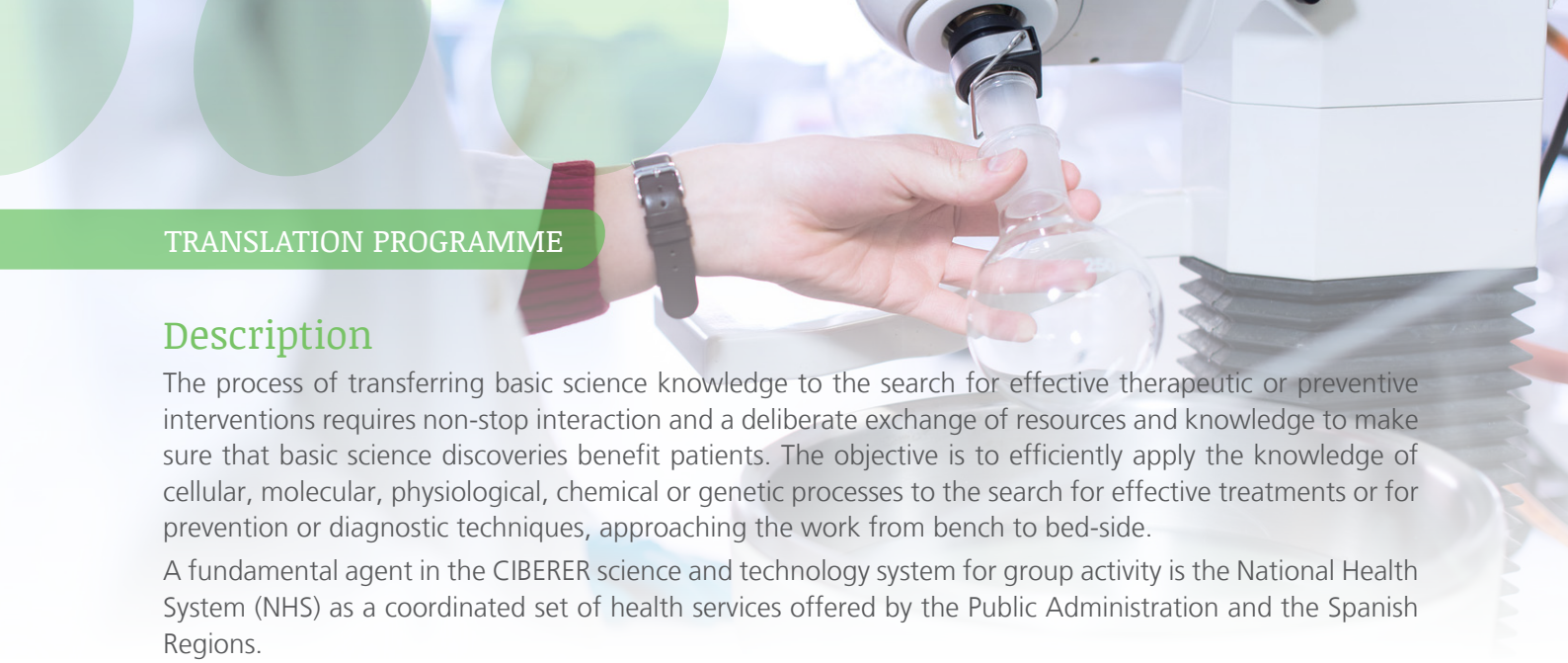
AID IN FORCE IN 2014

28 projects or initiatives that had been receiving a grant or aid since 2009 were carried out in 2014 and they were managed by CIBERER. The following table shows the type of project, the group and the name of the principal investigator, the title or reason for the funded initiative and the entity granting the aid, as well as the period in which they were carried out.

PROJECTS GRANTED IN COMPETITIVE CALLS FOR PROPOSALS ACTIVE IN 2014

Group	Project PI / Work Group	Title	Funding Agency	Period
International Scope				
CIBERER U750	Dr. Raúl Estévez	CLC chloride channels and Megalencephalic leukoencephalopathy: molecular mechanisms and therapeutics	CIBERER- E-RARE 2	2014-2017
CIBERER U708	Dr. Juan Bernal	THYRONERVE	CIBERER- E-RARE 2	2014-2017
CIBERER U762	Dra. Isabel Illa	ACAMIN	CIBERER- E-RARE 2	2014-2017
CIBERER (U746, U720, U737, U703)	Dra. Mª Luz Couce	European Network and Registry for Homocystinurias and Methylation Defects (E-HOD).	DG SANCO – Project	2013-2016
CIBERER	Dr. Francesc Palau	EUCERD JOINT ACTION	DG SANCO – Joint Action	2013-2015
CIBERER	Dr. Francesc Palau	RD-Connect. An integrated platform connecting databases, registries, biobanks and clinical bioinformatics for rare disease research	7PM. HEALTH	2012-2016
CIBERER (U746, U739, U737, U703)	Dra. Magdalena Ugarte	E-IMD. European registry and network for Intoxication type Metabolic Diseases	DG SANCO – Project	2011-2014
CIBERER	Miquel Calvet	CommHERE -Communication of European Health Research (CIBERER participa como tercera parte del ISCIII)	7PM. HEALTH	2011-2014
National Scope, Public Entity calling for proposals				
CIBERER U735	Dra. Ivón Cuscó	Study of the pathways involved in autistic spectrum disorders: Functional consequences of genetic and epigenetic variants	ISCIII – FIS Health Research Projects	2014-2016
CIBERER U701	Dr. Tomás Pinos	Advances in McArdle's disease: New therapeutic and developmental approaches of a new non-invasive diagnostic method in patients.	ISCIII – FIS Health Research Projects	2014-2016

CIBERER U732	Dra. Carmen Espinós	Miguel Servet Contract, Dr. Carmen Espinós (U732). Associated project: "Genetic and Disease Mechanisms in Inherited Neuropathies"	ISCIII – FIS Subprogramme HR -Miguel Servet	2008-2014
CIBERER U732	Dra. Carmen Espinós	Translational research and mechanisms of disease in inherited peripheral neuropathies	ISCIII – FIS Health Research Projects	2013-2015
CIBERER U753	Dr. Víctor Martínez-González	Genomic, epigenetic and transcriptional study of tumors in polymalformative genetic syndromes	MICINN-Non-oriented, Fundamental Research Project Subprogramme	2011-2014
CIBERER U722	Dra. Gloria Garrabou	Mitochondrial impairments in cellular models of Parkinson's disease (LRRK2 and Parkin): Therapeutic potential of mitochondrial function modulators	ISCIII – FIS Health Research Projects	2012-2014
CIBERER U732	Dra. María Pilar González Cabo	Axonal physiopathology of Friedreich's ataxia: Axonal transport and degeneration	ISCIII – FIS Health Research Projects	2012-2014
CIBERER U732, U733, U713, U743, U755	Dr. Francesc Palau	Translational Research, Experimental Medicine And Therapeutics on Charcot-Marie-Tooth Disease	ISCIII-IRDiRC	2012-2016
		Private Entity calling for proposals		
CIBERER U732	Dr. Francesc Palau	Integrated Research Consortium for Friedreich's ataxia: physiopathological and therapeutic approach (FAIR)	Fundaciò Maratò TV3	2010-2014
CIBERER U742	Dr. Pascual Sanz	Lafora progressive myoclonus epilepsy: Physiopathological basis of the disease and therapeutic approaches	Fundaciò Maratò TV3	2010-2014
CIBERER U710	Dr. Juan A. Bueren	Regenerative medicine for Fanconi anaemia: generation of disease-free patient-specific iPS cells, derived hematopoietic progenitors and platelets	Fundaciò Maratò TV3	2013-2015
CIBERER U735	Dra. Ivón Cuzco	Generation of iPSC cells to study neurodevelopmental disorders: Autism and Williams Syndrome	Fundación Ramón Areces	2012-2014
CIBERER U708	Dra. Beatriz Morte	Allan-Herndon-Dudley Syndrome: Molecular mechanisms and therapeutic approaches in the model of the disease	Fundación Ramón Areces	2012-2014
CIBERER U759	Dra. Aurora Pujol	Cellular and molecular characterisation of the interrelation between oxidative stress and inflammation in adrenoleukodystrophy: therapeutic implications	Fundación Mehuer	2014-2015
CIBERER U708	Dra. Beatriz Morte	Preclinical study of the effectiveness of the thyroid hormone analogue, TRIAC, in the treatment of Allan-Herndon-Dudley syndrome	Fundación Mehuer	2014-2015



Description

The process of transferring basic science knowledge to the search for effective therapeutic or preventive interventions requires non-stop interaction and a deliberate exchange of resources and knowledge to make sure that basic science discoveries benefit patients. The objective is to efficiently apply the knowledge of cellular, molecular, physiological, chemical or genetic processes to the search for effective treatments or for prevention or diagnostic techniques, approaching the work from bench to bed-side.

A fundamental agent in the CIBERER science and technology system for group activity is the National Health System (NHS) as a coordinated set of health services offered by the Public Administration and the Spanish Regions.

CIBERER is responsible for leading the research that is being carried out in the organisation into clinical practice so that it directly and effectively benefits society and the National Health System. In this regard, relations with the health sector and specifically with the National Health System (NHS) are the best way to implement the social return of research. CIBERER research groups, many of which are integrated in the hospital and healthcare field, seek to develop knowledge that can be applied as clinical solutions.

Objectives

The general objective is to promote top-quality translational research, translating the results of basic, clinical, epidemiological, health services and public health research to the National Health System (NHS), the Spanish System of Science and Technology, to patients and to society as a whole.

Resources Used

- Staff resources: Translation Manager with the support of the team of Scientific Activity Managers.

  CIBERER groups are involved in the different links of the value chain, ranging from developing basic knowledge to applying it in routine clinical practice. That potential of complementary profiles must be put to use to favour translation by means of networking.

Results

EXISTING COLLABORATIONS AND ESTABLISHING NEW COLLABORATIONS WITH LINKED CLINICAL GROUPS (LCGS) IN THE FRAMEWORK OF THE NHS

As established in the CIBERER bylaws, the Board of Trustees, subject to a report from the Scientific Director and a favourable report from the Permanent Commission, may associate NHS centre clinical groups with CIBERER. This association would be necessary to carry out CIBERER programmes by means of specific agreements.

Therefore, in the framework of its Strategic Plans in 2013, CIBERER opened up the possibility of including new Linked Clinical Groups (LCGs). This allows CIBERER groups to collaborate with groups that have vast clinical experience with RDs, accelerating the final translation of the research conducted by CIBERER groups into the NHS.

In summary, efforts are pooled within the framework of skills and expertise that are characteristic of each of them, i.e., health centres and CIBERER research groups, in developing cooperative, multidisciplinary and translational research activities, as well as working to transfer research and development results and handling scientific training specialised in Biomedicine, and specifically in the area of RDs.

There are currently 20 LCGs linked to the CIBERER relating to 4 RPs: Paediatric and Developmental Medicine, Inherited Metabolic Medicine, Endocrine Medicine and Hereditary Cancer and Related Syndromes. This undoubtedly shows the Centre's clear support for translating research to clinical practice by means of carrying out cooperative projects in specific pathologies.

The LCGs are currently the following:

- **Relating to Paediatric and Developmental Medicine RPs:**
  Dra. Encarna Guillén (Hospital Virgen de la Arrixaca, Murcia)
  Dr. Feliciano J. Ramos (Hospital Lozano Blesa, Zaragoza)
  Dr. Jordi Rosell (Hospital Son Espases, Palma de Mallorca)
  Dra. Isabel Tejada (Hospital Cruces, Bilbao)
- **Relating to Inherited Metabolic Medicine RPs:**
  Dr. Luis Aldámiz-Echevarría Azuara (Hospital Cruces, Bilbao)
  Dra. Mª Luz Couce (Hospital Clínico de Santiago de Compostela, La Coruña)
  Dr. Luis González Gutiérrez-Solana (Hospital Infantil Niño Jesús, Madrid)
  Dr. Eduardo López Laso (Hospital Reina Sofía, Córdoba)
  Dr. Guillem Pintos (Hospital Germans Trías i Pujol, Barcelona)
  Dra. Mireia del Toro (Hospital Vall d´Hebrón, Barcelona)
- **Relating to Endocrine Medicine RPs:**
  Dra. Irene Halperin (Hospital Clínic, Barcelona)
  Dra. Mónica Marazuela (Hospital La Princesa, Madrid)
  Dr. Antonio Picó (Hospital General de Alicante, Alicante)
  Dr. Manuel Puig Domingo (Hospital Germans Trías i Pujol)
  Dr. Alfonso Soto (Hospital Virgen del Rocío, Sevilla)
- **Relating to Hereditary Cancer and Related Syndromes RPs:**
  Dra. Isabel Badell (Hospital de la Santa Creu i Sant Pau, Barcelona)
  Dra. Cristina Beléndez (Hospital Gregorio Marañón, Madrid)
  Dr. Albert Català (Hospital San Joan de Déu, Barcelona)
  Dr. Julián Sevilla (Hospital Infantil Niño Jesús, Madrid)
  Dr. Joan-Lluis Vives-Corrons (Hospital Clínic, Barcelona)

SUPPORT FOR PREPARING CLINICAL PRACTICE GUIDELINES, PROTOCOLS AND INFORMATIVE MATERIAL FOR PATIENTS

The numerous CIBERER research groups work to develop products that are clearly useful in clinical practice in relation to RDs, such as clinical guidelines, operating protocols and informative material for patients.

Particularly noteworthy in the field of Clinical Practice Guidelines is the work being done by **Work Group on Cancer in Polymalformative Genetic Syndromes (gT-CSgP)** with the participation of several CIBERER units, coordinated by Dr. Víctor Martínez-González-U753. The objective of this group is to offer biohealthcare professionals up-to-date information about the clinical and molecular aspects of syndromes of this type and their associated neoplasias to serve as a leader in diagnosis, prevention and follow-up with patients and family members, an in teaching and research. In 2014, the group published the Guideline on Bannayan-Riley-Ruvalcaba (BRR) Syndrome.

By way of example, another one of the Guidelines drawn up in 2014 is the **Guideline on Lowe Syndrome for families**, published by CIBERER and Hospital Sant Joan de Déu. The medical team of researchers led by

Dr. Mercedes Serrano- U703 drew up the first guideline of these characteristics for Lowe Syndrome, also known as the oculocerebrorenal syndrome.

CIBERER Clinical Guidelines are regularly added to the CIBERER database ("documentation" section of the CIBERER web page or directly at

http://www.ciberer.es/index.php?option=com_docman&task=cat_view&gid=41&Itemid=194),

favouring their dissemination to other CIBERER groups, healthcare professionals and the general public. .

SUPPORT FOR THE DEVELOPMENT OF THERAPEUTIC SOLUTIONS: CLINICAL TRIALS, ADVANCED THERAPIES AND ORPHAN DRUG (OD) DESIGNATION

In keeping with its strategic objectives, CIBERER facilitates and encourages its research groups to participate in national and international trials, aimed at the development and validation of therapies for RD.

In 2013, CIBERER started to more actively boost research projects in advanced therapies (gene therapy, cell therapy and tissue engineering), preclinical research projects and research on the biology of stem cells, particularly iPS cells, to allow future personalised cell therapy and regenerative medicine developments.

Furthermore, CIBERER acts as an advisor and driving force in any initiative relating to orphan drug designation that may arise from its research groups.

In 2014, CIBERER sponsored an **orphan drug**: "Lentiviral vector containing the liver and erythroid pyruvate kinase gene (PKLR)" for the treatment of pyruvate kinase deficiency, a hereditary disease affecting erythrocytes or red blood cell energy metabolism. The work for this declaration was led by Dr. José Carlos Segovia-U710 of CIEMAT, which is led by Dr. Juan Bueren.

PARTICIPATION IN THE "RARE DISEASE STRATEGY OF THE NATIONAL HEALTH SYSTEM"

Since it was drawn up in 2009, the Scientific Coordinator of the Strategy is Dr. Francesc Palau, Scientific Director of the CIBERER. Furthermore, CIBERER itself is represented in the Follow-up and Implementation Committee of same. CIBERER participated in the work that led to the **update in 2014 of the Rare Disease Strategy of the National Health System (NHS)**. This strategy update incorporates all the knowledge and data available as of today on rare diseases, which is of interest for professionals, patients and their family members.

Within the framework of the Strategy, precisely the Ministry of Health, Social Services and Equality (MSSSI) approved in 2014 eight **Good Practices (GPs) on rare diseases in the National Health System (NHS)**. Four of these eight GPs have been developed by CIBERER research groups: implementation of a quality management system in the HHT Unit (H. Sierrallana), which is part of U707, the Metabolic Guidelines of U703 (H. Sant Joan de Déu) and two projects relating to the coordinated RD web page www.odimet.es coordinated by the Dr. María Luz Couce-U737 (Hospital Clínico Universitario de Santiago de Compostela).

PARTICIPATION IN THE "EUCERD JOINT ACTION:WORKING FOR RARE DISEASES"

The CIBERER takes part in the EUCERD Joint Action: Working for Rare Diseases (http://www.eucerd.eu/?page_id=284), constituted to give support to the Experts' Committee of the EU in www.ciberer.es 35 ER (EUCERD; " European Union Committee of Experts on Rare Diseases ", as partner and coordinator of the package of work 7 (WP7), on Vida's Quality and Experts' Centers.

In 2014, CIBERER continued working on this important translational activity in Europe, studying various initiatives of the Member States aimed at improving the quality of life in people suffering from a rare disease. This year the CIBERER focused on the identification of good practices existing in the health care systems of the Member States, placing particular emphasis on those activities located in the centres of expertise. Factors affecting political decisions relating to the quality of care on RDs, as well as the internal organisation of health care systems will be analyzed in the future in order to adapt them to RD policies and to patients with RDs.

The CIBERER organised a Workshop on 31 March and 1 April at the MSSSI for the purpose of examining the knowledge and improvement of the practices of European centres of expertise on RDs and debating on their participation in European Reference Networks. The preliminary results of WP7, as well as experiences of some Centres of Expertise were presented at this meeting.

In this sense, it must be pointed out that the CIBERER was designed in 2014 by the MSSSI as a partner in the new Rare Disease Joint Action (RD ACTION) 2015-2017, giving the maintenance and coordination work of both Orphanet-Spain and the EUCERD Joint Action a chance to continue.

MAINTENANCE OF HEALTHCARE TRANSLATION COLLABORATION AGREEMENTS, INCLUDING PATIENT REGISTRIES FOR CLINICAL RESEARCH

The CIBERER has been entering collaboration agreements with a number of entities, many of which work in the translational field, for some time.

The most noteworthy of such agreements are the general agreements entered into with the Federación Española de Enfermedades Raras (FEDER), Fundación Pública Andaluza Progreso or Fundación Medina, setting up stable channels for collaboration offering consistency and continuity to any initiatives, programmes, projects and actions aimed at the group of people with rare diseases that may be developed jointly by both Institutions.

The importance of registries in the field of rare diseases must be highlighted within the field of translational research.

The scarce documented information about the epidemiology of rare diseases makes it obvious that there is a need to estimate the total number of people affected and the prevalence of each disease, and to evaluate the natural history of these diseases for the purpose of adapting health care to it and being able to improve disease follow-up.

Therefore, in 2014 CIBERER continued working on the start-up and maintenance of various registries, such as:

- **Rare Disease Registry** of the Instituto de Investigación de Enfermedades Raras (IIER-ISCIII), whose coordinator is Dr. Posada-U758.
- Maintenance of the **Fanconi Anaemia Database**, whose coordinators are Dr. Surrallés-U745 and Dr. Bueren-U710, (together with the Fundación Centro Nacional de Investigaciones Oncológicas-CNIO and the Centro de Investigaciones Medioambientales y Tecnológicas-CIEMAT).
- **E-IMD European registry and network for Intoxication type Metabolic Diseases**. Led by Dr. Ugarte-U746 with the participation of Dr. Artuch-U703, Dr. Ribes-U737 and Dr. Rubio-U739.
- **E-HOD European network and registry for homocystinurias and methylation defects**. Led by Dr. Couce-U737 with the participation of Dr. Artuch-U703, Dr. Grinberg-U720 and Dr. Pérez-U746.
- **European Registry of Wolfram, Alstrom, Bardet Biedl and other rare diabetes syndromes-EURO-WABB**. Led by Dr. Nunes-U730, (together with the Institut d´Investigació Biomèdica de Bellvitge and the Universidad de Vigo).
- **aHUS/C3g registry: Registry of patients with atypical uremic haemolytic syndrome and C3 glomerulopathies**. Together with the "Iñigo Álvarez de Toledo" Fundación Renal and Dr. Rodríguez de Córdoba's group-U738
- **Glycogen storage disease type V registry**: Dr. Antoni Andreu-U701 and Dr. Miguel Ángel Martín-U723. .

In summary, updating RD registries is one of the translation activities with the most long-term added value because it allows knowing the epidemiology of these pathologies the knowledge of which is biased due to the low prevalence of RDs.

OTHER TRANSLATIONAL ACTIVITIES: CONFERENCES, ENCOUNTERS AND MEETINGS

Both CIBERER as a Research Centre and the researchers that are part of take part in a number of conferences, encounters and meetings in order to disclose the results of their research with other colleagues on a national level, and by inviting internationally known speakers to therefore achieve an exchange of knowledge that has a direct effect on the collective advancement in the understanding of processes causing the diseases they study. Some of these activities performed in 2014 were:

- **Conference on the treatment of Pyruvate Kinase Deficiency**, organised by Dr. José Carlos Segovia and Dr. Juan Bueren-U710 in the CIEMAT of Madrid on 1 April. Presentation of the latest novelties in gene therapy for the treatment of Pyruvate Kinase Deficiency as an example of erythropathy.
- CIBERER participated in the **7th European Conference on Rare Diseases and Orphan Drugs (ECRD 2014)**, organised by EURORDIS in Berlin on 8-10 May. CIBERER presented a poster on the work conducted as coordinator of the EJA WP7 with the intervention of Dr. Francesc Palau.
- The Adult Rare Disease Work Group of Hospital Clínic-CIBERER organised the **"IV Jornada del Grupo de Enfermedades Minoritarias del Adulto: de los aspectos básicas a las unidades expertas"** on 30 May in Hospital Clínic de Barcelona. In this encounter, research in intermittent acute porphyria, rare anaemias and Lafora disease was explained. Professor Santiago Rodríguez de Córdoba-U738 was responsible for the discussion of Lafora disease.
- **Familial Cancer Conference**, organised by Dr. Javier Benítez-U706 on 5-6 June in the CNIO of Madrid. The most recent advances and ongoing projects in relation to hereditary cancers were presented in this conference from a multidisciplinary viewpoint.
- Dr. José María Millán, Assistant Scientific Director of the CIBERER, claimed that there is a need for research at a **Conference for Exposure of Rare Diseases** organised by the enterprise Genagen, FEDER and CIBERER on 19 June in Valencia.
- **7th International Congress of the Spanish Fanconi Anaemia (FA) Research Network**, organised by Dr. Juan Bueren-U710 and Dr. Jordi Surrallés-U745, on 6-7 October at the Instituto de Biomedicina of Seville. The Congress brought together, on one hand, basic expert scientists in molecular biology of the FA DNA repair pathway and clinical experts in the field applying the newest therapies. On the other hand, members of the Asociación Española de la Anemia de Fanconi (AEAF) attended the congress to obtain first-hand updated information about the disease and about the first lines of research for the prevention or cure of this disease.
- CIBERER co-organised with INGEMM and AEGH a **Conference on Dysmorphology** on 8 October in Madrid. In this forum, there was a presentation and informal discussion of rather uncommon cases of dysmorphology aimed at specialists in the matter, such as clinical geneticists, paediatricians, surgeons or pathologists. The conference was coordinated by Dr. Pablo Lapunzina-U753, Dr. Sixto García-Miñaúr-INGEMM, and Dr. Encarna Guillén-Navarro-LCG-Hospital Universitario Virgen de la Arrixada of Murcia.
- CIBERER collaborated in the organisation of the **4th Conference on Fragile X Syndrome and other Genetic Disorders causing Autism**, at Hospital Materno Infantil of Malaga, on 10-11 October. The LCGs which work with CIBERER and led by Dr. Feliciano Ramos, Dr. Jordi Rosell and Dr. Isabel Tejada, as well as Dr. Montserrat Milà-U726, all participated in the conference.
- Dr. Pilar Giraldo-U752 organised the **2nd Aragon Conference on Pharmacological**

Chaperones in Lysosomal Diseases and other Applications on 27-28 November in Zaragoza. In this encounter, the purpose of which was to provide updated information about the use of pharmacological chaperones in this type of pathologies for professionals in biomedicine involved in the diagnosis and treatment. Dr. José Luis Urdiales-U741 also participated in the conference.

- **2nd National Day commemorating Xeroderma Pigmentosum and other Premature Skin Ageing Diseases**, organised by the CIBERER, Fundación Jiménez Díaz and the CIEMAT, on 10 December in Madrid, coordinated by Dr. Marcela del Río-U714. Advances in different lines of research were presented, offering discussions about the relationship between telomeres and disease, genetics and molecular diagnosis, basic and clinical research, the proposal of a national clinical trial with Imiquimod, telomere shortening or the role of the ERCC4 gene in xeroderma pigmentosum.
- CIBERER and the Fundación Ramón Areces organised an **International Symposium on Hereditary Peripheral Neuropathies** on 11-12 December in Madrid. This encounter addressed the clinical framework of peripheral neuropathies, Charcot-Marie-Tooth (CMT) disease, the most common type among them, genetic diagnosis, the physiopathology and neuropathology of CMT, animal models for research, biomarkers and the discovery of new drugs.
- Health care managers from hospitals in 10 Spanish Regions, basic researchers and members of the Asociación HHT España for patients participated in the **2nd Meeting of the HHT Network Project** held on 12 December in Madrid. The purpose of this initiative is the joint work for the diagnosis, treatment and follow-up of patients with Hereditary Haemorrhagic Telangiectasia (HHT). CIBERER collaborated in this meeting, through unit U707, with its two pillars: the basic research led by Dr. Carmelo Bernabéu at the CIC/CSIC, and the clinical research coordinated by Dr. Roberto Zarrabeitia in the HHT Unit of Hospital Sierrallana of Cantabria.

In some of these activities, patients with RDs, their family members or their associations also actively participated, even though they are not the specific target audience. In addition, CIBERER also potentiates and supports a number of conferences and meetings intended for patients, or it collaborates in those organised by their associations. See the section on Dissemination Activities.

DISSEMINATION OF THE TRANSLATIONAL ACTIVITY OF CIBERER

The act of par excellence of dissemination of the translational activity of CIBERER is the **Conference called "Investigar es Avanzar"**, comprised within the acts held on **World Rare Disease Day**. This year, the act was jointly organised by CIBERER and the Federación Española de Enfermedades Raras (FEDER) on 26 February at the Centro de Investigación Príncipe Felipe in Valencia. See the section on Dissemination Activities.

CIBERER sponsored together with the Centro Nacional de Análisis Genómica (CNAG) the **exposition entitled "Menos raras"** organised by the Associació Catalana de Comunicació Científica (ACCC). This exposition was about research on RDs where advances made in Usher, Lafora, Wolfram, Fragile X, Fanconi, Williams-Beuren, dyskeratosis, retinal dystrophies, Lowe, AME and ALS were disclosed. The exposition could be seen from 1-24 April in the Biblioteca de la Sagrada Familia of Barcelona.

Dr. Carmen Ayuso-U704 participated on behalf of the CIBERER in the **Conference called "Actualización de Recursos de Atención en Enfermedades Raras"** organised by the Centro de Referencia Estatal a Personas con Enfermedades Raras y sus Familias (CREER) of Burgos on 24 June, presenting the translational research work for CIBERER.

CIBERER also organised a Dissemination Conference in the Facultad de Medicina of Ciudad Real on 3 November, entitled **"Introducción a las Enfermedades Raras: el valor de la investigación traslacional"**.

In addition, CIBERER also collaborated in dissemination activities to provide information about the research that was conducted in 2014 jointly with the remaining CIBERs, such as **"Tapa con Ciencia"**, which was held on 5 November in the Círculo de Bellas Artes of Madrid, a scientific-gastronomic initiative within the acts held for the Semana de la Ciencia in Madrid. Dr. Víctor Martínez González-U753 presented the CIBERER Exome Server, a database with the most common non-pathological genetic variants in the Spanish population which will be extremely useful in the research depicted through the culinary arts by means of fried banana helices stuffed with sea bass and fresh cheese.

Description

In recent years, CIBERER has established strategic alliances with particularly important agents in approaching the productive sector relating to RDs, such as ASEBIO (Asociación Española de Bioempresas), and biotechnological companies or pharmaceutical companies.

Boosting RD knowledge transfer to the productive sector is a fundamental objective identified by CIBERER. Advancement in the scientific activity of the research groups must continue, and the economic investments made in research must be returned to society.

Objectives

CIBERER is a national and international leader in research on and knowledge about RDs, and works to directly and effectively strengthen relationships with the productive sector, keeping two clear objectives in mind:

- Consolidation of tools for suitable knowledge transfer processes.
- Promoting RD knowledge transfer activities and innovation.

Resources Used

- Staff resources: Transfer Manager with the support of the team of Scientific Activity Managers. Support from the company Clarke, Modet & Co.
- Services: CIBER Technical Office.

Results

PATENTS

One of the primary objectives of CIBERER is to promote transferring complementary knowledge to the already existing programmes in the Consortium Institutions. This drive to transfer knowledge is fundamental because of the advantages it involves both for research groups and for society as a whole.

We would first like to highlight the following patent applications filed in 2014 in collaboration with some of the institutions forming the consortium:

Group	Application No.	Type of Application	Title
U721/ U759	P10458EP00	European	New therapeutic uses of Temsirolimus for adreno-leukodystrophy
U742	P201431364	National	Indole derivatives for the prevention and/or treatment of diabetes and related metabolic disorders
U757	PCT/ ES2014/070803	International	Peptide derived from GSE24.2 for treating diseases caused by oxidative stress and damage to DNA
U757	PCT/ ES2014/070072	International	Biodegradable bionanoparticles for releasing the GSE24-2 peptide, method for the production thereof and use of same

The primary activities for promoting the Transfer performed by CIBERER are the following:

DEVELOPMENT OF TOOLS FOR TRANSFER PROCESSES

First, CIBERER continues providing advisory services relating to intellectual property and other aspects relating to the transfer. This task was coordinated by Scientific Management with the support of the company Clarke, Modet & Co. Researchers channelled all their queries relating to the protection of R&D&I activities generated while carrying out their projects, and received guidance and support about applying good practices in management of the measures for protecting project results.

Furthermore, extensive work has been done in order to identify and valorise products and services potentially transferable to the different CIBERER groups.

CIBERER is a **full member of ASEBIO** (Asociación Española de Bioempresas). In 2014, CIBERER continued its activity within the Innovate Drug group, the specific Rare Diseases and Advanced Therapies subgroups, as well as in the Molecular Diagnosis Work Group, actively participating in the different meetings. Since 2011, CIBERER has also been an associate member of **BIOVAL (Bioregión de la Comunidad Valenciana)**. Since 2013 it has been a collaborating partner in the Medical and Health Innovation Technologies (ITEMAS) Platform. The ITEMAS Platform seeks to encourage innovation in health technology as a fundamental tool to make the National Health System more sustainable, supporting the development of the innovative culture necessary to facilitate integrating the science-industry system in the field of medical technology.

PARTICIPATION IN FORUMS AND EVENTS ENABLING COLLABORATION WITH THE PRIVATE SECTOR

Finally, in 2014 the Management Office staff and the CIBERER Management attended and participated in other forums and events of particular interest enabling some type of collaboration with the private sector, such as:

- **TRANSFIERE** which took place on 13-14 February 2014 in Málaga.
- **BIOSPAIN 2014** held in Santiago de Compostela on 24-26 September 2014, numerous researchers of the centre also participating.
- **VI Spanish Drug Discovery Network Meeting** which took place in the Science Park of Madrid at the head office of Glaxo Smith Kline, 20-21 November 2014

Furthermore, CIBERER has participated in several conference and workshops, organising them in collaboration with companies to deal with different aspects relating to the aetiology, causes, clinical symptoms and treatment of RDs:

- **World Rare Disease Day, "Investigar es avanzar"** in the Instituto de Investigación Príncipe Felipe de Valencia,. Several companies and institutions representing the private sector attended.
- **DNA-Day CIBERER Workshop** at Hospital Universitario La Paz de Madrid with the collaboration of Roche, Genycell Biotech, Sistemas Genómicos, Agilent Technologies, Abyntek, Progenika and Perkin Elmer.
- **International symposium on nerve biology and inherited peripheral neuropathies** organised in collaboration with the Fundación Ramón Areces on 11 and 12 December in Madrid.

OTHER RD KNOWLEDGE AND INNOVATION TRANSFER ACTIVITIES

As part of the continuous activity of 2014, public-private collaboration was encouraged through work meetings with private companies or entities to present specific opportunities to collaborate with CIBERER. A number of meetings were held to explore the collaboration pathways in future projects. The companies that were contacted include: **Orphan Europe, Roche, CABANA genetics, CYDAN, Valentia Biopharma, Janus Developments and Pfizer**.

Furthermore one-time agreements were also maintained with different companies for R&D collaboration.

- Collaboration agreement with **Sistemas Genómicos, S.L** to manage samples obtained by Sistemas Genómicos, S.L. and the assignment thereof to CIBERER-BIOBANK.
- Agreement with **EVERIS** to participate in the collaborative AMER project in the CDTI Innterconecta call for proposals.
- Agreement with **Orphan Europe** for a pharmacovigilance study in the European homocystinuria registry (E-HOD).

CREATION OF THE FIRST CIBER SPIN-OFF

One of the main milestones of 2014 has been the launch of the first Spin-off with the participation of CIBER, **Epidisease S.L**. This Spin-off is the result of the work and the experience of its developers, U733 of the CIBERER headed by Dr. Federico Pallardó, and carried out by Dr. Garcia Gimenez, hired by CIBERER, in the field of epigenetics.

Description

The CIBERER Training Programme on rare diseases promotes and supports training for its researchers, in addition to supporting the initiatives the research groups undertake for this purpose.

The training offer consisted of:

CIBERER PRE-DOCTORAL AID: specific tool for attracting recent university graduates to CIBERER groups, allowing remuneration for work immediately after joining without having to wait until the general calls for proposals for pre-doctoral aid are resolved.

AID FOR MOBILITY: aid so that CIBERER researchers can hold internships for up to three months in other internal or external research groups.

COURSES: aid for internal CIBERER courses and for funding the attendance of members of the CIBERER groups to courses of specific interest for some of the strategic lines of the Centre.

Objectives

The objectives of the Training Programme are:

- To favour incorporating research staff in training to the CIBERER groups.
- To directly organise or help organise training courses and activities
- To promote mutual knowledge and collaboration between CIBERER groups.
- To collaborate in the internal dissemination of the CIBERER research activity.

Resources Used

STAFF RESOURCES: Training Manager, who works part-time in organising and controlling the CIBERER training activities. CIBERER staff of the Pre-doctoral Aid Programme.

SERVICES: Training Department.

Results

The following can be mentioned as the 2014 Training Programme activity results:

CALL FOR PROPOSALS FOR PREDOCTORAL AID:

The 2013 call for proposals for predoctoral aid was taken on in its entirety with CIBERER funds. This call for proposals allowed incorporating fourteen young graduates so they could do their predoctoral work. The results of the 2014 Call for Proposals for Predoctoral Aid, indicating the name of the awarded candidates, the Consortium Research Center where they will be working, and the project they joined, are presented below.

Name	Surnames	Group	Associated Project
Pau Bernat	Esparza Moltó	U713	La mitocondria y su disfunción en patología: Papel de IF1
María José	López Iniesta	U718	Identificación de nuevas dianas terapéuticas en distrofias hereditarias de retina: Análisis funcional in vivo e in vitro de genes causantes de ceguera
Victoria	Gálvez Cortés	U714	FIBRODRESS: Desarrollo de un apósito bioactivo basado en fibrina y bioingredientes activos
Aleyda	Benítez Amaro	U705	Modulating SMN2 splicing with dual inhibitors of Sam68 and hnRNP A1: A novel therapeutic approach for Spinal Muscular Atrophy
Chiara	de Rienzo	U730	Implicación de la L-ergotioneina en la litiasis renal de cistina: Posible aplicación terapeútica en cistinuria
Judit	Cabana Dominguez	U720	Análisis Cruzados de Trastornos Psiquiátricos: Contribución de Variantes Genéticas Raras y Comunes al Autismo, el TDHA y la Dependencia de las Drogas
Clara	López Montero	U754	Diagnóstico, caracterización y relevancia clínica de defectos en la familia factor H/CFHRs del Complemento en patología renal
María	Alcázar Fabra	U729	Terapia del síndrome de deficiencia de CoQ10
Marta	Martín Sánchez	U702	Identificación de nuevos genes responsables de la enfermedad de Hirschsprung y del cáncer de tiroides, y determinación de los mecanismos patogénicos asociados
Uxia-Saraiba	Esperon Moldes	U711	Estudio Clínico y Genético Molecular de las Ictiosis Congénitas Autosómicas Recesivas en España
Tania	Moreno Mármol	U709	Linajes y competición celular en el desarrollo y la enfermedad (CEL-DD)
Germán	Sánchez Díaz	U758	RD-CONNECT: An integrated platform connecting registries, biobanks and clinical bioinformatics for RD research
Ximena	Barraza García	U753	Identificación y caracterización de genes implicados en las displasias esqueléticas
Cristina	Mesa Núñez	U710	EUROFANCOLEN: Gene therapy trial of Fanconi anemia patients with a new Orphan Drug consisting of a lentiviral vector carrying the FANCA gene; a coordinated international action

The consideration of the set of grant data for the 2014 call for grant proposals and of the follow-up and closure of the 2013 call for grant proposals, allows affirming that the objectives have been reasonably achieved:

- Percentage of withdraws before finishing the year of the aid, with continuity in the group: There were no withdraws before the final of the period of the aid.
- Number of grants in the grant 2014 grant call: 14. Above the range established as optimal (8 to 12).
- Average mark of the academic records of the 2014 grant call: 2.71. More than two decimals higher than that of 2013 and well above the cut-off point of 2.2.

AID FOR MOBILITY

In 2014, aid for mobility remains open up to external, national and international mobility. Several researchers could therefore benefit from this programme to expand their training and advance the projects in which they were involved.

- Number of examples of mobility: 7 requests, which represents a significant drop in relation to previous years (2010= 11, 2011= 10, 2012= 13, 2013= 18). 6 candidates were awarded aids for mobility, because 1 of the requests for aid for mobility was for mobility within the same province, which cannot receive financial aid.

The following table shows the cases of mobility in 2014:

Name	Issuer Group	Receiving Group
Gallego Villar, Lorena	746	U Zurich, Switzerland
Cascajo Almenara, Mª Victoria	729	713
Sequedo Pérez, Mª Dolores	755	710
Vázquez Manrique, Rafael	755	710
Bogliolo, Massimo	745	715
Emperador, Sonia	727	723
Álvarez Mora, Mª Isabel	726	705

AID FOR THE ATTENDING AND/OR ORGANIZING COURSES

In 2014 CIBERER organized a training course:

- "Introduction to Genetically Modified Animals Research, 3rd Edition". School of Veterinary Science UCM. 6 to 7 November 2014.

Aid for attending this course were granted to members of CIBERER groups. A total of 14 aid packages were offered to cover total expenses for attending recipients. CIBERER furthermore collaborated in another 5 courses, resolving 5 additional calls for proposals for aid for attending external courses of special interest for the development of the work of its own investigators. A total of 31 aid packages were offered for attending the following activities:

- "Translational Genomics in Biomedicine". In the Centro Esther Koplowitz of the Fundació Clínic. Barcelona 13 and 14 March.
- Online Course: "MASTER CLASS EN ENFERMEDADES DE DEPÓSITO LISOSOMAL (EDL)". Organised by U752
- "6th Familial Cancer Conference" in the Centro Nacional de Investigaciones Oncológicas (CNIO). Madrid, 5 and 6 June.
- "Diseño, Análisis de datos de genotipado e Interpretation de Resultados Estadísticos" in the Escuela National de Salud. Madrid, 12 and 13 June.
- "6º Curso de Genética Humana de la Sociedad Española de Genética". In Hospital de Sant Pau. Barcelona, 21 November.

ORGANISATION OF THE ANNUAL CIBERER MEETING

The 7th Annual CIBERER Meeting took place in Euroforum, Escorial in Madrid on 10, 11 and 12 March. 190 people attended this plenary meeting, and most of the attendees were researchers from CIBERER groups. For a networking Centre like CIBERER, the Annual Meeting is a unique opportunity to meet with researchers, to learn about the latest advancements and to debate new actions.

The meeting served as a forum for presenting and debating the advancements made in the different lines of research of the CIBERER groups. It reflects the actions of the seven CIBERER research programmes, in addition to the activities of their horizontal programmes and platforms for supporting scientific activity. The participation of researchers undergoing training was paramount, and the junior attached researchers and hires present at the meeting played an important role.

The programme also included the presentation of the actions of the different CIBERER platforms and the pooling of the short- and mid-term objectives and strategies.

With its Communication plan, CIBERER continuously informs the society about the work of the research groups, their projects, the diseases they are researching and the new knowledge generated. Patients and support associations are the main targets of these communication actions.

For dissemination activities, the CIBERER, consisting of the Communication Department and its collaborator Miquel Calvet maintained continuous contact with the press, has prepared a scientific newsletter and a social newsletter, has managed a Twitter account and kept the CIBERER web updated.

CIBERER has also directly approached patients and their families with the periodic organisation of conferences or with their presence in scientific, institutional and social forums relating to RD.

The CIBERER Communication Plan is split into two large lines of action, the Internal Communication Service and the External Communication Service.

Internal Communication Service

With this service and through the researchers and professionals associated with the institution, CIBERER consolidated its activity and corporate image and brought together its networking structure.

CIBERER worked hard to turn its web page (**www.ciberer.es**) into an effective instrument. All the calls for proposals (employment, training, aid programmes, etc.) that may be of interest for the groups, all the events organised by CIBERER or relating to RDs, updated news relating to the Institution and press clips available on the Intranet have been included. This web page was updated every day.

The CIBERER **Electronic Newsletter** must also be highlighted. It is a very effective publication, on one hand, for disseminating the research on RDs conducted by CIBERER and on the other, for providing all the information of interest about RDs to researchers that are both hired by and attached to our Institution.

Therefore, in 2014 work was done to improve knowledge among the different CIBERER research groups and to tighten their scientific collaboration links.

MOST NOTEWORTHY ACTIVITIES PERFORMED IN 2014:

- The Electronic Newsletter used to periodically report CIBERER activity to associated researchers and also to external directors interested in RD. In 2014, 8 electronic newsletters were sent out.
- Services over the web for communicating funding opportunities and events for research on RDs has been updated daily with all the notices and events of interest for all the research groups

External Communication Service

The Communication Service has offered support to researchers so that their activity can be better understood both by people suffering from RDs and by society as a whole. With its External Communication Service, CIBERER has transmitted the scientific activity of its research groups, social and institutional activity of the Institution and the events it organised, in order to bring it closer to the reality of patients and family members.

CIBERER has used various means for that purpose. The Communication Department has acted as a **press office**, carrying out dissemination campaigns intended for the press and dealing with information professionals. CIBERER has also organised **dissemination events** and updated its **web page** every day to turn it into an effective communication platform on both an external and internal level. It has also periodically sent out the **Social Newsletter**, an electronic publication for providing all the information about CIBERER and its research on RDs to patients, associations that represent them and to anyone else interested in this field. CIBERER has also had an active **Twitter account** which it uses to interact with researchers, patients and the remaining groups of interest in RD.

MOST NOTEWORTHY ACTIVITIES PERFORMED IN 2014:

- Organisation of the **sixth conference entitled "Investigar es Avanzar"** for the dissemination of CIBERER research activity in the framework of the RDs Day. The act was organised in February in Valencia
- Daily update of the web of the CIBERER: in 2014, the web was visited by 115,445 users.
- In 2014, CIBERER had 864 hits in the press. This indicator clearly shows that it has become an unquestionable social reference in the field of research on Rare Diseases.
- Social Newsletter: 6 social newsletters where sent in 2014.
- Dissemination of the centre's events, research and activities to the outside world by carrying out press campaigns and continuing handling the press as a communication office. Six press campaigns were carried out in 2014.
- Representation of the CIBERER at the patient association conference.
- Furthermore, CIBERER participated in the activity TapaConCiencia organised within the framework of the Semana de la Ciencia, in which 8 research projects were presented corresponding to the thematic areas of the CIBER, that served as an inspiration to the cook Jorge Cuellar to design 8 elaborate "tapas". Dr. Víctor Martínez González-U753 presented before 250 people the CIBERER Exome Server, a project to determine new genes for RDs. The event was covered by more than 20 mainstream and specialised media outlets.
- CIBERER Twitter account statistics:

	January 2014	December 2014
Updates	1590	2437
Followers	1447	2626
Klout (level of influence, values between 1 and 100)	48	55

CIBERER in the press

MOST OUTSTANDING IMPACTS ON PRESS IN 2014:

Date	Headline/Subject addressed	CIBERER Member mentioned	No. Impacts
03/11/2014	Lowe's Syndrome, a pathology ultra rare of that only 20 cases are known in Spain	Mercedes Serrano -U703	74
31/12/2014	Start the first database that gathers genetic mutations of the Spanish	CIBERER	31
07/02/2014	Identification of the pathogenic mechanism of the Lafora disease	Santiago Rodríguez de Córdoba-U738	29
27/10/2014	Overgrowth syndrome caused by the RNF125 gene	Pablo Lampunzina-U753	27
15/10/2014	Ciudad Real receive the new UCLM-bq software manufacturing centre	CIBERER	26

CIBERER dissemination activities aimed at patients and society

The specific event in which CIBERER addresses patients and society as a whole is undoubtedly the **Rare Diseases Day**, entitled **"Investigar es Avanzar"**. This 2014 edition, took place in the Centro de Investigación Príncipe Felipe de Valencia. Researchers of the CIBERER assessed the high importance of rare disease registries in which they are participating on a European level, specifically in rare metabolic diseases, a model of research on RDs was presented to help fight against a disease as prevalent as sepsis, and furthermore the benefits of the collaboration between researchers and patients were explained in the case of the Cushing syndrome and Williams syndrome. Furthermore, the Federación Española de Enfermedades Raras (FEDER) presented its integral activities and also its collaboration with the Universitat de València. Finally, the documentary "Raras pero no invisibles", created to disclose Spanish research in this type of pathologies, was presented.

The research activity that is performed in CIBERER reaches society through events that the RD associations or the CIBERER groups working hand in hand with them organise, among other activities the following should be noted:

- The Asociación de Ayuda a Personas con Albinismo (ALBA) organised the "**2nd European Days of Albinism**" in Valencia the 5 and 6 April. CIBERER U756 led by Dr. Lluís Montoliu collaborated in this encounter.
- The nutritionist Cristina Montserrat and Dr. Maria Forga, of Hospital Clínic de Barcelona and of the Adult Metabolic Disease Work Group, together with HSJD and the CIBERER, organised the 1st Edition of the **Cooking workshop for young patents and adults requiring a protein-restricted diet** on 27 September, that furthermore counted on the collaboration of the Asociación Catalana de Fenilcetonuria y Trastornos Metabólicos Hereditarios.
- CIBERER collaborated in the organisation of the **Meeting of Family members with Williams Syndrome** through Dr. Jordi Rosell, leader of the CIBERER Linked Clinical Group, in Hospital Son Espases de Palma de Mallorca. Dr. Luis Pérez Jurado (U735) participated in the encounter which took place on 15 November.
- The Dr. Laura Audí and Dr. Diego Yeste-U712 participated in the **XIV GrApSIA Encounter** held on 22 November in Barcelona which this association that supports young people and adults with Androgen Insensitivity Syndrome (AIS) and others related syndromes organised.
- The **Asociación Española de Afectados por Acromegalia held its 4th National Encounter** on 13 and 14 December in Madrid and it also included the collaboration of the CIBERER. In this event, Dr. Susan Webb and Dr. Eugenia Resmini, both of U747, were present.

Service for handling queries by patients and professionals

CIBERER and Orphanet receives a large number of queries which we try to respond to provide guidance to patients in searching for the possible answers to the questions they are asking. To that end we have the immeasurable help of CIBERER researchers and clinicians and of the Orphanet Scientific Committee members as well as the FEDER Patient Information Service and Guidance, SIO.

In 2014 a total of 138 queries were received, half of which arrived through the Orphanet web page and approximately a third of the total came from patients from Central and south American countries.

Crowd Funding Campaigns

There is no doubt that in the last years we have lived through an explosion of information concerning the existence of rare disease and how patients and their families had been ignored before that. Fortunately, and although there is still much to discover, we are witnessing nowadays a steady increase in social, scientific and political awareness of the need for and importance of research on RDs and to support and give answers and solutions to those suffering from these pathologies.

RD patient associations have, by making their reality visible, raised awareness and involved society in the cause. Several research projects have been funded or co-funded with crowd funding initiatives that patients with rare diseases have led jointly with researchers CIBERER in 2014:

- Through the **Plataforma Precipita** started up by FECYT:

  - Dr. Montserrat Milà -U726 started up a crowd funding campaign for research which seeks to evaluate the costs and viability of neonatal screening of Fragile X Syndrome. With the new technologies, we can exploit the samples of blood taken from newborns with current neonatal screening to identify those affected by Fragile X Syndrome, which is the most common cause of familial intellectual disabilities.

  - Dr. Santiago Rodríguez de Córdaba-U738 CIBERER for a project to develop drugs for atypical haemolytic uremic syndrome.

  - Dr. Mercedes Serrano- U703 for instructive videos on RDs for families and patients

  - Dr. Cristina Fillat-U716 for the creation of a videogame for cognitive stimulation of people with intellectual disabilities

  - Dr. Daniel Grinberg- U720 for conducting research on the identification of the gene responsible for Opitz C syndrome.

- Dr. Mercedes Serrano and Dr. Belén Pérez, both of U703, are driven by the solidarity challenge #ultratorozos, in favour of research. The athlete Lisandro Caravaca ran 100 km in the area of the Montes Torozos for the purpose of raising money for biomedical research on Lowe syndrome, CDG syndrome and neurodegenerative diseases with an accumulation of iron in the brain

4. PLATFORMS

Orphanet

CIBERER has been Orphanet's Spanish partner since April 2010. Orphanet is the information portal of reference in relation to rare diseases and orphan drugs and is present in about 40 countries, most of which are in Europe.

The Orphanet portal today as a database of reference in Europe for RDs and orphan drugs, pools together information on 9,539 diseases, 6,675 queries specializing in pathologies with a low prevalence, 2,671 patient associations, 15,941 health professionals, and 1,699 laboratories from 39 countries. It has an average of 45,000 visitors a day.

In 2014, the Spanish team had a project manager, Dr. Corrochano, and one scientific documentalists, Mª Elena Mateo. The Orphanet-Spain Scientific Committee, which is responsible for validating most of the information generated in Spain, currently has 60 experts integrated in 31 different medical areas, after the integration during 2014 of the area of infectious diseases. The complete list of members of the Spanish Scientific Committee can be consulted at the following link:

http://www.orphanet-espana.es/national/data/ES-ES/www/uploads/ComiteCientifico.pdf

The Orphanet Platform carried out the following activities in 2014:

DATA COLLECTION AND UPDATE:

The team is responsible for continuously collecting and updating the directory listing the services offered in Spain. The following document includes the inclusion criteria and the sources of information used for each type of activity that is recorded:

http://www.orphanet-espana.es/national/data/ES-ES/www/uploads/criterios-ES.pdf

After the process of collecting and updating data throughout 2014, the Spanish activities included in the Orphanet database are the following:

Total of Spanish activities in 2014

Specialized clinical queries	395
Patient associations	265
Diagnostic tests	7141
Clinical trials	844
Research projects	428
Registries / Biobanks	68

TRANSLATIONS:

A total of 286 disease summaries and 722 names of new RDs, with the modification of another 2,882 RD names already included in the database have been translated to Spanish and incorporated in the web page.

To contribute to the translation of the Orphanet Patient Encyclopaedia, a series of texts containing abundant information about a number of RDs written so that the general public can understand it, CIBERER has allocated of part of the budget for this platform to translating and validating 12 of these articles, all of which are pending publication.

PROMOTING ACTIVE PARTICIPATION OF THE SCIENTIFIC COMMITTEE (SC)

Scientific Committee (SC) members were involved in different tasks in 2014, such as reviewing disease summaries, clinical guidelines belonging to Orphanet and external guidelines and the lists of expert centres, as well as answering patient queries. Furthermore, SC members collaborated as external reviewers in validating guidelines written by CIBERER.

PROMOTING THE COMMUNICATION AND DISSEMINATION PLAN:

Greater dissemination of the Orphanet project is essential for giving the portal greater exposure and therefore maximizing its usefulness. The following actions, among others, have been boosted for that purpose:

- Centro de Referencia Estatal de Atención a Personas con Enfermedades Raras y sus Familias de Burgos (Creer)

  - Contribution to the CREER newsletter with the publication of a presentation paper of the Orphanet portal and of the activities of Orphanet-Spain (nº 43, April 2014). (http://www.creenfermedadesraras.es/creer_01/documentacion/boletindigitalcreer/ano_2014/news_abril/profesionales_abril/index.htm)

  - Attendance to the Conference "Actualización de Recursos de Atención en Enfermedades Raras" (24 June 2014).

- Orphanet Spain staff together with CIBERER managers handle queries submitted by people with RDs and forward them to different experts on the Orphanet Scientific Committee depending on the pathology in question.
- Contributions to the Orphanews Europe newsletter.
- Maintenance of the Orphanet Spain web:

  The Orphanet-Spain web page, which is developed by the Spanish team of documentalists and transmits current situation, events and documentation of Orphanet, which are all relevant on a national level, published about 100 articles throughout 2014. In collaboration with patient associations, it disclosed events relating to RDs in Spain, particularly those relating to Rare Disease Day. It also provided access to documents in Spanish on these diseases, such as the various guidelines contained in the "Enciclopedia de Orphanet-España" (Orphanet-Spain Encyclopaedia), or specific documental resources to offer social, educational and health support for people suffering from rare diseases in Spain, compiled in the "Otros recusos" (Other resources) section.

  In collaboration with the communication office of the CIBERER, the news published in the Orphanet-Spain web boosts its visibility through its Twitter service. Furthermore, those that stand out the most in relation to the Orphanet portal itself are published on the CIBERER web site and in its institutional newsletter.

PROMOTING RESOURCES SHARED BY CIBERER AND ORPHANET, WORKING SO THAT THE RELATIONSHIP BETWEEN THE INSTITUTIONS IS AN ADDED VALUE FOR THEIR RESPECTIVE PROJECTS

In 2014:

- The list of rare diseases that CIBERER works with was reviewed and updated.
- Collaboration was offered to the Patient Care Service in managing of queries and information requests by patients.
- Collaboration was offered to the managers of CIBERER in preparing proposals for projects involving the Orphanet platform.
- The Research Programmes of the CIBERER have collaborated with Orphanet in various ways:

  - Updating CIBERER database information which was subsequently introduced in Orphanet.

  - Collaboration as members of the of Orphanet-Spain Scientific Committee, participating in the validation of translations, external guidelines and the directory of expert resources included in Orphanet.

CIBERER Biobank

In 2014, the CIBERER Biobank had a coordinator, Dr. Corrochano and a laboratory manager, Dr. Salvador Martí. The activities carried out by the CIBERER Biobank were in line with the strategic objectives listed in the 2014 Action Plan and strived towards enhancing the good operation of the platform. In general lines, the following points must be highlighted:

- New sample processing techniques have been implemented and external services developed. The Biobank's participation in several national and international projects has been promoted in 2014.
- Services continued to be provided to CIBERER researchers.
- The Biobank's work has been disseminated in various national and international forums.

As regards the Biobank's objectives defined in the 2014 Action Plan, the following stands out:

OBJECTIVE 1: TO PROVIDE BIOLOGICAL SAMPLES TO THE BIOBANK

The Biobank continued to receive samples from different hospital services from centres such as Hospital Universitario La Fe of Valencia, La Paz Hospital of Madrid, Hospital Clínic of Barcelona or the Fundación Jiménez-Díaz of Madrid, Hospital de Bellvitge of Barcelona or Hospital Virgen del Rocio of Seville.

Besides the samples collected through the campaign, different CIBERER groups expressed their interest in collaborating with the Biobank in the Action Plans pertaining to the medical subject matters to which they belong. That interest is manifested in sending samples and requesting services.

A total of 301 samples corresponding to 33 different pathologies were collected at the end of 2014. The biological material catalogue can be consulted at the Biobank's web page: http://www.ciberer-biobank.es

OBJECTIVE 2: TO PROMOTE A STRATEGIC ALLIANCE AND DISSEMINATION PLAN

The CIBERER Biobank maintains the following collaborations:

- Member of the Red Valenciana de Biobancos (Valencian Biobank Network) (RVB) since 2010, actively participating in the different work groups.
- Draft Collaboration Agreement with the Centro Superior de Investigación en Salud Pública-FISABIO of the Valencia Regional Government, entered into in 2009 in order to establish an operational framework that promotes collaboration in scientific research, technological development, staff training activities.
- Draft Agreement with the Banco Nacional de ADN in order to cooperate in the creation and development of the CIBERER Biobank and in the implementation of projects and research programmes to be carried out together. Active since 2008.
- Agreement with Sistemas Genómicos since 2012 for sending RD samples from the clinics of Sistemas Genómicos to the CIBERER Biobank.
- Member of the Blood Derivatives work group of the National Biobank Network since 2010.
- 'Associated Partner' in the 7PM RD-Connect project (HEALTH. 2012. 2. 1. 1-1-C: databases, biobanks and clinical bio-informatics hub for rare diseases) coordinated by H. Lochmüller, of Newcastle University.
- Agreement with the Fundación FEDER whereby the biobank has received funding for hiring technical staff to provide support in the development of human iPS generation technique.

Disseminating information about Biobank activity

In 2014, the biobank has participated and disseminated its knowledge in 5 conferences/meetings, namely: 'Investigar es Avanzar' Conference, the 7th Annual CIBERER Meeting, the 3rd Scientific Meeting of TREAT-CMT, Biobank Introduction Course in Hospital La Fe and the 5th National Biobank Congress.

OBJECTIVE 3: TO GENERATE ADDED VALUE FOR CIBERER GROUPS.

CIBERER groups value the importance of having the Biobank platform within the network. In 2014, several expressions of interest were received by CIBERER groups, including:

- **Group: U704. Dr. C. Ayuso / Dr. M. Cortón**.- Collaboration in immortalizing cell lines.
- **Group: U730. Dr. V. Nunes / Dr. M. López de Heredia**.- Within the framework of an international project (European and North American groups) to study Wolfram syndrome, samples of DNA, RNA and immortalized cell lines will be collected (from about 30 patients). CIBERER Biobank will handle processing, storing and safeguarding of these samples.
- **Group: U733. Dr. F. Pallardó / Dr. J. L. García-Giménez**.- The Biobank collects and manages samples for two projects led by these researchers.
- **Group: U745. Dr. J. Surrallés / Dr. M. J. Ramírez**.- Collaboration in immortalizing cell lines of patients with Fanconi anaemia.
- **Group: U753. Dr. P. Lapunzina**.- Collaboration in immortalizing cell lines of patients with different pathologies.
- **Group U760 Dr. V. L. Ruiz**.- Collaboration in immortalizing cell lines of patients with different pathologies.

- Furthermore, within the framework of the TREAT-CMT project, the Biobank maintains collaborations with the following units of the CIBERER: U732, U755, U733, U713, U743.
- The Biobank also participates in other CIBERER projects providing logistics and technical support (see Objective 4).

Services Provided

The Biobank has fine-tuned a lymphocyte immortalization service that all CIBERER researchers can benefit from and is fine tuning other techniques that can also be offered as a service (myoblast culture, iPS cell generation,..).

Nineteen requests were received from CIBERER groups in 2014.

OBJECTIVE 4: TO PROMOTE AND SUPPORT NEW LINES OF ACTION ON RARE DISEASES

Participation in projects:

In 2014, the Biobank has maintained collaborations started in the preceding years and has also started other new collaborations:

- FP7 HEALTH 2012-INNOVATION: **RD-Connect**: An integrated platform connecting registries, biobanks and clinical bioinformatics for RD. The biobank participates as an Associated Partner.
- Translational Research, Experimental Medicine and Therapeutics on Charcot Marie **Tooth, TREAT-CMT**. International Rare Diseases Research Consortium (IRDIRC). Within the framework of this project, the Biobank has processed about 150 samples and assigned about 100 of said samples.
- Participation, together with the CIBERER U730 (Dr. V. Nunes), in an international project (European and North American groups) to study the **Wolfram syndrome**. Within the framework of this study, samples of DNA, RNA and immortalized cell lines will be collected (from about 30 patients). CIBERER Biobank will handle processing, storing and safeguarding of these samples.
- Influence of epigenetic factors on the development of **Adolescent Idiopathic Scoliosis**. Dr. J. L. García Giménez (U733). Fundación Mapfre 2012 Grant Call.
- **AMER –Multidisciplinary Action on Rare Diseases and Personalized Medicine**. R&D Project of the FEDER-INTERCONECTA Programme. 2012-014. The Biobank participates in PT2: Registrations of patients, biobanks and knowledge management. In this work packet, the biobank provides consultancy services in relation to the development of standardized methods, sample management and bioethics problems derived from such activities.
- **Spanish Exomes Project**, SPANEX. Project funded by CIBERER with the participation of 9 CIBERER research groups and the CIBERER Biobank. 2014-2016. Besides providing consultancy services in the ethical/legal aspects of human biological sample collections, the Biobank also provides logistics support to the project for sample collection and storage.
- **Development and validation of possible biomarkers and therapeutic targets for Friedreich's ataxia.** ACCI calls for proposals for CIBERER intramural projects. PI: Dr. Javier Díaz-Nido-U748. Participating groups: U732 and U733. The Biobank collaborates by means of assigning samples and providing consultancy services in the ethical/legal aspects of the project.

Networking Laboratory Animal Phenotyping Service (SEFALer)

The Networking Laboratory Animal Phenotyping Service (SEFALer) main objective is to **characterize the phenotype of animal models of rare diseases** as a fundamental tool for studying the physiopathology, for understanding the underlying molecular mechanisms, for identifying diagnostic criteria and for evaluating and refining new therapies

SEFALer is a service coordinated by CIBERER through several of research groups, providing important support to the research activity of the CIBERER units.

The following detailed information show the activities performed in 2014 based on the objectives proposed for the year in each section:

OBJECTIVE 1. TO INCREASE THE PHENOTYPING OFFER AND SEFALER'S ACTIVITY

In 2014, the SEFALer service offer has been increased with the following proposals:

- **SEFALer F1 Unit**- Dr. Isabel Varela-U761: this unit has implemented a method for counting inner ear hair cells using stereological techniques, surgical techniques for determining the endocochlear potential in murine models and a vestibular phenotyping test panel. A noise exposure model in rat as well as surgical techniques for the local administration of drugs to the inner ear are being developed.
- **SEFALer F3 Unit** - Dr. Cristina Fillat and Dr. Mara Dierssen-U716: the unit has incorporated in its offer longitudinal analysis systems for analysing the progression of the ingestion, vertical activity and actual position of the animal. This allows a long-term study in which these variables are shown in real time during the data acquisition process . Furthermore, this unit has incorporated electrophysiological techniques (LTP) and intracranial injection techniques and developed models for compulsive behaviour study, drug abuse studies and computational modelling.
- **SEFALer F4 Unit**- Dr. Consuelo González Manchón U734: this unit has implemented methods for analysing different blood cell components and specific assays for evaluating the haemostasis in animal models, providing tools to recognize the condition of the coagulation pathways as well as to evaluate the platelet aggregation and thrombogenesis in vivo. Furthermore, the optimization of in vitro tubulogenesis assays which would allow evaluating the angiogenic capacity of primary endothelial cell cultures originating from genetically modified animals is being developed. With this technique, the effect of inhibitory or potentiating agents on the formation of blood vessels, as well as the study of the signal transduction and cytoskeleton remodelling of the endothelial cells of the study animals can also be evaluated.

All the services offered by each of the SEFALer units can be seen in

www.ciberer.es/sefaler

Among the many functional phenotyping assays performed by the SEFARLer units for different CIBERER units, as well as for other CIBER-RETICS and research units not related to CIBERER, the following stands out:

- evaluation and histopathological diagnosis in preclinical assays of new therapies for primary hyperoxaluria (see section on projects).
- various neurobehavioral phenotyping studies in murine models:

  - for type C Niemann-Pick disease, for the laboratory of Dr. Daniel Grinberg-U730

  - knockout mouse models for the PPARα, abcd1 and abcd2 genes (KO abcd1, KO PPARα),

  - double KO abcd1abcd2, triple KO abcd1abcd2PPARα)

  - a knockout mouse model for the SIRT2 gene (KO SIRT2)

  - William Beurens model for the Dr. Luis Perez-Jurado and Dr. Victoria Campuzano both of U735
- functional assays of platelets from patients with hemorrhagic syndromes for analyzing the role of endoglin in the platelet-endothelium interaction for Dr. Carmelo Bernabéu's group-U707
- trials performed for several IDIBELL researchers (not CIBERER) in murine models of RDs:

  - model of X-adrenoleukodystrophy (double knockout mice for the Abcd1 and Abcd2 genes)

  - mice model for Rett Syndrome, in collaboration with Dr. Manel Esteller of the Cancer Epigenetics and Biology Program (PEBC)

  - mdx dystrophic mice for the study of the invasive and metastatic phenotype of tumours, in collaboration with Dr. Roser López-Alemany.

OBJECTIVE 2.- TO IMPROVE COMMUNICATION AND COORDINATION BETWEEN SEFALER UNITS.

SEFALer units maintain communication through the service's web page and email, **sefaler@CIBERER.es**, which includes information about its activity, acting like a networking service. They also hold group meetings, taking advantage of the annual CIBERER meetings and SEFALer training courses.

SEFALer units can act in a coordinated manner to share animals and perform complete phenotyping on the animal model.

OBJECTIVE 3 TO IMPROVE RELATIONS WITH OTHER CIBER OR RETICS GROUPS

In 2014 relations were maintained with research support groups and services that are outside CIBERER, belonging to other CIBERS or RETICS and performing phenotyping activities on animal models for the mid-term establishment of a national animal model phenotyping network, particularly for rare diseases. The biggest upcoming challenge will be to integrate new nodes in the new CIBER structure that this CIBERER is a part of.

OBJECTIVE 4.- TO IMPROVE EXPOSURE OF SEFALER ACTIVITY.

The SEFALer **web page was kept updated** in 2014 with monthly notifications and information useful for CIBERER researchers. Relevant service activity has also been included in the "highlighted information" section on the CIBERER portal (publications, organisation of training courses, participation in events, etc.). It can be asserted that the knowledge possessed by CIBERER units about the SEFALer activity and offer has considerably increased this year. Proof of this is the increase in applications for trials by CIBERER researchers.

In addition, **continuous presence in different scientific forums and associations** relating to animal experiments, animal models, biomedical research, research on rare diseases, etc., was maintained.

Part of the result of this exposure of the platform and the new relations created by SEFALer units with other research groups and centres, and obviously on the basis of experience and high scientific quality of the researchers, the involvement of SEFALer in important research projects, in international networks and in national and international preclinical and clinical trials is increasingly more well-known. The following can be highlighted from 2014:

- **SEFALer Unit F1**- Dr. Isabel Varela-U761: Coordinates the Marie Curie "TARGEAR" project focusing on the study of hypoacusia by combining basic research with result transfer and translation activities as well as training activities for young researchers.
- **SEFALer Unit F2**- Dr. Eduardo Salido-U740. This unit collaborates in three projects, contributing experience in histopathological diagnosis. It collaborates with Dr. Juan Antonio Bueren' group -U710 in the project entitled "Evaluación de estudios de terapia celular basada en hepatocitos derivados de células iPS". The other two are preclinical trials for assessing new therapies for primary hyperoxaluria.
- **SEFALer Unit F3**- Dr. Cristina Fillat and Dr. Mara Dierssen-U716: Participates in a European obsessive-compulsive disorder phenotyping project and in a clinical trial: "Use of epigallocatechin gallate in modulating Dyrk1A and APP and assess its impact on the cognitive performance in patients with Down syndrome ".
- **SEFALer Unit F4**- Dr. Consuelo González Manchón U734: Participates in several national projects as well as projects funded by private foundations for the study of rare diseases of a haematological origin.
- **SEFALer Unit F5**- Dr. Aurora Pujol Onofre-U759: Participates in several national projects, European projects and projects funded by private foundations: "Pharmacological strategies targeting mitochondria for adrenoleukodystrophy", "Advanced chemical technologies and predictive experimental models leading to new treatments against rare diseases", "Phase II international, multicentric clinical trial with MD1003 for adrenomyeloneuropathy patients" and "Mechanism of action of MD1003 in mouse and cellular models of adrenoleukodystrophy",; "Pharmacological strategies for myelin regeneration and axon protection in X-ALD" or "Functional proteomics approach towards deciphering molecular pathology of adrenomyeloneuropathy", among others.

  Furthermore it participates in a Phase II clinical trial with the orphan drug pioglitazone (designation obtained in January 2014) and in an international and multicentre clinical trial.
- **SEFALer Unit F6**- Dr. Lluis Montoliu-U756: Participates in and coordinates the project of the Community of Madrid Visionanimal-CM, aimed at the generation and study of animal models for the study of vision diseases.

OBJECTIVE 5.- TO MAINTAIN AND ENHANCE THE ADVISORY AND INFORMATIVE ACTIVITIES.

The SEFALer portal is a fundamental tool for the network. In 2014, the "News" and "Courses, Conferences and Workshops" section **has been maintained and periodically updated** with information of interest about phenotyping with the collaboration of CIBERER managers. Presentations of training courses organised by SEFALer have also been added to the web page.

Queries **made by CIBERER researchers** and by researchers outside CIBERER relating to animal model phenotyping, primarily by direct telephone contact and by e-mail at **sefaler@CIBERER.es** have also been attended to. Thus, for example, advisory services have been provided concerning optimisation of protocols for taking blood, obtaining platelets from mice, and platelet aggregation assays by means of flow cytometry to Dr. José González Castaño's group in CIBERNED.

OBJECTIVE 6.- TO MAINTAIN AND IMPROVE THE TRAINING PLAN.

SEFALer continues giving at least one annual course on animal model phenotyping. The 5th instalment of the "Animal Model Phenotyping" course was successfully held in November 2014, in which several SEFALer units participated.

Bioinformatics Platform for Rare Diseases (BIER)

The Bioinformatics Platform for Rare Diseases (BIER) is a transverse Work Group whose primary mission is to collaborate with the experimental groups working with genomic data, offering them both IT and scientific support for the analysis and interpretation of said data.

The basis for this platform is the technical knowledge and strong lines of research of the CIBERER bioinformatics groups: functional genomics and genomic, transcriptomic and massive sequencing data analysis conducted by U715, led by Dr. Joaquín Dopazo, and the experience in proteomics and systems biology conducted by U741, led by Dr. Francisca Sánchez.

BIER began operating in 2012 and has become a binding and synergistic element within CIBERER. This involves promoting the formation of small temporary groups to work on common collaborative projects and incorporating groups with bioinformatic-related interests into the collaboration structure of the BIER.

Massive sequencing has led to a new generation of data in many CIBERER group laboratories that is hard to handle, hard to interpret, and requires bioinformatics. This trend is also a clearly growing trend. In 2011 CIBERER started up a **Programme on "Genes in Undiagnosed Rare Diseases"** that has led to a series of projects to reinforce the lines of work of the research groups in this regard to respond to a cases of samples from patients that still had no identified genetic diagnosis.

Finally, the peculiarity of RDs is that the availability of few samples in a genomic scenario requires developing methodologies of analysis and specific bioinformatic tools that are not available in conventional bioinformatics.

In this regard, the actions performed by the platform in 2014 include:

OBJECTIVE 1: TO GIVE EXPOSURE TO BIER, BOTH WITHIN CIBERER AND OUTSIDE IT:

- Maintain the specific informative web page with available analysis tools
- Launch of a tool for filtering genomic variants, BIERapp:

  http://bierapp.babelomics.org/ An interactive application for giving priority to candidate genes in whole exome sequencing studies.
- The system facilitating and enabling support for groups was maintained, primarily based on a collaborative plan, within the possibilities of the BIER.

OBJECTIVE 2: TO SUPPORT CIBERER'S WORK IN TOP-LEVEL COMPETITIVE STRATEGIC FIELDS:

- Support was offered to analyze ultrasequencing data of the CNAG (National Genomic Analysis Centre) and MGP (Medical Genome Product) from the familial genomic analysis project initiative promoted by CIBERER.
- More specific support was offered in the required cases: support at different levels, starting with primary data processing up until applying more sophisticated techniques with predictive target function and locating potential, such as applying different functional prediction methods and other methods based on interaction network mining, for example.

- Large-scale genotyping, transcriptomics with microarrays or RNA-seq, proteome analysis and their projection on interactomes, etc., were performed for some projects.

OBJECTIVE 3: TO GENERATE ADDED VALUE BY ENCOURAGING COLLABORATIONS BETWEEN CIBERER GROUPS.

This objective contemplates collaboration with CIBERER research groups for the joint development of intramural research projects and other types of research projects.

Several levels of aid offered throughout 2014 stand out among the collaborations with CIBERER groups:

- Advisory projects: BIER offered advisory services about analysis tools to be used to groups of expertise.
- Support projects: BIER has provided support and been involved in analyzing genomic data of one or several groups.
- Development projects: CIBERER groups suggested a development that BIER carried out.

The BIER platform aspires to have a high degree of interaction with Orphanet because a great deal of the information contained in this international database can be used for completing information about RDs and their possible aetiologies, genetic origin, symptomatology interrelation, etc., enabling an integrative study of diseases. In addition, many of the analysis tools could in turn be implemented in Orphanet. For now, this interrelation is still incipient.

Publications as a direct result of BIER activity, beyond those led by the groups with support of the filtering and interpretation of data done by BIER, are:

The role of the interactome in the maintenance of deleterious variability in human populations. Garcia-Alonso L, Jiménez-Almazán J, Carbonell-Caballero J, Vela-Boza A, Santoyo-López J, Antiñolo G, Dopazo J. Mol Syst Biol. 2014 Sep 26;10:752. doi: 10.15252/msb.20145222.

Acceleration of short and long DNA read mapping without loss of accuracy using suffix array. Tárraga J, Arnau V, Martínez H, Moreno R, Cazorla D, Salavert-Torres J, Blanquer-Espert I, Dopazo J, Medina I. Bioinformatics. 2014 Dec 1;30(23):3396-8. doi: 10.1093/bioinformatics/btu553. Epub 2014 Aug 20.

A web tool for the design and management of panels of genes for targeted enrichment and massive sequencing for clinical applications. Alemán A, Garcia-Garcia F, Medina I, Dopazo J. Nucleic Acids Res. 2014 Jul;42(Web Server issue):W83-7. doi: 10.1093/nar/gku472. Epub 2014 May 26.

A web-based interactive framework to assist in the prioritization of disease candidate genes in whole-exome sequencing studies. Alemán A, Garcia-Garcia F, Salavert F, Medina I, Dopazo J. Nucleic Acids Res. 2014 Jul;42(Web Server issue):W88-93. doi: 10.1093/nar/gku407. Epub 2014 May 6.

Combined genetic and high-throughput strategies for molecular diagnosis of inherited retinal dystrophies. de Castro-Miró M, Pomares E, Lorés-Motta L, Tonda R, Dopazo J, Marfany G, Gonzàlez-Duarte R. PLoS One. 2014 Feb 7;9(2):e88410. doi: 10.1371/journal.pone.0088410. eCollection 2014. Erratum in: PLoS One. 2014;9(6):e101641.

PROTEOmAb

PROTEOmAb is an energy metabolism phenotyping platform using protein array technology. It is located in CIBERER unit U713 Centro de Biología Molecular Severo Ochoa UAM and is led by Dr. José María Cuezva. The group has ample experience in this methodology that it has been offering as a service to the scientific community since 2012. It offers a service comprising the quantitative analysis of energy metabolism proteins in biological samples in a simple and reproducible manner using high-affinity and high-specificity monoclonal antibodies (mAbs).

METHODOLOGY: The analyses can be done on collections of up to 1,000 different biopsies, which allows establishing correlations with clinical parameters and parameters of response to certain treatments. A reverse-phase protein microarray platform is used, which allows quantifying the expression of energy metabolism proteins in biopsies of normal and pathological tissues.

PROTEOMAB SERVICES:

- Identification and validation of molecular markers of the disease and of the response to therapy.
- Identification of new diagnostic markers.
- Establishing correlations between biomarkers and disease progression.
- Establishing correlations between biomarkers and response to a specific treatment.

PROTEOMAB COLLABORATIONS/SERVICE DEVELOPED

Collaborations have been established with various CIBER groups and with other institutions:

- Dr. Francesc Palau-U732. -Pathology studied: Charcot-Marie Tooth.
- Dr. José María Millán-U755.- Pathology studied: Retinitis Pigmentosa.
- Dr. Lourdes Ruiz Desviat-U746 and Dr. Barry Michel, Clinical Mayo, Rochester, USA. Pathology studied: Propionic acidemia.
- Dr. Francesc Cardellach-U722. Pathology studied: Myositis in all its variants: dermatomyositis, polymyositis and myositis with inclusion bodies.
- Dr. Miguel A. Martín Casanueva-U723. Pathology studied: Mitochondriopathies due to Complex I deficiency.

5. RESEARCH GROUPS

Group U701

Programme: Mitochondrial and Neuromuscular Medicine

Lead Researcher: Martí Seves, Ramon

Group Members

STAFF MEMBERS: Camara Navarro, Yolanda | Pinos Figueras, Tomas

ASSOCIATED MEMBERS: Andreu Periz, Antonio Luis | Brull Cañagueral, Astrid | Carreño Gago, Lidia | García Arumi, Elena | Melia 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 dystrophhy caused by mutations in the TNPO3 gene (LGMD1F).

Most relevant scientific articles

- Cámara Y, González-Vioque E, Scarpelli M, Torres-Torronteras J, Caballero A, Hirano M, Martí R. Administration of deoxyribonucleosides or inhibition of their catabolism as a pharmacological approach for mitochondrial DNA depletion syndrome. Hum Mol Genet. 2014 May 1;23(9):2459-67. doi: 10.1093/hmg/ddt641.
- Torres-Torronteras J, Viscomi C, Cabrera-Pérez R, Cámara Y, Di Meo I, Barquinero J, Auricchio A, Pizzorno G, Hirano M, Zeviani M, Martí R. Gene therapy using a liver-targeted AAV vector restores nucleoside and nucleotide homeostasis in a murine model of MNGIE. Mol Ther. 2014 May;22(5):901-7. doi: 10.1038/mt.2014.6.
- Nogales-Gadea G, Santalla A, Brull A, de Luna N, Lucía A, Pinós T. The pathogenomics of McArdle disease-genes, enzymes, models, and therapeutic implications. J Inherit Metab Dis. 2015 Mar;38(2):221-30. doi: 10.1007/s10545-014-9743-2.
- Meseguer S, Martínez-Zamora A, García-Arumí E, Andreu AL, Armengod ME. The ROS-sensitive microRNA-9/9* controls the expression of mitochondrial tRNA-modifying enzymes and is involved in the molecular mechanism of MELAS syndrome. Hum Mol Genet. 2015 Jan 1;24(1):167-84. doi: 10.1093/hmg/ddu427.
- Santalla A, Nogales-Gadea G, Ørtenblad N, Brull A, de Luna N, Pinós T, Lucía A. McArdle disease: a unique study model in sports medicine. Sports Med. 2014 Nov;44(11):1531-44. doi: 10.1007/s40279-014-0223-5.

Highlights

During 2014 we have advanced significantly in our research lines devoted to study therapeutic strategies for different forms of mitochondrial DNA (mtDNA) depletion and deletions syndromes (MDDS). On the one hand, based on our results (Cámara et al, Hum Mol Genet 2014), we have proposed a new therapy for MDDS caused by changes in nucleotide metabolism based on the administration of nucleoside or by inhibiting their catabolism. Moreover, we demonstrated the feasibility of gene therapy for MNGIE using an adeno-associated vector (Torres-Torronteras et al, Mol Ther 2014), which improves the results obtained with another vector (Torres-Torronteras et al, Gene Ther 2011) in terms of biosafety and efficacy.

Also, in the field of MDDS, we are positioned as national experts and we are fostering collaboration with other CIBERER (723, 762, 727, 722, 714) groups. Our group is currently coordinating an international consortium for the implementation of a clinical trial using gene therapy for MNGIE, project proposal sent to H2020 (second stage in the topic New Therapies for rare diseases) using a vector for which we have recently obtained the orphan drug designation by the EMA (August 2014 EU / 3/14/1326) and the FDA (September, 2014, number 14-4410).

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Group U702

Programme: Genetic Medicine

Lead Researcher: Antiñolo, Guillermo

Group Members

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

ASSOCIATED MEMBERS: Borrego López, Salud | Bravo Gil, Nereida | Enguix Riego, María del Valle | González del Pozo, María | López Alonso, Manuel | Lozano Arana, María Dolores | Marcos Luque, Irene | Navarro González, Elena | Peciña López, Ana María | Rueda Rueda, Trinidad | Santoyo López, Javier | Torroglosa González, Ana

Main lines of research

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

Most relevant scientific articles

- Garcia-Alonso L, Jiménez-Almazán J, Carbonell-Caballero J, Vela-Boza A, Santoyo-Lopez J, Antinolo G, et al. The role of the interactome in the maintenance of deleterious variability in human populations. Molecular systems biology. 2014;10:752. PubMed PMID: 25261458. Pubmed Central PMCID: 4299661.
- Garcia-Diaz L, de Agustin JC, Ontanilla A, Marenco ML, Pavon A, Losada A, et al. EXIT procedure in twin pregnancy: a series of three cases from a single center. BMC pregnancy and childbirth. 2014;14:252. PubMed PMID: 25078677. Pubmed Central PMCID: 4124143.
- Gonzalez-del Pozo M, Mendez-Vidal C, Bravo-Gil N, Vela-Boza A, Dopazo J, Borrego S, et al. Exome sequencing reveals novel and recurrent mutations with clinical significance in inherited retinal dystrophies. PloS one. 2014;9(12):e116176. PubMed PMID: 25544989. Pubmed Central PMCID: 4278866.
- Lecerf L, Kavo A, Ruiz-Ferrer M, Baral V, Watanabe Y, Chaoui A, et al. An impairment of long distance SOX10 regulatory elements underlies isolated Hirschsprung disease. Human mutation. 2014 Mar;35(3):303-7. PubMed PMID: 24357527.
- Torroglosa A, Enguix-Riego MV, Fernandez RM, Roman-Rodríguez FJ, Moya-Jiménez MJ, de Agustin JC, et al. Involvement of DNMT3B in the pathogenesis of Hirschsprung disease and its possible role as a regulator of neurogenesis in the human enteric nervous system. Genetics in medicine : official journal of the American College of Medical Genetics. 2014 Sep;16(9):703-10. PubMed PMID: 24577265.

Highlights

The main research lines have been funded by external agencies (public and private) through 9 projects (including one Intrasalud project), and one ACCI project in collaboration with other CIBERER units. It is worth mentioning the collaboration of Guillermo Antiñolo and Salud Borrego in "Multidisciplinary Action on rare diseases and Personalized Medicine" (CDTI-FEDER-Innterconecta). His participation as Scientific Director of The Medical Genome Project (2010-2013) has contributed to the generation of the Exome Server. As for the translational research, it is remarkable the use of targeted NGS as a new tool for the genetic diagnosis of inherited retinal dystrophies. It should be noted the transfer of these outcomes to Sistemas Genómicos, S.L., which commercializes this panel with diagnostic purposes. Regarding the study of Hirschsprung disease (HSCR), a customized NGS panel has been validated. This has improved our knowledge about the genetic background of our HSCR patients. In addition, another 2 customized NGS panels, one for hereditary colon cancer and another for familial adenomatous polyposis haven been implemented.

The group has also developed new highly complex applications in fetal therapy, including an ex-utero intrapartum therapy (EXIT) procedure for a twin pregnancy with severe congenital diaphragmatic hernia.

A new experimental model has been generated, based on the isolation of enteric precursors from mice for studies with DNMT3B, a new gene linked to the ethiopathogenesis of HSCR through epigenetic processes. Additionally, a ChIP-Seq protocol has been optimized for the study of HSCR using neurospheres isolated from mice guts.

Finally, a clinical guide for FMR1-associated diseases (X-Fragile syndrome, primary ovarian insufficiency and tremor/ataxia syndrome), in collaboration with other CIBERER units has been published. In addition, the group participates in the registry of genetic variants on germinal line in Spanish patients. Also, three new medical consultations for pheochromocytomas, paragangliomas and congenital cardiopathies have been implemented in 2014.

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Group U703

Programme: Inherited Metabolic Medicine

Lead Researcher: Artuch, Rafael

Group Members

STAFF MEMBERS: Casado Río, Mercedes | Montero Sánchez, Raquel

AT THE EXPENSE OF THE PROJECT: González, Mª Julieta | Nafría Escalera, Begonya.

ASSOCIATED MEMBERS: Campistol Plana, Jaume | Fons Estupiña, María del Carmen | García Cazorla, María Ángeles | Jiménez Mallebrera, Cecilia | Martorell Sampol, Loreto | Nascimento Osorio, Andrés | Ormazabal Herrero, Aida | Pérez Dueñas, Belén

Main lines of research

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

Most relevant scientific articles

- Mutations in the lipoyltransferase LIPT1 gene cause a fatal disease associated with a specific lipoylation defect of the 2-ketoacid dehydrogenase complexes. Tort F, Ferrer-Cortès X, Thió M, Navarro-Sastre A, Matalonga L, Quintana E, Bujan N, Arias A, García-Villoria J, Acquaviva C, Vianey-Saban C, Artuch R, García-Cazorla À, Briones P, Ribes A. Hum Mol Genet; 2014 Apr 1. 23(7):1907-15.
- Two novel mutations in the BCKDK (branched-chain keto-acid dehydrogenase kinase) gene are responsible for a neurobehavioral deficit in two pediatric unrelated patients. García-Cazorla A, Oyarzabal A, Fort J, Robles C, Castejón E, Ruiz-Sala P, Bodoy S, Merinero B, Lopez-Sala A, Dopazo J, Nunes V, Ugarte M, Artuch R, Palacín M, Rodríguez-Pombo P, Alcaide P, Navarrete R, Sanz P, Font-Llitjós M, Vilaseca MA, Ormaizabal A, Pristoupilova A, Agulló SB. Hum Mutat; 2014 Apr. 35(4):470-7
- Follow-up of folinic acid supplementation for patients with cerebral folate deficiency and Kearns-Sayre syndrome. Quijada-Fraile P, O Callaghan M, Martín-Hernández E, Montero R, Garcia-Cazorla À, de Aragón A, Muchart J, Málaga I, Pardo R, García-Gonzalez P, Jou C, Montoya J, Emperador S, Ruiz-Pesini E, Arenas J, Martin M, Ormazabal A, Pineda M, García-Silva MT, Artuch R. Orphanet J Rare Dis; 2014 Dec 24. [Epub ahead of print];
- A capillary electrophoresis procedure for the screening of oligosaccharidoses and related diseases. Casado M, Altimira L, Montero R, Castejón E, Nascimento A, Pérez-Dueñas B, Ormazabal A, Artuch R Anal Bioanal Chem; 2014 Jul. 406(18):4337-43.
- Transcriptomic profiling of TK2 deficient human skeletal muscle suggests a role for the p53 signalling pathway and identifies growth and differentiation factor-15 as a potential novel biomarker for mitochondrial myopathies. Kalko SG, Paco S, Jou C, Rodríguez MA, Meznaric M, Rogac M, Jekovec-Vrhovsek M, Sciacco M, Moggio M, Fagiolari G, De Paepe B, De Meirleir L, Ferrer I, Roig-Quilis M, Munell F, Montoya J, López-Gallardo E, Ruiz-Pesini E, Artuch R, Montero R, Torner F, Nascimento A, Ortez C, Colomer J, Jiménez-Mallebrera C BMC Genomics; 2014 15:91.

Highlights

In 2015, we have found 2 new research projects, that it will lead us to cosolidate 2 research lines: 1) the congenital disorders of glycosylation and 2) the Analyses of different biochemical markes in cerebrospinal fluid for the study of neuropediatric diseases.

The collaborations of our gruop inside the CIBERER have been growing in the last years, and include gruops 705, 708, 715, 717, 720, 722, 723, 726, 727, 730, 731, 732, 736, 737, 746, 753, 759. We have also participate in teh creation and consolidation of the first Spanish Unit for the follow-up of adult patients with inborn errors of metabolism, together with the Hospital Clinic and IBC from Barcelona. Our group has been designed as one of the 2 reference centers in Catalonia for the clinical management of patients with inborn errors of metabolism detected in the expanded newborn screening program (since february 2013). We also have stable and godo collaborations with several clinical groups recently associated with the CIBERER (GCV03, 05, 07, 08, 09 and 10).

Regarding the future actions, our Hospital is sufering a deep transformation with the creation of a new Pediatric Institute for rare diseases, which will include 5 areas: 1) Assistential, 2) Diagnostic platforms. 3) research. 4) Big data. 5) Family associations and other social groups relationship. Inside this institute, our research line will be inborn errors of metabolism but we will reinforce the genetic diagnosis of these diseases. Furthermore, the clinical trials in inborn errors of metabolism will be one of our main interests.

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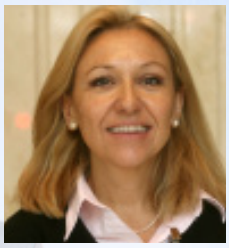
Group U704

Programme: Sensorineural Pathology



Lead Researcher: Ayuso, Carmen

Group Members

STAFF MEMBERS: Avila Fernández , Almudena | Zurita Muñoz, Olga

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

Main lines of research

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

Most relevant scientific articles

- Corton M, Avila-Fernandez A, Vallespín E, López-Molina MI, Almoguera B, Martín-Garrido E, Tatu SD, Imran Khan M, Blanco-Kelly F, Riveiro-Alvarez R, Brión M, García-Sandoval B, P.M. Cremers F, Carracedo A, Ayuso C. Involvement of LCA5 in Leber Congenital Amaurosis and Retinitis Pigmentosa in the Spanish Population. Ophthalmology 2014 Jan;121(1):399-407 Epub 2013 Oct 18 PMID: 24144451 doi:pii: S0161-6420(13)00776-8. 10.1016/j.ophtha.2013.08.028. IF(2013): 6,170 5-Year Impact Factor (2013): 6,195 Q(2013) Q1 D1 (2:58)
- Dal-Ré Rafael, Katsanis Nicholas, Katsanis Sara, Parker Lisa S, Ayuso C. Managing incidental genomic findings in clinical trials: fulfillment of the principle of justice in human subjects research. PLoS Medicine. 2014 Jan 11;1:e1001584. PMID: 24453945. IF(2013): 14,000 5-Year Impact Factor (2013): 17,945 Q(2013) Q1 D1 (6:156)
- Nishiguchi KM; Avila-Fernandez A; van Huet RAC, Corton M, Perez-Carro R, Martin-Garrido E, Lopez-Molina MI, Blanco-Kelly F, Hoefsloot LH, van Zelst-Stams WA, Garcia-Ruiz PJ, del Val J, Di Gioia SA, Klevering BJ, van de Warrenburg Bart PC, Vazquez C, Cremers FPM, Garcia-Sandoval B, Hoyng CB, Collin RWJ, Rivolta C , Ayuso C. Exome sequencing extends the phenotypic spectrum for ABHD12 mutations: from syndrome to non-syndromic retinal degeneration. Ophthalmology 2014 Mar 31 S0161-6420(14)00138-9 PMID: 24697911. IF(2013): 6,170 5-Year Impact Factor (2013): 6,195 Q(2013) Q1 D1 (2:58)
- Sánchez-Alcudia R, Corton M, Avila-Fernandez A, Zurita O, Tatu SD, Perez-Carro R, Fernandez-San Jose P, Lopez-Martinez MA, Del Castillo FJ, Millan JM, Blanco-Kelly F, Garcia-Sandoval B, Lopez-Molina MI, Riveiro-Alvarez R, Ayuso C. Contribution of mutation load to the intrafamilial genetic heterogeneity in a large cohort of Spanish retinal dystrophies families. Invest Ophthalmol Vis Sci. 2014 Oct 23. 55(11):7562-71: doi: 10.1167/iovs.14-14938. PMID: 25342620. IF(2013): 3,661 5-Year Impact Factor (2013): 3,754 Q(2013) D1 (6:58)
- Ayuso C, Millan JM, Dal-Re R. Management and return of incidental genomic findings in clinical trials. Pharmacogenomics J. 2014 Oct 28 . PMID: 25348616. IF(2013): 5,513 5-Year Impact Factor (2013): 4,531 Q(2013) Q1 D1 (14:256)

Highlights

The U704 is set up by a group of professionals with a wide experience in research projects, mainly coordinated and translational. The U704 contributes to the study of many hereditary diseases and is crucial for the clinical activity (diagnosis and prevention of genetic diseases) and for the development of research by other CIBERER groups with which it collaborates. It contributes to the translation into clinical practice applied to hereditary diseases (Ophthalmology, Oncology, Neuroscience, Cardiovascular, Reproductive and Fetal Health) by developing algorithms and diagnostic techniques, new therapies (cellular, genetic and pharmacological) and prevention strategies for comprehensive patient care.

Among 2014, the group's activity has allowed the implementation of new technologies, as next generation sequencing (NGS) and CGH array, to the genetic study of Rare Diseases leading to a fast and cost-efficient diagnosis. Five panel genes (NGS) have been validated for clinical practice (Macular Dystrophies, Retinitis Pigmentosa, Heart Disease, Oncogenetics and Eye Malformations) and the diagnostic algorithms have been combined with array CGH to detect genomic deletions-inserts.

The application of Whole Exome Sequencing (WES) in patients affected by different rare diseases as ophthalmogenetic disorders, main line of research, has allowed establishing new genotype-phenotype associations, in collaboration with national and international groups, and identifying new genes as cause of different rare diseases.

Currently, U704 is part of two European projects:

1) New cost-effective techniques by the use of gene panels (NGS) applying the Molecular Inversion Probes (MIPs) technique as part of the European Retinal Diseases Consortium (ERDC).
2) WGS as a strategy for identifying new genetic alterations in monogenic diseases (NEXOME Project, Prof Carlo Rivolta, Lausanne University).

In collaboration with other CIBERER groups has been involved in legal ethics-translational aspects of the massive sequencing (U755), in the ethical and legal aspects of genetic databases (U711) and in the design of informed consent and ethical-legal studies (SPANEX Project).

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Group U705

Programme: Genetic Medicine

Lead Researcher: Baiget Bastus, Montserrat

Group Members

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

ASSOCIATED MEMBERS: Barceló Rubira, María Jesús | Cornet Ciurana, Mónica | Domenech María, Montserrat | Gallano Petit, María Pia | Juan Mateu, Miquel Jonas | Lassa Laborde, Adriana | Páez López-Bravo, David | Río Conde, Elisabeth Del | Rodríguez Fernández, María José | Tizzano Ferrari, Eduardo

Main lines of research

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

Most relevant scientific articles

- "EGFR ligands and DNA repair genes: genomic predictors of complete response after capecitabine-based chemoradiotherapy in locally advanced rectal cancer." Sebio A, Salazar J, Páez D, Berenguer-Llergo A, Del Río E, Tobeña M, Martín-Richard M, Sullivan I, Targarona E, Balart J, Baiget M, Barnadas A. Pharmacogenomics J. 2015 Feb;15(1):77-83. doi: 10.1038/tpj.2014.33. PMID: 25026457.
- "Intergenic polymorphisms in the amphiregulin gene region as biomarkers in metastatic colorectal cancer patients treated with anti-EGFR plus irinotecan." Sebio A, Páez D, Salazar J, Berenguer-Llergo A, Paré-Brunet L, Lasa A, Del Río E, Tobeña M, Martín-Richard M, Baiget M, Barnadas A. Pharmacogenomics J. 2014 Jun;14(3):256-62. doi: 10.1038/tpj.2013. PMID: 23959273.
- "Pharmacogenetics of the DNA repair pathways in advanced non-small cell lung cancer patients treated with platinum-based chemotherapy." Sullivan I, Salazar J, Majem M, Pallarés C, Del Río E, Páez D, Baiget M, Barnadas A. Cancer Lett. 2014 Oct 28;353(2):160-6. doi: 10.1016/j.canlet.2014.07.023. PMID: 25069034.
- "Abnormalities in early markers of muscle involvement support a delay in myogenesis in spinal muscular atrophy." Martínez-Hernández R, Bernal S, Alias L, Tizzano EF. J Neuropathol Exp Neurol. 2014 Jun;73(6):559-67. doi: 10.1097/NEN. PMID: 24806300.
- "Improving detection and genetic counseling in carriers of spinal muscular atrophy with two copies of the SMN1 gene." Alías L, Barceló MJ, Bernal S, Martínez-Hernández R, Also-Rallo E, Vázquez C, Santana A, Milián JM, Baiget M, Tizzano EF. Clin Genet. 2014 May;85(5):470-5. doi: 10.1111/cge.12222. PMID: 23799925

Highlights

The U705 has vast experience in research and in clinical diagnosis of rare diseases, particularly in neuromuscular and hematological diseases, Pharmacogenetics and Oncogenetics.Due to the results of their research activity in 2014, the Unit has published a large number of articles in prestigious scientific journals. The capacity of attracting national and international funding is considerable both from competitive agencies (FIS/ISCIII, MICINN, MINCYT, Fundación Mutua Madrileña and SMA Europe), and also donations from private companies.

Furthermore, the Unit has worked directly with CIBERER units U702 and U715 (Program of Genetic Medicine) on the study of discordant families with neuromuscular diseases using next generation sequencing. The Unit also collaborates with other CIBERER units (U702, U755, U704, U753) working on the project "Creación de una base de datos nacional de mutaciones en línea germinal" (http://www.humanvariomeproject.org/).

On the topic of translational research, the U705 is conducting two new clinical trials in SMA, in addition to the trials that started in previous years in the field of Pharmacogenetics. The Unit also contributes to international organisations such as the DMD Registry (TREAT-NMD) and the Registry of SMA patients, and collaborates with scientific societies and patient associations (ASEM and SEN).The Unit has organized conferences and meetings, in order to raise awareness of rare diseases ("II Jornada de la Sociedad Española de Farmacogenética y Farmacogenómica", Jornada "Defining targets for therapeutics in SMA" y "XI Jornada de Actualización en Genética Humana AEGH").On a final note, the Unit continues training researchers, two of which have subsequently completed their PhD thesis, and another who has been awarded the Juan Rodés contract. The Unit coordinates the postgraduate course in Clinical Pharmacogenetics and Pharmacogenomics (IL3-UB).

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Group U706

Programme: Hereditary Cancer and Related Syndromes

Lead Researcher: Benítez, Javier

Group Members

STAFF MEMBERS: Calvete Torres, Oriol | Gayarre Navarro, Javier | Inglada Pérez, Lucía

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

Main lines of research

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

Most relevant scientific articles

- Saucedo-Cuevas, Laura P., Isabel Ruppen, Pilar Ximénez-Embún, Samuel Domingo, Javier Gayarre, Javier Muñoz, Jose M. Silva, María J. García, and Javier Benítez. CUL4A contributes to the biology of basal-like breast tumors through modulation of cell growth and antitumor immune response. Oncotarget 5, no. 8 (2014): 2330.
- Osorio, Ana, Roger L. Milne, Karoline Kuchenbaecker, Tereza Vaclová, Guillermo Pita, Rosario Alonso, Paolo Peterlongo et al. DNA glycosylases involved in Base Excision Repair may be associated with cancer risk in BRCA1 and BRCA2 mutation carriers. PLoS Genetics 10, no. 4 (2014): e1004256.
- Kamieniak, Marta M., Daniel Rico, Roger L. Milne, Ivan Muñoz-Repeto, Kristina Ibáñez, Miguel A. Grillo, Samuel Domingo et al. Deletion at 6q24. 2–26 predicts longer survival of high-grade serous epithelial ovarian cancer patients. Molecular oncology 9, no. 2 (2015): 422-436.
- Mancikova, Veronika, Raquel Buj, Esmeralda Castelblanco, Lucía Inglada-Pérez, Anna Diez, Aguirre A. Cubas, Maria Curras-Freixes et al. DNA methylation profiling of well-differentiated thyroid cancer uncovers markers of recurrence free survival. International Journal of Cancer 135, no. 3 (2014): 598-610
- Apellániz-Ruiz, M., L. Inglada-Pérez, M. E. G. Naranjo, L. Sánchez, V. Mancikova, M. Currás-Freixes, A. A. de Cubas et al. High frequency and founder effect of the CYP3A4* 20 loss-of-function allele in the Spanish population classifies CYP3A4 as a polymorphic enzyme. The pharmacogenomics Journal (2014).

Highlights

Projects. The Unit 706 obtained more tan 2M euros of funding from competitive projects that were ongoing in 2014. It is worthy to note that people funded by CIBERER participate as research team in 25% of projects.

Regarding with agreements with Pharma industry, in 2014 we had two ongoing projects (with CELGENE and Pfizer), which aims were to characterize nab-paclitaxel neurotoxicity, and to identify microRNA predictors of response to TKIs in clear cell renal cell carcinoma.

In addition, we participated in 3 intra-CIBERER initiatives, one of them acting as Coordinator.

Results. Research performed during 2014 led to: 1- identification of new susceptibility genes related to breast cancer and phenotype modulators, 2- identification of por prognosis predictors on rare diseases, 3- establish the prevalence and the effect of genetic alterations in new genes related to neuroendocrine tumours develoment, and 4- identificatio of variants in drug metabolizing enzymes associated with treatment response prediction. Our activity in 2014 has led to the identification of two new major susceptibility genes, which will be published in high impact factor journal in 2015.

Technology transfer. In 2014 we have provided services based on arrays and other high-throughput platforms to clinical groups, hospitals and Universities. The consultancy on Familial Cancer dealt with 250 patients referred by other hospitals and centers in Spain.

Clinical transfer. The U-706 has continued to participate in the development of clinical guidelines. In 2014, in the production of the Bannayan-Riley-Ruvalcaba syndrome Guide.

Training and visibility. We organized three training courses (one of them international), and an International Symposium on rare diseases. Two of them were co-financed by CIBERER. As in previous years, the training activity of the Group on rare diseases culminated with obtaining the degree of doctor by 3 students.

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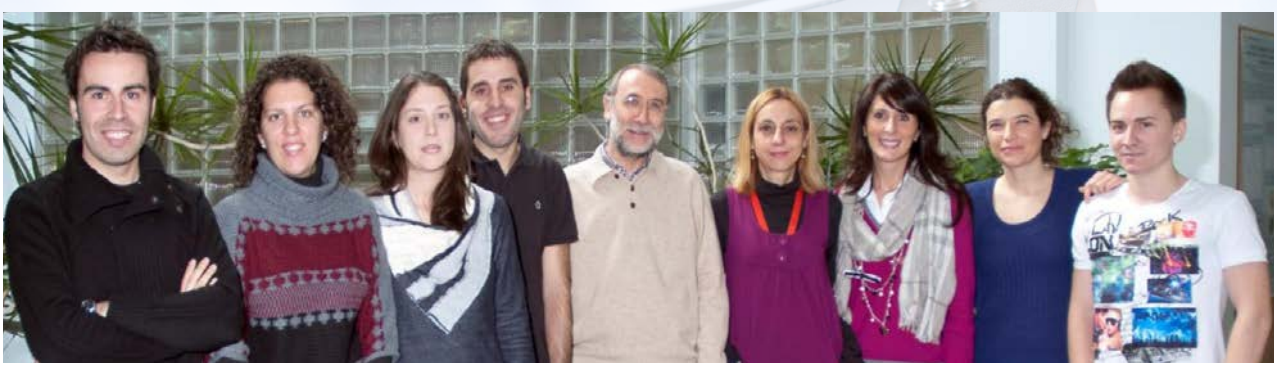
Group U707

Programme: Genetic Medicine



Lead Researcher: Bernabéu, Carmelo

Group Members

STAFF MEMBERS: Ojeda Fernández, Mª Luisa | Ruiz Llorente, Lidia

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

Main lines of research

- Studies of expression, function and structure of endoglin and ALK1 and their 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.

Most relevant scientific articles

- Pérez-Gómez E, Jerkic M, Prieto M, Del Castillo G, Martín-Villar E, Letarte M, Bernabeu C, Pérez-Barriocanal F, Quintanilla M, López-Novoa JM. Impaired Wound Repair In Adult Endoglin Heterozygous Mice Associated With Lower NO Bioavailability. J. Invest. Dermatol. (2014) 134(1): 247-255. doi: 10.1038/jid.2013.263.
- Tobar N, Avalos MC, Méndez N, Smith PC, Bernabeu C, Quintanilla M, Martínez J. Soluble MMP-14 produced by bone marrow-derived stromal cells sheds epithelial endoglin modulating the migratory properties of human breast cancer cells. Carcinogenesis. (2014) 35(8): 1770-1779. doi: 10.1093/carcin/bgu061.
- Aristorena M, Blanco FJ, de Las Casas-Engel M, Ojeda-Fernandez L, Gallardo-Vara E, Corbi A, Botella LM, Bernabeu C. Expression of endoglin isoforms in the myeloid lineage and their role during aging and macrophage polarization. J. Cell Sci. (2014) 127(Pt 12): 2723-2735. doi: 10.1242/jcs.143644.
- Oujo B, Muñoz-Félix JM, Arévalo M, Núñez-Gómez E, Pérez-Roque L, Pericacho M, González-Núñez M, Langa C, Martínez-Salgado C, Perez-Barriocanal F, Bernabeu C, Lopez-Novoa JM. L-Endoglin Overexpression Increases Renal Fibrosis after Unilateral Ureteral Obstruction. PLoS One. (2014) Oct 14; 9(10): e110365. doi: 10.1371/journal.pone.0110365. eCollection 2014.

Highlights

- HHT NETWORK. In order to create a Spanish network of clinical units in Hereditary Hemorrhagic Telangiectasia (HHT), we have organized, with the support of CIBERER and the Spanish Society of Internal Medicine, a meeting in Madrid (December 2014) where clinicians from different hospitals in Spain and Portugal, as well as representatives of Patients Associations, shared their experience. An agreement was reached regarding HHT assessment protocols, establishing a solid base to create a clinical network of HHT.
- ORPHAN DRUG. In November 2014, we managed to obtain the designation by the EMA (European Medicines Agency) of Bazedoxifene acetate (Conbriza) as an orphan drug for HHT. We are currently negotiating with Pfizer the development of a clinical trial.
- PATHOGENIC MECHANISM. We have made progress in understanding the role of endoglin, a protein that is mutated in HHT. We have characterized its functional involvement in the myeloid lineage (monocytes and macrophages) and we have described that haploinsufficiency of endoglin interferes with the wound repair mechanism. We have also described the implication of soluble endoglin in the migration of breast cancer cells and that overexpression of endoglin increases renal fibrosis after unilateral ureteral obstruction.
- PARTNERSHIPS AND OTHERS. We have maintained an active collaboration with the the Spanish Patient Association of HHT, FEDER, European associations of HHT through EURORDIS and the American international association. We have actively participated in the presentation of results in various scientific conferences. In 2014, Carmelo Bernabeu received funding from the National Plan (SAF2013-43421-R) to continue studies of HHT genes until the end of 2016. In October 2014, we received the Prize Iñigo Alvarez de Toledo (XXV edition) to the Basic Research in Nephrology through labor "Oxysterol-induced soluble endoglin release and Its Involvement in hypertension".

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Group U708

Programme: Endocrine Medicine

Lead Researcher: Bernal, Juan

Group Members

STAFF MEMBERS: Morte Molina, Beatriz

ASSOCIATED MEMBERS: Gil Ibáñez, Pilar | Guadaño Ferraz, Ana Cristina | Martn Belinchon, Mónica

Main lines of research

- CONGENITAL HYPOTHYRODISM: Mechanisms of action of the thyroid hormone in the brain. Physiopathology of neural alterations over thyroid hormone deprivation during the fetal and neonatal periods. Influence of maternal thyroid hormones and consequences of maternal hypotiroxinemia over gene expression in the fetal brain.
- SLC16A2 MUTATIONS: Physiopathology of the Allan-Herndon-Dudley syndrome and deficiency of T3 transport in the syndrome using transporter knock out mice. Development of new therapeutic approaches based on thyroid hormone analogues with alternative transport.
- 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

- López-Espíndola D, Morales-Bastos C, Grijota-Martínez C, Liao XH, Lev D, Sugo E, Verge CF, Refetoff S, Bernal J, Guadaño-Ferraz A. Mutations of the thyroid hormone transporter MCT8 cause prenatal brain damage and persistent hypomyelination. J Clin Endocrinol Metab. 2014;99(12):E2799-804.
- Núñez B, Martínez de Mena R, Obregon MJ, Font-Llitjós M, Nunes V, Palacín M, Dumitrescu AM, Morte B, Bernal J. Cerebral cortex hyperthyroidism of newborn mct8-deficient mice transiently suppressed by lat2 inactivation. PLoS One. 2014;9(5):e96915.
- Navarro D, Alvarado M, Morte B, Berbel D, Sesma J, Pacheco P, Morreale de Escobar G, Bernal J, Berbel P. Late maternal hypothyroidism alters the expression of Camk4 in neocortical subplate neurons: a comparison with Nurr1 labeling. Cereb Cortex. 2014;24(10):2694-706.
- Gil-Ibáñez P, Bernal J, Morte B. Thyroid hormone regulation of gene expression in primary cerebrocortical cells: role of thyroid hormone receptor subtypes and interactions with retinoic acid and glucocorticoids. PLoS One. 2014;9(3):e91692.
- Morte B, Bernal J. Thyroid hormone action: astrocyte-neuron communication.Front Endocrinol (Lausanne). 2014;5:82.

Highlights

The Ciberer group 708 works in three rare diseases due to defects of thyroid hormone signaling: Congenital hypothyroidism, Syndromes of Resistance to thyroid hormones due to receptor mutations, and Allan-Herndon-Dudley syndrome, due to mutations in the thyroid hormone transporter MCT8/SLC16A2. We use animal models to understand the pathophysiology of the syndrome, and we have contributed with contributions that have enhanced our knowledge of these diseases and also of normal physiology. We collaborated with U730 and U731 in one Doctoral Thesis.

We also provide genetic diagnosis of MCT8, THRA and THRB mutations, and counseling. Of special relevance, we have diagnosed the first case in Spain, and most cases diagnosed to date.

Juan Bernal Has participated in the International Committee for the classification and nomenclature of these syndromes, and has organized the 11th International Workshop on Thyroid Hormone Resistance and Thyroid Hormone Action in September 2014, in El Escorial, with support from patients families (Sherman Family), Mapfre Foundation, Ciberer, and the European and American Thyroid Associations. Collaborating with Ciberer, Fulbright Foundation, and U753 we organized a workshop at the Hospital La Paz. Group 708 is one of the few groups from Ciberer participating in an E-RARE proyect (2014-2017). It is very well positioned internationally in the study of the Allan-Herndon-Dudley syndrome (presently is writing an invited review for Nature Reviews in Endocrinology), and collaborates with the Sherman Family Association. Collaborates with Prof Refetoff (Chicago) and Dr Moreno (INGEMM) in therapy development, and is the only group in the world with brain samples (from Australia) suitable for histopathology.

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Group U709

Programme: Sensorineural Pathology

Lead Researcher: Bovolenta, Paola

Group Members

STAFF MEMBERS: Sandonís Consuegra, África

ASSOCIATED MEMBERS: Cardozo Ruiz, Marcos Julian | Esteve Pastor, Pilar

Main lines of research

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

Most relevant scientific articles

- Gayarre J*, Duran-Trío, L.*, Criado Garcia O.*, Aguado C, Juana-López L., Crespo I., Knecht E., Bovolenta P. and Rodríguez de Córdoba S. (2014) The glycogen phosphatase activity of laforin is dispensable to rescue the Lafora disease phenotype of Epm2a-/- mice. Brain 137, 806-18. (Comment in Brain 137, 646-648)
- Conte I, Merella S., Garcia Manteiga JM, Migliore C., Lazarevic D., Carrella S, Marco-Ferreres R., Avellino R., Emmett W., Sanges R., Bockett N., Van Heel D., Meroni G., Bovolenta P., Banfi S., Stupka E. (2014) The combination of transcriptomics and informatics identifies pathways targeted by miR-204 during neurogenesis and axon guidance. Nuc. Acid Res. 42, 7793-806.
- Cardozo M., Sánchez-Arrones L., Sandonis A., Sánchez-Camacho C., Gestri G., Wilson SW, Guerrero, I. and Bovolenta P. (2014) Cdon acts as a Hedgehog decoy receptor during proximal-distal patterning of the optic vesicle. Nature Comm. 5:4272. doi: 10.1038/ncomms5272. (Selected in The Faculty of 1000)
- Cavodeassi F and Bovolenta P. (2014) New functions for old genes: Pax6 and Mitf in eye pigment biogenesis. Pigment Cell & Melanoma Res. 27, 1005-1007.
- Bovolenta, P., Gorny, A., Esteve P. and Steinbeisser, H. (2014). Secreted Wnt inhibitors or modulators. Chapter 13 in "Wnt Signaling in Development and Disease: Molecular Mechanisms and Biological Functions. Stefan Hoppler and Randall T Moon, Editors.

Highlights

Our group investigates the mechanisms that control the early development of the vertebrate nervous system, mostly focusing on the visual system. We are particularly interested in those aspects that may help pinpointing the causes of congenital malformations or those related to the onset of neurodegenerative diseases. During this period, we have identified a new role for Boc and Cdon, two cell adhesion molecules that bind the morphogen Shh. During eye development these molecules are mostly localised to the basal end-foot of neuroepithelial cells favouring the enlargement of the basal site and the formation/stabilization of filopodial-like processes. In this location, Cdon and Boc act as Shh decoy receptors, limiting the effects of this morphogen. Loss of Cdon function leads to coloboma in zebrafish, suggesting that this gene Could be a new candidate for this congenital malfromation of the eye. In parallel, we have also contributed to identify the role of a few miRNA in eye development and to develop a model in medaka fish for "microphthalmia with skin lesions", pinpointing to the molecular mechanism underlying this rare hereditary disease. On another side, we have collaborated with other members of the CIBERER, to elucidate the molecular basis of Lafora Disease, a rare and neurodegenerative disease.

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Group U710

Programme: Hereditary Cancer and Related Syndromes

Lead Researcher: Bueren, Juan Antonio

Group Members

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

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

Main lines of research

General research lines of our group are:

- Cell and gene therapy for rare diseases. • Stem cell research and applications. • Research of the molecular and genetic bases of rare diseases affecting the hematopoietic system. • Biology of hematopoietic transplantation.

During 2014, our work has focused on developing innovative therapies for aplasias, anemias and congenital immunodeficiencies. Specifically we have worked in the following research areas:

- Gene therapy of patients with Fanconi anemia subtype A. • Applications of cellular reprogramming and directed gene therapy in Fanconi anemia (FA) and erythrocyte pyruvate kinase deficiency (PKD). • Development of an orphan drug for the treatment of erythrocyte pyruvate kinase deficiency (PKD). • - Preclinical studies for the gene therapy of the leukocyte adhesion deficiency type 1 (LAD-1).

Our research has been conducted in the context of the National Research Plan and the EU Framework Programme FP7 (PERSIST Project; REGENERATE and EUROFANCOLEN). For the same purpose, we participate in the International Consortium "Transatlantic Gene Therapy Consortium" promoted by Drs Williams (Harvard Medical School), Thrasher (UCL, London) and Baum (Hannover Medical School). The interest in conducting translational biomedical research has resulted in the signing of a 5 year period agreement with the Health Research Institute-Fundación Jiménez Díaz (January 2014-December 2017), in which we created a Joint Unit for Advanced Therapies CIEMAT / IIS-Fundación Jiménez Díaz to give clinical applicability to our gene and cell therapy studies.

The work done by our team within the CIBERER and through collaboration with other CIBERER groups and Linked Clinical Groups (H. Niño Jesus and H. Vall d'Hebron), is allowing us to lead global gene therapy programs in AF, and trust also do so in other rare diseases that affect blood cells. At the same time we offer collaboration to our CIBERER collaborators for the development of new advanced therapies for rare diseases.

Most relevant scientific articles

- Leon-Rico D, Aldea M, Sanchez R, Segovia JC, Weiss LA, Hidalgo A, et al. Brief report: reduced expression of CD18 leads to the in vivo expansion of hematopoietic stem cells in mouse bone marrow. Stem cells. 2014 Oct;32(10):2794-8. PubMed PMID: 24906078.
- Rio P, Banos R, Lombardo A, Quintana-Bustamante O, Alvarez L, Garate Z, et al. Targeted gene therapy and cell reprogramming in Fanconi anemia. EMBO molecular medicine. 2014 Jun;6(6):835-48. PubMed PMID: 24859981. Pubmed Central PMCID: 4203359.
- Navarro S, Moleiro V, Molina-Estevez FJ, Lozano ML, Chinchon R, Almarza E, et al. Generation of iPSCs from genetically corrected Brca2 hypomorphic cells: implications in cell reprogramming and stem cell therapy. Stem cells. 2014 Feb;32(2):436-46. PubMed PMID: 24420904.
- Pulecio J, Nivet E, Sancho-Martinez I, Vitaloni M, Guenechea G, Xia Y, et al. Conversion of human fibroblasts into monocyte-like progenitor cells. Stem cells. 2014 Nov;32(11):2923-38. PubMed PMID: 25175072. Pubmed Central PMCID: 4198469.
- Liu GH, Suzuki K, Li M, Qu J, Montserrat N, Tarantino C, et al. Modelling Fanconi anemia pathogenesis and therapeutics using integration-free patient-derived iPSCs. Nature communications. 2014;5:4330. PubMed PMID: 24999918. Pubmed Central PMCID: 4291073

Highlights

As a result of gene complementation studies performed in our laboratory and in collaboration with the team of Dr. Surrallés (U745), we described the XPF/ERCC4 gene as a new gene involved in Fanconi anemia pathway, known as the FANCQ gene (Bogliolo et al, 2014). Thanks to the Orphan Drug designation to our lentiviral vector PGK-FANCA-WPRE, we obtained funding for the development of the first clinical trial of lentiviral gene therapy of hematopoietic stem cells mobilized in patients with FA subtype A and in 2014, the IMPD was approved for the manufacture of the gene therapy cellular drug.

We have shown that gene edition on FA cells is possible and those cells were reprogrammed to generate iPSCs, which later were differentiated into the hematopoietic lineage (Rio et al. EMBO Mol Med 2014 Dew Thesis Bathrooms 2014). In a similar work done in Fanca-/- mouse cells, we demonstrated the advantages and limitations of cellular reprogramming techniques for the development of hematopoietic cell therapy protocols (Navarro et al Stem Cells 2014).

In the field of PKD anemia, genetically edited iPSCs derived from two patients with this deficiency have been described. The gene modification was performed by homologous recombination enhanced by TALE nucleases (Thesis Zita Garate 2014). In August 2014 one of our lentiviral vectors was designated as a new orphan drug for the treatment of PKD (EU / 3/14/1130).

In 2014 it has been possible to complete the development of four lentiviral vectors candidates for the treatment of leukocyte adhesion deficiency type I. These vectors have been tested in vitro and in vivo, using different models of the disease, and have proved to be effective to correct the disease phenotype in both human and mouse cells (Leon et al. Stem Cells 2014).

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Group U711

Programme: Genetic Medicine

Lead Researcher: Carracedo, Ángel

Group Members

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

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

Main lines of research

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

Most relevant scientific articles

- De Rubeis S, He X, Goldberg AP, Poultney CS, Samocha K, Cicek AE, Kou Y, Liu L, Fromer M, Walker S, Singh T, Klei L, Kosmicki J, Shih-Chen F, Aleksic B et al. Synaptic, transcriptional and chromatin genes disrupted in autism. Nature; 2014 Nov 13. 515(7526):209-15;
- Arking DE, Pulit SL, Crotti L, van der Harst P, Munroe PB, Koopmann TT, Sotoodehnia N, Rossin EJ, Morley M, Wang X, Johnson AD, Lundby A, Gudbjartsson DF, Noseworthy PA, Eijgelsheim M, et al. Genetic association study of QT interval highlights role for calcium signaling pathways in myocardial repolarization.. Nat Genet; 2014 Aug. 46(8):826-36;
- Fachal L, Gómez-Caamaño A, Barnett GC, Peleteiro P, Carballo AM, Calvo-Crespo P, Kerns SL, Sánchez-García M, Lobato-Busto R, Dorling L, Elliott RM, et al. A three-stage genome-wide association study identifies a susceptibility locus for late radiotherapy toxicity at 2q24.1. Nat Genet; 2014 Aug. 46(8):891-4;
- Rosmarin D, Palles C, Pagnamenta A, Kaur K, Pita G, Martin M, Domingo E, Jones A, Howarth K, Freeman-Mills L, Johnstone E, Wang H, Love S, Scudder C, Julier P, et al. A candidate gene study of capecitabine-related toxicity in colorectal cancer identifies new toxicity variants at DPYD and a putative role for ENOSF1 rather than TYMS. Gut ;2014 Mar 19.
- Kinnersley B, Buch S, Castellví-Bel S, Farrington SM, Forsti A, Hampe J, Hemminki K, Hofstra RM, Northwood E, Palles C, Pinheiro M, Ruiz-Ponte C, et al.. Re: Role of the oxidative DNA damage repair gene OGG1 in colorectal tumorigenesis. J Natl Cancer Inst ;May. 106(5):

Highlights

During 2014 we started, a collaboration with Actelion Pharmaceuticals to develope an specific line for the study of Newman Pick type C and led an international consortium on cerebrotendinous xanthomatosis.

In terms of competitive resources, we must highlight that the effort of this year has allowed us to obtain financing for two H2020 projects, one of them as coordinators.

Regarding the application of knowledge, we have produced two systematic reviews (Primary Familial Brain Calcification, (MJ Sobrido et al and Spinocerebellar Ataxia Type 36, M Arias et al), collaborated on several reports and opinions (basically IRDiRC) or consensus documents (Reference for establishing clinical criteria of suspected CMMR-D. Wimmer et al) and have collaborated with an international consortium in the identification of new genes for autism. Other findings have been published in A novel stop mutation in the vascular endothelial growth factor-C gene (VEGFC) results in Milroy-like disease". (Balboa-Beltran E et al. J Med Genet) y "A three-stage genome-wide association study identifies a susceptibility locus for late radiotherapy toxicity at 2q24.1". (Fachal L et al, Nat Genet).

The research group has also implemented a database for historical description of variants sequenced and elimination of systematic errors and designed a pipeline for NGS analysis for processing raw ultrasequencing results.

Finally, one member of our group, Dr. Sobrido, has been appointed coordinator of the Study of Ataxia and degenerative Spastic parapareglias (Spanish Society of Neurology) and has been invited to participate as an expert in the Scientific Panel of Neurogenetics Subspecialty (European Academy of Neurology).

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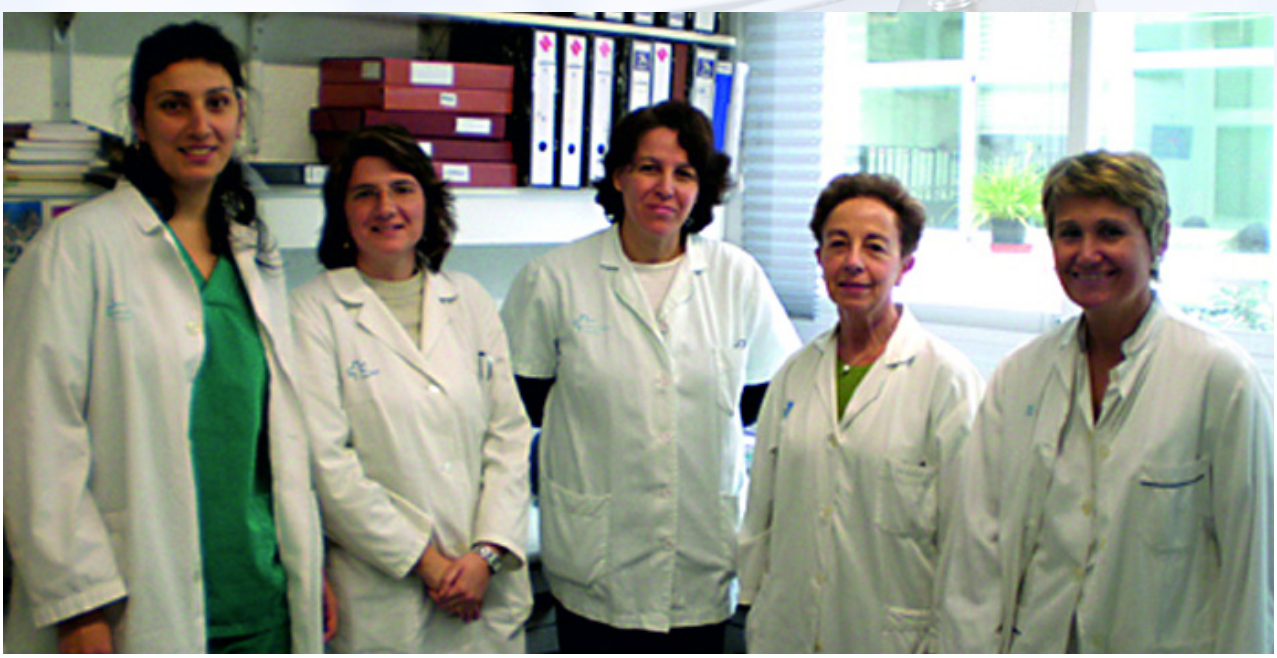
Group U712

Programme: Endocrine Medicine



Lead Researcher: Carrascosa, Antonio

Group Members

STAFF MEMBERS: Fernández Cancio, Mónica

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

Main lines of research

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

Most relevant scientific articles

- Malikova J, Camats N, Fernández-Cancio M, Heath K, González I, Caimarí M, del Campo M, Albisu M, Kolouskova S, Audí L, Flück CE. Human NR5A1/SF-1 mutations show decreased activity on BDNF (brain-derived neurotrophic factor), an important regulator of energy balance: testing impact of novel SF-1 mutations beyond steroidogenesis. PLoS One. 2014 Aug 14;9(8):e104838. doi: 10.1371/journal.pone.0104838. eCollection 2014. PubMed PMID: 25122490; PubMed Central PMCID: PMC4133263.
- Akcay T, Fernandez-Cancio M, Turan S, Güran T, Audi L, Bereket A. AR and SRD5A2 gene mutations in a series of 51 Turkish 46,XY DSD children with a clinical diagnosis of androgen insensitivity. Andrology. 2014 Jul;2(4):572-8. doi: 10.1111/j.2047-2927.2014.00215.x. Epub 2014 Apr 16. PubMed PMID: 24737579.
- Cox K, Bryce J, Jiang J, Rodie M, Sinnott R, Alkhawari M, Arlt W, Audi L, Balsamo A, Bertelloni S, Cools M, Darendeliler F, Drop S, Ellaithi M, Guran T, et al. Novel associations in disorders of sex development: findings from the I-DSD Registry. J Clin Endocrinol Metab. 2014 Feb;99(2):E348-55. doi: 10.1210/jc.2013-2918. Epub 2013 Dec 3. PubMed PMID: 24302751; PubMed Central PMCID: PMC3955252.
- Gimeno A, García-Giménez JL, Audí L, Toran N, Andaluz P, Dasí F, Viña J, Pallardó FV. Decreased cell proliferation and higher oxidative stress in fibroblasts from Down Syndrome fetuses. Preliminary study. Biochim Biophys Acta. 2014 Jan;1842(1):116-25. doi: 10.1016/j.bbadis.2013.10.014. Epub 2013 Oct 31. PubMed PMID: 24184606.
- Camats N, Pandey AV, Fernández-Cancio M, Fernández JM, Ortega AM, Udhane S, Andaluz P, Audí L, Flück CE. STAR splicing mutations cause the severe phenotype of lipoid congenital adrenal hyperplasia: insights from a novel splice mutation and review of reported cases. Clin Endocrinol (Oxf). 2014 Feb;80(2):191-9. doi: 10.1111/cen.12293. Epub 2013 Aug 17. Review. PubMed PMID: 23859637.Casteràs A, Kratzsch J, Ferrández A, Zafón C, Carrascosa A, Mesa J. Clinical challenges in the management of isolated GH deficiency type IA in adulthood. Endocrinol Diabetes Metab Case Rep. 2014;2014:130057. doi: 10.1530/EDM-13-0057. Epub 2014 Feb 1. PubMed PMID: 24683479; PubMed Central PMCID: PMC3965272.

Highlights

Translational activities: Specialized paediatric endocrinology consultations on skeletal growth, disorders of sex development (DSD), familial glucocorticoid deficiency and factors predisposing to rickets.

Vall d'Hebron Institut de Recerca (VHIR) Biobank: paediatric endocrinology colection.

Colaborations: Spanish Societies (SEEP, SEEN and SEQC), European Society (ESPE) for clinical, biochemical and genetic Guidance and Recommendations.

Reference Centre for Congenital Hypothyroidism Diagnosis and Therapy.

Catalan Advisory Commission for GH therapy.

European Project COST BM1303 for DSD international studies.

Transfer activities: auxological growth data informatization (Auxolog Programme).

Databases: 1) DSD in the ISCIII, coordinated by the Group; 2) International DSD Registry.

CIBERER Activities: Orphanet advisory for paediatric endocrinology. CIBER advisory for paediatric endocrinology.

Colaboration with paediatric groups in our hospital (neumology, neurology and metabolic diseases, clinical genetics and immunodeficiencies.

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Group U713

Programme: Mitochondrial and Neuromuscular Medicine

Lead Researcher: Cuezva, José M.

Group Members

STAFF MEMBERS: Núñez de Arenas Flores, Cristina | Sánchez Arago, María

AT THE EXPENSE OF THE PROJECT: Cueva Martín, Mª del Carmen

ASSOCIATED MEMBERS: Formentini, Laura | García Bermúdez, Javier | Martínez Jover, Estefanía | Martínez Reyes, Inmaculada | Santacatterina, Fulvio

Main lines of research

- Alterations of biogenesis and/or mitochondrial functions in human pathology due to genetic or epigenetic causes.
- Biosynthesis, assembling and degradation of the mitochondrial oxidative phosphorylation Complex V. Identification and functional characterization of the mRNA binding proteins from the beta-F1-ATPasa subunit.
- Development of cellular and mouse models of disease with alterations in mitochondrial oxidative phosphorylation.
- Development of proteomic platforms for the identification of molecular markers of diagnosis on 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

- Sanchez-Arago M, Garcia-Bermudez J, Martinez-Reyes I, Santacatterina F, Cuezva JM. Degradation of IF1 controls energy metabolism during osteogenic differentiation of stem cells. EMBO Rep. 2013;14(7):638-44.
- Sanchez-Arago M, Formentini L, Cuezva JM. Mitochondria-mediated energy adaption in cancer: the H(+)-ATP synthase-geared switch of metabolism in human tumors. Antioxid Redox Signal. 2013;19(3):285-98.
- Martínez-Reyes I, Cuezva JM. The H(+)-ATP synthase: a gate to ROS-mediated cell death or cell survival. Biochim Biophys Acta. 2014;1837(7)
- Formentini L, Pereira MP, Sanchez-Cenizo L, Santacatterina F, Lucas JJ, Navarro C, et al. In vivo inhibition of the mitochondrial H+-ATP synthase in neurons promotes metabolic preconditioning. Embo J. 2014;33(7):762-78.
- Santacatterina F, Chamorro M, de Arenas CN, Navarro C, Martín MA, Cuezva JM, Sánchez-Aragó M. Quantitative analysis of proteins of metabolism by reverse phase protein microarrays identifies potential biomarkers of rare neuromuscular diseases. J Transl Med. 2015;13:424.

Highlights

PROJECTS

• Reference: S2010/BMD-2402. Title: La mitocondria y su implicación en patología humana. Budget: 795.800€. 2012-2015. PI: José M. Cuezva Marcos. • Reference: 13-713/438.00. Title: Traslational Research, experimental Medicine and Therapeutics on Charcot-Marie-Tooth disease (TREAT-CMT). International Rare Diseases Research Consortium (IRDiRC). Budget: 3.084.664€. 2012-2016. Co-PI: José M. Cuezva Marcos. • Reference: SAF2013-41945-R. Title: La mitocondria y su disfunción en patología: papel de IF1. Budget: 335000€. 2014-2016. PI: José M. Cuezva Marcos. • Reference: Fundación Ramón Areces. Title: Función oncogénica de IF1, el inhibidor de la H+ATP sintasa de la mitocondria. Budget: 125760€. 2015-2017. PI. José M. Cuezva Marcos.

PATENTS

• Inventors: Fulvio Santacatterina, María Sánchez-Aragó and José M. Cuezva. Title: "Un proceso y kit para el diagnóstico diferencial de una enfermedad que cursa con afectación muscular". Application number: 201230771. Publication number: ES2432653. Country: Spain. Publication date: 23/05/2012. Applicants: Universidad Autónoma de Madrid-CIBERER. • BRAND REGISTRY NUMBER: PROTEOmAb. Owner: Universidad Autónoma de Madrid. Brand number: 3.055.803. Application date: 12/12/2012. Authorization date: 14/03/2013. • The lab has developed PROTEOmAb Platform, focused on the identification and quantification of new disease molecular markers and/or therapy response. Based on "Reverse Phase Protein Microarray" technology. Analysis of 1.000 different biopsies, that provides correlations with clinical and treatment response parameters. (i) "Translation of Energy Metabolism" group in Cancer field of the Instituto de Investigación Hospital 12 de Octubre (i+12) (ii) We belong to MITOLAB Consortium, Comunidad de Madrid. J.M. Cuezva is the Coordinator.

ABSTRACT OF SELECTED PUBLICATIONS

• We have demonstrate that the ATPase Inhibitory Factor 1 (IF1) is a potential therapeutic target in muscular mitochondriopathies (J Trans Med, 2015). In a transgenic mouse model the expression of IF1 in neurons inhibits oxidative phosphorylation and regulates the activity of aerobic glycolysis. Our findings provide the first demonstration that links the inhibition of the H+-ATP synthase with protection from neuronal damage in vivo. In the liver mouse model, we demonstrate in vivo that a metabolic phenotype with a restrained OXPHOS is prone to the development of cancer (Hepathology, 2014, submitted).

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Group U714

Programme: Hereditary Cancer and Related Syndromes

Lead Researcher: Del Río Nechaevsky, Marcela

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, Nuria | 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: Epidermolisis Bullosa and Kindler síndrome.
- Development of humanized animal models of rare skin diseases.
- Bone regeneration through tissue engineering.

Most relevant scientific articles

- Zapatero-Solana E, García-Giménez J, Guerrero-Aspizua S, García M, Toll A, Baselga E, Durán-Moreno M, et al. Oxidative stress and mitochondrial dysfunction in Kindler syndrome. Orphanet J Rare Dis. 2014 Dec 21;9(1):211.
- Duarte B, Miselli F, Murillas R, Espinosa-Hevia L, Cigudosa JC, Recchia A, et al. Long-term skin regeneration from a gene-targeted human epidermal stem cell clone. Mol Ther. 2014 Nov;22(11):1878-80.
- Kiritsi D, Garcia M, Brander R, Has C, Meijer R, Escámez MJ, et al. Mechanisms of natural gene therapy in dystrophic epidermolysis bullosa. J Invest Dermatol. 2014 Aug;134(8):2097-104.
- Puig-Butille JA, Escámez MJ, Garcia-Garcia F, Tell-Marti G, Fabra À, Martínez-Santamaría L, et al. Capturing the biological impact of CDKN2A and MC1R genes as an early predisposing event in melanoma and non melanoma skin cancer. Oncotarget. 2014 Mar 30;5(6):1439-51.
- Gostynski A, Llames S, García M, Escamez MJ, Martinez-Santamaria L, Nijenhuis M, et al. Long-term survival of type XVII collagen revertant cells in an animal model of revertant cell therapy. J Invest Dermatol. 2014 Feb;134(2):571-4.

Highlights

- **Orphan drug designation:** "Allogeneic adipose-derived adult mesenchymal stem cells contained in a fibrin-based bioengineered dermis" (EU/3/14/1407). Indication: Treatment of epidermolysis bullosa. EMEA: EMA/OD/197/14
- **Cátedra de Investigación** in Regenerative Medicine and Tissue Engineering with the IIS-Fundación Jiménez Díaz to enhance translational research on rare diseases.
- **Research projects granted:** project SAF2013-43475-R (PI: M. Del Río), clinical research project ICC114/032 (led by MJ. Escamez) y project IP14/00931 (led byF. Larcher).
- **Clinical trials:** - Start-up of phase I/II clinical trial at the Hospital La Paz in Madrid that consist on the use of mesenchymal stem cells for the treatment of mucosal fragility in patients with epidermolysis bullosa - Recruitment of patients in the European project GENEGRAFT ("Phase I/II ex vivo gene therapy clinical trial for recessive dystrophic epidermolysis bullosa using skin equivalent grafts genetically corrected with a COL7A1-encoding SIN retroviral vector") - Proposed clinical trial for lamellar ichthyosis that has been submitted and selected for the "2nd Stage" in the H2020 program, topic: PHC-14-2015: "New therapies for rare diseases". This proposal involves basic and clinical groups and the company Pierre Fabre (France).
- 3 **ACCI projects** (CIBERER) in which our unit collaborate with other CIBERER units (u701, u715, u726 and u733)
- **Transfer of research to the industry:** generation of a spin-off, license of 2 patents, know-how transfer of the orphan drug EU/3/14/1407 to the GMP facility of the Hospital Niño Jesús.
- **Organization of seminars and conferences:**

- "II International Day of Xeroderma Pigmentosum and other DNA repair and premature aging diseases", held at the Fundación Jiménez Díaz (10/12/2014). Event cofinancied by CIBERER.
- Sponsorship (in 2014) by the Ramón Areces Foundation for the symposium: "Rare Diseases: breaking paradigms", that we are organizing nowadays.

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Group U715

Programme: Genetic Medicine

Lead Researcher: Dopazo, Joaquín

Group Members

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

ASSOCIATED MEMBERS: Conesa Cegarra, Ana Victoria | García García, Francisco | Montaner González, David | Tarraga Giménez, Joaquín

Main lines of research

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

Most relevant scientific articles

- Alemán A, Garcia-Garcia F, Salavert F, Medina I, Dopazo J. 2014 A web-based interactive framework to assist in the prioritization of disease candidate genes in whole-exome sequencing studies. Nucleic Acids Res. 42:W88-W93.
- Alemán A, Garcia-Garcia F, Medina I, Dopazo J. 2014 A web tool for the design and management of panels of genes for targeted enrichment and massive sequencing for clinical applications." Nucleic Acids Res. 42:W83-W87
- Garcia-Alonso L, Jiménez-Almazán J, Carbonell-Caballero J, Vela-Boza A, Santoyo-López J, Antiñolo G, Dopazo J. 2014 The role of the interactome in the maintenance of deleterious variability in human populations. Mol. Syst. Biol. 10(9):752
- Sebastian-Leon P, Vidal E, Minguez P, Conesa A, Tarazona S, Amadoz A, Armero C, Salavert F, Vidal-Puig A, Montaner D, Dopazo J. 2014 Understanding disease mechanisms with models of signaling pathway activities." BMC Syst Biol. 8(1):121
- Su Z, Labaj PP, ...Dopazo, J..., et al. 2014 A comprehensive assessment of RNA-seq accuracy, reproducibility and information content by the Sequencing Quality Control Consortium. Nat. Biotechnol. 32:903-914.

Highlights

During 2014 the group has had an intense activity in two fronts. On one hand, the group has continued providing support to the collaborative intra-CIBERER programme for rare disease patients sequencing. Only in this year 212 exomes from 131 families have been analysed. The analysis has resulted in 9 publications (out of a total of 24 already produced in this collaborative programme).

On the other hand, software specifically oriented to the analysis of genomic data in the context of rare diseases has been developed. The BiERapp program (http://bierapp.babelomics.org), for disease candidate gene prioritization, has been released. BiERapp has been used in the above mentioned collaborative programme as well as in other projects. The TEAM (http://team.babelomics.org) application for the management of panels of genes for diagnostic by targeted enrichment sequencing has also been delivered. Finally, we have worked on the set up of a database of variability of Spanish population. The database is crucial for the discovery of new disease genes as well as for diagnostic by targeted resequencing.

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Group U716

Programme: Paediatric and Developmental Medicine

Lead Researcher: Fillat, Cristina

Group Members

STAFF MEMBERS: Luna Cornado, Jerónimo | Rozen, Esteban Javier

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

Main lines of research

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

Most relevant scientific articles

- DYRK1A promotes dopaminergic neuron survival in the developing brain and in a mouse model of Parkinson's disease. Barallobre MJ, Perier C, Bové J, Laguna A, Delabar JM, Vila M, Arbonés ML. Cell Death Dis. 2014 Jun 12;5:e1289.
- Epigallocatechin-3-gallate, a DYRK1A inhibitor, rescues cognitive deficits in Down syndrome mouse models and in humans. De la Torre R, De Sola S, Pons M, Duchon A, de Lagran MM, Farré M, Fitó M, Benejam B, Langohr K, Rodríguez J, Pujadas M, Bizot JC, Cuenca A, Janel N, Catuara S, Covas MI, Blehaut H, Herault Y, Delabar JM, Dierssen M. Mol Nutr Food Res. 2014 Feb;58(2):278-88.
- The role of nicotinic receptors in shaping and functioning of the glutamatergic system: a window into cognitive pathology. Molas S, Dierssen M. Neurosci Biobehav Rev. 2014 Oct;46 Pt 2:315-25.
- A genetic fiber modification to achieve matrix-metalloprotease-activated infectivity of oncolytic adenovirus. José A, Rovira-Rigau M, Luna J, Giménez-Alejandre M, Vaquero E, García de la Torre B, Andreu D, Alemany R, Fillat C. J Control Release. 2014 Oct 28;192:148-56.
- miR-148a- and miR-216a-regulated oncolytic adenoviruses targeting pancreatic tumors attenuate tissue damage without perturbation of miRNA activity. Bofill-De Ros X, Gironella M, Fillat C. Mol Ther. 2014 Sep;22(9):1665-77.

Highlights

The team focuses its research in the study of the molecular basis, the pathophysiological mechanisms and therapeutic research of genetic and developmental disorders affecting the central nervous system. Of special interest are the set of rare diseases that present with intellectual disabilities and in particular, those associated with total / partial trisomy of chromosome 21 (HSA21) responsible for Down syndrome (DS) and monosomy of this chromosome such as the "autosomal dominant Mental retardation-7" (MRD7; OMIM # 614104), resulting from heterozygous mutations in the HSA21 gene DYRK1A. In addition, the group develops therapeutic strategies against rare tumors.

In 2014 main contributions have demonstrated that DYRK1A kinase promotes the survival of dopaminergic neurons in the developing brain. In addition we have shown that DYRK1A attenuates neuronal death, under induced neuronal toxicity in a mouse model of Parkinson's disease.

We also note the publication of the first data derived from clinical trial (NCT01699711) in collaboration with the IMIM-Hospital del Mar on the "use of epigallocatechin gallate (EGCG) to modulate DYRK1A and APP and assess their impact on cognitive performance in patients with Down syndrome. " This pilot study suggests that treatment with EGCG bring benefits in memory processes and the quality of life of people with DS.

Regarding the development of new therapies for the treatment of rare tumors we have advanced in the design and preclinical studies of gene virotherapy by developing oncolytic adenovirus with high selectivity and potency against pancreatic tumors, leading to a patent application, currently in PCT phase.

It should be noted the active contribution of the group to SEFALER unit with the performance of behavioral phenotyping in mouse models of rare diseases in collaboration with diverse groups of CIBERER.

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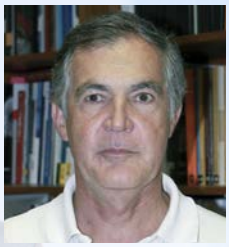

Group U717

Programme: Mitochondrial and Neuromuscular Medicine

Lead Researcher: Garesse, Rafael

Group Members

STAFF MEMBERS: Gallardo Pérez, María Esther

ASSOCIATED MEMBERS: Bornstein Sánchez, Belen | Fernández Moreno, Miguel Ángel | Galera Monge, Teresa

Main lines of research

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

Most relevant scientific articles

- Zambrano A, García-Carpizo V, Gallardo ME, Villamuera R, Gómez-Ferrería MA, Pascual A et al., The thyroid hormone receptor ß induces DNA damage and premature senescence. J Cell Biol. 2014; 204(1):129-46.
- González-Vioque E, Bornstein B, Gallardo ME, Fernández-Moreno MÁ, Garesse R. The pathogenicity scoring system for mitochondrial tRNA mutations revisited. Mol Genet Genomic Med. 2014; 2(2):107-14.
- Gallego-Delgado M, Cobo-Marcos M, Bornstein B, Hernández-Laín A, Alonso-Pulpón L, Garcia-Pavia P. Mitochondrial Cardiomyopathies Associated With the m.3243A>G Mutation in the MT-TL1 Gene: Two Sides of the Same Coin. Rev Esp Cardiol (Engl Ed). 2014; Epub ahead of print].
- Zabalza R, Nurminen A, Kaguni LS, Garesse R, Gallardo ME, Bornstein B. Co-occurrence of four nucleotide changes associated with an adult mitochondrial ataxia phenotype. BMC Res Notes. 2014;7:883.
- Echevarría L, Clemente P, Hernández-Sierra R, Gallardo ME, Fernández-Moreno MA, Garesse R. Glutamyl-tRNAGln amidotransferase is essential for mammalian mitochondrial translation in vivo. Biochem J. 2014; 460(1):91-101.

Highlights

During 2014, the unit U717 has been funded by three different projects: one provided by the ISCIII (PI13/00556), one by the CAM (S2010/BMD-2402) and other by the FMM (FMM2011-0060). Our work has been focused on different aspects of the mitochondrial physiopathology. Among them: 1) The biochemical characterization of transmitochondrial cybrids from patients with several mitochondrial diseases. 2) Molecular and functional characterization of mutations in the mitochondrial and nuclear genome in patients with mitochondrial cardiomyopathy. 3) Regarding to the transfer and translational assistance in our lab and in the Puerta de Hierro Hospital in Madrid, several molecular diagnostic platforms are being implemented. Among them, platforms for the diagnosis of sarcomeric genes in cardiomyopathies and for intergenomic communication defects genes, like the POLG gene. For the diagnosis of this gene we are considered as a reference center. Besides, in collaboration with other CIBERER units we have participated in a) the elaboration of a normalized method for the quantification of the mtDNA and b) for the standardization of clinical diagnosis of human mitochondrial respiratory chain defects. Both methods are being used now for the molecular diagnosis of mitochondrial disorders. 4) Identification and characterization of new genes involved in the OXPHOS function. Until now, two genes (GatC and hCOA3) have been identified and characterized. 5) Generation of induced pluripotent stem cells (iPSCs) like a model for the study of mitochondrial diseases and as an approximation to the development of therapeutical strategies for these diseases. Up to now, we have generated iPSCs from patients with Leigh syndrome caused by mutations in the mtDNA, from patients with a plus optic atrophy and from patients with mutations in the POLG gene. The use of this technology together with the identification of new OXPHOS genes will be the priority research topics of our lab.

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Group U718

Programme: Sensorineural Pathology

Lead Researcher: González Duarte, Roser

Group Members

STAFF MEMBERS: Andrés Ventura, María Rosa

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

Main lines of research

- Study of the genetic and molecular basis for retinal dystrophies.
- Direct mutational analysis of the genes responsible for hereditary retinal dystrophies.
- Construction and optimization of DNA chips for indirect diagnosis of the genes causing hereditary retinal dystrophies in isolated families. Application of the last version of the chip for the genetic diagnosis for 100 genes of retinal dystrophies.
- Search for new genes causing retinal dystrophies in affected families by means of exome/enrichment and massive DNA sequencing.
- Functional analysis of CERKL by means of studies in cell lines and of the animal model created by the team, knockout CERKL-/- mice.

Most relevant scientific articles

- Fathinajafabadi A, Pérez-Jiménez E, Riera M, Knecht E, Gonzàlez-Duarte R. CERKL, a retinal disease gene encodes an mRNA-binding protein that localizes in compact and untranslated mRNPs associated with microtubules. PLoS One 9 (2):e87898.
- de Castro-Miró M, Pomares E, Lorés-Motta L, Tonda R, Dopazo J, Marfany G, Gonzàlez-Duarte R. Combined genetic and high-throughput strategies for molecular diagnosis of inherited retinal dystrophies. PLoS One 9 (2):e88410.

Highlights

The research activity of the U718 group is focused on the genetic and functional study of the inherited retinal dystrophies (IRDs), novel gene identification and high-yield genetic diagnosis using costumized DNA chips, massive exome sequencing (WES) and bioinformatic tools. The functional analysis of CERKL, a retinitis pigmentosa (RP) causing gene, has revealed that the encoded protein forms ribonucleoprotein aggregates associated to microtubules in several human cell lines, murine photoreceptors and retinal ganglion cells. The putative CERKL role on mRNAs transport and protection, previously unreported for RP genes, opens new scenarios to study the cellular pathways relevant to visual disorders and highlights novel therapeutic targets. We are studying the functional effects of post-translational modifications of key transcription factors for photoreceptor development, CRX and NR2E3 among others, which are frequently associated to severe retinal disorders.

New tools are needed to analyse complex sensorial disorders such as IRDs. To that end, we have designed and develped an interactive webapp that integrates all the molecular and biochemical data concerning the non-syndromic Retinitis Pigmentosa genes (62 reported so far). This information underscores previously unknown nodes and proteins in the metabolic and signalling cellular pathways, which are valuable clues to identify disease candidates and devise efficient therapies. Furthermore, we have established organotypic and primary cultures of murine retinal tissue and optimized tissular transient transfection to further our genetic studies with innovative in vitro and in vivo super resolution imaging approaches. We are also involved in the construction of two knockout models (Cerkl and Nr2e3) using the CRIPSR/Cas9 system.

Currently, our research is funded by the SAF2013-49069-C2-1-R (2014-2016) and La Marató TV3 (2014-2017) agencies. Also, the group was recently awarded as a distinguished research group and is additionally supported by two private foundations. At present, we have 6 predoctoral students.

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Group U719

Programme: Paediatric and Developmental Medicine

Lead Researcher: Gratacòs, Eduard

Group Members

STAFF MEMBERS: Acosta Rojas, Emilia R. | Demicheva, Elena | 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 Cortes, 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

- Batalle D, Muñoz-Moreno E, Arbat-Plana A, Illa M, Figueras F, Eixarch E, Gratacós E. Long-term reorganization of structural brain networks in a rabbit model of intrauterine growth restriction. Neuroimage. 2014 Jun 2;100:24–38.
- Crispi F, Bijnens B, Sepulveda-Swatson E, Cruz-Lemini M, Rojas-Benavente J, González-Tendero A, Garcia-Posada R, Rodríguez-Lopez M, Demicheva E, Sitges M, Gratacós E. Post-Systolic Shortening by Myocardial Deformation Imaging as a Sign of Cardiac Adaptation to Pressure Overload in Fetal Growth Restriction. Circ Cardiovasc Imaging. 2014 Jun 13;7(5):781–7.

- Garcia-Canadilla P, Rudenick PA, Crispi F, Cruz-Lemini M, Palau G, Camara O, Gratacós E, Bijnens B. A Computational Model of the Fetal Circulation to Quantify Blood Redistribution in Intrauterine Growth Restriction. PLoS Comput Biol. 2014 Jun;10(6):e1003667.
- Cruz-Lemini M, Crispi F, Valenzuela-Alcaraz B, Figueras F, Gómez O, Sitges M, Bijnens B, Gratacós E. A fetal cardiovascular score to predict infant hypertension and arterial remodeling in intrauterine growth restriction. Am J Obstet Gynecol. 2014 Dec 22;210(6):552.e1–552.e22.
- Sanz-Cortés M, Egaña-Ugrinovic G, Zupan R, Figueras F, Gratacós E. Brainstem and cerebellar differences and their association with neurobehavior in term small-for-gestational-age fetuses assessed by fetal MRI. Am J Obstet Gynecol. 2014 Dec 4;210(5):452.e1–8.

Highlights

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

Some of our major scientific and translational milestones achieved in 2014 include:

- Identification and diagnosis of pregnancy complications: set of criteria to improve the management of fetal diseases with prenatal brain damage implications.
- Perinatal brain damage biomarkers: characterization of the effects of preeclampsia and congenital heart disease with MR diffusion-tractography and computer analysis of cortical development.
- Fetal Cardiology: new methods for the study of fetal cardiac function.
- Coordination of an international multicentre study to assess the prediction of neonatal respiratory distress syndrome by non-invasive ultrasound.
- Consolidation of the first fetal neurology unit, with application of new biomarkers and screening protocols of fetal CNS.
- Clinical calculators that integrate the management of various rare diseases are available on the web, in addition to all our clinical protocols, most of them on rare diseases.
- First unit on fetal cardiac function in Spain, which uses our algorithms for predicting prognosis in congenital heart disease.
- Development of a new predictive algorithm for preeclampsia, patented in collaboration with industry (Siemens Healthcare).
- Collaboration with Perkin Elmer for the development of new set of biomarkers for predicting growth restriction and preeclampsia in the third trimester of pregnancy.
- New quantitative image analysis method for predicting neonatal respiratory distress risk. In collaboration with our spin-off TMB, both the patent and the product (Quantus FML) are in the market since 2014.

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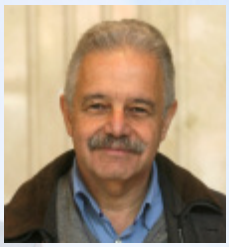
Group U720

Programme: Inherited Metabolic Medicine



Lead Researcher: Grinberg, Daniel

Group Members

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

ASSOCIATED MEMBERS: Balcells Comas, Susana | Carreño, Oriel | Cormand Rifa, Bru | Gómez Grau, Marta | Rodríguez Pascau, Laura | Sánchez Olle, Gessami | Sarrión Pérez-Caballero, Patricia | Serra Vinardell, Jenny | Sintas Vives, Celia | Torrico Avilés, Barbara | Vilageliu Arques, Lluisa

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

- Genetic analysis of high bone mass cases from the BARCOS cohort of Spanish postmenopausal women. Sarrión P, Mellibovsky L, Urreizti R, Civit S, Cols N, García-Giralt N, Yoskovitz G, Aranguren A, Malouf J, Di Gregorio S, Río LD, Güerri R, Nogués X, Díez-Pérez A, Grinberg D, Balcells S. PLoS One. 2014; 9(4):e94607.
- Toma C, Torrico B, Hervás A, Valdés-Mas R, Tristán-Noguero A, Padillo V, Maristany M, Salgado M, Arenas C, Puente XS, Bayés M, Cormand B. Exome sequencing in multiplex autism families suggests a major role for heterozygous truncating mutations. Mol Psychiatry. 2014; 19(7):784-90.
- Genetic variation associated with euphorigenic effects of d-amphetamine is associated with diminished risk for schizophrenia and attention deficit hyperactivity disorder. Hart AB, Gamazon ER, Engelhardt BE, Sklar P, Kähler AK, Hultman CM, Sullivan PF, Neale BM, Faraone SV; Psychiatric Genomics Consortium: ADHD Subgroup, de Wit H, Cox NJ, Palmer AA. Proc Natl Acad Sci U S A. 2014; 111(16):5968-73.
- Cholesterol regulates Syntaxin 6 trafficking at trans-Golgi network endosomal boundaries. Reverter M, Rentero C, Garcia-Melero A, Hoque M, Vilà de Muga S, Alvarez-Guaita A, Conway JR, Wood P, Cairns R, Lykopoulou L, Grinberg D, Vilageliu L, Bosch M, Heeren J, Blasi J, Timpson P, Pol A, Tebar F, Murray RZ, Grewal T, Enrich C. Cell Rep. 2014; 7(3):883-97
- Therapeutic strategies based on modified U1 snRNAs and chaperones for Sanfilippo C splicing mutations. Matos L, Canals I, Dridi L, Choi Y, Prata M, Jordan P, Desviat LR, Pérez B, Pshezhetsky AV, Grinberg D, Alves S, Vilageliu L. Orphanet J Rare Dis. 2014; 9(1):180

Highlights

In the research line on lysosomal diseases, a neuronal cellular model for Sanfilippo C disease was generated, using induced pluripotent stem (iPS) cells derived from patients' fibroblasts. A model of osteoblasts for Gaucher disease is also being generated using iPS cells. A mouse model carrying a splicing mutation responsible for Niemann-Pick C disease was generated and is being characterized to test future therapies.

In the line of bone diseases two genes, WNT16 and FLJ42280, previously identified as genes involved in osteoporosis by GWAs studies (in which our group has participated), are being studied by resequencing. On the other hand, we have identified by exome sequencing a mutation responsible for atypical femoral fractures in patients taking bisphosphonates. This result has led to a patent that has been submitted.

In the field of neurological diseases, several studies have been conducted within the Psychiatric Genomics Consortium (PGC), focused on the analysis of the genetic basis of psychiatric disorders. One has demonstrated the association between common genetic variants involved in the response to amphetamines and risk for schizophrenia or attention deficit and hyperactivity disorder. Another study has sequenced the entire exome of families with several autistic children in which truncating mutations associated with neuronal migration and myelination genes have been identified. Some of these genes and their mutations are being studied in cell and animal models.

Furthermore, an exome study of patients diagnosed with Opitz C-trigonocephaly syndrome has been performed. The pathogenic mutations in two patients was identified, allowing their new diagnosis as patients of two different diseases: Bohring-Opitz (ASXL1 gene) and congenital myopathy (RYR1 gene), respectively. The search for the Opitz C gene is still ongoing.

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Group U721

Programme: Genetic Medicine

Lead Researcher: Knecht, Erwin

Group Members

STAFF MEMBERS: Aguado Muñoz, Carmen

ASSOCIATED MEMBERS: Armengod González, María Eugenia | Montaner Fayos, Asunción

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.
- Regulation by PTEN of autophagy in hereditary breast cancer.
- Role of mitochondrial tRNAs modification enzymes in MELAS and other OXPHOS syndromes.
- Alterations in intracellular protein degradation in X-linked adrenoleukodistrophy.
- Lysosomal alterations in Danon disease.

Most relevant scientific articles

- Launay N*, Aguado C*, Fourcade S, Ruiz M, Grau L, Riera J, Guilera C, Giròs M, Ferrer I, Knecht E, Pujol A. Autophagy induction halts axonal degeneration in a mouse model of X-adrenoleukodystrophy. Epub 2014 Dec 31. *equal contribution.
- Moukadiri I, Garzón MJ, Björk GR, Armengod M.E. The output of the tRNA modification pathways controlled by the Escherichia coli MnmEG and MnmC enzymes depends on the growth conditions and the tRNA species. Nucleic Acids Res. 2014; 42(4): 2602-23.
- Fathinajafabadi A*, Pérez-Jiménez E*, Riera M, Knecht E, Gonzàlez-Duarte R. CERKL, a retinal disease gene, encodes an mRNA-binding protein that localizes in compact and untranslated mRNPs associated with microtubules. PLoS One 2014; 9(2): e87898. *equal contribution.
- Gayarre J, Durán-Trío L, Criado García O, Aguado C, Juana-López L, Crespo I, Knecht E, Bovolenta P, Rodríguez de Córdoba S. The phosphatase activity of laforin is dispensable to rescue Epm2a-/- mice from Lafora disease. Brain 2014; 137: 807-18.
- Romá-Mateo C*, Aguado C*, García-Giménez JL*, Ibáñez-Cabellos JS, Seco-Cervera M, Pallardó FV, Knecht E, Sanz P. Increased oxidative stress and impaired antioxidant response in Lafora Disease. Molecular Neurobiol 2014; [Epub ahead of print] PubMed PMID: 24838580.*equal contribution.

Highlights

- **Neuronal Ceroid Lipofuscinoses (NCL):** besides alterations in the formation of autophagosomes and in their fusion with endosomes/lysosomes, other consequences of the observed lysosomal pH increase in the CLN3 variant are a reduction in vesicular trafficking and in the maturation of lysosomal enzymes. We also collaborate with the Neuroimmunology Unit of the La Fe Hospital (Valencia) in the diagnosis of patients with suspected LCN and we have developed protocols to quantify the activity of enzymes (PPT-1, TTP-1, cathepsin D) implicated in three of the most prevalent forms of the disease (CLN1, CLN2, CLN10, respectively), in dried samples on filter paper.
- **Lafora disease (LD):** the most relevant results obtained in collaboration with other CIBERER units (U709, U733, U738, U742 y U744) were a reduced formation of autophagosomes in all models of the disease, probably related with p38 signalling, and an increased oxidative stress due to defects in autophagy and in the stress response. Furthermore, the phosphatase activity of laforin does not rescue disease symptoms. Finally, we participate in an ACCI grant with three other CIBERER units (U732, U733 and U742) to develop iPS models of the disease.
- **X-Adrenoleukodystrophy (X-ALD:** in collaboration with U-759, we described, an impairment in the formation of autophagosomes and that temsiroloimus (an mTOR inhibitor) restores alterations that occur in an X-ALD mouse model. Therefore, we have patented a repositioning of this drug for the treatment of the disease.
- **Retinitis pigmentosa (RP):** in collaboration with U-718 we have demonstrated that the protein CERKL, implicated in RP, binds to specific not translated mRNAs in compact particles of RNPs associated to microtubules for their polarized transport.
- Finally, Dr. Armengod, adscribed to our unit, collaborates with other units (U-701, U723) in the study of the implication of mitochondrial tRNAs and micro-RNAs in **mitochondrial diseases (MERRF and MELAS).** For instance, the micro-RNA 9/9* has been shown to be involved in the molecular mechanism of MELAS syndrome through the negative regulation of the expression of U34 modifying enzymes.

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Group U722

Programme: Mitochondrial and Neuromuscular Medicine

Lead Researcher: Cardellach, Francesc

Group Members

STAFF MEMBERS: Garrabou Tornos, Gloria

AT THE EXPENSE OF THE PROJECT: Morén Núñez, Constanza | González Casabuerta, Ingrid

ASSOCIATED MEMBERS: Catalán García, Marc | Grau Junyent, Josep Maria

Main lines of research

- Creation of the Group for Medical Assistance of Adult Patients with Rare Diseases (basically of metabolic and mitochondrial origen, among others).
- Mitochondrial Pathology: Mitochondrial basis of disease and cell processes.
- Muscular Pathology (mitochondrial, inflammatory, autoinmune and toxic, especially due to statin treatment).
- Toxicity induced by drugs that cause clinic manifestations of mitochondrial origen (Lipodystrophy, hyperlactatemia, peripheral neuropathy, infertility, obstetric problems, miopathy).
- Toxicity induced by tobacco and carbon monoxide that cause clinic manifestations of mitochondrial origen.
- Mitochondrial basis of Parkinson disease associated to mutations in Parkin and LRRK2 genes (rare forms of the disease).
- Mitochondrial basis of body inclusion myositis.
- Mitochondrial function in the study of gene therapy in MNGIE.
- Mitochondrial implication in X-Fragile Syndrome.
- Mitochondrial basis on intrauterine growth restriction and cardiovascular fetal remodeling.

Most relevant scientific articles

- Garrabou G, Hernàndez AS, Catalán García M, Morén C, Tobías E, Córdoba S, López M, Figueras F, Grau JM, Cardellach. Molecular basis of reduced birth weight in smoking pregnant women: mitochondrial dysfunction and apoptosis. Addict Biol 2014; In press. PMID 25186090. IF 5.93 Q1D1
- Prieto-González S, Depetris M, García-Martínez A, Espígol-Frigolé G, Tavera-Bahillo I, Corbera-Bellata M, Planas-Rigol E, Alba MA, Hernández-Rodríguez J, Grau JM, Lomeña F, Cid MC. Positron emission tomography assessment of large vessel inflammation in patients with newly diagnosed, biopsy-proven giant cell arteritis: a prospective, case-control study. Ann Rheum Dis ;Jul. 73(7):1388-92. PMID 24665112. IF 9.27 Q1D1
- Selva-O'Callaghan A, Trallero-Araguás E, Grau JM. Eosinophilic myositis: an updated review. Autoimmun Rev ;13(4-5):375-8. PMID 24424174. IF 7.095 Q1D1
- Labrador-Horrillo M, Martínez MA, Selva-O'Callaghan A, Trallero-Araguás E, Grau-Junyent JM, Vilardell-Tarrés M, Juarez C. Identification of a novel myositis-associated antibody directed against cortactin. Autoimmun Rev ;Oct. 13(10):1008-12. PMID 25182205. IF 7.095 Q1D1
- Catalán M, Selva-O'Callaghan A, Grau JM. Diagnosis and classification of sporadic inclusion body myositis (sIBM). Autoimmun Rev ;13(4-5):363-6. PMID 24424185. IF 7.095 Q1D1

Highlights

The Unit U722 is a multidisciplinary team with both clinicians and basic researchers that focuses its research interests in the clinical assistance and translational research. We parallelaly diagnose and follow up patients with RD and research about the molecular basis, diagnostic/prognostic biomarkers and potential treatments for these diseases. We collaborate in:(i)PIBER-1:genomic medicine of Mitochondrial Medicine Program for the study of the EXOMA of patients with mitochondrial RD (TK2 mutations in adulthood);(ii)PIBER-2:physiopathology of RD (mtDNA maintenance syndromes) with U701,U717,U723 and U727; as well as (iii) in PIBERs 3 and 4:clinic and therapeutic research in RD specialized into to the following categories: (a) obstetric problems:intrauterine growth restriction with U719 (FIS1201199); (b)neurodegeneration:novel biomarkers for X-fragile syndrome with U726 (FIS1200879); familial Parkinson disease with CIBERNED (FIS1100462); common molecular mechanisms among RD,Parkinson,diabetes and Alzheimer (InterCIBER PIE1400061,12 groups CIBER); (c) myopathies: novel biomarkers for sporadic inclusion body myositis with U713 and U703; (d)mitochondrial toxicity (FIPSE 360982); (e)myocardiopathies:mitochondrial base of cardiac insufficiency; (f) mitochondrial genetic diseases: genetic therapy in MNGIE with U701 and U714 (ACCI). We administer 2 orphan drugs for rare myopathies and Pompe disease. Cellex Foundation allowed facility and human resources private funding. We also collaborate in PITER-1:(a)diagnosis of RD (with U701;U729;U717);(b)translation to the NHS of new diagnostic methods (with U717,U737,U701,U723,U727,U729);(c)clinical guide redaction for family/specialist clinicians; (d) creation of the 'Medical Assistance Group of Adult Patients with Rare Diseases' and the 'Attention Unit for Patients with Inborn Errors of Metabolism' (U703,U737 and U722) and the Internal Medicine/Endocrinology/Nutrition/Neurology/Gineacology services of the Hospital Clinic of Barcelona (intramural/CIBERER-2010), PITER-2: we collaborate through the donation of samples to the CIBERER Biobank and PITER-3: practical student training (grade;master ;PhD;MD;residents), tutorial CIBERER program and university classes (grade/master). Our researchers participate in mobility programs, CIBERER courses and meetings, diffusion of collaborative publications, international congresses and clinical assistance of consultancies directed to the CIBERER/Orphanet.

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Group U723

Programme: Mitochondrial and Neuromuscular Medicine

Lead Researcher: Martín Casanueva, Miguel A.

Group Members

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

ASSOCIATED MEMBERS: Atencia Cibreiro, María Gabriela | Delmiro Magdalena, Aitor | Domínguez González, Cristina | Esteban Pérez, Jesús | García Consuegra Galiana, Inés | García Redondo, Alberto | García Silva, María Teresa | Hoyo Gordillo, Pilar Del | Martínez Azorín, Francisco | Moran Bermejo, María Jesús | Rubio Muñoz, Juan Carlos | Rufian Vázquez, Laura | Ugalde Bilbao, Cristina

Main lines of research

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

Most relevant scientific articles

- Moran M, Delmiro A, Blazquez A, Ugalde C, Arenas J, Martin MA. Bulk autophagy, but not mitophagy, is increased in cellular model of mitochondrial disease. Biochim Biophys Acta - Molecular Basis of Disease. 2014;1842:1059 -1129
- Castro-Gago M, Dacruz-Alvarez D, Pintos-Martínez E, Beiras-Iglesias A, Delmiro A, Arenas J, Martín MÁ, Martínez-Azorín F. Exome sequencing identifies a CHKB mutation in Spanish patient with megaconial congenital muscular dystrophy and mtDNA depletion. Eur J Paediatr Neurol. 2014;18:796-800.
- Dols-Icardo O, García-Redondo A, Rojas-García R, Sánchez-Valle R, Noguera A, Gómez-Tortosa E, Pastor P, Hernández I, Esteban-Pérez J, Suárez-Calvet M, Antón-Aguirre S, Amer G, Ortega-Cubero S, Blesa R, Fortea J, Alcolea D, Capdevila A, Antonell A, Lladó A, Muñoz-Blanco JL, Mora JS, Galán-Dávila L, Rodríguez De Rivera FJ, Lleó A, Clarimón J. Characterization of the repeat expansion size in C9orf72 in amyotrophic lateral sclerosis and frontotemporal dementia.Hum Mol Genet 2014;23:749-54
- Toivonen JM, Manzano R, Oliván S, Zaragoza P, García-Redondo A, Osta R. MicroRNA-206: a potential circulating biomarker candidate for amyotrophic lateral sclerosis. PLoS One 2014;9:e89065
- Miguel A. Martin; Alejandro Lucía; Joaquín Arenas; Antoni L Andreu. Glycogen Storage Disease Type V. [Updated 2014 Jun 26]. GenReviews [Internet] Avalailable from http://www.ncbi.nlm.nih.gov/books/NBK1344/. Seattle (WA)(Estados Unidos de América): Pagon RA, Adam MP, Ardinger, et al, Editors. Seattle (WA), University of Washington.

Highlights

At translational-clinical level we are working to be involved as Natiornal Rerfence Unit (CSUR) for mitochondrial and hereditary metabolic diseases (Dr. García-Silva). This year the group has been very active in ALS and Fronto-Temporal Dementia (FTD) research line, identifying potential miRNAs as biomarkers, contributing remarkably to the characterization in Spain of the repeat expansion in the C9orf72 gene, and contributing on international cooperation to discover a novel gene associated with this disease, TUBA4A gene. As for mitochondrial disorders, we have studied the mechanisms of deregulation of the mitophagy/autophagy in cellular models derived from patients with different pathogenic mutations in different nuclear and mtDNA genes, and we have revealed some new mutations and correlations with paediatric phenotypes using exome sequencing (CHKB gen and megaconial congenital muscular dystrophy). We are working in collaboration with U701-CIBERER on a ISCIII project aimed to improve the molecular characterization of patients with OXPHOS disorder by different methods including next generation sequencing. We collaborated internationally identifying patients with mutations in the glycogenin-1 gene, a recent novel muscle glycogenoses. We updated the clinical and genetic characteristics of type V glycogenosis (GSDV) or McArdle disease in the GeneReviews (Washington University). We are leading a WP in an EAHC-EU project regarding European Registry of patients with McArdle disease (EUROMAC), which is intended to start its operability in early 2015. We kept the alliance with Prof. A. Lucia, Univ Europea de Madrid in approaches related to physical exercise, i.e McArdle patients, in aging, and in a graft-versus-host-disease mouse model.

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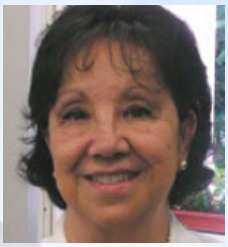
Group U724

Programme: Paediatric and Developmental Medicine



Lead Researcher: Martínez-Frías, Ma Luisa

Group Members

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Main lines of research

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

Most relevant scientific articles

- A new overgrowth syndrome is due to mutations in RNF125. Tenorio J, Mansilla A, Valencia M, Martínez-Glez V, Romanelli V, Arias P, Castrejón N, Poletta F, Guillén-Navarro E, Gordo G, Mansilla E, García-Santiago F, González-Casado I et al. Hum Mutat. 2014 Dec;35(12):1436-41. doi: 10.1002/humu.22689. PMID: 25196541
- European recommendations for primary prevention of congenital anomalies: a joined effort of EUROCAT and EUROPLAN projects to facilitate inclusion of this topic in the National Rare Disease Plans. Taruscio D, Arriola L, Baldi F, Barisic I, Bermejo-Sánchez E, Bianchi F, Calzolari E, Carbone P, Curran R, et al.. Public Health Genomics. 2014;17(2):115-23. doi: 10.1159/000360602. Epub 2014 Apr 3. PMID: 24714026
- Interstitial deletion 14q22.3-q23.2: genotype-phenotype correlation. Martínez-Frías ML, Ocejo-Vinyals JG, Arteaga R, Martínez-Fernández ML, Macdonald A, Pérez-Belmonte E, Bermejo-Sánchez E, Martínez S. Am J Med Genet A. 2014 Mar;164A(3):639-47. doi: 10.1002/ajmg.a.36330. Epub 2013 Dec 19. PMID: 24357464
- Haploinsufficiency of BMP4 gene may be the underlying cause of Frías syndrome. Martínez-Fernández ML, Bermejo-Sánchez E, Fernández B, MacDonald A, Fernández-Toral J, Martínez-Frías ML. Am J Med Genet A. 2014 Feb;164A(2):338-45. doi: 10.1002/ajmg.a.36224. Epub 2013 Dec 5. Review. PMID: 24311462

Highlights

• Maintenance of Clinical Network of ECEMC (> 400 physicians throughout Spain). • Clinical-dysmorphological evaluation of 757 newborns with congenital defects (CD) in Spain. • Cytogenetic study (high resolution and molecular): 215 samples from ECEMC network. • Attending 538 medical consultations to SITTE (Teratology Information Service, Spain) and 3,988 calls to SITE (Teratology Information Service for general public). • Epidemiological Surveillance of CD in Spain. • European Surveillance of CD in the EUROCAT network (www.eurocat-network.eu). • Worldwide epidemiological surveillance of CD in the ICBDSR network (www.icbdsr.org). • Continuation of work developed in the WP7 of "EUROCAT Joint Action (2011-2013)", EAHC, EU Health Programme 2008-2013. IP: Helen Dolk. Ref.2010 22 04. • Development of the Project: "Research on the clinical and etiological aspects of atypical congenital craniofacial clefts". IP: E. Bermejo-Sánchez. PI12 /00759. • Vice-Chair of the Executive Committee of ICBDSR. • Publication of 5 "Propositus: ECEMC Information Factsheets" (16,613 downloads in http://www.fundacion1000.es/boletines-ecemc). • Professor of the Official Master "Current knowledge on Rare Diseases". Universidad Internacional de Andalucía. • Professor of "Specialist Course in Childhood Disability" Universidad Complutense de Madrid • Multiple teaching activities and attendance of national and international conferences in the CD field. • Organisation of the "XXXVII Annual ECEMC Meeting" and "Update Course of CD Investigation". Toledo, 23 to 25 October 2014 [2,2 CME credits Madrid-NHS. File: 07-AFOC-04934.1 / 2014]. • Participation and organisation of the "41st Annual Meeting of the International Clearinghouse for Birth Defects, Surveillance and Research", Helsinki (Finland), 14-16 September 2014. • Four meetings of the "Clinical Teratology Conference". Organised by the Training Service of the General Directorate (GD) of Human Resources and the Public Health Observatory of the Public Health GD, Health Administration of Castilla and Leon, and the Research Center on Congenital Anomalies (CIAC). Valladolid, Leon, Burgos and Segovia.

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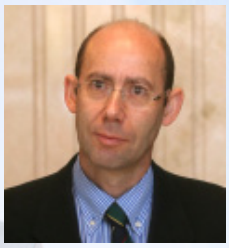
Grupo Asociado U725A

Programme: Endocrine Medicine



Lead Researcher: Castaño, Luis

Group Members

ASSOCIATED MEMBERS: Aniel Quiroga Rodríguez, María Ángeles | Bilbao Catalá, José Ramón | Busturia Jimeno, María Ángeles | Cortazar Galarza, Alicia | Gaztembide Sáenz, Sonia | Martul Tobio, Pedro | Rica Etxebarria, Itxaso | Vázquez San Miguel, Federico | Vela Desojo, Amaia

Main lines of research

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

Most relevant scientific articles

- Improving coeliac disease risk prediction by testing non-HLA variants additional to HLA variants. Romanos J, Rosén A, Kumar V, Trynka G, Franke L, Szperl A, Gutierrez-Achury J, van Diemen CC, Kanninga R, Jankipersadsing SA, Steck A, Eisenbarth G, van Heel DA, Cukrowska B, Bruno V, Mazzilli MC, Núñez C, Bilbao JR, Mearin ML, Barisani D, Rewers M, Norris JM, Ivarsson A, Boezen HM, Liu E, Wijmenga C. Gut; 2014 Mar. 63(3):415-22; PMID: 23704318 Doi: 10.1136/gutjnl-2012-304110.
- RET Cys634Arg mutation confers a more aggressive multiple endocrine neoplasia type 2A phenotype than Cys634Tyr mutation.. Valdés N, Navarro E, Mesa J, Casterás A, Alcázar V, Lamas C, Tébar J, Castaño L, Gaztambide S, Forga Llenas L. Eur J Endocrinol; 2014 Dec 16. [Epub ahead of print];. PMID: 25515555 Doi: 10.1530/EJE-14-0818 . .
- Hydrolyzed infant formula and early ß-cell autoimmunity: a randomized clinical trial.. Knip M, Åkerblom HK, Becker D, Dosch HM, Dupre J, Fraser W, Howard N, Ilonen J, Krischer JP, Kordonouri O, Lawson ML, Palmer JP, Savilahti E, Vaarala O, Virtanen SM. JAMA; 2014 Jun 11. 311(22):2279-87;. PMID: 24915259 Doi: 10.1001/jama.2014.5610. .
- Highly sensitive diagnosis of 43 monogenic forms of diabetes or obesity through one-step PCR-based enrichment in combination with next-generation sequencing. Bonnefond A, Philippe J, Durand E, Muller J, Saeed S, Arslan M, Martínez R, De Graeve F, Dhennin V, Rabearivelo I, Polak M, Cavé H, Castaño L, Vaxillaire M, Mandel JL, Sand O, Froguel P. Diabetes Care; 2014 Feb. 37(2):460-7;. PMID: 24041679 Doi: 10.2337/dc13-0698.
- Coregulation and modulation of NF?B-related genes in celiac disease: uncovered aspects of gut mucosal inflammation.. Fernandez-Jiménez N, Castellanos-Rubio A, Plaza-Izurieta L, Irastorza I, Elcoroaristizabal X, Jauregi-Miguel A, Lopez-Euba T, Tutau C, de Pancorbo MM, Vitoria JC, Bilbao JR. Hum Mol Genet; 2014 Mar 1. 23(5):1298-310;. PMID: 24163129 Doi: 10.1093/hmg/ddt520 .

Highlights

- Participation in the RENALTUBE Project (www.renaltube.com). "Maintenance, extension and improvement of RENALTUBE, clinical and molecular characterization system for renal Tubulopathies". ISCIII -PI11/01412 (2012-2014). Researchers: G Ariceta (IP), Castano L.
- Development of projects related to molecular characterization of monogenic diabetes (Basque Education Department GV IT795-13 and Basque Health Department GV 2010111185).
- Global prevalence of vitamin D levels of Gohierri-Urola-Gipuzkoa region in children. (Basque Health Department (2011111107), 2012-2015). Researchers: Elizabeth Blarduni, Castano L.
- Molecular characterization of hyperinsulinism, gonadal dysgenesis, pseudohypoparathyroidism and other endocrine diseases (Basque Education Department GV, IT795-13 (2013-2018). Researchers: Castano L (IP), Vitoria JC, Gaztambide S, Bilbao JR, Ariceta G, Vázque F).
- Participation in projects for the genetic characterization of celiac disease. "Functional characterization of the genomic regions associated with the risk of celiac disease in cells in the intestinal mucosa" (ISCIII-MICINN PI13/01201, 2014-2016); "Functional study of candidate genes for celiac disease and its potential application as a diagnostic tool." (Basque Government Health Department (2011111034), 2013-2015); "Systems Biology of autoimmunity. Celiac disease as a model" (ISCIII-MICINN PI10/00310, 2011-2014).

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Group U726

Programme: Paediatric and Developmental Medicine

Lead Researcher: Milà, Montserrat

Group Members

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Main lines of research

- Mental retardation of genetic origin.
- Familial cutaneous melanoma.
- Genodermatosis.
- Autism.
- Fragile X síndrome.

Most relevant scientific articles

- Griewank KG, Murali R, Puig-Butille JA, Schilling B, Livingstone E, Potrony M, Carrera C, Schimming T, Möller I, Schwamborn M, Sucker A, Hillen U, Badenas C, Malvehy J, Zimmer L, Scherag A, Puig S, Schadendorf D. TERT promoter mutation status as an independent prognostic factor in cutaneous melanoma. J Natl Cancer Inst; 2014 Sep. 106(9). PubMed; PMID: 25217772 Doi: 10.1093/jnci/dju246
- Puig-Butille JA, Escámez MJ, Garcia-Garcia F, Tell-Marti G, Fabra À, Martínez-Santamaría L, Badenas C, Aguilera P, Pevida M, Dopazo J, del Río M, Puig S. Capturing the biological impact of CDKN2A and MC1R genes as an early predisposing event in melanoma and non melanoma skin cancer. Oncotarget; 2014 Mar 30. 5(6):1439-5. PMID: 24742402
- Alarcon I, Carrera C, Alos L, Palou J, Malvehy J, Puig S. In vivo reflectance confocal microscopy to monitor the response of lentigo maligna to imiquimod. J Am Acad Dermatol; 2014 Jul. 71(1):49-55. PMID: 24725478 Doi: 10.1016/j.jaad.2014.02.043
- Potrony M, Puig-Butillé JA, Aguilera P, Badenas C, Carrera C, Malvehy J, Puig S. Increased prevalence of lung, breast, and pancreatic cancers in addition to melanoma risk in families bearing the cyclin-dependent kinase inhibitor 2A mutation: implications for genetic counseling. J Am Acad Dermatol; 2014 Nov. 71(5):888-95. PMID: 25064638 Doi: 10.1016/j.jaad.2014.06.036
- Alarcon I, Carrera C, Turegano P, Malvehy J, Puig S. Basal cell carcinoma with spontaneous regression: added value of reflectance confocal microscopy when the dermoscopic diagnosis is uncertain. J Am Acad Dermatol; 2014 Jul. 71(1):e7-9. PMID: 24947714 Doi: 10.1016/j.jaad.2014.01.877

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Group U727

Programme: Mitochondrial and Neuromuscular Medicine

Lead Researcher: Montoya, Julio

Group Members

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

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

Main lines of research

- Genetic and molecular diagnosis of mitochondrial DNA disorders and study of the physiopathogenic mechanism of mutations.
- Study of mtDNA population genetic variants conferring susceptibility to multifactorial diseases.
- Characterization of environmental 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 dtam cell as a model for he study of Physiopatologic mechanism of thr 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

- Kalko, G. S., Paco, S., Jou, C., Rodríguez, A. M., Meznaric, M., Rogac, M., Jekovec-Vrhovsek, M., Sciacco, M., Moggio, M., Fagiolari, G., De Paepe, B., De Meirleir, L., Ferrer, I., Roig-Quilis, M., Munell, F., Montoya, J., López-Gallardo, E., Ruiz-Pesini, E., Artuch, R., Montero, R., Torner, F., Nascimento, A., Ortez, C., Colomer, J., Jiménez-Mallebrera, C. "Transcriptomic profiling of TK2 deficient human skeletal muscle suggests a role for the p53 signalling pathway and identifies growth and differentiation factor-15 as a potential novel biomarker for mitochondrial myopathies" BMC Genomics. 15:91 (22 páginas), 2014. DOI: 10.1186/1471-2164-15-91
- Pesini, A., Iglesias E., Garrido N., Bayona-Bafaluy, M. P., Montoya, J., Ruiz-Pesini, E. "OXPHOS, pyrimidine nucleotides and Alzheimer disease: A pharmacogenomics approach". Journal of Alzheimer's Disease 42, 87-96, 2014.
- Martínez-Romero, I., Herrero-Martín, M. D., Llobet, L., Emperador, S., Martín-Navarro, A., Narberhaus, B., Ascaso, F. J., López-Gallardo, E., Montoya, J., Ruiz-Pesini, E. "A new MT-ND1 pathologic mutation for Leber hereditary optic neuropathy" Clin Exp Ophthalmol 42, 856-864, 2014. DOI: 10.1111/ceo.12355
- Lorente, L., Matín, M. M., López-Gallardo, E., Iceta, R., Blanquer, J., Solé-Violán, J., Labarta, L., Díaz, C., Jiménez, A., Montoya, J., Ruiz-Pesini, E. "Higher platelet cytochrome oxidase specific activity in surviving than in non-surviving septic patients". Crit. Care 18(3), R136 (7 páginas), 2014
- López-Gallardo, E., Emperador, S., Solano, S., Llobet, L., Martín-Navarro, A., López-Pérez, M. J., Briones, P., Pineda, M., Artuch, R., Barraquer, E., Jericó, I., Ruiz-Pesini, E., Montoya, J. "Expanding the clinical phenotypes of MT-ATP6 mutations" Hum Mol Genet. 23, 6191-6200, 2014. doi:10.1093/hmg/ddu339 Portada del número 23 de este volumen, dedicada a este artículo (figura 4).

Highlights

New mutations in the mitochondrial DNA (mtDNA) associated with new and already known phenotypes have been described. In particular, mutations in the MT-ATP6 gene), until now related only with syndromes of striatal necrosis, have been associated with metilglutaconica aciduria, LHON and NARP. These results show the importance of sequencing the gene or the complete mtDNA, at least, in patients with suspiction of suffering disease related to the mtDNA and that do not present histochemical and biochemical damage in the oxidative phosphorylation system and, therefore, not used to analyze. A figure of this article was the cover of the issue of Hum. Mol. Genet in which it was published. In addition, new nuclear genes related to mitochondrial disease have been described.

The results obtained in this period have allowed to reveal the molecular basis of several mitochondrial diseases. This was reaized in collaboration with groups intraCIBERER and other hospitals that do not belong to CIBERER, reflecting care clinical results, treatment, and basic research, providing a strong translational character. In addition, neural cybrids have been generated to study the effect of variations of the OXPHOS system in these diseases. Beside this, we have carried out experiments in order to study the interaction between mutations of mtDNA with different drugs and xenobiotics.

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Group U728

Programme: Sensorineural Pathology

Lead Researcher: Moreno Pelayo, Miguel Ángel

Group Members

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

ASSOCIATED MEMBERS: Borreguero Escribano, Lucía | Charaf Hasbani, Sara Romina | Del Castillo Fernández del Pino, Francisco Javier | Del Castillo Fernández del Pino, Ignacio | Domínguez Ruiz, María | Hernández Chico, Concepcion | Hernández Imaz, Elisabete | Hernández López, Alba Marina | Martín Santo Domingo, Yolanda | Melean Gumiel, Germán Ernesto | Moreno Herrero, Felipe | Olavarrieta Scappini, Luz Leticia | Pardo Merino, Beatriz | Rodríguez Álvarez, Francisco Javier | Rodríguez Ballesteros, Montserrat | Ruiz Palmero, Laura | Santos Serrao de Castro, Luciana | Villamar López, Manuela

Main lines of research

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

Most relevant scientific articles

- Three deaf mice: mouse models for TECTA-based human hereditary deafness reveal domain-specific structural phenotypes in the tectorial membrane. Legan PK, Goodyear RJ, Morín M, Mencia A, Pollard H, Olavarrieta L, Korchagina J, Modamio-Hoybjor S, Mayo F, Moreno F, Moreno-Pelayo MA, Richardson GP. Hum Mol Genet; 2014 May 15. 23(10):2551-68.
- Mutations in PRPS1 causing syndromic or non-syndromic hearing impairment: intrafamilial phenotypic variation complicates genetic counselling. Marta Gandía, Joaquín Fernández-Toral, Juan Solanellas, María Domínguez-Ruiz, Elena Gómez-Rosas, Francisco J. del Castillo, Manuela Villamar, Miguel A. Moreno-Pelayo, Ignacio del Castillo. Pediatric Research; 2014.
- Contribution of mutation load to the intrafamilial genetic heterogeneity in a large cohort of Spanish retinal dystrophies families. Sánchez-Alcudia R, Cortón M, Ávila-Fernández A, Zurita O, Tatu SD, Pérez-Carro R, Fernandez-San Jose P, Lopez-Martinez MÁ, del Castillo FJ, Millan JM, Blanco-Kelly F, García-Sandoval B, Lopez-Molina MI, Riveiro-Alvarez R, Ayuso C. Invest Ophthalmol Vis Sci; 2014 Nov. 55(11):7562-71.
- Similar phenotypes caused by mutations in OTOG and OTOGL. Oonk AM, Leijendeckers JM, Huygen PL, Schraders M, del Campo M, del Castillo I, Tekin M, Feenstra I, Beynon AJ, Kunst HP, Snik AF, Kremer H, Admiraal RJ, Pennings RJ. Ear Hear; 2014 35(3):e84-91.
- Progressive hearing loss and vestibular dysfunction caused by a homozygous nonsense mutation in CLIC5. Seco CZ, Oonk AM, Domínguez-Ruiz M, Draaisma JM, Gandía M, Oostrik J, Neveling K, Kunst HP, Hoefsloot LH, Del Castillo I, Pennings RJ, Kremer H, Admiraal RJ, Schraders M. Eur J Hum Genet; 2014 en prensa.

Highlights

- It has been activated the regularization procedure on group size that is currently composed of 11 members.
- We are picking up the publication pace by means of 5 manuscripts currently in preparation / publication. To emphasize the identification of the first gene associated with unilateral deafness in collaboration with the team of Prof. Hannie Kremer.
- Attempt to establish new collaborations both within the program Sensorineural pathology (reference group ACCI with Isabel Varela) as the gestation of SPÄNEX project (IPs. Pablo Lapunzina and Miguel Angel Moreno) as an example of leadership of a project resulting the benefit of the consortium and the rest of the extramural scientific community.
- Organization of an international symposium in collaboration with Professor Isabel Varela within the Ramón Areces Foundation due to scheduling conflicts has been taken place on 5-6 March 2015.
- We have received in the last annual two researchers from the University of Campinas (CNPQ program). This program (visitor Pesquisador) allowed in this case my shift at the University of Campinas for 1 month for the implementation of the latest techniques in the field of hearing loss (OTO-NGS-panel and OTO-array-CGH) we have generated in our laboratory.
- Fund raising in the last call of FIS with projects (PI14 / 1162; IP Ignacio del Castillo and PI14 / 0948, IP: Miguel Angel Moreno).
- As a consolidated group I lead in our research institute IRYCIS, we are part of consoricio IRYCIS who has received one of the projects of excellence granted to research institutes call 2013 (PE13 / 00040). In the field of innovation we hane renovated the innovation platform ITEMAS (node IRYCIS, PT13 / 0006/0002) of which I am IP in the Ramón y Cajal Hospital.

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Group U729

Programme: Mitochondrial and Neuromuscular Medicine

Lead Researcher: Navas, Plácido

Group Members

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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

- Yubero D, O Callaghan M, Montero R, Ormazabal A, Armstrong J, Espinos C, Rodríguez MA, Jou C, Castejon E, Aracil MA, Cascajo MV, Gavilan A, Briones P, Jiménez-Mallebrera C, Pineda M, Navas P, Artuch R. Association between coenzyme Q 10 and glucose transporter (GLUT1) deficiency. BMC Pediatr. 2014 Nov 8;14(1):284.
- Doimo M, Trevisson E, Airik R, Bergdoll M, Santos-Ocaña C, Hildebrandt F, Navas P, Pierrel F, Salviati L. Effect of vanillic acid on COQ6 mutants identified in patients with coenzyme Q10 deficiency. Biochim Biophys Acta. 2014 Jan;1842(1):1-6. doi: 10.1016/j.bbadis.2013.10.007.
- Siendones E, SantaCruz-Calvo S, Martín-Montalvo A, Cascajo MV, Ariza J, López-Lluch G, Villalba JM, Acquaviva-Bourdain C, Roze E, Bernier M, de Cabo R, Navas P. Membrane-bound CYB5R3 is a common effector of nutritional and oxidative stress response through FOXO3a and Nrf2. Antioxid Redox Signal. 2014 Oct 20;21(12):1708-25. doi: 10.1089/ars.2013.5479.
- Buján N, Arias A, Montero R, García-Villoria J, Lissens W, Seneca S, Espinós C, Navas P, De Meirleir L, Artuch R, Briones P, Ribes A. Characterization of CoQ□□ biosynthesis in fibroblasts of patients with primary and secondary CoQ□□ deficiency. J Inherit Metab Dis. 2014 Jan;37(1):53-62.
- Nguyen TP, Casarin A, Desbats MA, Doimo M, Trevisson E, Santos-Ocaña C, Navas P, Clarke CF, Salviati L. Molecular characterization of the human COQ5 C-methyltransferase in coenzyme Q10 biosynthesis. Biochim Biophys Acta. 2014 Nov;1841(11):1628-38. doi: 10.1016/j.bbalip.2014.08.007.

Highlights

We have maintained the group's activity with intense collaboratios with Rafael Artuch's and Antonia Ribes's groups in CEBERER, including collaboration with Leonardo Salviati (Padova), Sandra Jacson (Dresden), Iain Hargreaves (London) and Salvatore DiMauro (USA). We have advanced in the basic knowledgement of coenzyme Q synthesis regulation and have developed the following points. 1. We have shown a new version of our proposal for the consideration of ubiquinol as orfan medicament for primary deficiency in CoQ10 to the European Medicament Agency and we are developing a preclinical assay in mice showing deficiency in CoQ (ADCK2+/-) and a clinical assay in the San Juan de Dios Hospital in Barcelona, in cooperation with Rafael Artuch group. 2. We are developing the project eRARE2 coordinated by Pablo Menéndez and the internal project ACCI 2012 with Rafael Garesse (IP, U717) and Belén Pérez (U746) in which iPSCs are produced and differentiated from fibroblasts showing deficiency in CoQ synthesis. 3. In the ACCI 2014 call, we showed the proposal entitled "Study of the implication of the permeability transition pore in models of diseases secondarily affecting mitochondrial activity: putative use in diagnostic and therapy" with the participation of Jorgina Satrústegui (U743) (IP) and María Morán (U723). 4. We maintain the service of diagnostic of mitochondrial pathology and analysis of CoQ in muscle biopsies and/or primary fibroblasts of patients of public and private hospitals of Andalucía. 5. We have characterized a patient with haploinsuficiency of CoQ4, a gene involved in CoQ synthesis (Salviati et al. 2012) and have participated in the characterization of the only patients described showing punctate mutations in COQ4 (Brea-Calvo et al 2015). 6. We have also phenotypicaly characterized a KO mouse for ADCK2 gene. This mouse was developed by our group in 2012 and it mimics a muscle-specific deficiency in CoQ without affecting neuronal function.

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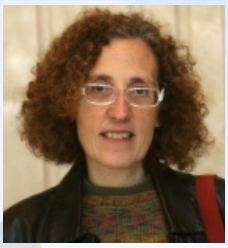
Group U730

Programme: Inherited Metabolic Medicine



Lead Researcher: Nunes, Virginia

Group Members

STAFF MEMBERS: González Simarro, Laura | López de Heredia Alonso, Miguel

ASSOCIATED MEMBERS: Prat Pedrola, Esther | Vilches Caubet, Clara

Main lines of research

- Heteromeric aminoacid transporters (cystinuria and lysinuria).
- Knockout model for megalencephalic leukoencephalopathy (MLC1).
- Molecular study of Wolfram Syndrome.
- News biochemical and genetis essays to identify MLC1 interactome.
- Characterization of the knockout mouse for LAT-2 transporter.
- Generation and characterization of the double LAT-2/Tat1 knockout mouse.

Most relevant scientific articles

- Megalencephalic leukoencephalopathy with subcortical cysts protein 1 regulates glial surface localization of GLIALCAM from fish to humans. Sirisi S, Folgueira M, López-Hernández T, Minieri L, Pérez-Rius C, Gaitán-Peñas H, Zang J, Martínez A, Capdevila-Nortes X, De La Villa P, Roy U, Alia A, Neuhauss S, Ferroni S, Nunes V, Estévez R, Barrallo-Gimeno A. Hum Mol Genet. 2014 Oct 1;23(19):5069-86. doi: 10.1093/hmg/ddu231. Epub 2014 May 12. (PMID:24824219)
- Cerebral cortex hyperthyroidism of newborn mct8-deficient mice transiently suppressed by lat2 inactivation. Núñez B, Martínez de Mena R, Obregon MJ, Font-Llitjós M, Nunes V, Palacín M, Dumitrescu AM, Morte B, Bernal J.PLoS One. 2014 May 12;9(5):e96915. doi: 10.1371/journal.pone.0096915. eCollection 2014. (PMID:24819605)
- Two novel mutations in the BCKDK (branched-chain keto-acid dehydrogenase kinase) gene are responsible for a neurobehavioral deficit in two pediatric unrelated patients.García-Cazorla A, Oyarzabal A, Fort J, Robles C, Castejón E, Ruiz-Sala P, Bodoy S, Merinero B, Lopez-Sala A, Dopazo J, Nunes V, Ugarte M, Artuch R, Palacín M, Rodríguez-Pombo P, Alcaide P, Navarrete R, Sanz P, Font-Llitjós M, Vilaseca MA, Ormaizabal A, Pristoupilova A, Aguló SB. Hum Mutat. 2014 Apr;35(4):470-7. doi: 10.1002/humu.22513. Epub 2014 Mar 5.(PMID:24449431)
- Disrupting MLC1 and GlialCAM and ClC-2 interactions in leukodystrophy entails glial chloride channel dysfunction. Hoegg-Beiler MB, Sirisi S, Orozco IJ, Ferrer I, Hohensee S, Auberson M, Gödde K, Vilches C, de Heredia ML, Nunes V*, Estévez R*, Jentsch TJ* (*Sharing corresponding authorship) Nat Commun. 2014 Mar 19;5:3475. doi: 10.1038/ncomms4475. (PMID:24647135)

Highlights

During the year 2014 we have continued working in our three lines of research on rare diseases: Wolfram Syndrome, Cystinuria and Megalencephalic Leukoencephalopathy with Subcortical cysts (MLC), in two of them in collaboration with other CIBERER units. We have created and participated respectively in the creation of the Spanish and European registries for the syndromes of Bardet-biedl, Alstrom and Wolfram. We are members of the international consortium for the advancement in the syndrome of Wolfram, sponsored by the French Association for 6 years. We have been until June 2014 Spanish partner of a European project (EURO-WABB), we have actively participated in the generation of guidelines for these syndromes and in the update of the entry for Wolfram Syndrome in Orphanet.

We have worked on the development of a functional assay, in which we are already working, to test the pathogenicity of different mutations in the WFS1 gene. Since last year we have continuing developing our FIS project which aim is to demonstrate the possible therapeutic role of a molecule with characteristics for modulating lithiasis of cystine in patients with Cystinuria using our murine Knockout model Slc7a9-/-. . We have characterized the animal model for other amino acids transporter, LAT-2, as well as its interaction with another amino acid transporter TAT1.We have participated in the elaboration of clinical guidelines for Cystinuria.

We keep on working in a project of the ELA Research Foundation which aim is to identify MLC 1 partners using the Mlc1 Knockout mouse model we have generated. We want to highlight a recent collaboration with MedDay Pharmacueticals to carry out a pilot trial to test a molecule as a possible therapy for MLC in this model. In two of the three projects we work actively on the lines proposed by Horizon 2020 trying to identify molecules with therapeutic effect.

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Group U731

Programme: Inherited Metabolic Medicine

Lead Researcher: Palacín, Manuel

Group Members

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

ASSOCIATED MEMBERS: Bodoy Salvans, Susana | Chillarón Chaves, Josep | Kowalczyk Mieczyslaw, Lukasz | Ratera Bastardas, Maria Mercè | Rodríguez de la Ballina, Laura | Rosell Febres, Albert | Valencia Sanmiguel, Eva María | Vázquez Ibar, José Luis

Main lines of research

- Structure and function of heteromeric aminoacid transporters. Physiopathology or renal reabsorption of aminoacids.

Most relevant scientific articles

- Structural bases for the interaction and stabilization of the human amino acid transporter LAT2 with its ancillary protein 4F2hc. Rosell A, Meury M, Álvarez-Marimon E, Costa M, Pérez-Cano L, Zorzano A, Fernández-Recio J*, Palacín M*, Fotiadis D*. (*; correspondence authors) Proc Natl Acad Sci U S A. 2014 Feb 25;111(8):2966-71. doi: 10.1073/pnas.1323779111. Epub 2014 Feb 10. PMID: 24516142
- Detergent-induced stabilization and improved 3D map of the human heteromeric amino acid transporter 4F2hc-LAT2. Meury M, Costa M, Harder D, Stauffer M, Jeckelmann JM, Brühlmann B, Rosell A, Ilgü H, Kovar K, Palacín M*, Fotiadis D*. (*; correspondence authors) PLoS One. 2014 Oct 9;9(10):e109882. doi: 10.1371/journal.pone.0109882. eCollection 2014.PMID: 25299125 [PubMed - in process]
- Two novel mutations in the BCKDK (branched-chain keto-acid dehydrogenase kinase) gene are responsible for a neurobehavioral deficit in two pediatric unrelated patients. García-Cazorla A, Oyarzabal A, Fort J, Robles C, Castejón E, Ruiz-Sala P, Bodoy S, Merinero B, Lopez-Sala A, Dopazo J, Nunes V, Ugarte M, Artuch R*, Palacín M*, Rodríguez-Pombo P* (*; correspondence authors)and the working group: Alcaide P, Navarrete R, Sanz P, Font-Llitjós M, Vilaseca MA, Ormaizabal A, Pristoupilova A, Agulló SB. Hum Mutat. 2014 Apr;35(4):470-7. doi: 10.1002/humu.22513. Epub 2014 Mar 5.PMID: 24449431
- Cerebral cortex hyperthyroidism of newborn mct8-deficient mice transiently suppressed by lat2 inactivation. Núñez B, Martínez de Mena R, Obregon MJ, Font-Llitjós M, Nunes V, Palacín M, Dumitrescu AM, Morte B, Bernal J.PLoS One. 2014 May 12;9(5):e96915. doi: 10.1371/journal.pone.0096915. eCollection 2014.PMID: 24819605 [PubMed - indexed for MEDLINE] Free PMC Article
- Autophagy-regulating TP53INP2 mediates muscle wasting and is repressed in diabetes. Sala D, Ivanova S, Plana N, Ribas V, Durán J, Bach D, Turkseven S, Laville M, Vidal H, Karczewska-Kupczewska M, Kowalska I, Straczkowski M, Testar X, Palacín M, Sandri M, Serrano AL, Zorzano A. J Clin Invest. 2014 May;124(5):1914-27. doi: 10.1172/JCI72327. Epub 2014 Apr 8.PMID: 24713655 [PubMed - indexed for MEDLINE] Free PMC Article

Highlights

We had generated and validated the first structural model at low resolution of a Heteromeric Amino acid Transporter (HAT), the human 4F2hc/LAT2 (publications 1 and 2). This model offers the first structural clues for the molecular recognition and stabilization of the light subunit (LAT2) by the heavy subunit (4F2hc). This model should also apply for HAT involved on rare diseases like lysinuric protein intolerance (4F2hc/y+LAT1) and cystinurias (rBAT/b0,+AT) (Fotiadis, Kanai y Palacín. Mol Aspects Med. 34:139-58, 2013).

In collaboration with a group of CIBERER units (U703, U715, U730 y U746) we had studied the activity associated to mutations causing BCKDK deficiency (publication 3) and with units U708 y U730 we performed the phenotyping of the double KO for the thyroid hormone transporters MCT8 and LAT2 (Publication 4). BCKDK deficit causes a form of inherited autism (Novarino et al. Science 338:394–397, 2012).In our work we did identify new BCKDK mutations that add epilepsy and neural developmental defects to the syndrome. Our unit U731 expressed and purifies to homogeneity for the first time human BCKDK, which allowed a direct determination of the intrinsic activity of BCKDK mutants and demonstrated loss-of-function of the identified mutations.

Mutations in MCT8 cause Allan-Herndon-Dudley syndrome, but MCT8 KO do not phenocopy the syndrome in mice, suggesting compensation by other thyroid hormone transporters. Because 4F2hc/LAT2 is also a thyroid hormone transporter the double KO for MCT8 and LAT2 was generated. These mice did not developed Allan-Herndon-Dudley syndrome but uncover an early postnatal role of 4F2hc/LAT2 in the supply of thyroid hormones to cerebral cortex.

Finally, in collaboration with Prof. Antonio Zorzano lab (CIBERDEM) we had demonstrated the role of TP53INP2-modulated autophagy on skeletal muscle wasting in type 2 diabetes (publication 5). This mechanism might be operative in other conditions with defective insulin action.

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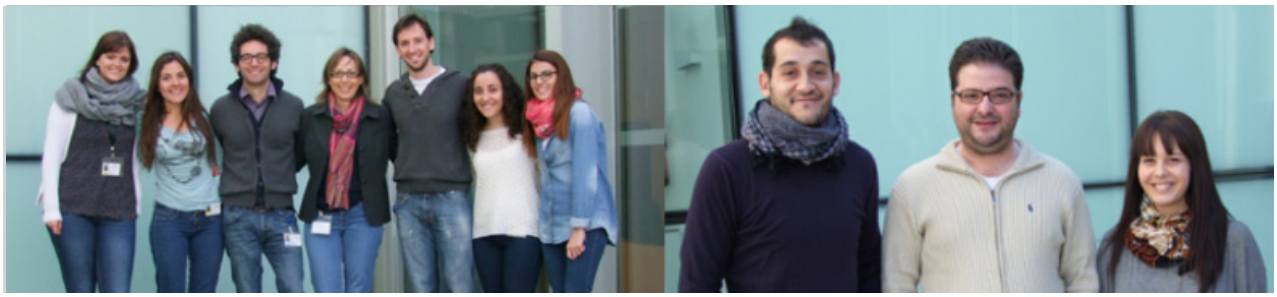
Group U732

Programme: Genetic Medicine



Lead Researcher: Palau, Francesc

Group Members

STAFF MEMBERS: González Cabo, Mª Pilar | Martínez Rubio, Mª Dolores | Molla Moliner, Belén.

AT THE EXPENSE OF THE PROJECT: Civera Tregón, Azahara | Juárez Gómez, Paula | Lupo Barretta, Vincenzo | Estela Bolta, Anna | López, Víctor | Riverio Arjomil, Fátima | Calpena, Eduardo.

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

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

Main lines of research

- Genetics and molecular epidemiology of neurological and pediatric rare diseases.
- Neurobiology and cellular physiopathology of mitochondrial-associated Charcot-Marie-Tooth neuropathies, Friedreich ataxia and Duchenne muscular dystrophy.
- Animal and cellular models of genetic disorders: comparative and functional genomics of Charcot-Marie-Tooth disease and cerebellar ataxias.

Most relevant scientific articles

- Pérez-Garrigues H, Sivera R, Vílchez JJ, Espinós C, Palau F, Sevilla T. Vestibular impairment is a relevant feature in SH3TC2 Charcot Marie Tooth disease (CMT4C). J Neurol Neurosurg Psychiatr 2014; 85: 824-827
- Calpena EL, Martínez-Rubio D, Sanz I, Montaner D, Rivolta C, García-Peñas JJ, Arpa J, Dopazo J, Palau F, Espinós C. Characterization of a new clinical form of hereditary recurrent neuropathy. Neuromusc Dis 2014; 24:660-665
- Bolinches-Amorós A, Mollá B, Pla-Martin D, Palau F, González-Cabo P. Mitochondrial dysfunction induced by frataxin deficiency is associated with cellular senescence and abnormal calcium metabolism. Front Cell Neurosci 2014;8:124
- Yubero D, O Callaghan M, Montero R, Ormazabal A, Armstrong J, Espinos C, Rodríguez MA, Jou C, Castejon E, Aracil MA, Cascajo MV, Gavilan A, Briones P, Jiménez-Mallebrera C, Pineda M, Navas P, Artuch R. Association between coenzyme Q 10 and glucose transporter (GLUT1) deficiency. BMC Pediatr 2014;14:284
- Ministerio de Sanidad, Servicios Sociales e Igualdad. Palau F (coordinador científico) et al. Estrategia en Enfermedades Raras del Sistema Nacional de Salud - Actualización aprobada por el Consejo Interterritorial del Sistema Nacional de Salud el 11 de junio de 2014.

  http://www.msssi.gob.es/organizacion/sns/planCalidadSNS/pdf/Estrategia_Enfermedades_Raras_SNS_2014.pdf

Highlights

The group has achieved several scientific milestones in 2014, although some of them were published in early 2015. These accomplishments are summarized: 1) We have shown that frataxin depletion associated with Friedreich's ataxia presents a bioenergetic deficit and a defect in the mitochondrial calcium handling with induction of cellular senescence; 2) we have shown that lack of GDAP1 in a murine KO model of recessive Charcot-Marie-Tooth disease type 2K disease affects mitochondrial alterations with depleted cytosolic calcium and that this may lead to axonal neuropathy (Barneo-Muñoz et al. PLoS Genet 2015); 3) we have shown by genetic and functional studies that JPH1 gene encoding the juntophilin-1 is a modifier gene in the clinical expression and severity of CMT2K dominant forms of neuropathy Charcot-Marie-Tooth disease due to R120W mutation in the GDAP1 gene (Pla-Martin et al. Hum Mol Genet 2015).

Under the EUCERD Joint Action No. 20112201, we have organized the Workshop on the preliminary results of the survey on expert centres in Europe, part of WP7 aimed at studying these centers as actions healthcare quality for rare diseases in the European context of the coming European Reference Networks (March 31-April 1, 2014, Madrid).

Along with CIBERER Unit 762 we have organized the International Symposium on 'Peripheral inherited neuropathies: from biology to therapy' at the Ramon Areces Foundation in Madrid.

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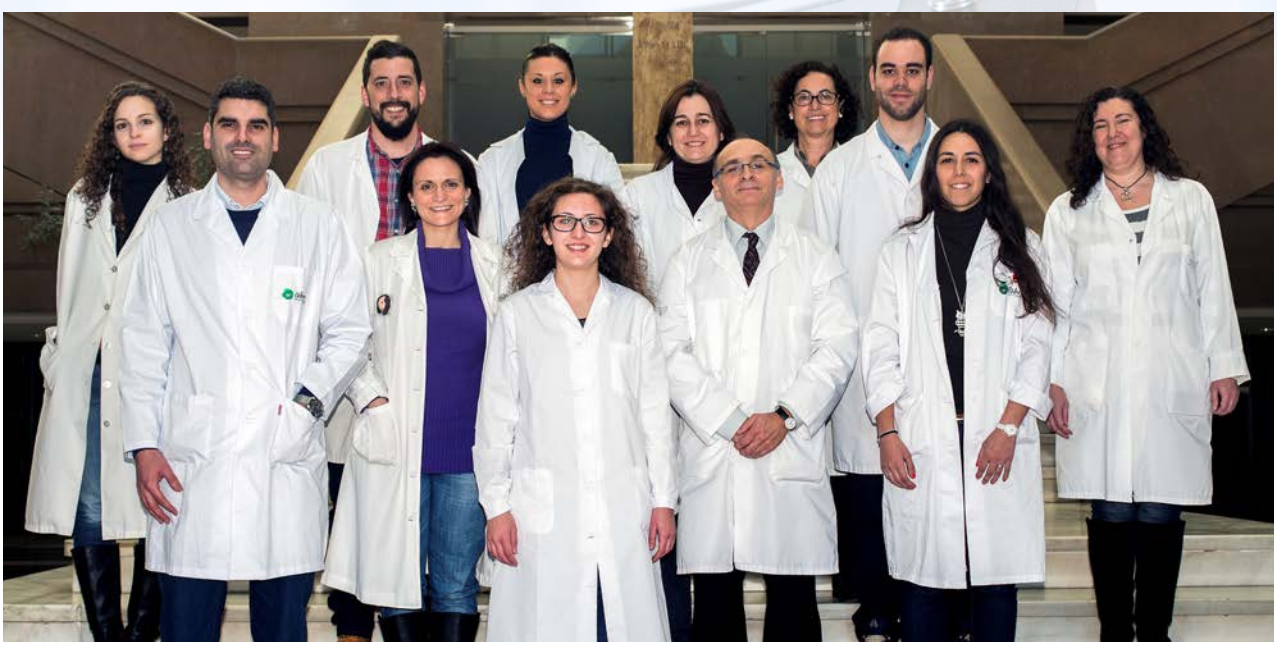
Group U733

Programme: Hereditary Cancer and Related Syndromes



Lead Researcher: Pallardó, Federico

Group Members

STAFF MEMBERS: García Giménez, José Luis

AT THE EXPENSE OF THE PROJECT: Seco Rivera, Marta

ASSOCIATED MEMBERS: Markovic, Jelena | Rus Rus, Ariana Diana | Santangelo Magrini, Gustavo

Main lines of research

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

Most relevant scientific articles

- García-Giménez JL. Seco-Cervera M, Aguado C, Romá-Mateo C, Dasí F, Priego S, Markovic J, Knecht E, Sanz P, Pallardó FV. Lafora disease fibroblasts exemplify the molecular interdependence between thioredoxin 1 and the proteasome in mammalian cells. Free Radic Biol Med. 2013 65C:347-359.
- Romá-Mateo C, Aguado C, García-Giménez JL, Ibáñez-Cabellos JS, Seco-Cervera M, Pallardó FV, Knecht E, Sanz P. Increased Oxidative Stress and Impaired Antioxidant Response in Lafora Disease. Mol Neurobiol. 2014 May 17. doi:10.1016/j.freeradbiomed.2015.01.034
- Manguan-Garcia C, Pintado-Berninches L, Carrillo J, Machado-Pinilla R, Sastre L, Pérez-Quilis C, Esmoris I, Gimeno A, García-Giménez JL, Pallardó FV, Perona R. Expression of the genetic suppressor element 24.2 (GSE24.2) decreases DNA damage and oxidative stress in X-linked dyskeratosis congenita cells. PLoS One. 2014 Jul 2;9(7):e101424. doi: 10.1371/journal.pone.0101424.
- López Del Amo V, Seco-Cervera M, García-Giménez JL, Whitworth AJ, Pallardó FV, Galindo MI. Mitochondrial defects and neuromuscular degeneration caused by altered expression of Drosophila Gdap1: implications for the Charcot-Marie-Tooth neuropathy. Hum Mol Genet. 2014 Aug 13. pii: ddu416.
- Seco-Cervera M, Spis M, García-Giménez JL, Ibañez-Cabellos JS, Velázquez-Ledesma A, Esmorís I, Bañuls S, Pérez-Machado G, Pallardó FV. Oxidative stress and antioxidant response in fibroblasts from Werner and Atypical Werner Syndromes. Aging (Albany NY). 2014 Mar;6(3):231-45.

Highlights

Unit 733 maintains a close collaboration with the following CIBERER groups, U721, U742, U714 and U757. In 2014 we have performed the following financed projects:" Study of miRNAs in Friedreich Ataxia patients. Diagnostic and therapeutic implications (FIS PI12/02263), patient samples have been stored at the CIBERER-Biobank, IRDiRC Project "TREAT-CMT" togheter with other CIBERER groups, two ACCI from CIBERER, an international Project financed by the "Saving Lives at Birth-Grand Challenges Canada Consortium" entitled: "Hist- Birth: Innovative and Rapid point-of-care histone test strips for early diagnosis of sepsis in pregnancy and childbirth" and two projects related to severe sepsis financed by Institute of Health Research INCLIVA and Generalitat Valenciana. We have launch teaching activities like the subject "Physiopathology of rare diseases" in the Master of Physiology (Quality course) and master of Biomedical Research from 2011 to 2015, we have also organized the course entitled: Rare diseases: research, clinical care and social consciousness" in the Escuela Valenciana de Estudios Sanitarios (EVES). Dr. Pallardó is the director of the ADEIT-Universitat de València (13721390) "master on rare diseases". In the section about knowledge transfer our group has developed "EpiDisease S.L." the first Spin-off in CIBER which main objective is to study epigenetic biomarkers in human diseases (26th June 2014). In this period our group has been awarded with the following prizes: National Award to Young from INJUVE (Ministry of Health, Social Services and Equity 201 and the award to the best business in R+D+i from "premios EmprenJove" by IVAJ Generalitat Valenciana in 2014.

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Group U734

Programme: Genetic Medicine

Lead Researcher: González Manchón, Consuelo

Group Members

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

Main lines of research

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

Most relevant scientific articles

- Sánchez-Guiu I, Antón AI, Padilla J, Velasco F, Lucía JF, Lozano M, Cid A, Sevivas T, Lopez-Fernandez MF, Vicente V, González-Manchón C, Rivera J, Lozano ML. Functional and molecular characterization of inherited platelet disorders in the Iberian Peninsula: results from a collaborative study. Orphanet J Rare Dis 2014 Dec, 9: 213-224
- de la Encarnación A, Alquézar C, Esteras N, Martín-Requero A. Progranulin deficiency reduces CDK4/6/pRb activation and survival of human neuroblastoma SH-SY5Y cells. Mol Neurobiol 2014, Nov 7 [Epub ahead of print] PMID:25377796
- Horrillo A, Fontela T, Arias-Salgado EG, Llobat D, Porras G, Ayuso MS, González-Manchón C. Generation of mice with conditional ablation of the Cd40lg gene: new insights on the role of CD40L. Transgenic Res 2014 Feb, 23(1):53-66
- Esteras N, Alquézar C, Bartolomé F, de la Encarnación A, Bermejo-Pareja F, Molina JA, Martín-Requero A. G1/S cell cycle checkpoint dysfunction in lymphoblasts fromSporadic Parkinson's disease patients. Mol Neurobiol 2014, Sep 3. [Epub ahead of print] PMID:25182869
- Alquezar C, Esteras N, de la Encarnación A, Moreno F, Lopez de Munain A, Martin-requero A. Increasing PGRN levels and blockade of the ERK pathway: Upstream and downstream strategies for the treatment of PGRN deficient frontotemporal dementia. Eur Neuropsychopharmacology, doi:10.1016/j.euroneuro.2014.12.007

Highlights

- The generation and phenotypic characterization of "knockout" mice with conditional ablation of CD40L at different stages of hematopoietic development has provided relevant results to understand the pathogenesis and clinical manifestations of X-linked hyper-IgM syndrome due to mutations in the Cd40lg gene (ORPHA # 69712).
- We have developed a mouse model lacking podocalicina (Podxl) in the vascular endothelium that represents an excellent tool for studying human vasculitis (ORPHA52759) and the mechanisms controling vascular permeability.
- We conducted an epidemiological study in collaboration with the research group of doctors Vincent and Rivera (Hospital Morales Meseguer, Murcia) on the incidence and identification of new mutants and diagnostic difficulties of inherited platelet diseases in the Iberian Peninsula. In this study, 14 hospitals have provided a total of 70 cases of 8 different disorders.
- We are interested in mechanisms that cause cell death in disorders such as Alzheimer's disease (AD), frontotemporal dementia (FTLD) and other neurodegenerative disorders, in order to identify potential therapeutic targets and to find useful biomarkers for the early diagnosis and/or track disease status. The work focuses on cell cycle dysfuntion, apoptosis, mitochondrial impairment, oxidative damage, and protein degradation using in vivo models of neurodegeneration and in vitro culture of cells, including peripheral cells from patients. Main findings can be summarized as follows:

  1) We have detected altered gene expression in lymphocytes and brain of a murine model of familial AD, as well as in lymphocytes of AD patients.

  2) The increased levels of calmodulin found in lymphocytes and plasma of AD patients may serve as a biomarker for early diagnosis of AD.

  3) We have identified potential therapeutic targets in the Wn5a/CamKII/ERK1/2/CDK6/pRB signaling pathway for the treatment of progranulin-linked FTLD (ORPHA#98929).

  4) We began studies aimed at the repositioning of drugs for the treatment of idiopathic Parkinson disease.

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http://www.cib.csic.es/es/grupo.php?idgrupo=58" - https://www.cib.csic.es/es/grupo.php?idgrupo=57

Group U735

Programme: Paediatric and Developmental Medicine

Lead Researcher: Pérez Jurado, Luis A.

Group Members

STAFF MEMBERS: Cusco Martí, Ivon | Gutiérrez Arumi, Armand | Serra Juhe, Clara

ASSOCIATED MEMBERS: Campuzano Uceda, Victoria | Del Campo Casanelles, Miguel | Flores Peirats, Raquel | Palacios Verdú, María Gabriela | Pérez García, Débora | Rodríguez Santiago, Benjamín

Main lines of research

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

Most relevant scientific articles

- Argente J, Flores R, Gutiérrez-Arumí A, Verma B, Martos-Moreno GÁ, Cuscó I, Oghabian A, Chowen JA, Frilander MJ, Pérez-Jurado LA. Defective minor spliceosome mRNA processing results in isolated familial growth hormone deficiency. EMBO Mol Med 6:299-306 (2014).
- González JR, A Cáceres A, Esko T, Cuscó I, (7 more authors), Pérez-Jurado LA. A common inversion polymorphism at 16p11.2 underlies the joint susceptibilityto asthma and obesity. Am J Hum Genet 94(3):361-72 (2014).
- Segura-Puimedon M, Sahún I, Velot E, Dubus P, Borralleras C, Rodrigues AJ, Valero MC, Valverde O, Sousa N, Herault Y, Dierssen M, Pérez-Jurado LA, Campuzano V. Heterozygous deletion of the Williams-Beuren syndrome critical interval in mice recapitulates most features of the human disorder. Hum Mol Genet. 23:6481-6494 (2014).
- Binelli C, Subira, Batalla A, Muñiz A, Sugranyes G, Crippa JA, Farre M, Pérez-Jurado LA, Martín-Santos R. Common and distinct neural correlates of facial emotion processing in Social Anxiety Disorder and Williams Syndrome: a systematic review and voxel-based meta-analysis of functional resonance imaging studies. Neuropsychologia, 64C:205-217 (2014).
- Pérez-García D, Flores R, Brun-Gasca C, Pérez-Jurado LA. Lateral preference in Williams-Beuren syndrome is associated with cognition and language. Eur Child Adolesc Psychiatry. 2014 Nov 28. [Epub ahead of print]

Highlights

Our group has contributed over the years to unravel the pathophysiologic mechanisms of Williams-Beuren syndrome (WBS). Recent clinical research led to a better description of novel metabolic and neurobehavioral features of the disease (Palacios JMG 2015, Pérez-García ECAP 2014), and abnormal brain activation related to anxiety disorder (Binelli NeuroPsy 2014). We have also generated the best mouse model for WBS showing neurobehavioral and craniofacial anomalies (Segura-Puimedon HMG 2014). We have obtained funding for searching therapeutic targets for the cardiovascular and cognitive features (Innopharma) and for the simultaneous study of WBS and the reciprocal microduplication syndrome (Todos Somos Raros). We have consolidated a referral clinical unit for the multidisciplinary management of these disorders in the Hospital del Mar, Barcelona.

Our work on structural variants of the human genome has contributed to the identification of clonal mosaicism for chromosomal rearrangements as a strong and aging-related susceptibility factor (and marker) for hematological and solid cancer (Machiela AJHG 2015). We have also found that submicroscopic inversions can behave as contiguous gene susceptibility syndromes explaining joint genetic susceptibility to some disorders and common traits, such as the novel 16p11.2 inversion related to asthma and obesity (Gonzalez AJHG 2014).

In terms of clinically driven research we have identified and characterized a novel syndrome associated with pituitary hypoplasia and growth hormone deficiency caused by mutations in a protein of the minor spliceosome that regulates the processing of hypophyseal genes (Argente EMM 2014) and participated in the clinical-molecular definition of several other disorders.

In addition to the diverse scientific contributions as publications, our research has obtained relevant translational results, contributing to the diagnosis of patients and their genetic counseling, the development of novel tools useful for the clinical labs, the consolidation of the spin-off company qGenomics, and the evaluation of potential therapeutic agents for a rare disease, WBS.

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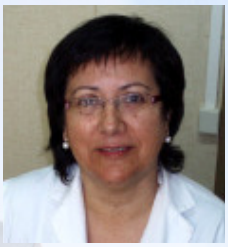

Group U737

Programme: Inherited Metabolic Medicine

Lead Researcher: Ribes, Antonia

Group Members

STAFF MEMBERS: Matalonga Borrel, Lesley | Tort Escalé, Frederic

AT THE EXPENSE OF THE PROJECT: Oreiro García, Mª Teresa | Barbosa Sousa Gouveia, Sofía Isabel

ASSOCIATED MEMBERS: Briones Godino, María Paz | Bujan Murla, Nuria | Coll Rosell, María José | Fernández Sierra, Cristina | Ferrer Cortes, Xenia | Giros Blasco, María Luisa | Gort Mas, Laura | Lluch Mir, Montserrat | Macias Vidal, Judit | Pampols Ros, Teresa

Main lines of research

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

Most relevant scientific articles

- Tort F, Ferrer-Cortès X, Thió M, Navarro-Sastre A, Matalonga L, Quintana E, et al. Mutations in the lipoyltransferase LIPT1 gene cause a fatal disease associated with a specific lipoylation defect of the 2-ketoacid dehydrogenase complexes. Hum Mol Genet. 2014; 23(7):1907-15.
- Mayr JA, Feichtinger RG, Tort F, Ribes A, Sperl W. Lipoic acid biosynthesis defects. J Inherit Metab Dis. 2014; 37(4): 553-63.
- Cañueto J, Girós M, González-Sarmiento R. The role of the abnormalities in the distal pathway of cholesterol biosynthesis in the Conradi-Hünermann-Happle syndrome. Biochim Biophys Acta. 2014; 1841(3): 336-44.
- Buján N, Arias A, Montero R, García-Villoria J, Lissens W, Seneca S, et al. Characterization of CoQ10 biosynthesis in fibroblasts of patients with primary and secondary CoQ10 deficiency. J Inherit Metab Dis. 2014; 37(1): 53-62.
- Matalonga L, Arias A, Coll MJ, Garcia-Villoria J, Gort L, Ribes A. Treatment effect of coenzyme Q(10) and an antioxidant cocktail in fibroblasts of patients with Sanfilippo disease. J Inherit Metab Dis. 2014; 37(3): 439-46.

Highlights

In 2011 our group identified a new gene, NFU1, in humans. Thanks to this finding the knowledge of the metabolic pathway of lipoic acid biosynthesis in humans started to grow. Using the biochemical stratification proposed in previous study and thanks to the previous knowledge in yeast, our group identified mutations in another new gene in this metabolic pathway, LIPT1, in 2014 . In addition we would like to remark that the modification of this metabolic pathway, thanks to our work, has been accepted by the scientific community and we have been invited recently to participate in a review about the defects in the biosynthesis of lipoc acid (JIMD 2014, 37:553-563).

On the other hand, we have identified new disease-causing genes through exome sequencing or other NGS strategies. It is remarkable the study of families with 3-methylglutaconic aciduria. Among them we have found a family with mutations in a candidate gene, of which there is still no evidence in the literature that associates it to human disease. Moreover, also in this large subgroup, we identified mutations in other genes associated with disease (DNAJC19, TMEM70, ATP12, SERAC1, ECHS1, NDUFAF4, NADK2). We have identified mutations in another gene associated with disorders of protein glycosylation and complex V deficiency, yet not associated with human pathology and in which we are conducting functional studies. These works are pendent of imminent publication.

Concerning therapies, we have found a compound that could potentially act as a pharmacological chaperone for glutaric aciduria type I. In the study of treatments for lysosomal diseases we found a compound capable of inducing exocytosis . This compound is currently patented and licensed in collaboration with the company BCN-peptides.

Current projects in 2014: 2 projects FIS; 1 DG-SANCO; 1 AGAUR Autonomous Community, 1 Project CNAG and 1 non-competitive project BIOMARIN.

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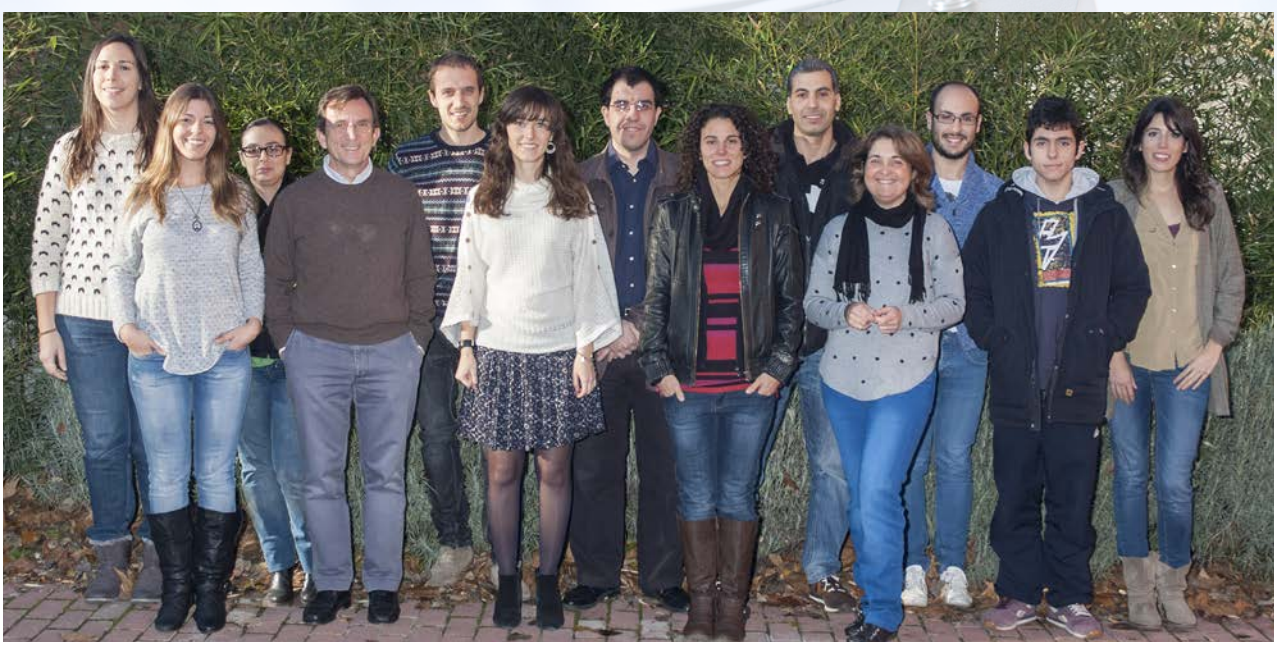
Group U738

Programme: Genetic Medicine



Lead Researcher: Rodríguez de Córdoba, Santiago

Group Members

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

ASSOCIATED MEMBERS: Durán Trío, Lara | Navarro Fernández-Balbuena, Carmen | 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

- Subías Hidalgo M., Tortajada A., Gastoldi S., Galbusera M., López-Perrote A., de Juana López L., González-Fernández FA., Villegas-Martínez A., Domínguez M., Llorca O., Noris M., Morgan PB. and Rodríguez de Córdoba S. A novel antibody against human factor B that blocks formation of the C3bB proconvertase and inhibits complement activation in disease models. J. Immunol. 193(11):5567-75 (2014)
- Sánchez-Chinchilla D.#, Pinto S.#, Hoppe B., Adragna M., López L., Justa Roldan ML., Peña A., López-Trascasa M., Sánchez-Corral P. and Rodríguez de Córdoba S. Complement Mutations in Diacylglycerol Kinase-ε-Associated atypical Hemolytic Uremic Syndrome. Clin J Am Soc Nephrol. 9:1611-1619 (2014) (# Equal contribution authors)
- Sánchez-Moreno A., de la Cerda F., Cabrera R., Fijo J., López-Trascasa M., Bedoya R., Rodríguez de Córdoba S. and Ybot-González P. Eculizumab in Dense-Deposit Disease after renal transplantation. Pediatr. Nephrol. 29:2055-2059 (2014)
- Rodríguez de Córdoba S., Subías-Hidalgo M., Pinto S. and Tortajada A. Genetics of atypical Hemolytic Uremic Syndrome (aHUS). Semin Thromb. Hemost. 40:422-430 (2014)
- Gayarre J., Durán-Trío L., Criado García O., Aguado C., Juana-López L., Crespo I., Knecht E., Bovolenta P. and Rodríguez de Córdoba S. The phosphatase activity of laforin is dispensable to rescue Epm2a-/- mice from Lafora disease. Brain. 137:806-18 (2014)

Highlights

Our research and translational activity focus in the study of rare diseases associated with complement dysregulation and in Lafora disease. Our 2014 contributions, identifying new genetic associations or characterizing novel pathogenic mechanisms, represent important advances in our understanding of these disorders and provide new therapeutic possibilities. In different reviews and consensus reports published, or submitted for publication, during this period we have summarized our opinion in relation to the association between complement and disease, highlighting the importance contribution that complement dysregulation plays in diseases like atypical Uremic Hemolytic Syndrome and C3-glomerulopathies and how this improved knowledge of rare diseases have also important consequences in prevalent diseases like Age-related Macular Degeneration and IgA Nephropathy. During 2014 our laboratory lectured 25 educational talks or seminars to different clinical groups (national and international), where we emphasized these important advances in the complement field and the usefulness of this knowledge in the clinical practice. During 2014 we have continue developing diagnostics strategies, including, a CGH array for the detection of CNV in complement genes and a platform for the screening by NGS of the genes associated with aHUS.

Also, we begin a research study in order to generate complement inhibitors with therapeutic interest, which has already generated a patent for an anti-FB antibody. 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 88 during 2014) with a genetic and molecular analysis of the complement system and specific suggestions related to their treatments. Also of strategic interest is the registry of patients with renal pathology that we have developed with the supervision and support of CIBERER.

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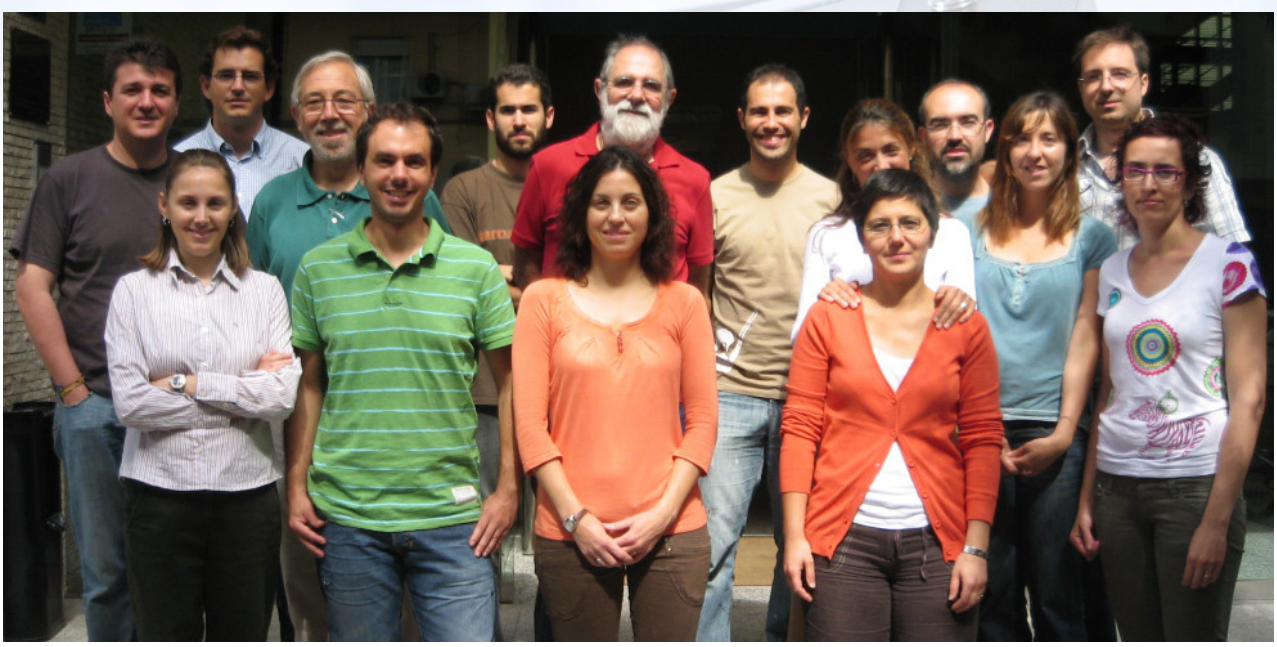
Group U739

Programme: Inherited Metabolic Medicine



Lead Researcher: Rubio, Vicente

Group Members

STAFF MEMBERS: De Cima Martín, Sergio | Gougeard, Nadine

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

- Hu L, Diez-Fernandez C, Rüfenacht V, Hismi BÖ, Ünal Ö, Soyucen E, Çoker M, Bayraktar BT, Gunduz M, Kiykim E, Olgac A, Pérez-Tur J, Rubio V, Häberle J. Recurrence of carbamoyl phosphate synthetase 1 (CPS1) deficiency in Turkish patients: characterization of a founder mutation by use of recombinant CPS1 from insect cells expression. Mol Genet Metab. 2014;113(4):267-273.
- Díez-Fernández C, Hu L, Cervera J, Häberle J, Rubio V. Understanding carbamoyl phosphate synthetase (CPS1) deficiency by using the recombinantly purified human enzyme: effects of CPS1 mutations that concentrate in a central domain of unknown function. Mol Genet Metab. 2014;112:123-132.
- Casino P, Miguel-Romero L, Marina A. Visualizing autophosphorylation in histidine kinases. Nat Commun. 2014;5:3258.
- Häberle J, Rubio V. Hyperammonemia and related disorders. In: Blau N, Durán R, Gibson KM, Blaskovics M and Dionisi-Vici C, eds. Physician's Guide to the Diagnosis, Treatment, and Follow-Up of Inherited Metabolic Diseases. Heidelberg: Springer -Verlag; 2014. pgs. 47-62
- Sanjurjo P, Rubio V. Diagnóstico y tratamiento de las enfermedades del ciclo de la urea. En: Sanjurjo P, Balldellou A, eds. Diagnóstico y tratamiento de las enfermedades metabólicas hereditarias. 4ª ed. Majadahonda, Madrid: Ergon; 2014. pgs. 713-728.

Highlights

The five publications selected aim at reflecting different lines of our action within CIBERER, rather than bibliographic impact factors. They try to exemplify basic advances (Nature Communications paper), translational science (see both papers in Molecular Genet Metab) and plain translation of international reach (chapter of the paradigmatic Blau book on Inherited Metabolic Diseases) and of hispanic reach (chapter in the Spanish bible on inborn metabolic errors, the book edited by Sanjurjo). I will highlight here that our commitment and experience on urea cycle disorders and of structure-function studies (based on our abilities on crystallography and on recombinant protein expression) has focused this year on cracking carbamoyl phosphate synthetase deficiency (a urea cycle disorder). Our initial breakthough of 2013, the in vitro expression of abundant and highly pure human carbamoyl phosphate synthetase 1 (CPS1), has enabled us to attack this year the experimental study in collaboration with the most important clinical group in Europe for CPS1 deficiency (led by Prof. Johannes Häberle, Hospital Pediátrico de Zürich) of the consequences of the numerous clinical mutations found in patients with CPS1 deficiency. This translational research activity of our group is in its high, and is bound to give further highly relevant clinical and scientific fruits in 2015, with one paper accepted already, a PhD Thesis deposited which has as exclusive subject CPS1 deficiency, and another two papers on this disorder at the writing stage, one of them a great structural breaktrough of high translational relevance. All of this stems from our activity in 2014. The group is involved in the current updating of our prior European clinical guideline on urea cycle disorders; in preparing the AECOM's (Asociación Española sobre Errores Congénitos del Metabolismo) guide on inborn hyperammonemia; and is working very actively on translational studies on pyrrolin-5-carboxylate synthetase and acetilglutamate synthase deficiencies.

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Group U740

Programme: Inherited Metabolic Medicine

Lead Researcher: Salido, Eduardo

Group Members

STAFF MEMBERS: Rodríguez Rodríguez, Bárbara

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

Main lines of research

- Inherited metabolic disease.
- Inherited renal diseases.

Most relevant scientific articles

- Mesa-Torres N, Salido E, Pey AL. The lower limits for protein stability and foldability in primary hyperoxaluria type I. Biochim Biophys Acta. 2014 Oct 18;1844(12):2355-2365.
- Mesa-Torres N, Yunta C, Fabelo-Rosa I, Gonzalez-Rubio JM, Sánchez-Ruiz JM, Salido E, Albert A, Pey AL. The consensus-based approach for gene/enzyme replacement therapies and crystallization strategies: the case of human alanine-glyoxylate aminotransferase. Biochem J. 2014 Sep 15;462(3):453-63.
- Hernández-Guerra M, González-Méndez Y, de Ganzo ZA, Salido E, García-Pagán JC, Abrante B, Malagón AM, Bosch J, Quintero E. Role of gap junctions modulating hepatic vascular tone in cirrhosis. Liver Int. 2014 Jul;34(6):859-68.
- Luis-Lima S, Gaspari F, Porrini E, García-González M, Batista N, Bosa-Ojeda F, Oramas J, Carrara F, González-Posada JM, Marrero D, Salido E, Torres A. Measurement of glomerular filtration rate: internal and external validations of the iohexol plasma clearance technique by HPLC. Clin Chim Acta. 2014 Mar 20;430:84-5.
- Tippin BL, Kwong AM, Inadomi MJ, Lee OJ, Park JM, Materi AM, Buslon VS, Lin AM, Kudo LC, Karsten SL, French SW, Narumiya S, Urade Y, Salido E, Lin HJ. Intestinal tumor suppression in ApcMin/+ mice by prostaglandin D2 receptor PTGDR. Cancer Med. 2014 Aug;3(4):1041-51.

Highlights

Research projects:

- SAF2011-23933 Molecular therapy of primary hyperoxaluria. MINECO.
- REGPOT-FP7-2012-CT2012-316137 Improvement of biomedical research and innovation in the Canary Islands. EU-FP7

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Group U741

Programme: Inherited Metabolic Medicine

Lead Researcher: Sánchez Jiménez, Francisca Mª

Group Members

STAFF MEMBERS: Reyes Palomares, Armando | Rodríguez López, Rocío.

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

Main lines of research

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

Most relevant scientific articles

- Rodríguez-López R, Reyes-Palomares A, Sánchez-Jiménez F, Medina M. PhenUMA: a tool for integrating the biomedical relationships among genes and diseases. BMC Bioinformatics. 2014; 15(1): 375. PMID: 25420641.
- Perkins JR, Ayuso P, Cornejo-García JA, Ranea JA. The study of severe cutaneous drug hypersensitivity reactions from a systems biology perspective. Curr Opin Allergy Clin Immunol. 2014; 14(4): 301-6. PMID: 24905771.
- Castro-Oropeza R, Pino-Ángeles A, Khomutov MA, Urdiales JL, Moya-García AA, Vepsäläinen J, Persson L, Sarabia F, Khomutov A, Sánchez-Jiménez F. Aminooxy analog of histamine is an efficient inhibitor of mammalian L-histidine decarboxylase: combined in silico and experimental evidence. Amino Acids. 2014; 46(3): 621-31. PMID: 24129980.
- Sánchez-Jiménez F, Reyes-Palomares A, Moya-García AA, Ranea JA, Medina MÁ. Biocomputational resources useful for drug discovery against compartmentalized targets. Curr Pharm Des. 2014; 20(2): 293-300. PMID: 23701544.
- García-Caballero M, Cañedo L, Fernández-Medarde A, Medina MÁ, Quesada AR. The marine fungal metabolite, AD0157, inhibits angiogenesis by targeting the Akt signaling pathway. Mar Drugs. 2014; 12(1): 279-99. PMID: 24441613

Highlights

In 2014, the unit 741 has accomplished a first phase of PhenUMA development (www.phenuma.uma.es; Rodríguez-López et al., 2014). We continue implementing the tool with genetic variant and metabolic data. We have established partnerships with various CIBERER groups (and others, eg. Perkins et al, 2014). They are giving promising results (unpublished results). The PhenUMA developers (CIBERER staff members) were awarded with the Malaga Young 2014 prize (Junta de Andalucia).

The group also maintains experimental activity in the field of biogenic amines. These biomolecules are involved in many low prevalence diseases (rare tumors, idiopathic inflammations, neuropathology, etc). We have published on the adverse effects of overproduction of histamine and we have found a new family of compounds with pharmacological potential as modulators of the histamine production (Castro-Oropeza et al., 2014). In some of the recent reviews published by the group, we express our perspective on advances in biogenic amine systems biomedicine (eg. Sánchez-Jiménez et al, 2014).

A part of our unit works in angiogenesis drug development, with translational potential for many rare diseases. We located a couple of promising compounds (eg. García-Caballero et al, 2014.).

Within the CIBERER framework, we have participated in various training events and promotion of in silico technology (molecular modeling and dynamics) for the development of pharmacological chaperones, as we were taking part in the development of pharmacological chaperones against Gaucher disease.

The CIBERER staff member Armando Reyes-Palomares defended his doctoral thesis with European mention and the highest qualification.

We consider that our group is perfectly into CIBERER. As our activity has essentially a holistic nature, it can work synergistically with other basic and clinical CIBERER groups.

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Group U742

Programme: Genetic Medicine

Lead Researcher: Sanz, Pascual

Group Members

STAFF MEMBERS: García Gimeno, Adelaida | Heredia Pérez, Miguel

ASSOCIATED MEMBERS: Berthier, Arnaud

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

- Romá-Mateo, C., Aguado, C., Garcia-Gimenez, J.L., Ibañez-Cabellos, S., Seco-Cervera, M. Pallardo, F.V., Knecht, E., Sanz, P. "Increased oxidative stress and impairment of antioxidant systems in Lafora disease models". Mol. Neurobiol. PMID: 24838580 (2014).
- Raththagala M, Brewer K.M., Parker M.W., Sherwood A.R., Wong B.K., Hsu S., Bridges T.M., Paasch B.C, Hellman L.M, Husodo S., Meekins D.A., Taylor A.O., Turner B.D., Auger K.D., Dukhande V.V., Chakravarthy S., Sanz P., Woods V.V., Li S., Vander Kooi C.W. and Gentry M.S. "Structural Mechanism of Laforin Function in Glycogen Dephosphorylation and Lafora Disease". Molecular Cell. PMID: 25544560 (2014).

Highlights

- We have demonstrated that in fibroblasts from Lafora disease (LD) patients there is increase oxidative stress, due probably to a mitochondrial dysfunction. These results were confirmed in mouse models of Lafora disease, suggesting that oxidative stress should be considered as a new parameter in the pathophysiology of LD (Romá-Mateo et al., 2014 Mol. Neurobiol, PMID: 24838580).
- We have solved the crystal structure of laforin. This protein has two characteristic structural domains, a carbohydrate binding module (CBM) and a dual specificity phosphatase domain (DSP). The solved structure allows the localization of the amino acid residues that are mutated in LD patients y their pathologic potential (Raththagala et al., 2014, Mol Cell, PMID: 25544560).
- We have presented a patent on new AMP-activated protein kinase (AMPK) activators. Due to the importance of AMPK in metabolic, cardiovascular, inflammatory and neurological diseases, we expect to attract pharmaceutical companies interested in developing these compounds (Castro et al., 2014 P201431364).
- In collaboration with the groups of Dr. Knecht and Pallardó, we have given an R+D service to the Khondrion Company, to evaluate the antioxidant capacity of two compounds from the company and the potential benefits on fibroblasts from LD patients.

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Group U743

Programme: Mitochondrial and Neuromuscular Medicine

Lead Researcher: Satrústegui, Jorgina

Group Members

STAFF MEMBERS: Contreras Balsa, Laura

CONTRATADOS A CARGO DE PROYECTO: Martínez Valero, Paula

ASSOCIATED MEMBERS: De Arco Martínez, Araceli

Main lines of research

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

Most relevant scientific articles

- Rueda CB, Traba J, Amigo I, Llorente-Folch I, González-Sánchez P, Pardo B, Esteban JA, Del Arco A, Satrústegui J. Mitochondrial ATP-Mg/Pi Carrier SCaMC-3/Slc25a23 Counteracts PARP-1-Dependent Fall in Mitochondrial ATP Caused by Excitotoxic Insults in Neurons. J Neurosci. 2015 35(8):3566-81.
- Lindsay KJ, Du J, Sloat SR, Contreras L, Linton JD, Turner SJ, Sadilek M, Satrústegui J, Hurley JB. Pyruvate kinase and aspartate-glutamate carrier distributions reveal key metabolic links between neurons and glia in retina. Proc Natl Acad Sci U S A. 2014 111(43):15579-84.
- Rueda CB, Llorente-Folch I, Amigo I, Contreras L, González-Sánchez P, Martínez-Valero P, Juaristi I, Pardo B, del Arco A, Satrústegui J. Ca(2+) regulation of mitochondrial function in neurons. Biochim Biophys Acta. 2014 1837(10):1617-24.
- Cascón A, Comino-Méndez I, Currás-Freixes M, de Cubas AA, Contreras L, Richter S, Peitzsch M, Mancikova V, Inglada-Pérez L, Pérez-Barrios A, Calatayud M, Azriel S, Villar-Vicente R, Aller J, Setién F, Moran S, Garcia JF, Río-Machín A, Letón R, Gómez-Graña Á, Apellániz-Ruiz M, Roncador G, Esteller M, Rodríguez-Antona C, Satrústegui J, Eisenhofer G, Urioste M, Robledo M. Whole-Exome Sequencing Identifies MDH2 as a New Familial Paraganglioma Gene. J Natl Cancer Inst. 2015 107(5).

Highlights

Our goal is calcium signaling to mitochondria and their involvement in human pathology, focused on the study of mitochondrial signaling systems that do not require entry into the organelle; the mitochondrial carriers of aspartate/glutamate (AGCs) and ATP-Mg/Pi (SCaMCs). We found that in neurons the Ca2+-dependent mitochondrial carrier of ATP-Mg/Pi, SCaMC-3, is involved in the response to intense stimulations intervening in the acute response to glutamate, during which performs the transport of ATP or ADP in mitochondria. The transport of nucleotides into mitochondria counteracts the nucleotide depletion caused by PARP1 activity and avoids its loss preventing the PTP opening and confers protection against neuronal excitotoxicity in vitro and against seizures induced by kainate in vivo. For these studies we have an intramural project of the CIBERER 14-11 call for the study of the involvement of the permeability transition pore (PTP) in models of diseases affecting the mitochondria for a possible diagnostic and therapeutic use.

Furthermore, progress has been achieved in understanding the glutamate-glutamine cycle and the role of the carrier Aralar/AGC1 in the synthesis of aspartate as neuronal precursor of glial glutamine and glutamate moving our study to the retina. There it has been demonstrated the function of aspartate generated in photoreceptors for glutamate-glutamine synthesis in Müller glia, showing a symbiotic relationship between the two cell types that will help in the understanding of retinal metabolism. Recently our group has joined to the Instituto de Investigación Sanitaria de la Fundación Jiménez (IIS-FJD) which has been granted a UAM-IIS-FJD intramural collaborative project to study the involvement of Aralar/AGC1 in the glutamate-glutamine cycle and in epilepsy.

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Group U744

Programme: Genetic Medicine

Lead Researcher: Serratosa, José M.

Group Members

STAFF MEMBERS: Guerrero López, Rosa

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

Main lines of research

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

Most relevant scientific articles

- Ortega-Moreno L, Giraldez BG, Verdu A, Garcia-Campos O, Sanchez-Martin G, Serratosa JM, et al. Novel mutation in STXBP1 gene in a patient with non-lesional Ohtahara syndrome. Neurologia 2015.
- Giraldez BG, Guerrero-Lopez R, Ortega-Moreno L, Verdu A, Carrascosa-Romero MC, Garcia-Campos O, et al. Uniparental disomy as a cause of spinal muscular atrophy and progressive myoclonic epilepsy: Phenotypic homogeneity due to the homozygous c.125C>T mutation in ASAH1. Neuromuscular disorders : NMD 2015;25:222-4.
- Guerrero-Lopez R, Ortega-Moreno L, Giraldez BG, Alarcon-Morcillo C, Sanchez-Martin G, Nieto-Barrera M, et al. Atypical course in individuals from Spanish families with benign familial infantile seizures and mutations in the PRRT2 gene. Epilepsy research 2014;108:1274-8.
- Ferlazzo E, Canafoglia L, Michelucci R, Gambardella A, Gennaro E, Pasini E, et al. Mild Lafora disease: clinical, neurophysiologic, and genetic findings. Epilepsia 2014;55:e129-33.

Highlights

Unit 744 of CIBERER aims: a) to identify and characterize genes involved in sporadic or familial genetic epilepsies (fundamentally epileptic encephalopathies in childhood), b) to generate diagnostic and therapeutic tools that improve the quality of life of patients and family members affected by these diseases, and c) to achieve progress in the knowledge and treatment of Lafora disease by means of studying animal models.

In 2014 a selected group of patients has been analyzed by means of a multigene panel designed for the analysis of genes related to familial genetic epilepsies and epileptic encephalopathies in childhood in order to validate and transfer this diagnostic tool. Furthermore, we have described new mutations in the PRRT2 gene in the Spanish population in benign familial neonatal seizures and characterized one case of progressive myoclonus epilepsy with spinal muscular atrophy with ASAH1 mutation.

Unit 744 continued to lead the Spanish Group of Genetics of Childhood Epilepsies, GEGEI (www.gegei.es). In this year, drugs have been tested in animal models of Lafora disease in order to prepare a clinical trial in patients and the corresponding clinical trial for studying the efficacy of Lacosamide in nocturnal attacks has continued, developing devices for quantifying the frequency of nocturnal epileptic fits in the patient's home.

On an international level, we represented Spain in the "Collaborative Research Project (CRP) on Rare Epilepsy Syndromes" of EUROEPINOMICS (European Science Foundation) participating in the identification of new susceptibility genes in different types of rare epileptic syndromes.

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

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Group U745

Programme: Hereditary Cancer and Related Syndromes

Lead Researcher: Surrallés, Jordi

Group Members

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

ASSOCIATED MEMBERS: Cabre Fabre, Oriol | Castella Castella, Maria | Hernández Viedma, Gonzalo | Marín Vilar, María | Mina, Leonardo | Minguillón Pedreño, Jordi | Montanuy Escribano, Helena | Umbert Mestres, Gloria

Main lines of research

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

Most relevant scientific articles

- G.Liu, K.Suzuki, M.Li, J.Qu, N.Montserrat, C.Tarantino, Y.Gu, F.Yi, X.Xu, W. Zhang, S.Ruiz, N.Plongthongkum, K.Zhang, S.Masuda, E.Nivet, Y.Tsunekawa, R. D.Soligalla, A.Goebl, E.Aizawa, N.Y.Kim, J.Kim, I.Dubova, Y.Li, R.Ren, C. Benner, A.del Sol, J.Bueren, J.P.Trujillo, J.Surralles, E.Cappelli, C.Dufour, C.Rodríguez Esteban and J. C.Izpisua. Modeling Fanconi Anemia pathogenesis and therapeutics using integration-free patient iPSCs. Nature Communications 2014, 5:4330-4336.
- Río P, R.Baños, A.Lombardo, O.Quintana-Bustamante, L.Alvarez, Z.Garate1, P.Genovese, E.Almarza, A.Valeri, B.Díez, S.Navarro, Y.Torres, J.P.Trujillo, R.Murillas, J.C.Segovia, E.Samper, J. Surralles, P.D.Gregory, M.C.Holmes, L.Naldini, J.A.Bueren (2014). Targeted Gene Therapy and Cell Reprogramming in FanconiAnemia. EMBO Mol Therapy 6:835-48
- A.Aulinas, M.J.Ramírez, M.J.Barahona, E.Valassi, E.Resmini, E.Mato, A.Santos, I.Crespo, O.Bell, J.Surralles, and S.Webb (2014) Telomere length analysis in Cushing's syndrome. Eur J Endocrinol. 171:21-9.
- Trujillo JP and J Surralles (2014) Savior siblings and Fanconi anemia: analysis of success rates from the family's perspective. Genetics in Medicine (acceptado)
- Bogliolo M and J Surrallés (2014) Fanconi anemia: from novel genes to advanced therapies. Current Opinion in Genetics and Development (invited review; aceptado)

Highlights

During 2014 we developed new therapeutic strategies in Fanconi anemia based on genome editing. We performed therapeutic research both in vitro (cell based screening system development to test libraries o selected compunds) and in vivo, both in mice models and as part of a gene therapy clinical trial where our team participates. In this framework, five Fanconi anemia patients have been recruited in the first phase of the clinical trial aimed to mobilize and collect hematopoietic stem cells from Fanconi anemia patients. We also discovered additional components involved in interstrand cross link repair and homologous recombination with a role in cancer predisposition and prognosis that are currently under patentability study. Whole exome sequencing of 60 Fanconi anemia and Fanconi anemia-like individuals have been done in order to genetically characterize patients and find new candidate genes. We finalized the SNP array analysis of 135 patient's samples to detect bone marrow clonal cytogenetic events in blood DNA. We finally collaborated in a research project on the pathophysiology of Cushing syndrome.

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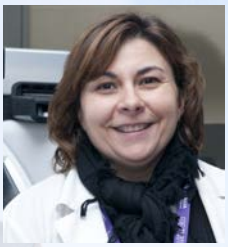

Group U746

Programme: Inherited Metabolic Medicine

Lead Researcher: Pérez González, Belén

Group Members

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

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

Main lines of research

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

Most relevant scientific articles

- Trujillano D*, Perez B*, González J, Tornador C, Navarrete R, Escaramis G, Ossowski S, Armengol L, Cornejo V, Desviat LR, Ugarte M, Estivill X. Accurate molecular diagnosis of phenylketonuria and tetrahydrobiopterin-deficient hyperphenylalaninemias using high-throughput targeted sequencing. European Journal of Human Genetics (2014) 22(4):528-34. * These authors contributed equally to this work.
- García-Cazorla A, Oyarzabal A, Fort J, Robles C, Castejón E, Ruiz-Sala P, Bodoy S, Merinero B, Lopez-Sala A, Dopazo J, Nunes V, Ugarte M, Artuch R, Palacín M, Rodríguez-Pombo P. Hum Mutat. 2014 35(4):470-7.
- Yuste P, Medrano C, Gamez A, Desviat LR,, Matthijs G, Ugarte M, Pérez-Cerdá C, Pérez. Antisense Mediated Therapeutic Pseudoexon Skipping In TMEM165-CDG.. Clinical Genetics (2014)
- Gallego-Villar L, Viecelli HM, Pérez B, Harding CO, Ugarte M, Thöny B, Desviat LR. A sensitive assay system to test antisense oligonucleotides for splice suppression therapy in the mouse liver. Mol Ther Nucleic Acids. 2014 Sep 16.
- Alcaide P, Krijt J, Ruiz-Sala P, Ješina P, Ugarte M, Kozich V, Merinero B. Enzymatic diagnosis of homocystinuria by determination of cystathionine-ß-synthase activity in plasma using LC-MS/MS. Clinica Chimica Acta(2014)

Highlights

The research projects of the Diagnostic and Research of Inherited Metabolic diseases (IMD) are aimed at improving the diagnosis and to the development of therapeutic strategies based on the analysis of the mechanisms of action of the mutations identified in patients. During this year we have incorporated new biomarkers analized in physiological fluids and new enzymatic activities assays in order to improve the diagnosis and patient stratification for future genetic studies. At the genetic level we have implemented routinely massive parallel sequencing as a diagnostic tool in IMD. In particular we highlight the incorporation of genetic analysis of hyperphenylalaninemias (HPA). We have developed a gene panel for analyzing the four genes that cause HPA generating a proof of concept that certifies the diagnostic utility of the complete capture of candidate genes for detection of complete mutational spectrum including nucleotide changes and copy number variations. We also highlight the first identification of new genes. We have identified and functional characterized for first time mutations in the gene BCKDK in two autistic patients. We have reported the successfully nutritional therapy. Regarding therapies we have reported the characterization of mitochondrial dysfunction in organic acidurias as novel therapeutic target. The results have revealed that oxidative damage may produce an alteration in the morphology of mitochondria and mitochondrial respiration. Concerning the mutation specific therapies we highlight the successful application of antisense therapy for exonic and intronic rescue of splicing motions hat affect splicing and in vivo analysis of the effectiveness of treatment in a murine model of PKU.

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Group U747

Programme: Endocrine Medicine

Lead Researcher: Webb, Susan

Group Members

STAFF MEMBERS: Resmini, Eugenia

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

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.
- Neuromyopathy due to adult GH deficiency as a model of muscle atrophy.
- 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 900 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.
- 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

- Crespo I, Granell-Moreno E, Santos A, Valassi E, de Juan-Delago M, Vives-Gilabert Y, Webb SM, Gomez-Anson B, Resmini E. Impaired decision-making process and thinner prefrontal cortex in patients with Cushing's syndrome. Clin Endocrinol. 2014; 81(6): 826 - 833.
- Mo D, Blum WF, Rosilio M, Webb SM, Qi R, Strasburger CJ. Ten-year change in quality of life in adults on growth hormone replacement for growth hormone deficiency: an analysis of the hypopituitary control and complications study. J Clin Endocrinol Metab 2014; 99 (12): 4581 – 4588.
- Santos A, Resmini E, Crespo I, Pires P, Vives Gilabert Y, Granell E, Valassi E, Gómez Anson B, Martínez Momblán MA, Mataró M, Webb SM. Small cerebellar cortex volume in patients with active Cushing's syndrome. Eur J Endocrinol 2014; 171 (4): 461 – 469.
- Crespo I, Webb SM. Perception of health and cognitive dysfunction in acromegaly patients. Endocrine 2014; 46 (3): 365 - 367.
- Aulinas A, Ramírez MJ, Barahona MJ, Valassi E, Resmini E, Mato E, Santos A, Crespo I, Bell O, Surrallés J, Webb SM. Telomere length analysis in Cushing's syndrome. Eur J Endocrinol 2014; 171 (1):21 – 30.

Highlights

The U747 performs clinical research oriented to Rare Pituitary Diseases, with translation to the NHS, registries and collaborations with patient associations. In translation we have continued to collaborate with EPIRARE, Orphanet-Spain and the PI is the coordinator of the CIBERER program "Endocrine Medicine"; in 2014, 5 clinical groups have been linked to this program, strengthening its translational activity. Since 1982, the PI is responsible of specialized clinics for Rare Pituitray Diseases, and is a recognized reference centre due to its professional excellence.

We have obtained a new publically funded research project PI 14/000194, ISCIII: "Study of bone microarchitecture and resistance and their determining factors in Cushing syndrome or acromegaly in remission. Model to investigate the interaction bone- body fat".

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

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

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

In 2014 the Agencia de Gestió d'Ajuts Universitaris i de Recerca (AGAUR) recognized the Group (355) in the call for Support for Research Groups , and classified this Group as the 4th (the first clinical group) of the 60 groups of the IIB-S Pau, demonstrating its internal and external value.

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Group U748

Programme: Genetic Medicine

Lead Researcher: Díaz Nido, Javier

Group Members

STAFF MEMBERS: Pérez Luz, Sara

ASSOCIATED MEMBERS: Gimenez Cassina Sendón, Alfredo | Katsu Jiménez, Yurika María | Lim Siok, Filip |

Main lines of research

- Neural cell models of frataxin deficiency.
- Molecular and cellular physiopathology of Friedreich's ataxia.
- Gene therapy in models of Friedreich's ataxia.
- Biology of stem cells of the olfactory mucosa.
- Application in cell therapy and regenerative medicine.

Most relevant scientific articles

- Loría F, Díaz-Nido J. Frataxin knockdown in human astrocytes triggers cell death and the release of factors that cause neuronal toxicity. Neurobiol Dis 2014; Dec 29. [Epub ahead of print].PubMed
- Tello Velasquez J, Watts ME, Todorovic M, Nazareth L, Pastrana E, Diaz-Nido J, Lim F, Ekberg JA, Quinn RJ, St John JA. Low-dose curcumin stimulates proliferation, migration and phagocytic activity of olfactory ensheathing cells. PLoS One 2014; 9(10):e111787. PubMed

Institution: Universidad Autónoma de Madrid

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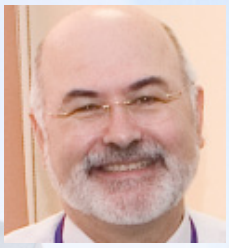
Group U749

Programme: Hereditary Cancer and Related Syndromes



Lead Researcher: Fernández Piqueras, José

Group Members

STAFF MEMBERS: Cobos Fernández, María de los Ángeles | González Sánchez, Laura

ASSOCIATED MEMBERS: Santos Hernández, Javier | Villa Morales, María

Main lines of research

In the last year we have been working on genetics and epigenetics cancer susceptibility, with particular reference to T-cell lymphoblastic lymphomas (T-LBL). Precursor T-cell lymphoblastic neoplasms are aggressive haematological malignancies, which mainly develop in children (in particular adolescent males) but can also affect adults. The molecular basis of these neoplasms has been well established in T-cell lymphoblastic leukaemia (in particular T-ALL) but to a lesser extent in T-LBL, which consists of a rare subtype. The integration of genomic approaches has enabled us to reveal a map of genetic alterations in coding and non-coding genes (microRNAs), which provided new insights about T-LBL development. Specifically, we have been working with specific mutations or deregulations of several members of the Fas/FasL apoptotic signalling pathway to assess about the involvement of this apoptotic pathway. Another interesting initiative was to unravel how activating JAK2 mutations may be contributing to T-LBL development. In addition our team has collaborated with other groups in the study of the cannabinoid receptor CB2 as a pivotal regulator in breast cancer. Finally, we have been working with some rare forms of psychiatric illnesses to identified new susceptibility genes involved in alcohol use disorders. Present and future initiatives of our group are to assess a role for key genes as NOTCH1, FBXW7 and other members of the JAK/STAT pathways (in particular JAK1, and JAK3), combining/integrating mutational screening and changes of expression due to epigenetic mechanisms and microRNA deregulation; and to exploit the collateral damage of common deletions for the development of more effective therapies to specifically killing lymphoma cells, avoiding the damage of normal accompanying cells (ACCI project).

Most relevant scientific articles

- Villa-Morales M, Cobos MA, Gonzalez-Gugel E, Alvarez-Iglesias V, Martinez B, Piris MA et al. FAS system deregulation in T-cell lymphoblastic lymphoma. Cell Death Dis 2014; 5: e1110.
- Vaquero-Lorenzo C, Lopez-Castroman J, Bermudo-Soriano CR, Saiz-Ruiz J, Fernandez-Piqueras J & Baca-Garcia E. Putative association between the -1415 T/C polymorphism of spermidine/spermine N1-acetyltransferase (SSAT1) gene and alcohol use disorders in women and men. Am J Drug Alcohol Abuse 2014; 40: 240-243.
- Pérez-Gómez E, Andrada C, Caffarel MM, Blasco-Benito S, García-Taboada E, Villa-Morales M et al. Cannabinoid receptor CB2 is a pivotal regulator of HER2 oncogenic signaling in breast cáncer. J Natl Cancer Inst 2015.
- Roncero AM, López-Nieva P, Cobos-Fernández MA, Villa-Morales M, González-Sánchez L, López-Lorenzo JL et al. Contribution of JAK2 mutations to T-cell lymphoblastic lymphoma development. Leukemia 2015.
- López-Nieva P, Malavé M, González-Sánchez L, Fernández-Piqueras J, Fernández-Navarro P & Hernandez. JS. Phosphorylation of Trp53 at serine 389 plays a key role in the radioadaptive response in mouse thymocytes. Mutation Research 2015.

Highlights

The most remarkable major achievements were focused on the deregulation of FAS/FASL pathway and in the contribution of JAK2 mutations to T-LBL development. Specifically, we have demonstrated that the FAS-FASL system is impaired in a significant fraction of lymphomas through inactivating mutations and/or deregulation of FAS and/or other members of the pathway rendering T-LBL tumour cells more resistant to apoptotic cell death. Regarding JAK2 we have identified one activating TEL-JAK2 translocation and six missense mutations, identifying intra-tumour heterogeneity (subclonal heterogeneity) with implications for targeted therapies and accurately diagnosis. Functional approaches revealed that several JAK2 mutations may activate JAK-STAT signalling pathway and to induce the expression of the potent oncogene LMO2. Aberrant hypermethylation of SOCS3 also contributes to enhance activation of JAK-STAT signalling in these tumours. We therefore proposed that the use of pan-JAK inhibitors in combination with epigenetic drugs should be considered in future treatments. In addition our team has collaborated in the demonstration that the cannabinoid receptor CB2 is a pivotal regulator of HER2 oncogenic signalling in breast cancer; and in the identification of new susceptibility genes involved in alcohol use disorders.

With regard to projects, our team has participated in a European initiative (OPERRA-604984) (2014-16) and in an ACCI-CIBERER-12-03 project; and directed several projects: (1) from the Spanish Nuclear Security Council; (2) the Spanish National Plan (SAF2012-36566); (3) and from the IIS-FJD.

Additional results were a doctoral thesis, our participation in one training course, and in several Masters and Post-graduates degrees at several Universities or Institutions (UAM, UCM, CNIO etc.). Members employed by the CIBERER have participated in multiple training courses organized by the CIBERER itself or other Institutions from the del SNS. Finally, as a member of the IIS-FJD, our team have performed genetic and epigenetic analyses of all T-LBL samples attended in the FJD Hospital.

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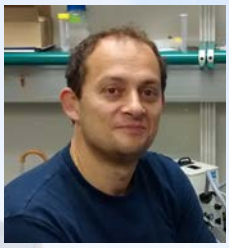
Group U750

Programme: Inherited Metabolic Medicine



Lead Researcher: Estévez Povedano, Raúl

Group Members

STAFF MEMBERS: Gaitán Peñas, Hector

ASSOCIATED MEMBERS: Arnedo Llena, 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

- Pérez-Rius C, Gaitán-Peñas H, Estévez R, Barrallo-Gimeno A. Identification and characterization of the zebrafish ClC-2 chloride channel orthologs. Pflugers Arch. 2014 Sep 20. [Epub ahead of print] PubMed PMID: 25236920.
- Jeworutzki E, Lagostena L, Elorza-Vidal X, López-Hernández T, Estévez R, Pusch M. GlialCAM, a CLC-2 Cl(-) channel subunit, activates the slow gate of CLC chloride channels. Biophys J. 2014 Sep 2;107(5):1105-16. doi: 10.1016/j.bpj.2014.07.040. PubMed PMID: 25185546; PubMed Central PMCID: PMC4156679.
- Arnedo T, López-Hernández T, Jeworutzki E, Capdevila-Nortes X, Sirisi S, Pusch M, Estévez R. Functional analyses of mutations in HEPACAM causing megalencephalic leukoencephalopathy. Hum Mutat. 2014 Oct;35(10):1175-8. doi: 10.1002/humu.22622. Epub 2014 Aug 18. PubMed PMID: 25044933.
- Sirisi S, Folgueira M, López-Hernández T, Minieri L, Pérez-Rius C, Gaitán-Peñas H, Zang J, Martínez A, Capdevila-Nortes X, De La Villa P, Roy U, Alia A, Neuhauss S, Ferroni S, Nunes V, Estévez R, Barrallo-Gimeno A. Megalencephalic leukoencephalopathy with subcortical cysts protein 1 regulates glial surface localization of GLIALCAM from fish to humans. Hum Mol Genet. 2014 Oct 1;23(19):5069-86. doi: 10.1093/hmg/ddu231. Epub 2014 May 12. PubMed PMID: 24824219.
- Hoegg-Beiler MB, Sirisi S, Orozco IJ, Ferrer I, Hohensee S, Auberson M, Gödde K, Vilches C, de Heredia ML, Nunes V, Estévez R, Jentsch TJ. Disrupting MLC1 and GlialCAM and ClC-2 interactions in leukodystrophy entails glial chloride channel dysfunction. Nat Commun. 2014 Mar 19;5:3475. doi: 10.1038/ncomms4475. PubMed PMID: 24647135.

Highlights

- E-RARE2 project: "CLC channels and megalencephalic leukoencephalopathy"
- ICREA Academia prize for Raúl Estévez Povedano
- ELA Research project: ELA 2012-014C2 "MLC disease: identification of proteins which could modulate the disease phenotype"

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Group U751

Programme: Genetic Medicine

Lead Researcher: Giménez Martín, Cecilio

Group Members

ASSOCIATED MEMBERS: Aragón Rueda, Carmen | López Corcuera, Beatriz | Núñez Balbuena, Enrique | Zafra Gómez, Francisco

Main lines of research

- Study of mutations in the sodium channel Nav1.1 in patients whith Dravet Syndrome.
- Study of glycine-mediated neurotransmission in the brain stem and spinal cord. Neuromuscular system disorders relating to the glycinergic system: hyperekplexia.
- Molecular basis for glutamatergic neurotransmission involved in memory and learning processes and in pathological processes.

Most relevant scientific articles

- Jiménez E, Núñez E, Ibáñez I, Draffin JE, Zafra F, Giménez C.Differential regulation of the glutamate transporters GLT-1 and GLAST by GSK3ß. 2014, Neurochem Int 79, 33-43.
- Jiménez E, Núñez E, Ibáñez I, Zafra F, Aragón C, Giménez C. Glycine transporters GlyT1 and GlyT2 are differentially modulated by glycogen synthase kinase 3ß. 2014, Neuropharmacology, 89:245-254
- Rodríguez A, Ortega A, Berumen LC, García-Alcocer MG, Giménez C, Zafra F. Expression of the System N transporter (SNAT5/SN2) during development indicates its plausible role in glutamatergic neurotransmission. 2014 Neurochem Int 73, 166-171.
- Cubelos B, Leite C, Giménez C, Zafra F. Localization of the glycine transporter GLYT1 in glutamatergic synaptic vesicle. 2014, Neurochem Int 73, 204-210.
- Hernandez D, Fuentes A, Ortega A, Zafra F; Gimenez C, Rodríguez A. 2014, Glutamine transporter SNAT5 ontogeny in rat cerebral cortex. 2014, J Neurochem. 125, 181-182.

Highlights

Hereditary hyperekplexia is a complex genetic disease in which different genes may be involved (GLRA1, GLRB, ARHGEF9, GPHN and SLC6A5) that encode proteins involved in inhibitory glycinergic neurotransmission. So far, two major proteins identified as responsible hyperkplexia, the strychnine sensitive glycine (GlyR) and the neuronal glycine transporter Glyt2. Since our entry into CIBERER began the search for mutations in glycinergic systems (receptors, transporters, accessory proteins) that may be involved in hyperplexia. In coordination with the group led by Dr Lapunzina (Hospital La Paz) we initiated a study to identify mutations in the SLC6A5 gene of patients diagnosed with hyperekplexia. So far we have found new mutations of SLC6A5 and we are studying their impact in transport activity of the mutated protein its biogenesis and itselectrophysiological properties . Latest publications of the group demonstrate how mutations affect not only the transport properties of Glyt2, but also alter their intracellular trafficking properties and their interaction with other scaffolding proteins.

Two years ago we began the study of mutations in the SCN1A gene encoding the sodium channel Nav1.1 in patients with Dravet syndrome. We studied a large number of patients (over 500) found mutations in 70 of them. Of these mutated forms of the channel found in patients, we selected 12 possible impact on the regulation of protein. Our interest is in the study of intracellular trafficking and functionality of the native and mutated protein in different positions.

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Group U752

Programme: Inherited Metabolic Medicine

Lead Researcher: Giraldo, Pilar

Group Members

STAFF MEMBERS: Alfonso Palacín, María Pilar | Irún Irún, María Pilar

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

Main lines of research

- Gaucher disease epidemiology, in Spain: National Registry acredited by ISO 9001 (Num EC2751/07).
- Genetic analysis and search of genes related to clinical heterogeneity. Directed mutagenesis. DNA, serum, plasma and leukocyte patient samples biobank.
- Study of biomarkers and inflammatory cytokines and its relationship with response to treatment.
- Study of bone disease by imaging techniques and its relationship with plasma biomarkers.
- Neurological disease evaluation by clinical, neurophysiological and imaging methods.
- Clinical research of new drugs on clinical trials (OGT-011, TKT034, TKT039, Protalix). Independent clinical trial.

- Epidemiology of hematological neoplasias. Gene expression marker study and search of polymorphisms accounting for familial aggregations.
- Approach to study of internalization of nanoparticles containing small drug molecules on monocytes and macrophages and application to treat deposit diseases.
- Analysis of the effect of pharmacological chaperones on protein mutants in Gaucher Disease.
- Plasma miRNAs profile in Haematological malignancies and predictor use to developed acute leukaemia.

Most relevant scientific articles

- Pastores GM, Petakov M, Giraldo P, Rosenbaum H, Szer J, Deegan PB, Amato DJ, Mengel E, Tan ES, Chertkoff R, Brill-Almon E, Zimran A. A Phase 3, multicenter, open-label, switchover trial to assess the safety and efficacy of taliglucerase alfa, a plant cell-expressed recombinant human glucocerebrosidase, in adult and pediatric patients with Gaucher disease previously treated with imiglucerase. Blood Cells Mol Dis 2014; 2014 Dec. 53(4):253-60. PubMed
- García-Gutiérrez V, Puerta JM, Maestro B, Casado Montero LF, Muriel A, Molina Hurtado JR, Perez-Encinas M, Moreno Romero MV, Suñol PB, Sola Garcia R, De Paz R, Ramirez Sanchez MJ, Osorio S, Mata Vazquez MI, Martinez López J, Sastre JL, Portero Mde L, Bautista G, Durán Nieto MS, Giraldo P, Jiménez Jambrina M, Burgaleta C, Ruiz Aredondo J, Peñarrubia MJ, Requena MJ, Fernández Valle Mdel C, Calle C, Paz Coll A, Hernández-Rivas JÁ, Franco Osorio R, Cano P, Tallón Pérez D, Fernández de la Mata M, Garrido PL, Steegmann JL. Do chronic myeloid leukemia patients with late "warning" responses benefit from "watch and wait" or switching therapy to a second generation tyrosine kinase inhibitor? Am J Hematol 2014; Nov. 89(11):E206-11. PubMed
- Oriol A, Giraldo P, Kotsianidis I, Couturier C, Olie R, Angermund R, Corso A. Efficacy and safety of bortezomib-based retreatment at the first relapse in multiple myeloma patients: a retrospective study. Hematology 2014; Dec 10. [Epub ahead of print]. PubMed
- Medrano-Engay B, Irun P, Gervas-Arruga J, Andrade-Campos M, Andreu V, Alfonso P, Pocovi M, Giraldo P. Iron homeostasis and inflammatory biomarker analysis in patients with type 1 Gaucher disease. Blood Cells Mol Dis 2014; 2014 Dec. 53(4):171-5. PubMed
- Benboubker L, Dimopoulos MA, Dispenzieri A, Catalano J, Belch AR, Cavo M, Pinto A, Weisel K, Ludwig H, Bahlis N, Banos A, Tiab M, Delforge M, Cavenagh J, Geraldes C, Lee JJ, Chen C, Oriol A, de la Rubia J, Qiu L, White DJ, Binder D, Anderson K, Fermand JP, Moreau P, Attal M, Knight R, Chen G, Van Oostendorp J, Jacques C, Ervin-Haynes A, Avet-Loiseau H, Hulin C, Facon T. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N Engl J Med 2014; Sep 4. 371(10):906-17. PubMed

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Group U753

Programme: Paediatric and Developmental Medicine

Lead Researcher: Lapunzina Badía, Pablo D.

Group Members

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

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

Main lines of research

- Congenital alterations of purine metabolism.
- Subtelomeric rearrangements in patients with idiopathic mental retardation.
- Genetic and functional analysis of genes SHOX and SHOX2 in human growth.
- Overgrowth syndromes. Epidemiology. Clinical presentations and molecular analysis.
- Genetic factors in harmonic hypo.
- Determinants and genetic modifiers of monogenic diabetes.
- Genetic analysis of the ghrelin axis in childhood obesity.
- 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 tumors.

- Molecular genetics of hypertrophic myocardiopathy.
- Functional characterization of CLCN1 mutations causing congenital myotonia.
- Molecular study of endothelial dysfunction in human cell models for diabetes and aging.
- Molecular characterization of the 22q11.2 region by MLPA techniques and its correlation with micro-satellite 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 síndromes.
- Dravet Syndrome.

Most relevant scientific articles

- Tenorio J, Mansilla A, Valencia M, Martínez-Glez V, Romanelli V, Arias P, Castrejón N, Poletta F, Guillén-Navarro E, Gordo G, Mansilla E, García-Santiago F, González-Casado I, Vallespín E, Palomares M, Mori MA, Santos-Simarro F, García-Miñaur S, Fernández L, Mena R, Benito-Sanz S, Del Pozo A, Silla JC, Ibañez K, López-Granados E, Martín-Trujillo A, Montaner D, Heath KE, Campos-Barros A, Dopazo J, Nevado J, Monk D, Ruiz-Pérez VL, Lapunzina P. A New Overgrowth Syndrome is due to Mutations in RNF125. Hum Mutat; 2014 Dec. 35(12):1436-41. PMID: 25196541 Doi: 10.1002/humu.22689
- Court F, Tayama C, Romanelli V, Martin-Trujillo A, Iglesias-Platas I, Okamura K, Sugahara N, Simón C, Moore H, Harness JV, Keirstead H, Sanchez-Mut JV, Kaneki E, Lapunzina P, Soejima H, Wake N, Esteller M, Ogata T, Hata K, Nakabayashi K, Monk D. Genome-wide parent-of-origin DNA methylation analysis reveals the intricacies of human imprinting and suggests a germline methylation-independent mechanism of establishment. Genome Res; 2014 Apr. 24(4):554-69. PMID: 24402520 Doi: 10.1101/gr.164913.113
- Eggermann T, Binder G, Brioude F, Maher ER, Lapunzina P, Cubellis MV, Bergadá I, Prawitt D, Begemann M. CDKN1C mutations: two sides of the same coin. Trends Mol Med; 2014 Nov. 20(11):614-22. PMID: 25262539 Doi: 10.1016/j.molmed.2014.09.001
- Yuen M, Sandaradura SA, Dowling JJ, Kostyukova AS, Moroz N, Quinlan KG, Lehtokari VL, Ravenscroft G, Todd EJ, Ceyhan-Birsoy O, Gokhin DS, Maluenda J, Lek M, Nolent F, Pappas CT, Novak SM, D'Amico A, Malfatti E, Thomas BP, Gabriel SB, Gupta N, Daly MJ, Ilkovski B, Houweling PJ, Davidson AE, Swanson LC, Brownstein CA, Gupta VA, Medne L, Shannon P, Martin N, Bick DP, Flisberg A, Holmberg E, Van den Bergh P, Lapunzina P, Waddell LB, Sloboda DD, Bertini E, Chitayat D, Telfer WR, Laquerrière A, Gregorio CC, Ottenheijm CA, Bönnemann CG, Pelin K, Beggs AH, Hayashi YK, Romero NB, Laing NG, Nishino I, Wallgren-Pettersson C, Melki J, Fowler VM, MacArthur DG, North KN, Clarke NF. Leiomodin-3 dysfunction results in thin filament disorganization and nemaline myopathy. J Clin Invest; 2014 Nov 3. 124(11):4693-708. PMID: 25250574 Doi: 10.1172/JCI75199
- Corton M, Avila-Fernandez A, Vallespín E, López-Molina MI, Almoguera B, Martín-Garrido E, Tatu SD, Khan MI, Blanco-Kelly F, Riveiro-Alvarez R, Brión M, García-Sandoval B, Cremers FP, Carracedo A, Ayuso C. Involvement of LCA5 in Leber congenital amaurosis and retinitis pigmentosa in the Spanish population. Ophthalmology; 2014 Jan. 121(1):399-407. PMID: 24144451 Doi: 10.1016/j.ophtha.2013.08.028

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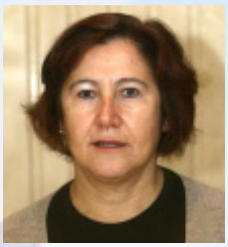
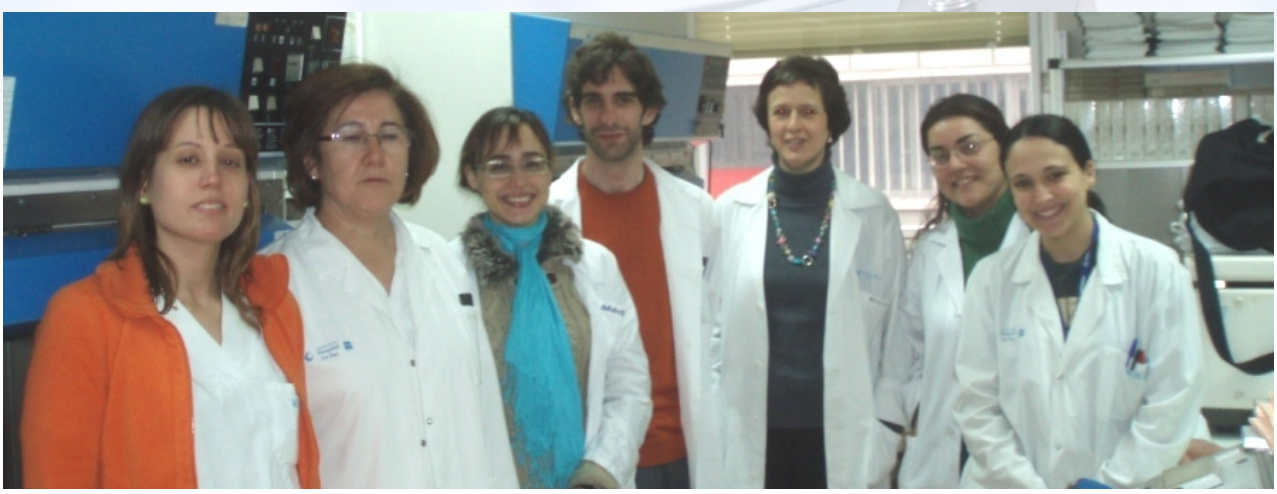
Group U754

Programme: Genetic Medicine





Lead Researcher: López Trascasa, Margarita

Group Members

STAFF MEMBERS: López Lera, Alberto

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

Main lines of research

- The complement system: diagnosis and characterization of pathologies associated with congenital deficiencies of the system and/or their regulation.
- Complement system disorders in renal pathology.
- Identification of modifying genes in clinical manifestations in patients with hereditary angioedema by means of gene expression studies with microarrays.

Most relevant scientific articles

- López-Lera A, M Torres-Canizales J, Garrido S, Morales A, López-Trascasa M. Rothmund-Thomson syndrome and glomerulonephritis in a homozygous C1q-deficient patient due to a Gly164Ser C1qC mutation. J Invest Dermatol; 2014 Apr. 134(4):1152-4. PMID: 24157463 Doi: 10.1038/jid.2013.444
- Sánchez Chinchilla D, Pinto S, Hoppe B, Adragna M, Lopez L, Justa Roldan ML, Peña A, Lopez Trascasa M, Sánchez-Corral P, Rodríguez de Córdoba S. Complement mutations in diacylglycerol kinase-e-associated atypical hemolytic uremic syndrome. Clin J Am Soc Nephrol; 2014 Sep 5. 9(9):1611-9. PMID: 25135762 Doi: 10.2215/CJN.01640214
- Cicardi M, Aberer W, Banerji A, Bas M, Bernstein JA, Bork K, Caballero T, Farkas H, Grumach A, Kaplan AP, Riedl MA, Triggiani M, Zanichelli A, Zuraw B. Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International Working Group. Allergy; 2014 May. 69(5):602-16. PMID: 24673465 Doi: 10.1111/all.12380
- Aberer W, Maurer M, Reshef A, Longhurst H, Kivity S, Bygum A, Caballero T, Bloom B, Nair N, Malbrán A. Open-label, multicenter study of self-administered icatibant for attacks of hereditary angioedema. Allergy; 2014 Mar. 69(3):305-14. PMID: 24438203 Doi: 10.1111/all.12303
- Charignon D, Ghannam A, Defendi F, Ponard D, Monnier N, López Trascasa M, Launay D, Caballero T, Djenouhat K, Fain O, Cichon S, Martin L, Drouet C. Hereditary angioedema with F12 mutation: factors modifying the clinical phenotype. Allergy; 2014 Dec. 69(12):1659-65. PMID: 25134986 Doi: 10.1111/all.12515

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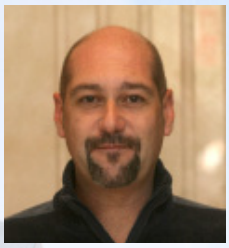
Group U755

Programme: Sensorineural Pathology



Lead Researcher: Millán Salvador, José M.

Group Members

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

ASSOCIATED MEMBERS: Aparisi Navarro, Mª José | Jaijo Sanchis, Teresa | Morera Pérez, Constantino | Pérez Garrigues, Herminio | Rodrigo Nicolas, Regina | Sequedo Pérez, Mª 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

- Alias L, Barceló MJ, Bernal S, Martinez R, Alsó E, Millán JM, Baiget M, Tizzano E. Improving detection and genetic counseling in carriers of spinal muscular atrophy with two copies of the SMN1 gene. Clin Genet. 2014 85: 470-475.
- García-García G, Aller E, Jaijo T, Aparisi MJ, Larrieu L, Faugère V, Blanco-Kelly F, Ayuso C, Roux AF, Millán JM. Novel deletions involving the USH2A gene in patients with Usher syndrome and retinitis pigmentosa. Mol Vis. 2014 20: 1398-1410.
- Cristina Martinez-Fernandez de la Camara C, Olivares-Gonzalez L, Hervas D, Salom D, Millan JM, Rodrigo R. Infliximab reduces Zaprinast-induced retinal degeneration in cultures of porcine retina. J Neuroinflammation. 2014 11:172.
- Sánchez-Alcudia R, Cortón M, Ávila-Fernández A, Zurita O, Tatu SD, Pérez-Carro R, Fernandez-San Jose P, Lopez-Martinez MA, del Castillo FJ, Millan JM, Blanco-Kelly F, García-Sandoval B, Lopez-Molina MI, Riveiro-Alvarez R, Ayuso C. Contribution of mutation load to the intrafamilial genetic heterogeneity in a large cohort of Spanish retinal dystrophies families. Invest Ophthalmol Vis Sci. 2014 55: 7562-7571.
- Aparisi MJ, Aller E, Fuster-García C, García-García G, Rodrigo R, Vazquez-Manrique RP, Blanco-Kelly F, Ayuso C, Roux AF, Jaijo T, Millan JM. Targeted next generation sequencing for molecular diagnosis of Usher syndrome. Orphanet J Rare Dis. 2014 9: 168.

Highlights

- The development of a Platform for Genomics within the IIS-La Fe coordinated by the PI of the group. This is a NGS-based platform capable to sequence by panels of genes responsible for genetically heterogeneous diseases and whole human exomes and is playing a key role in genetic diagnosis at both care level and research for the unit U755 and other groups of IIS.
- Projects like TREAT-CMT, ACCII and collaboration CIBERER-CNAG have allowed us i) to familiarize with and to interpret whole exome sequencing (WES). A WES from a family with Usher (USH) syndrome has allowed us to identify a potential new disease-associated gene (manuscript in preparation); ii) to start the epigenetic analysis (directed and whole genome methylation) of patients with CMT with similar genotypes and discordant phenotypes; iii) to carry out functional studies on the effect of mutations in the splicing by minigenes technology and extracting mRNA from epithelial hair cells of USH patients.
- The consolidation of research in cell biology by studying the processes of apoptosis, oxidative stress and inflammation in the death of photoreceptors in both cell models (organotypic cultures of porcine retinas), animals (mice rd10) and patients (serum and aqueous humour of patients with retinitis pigmentosa (RP).
- Initiation of genomic technology edition by CRISPR/Cas9 in cellular models. We have obtained a project to be performed in fibroblasts from patients with USH and RP.
- Generation of a model of C.elegans to identify modifier genes in Huntington's disease (manuscript in preparation). We sequenced the complete genome of this model and we are analyzing the results.
- Translation to care system: the group maintains close relationship with several of patients' associations, regular activity with Orphanet and CIBERER-Biobank and has participated in the development of a diagnostic guideline for aniridia in collaboration with another CIBERER group.
- Transferibility: A member of the unit has filed a patent about Menière's disease that has benn extended to Europe and the United States but is not yet in operation.

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Group U756

Programme: Sensorineural Pathology

Lead Researcher: Montoliu José, Lluís

Group Members

STAFF MEMBERS: Fernández López, Almudena

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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

- Harms DW, Quadros RM, Seruggia D, Ohtsuka M, Takahashi G, Montoliu L, Gurumurthy CB. Mouse Genome Editing Using the CRISPR/Cas System. Curr Protoc Hum Genet. 2014; 83:15.7.1-15.7.27.
- Seruggia D, Montoliu L. The new CRISPR-Cas system: RNA-guided genome engineering to efficiently produce any desired genetic alteration in animals. Transgenic Res. 2014; 23(5):707-16.
- Moreira PN, Montoliu L. Intracytoplasmic sperm injection (ICSI)-mediated transgenesis in mice. Methods Mol Biol. 2014;1194:141-56.
- Montoliu L, Kelsh RN. Do you have to be albino to be albino? Pigment Cell Melanoma Res. 2014; 27(3):325-6.
- Montoliu L, Grønskov K, Wei AH, Martínez-García M, Fernández A, Arveiler B, Morice-Picard F, Riazuddin S, Suzuki T, Ahmed ZM, Rosenberg T, Li W. Increasing the complexity: new genes and new types of albinism. Pigment Cell Melanoma Res. 2014;27(1):11-8.

Highlights

CIBERER Unit U756 focuses its activities in research on albinism, a rare genetic condition affecting 1:17000 in Europe and North-America. At least 18 heterogeneous types of albinism group in this rare disease, globally characterized by a fundamental visual deficit, associated with mutations present in, at least, 18 loci. People with albinism can manifest alterations in pigmentation, affecting skin, hair and eyes (oculocutaneous albinism, OCA) o only the eyes (ocular albinism). These symptoms can be presented in a syndromic form (Hemansky-Pudlak, Chediak-Higashi). In collaboration with the Spanish association in support of people with albinism (ALBA, www.albinismo.es) and with unit U711 Angel Carracedo (USC) we are developing an initiative called albinochip, aiming to genetically diagnose, universally, all known mutations associated with albinism. We also offer support and information to everyone interested through a dedicated web page (www.cnb.csic.es/~albino/). In the laboratory, we have generated various animal models of albinism, essentially mice, whose genome has been genetically altered to reproduce the visual and pigment deficits observed in humans. Using these animal models for different types of albinism, mainly OCA1, we have explored the functional relevance of non-coding genomic sequences, using the innovative CRISPR-Cas9 technology, and described phenotypes that are similar to those observed in mutations usually located within the coding areas. We have also reported new animal models of additional visual alterations, such as achromatopsia, and started to explore potential treatments for certain types of albinism, analyzing the usefulness of some drugs whose activity has been recently proposed to recover, at least partially, some deficits associated with albinism. Finally, through our participation in International Mouse Functional Genomic consortia, we offer from our laboratory the possibility to cryopreserve, archive, disseminate and import many mouse mutant lines of interest in biomedicine, through the platform EMMA/INFRAFRONTIER (http://www.infrafrontier.eu).

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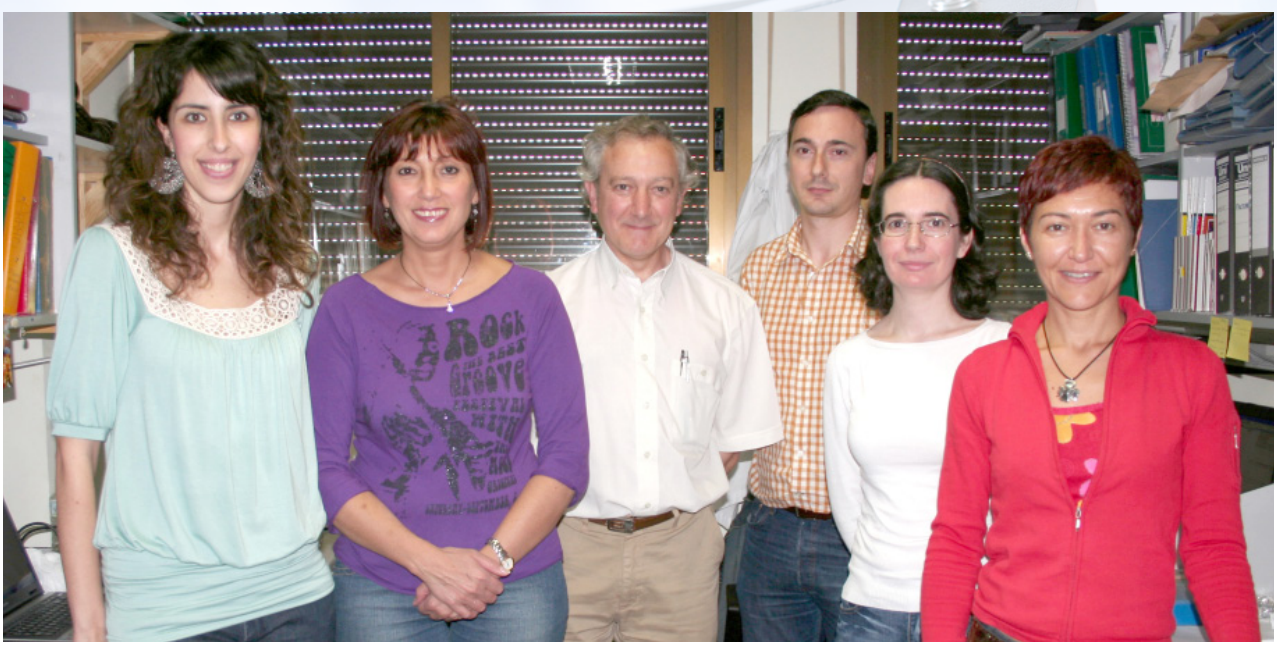
Group U757

Programme: Hereditary Cancer and Related Syndromes



Lead Researcher: Perona, Rosario

Group Members

STAFF MEMBERS: Manguán García, Cristina

ASSOCIATED MEMBERS: Carrillo García, Jaime | Sánchez Pérez, Isabel | Sastre Garzón, Leandro

Main lines of research

- Application of a rescue therapy in diseases associated with telomerase activity deficiency. Signalling pathways active in dyskeratosis congenita in response to DNA damage. Improve the activity of nanoparticles and lentiviral vectors for gene therapy.
- Development of a therapy base in the GSE24.2 peptide fro the treatment of short telomeres associated diseases, increase oxidative stress and geentic instability.
- Genetic diagnosis of DC y study of telomere lenght in patients of DC and idiophatic pulmonary fibrosis. Study of models of idiopathic pulmonary fibrosis using stem cells and KO mouse models for DUSP1.
- Investigation about the activity of GSE24.2 for the treatment of idiophatic pulmonary fibrosis.
- Use of GSE24.2 for the treatment of ataxia telangiectasia.

Most relevant scientific articles

- Jorge Oliver-De La Cruz, Josefa Carrión-Navarro, Noemí García-Romero, Antonio Gutiérrez-Martín, Elisa Lázaro-Ibañez, Carmen Escobedo-Lucea, Rosario Perona, Fernando López-Ríos, Cristobal Belda-Iniesta and Ángel Ayuso-Sacido. (2014) SOX2+ cells from the normal human white matter are able to generate mature oligodendrocytes. Plos One 9(6):e99253. IF 3,73. IF 3,73
- C Manguan-Garcia, L. Pintado-Berninches, J. Carrillo, R Machado-Pinilla, L Sastre, Carmen Pérez-Quilis, Isabel Esmoris, Amparo Gimeno, José Luis García-Giménez, Federico V. Pallardó and R Perona (2014) Expression of the genetic suppressor element 24.2 (GSE24.2) decreases DNA damage and oxidative stress in X-linked dyskeratosis congenita cells. Plos One 9(7):e101424. doi: 10.1371/journal.pone.0101424. eCollection 2014.. IF 3,73
- S.P. Egusquiaguirre, C. Manguán-García, R. Perona, R.M. Hernández, M. Igartua, J.L. Pedraz. Development and validation of a rapid HPLC method for the quantification of GSE4 peptide in biodegradable PEI-PLGA nanoparticles. Journal of Chromatography B 2014 972:95-101. IF: 2.862
- Egusquiaguirre, C. Manguán-García, L. Pintado-Berninches, L. Iarriccio, D. Carbajo, F. Albericio, M. Royo, J.L. Pedraz, R.M. Hernández, R. Perona*, M. Igartua*.(2014) Development of surface modified biodegradable polymeric nanoparticles to deliver GSE24.2 peptide to cells: a promising approach for the treatment of defective telomerase disorders. Submitted to: European Journal of Pharmaceutics and Biopharmaceutics, TP: Feb 7. pii: S0939-6411(15)00044-2 A. IF: 3.826.* corr authors
- C.Benitez-Buelga, MS, L.Sanchez-Barroso, MS, M.Gallardo, PhD, María Apellániz-Ruiz, MS , L. Inglada-Pérez, PhD, K.Yanowski, J.Carrillo, L.Garcia-Estevez, I.Calvo, R.Perona, M.Urioste, A.Osorio, MA.Blasco, C.Rodríguez-Antona, J.Benitez, (2014). Impact of chemotherapy on telomere-length in sporadic and familial breast cancer patients. Breast Cancer Research and Treatment. 2014 Dec 21. 149(2):385-94

Highlights

We have identified a short sequence within the GSE24.2 peptide of 11 AA termed GSE4 that holds an equivalent biological activity than GSE24.2. The in vivo assays in a rat model of pulmonary fibrosis and using PLGA-PEI nanoparticles loaded with GSE4 indicate an antifibrotic activity of this peptide. We have performed genetic diagnosis for dysketatosis congenita in colaboration with the U753 group of CIBERER and detected new mutations within the spanish patients. For pulmonary fibrosis we colaborate with Dr. Maria Molina Molina (CIBERES) to make a non invasive methos of telomere lenght measurement. Our preliminary results of the use og GSE24.2 in ataxia telangiectasia patient cells indicate that expresion of GSE24.2 is able to rescue some of the alteration of these cells.

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Group U758

Programme: Paediatric and Developmental Medicine

Lead Researcher: Posada De la Paz, Manuel

Group Members

STAFF MEMBERS: Monzón Fernández, Sara

ASSOCIATED MEMBERS: Abaitua Borda, Ignacio | Alonso Ferreira, Verónica | Hens Pérez, Manuel | Morales Piga, Antonio | Villaverde Hueso, Ana

Main lines of research

- Epidemiology and risk factors in autism: Early diagnosis (screening); case-cohort studies; case-control studies.
- Epidemiology and risk factors in connective tissue diseases and autoimmune diseases: Risk factor analysis; search for drugs; quality of life; registry; costs.
- General epidemiology of rare diseases: Rare disease registry; health costs; quality of life.
- Progressive spastic paraplegia and ataxias.
- National Rare Disease Registry (SpainRDR).
- 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

- García-Primo P, Hellendoorn A, Charman T, Roeyers H, Dereu M, Roge B, Baduel S, Muratori F, Narzisi A, Van Daalen E, Moilanen I, de la Paz MP, Canal-Bedia R. Screening for autism spectrum disorders: state of the art in Europe. Eur Child Adolesc Psychiatry. 2014 Nov;23(11):1005-21. doi: 10.1007/s00787-014-0555-6. Epub 2014 Jun 10.
- Lara B, Martínez MT, Blanco I, Hernández-Moro C, Velasco EA, Ferrarotti I, Rodríguez-Frias F, Perez L, Vazquez I, Alonso J, Posada M, Martínez-Delgado B. Severe alpha-1 antitrypsin deficiency in composite heterozygotes inheriting a new splicing mutation QOMadrid. Respir Res. 2014 Oct 7;15:125. doi: 10.1186/s12931-014-0125-y.
- Mora M, Angelini C, Bignami F, Bodin AM, Crimi M, Di Donato JH, Felice A, Jaeger C, Karcagi V, LeCam Y, Lynn S, Meznaric M, Moggio M, Monaco L, Politano L, de la Paz MP, et al. The EuroBioBank Network: 10 years of hands-on experience of collaborative, transnational biobanking for rare diseases. Eur J Hum Genet. 2014 Dec 24. doi: 10.1038/ejhg.2014.272.
- Thompson R, Johnston L, Taruscio D, Monaco L, Béroud C, Gut IG, Hansson MG, 't Hoen PB, Patrinos GP, Dawkins H, Ensini M, Zatloukal K, Koubi D, Heslop E, et al. RD-Connect: an integrated platform connecting databases, registries, biobanks and clinical bioinformatics for rare disease research. J Gen Intern Med. 2014 Aug;29 Suppl 3:S780-7. doi: 10.1007/s11606-014-2908-8.
- López-Bastida J, Linertová R, Oliva-Moreno J, Posada-de-la-Paz M, Serrano-Aguilar P. Social economic costs and health-related quality of life in patients with systemic sclerosis in Spain. Arthritis Care Res (Hoboken). 2014 Mar;66(3):473-80. doi: 10.1002/acr.22167.

Highlights

U-758 researchers have participated in 12 projects in 2014 (9 ongoing + 3 new). It is important to point out the role of coordinator of the EU project "Autism Spectrum Disorders in the European Union" from DG-SANCO, and the participation in RD-Connect and RARE-BestPractices, both from FP7. The head of the unit is also coordinator of the RD registries network SpainRDR, funding by IRDiRC consortium.

In 2014 Manuel Posada was appointed member of the group of experts in RD of the European Commission, and named President-Elect of the International Conference on RD and Orphan Drugs (ICORD). U-758 international projection on RD field is completed with the NIH collaboration (ORD-NCATS) and the international group of undiagnosed cases.

U-758 develops and maintains two national platforms which support RD research: the National RD Biobank and the National RD Registry. The intraCIBERER collaboration is related to epidemiology and the National RD Registy.

IIER has recently increases the possibilities of collaboration with basic research groups, thanks to its new human genetics department. Unfortunately, our request for inclusion those researchers in unit 758 CIBERER has been rejected in 2014, despite having been approved by the CIBER and the director of ISCIII.

In these circumstances, we have maintained the activities outlined in the previous years and developed new ones: SpainMDB database of mutations; new collaborative projects; inclusion in the ISCIII platform of biobanks, being coordinators of RD biobanks work package; application and success of a CIBERER "beca lanzadera"; and ongoing collaboration with CIBERER groups participating in the National RD Registry.

Finally, U-758 also collaborates with other CIBER such as CIBERESP and CIBERES.

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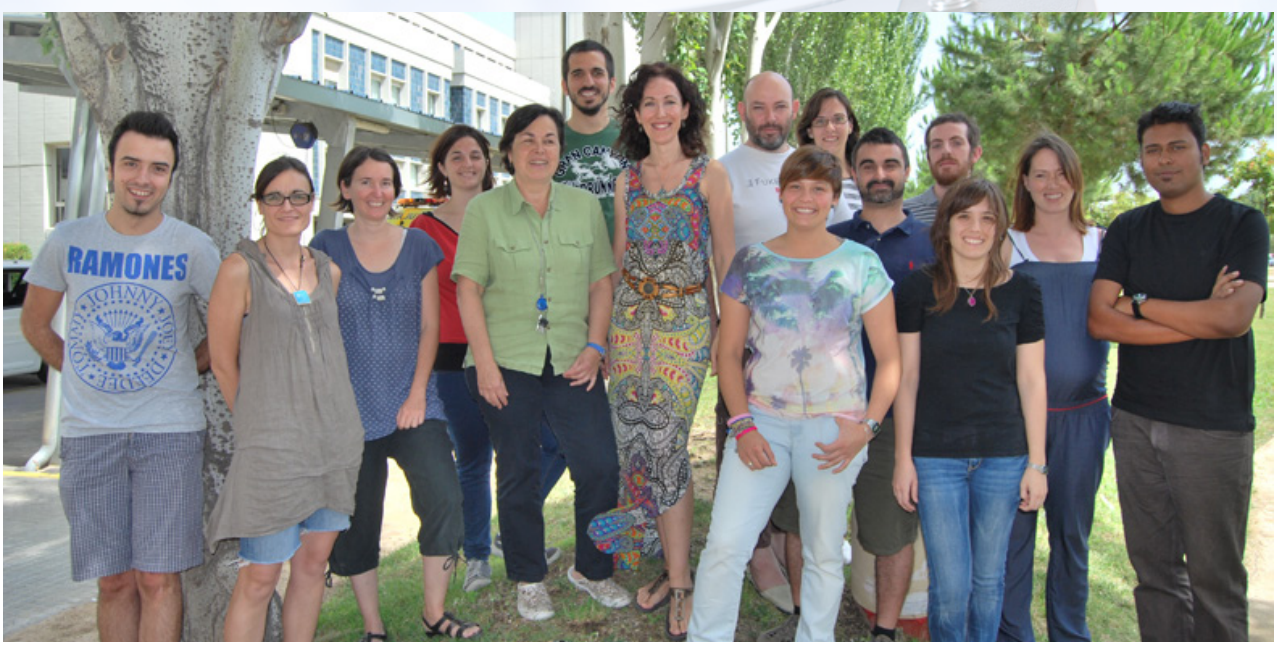
Website: http://www.isciii.es/ISCIII/es/contenidos/fd-el-instituto/fd-organizacion/fd-estructura-directiva/fd-subdireccion-general-servicios-aplicados-formacion-investigacion/fd-centros-unidades/instituto-investigacion-enfermedades-raras.shtml

Group U759

Programme: Inherited Metabolic Medicine



Lead Researcher: Pujol Onofre, Aurora

Group Members

STAFF MEMBERS: Launay, Nathalie | Ruiz Sales, Montserrat

ASSOCIATED MEMBERS: Coppa, Andrea | Dalfo Capella, Esther | 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, Aguado C, Fourcade S, Ruiz M, Grau L, Riera J, Guilera C, Giròs M, Ferrer I, Knecht E, Pujol A*. Autophagy induction halts axonal degeneration in a mouse model of X-adrenoleukodystrophy. Acta Neuropathol. 2015 Mar;129(3):399-415. IF : 9.777 (Q1 Neurosciences 13/252)
- Szczesna K, de la Caridad O, Petazzi P, Soler M, Roa L, Saez MA, Fourcade S, Pujol A, Artuch-Iriberri R, Molero-Luis M, Vidal A, Huertas D, Esteller M. Improvement of the Rett syndrome phenotype in a MeCP2 mouse model upon treatment with levodopa and a dopa-decarboxylase inhibitor. Neuropsychopharmacology. 2014. Nov;39(12):2846-56. IF: 8.678. (Q1 Neurosciences 17/252).
- Pirinen E, Canto C, Jo YS, Morató L, Zhang H, Menzies K, Williams EG, Mouchiroud L, Moullan N, Hagberg C, Li W, Timmers S, Imhof R, Verbeek J, Pujol A, van Loon B, Viscomi C, Zeviani M, Schrauwen P, Sauve A, Schoonjans K, Auwerx J. Pharmacological inhibition of Poly(ADP-Ribose) Polymerases improves fitness and mitochondrial Function in Skeletal Muscle. Cell Metab. 2014 Jun 3;19(6):1034-41. IF: 16.747 (Q1 Cell Biology 8/185).
- Morató L, Bertini E, Verrigni G, Ardissone A, Ruiz M, Ferrer I, Uziel G and Pujol A*. Mitochondrial dysfunction in white matter disorders. Glia. 2014 Nov;62(11):1878-94. IF: 5.066 (Q1 Neurosciences 43/252).
- Stack C, Jainuddin S, Elipenahli C, Gerges M, Starkova N,. Starkov AA, Portero-Otin M, Launay N, Pujol A, Kaidery, N; Thomas B; Beal MF, Dumont M. Methylene blue upregulates Nrf2/ARE genes and prevents tau-related neurotoxicity. Hum Mol Genet 2014 Jul 15;23(14):3716-32. IF 7.692 (D1, Biochemistry and Molecular Biology 28/290).

Highlights

In 2014 we achieved to: i) increase the knowledge of molecular basis and pathophysiology in X-ALD; ii) identifiy new therapeutic targets as the mitochondrial biogenesis drivers (Sirt1/PGC-1/PPARy axis) and autophagic flux (via mTOR); iii) identify drugs like resveratrol or temsirolimus, able to reverse the axonal degeneration in the mouse model, and iv) develop a biostatistical method for the diagnosis and study of new genes associated to leukodystrophies and spastic paraparesis, using new generation sequencing technologies.

We also started a multicenter international phase II clinical trial with biotin for AMN patients and promoted a phase II clinical trial with pioglitazone, for which we got the AEMPS and CEIC authorizations and funding in 2014 to start in 2015. We have also licensed the pioglitazone patent and obtained the orphan drug designation. In addition, we also obtained an international patent for temsirolimus along with U721.

In the ACCI 2014 call, we achieved an intramural project together with U703 and U711 units for exome and genome sequencing and functional validation in zebrafish, with the highest score by the ISCIII among all the applicant groups.

In addition to the aforementioned intraCIBERER collaborations, within the INFRAFRONTIER-I3 European project coordinated by Ll Montoliu (U756) we managed to generate a conditional KO IL10 mouse model, which is currently crossing with our X-ALD models to generate a model that mimics the cerebral X-ALD phenotype. Internationally, we started in 2013 a collaboration with Dr. J. Auwerx in Lausanne, with a first publication in Cell Metabolism in 2014.

Finally, as members of the SEFALer platform, we performed phenotyping services of locomotor disorders and neuromuscular coordination for the interested groups.

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Group U760

Programme: Paediatric and Developmental Medicine

Lead Researcher: Ruiz-Pérez, Víctor L

Group Members

STAFF MEMBERS: Caparrós Martín, José Antonio.

ASSOCIATED MEMBERS: Valencia Benítez, Maria

Main lines of research

- Análisis molecular y mecanismos fisiopatológicos del síndrome de Ellis-van Creveld y Weyer´s acrodental disostosis.
- Análisis molecular de casos con osteogénesis imperfecta autosómica recesiva y autosómica dominante.
- Identificación y caracterización de nuevos genes responsables de síndromes pediátricos.

Most relevant scientific articles

- Tenorio J, Mansilla A, Valencia M, Martínez-Glez V, Romanelli V, Arias P, Castrejón N, Poletta F, Guillén-Navarro E, Gordo G, Mansilla E, García-Santiago F, González-Casado I, Vallespín E, Palomares M, Mori MA, Santos-Simarro F, García-Miñaur S, Fernández L, Mena R, Benito-Sanz S, del Pozo Á, Silla JC, Ibañez K, López-Granados E, Martín-Trujillo A, Montaner D; SOGRI Consortium, Heath KE, Campos-Barros Á, Dopazo J, Nevado J, Monk D, Ruiz-Pérez VL, Lapunzina P. A new overgrowth syndrome is due to mutations in RNF125. Hum Mutat. 2014 Dec;35(12):1436-41
- Valencia M, Caparrós-Martin JA, Sirerol-Piquer MS, García-Verdugo JM, Martínez-Glez V, Lapunzina P, Temtamy S, Aglan M, Lund AM, Nikkels PG, Ruiz-Perez VL, Ostergaard E. Report of a newly indentified patient with mutations in BMP1 and underlying pathogenetic aspects. Am J Med Genet A. 2014 May;164A(5):1143-50.
- Guillén-Navarro E, Ballesta-Martínez MJ, Valencia M, Bueno AM, Martinez-Glez V, López-González V, Burnyte B, Utkus A, Lapunzina P, Ruiz-Perez VL. Two mutations in IFITM5 causing distinct forms of osteogenesis imperfecta. Am J Med Genet A. 2014 May;164A(5):1136-42.

Highlights

Osteogenesis imperfecta (OI) is a genetic condition characterized by bone fragility and recurrent fractures. In 2012 we described for the first time that mutations in BMP1, the gene encoding bone morphogenetic protein 1, are responsible for OI (Martinez-Glez et al Hum Mut 2012). In 2014 we have reported an additional patient with mutations in BMP1 (Valencia et al., AJMG 2014). Functional analysis in dermal fibroblasts demonstrated that the mutation in this patient resulted in decreased protein levels of the two alternatively spliced products of BMP1 and abnormal cleavage of the C-terminal propeptide of type I procollagen. In addition, fluorescence and electron microscopy showed impaired assembly of type I collagen fibrils in the extracellular matrix of cultured fibroblasts derived from two patients indicating that BMP1 is essential for human type I collagen fibrilogenesis. Further to this ongoing mutation screening in our lab identified one Spanish patient with a de novo Ser40Leu heterozygous mutation in IFITM5, a gene associated with OI type V, and another patient with the recurrent c.-14C>T transition in this gene also generated de novo (Guillen-Navarro et al AMJMG 2014). Patients with OI-V were previously found exclusively with the c.-14C>T change. Interestingly the Ser40Leu patient had none of the typical signs of OI type V and was diagnosed with limb shortening at prenatal stages. This study challenged the lack of allelic and clinical heterogeneity in IFITM5 mutations. Both BMP1 and IFITM5 publications were the product of a collaborative effort between several CIBERER units, a CIBERNED group and international teams. Lastly, in 2014 we collaborated with the U753 CIBERER unit in the description of a novel gene, RNF125, mutated in a new overgrowth syndrome (Tenorio et al Hum Mut 2014).

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Group U761

Programme: Sensorineural Pathology

Lead Researcher: Varela Nieto, Isabel

Group Members

STAFF MEMBERS: Murillo Cuesta, Silvia | Rodríguez de la Rosa, Lourdes

ASSOCIATED MEMBERS: Baeza Ochoa de Ocariz, María Luisa | Cediel Algovia, Rafael | Celaya Puertolas, Adelaida | Contreras Rodríguez, Julio | De Iriarte Rodríguez, Rocío | García Alcántara, Fernando | Magariños Sánchez, Marta | Martínez Vega, Raquel | Pajares Tarancón, María de los Ángeles | Rivera Rodríguez, Teresa | Sanz López, Lorena | Zubeldia Ortuño, José Manuel

Main lines of research

- Characterization of animal and cellular models of sensorineural hearing loss.

  - Genetics. Physiopathology of IGF-I deficit using animal and cellular models. Neuroinflammatory signature and redox balance.

  - Environment-genome interaction in animal models of hereditary hearing loss subjected to environmental stress: ototoxic agents, noise and vitamin deficiency.

  - Associated with aging.

- Identification of potential therapeutic targets and hearing loss progression markers. Role of the activity of pro-inflammatory kinase p38 MAPK in auditory damage and of the loss of function of genes from the RAF (RASopathy) family.
- Testing new therapies with small molecules and stem cells in animal models of sensorineural hearing loss.
- Animal models of retinal degeneration associated with IGF-I deficit and intracellular targets.

Most relevant scientific articles

- Folic acid deficiency induces premature hearing loss through mechanisms involving cochlear oxidative stress and impairment of homocysteine metabolism. Martínez-Vega R, Garrido F, Partearroyo T, Cediel R, Zeisel SH, Martínez-Álvarez C, Varela-Moreiras G, Varela-Nieto I, Pajares MA. FASEB J. 2015 Feb;29(2):418-32. doi: 10.1096/fj.14-259283. Epub 2014 Nov 10. PMID: 25384423
- IGF-1 deficiency causes atrophic changes associated with upregulation of VGluT1 and downregulation of MEF2 transcription factors in the mouse cochlear nuclei. Fuentes-Santamaría V, Alvarado JC, Rodríguez-de la Rosa L, Murillo-Cuesta S, Contreras J, Juiz JM, Varela-Nieto I. Brain Struct Funct. 2014 Nov 7. PMID: 25378055
- Differential organ phenotypes after postnatal Igf1r gene conditional deletion induced by tamoxifen in UBC-CreERT2; Igf1r (fl/fl) double transgenic mice. López IP, Rodríguez-de la Rosa L, Pais RS, Piñeiro-Hermida S, Torrens R, Contreras J, Varela-Nieto I, Pichel JG. Transgenic Res. 2015 Apr;24(2):279-94. doi: 10.1007/s11248-014-9837-5. Epub 2014 Sep 20. PMID: 25238791
- Loss of lysophosphatidic acid receptor LPA1 alters oligodendrocyte differentiation and myelination in the mouse cerebral cortex. García-Díaz B, Riquelme R, Varela-Nieto I, Jiménez AJ, de Diego I, Gómez-Conde AL, Matas-Rico E, Aguirre JA, Chun J, Pedraza C, Santín LJ, Fernández O, Rodríguez de Fonseca F, Estivill-Torrús G. Brain Struct Funct. 2014 Sep 17. PMID: 25226845
- Treatment with N- and C-terminal peptides of parathyroid hormone-related protein partly compensate the skeletal abnormalities in IGF-I deficient mice. Rodríguez-de la Rosa L, López-Herradón A, Portal-Núñez S, Murillo-Cuesta S, Lozano D, Cediel R, Varela-Nieto I, Esbrit P. PLoS One. 2014 Feb 4;9(2):e87536. doi: 10.1371/journal.pone.0087536. eCollection 2014.

Highlights

This year we have made progress in participation in projects and European networks focused on the study of the genetic basis of auditory aging. The FP7 AFHELO project for the preclinical study of a new family of molecules derived from cholesterol and two networks. The net COST MouseAge focused on the characterization of animal models of human diseases; and the network TARGEAR which we coordinate (www.targear.eu) and that it has a strong translational component with the Hospital de La Paz (Madrid) and transfer with two international biotechnology and electronics companies, we collaborate in the framework of the FP7-PEOPLE program "Industry-Academia Partnerships and Pathways (IAPP) - Marie Curie Action".

Scientific milestones include the description of the importance of diet in the progression of age-related hearing loss. Thus, we describe for the first time that folic acid and vitamin B derivatives are essential to maintaining a good hearing and cochlear redox state. Finally, they indicate that hyperhomocysteinemia in plasma may be a diagnosis tool for deafness progression. In parallel, we have further understood of the molecular basis of syndromes associated with deficits in the insulin-like growth factor type 1 (IGF-1) using animal models of deficit on the factor and its high affinity receptor. The total deficit is a rare human disease that causes neurosensorial deafness and alterations in bone growth. We have described in these animal models alterations in the central neurotransmission in the auditory pathway, as well as impaired bone growth caused by the loss of activity of cell survival AKT kinase signaling pathways.

The clinical doctors of the group maintained their specialized healthcare activity.

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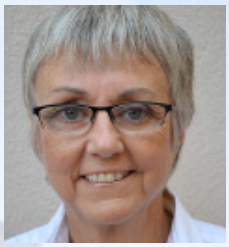
Group U762

Programme: Mitochondrial and Neuromuscular Medicine



Lead Researcher: Illa Sendra, Isabel

Group Members

STAFF MEMBERS: Araque Palacios, Josefa | Piñol Jurado, Patricia

ASSOCIATED MEMBERS: Alejaldre Monforte, Aida | Díaz Manera, Jorge Alberto | Gallardo Vigo, Eduardo | Navas Madroñal, Miquel | Nogales Gadea, Gisela | Ortiz Losada, Esther | Querol Gutiérrez, Luis Antonio | Ramos Fransi, Alba | Rojas García, Ricardo | Suárez Calvet, Xavier

Main lines of research

- **Search for biomarkers in neuromuscular disorders:** A) Search for new autoantibodies in immune-mediated NMD (Myasthenia, CIDP, NMM,..) and its correlation with specific phenotypes and new treatments. B) Analysis of miRNA profile in plasma/serum of patients with muscular dystrophies, Pompe's disease and myasthenia as biomarkers of the progresión of the different diseases C) Study of the secretome in human primary cultures of skeletal muscle from patients with well- characterized to determine its utility as a biomarker of clinical progression and to gain knowledge of the pathogenesis of these diseases D) Serial studies of muscle MRI in patients with muscular dystrophies to establish patterns of involvement that may be useful for the differential diagnosis and etiology of these diseases. In addition, quantitative studies of changes in muscle involvement to determine its utility as a non-invasive follow up test to monitor the efficacy of future treatments.
- **Research of pathogenic mechanisms of NMD:** A) Study of pericytes from skeletal muscle as a source of cells for physiological muscle regeneration and as a source of cells for cell therapy in patients with muscular dystrophies. B) To study factors involved in muscle regeneration and fibrosis.C) To study the role of innate immunity in inflammatory myopathies. D) Analysis of subpopulations of B cells in patients with autoimmune NMD. E) Estudios epidemiológicos y genéticos en ELA.
- **Spanish registry of NMD**. A nationwide registry of patients with NMD in Spain is in progress with epidemiological and research purposes (e.g search for new genes, clinical guidelines,...) At present, 4.500 patients have been registered. Twenty-seven hospitals in Spain participate in the registry and curator is in charge of the quality control of all data included in it (as part of CIBERER facilities).

Most relevant scientific articles

- Aragones JM, Roura-Poch P, Hernandez-Ocampo EM, Alonso F, Pont-Llluelles M, Xandri I, et al. Myasthenia gravis: a disease of the very old. J Am Geriatr Soc2014 Jan;62(1):196-7.FI: 4,22 Primer decil
- Gallardo E, Ankala A, Nunez-Alvarez Y, Hegde M, Diaz-Manera J, Luna ND, et al. Genetic and epigenetic determinants of low dysferlin expression in monocytes. Hum Mutat2014 Aug;35(8):990-7. FI: 5.05 Primer cuartil
- Gallardo E, Martinez-Hernandez E, Titulaer MJ, Huijbers MG, Martinez MA, Ramos A, et al. Cortactin autoantibodies in myasthenia gravis. Autoimmun Rev2014 Oct;13(10):1003-7. FI: 7.09 Primer decil
- Querol L, Nogales-Gadea G, Rojas-Garcia R, Diaz-Manera J, Pardo J, Ortega-Moreno A, et al. Neurofascin IgG4 antibodies in CIDP associate with disabling tremor and poor response to IVIg. Neurology2014 Mar 11;82(10):879-86.FI: 8.3 Primer decil
- Suarez-Calvet X, Gallardo E, Nogales-Gadea G, Querol L, Navas M, Diaz-Manera J, et al. Altered RIG-I/DDX58-mediated innate immunity in dermatomyositis. J Pathol2014 Jul;233(3):258-68. FI: 7.33 Primer decil

Highlights

PROJECTS

NATIONALS

- 2009 SGR1004. Research on neuromuscular diseases. Grup de recerca consolidat de la Generalitat. 2010-2014 PI: Dr Gallardo • AC365. Fundación Gemio. Research on advanced therapies in muscular dystrophy: Bone marrow transplantation and mesoangioblasts in murine models. 2009-2014. 400.000 euros PI: Dr ILLA • FIS 12/02291 Search for biomarkers in muscular dystrophies with limb girdle weakness. 2012-2015. 109.550 euros PI: Dr Gallardo • FIS 13/0937 New antigenic reactivities and innate immunity studies in autoimmune neuromuscular diseases (IMMUN-ENM). 2013-2015. 160.250 euros PI: Dr ILLA • FIS 13/0772 Spanish database of neuromuscular disorders. 2013-2015. 25.000 euros PI: Dr. Rojas • Duchenne Parents Project Nintedanib as at treatment for a murine model of dystrophinopathy. 25.000 euros PI: Dr Diaz • 2014 SGR 272 Research on neuromuscular diseases. 30.000 euros PI: Dr Gallardo

INTERNATIONALS

- Jain Foundation 2011-2016. Clinical Outcome Study for Dysferlinopathy. 2011-2016. 216.000 euros PI: Dr ILLA • IGOS. International GBS Outcome Study (IGOS). 2012- PI: Dr ILLA • AFMTÉLÉTHON. Nodal and paranodal cell adhesión molecules as immune targets in inflammatory neuromuscular diseases. 204-2016 PI: Dr ILLA • E-Rare Call. Autoantibodies to cell adhesion molecules in inflammatory neuropathies. ACAMIN. 2014-2016. 80.000 euros PI: Dr ILLA

CLINICAL GUIDELINES

- A manuscript of an international clinical guide for autoimmune Myasthenia gravis is in progress. The guide has been designed using the Delphi method and nine experts from the following countries have participated: USA (3), Canada (1), Japan (1), Italy (1), Germany (1), Denmark (1), Spain (1, Dr Illa).

PATENTS

- AUTHORS: RH Brown, MF Ho, I Illa, E Gallardo TITLE: Blood-Based Assay for Dysferlinopathies REGISTRY Nº: 7,172,858 PRIORITY DATE: 6 de Febrero de 2007 ENTITIES: Massachusetts General Hospital, Boston/ Hospital de Sant Pau, Barcelona COUNTRIES: USA, CANADA, JAPON. EXPLOITED BY: Athena Diagnostics.

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Group U763

Programme: Mitochondrial and Neuromuscular Medicine

Lead Researcher: Vílchez Padilla, Juan Jesús

Group Members

STAFF MEMBERS: Azorín Villena, Inmaculada Concepción | Gómez Perpiña, Lorena |

ASSOCIATED MEMBERS: Bataller Alberola, Luis | Chumillas Luján, Josefina | Marti Martínez, María Pilar | Mayordomo Fernández, Fernando | Muelas Gómez, Nuria | Sevilla Mantecón, María Teresa

Main lines of research

- Clinical and genetic characterization of hereditary motor and sensory neuropathies.
- Cutaneous innervation study and its application in the diagnosis of genetic and acquired neuropathies.
- Clinical studies and therapeutic trials in muscular dystrophies.
- Immunopathogenesis of hereditary and acquired ataxias.
- Clinical and genetic characterization of congenital myasthenias.

Most relevant scientific articles

- Lamont PJ, Wallefeld W, Hilton-Jones D, Udd B, Argov Z, Barboi AC, Bonneman C, Boycott KM, Bushby K, Connolly AM, Davies N, Beggs AH, Cox GF, Dastgir J, DeChene ET, Gooding R, Jungbluth H, Muelas N, Palmio J, Penttilä S, Schmedding E, Suominen T, Straub V, Staples C, Van den Bergh PY, Vilchez JJ, Wagner KR, Wheeler PG, Wraige E, Laing NG. Novel mutations widen the phenotypic spectrum of slow skeletal/ß-cardiac myosin (MYH7) distal myopathy. Hum Mutat; 2014 Jul. 35(7):868-79. PMID: 24664454 Doi: 10.1002/humu.22553.
- Pérez-Garrigues H, Sivera R, Vílchez JJ, Espinós C, Palau F, Sevilla T. Vestibular impairment in Charcot-Marie-Tooth disease type 4C. J Neurol Neurosurg Psychiatry; 2014 Jul. 85(7):824-7. PMID: 24614092 Doi: 10.1136/jnnp-2013-307421.
- Kornak U, Mademan I, Schinke M, Voigt M, Krawitz P, Hecht J, Barvencik F, Schinke T, Giesselmann S, Beil FT, Pou-Serradell A, Vílchez JJ, Beetz C, Deconinck T, Timmerman V, Kaether C, De Jonghe P, Hübner CA, Gal A, Amling M, Mundlos S, Baets J, Kurth I. Sensory neuropathy with bone destruction due to a mutation in the membrane-shaping atlastin GTPase 3. Brain; 2014 Mar. 137(Pt 3):683-92. PMID: 24459106 Doi: 10.1093/brain/awt357.
- Sabater L, Gaig C, Gelpi E, Bataller L, Lewerenz J, Torres-Vega E, Contreras A, Giometto B, Compta Y, Embid C, Vilaseca I, Iranzo A, Santamaría J, Dalmau J, Graus F. A novel non-rapid-eye movement and rapid-eye-movement parasomnia with sleep breathing disorder associated with antibodies to IgLON5: a case series, characterisation of the antigen, and post-mortem study. Lancet Neurol; 2014 Jun. 13(6):575-86. PMID: 24703753 Doi: 10.1016/S1474-4422(14)70051-1.
- Petit-Pedrol M, Armangue T, Peng X, Bataller L, Cellucci T, Davis R, McCracken L, Martinez-Hernandez E, Mason WP, Kruer MC, Ritacco DG, Grisold W, Meaney BF, Alcalá C, Sillevis-Smitt P, Titulaer MJ, Balice-Gordon R, Graus F, Dalmau J. Encephalitis with refractory seizures, status epilepticus, and antibodies to the GABAA receptor: a case series, characterisation of the antigen, and analysis of the effects of antibodies. Lancet Neurol; 2014 Mar. 13(3):276-86. PMID: 24462240 Doi: 10.1016/S1474-4422(13)70299-0.

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