RES

Annual Report 2016

ciberes

Centro de Investigación Biomédica en Red

Enfermedades Respiratorias

Index

Ferran Barbé, Scientific Director

Scientific Director's Presentation

Dear researchers,

We are now presenting our area's results for 2016. Please allow me to stress the two aspects which I consider to have been of greatest importance in our work over these last twelve months.

On one hand, our scientific results are yet again excellent, thanks to you all. We are keeping up our level of production and quality in both publications and projects and we have also got some very good results as CIBERES in competitive calls. One good example of this could be the fact that in 2016 we were granted four of the nine applications for FIS projects presented by us, which represents double the results obtained in 2015, as well as a type I Miguel Servet contract, the only one granted to a CIBER area in this call.

I would secondly like to highlight the work that we have done in developing a Strategic Plan to steer our work until 2019. This Plan redefines both our mission and vision and our strategic objectives, which can now finally be expressed as follows:

CIBERES Mission: *to join forces to tackle respiratory diseases, by fostering excellence research and innovation and its prompt and safe transfer to clinical practice, encouraging training and compiling knowledge and research talent state-wide, as a driving-force research centre and benchmark in the field of respiratory diseases.*

CIBERES Vision: *CIBERES vision is to be an excellence network research centre on the international level, competitive, sustainable and a reference in the work done for prevention in the field of respiratory diseases.*

Strategic objectives:

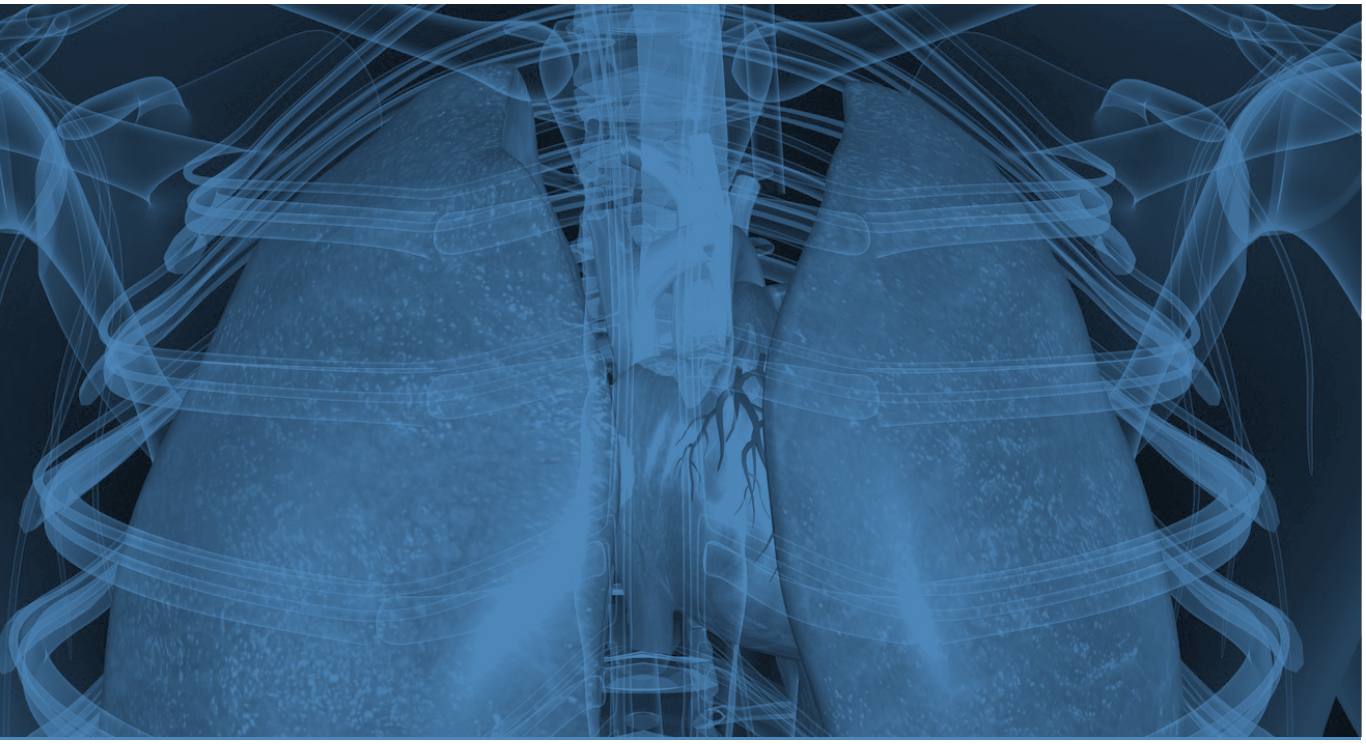
- *Excellence research in respiratory diseases: encouraging excellence research in respiratory diseases combining talent and the best human resources available state-wide.*
- *Translational calling: contributing to solving problems in everyday clinical practice in the field of respiratory diseases.*
- *International presence: encouraging participation and leadership of CIBERES research groups in international-scale research work.*
- *Transfer of results in innovation: promoting the transfer of research results to society in general and to the production sector in particular.*
- *Training: reinforcing the skills and competence of researchers in respiratory medicine: helping to increase their capacities for research and innovation and their competitiveness in respiratory diseases.*
- *Dissemination and visibility: raising awareness about CIBERES, spreading news of its activities and main results of respiratory research to society.*

- *Cooperation and alliances: establishing relations and stable synergies with public and private agents in the field of respiratory medicine.*

Our work over the coming years will thus be focussed on attaining the objectives set, to which end I hope to go on relying on your backing.

Congratulations to you all for your excellent work and for your commitment to cooperative research.

Many thanks.



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Organisation

Organisational structure

The CIBERES is one of the thematic areas forming the *Centro de Investigación Biomédica en Red* (CIBER), a Spanish research consortium in the field of biomedical research with great scientific potential, under the Instituto de Salud Carlos III (ISCIII) – Ministry of the Economy and Competitiveness. In 2016 it was made up of 8 thematic areas, which were extended to 11 in 2017.

The CIBERES is made up of 32 research groups, belonging to institutions of many different kinds: university hospitals, universities, Public Research Organizations (OPI), such as the Instituto de Salud Carlos III (ISCIII) itself and the Consejo Superior de Investigaciones Científicas (CSIC), and research centres of Spain's regional 'autonomous communities'.

CIBERES has a large team of human resources consisting of over 400 people, including a sizeable staff of its own researchers and members of groups as personnel associated to the CIBERES. This extensive team is made up of basic and clinical biomedical researchers, research technicians and management staff.

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

Steering Committe Members

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

Name	Post
Ferran Barbé Illá	Scientific Director
Jesús Ruiz-Cabello Osuna	Scientific Assistant Director
Antoni Torres Martí	Coordinator of the Infectious Disease Programme
Juan Fernando Masa Jiménez	Coordinator of the Respiratory Disease Programme
Francisco Pérez Vizcaíno	Coordinator of the Diffuse Respiratory Disease Programme
Cristina Prat Aymerich	Coordinator of the Teaching Programme
Javier Muñoz Bravo	Management of Scientific Programmes
Roser Mías Carballal	Attached to Scientific Director
Manuel Sánchez Delgado	Manager

External Advisory Scientific Committee

The External Advisory Scientific Committee is a body for scientific assessment and support, made up of relevant personalities in the field of health sciences standing out for their professional or scientific careers in line with the objectives of the Consortium. This is the body which carries out the annual appraisal of the work done by CIBERES and its research groups.

Name	Post
Dr. David Gozal	President. Univ Chicago, USA
Prof. Francesco Blasi	Member Univ. Milano.
Prof. Antonio Azueto	Member. Texas, USA
Prof. Kenneth BM Reid	Member. Univ. Oxford, United Kingdon
Prof. Michael S. Niederman	Member. New York, USA

Name	Post
Dr. Marc Humbert	Member C. National de Référence de l'Hypertension Pulmonaire Sévère. París
Prof. Bruno Crestaní	Member. Univ. Paris Diderot
Dr. Miguel Viveiros	Member Instituto de Higiene e Medicina Tropical Universida de NOVA de Lisboa

Scientific Management

Name	Post
Roser Mías	Attached to Scientific Director
Javier Muñoz	Manager of Scientific Programmes
Cristina Broceño	Technology Transfer and Bussiness Collaboration Manager
Cristina Villena	Coordinator of the Pulmonary Biobank Consortium

Contact: http://www.ciberes.org/en/about-us/contact

Technical Unit

List of personnel: http://www.ciberes.org/en/about-us/structure/head-office

Directory of Groups and Institutions

Group Leader	Institution	Centre	Centre Prov.
Agustí García Navarro, Álvar	Hospital Clínico y Provincial de Barcelona	Hospital Clínico y Provincial de Barcelona	Barcelona
Álvarez Martínez, Carlos José	Servicio Madrileño de Salud	Hospital Universitario 12 de Octubre	Madrid
Ardanuy Tisaire, Mª Carmen	Fundación IDIBELL	Hospital Universitario de Bellvitge	Barcelona
Barbé Illa, Ferrán	Instituto de Investigación Biomédica de Lleida. Fundación Dr. Pifarré	Instituto de Investigación Biomedica de Lleida	Lleida
Barberá Mir, Joan Albert	Hospital Clínico y Provincial de Barcelona	Hospital Clínico y Provincial de Barcelona	Barcelona
Blanch Torra, Lluis	Corporación Sanitaria Parc Taulí	Corporación Sanitaria Parc Taulí	Barcelona
Bouza Santiago, Emilio	Servicio Madrileño de Salud	Hospital Gregorio Marañon	Madrid
Cardona Iglesias, Pere Joan	Fundación Instituto de Investigación Germans Trias i Pujol	Hospital Universitario Germans Trias i Pujol.	Barcelona
Casals Carro, Cristina	Universidad Complutense de Madrid	Facultad de Biología	Madrid
Farré Ventura, Ramon	Universidad de Barcelona	Facultad de Medicina	Barcelona
García López, Ernesto	Agencia Estatal Consejo Superior de Investigaciones Científicas	Centro de Investigaciones Biológicas	Madrid
García Río, Francisco José	Servicio Madrileño de Salud	Hospital La Paz	Madrid
Gea Guiral, Joaquim	Consorci Mar Parc Salut de Barcelona	Hospital del Mar	Barcelona
González Mangado, Nicolás	Fundación Instituto de Investigación Sanitaria Fundación Jiménez Díaz	Instituto de Investigación Sanitaria - Fundación Jiménez Díaz	Madrid
Lorente Balanza, José Ángel	Servicio Madrileño de Salud	Hospital Universitario de Getafe	Madrid

Group Leader	Institution	Centre	Centre Prov.
Marimón Ortiz de Zarate, José Maria	Asociación Instituto Biodonostia	Hospital Donostia	San Sebastian
Martín Montañés, Carlos	Universidad de Zaragoza	Universidad de Zaragoza	Zaragoza
Masa Jiménez, Juan Fernando	Fundación para la Formacion y la Investigación de los Profesionales de la Salud (FUNDESALUD)	Hospital San Pedro de Alcantara	Cáceres
Menéndez Fernández, Margarita	Agencia Estatal Consejo Superior de Investigaciones Científicas	Instituto de Química Física Rocasolano	Madrid
Monsó Molas, Eduard	Corporación Sanitaria Parc Taulí	Corporación Sanitaria Parc Taulí	Barcelona
Montserrat Canal, Josep Mª	Hospital Clínico y Provincial de Barcelona	Hospital Clínico y Provincial de Barcelona	Barcelona
Morcillo Sánchez, Esteban Jesús	Universidad de Valencia	Facultad de Medicina de Valencia	Valencia
Muñoz Gall, Xavier	Fundación Hospital Universitario Vall d'Hebron - Institut de Recerca (VHIR)	Hospital Valle Hebron	Barcelona
Nieto Martín, Amelia	Agencia Estatal Consejo Superior de Investigaciones Científicas	Centro Nacional de Biotecnologia	Madrid
Obeso Caceres, Ana	Universidad de Valladolid	Facultad de Medicina	Valladolid
Pérez Vizcaíno, Francisco	Universidad Complutense de Madrid	Facultad de Medicina	Madrid
Picado Vallés, César	Hospital Clínico y Provincial de Barcelona	Hospital Clínico y Provincial de Barcelona	Barcelona
Pozo Abejón, Mª Victoria del	Fundación Instituto de Investigación Sanitaria Fundación Jiménez Díaz	Instituto de Investigación Sanitaria - Fundación Jiménez Díaz	Madrid
Rello Condomines, Jordi	Fundación Hospital Universitario Vall d'Hebron - Institut de Recerca (VHIR)	Hospital Valle Hebron	Barcelona
Regueiro Comesaño, Verónica	Fundación de Investigación Sanitaria de las Islas Baleares Ramón Llull (FISIB)	Hospital Universitario Son Espases	I. Baleares
Ruiz Cabello Osuna, Jesús	Fundación Centro Nacional de Investigaciones Cardiovasculares	Fundación Centro Nacional de Investigaciones Cardiovasculares	Madrid
Torres Martí, Antoni	Hospital Clínico y Provincial de Barcelona	Hospital Clínico y Provincial de Barcelona	Barcelona
Villar Hernández, Jesús	Fundación Canaria de Investigación Sanitaria (FUNCANIS)	Hospital Universitario de Gran Canaria Dr. Negrín	Las Palmas

Budget

INCOME					
ISCIII TRANSFER	GRANTS PROJECTS	SERVICES RENDERED	OTHER INCOME	CARRYOVERS	TOTAL
2.632.420,00	329.515,82	159.402,93	19.000,00	334.738,17	3.475.076,92

EXPENDITURE				
Project	Inventoriable	Supplies and other activity expenses	Personnel	TOTAL
Scientific Management, Scientific Secretariat, Communication	0,00	84.310,53	55.543,34	139.853,87
Groups	259.452,26	446.877,45	1.632.591,55	2.338.921,40
Training	0,00	24.422,20	80.021,41	104.443,61
Programmes	0,00	19.550,34	1.307,59	20.857,93
Platforms	15.436,53	2.642,37	88.533,64	106.612,54
Intramural Projects	3.359,05	2.187,99	0,00	5.547,04
External Projects	11.413,24	494.307,71	253.119,48	758.840,53
TOTAL	**289.661,08**	**1.074.298,59**	**2.111.117,01**	**3.475.076,92**

Personnel

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

	MEN	WOMEN	Overall total
Diploma holders	2	7	9
Doctors	6	23	29
Graduates	10	17	27
Technical	2	9	11
TOTAL	**20**	**56**	**76**

Significant activities

Projects

NATIONAL

Financing Agency: Instituto de Salud Carlos III

Role of innate immune receptors in vascular alterations associated with acute lung damage and pulmonary hypertension. The implication of endogenous danger-associated molecular patterns.
Role of FAS-mediated apoptosis in damage of the pulmonary epithelium.
Identification of markers of very severe COPD activity in experimental models, and assessment of therapeutic intervention with soluble guanylate cyclase.
National Biobanks Network.
Molecular profile of cardiovascular risk in patients with obstructive sleep apnoea: Personalised predictive model.
FPI Cohort: Telomere Shortening and its regulation.
Therapeutic potential of exosomes derived from mesenchymal cells and late endothelial progenitor cells in bronchopulmonary dysplasia and pulmonary hypertension.
Tight junctions of the alveolar epithelium in the development of the Acute Respiratory Distress Syndrome: Clinical and experimental study.

Financing Agency: Ministry of the Economy and Competitiveness:

Post-Doctoral Grant Contract 2013.
Technical Support staff Contract 2015.

Other financing organisations:

Fundación Astrazeneca.
Development and application of network medicine to tackle pathobiological heterogeneity and clinical complexity of COPD.
Impact of the Sleep apnoea-hypopnea syndrome in the evolution of the acute coronary syndrome.
Effect of intervention with continuous positive airway pressure (CPAP).

INTERNATIONAL PROJECTS EU

FP7-PEOPLE-2011-COFUND Proyecto M+VISION.

Transfer

One of the CIBER's main aims is the transfer of the knowledge generated by its researchers, so that its research results can be developed in protocols, services and products for improving clinical practice and people's quality of life.

To this end the CIBER Technology Transfer department acts as a liaison between our researchers and companies, private institutions, public research centres and other innovation agents to make cooperation with them more effective and ensure that the results of research are actually applied.

Work is done in several approaches to achieve this aim:

- Continuous contact with our researchers to monitor their results and train them in innovation management.
  On 29 and 30 November 2016 a Technology Transfer Session was arranged to this end as part of the 30th anniversary of the ISCIII. At this event experts in different areas shared their knowledge on industrial property, company creation, licencing processes, venture capital, grants for internationalisation, etc.
- Protection of the results of research and management of cooperation with other agents, as displayed by the application for patents and signing licence contracts, amongst other agreements.

Throughout 2016 eleven new patent applications and a registration of software were thus submitted at the CIBER. Seven inventions are in the patentability study and one in the drafting stage, and these are expected to be submitted in early 2017.
Apart from this, eight licence contracts have been signed. Furthermore, during 2016 several negotiations started and we expect to end successfully in the first quarter 2017.
At CIBERES a licence contract was signed with a company in 2016.

- The presentation of the results of research and technological capacities of our groups in technology transfer sessions. Among many other measures, and just as an example of this, CIBER had a stand and institutional presence at BIOSPAIN 2016 (28-30 September, Bilbao).
- Support for technology-based company creation stemming from CIBER groups.
- Other activities connected with innovation, public-private cooperation and industrial and intellectual property. As an example we could mention:
  - The call for Caixaimpulse 2016 projects at which a CIBERES project won an award.
  - Several MTAs (material transfer agreements) were signed, one with a company and thus with economic compensation for the CIBERES), CDAs (confidentiality agreements) and several scientific cooperation agreements as well as the ones mentioned).
  - Participation in internal and external forums and conferences.

Dissemination

In 2016 the CIBER'S Communication Department performed different measures for dissemination and disclosure in order to raise awareness of the Centre, as well as to spread knowledge about the research work done by the groups in its eight thematic areas.

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

- **The CIBERES in the media:**
  In this period 67 CIBER press releases were published, 4 of these from the CIBERES and 1 in cooperation between several CIBER areas.

Date	Thematic area	Title
16/03/2016	CIBERES	El uso de viejos antibióticos con nuevos dispositivos para aerosolizar emerge como estrategia terapéutica en infecciones respiratorias graves
04/07/2016	CIBERES	Las apneas de sueño de extrema gravedad paradójicamente disminuyen el riesgo cardiovascular en pacientes obesos con insuficiencia respiratoria
06/07/2016	CIBERES	Diseñan un sistema de uso sencillo para predecir el pronóstico de pacientes con lesión pulmonar grave
30/08/2016	CIBERES	El tratamiento con CPAP no previene los problemas cardiovasculares graves de pacientes con apnea de sueño
16/11/2016	VARIOS CIBER	El CIBER acerca su investigación a la sociedad de la mano de la improvisación teatral en #ImproCiencia

343 appearances in the media were also recorded:

2016	News items	Audience
CIBERES	343	26.691.400

- **CIBER Newsletter**
  This year 5 CIBER newsletters were edited and disseminated, including relevant content about the CIBERES and other thematic areas. The digital newsletters were sent to around 4000 subscribers. http://www.ciberisciii.es/en/press/newsletter

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

- **CIBERES Web site**
  The CIBERES web site published 60 news items and 49 events on the agenda in 2016.

Statistics on visits on the web 2016							
	No. of visits to page	Sessions*	Users	Pages / session	Average duration of session	% rebound**	% new sessions
CIBERES	66.082	27.218	18.113	2,43	1:55	64,36	65,52

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

- **Social Networks**
  Main indicators of the presence of CIBERES en Twitter:

	followers		Updates		Klout (Influencia)	
	January	December	January	December	January	December
CIBERES	1528	2024	2484	2692	44	44

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

- **CIBER Science Week #ImproCiencia**
  The #ImproCiencia dissemination event, held on 16 November in Madrid, combined science and theatre improvisation to give a light-hearted explanation of the biomedical research work done by the CIBER in its eight thematic areas. CIBERES also presented the Pulmonary Biobank Consortium, coordinated by Dr. Cristina Villena.

- **CIBERES Scientific Sessions**
  The results of the different research lines of the CIBERES were presented at the 10th CIBERES Scientific Sessions, held on 30 June and 1 July at the Escuela Nacional de Sanidad of the Instituto de Salud Carlos III.
  Programme: http://www.ciberes.org/media/657938/programa-x-jornadas-cientificas-ciberes.pdf

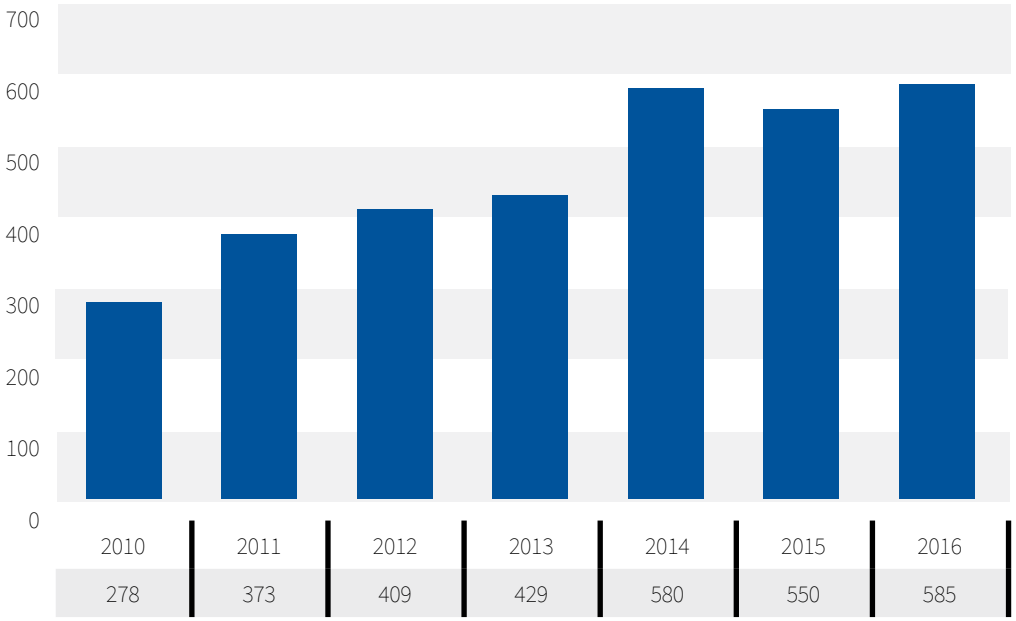
Scientific Production

The graphic evolution of CIBERES publications can be seen from the following tables, in which the data from 2010 to 2016 is analysed. They also detail the publications by group for this year, as well as the interCIBER and intraCIBER cooperation work done.

NO. OF AFFILIATED PUBLICATIONS 2016

Nº. of affiliated publications	2015	2016
No. of affiliated publications	561	585
Q1	303	287
D1	143	126

EVOLUTION OF PUBLICATIONS 2010-2016



Most relevant CIBERES publications in 2016 according to the Impact Factor

Publication	Impact Factor
McEvoy R.D., Antic N.A., Heeley E., Luo Y., Ou Q., Zhang X. et al. CPAP for prevention of cardiovascular events in obstructive sleep apnea. New England Journal of Medicine. 2016;375(10):919-931.	59,558
Cunha BA, Burillo A, Bouza E. Legionnaires' disease. Lancet (London, England). 2016;387(10016).	44,002
Latorre-Pellicer A., Moreno-Loshuertos R., Lechuga-Vieco A.V., Sanchez-Cabo F., Torroja C., Acin-Perez R. et al. Mitochondrial and nuclear DNA matching shapes metabolism and healthy ageing. Nature. 2016;535(7613):561-565.	38,138
Bellani G., Laffey J.G., Pham T., Fan E., Brochard L., Esteban A. et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA - Journal of the American Medical Association. 2016;315(8):788-800.	37,6840
Hernandez G., Vaquero C., Gonzalez P., Subira C., Frutos-Vivar F., Rialp G. et al. Effect of postextubation high-flow nasal cannula vs conventional oxygen therapy on reintubation in low-risk patients: A randomized clinical trial. JAMA - Journal of the American Medical Association. 2016;315(13):1354-1361.	37,6840
Hernández G, Vaquero C, Colinas L, Cuena R, González P, Canabal A et al. Effect of Postextubation High-Flow Nasal Cannula vs Noninvasive Ventilation on Reintubation and Postextubation Respiratory Failure in High-Risk Patients: A Randomized Clinical Trial.JAMA. 2016.	37,6840
Sunyer R., Conte V., Escribano J., Elosegui-Artola A., Labernadie A., Valon L. et al. Collective cell durotaxis emerges from long-range intercellular force transmission. Science. 2016;353(6304):1157-1161.	34,661
Jimenez D., De Miguel-Diez J., Guijarro R., Trujillo-Santos J., Otero R., Barba R. et al. Trends in the Management and Outcomes of Acute Pulmonary Embolism Analysis from the RIETE Registry. Journal of the American College of Cardiology. 2016;67(2):162-170.	17,759
Delcroix M., Lang I., Pepke-Zaba J., Jansa P., D'Armini A.M., Snijder R. et al. Long-Term Outcome of Patients with Chronic Thromboembolic Pulmonary Hypertension: Results from an International Prospective Registry. Circulation. 2016;133(9):859-871.	17,047
Neto AS, Barbas CS, Simonis FD, Artigas-Raventós A, Canet J, Determann RM et al. Epidemiological characteristics, practice of ventilation, and clinical outcome in patients at risk of acute respiratory distress syndrome in intensive care units from 16 countries (PRoVENT): an international, multicentre, prospective study.The Lancet. Respiratory medicine. 2016.	15,328

Nº. of publications per group 2016

Group Leader	Total Publications	Q1	D1
Agustí García Navarro, Álvar	39	17	10
Álvarez Martínez, Carlos José	20	14	3
Ardanuy Tisaire, María Carmen	14	10	4
Barbé Illa, Ferrán	51	21	8
Barberá Mir, Joan Albert	27	19	10
Blanch Torra, Lluis	43	31	17
Bouza Santiago, Emilio	45	22	8
Cardona Iglesias, Pere Joan	24	9	2
Casals Carro, Cristina	2	2	0
Farré Ventura, Ramon	20	13	2
García López, Ernesto	7	5	1
García Río, Francisco José	19	8	5
Gea Guiral, Joaquim	36	10	1
González Mangado, Nicolás	16	9	1
Lorente Balanza, José Ángel	12	7	6
Marimón Ortiz de Zarate, José Maria	10	5	1
Martín Montañés, Carlos	9	4	2
Masa Jiménez, Juan Fernando	21	10	4
Menéndez Fernández, Margarita	4	3	2
Monsó Molas, Eduard	24	6	3
Montserrat Canal, Josep Maria	20	10	3
Morcillo Sánchez, Esteban Jesús	6	6	2
Muñoz Gall, Xavier	62	18	11
Nieto Martín, Amelia	13	9	1
Obeso Cáceres, Ana	3	2	1
Pérez Vizcaíno, Francisco	7	5	2
Picado Vallés, César	32	10	3
Pozo Abejón, María Victoria del	10	4	4
Regueiro Comesaño, Verónica	2	2	1
Relló Condomines, Jordi	51	23	7
Ruiz Cabello Osuna, Jesús	11	8	4
Torres Martí, Antoni	55	33	15
Villar Hernández, Jesús	22	12	5

COLLABORATIVE WORK

Collaborative work	2015	2016
intraCIBER publications	174	166
interCIBER publications	78	86

Patents with CIBER ownership 2016:

- APPLICATION FOR – international and national. PCT for the same P201531409 6% CIBER/ES "Integrated filter-holder and procedure for concentrating and detecting microorganisms"
- GRANTED – international and national. Granting of patents US9297034 and EP2514833 24%CIBER/ES for priority patent P200931177 "Detection of Streptococcus pneumoniae through magneto-amperometric genosensors employing specific primers and probes for the lytA gene".

Clinical guidelines 2016:

- *"Risk and safety requirements for diagnostic and therapeutic procedures in allergology: World Allergy Organization Statement".*
- *"A review of national guidelines for management of COPD in Europe".*
- *"Guidelines for the use of interferon-gamma release assays in the diagnosis of tuberculosis infection".*
- *"Recomendaciones para la interpretación del anexo IV del Reglamento General de conductores aprobado por RD 818/2009 modificado por el RD 1055/2015 sobre apnea del sueño y conducción de vehículos."*
- *"Triage decisions for ICU admission: Report from the Task Force of the World Federation of Societies of Intensive and Critical Care Medicine".*
- *"The Intensive care unit specialist: Report from the Task Force of World Federation of Societies of Intensive and Critical Care Medicine".*
- *"Esophageal and transpulmonary pressure in the clinical setting: meaning, usefulness and perspectives".*
- *"Does this ventilated patient have asynchronies? Recognizing reverse triggering and entrainment at the bedside".*
- *"The Intensive Care Global Study on Severe Acute Respiratory Infection (IC-GLOSSARI): a multicenter, multinational, 14-day inception cohort study".*
- *"Criteria for initiation of invasive ventilation in septic shock: An international survey".*
- *"Delay in diagnosis of influenza A (H1N1) pdm09 virus infection in critically ill patients and impact on clinical outcome".*
- *"14. SEPsis REcognition and MAnagement (SEPREMA survey)".*

3

Scientific Programmes

Chronic Respiratory Diseases Programme

Coordinator: **Juan Fernando Masa**

Sleep line

a) We have a population of 70,000 patients with CPAP and a collection of samples of 550 patients for BigData analysis and clusters in SAOS; b) A commercial transfer has been generated which predicts the response to treatment based on biomarkers (HIPARCO-Score); c) In SAOS manipulation, 5 publications have been obtained and 5 studies completed; d) A virtual sleep unit has been got under way and a platform for monitoring patients with SAOS, generating 5 publications; e) 16 articles have been published on the SAOS-cancer relationship, intermittent hypoxia being responsible for the increase in tumor incidence; f) 3 papers have been given at congresses on the SAOS- Alzheimer relationship and there are 3 projects under way; and g) The SAOS-cardiovascular relationship has been explored, generating 7 articles, one at the NEJM.

COPD line

Progress has been made in the cohorts of the line (DELICATO-BIOMEPOC, EARLY-EPOC and PESA-CNIC) and in the following activity biomarkers: a) Transcriptome analysis of the DELICATO-BIOMEPOC cohort, now in the biostatistical analysis stage; b) Analysis of networks displaying the participation of B lymphocytes in serious emphysema; c) Microbiome: definition of the microbiome by analysis of 16S-rRNA. Adaptive traits of the virulence of NTHi identified. Cover of anti-pneumococcal vaccine PCV13 in COPD defined; d) Biomarkers of systemic inflammation connected with exacerbation of COPD defined; e) Identification of individuals with poor pulmonary development having lower development and more comorbidities; and f) Experimental treatments: progress in treatment of emphysema with LGF and guanylate cyclase.

Asthma Line

a) Starting a multicentre study to determine the events giving rise to an asthmatic population, long-term parameters which may determine changes in patients' severity and what treatments are of influence in the progression of asthma, the causes of exacerbations and how these affect asthma's evolution; b) A cohort of 450 patients has been got under way with 250 already included. The first results have been sent to SEPAR and ERS. Financing for the project has been obtained from the FIS (PI15/01900) (140,000 €) and from SANOFI (120,000 €); and c) In 2016 the members of the group took part in 31 publications, 12 international and 19 national.

Cancer Line

a) Cohorts (IASLC, CIBERES and Early-COPD) of patients with LC in the Ip/IIp stages: the inflammatory and tumour stroma biomarkers are associated with a bad prognosis and there is an overexpression of miARNs in patients with prolonged survival; b) 207 patients with lung cancer in more advanced early stage (FIS grant), had a greater CRP and TNF-2 receptor. An associated project (SEPAR) has produced two publications; c) The results of a screening cohort using low doses of CT (LD-CT) (>500 individuals) have been presented at national congresses and ATS 2017; d) The recruiting of patients with lung cancer diagnosed/staged by EBUS-TBNA started; e) In the LC cohort (>200 subjects) and in 50 patients with lung cancer a high prevalence of sleep-related breathing disorders was found. The results are presented in SEPAR, ERS and ATS.

Infectious Respiratory Diseases Programme

Coordinator: **Antoni Torres**

Tuberculosis Line

The strategic programme on tuberculosis (TB) is focussed on:

Prevention: the design of new candidates for vaccination: clinical development of MTBVAC; construction of multivalent live-attenuated vaccines based on three modern families of M. tuberculosis; design of a hyper-attenuated vaccine for the immunocompromised; new strategic therapies for preventing infection and active disease: methods for fast monitoring of the transmission of TB by genome sequencing and species-specific CRPs.

Diagnosis: study of lesions caused by TB obtained by surgical procedures to seek biomarkers better correlating with TB pathology, clinical aspects, multi-resistance to drugs and prognosis; evaluation of new immunological and molecular tests for diagnosis of latent TB infection and disease: development of tests that are useful in low-income countries; integration of genomic and epidemiological strategies.

Treatment: basic research and development of new anti-tuberculosis drugs; evaluation of therapies addressing the host; development of new approaches for studying pathogen-host interactions with new anti-tuberculosis formulations.

Host-Pathogen Interactions Line

The host-pathogen interaction line works on identifying new therapeutic targets based on knowledge of the biological bases of infection for their later exploitation in the development of antimicrobials. To this end it uses multiple pathogen-specific approaches currently in the therapeutic discovery and/or preclinical evaluation phase. This line is having significant results in its three areas:

- Genes of *K. pneumoniae*, *S. aureus*, *H. influenzae*, *S. pneumoniae*, *influenza* and *Mycobacterium* implicated in patho-adaptive evolution during respiratory infection have been identified and/or characterised on the genomic and phenotypic level;
- Strategies in eukaryotic subversion by *Mycobacterium*, *K. pneumoniae*, the influenza virus and RSV, and of immunomodulation by pulmonary surfactant have been characterised;
- Progress has been made in the preclinical valuation of pulmonary surfactant proteins, natural polyphenols, aptamers and enzybiotics as antimicrobials, as well as in the optimisation of pharmacological release systems.

In 2016, the work done in this line generated 36 scientific publications, 2 patents, and gave rise to the defence of 7 doctoral theses.

Pneumonia Line

The “Pneumocoper” project is the project of the Pneumonia Line Programme for the 2016-2018 period. This project includes the following 9 sub-programmes:

- *WP1-Pneumonia caused by MDR pathogens. Rosario Menéndez*
- *WP2-Community-acquired Pneumonia in non neutropenic oncological patients. Maria Luisa Pedro-Botet*
- *WP3-S. Pneumoniae from bench to bedside. Carmen Ardanuy*
- *WP4-Rapid microbiological tests to improve the management of respiratory infections. Emilio Bouza*
- *WP5-Treatment of pneumonia:reviewing the current Guidelines, amd what´s in the pipe line.Jordi Rello*
- *WP6-Prevention of Hospital-acquired pneumonia. Antoni Torres*
- *WP7-Animal models of pneumonia. Gian Luigi li Bassi*

- *WP8-Other pathogens causing CAP. Txema Marimón*
- *WP9-Dissemination. Antoni Artigas*

The "Pneumocoper" programme made satisfactory progress in most of the 9 sub-programmes in 2016, with the publication of diverse articles in the first decile and quartile, doctoral theses, official and unofficial research projects, clinical guides and interaction with private companies.

Diffuse Respiratory Disease Programme

Coordinator: **Francisco Pérez Vizcaíno**

Lines:

ACUTE LUNG INJURY (ALI)

PULMONARY FIBROSIS (PF)

PULMONARY HYPERTENSION (PH)

CLINICAL GUIDES

- European and Spanish clinical guides on the diagnosis and treatment of PH.
- Redefinition of the Acute Respiratory Distress Syndrome (ARDS).

GENETICS

- Genome analysis (GWAS) of patients at risk of ARDS. Development of the PH biobank.
- Participation in the *International PAH Genetics Consortium*.

GENOMIC, TRANSCRIPTOMIC AND METABOLOMIC BIOMARKERS

- Profile of expression of angiogenic factors in vascular remodelling in COPD.
- Metabolomic characterisation in PH and ARDS.
- Changes in microparticles, microRNAs and endothelium progenitor cells circulating in arterial and thromboembolic PH.

EPIDEMIOLOGY

- Strategies for ventilation and prognosis of patients at risk of ARDS.
- Therapeutic handling and prognosis of patients with chronic thromboembolic PH.
- Predictive and prognostic factors of telomere shortening in PF.

IMAGING

- Utility of (68) Ga-DOTA PET for measuring regional pulmonary blood flow.
- Development of microCT, microCT-PET, microCT-SPECT to evaluate pulmonary structure, inflammation and vascular remodelling.
- In vivo imaging with new biocompatible systems of metallic nanoparticles.
- Marking of autologous erythrocytes with 18F-FDF.

PHYSIOPATHOLOGY

- The role of angiopoietin-2 in PH associated with COPD.
- Acid sphingomyelinase and IL-6 in endotoxin-induced vascular dysfunction.
- Role of Slug in vascular proliferation and remodelling.

- Transdifferentiation of endothelial cells to smooth muscle cells in vascular proliferation and remodelling.
- Haemodynamic characterisation in patients with COPD.
- Role of Fas ligand in acute pulmonary damage.
- Changes in expression and distribution of tight-junction proteins ZO1 and occludin in ARDS.
- Specific MicroRNAs induce endothelial dysfunction and ionic remodelling in pulmonary arteries.
- Brain-lung communication in the critical patient.
- Meaning of patient-ventilator asynchronies.
- Identification of the mechanisms involved in collective cell migration.
- Changes in 3D structure have a role in losing pulmonary compliance.
- Characterisation of vascular resistance in the decellularized lung.

NEW THERAPIES

- Telomerase-inhibiting peptides for treatment of PF.
- Acid sphingomyelinase and IL-6 inhibitors in PH and endotoxin-induced ventilation-perfusion uncoupling.
- Quercetin flavonoid prevents pulmonary oedema in a haemorrhagic shock model.
- Anti-inflammatory effects of heparin and antithrombin III in human lung cells.
- Effectiveness of methotrexate in animal models of sepsis.
- Intestinal decontamination attenuates the inflammation induced by aggressive mechanical ventilation.
- Transplanting type II alveolar cells reduces alveolar-capillary permeability and cell infiltration.
- Therapy of combining ambrisentan and tadalafil in PH.
- Effectiveness of sildenafil in models of COPD and PF.
- Preclinical utility of ß3 adrenergic agonists in PH.

UTILITY MODELS AND INNOVATION

- New long-term ARDS models.
- Cell models with mutations of the telomerase complex of patients with idiopathic PF.
- Cultures of endothelial cells from endarterectomies.
- Administration protocols.

4

Transversal Programmes

Training Programme

Coordinator: **Cristina Prat**

In 2016, the teaching Programme was considered to be a strategic measure in the 2016 CIBERES Action Plan which focussed on “Encouraging the training of new researchers” and “Fostering internationalisation”. The main objectives of the Teaching Programme are:

- To increase our researchers’ basic, clinical and technological knowledge by creating synergies with receiving organisations.
- To increase the interest for research in respiratory diseases of young researchers in their training period to integrate these into CIBERES groups by fostering talent recruitment.
- To further the mobility of research staff.
- To boost researchers’ intensification measures to enable the presentation of European/international projects.

Training Programme for Research Staff

GRANTS FOR INITIATION TO RESEARCH

This programme proved to be of great interest as in earlier editions. The aim of the grants is to help young researchers in their initial training to join a research programme financed by public institutions for one year and associate this with one of the CIBERES research groups. The official Programme for training research staff (FPI) keeps its co-financing ratio at 66% by the teaching training programme and 33% by the receiving group itself.

Thanks to the increase in the budget, a further 2 calls for 9 grants were launched in 2016.

Improvement and Mobility Programme

In 2016, a further line of action was added to the mobility programme focussing on co-financing the enrolment dues of Doctorate Programmes. 7 applications for payment of dues (500 € per application) and 3 applications for stays in another city were co-financed. Longer stays were encouraged with an increase in the economic endowment of the grants to 600 € per month plus 80% of the return trip, approving a further 2 applications (London and Toronto), which will be financed in 2017.

Intensification Programme

The Intensification programme was proposed in order to strengthen Internationalisation at CIBERES, helping the researcher in drafting and submitting proposals for European/international projects. The final aim of this is to increase the input of external resources by raising the number of projects financed. 2 applications were presented in 2016.

Programme for Fostering Interest in Respiratory Research

TRAINING SESSIONS

On 29 and 30 September 2016 the 9th Training Sessions were held in Madrid, at the Sala Auditorio of the Centro Nacional de Investigaciones Cardiovasculares (CNIC).

One innovation that we should mention was the participation of CIBERBBN researchers who shared the presentation of 6 cooperative projects undertaken in the framework of CIBERES-CIBERBBN- SEPAR cooperation displaying the bonds already existing between the two CIBER areas. 48 junior CIBERES and CIBER-BBN researchers took part, presenting 10 oral papers and 38 posters, as well as the value contributed by senior researchers and managers.

3 prizes for the best posters and oral communication were awarded as well as a special “Dr. Constancio González“ prize for the most highly-considered oral paper.

Internationalisation Programme

Coordinator: **Cristina Rodríguez**

Last 11 May 2015 the **CIBER Platform for Assistance for Internationalisation** was set up. The Platform for Assistance for Internationalisation (PAI) came about as a joint initiative of the **Bioengineering, Biomaterials and Nanomedicine areas (CIBER-BBN), Rare Diseases (CIBERER) and Respiratory Diseases (CIBERES), of the Centro de Investigación Biomédica en Red (CIBER)**, with the aim of underpinning and coordinating endeavours intended to promote its researchers' participation in European programmes and creating a common structure **to further internationalisation and leadership of research and innovation in these three thematic areas**.

In 2016 the platform focussed its work on two main areas: fostering the participation of CIBER groups in international projects and improving the international visibility of the CIBER.

As regards fostering the participation of CIBER groups in international projects and, in order to improve the quality of the proposals put forward, the PAI has carried out 4 specific events for disseminating the advantages of internationalisation and given **3 specific courses** on drafting and managing European projects intended for researchers and managers in the CIBER environment (Aspects of relevance in presentation and justification of European proposals in the CIBER environment" (April 2016, with 70 persons attending) and "Drafting successful cooperation proposals in the framework of H2020" (Madrid edition. June 2016, with 40 attending, and Barcelona edition, September 2016, 44 attending) both a great success for all those taking part.

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

Thanks to this, in **2016 CIBER put forward 36 new proposals, 4 new projects being granted**. Expressions of interest were received for the presentation of 10 new proposals. In this field it should be stressed that CIBER has received 5 new contacts from research groups or companies in order to set up agreements for joint presentation of proposals in the H2020 setting, and currently 2 of these contacts have materialised in the real presentation of two H2020 proposals.

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

5

Platforms

Pulmonary Biobank Consortium

Coordinator: **Germán Peces Barba**

Head: **Cristina Villena**

Most relevant milestones in 2016:

- Improvement of external visibility:
  - Development and publication of new web page addressing researchers and donors.
  - Drafting and distribution of new updated triptychs.
  - Attendance at scientific events (sessions for training researchers, university master courses, meetings of experts in respiratory pathologies), and in cooperative activities (congresses, dissemination work, projects, etc.).
- Increase in collection of deficient samples (lung explants, organ donors, other collections), with 6781 new samples being collected.
- Management and inclusion of the multicentre collection of over 900 patients recruited in the ISAAC project, coordinated by the Obstructive Sleep Apnoea line of CIBERES and SEPAR.
- Increase in the requests for samples, both internal and external, with a rise in the number of projects requiring prospective collections.
- Cooperation and compliance with the objectives undertaken with the National Biobanks Network Platform of the AES 2013 (PRNB), taking part in its 5 work programmes.
  - Member of the management committee - PRNB.
  - Member of the quality commission - PRNB.
  - Co-coordination of the R+D+i in human tissue Line (Programme 3: Research, Development and Innovation). This group has already published the following works:

    Villena C, Artiga MJ, Bahamonde O, Belar O, Bermudo R, Castro E, De la Puente R, Escámez T, Fraga M, Jauregui L, Novoa I, Peiró-Chova L, Piñero E, Rejón JD, Ruiz M, Vieiro P, Zazo S, Villar V and Rábano A. Optimization of tissue samples for the development and validation of disease biomarkers: the OPTIMARK Project. Europe Biobank Week, Vienna, 2016. Poster presentation. PRIZE for the best poster presentation.

    Villena C, Artiga MJ, Bahamonde O, Belar O, Bermudo R, Castro E, De la Puente R, Escámez T, Fraga M, Jauregui L, Novoa I0, Peiró-Chova L, Piñero E, Rejón JD, Ruiz-Miró M, Vieiro P, Zazo S, Villar V, and Rábano A. Optimización de muestras de tejido para el desarrollo y la validación de biomarcadores de enfermedad: proyecto OPTIMARK. VII Congreso Nacional de Biobancos and I Congreso Latinoamericano de Biobancos, Santiago de Compostela, 2016. ORAL paper. PRIZE for the best oral paper.

    Villena C, Artiga MJ, Bahamonde O, Belar O, Bermudo R, Castro E, De la Puente R, Escámez T, Fraga M, Jauregui L, Novoa I0, Peiró-Chova L, Piñero E, Rejón JD, Ruiz-Miró M, Vieiro P, Zazo S, Villar V, and Rábano A. Cuestiones ético-legales y problemas de tramitación planteados en un proyecto colaborativo de biobancos. VII Congreso Nacional de Biobancos and I Congreso Latinoamericano de Biobancos, Santiago de Compostela, 2016. Poster presentation.
  - Coordination of RESPIRATORY DISEASES work group (Programme 1: Strategic Collections).
  - Co-Coordination of LEGAL line and participation in the ETHICS line (Programme 4: ELSI).
  - Participation in other lines, such as:

    Quality management system (Programme 2: Service management).

    Standardisation of database (Programme 3).

Obtaining the classification of distinction for its contribution to the development of objectives of the PRNB programmes.

- Granting of the FIS project: Optimization of tissue samples for the development and validation of disease biomarkers: OPTIMARK project.
- CIBERES research initiation pre-doctoral grant awarded as part of the FIS project.

Technology Development and Transfer Platform

Coordinator: **LLuis Blanch**

Head: **Cristina Broceño**

The main aim of the **CIBERES Technology Development and Transfer Platform (PDTT) is the promotion and coordination of projects intended for innovation in respiratory diseases, ensuring in turn operative management and protection of CIBER/ES rights and those of its researchers.**

The PDTT's work thus involves all the measures intended to foster innovation at CIBERES and maintenance and improvement of the CIBERES relationship with the production network of the biomedical area for respiratory diseases.

The **main achievements attained by the PDTT over 2016** are:

- **1 Licence contract** for CIBER/ES P201531409 patent "Integrated filter-holder and procedure for concentrating and detecting microorganisms" to the Waterologies company.
- Obtaining the **grant for** CIBER/ES US9297034 and EP2514833 patents from priority P200931177 "Detection of Streptococcus pneumoniae by means of magneto-amperometric genosensors employing specific primers and probes for the lytA gene".
- **Negotiating and signing two CIBER cooperation agreements** with Menarini Laboratories for projects: "Structured care Programme for COPD exacerbations in the emergency service" and "Impact of telemedicine on the rate of readmissions for COPD and cost-effectiveness analysis".
- **Negotiating and signing two CIBER service contracts** with companies: CIBER-PHILIPS project "Effectiveness of automatically adjusted NIV in the OHS" and CIBER-MODERNA "Isolation, purification, characterisation and production of fusion protein of the human metapneumovirus established in the pre-fusion conformation.
- Signing the CIBER-ISCIII- VALNEVA **MTA** (Material Transfer Agreement).
- **Application and Grant of a Caixaimpulse project** for the Valorisation and commercialisation of HIPARCO-Score technology as a predictor of personalised treatment for patients with resistant hypertension.
- **Promotion of the clinical assay sponsored by CIBER/ES** and financed by ROCHE "The effect of the diet on adverse effects of patients with IPF treated with pyrophenidone".
- Meeting and **interviews** with IPs CIBERES for monitoring CIBERES ideas and interests. Preparing a list of CIBERES services.
- **Cooperation with ITEMAS** in preparing the "ITEMAS Manual for Good Practice in Valorisation".
- Drafting the 2017 proposal for the 1st Forum for Public-Private Innovation in Respiratory Diseases, along with ITEMAS, ASEBIO, FENIN.
- Drafting the proposal for the 1st intraCIBERES Call in Innovation 2017 for supporting the valorisation of innovative projects carried out by CIBERES groups.
- **Maintenance and extension of the CIBERES network**. Drafting the new CIBERES triptych and dossier and dissemination of CIBERES capacities at meetings with companies from the sector: Biospain, Caixaimpulse, ITEMAS.
- Participation in measures of the **CIBERES/BBN/ER Internationalisation Platform** for promoting internationalisation at CIBERES, dissemination and recruitment of interest.
- **Drafting and submitting of CIBERES interests for the 5 European Joint Actions on**: quality of prevention and attendance in HIV/AIDS/STD, viral hepatitis and tuberculosis; chronic diseases; tobacco control; antimicrobial resistances and infections associated with healthcare; processes for preparation in the blood, cells and tissues.
- Participation in drafting the proposal for inter-CIBERES/BBN/ER European projects and preparing training courses on justifying and writing European projects.

6

Research Groups

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Group website

PROGRAMMES

Chronic Respiratory Diseases
Diffuse Respiratory Diseases
Infectious Respiratory Diseases

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Associated members: Barceló Martín, Bernardino | Cruz Santacruz, Tamara | Ferrer Balaguer, Joana Mª | García-Cosío Piqueras, Fco. de Borja | López Giraldo, Alejandra | López Zamora, Meritxell | Molins López Rodo, Laureano | Noguera Bennaser, Francisca Ana | Pons de Ves, Jaiem | Ríos Olivencia, Ángel | Sala Llinas, Ernest | Sauleda Roig, Jaume | Sibila Vidal, Oriol | Soler Cataluña, Juan José | Valera Felices, José Luis

Main lines of research

- Line called “Natural History “ which seeks to deepen into the different clinical , pathophysiological and structural aspects of COPD , with emphasis on discovering predictors of evolution.
- Line called “Pathobiology” focuses on aspects related to the origin or cause of the disease and the changes at the molecular and cellular level, including the initial effects of tobacco to subsequent inflammatory immune mechanisms and remodelling.
- Thirdly, the study of “Systemic effects and multimorbility “ of COPD wants to identify mechanisms of extra pulmonary entity and its clinical consequences . Basically , this line goes to the cardiovascular effects and skeletal muscle.
- Line “ Exacerbations “ refers to the phenomenon of exacerbation of COPD , from its causes to the consequences of behaviour in the evolution of the disease.

Most relevant scientific articles

- Agusti A. Simple versus complex COPD: Implications for health-care management. The Lancet Respiratory Medicine. 2016;4(2):e6-e7.
- Faner R., Cruz T., Casserras T., Lopez-Giraldo A., Noell G., Coca I. et al. Network analysis of lung transcriptomics reveals a distinct b-cell signature in emphysema. American Journal of Respiratory and Critical Care Medicine. 2016;193(11):1242-1253.
- Singh D., Roche N., Halpin D., Agusti A., Wedzicha J.A., Martinez F. J Current controversies in the pharmacological treatment of chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine. 2016;194(5):541-549.
- Agusti A., Bel E., Thomas M., Vogelmeier C., Brusselle G., Holgate S. et al. Treatable traits: Toward precision medicine of chronic airway diseases. European Respiratory Journal. 2016;47(2):410-419.
- Cosio B.G., Shafiek H., Iglesias A., Yanez A., Cordova R., Palou A. et al. Oral Low-dose Theophylline on Top of Inhaled Fluticasone-Salmeterol Does Not Reduce Exacerbations in Patients With Severe COPD: A Pilot Clinical Trial. Chest. 2016;150(1):123-130.

Highlights

During this year, the principal investigator of the group (Dr. Alvar Agusti) has been designated as the chair of the GOLD (Global Initiative for Chronic Obstructive Lung Disease), entity designated to generate global consensus for the diagnosis, treatment and prevention of COPD.
Dr. Borja Cosío has been included in the Scientific Committee of the Spanish COPD guideline, participating in the actualization that will be released in 2017. Furthermore, a non-commercial clinical study promoted from this Ciberes group, with the participation of several groups, has clarified the role of Theophylline in severe COPD patients, these observations have been included in the new Gold guideline.
Rosa Faner, member of the group, this year has been awarded with a Miguel Servet I grant, and the young investigator grant in COPD from AstraZeneca.
The group has been involved with other CIBERES groups in the organization of the international symposium “The Microbiome in Respiratory Medicine”.

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PROGRAMMES

Chronic Respiratory Diseases

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Main lines of research

- Line NEOPLASIAS TORÁCCICAS LUNG CANCER AND PLEURA: Identify a set of clinical-molecular variables that improve the prognostic and predictive capacity of TNM and clinical translation of these results.
- Line CHRONIC OBSTRUCTIVE PULMONARY DISEASE: To study the clinical, biological, microbiological, radiological, functional determinants of progression and severity. Evaluate new endoscopic treatment in obstructive airway disease and the impact of different approaches to health care in the management of disease activity.
- Line PULMONARY HYPERTENSION (HP): Establish a network of groups with complementary capabilities of research aimed at identifying new markers for assessing disease activity and new therapeutic targets for the treatment of pulmonary hypertension following a strategy of translational research, with the ultimate aim of contributing to alleviate and cure the disease.
- Line INSTERSTICIALES DISEASES AND FIBROSIS: Create a record of well-characterized patients, and incorporate new treatments in their care, measuring the impact on quality of life, progression and prevention of exacerbations.

- Line SAHS & NO INVASIVE VENTILATION (NIV): Develop new ways of simplified diagnosis, deepen treatment indications and establish new indications for NIV outside the critical care units. Investigate the causes of failure of NIV and asynchrony.
- Line RESEARCH IN LUNG TRANSPLANTATION: Advance knowledge of the causes of rejection and infection and diagnosis, and expand the selection criteria organ donor and recipient.

Most relevant scientific articles

- Delcroix M., Lang I., Pepke-Zaba J., Jansa P., D'Armini A.M., Snijder R. et al. Long-Term Outcome of Patients with Chronic Thromboembolic Pulmonary Hypertension: Results from an International Prospective Registry. Circulation. 2016;133(9):859-871.
- Hartl S., Lopez-Campos J.L., Pozo-Rodriguez F., Castro-Acosta A., Studnicka M., Kaiser B. et al. Risk of death and readmission of hospital-admitted COPD exacerbations: European COPD Audit. European Respiratory Journal. 2016;47(1):113-121.
- Masa J.F., Corral J., Caballero C., Barrot E., Teran-Santos J., Alonso-alvarez M.L. et al. Non-invasive ventilation in obesity hypoventilation syndrome without severe obstructive sleep apnoea. Thorax. 2016.
- Eberhardt W.E.E., Mitchell A., Rami-Porta R.Reply to the letter to the editor by Hendriks et al.Journal of Thoracic Oncology. 2016;11(3): e43-e44.
- Goldstraw P., Chansky K., Crowley J., Rami-Porta R., Asamura H., Eberhardt W.E.E. et al. The IASLC lung cancer staging project: Proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM Classification for lung cancer. Journal of Thoracic Oncology. 2016;11(1):39-51.

Highlights

All research lines of Group 21 continue their scientific activity. Highlights from this work are:

- Coordination Pulmonary Circulation Group of the European Society of Cardiology
- The International prospective registry of Chronic thromboembolic pulmonary hypertension (CTEPH) colaboration
- Presidency of the International Statistical Committee at IASLC
- Strengthening of a Spanish hospital network of research in EPOC that fulfills 10 years of joint and continuous work.
- Consolidation of clinical audit of histories as a standardized tool for the collection of clinical information in network research studies
- Active participation in the pathologists panel of the CIBERES Strategic Cancer Project for the evaluation of clinical and molecular biomarkers in early lung cancer.

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PROGRAMMES

Infectious Respiratory Diseases
Chronic Respiratory Diseases

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Main lines of research

Our research interests are mainly microorganisms that cause respiratory infections in both the general population and patients with chronic respiratory diseases. We use classical typing approaches, whole genome sequencing and different in vivo and in vitro models to analyze the bacterial pathogenesis.

- Host-pathogen interaction in the invasive and non-invasive pneumococcal diseases.
- Molecular characterization of resistance mechanisms and their surroundings.
- Microbial diversity in respiratory samples of patients with chronic obstructive pulmonary disease (COPD).
- Role of biofilm formation in the pathogenesis and persistence of chronic respiratory infections.
- Bacterial adaptative mechanisms in the persistence and infection.
- Cardiovascular changes and vascular remodeling associated with COPD.

Most relevant scientific articles

- Marti S, Puig C, de la Campa AG, Tirado-Velez JM, Tubau F, Domenech A et al. Identification of Haemophilus haemolyticus in clinical samples and characterization of their mechanisms of antimicrobial resistance.The Journal of antimicrobial chemotherapy. 2016;71(1):80-4.
- Mell J.C., Viadas C., Moleres J., Sinha S., Fernandez-Calvet A., Porsch E.A. et al. Transformed Recombinant Enrichment Profiling Rapidly Identifies HMW1 as an Intracellular Invasion Locus in Haemophilus influenza. PLoS Pathogens. 2016;12(4).
- Munoz-Esquerre M., Lopez-Sanchez M., Escobar I., Huertas D., Penin R., Molina-Molina M. et al. Systemic and pulmonary vascular remodelling in chronic obstructive pulmonary disease. PLoS ONE. 2016;11(4).
- Grau I., Ardanuy C., Cubero M., Benitez M.A., Linares J., Pallares R. Declining mortality from adult pneumococcal infections linked to children's vaccination. Journal of Infection. 2016-.
- Domenech A., Moreno J., Ardanuy C., Linares J., De La Campa A.G., Martin-Galiano A.J. A novel typing method for Streptococcus pneumoniae using selected surface proteins. Frontiers in Microbiology. 2016;7(MAR).

Highlights

The introduction of pneumococcal conjugate vaccines for childhood vaccination has been associated with a decrease in the young adult mortality due to invasive pneumococcal disease, showing herd protection.
The surfotyping is a new approach for the study of pneumococcal diseases that use surface protein combinations to define pathogenic lineages.
"Transformed recombinant enrichment profiling" (TREP) is a new methodology for the analysis of the genetic basis of phenotypic variation in order to identify new targets for antimicrobial development.
Among respiratory samples, the frequency of *Haemophilus haemolyticus* is low being most relevant in genital samples. Moreover, the antimicrobial resistance mechanisms of this emergent pathogen have been described.
In the 2016 call of "Acción Estratégica en Salud", two new projects have been funded to study several aspects of COPD. The first one, based in omics tools will analyze the inflammatory markers in COPD. The second one will study the cardiovascular alterations and the vascular remodeling associated with this chronic disease.
A PhD thesis analyzing the virulence and resistance mechanisms of *Klebsiella pneumoniae* has been defended.

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PROGRAMMES

Chronic Respiratory Diseases
Diffuse Respiratory Diseases
Infectious Respiratory Diseases

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Contributors: Casas Méndez, Luis Fernando | Seminario Ruiz, María Asunción

Main lines of research

Sleep disorders breathing:

- Evaluation of new diagnostic and treatment methods.
- Pathogenesis of cardiovascular and metabolic complications
- Thecnologic development

Most relevant scientific articles

- McEvoy R.D., Antic N.A., Heeley E., Luo Y., Ou Q., Zhang X. et al. CPAP for prevention of cardiovascular events in obstructive sleep apnea. New England Journal of Medicine. 2016;375(10):919-931.
- Lee C.-H., Barbe F. Adaptive servoventilation for central sleep apnoea in heart failure: a broken dream. The Lancet Respiratory Medicine. 2016;4(11):846-847.
- Campos-Rodriguez F., Queipo-Corona C., Carmona-Berna C., Jurado-Gamez B., Cordero-Guevara J., Reyes-Nunez N. et al. Continuous positive airway pressure improves quality of life in women with obstructive sleep apnea a randomized controlled trial. American Journal of Respiratory and Critical Care Medicine. 2016;194(10):1286-1294.
- Martinez-Ceron E., Barquiel B., Bezos A.-M., Casitas R., Galera R., Garcia-Benito C. et. al. Effect of continuous positive airway pressure on glycemic control in patients with obstructive sleep apnea and type 2 diabetes a randomized clinical trial. American Journal of Respiratory and Critical Care Medicine. 2016;194(4):476-485.
- Vicente E., Marin J.M., Carrizo S.J., Osuna C.S., Gonzalez R., Marin-Oto M. et. al. Upper airway and systemic inflammation in obstructive sleep apnoea. European Respiratory Journal. 2016;48(4):1108-1117.

Highlights

The G35 (CIBERES) led by Ferran Barbé focuses his activity on the study of Sleep Apnea Syndrome (SAHS). During 2016 I publish 51 original publications. In addition, it received funding in competitive calls for the development of 22 new research projects and 18 clinical trials. The projects develop the objectives of the CIBERES 2016-18 Sleep Line, being: i) To characterize different SAHS phenotypes and to improve the management of the disease. Ii) To evaluate the impact of SAHS and its treatment in the development of comorbidities with high mortality and high social impact. He has obtained recognition of the Caixaimpulse program for the development of the first technology for application of personalized medicine in the SAHS, which evaluates the response to CPAP treatment in patients with resistant hypertension and SAHS. The papers have been published in the first journal of the category of Cardiac & Cardiovascular Systems (Journal of the American College of Cardiology (JACC)) and recognized with Best Publication of the SES 2016. Moreover, it has led nationally, The most relevant international study so far for evaluating the impact of CPAP treatment on secondary prevention of cardiovascular disease. The results were published in New England Jounal or Medicine. In addition, in 2017, the first global study, conducted by Group 35, was completed to determine the prevalence of sleep disorders in COPD. Group 35 continues its involvement in the development of several simplified device transfer contracts for the diagnosis of SAHS. Finally, to highlight different acknowledgments received such as the Young Researcher Award AstraZeneca 2016, Young Lesson SEPAR 2015 and ATS Young Researcher 2016, as well as participation in national meetings and more prestigious internationals through conferences by invitation.

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Diffuse Respiratory Diseases

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Main lines of research

PULMONARY HYPERTENSION

- Identification of new biomarkers and therapeutic targets.
- Experimental models
- Biopathology, mechanisms of injury and repair: progenitor cells, microparticles, microRNA

COPD

- Physical activity and cellular biogenetic
- Experimental models
- New therapeutic strategies

OBESITY AND LUNG

- Regulation of gas exchange

CONTINUITY OF CARE AND INFORMATION AND COMMUNICATION TECHNOLOGIES (ICT) IN CHRONIC RESPIRATORY DISEASES

- ICTs in the clinical management of chronic diseases
- Clinical decision support tools

Most relevant scientific articles

- Hoeper M.M., McLaughlin V.V., Barbera J.A., Frost A.E., Ghofrani H.-A., Peacock A.J. et al. Initial combination therapy with ambrisentan and tadalafil and mortality in patients with pulmonary arterial hypertension: a secondary analysis of the results from the randomised, controlled AMBITION study. The Lancet Respiratory Medicine. 2016;4(11):894-901.
- Delcroix M., Lang I., Pepke-Zaba J., Jansa P., D'Armini A.M., Snijder R. et. al. Long-Term Outcome of Patients with Chronic Thromboembolic Pulmonary Hypertension: Results from an International Prospective Registry. Circulation. 2016;133(9):859-871.
- Watz H., Tetzlaff K., Wouters E.F.M., Kirsten A., Magnussen H., Rodriguez-Roisin R. et. al. Blood eosinophil count and exacerbations in severe chronic obstructive pulmonary disease after withdrawal of inhaled corticosteroids: A post-hoc analysis of the WISDOM trial. The Lancet Respiratory Medicine. 2016;4(5):390-398.
- Ambrosino N., Vitacca M., Dreher M., Isetta V., Montserrat J.M., Tonia T. et. al. Tele-monitoring of ventilator-dependent patients: A European Respiratory Society Statement. European Respiratory Journal. 2016;48(3):648-663.
- Scioscia G., Blanco I., Arismendi E., Burgos F., Gistau C., Barbaro M.P.F. et al. Different dyspnoea perception in COPD patients with frequent and infrequent exacerbations. Thorax. 2016.

Highlights

- Participation in the European Reference Network on Rare Respiratory Diseases (ERN-LUNG), Pulmonary Hypertension
- Participation in the ERS / ATS Task Force for the standardization of measurement of carbon monoxide diffusion capacity (F. Burgos).
- Participation in Task Forces of the European Respiratory Society (ERS): Pulmonary Hemodynamics During Exercise (J.A. Barberà); Exercise Training and Rehabilitation in Patients with Severe Chronic Pulmonary Hypertension (I. Blanco, J.A. Barberà).
- Participation in the International Consortium for Genetic Studies in Pulmonary Arterial Hypertension (PAH).
- Development of the project: Network Management of Patients with Rare Diseases: Pulmonary Hypertension as a use case (GERAR) within the RETOS Program of the Ministry of Economy, Industry and Competitiveness.

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Main lines of research

The main research lines of our group combine preclinical and clinical studies from a translational perspective and are integrated into two main programs: 1) Diffused Respiratory Diseases, including projects related to Acute Lung Injury and 2) Respiratory Infectious Diseases: which includes Translational Multidisciplinary Research in Respiratory Tract Infections.
We are interested in the diagnosis and characterization of molecular, cellular and physiological changes related to the development of acute lung injury and respiratory infections, as well as the impact on other organs or systems and the development of new therapeutic strategies.

- Management and monitoring of critically ill patients:
  ARDS/ALI, mechanical ventilation (MV), patient-ventilator interaction, weaning. / Development of software for continuous monitoring of critically ill patients on MV. Processing and storing digital signals from monitoring equipment or ventilators. / Software for interpretation, analysis and multimodal-multichannel physiological-diagnosed computerized interpretation of biomedical signals. / Design and application of a smart data display to help clinical decision making. / Early diagnosis and treatment of ventilator-associated pneumonia.
- Development of experimental models (animals and cell cultures) for the characterization of new mechanisms involved in acute lung injury (ALI) and prevention strategies.
- Development of new therapeutic strategies for ALI and ARDS management.
  Pharmacological approach (systemic or inhaled) by administering anticoagulants, heparin, AT-III, thrombomodulin or immunomodulators in animal and cell culture models. / Cell therapy based on local

instillation of mesenquimal stem cells or type II alveolar cells in animal models of ALI.

- Clinical and experimental approach of the axis brain-lung during mechanical ventilation (CIBERES Groups 29 and 33; GTC I3A CIBER-BBN and SEPAR):
  Molecular alterations in brain and lung during MV / Characterization of neuropsychological / psychopathology alterations and cognitive assessment in MV patients. / Integrity of the autonomic nervous system during VM collaboration with CIBER-BBN-SEPAR. / Feasibility, safety and efficacy of neurocognitive rehabilitation in patients with VM.
- Study of the patient-ventilator interaction during VM.

Most relevant scientific articles

- Hernandez G., Vaquero C., Gonzalez P., Subira C., Frutos-Vivar F., Rialp G. et al. Effect of postextubation high-flow nasal cannula vs conventional oxygen therapy on reintubation in low-risk patients: A randomized clinical trial. JAMA - Journal of the American Medical Association. 2016;315(13):1354-1361.
- Hernández G, Vaquero C, Colinas L, Cuena R, González P, Canabal A et. al. Effect of Postextubation High-Flow Nasal Cannula vs Noninvasive Ventilation on Reintubation and Postextubation Respiratory Failure in High-Risk Patients: A Randomized Clinical Trial.JAMA. 2016.
- Garcia-Prieto E., Lopez-Aguilar J., Parra-Ruiz D., Amado-Rodriguez L., Lopez-Alonso I., Blazquez-Prieto J. et al. Impact of Recruitment on Static and Dynamic Lung Strain in Acute Respiratory Distress Syndrome. Anesthesiology. 2016;124(2):443-452.
- Murias G., Montanya J., Chacon E., Estruga A., Subira C., Fernandez R. et al. Automatic detection of ventilatory modes during invasive mechanical ventilation. Critical Care. 2016;20(1).
- Puig F, Herrero R, Guillamat-Prats R, Gómez MN, Tijero J, Chimenti L et al. A New Experimental Model of Acid and Endotoxin-Induced Acute Lung Injury in Rats.American journal of physiology. Lung cellular and molecular physiology. 2016; ajplung.00390.2015.

Highlights

- Strategic Health Action ISCIII: Implementation of a “Smart Data Display” to support decision making in the critical patient. Application in patient-ventilator interaction and weaning from mechanical ventilation (PI16/01606). / Immunomodulatory cell therapy in sepsis (PI15/02204). / Influence of persistent patient/ventilator decoupling on the cognitive and psychopathological status in the critical patient (PI13/02204): Characterization of asynchronies and cognitive/psychopathological alterations (1-24 months after ICU) in mechanically ventilated patients. Experimental model of asynchronies. / Alveolar type II cell transplant and experimental models of acute lung injury (PI12/02548): New experimental model of ALI and anti-inflammatory effect of transplanted AT2 cells (Catalan Society of Pulmonology Grant).
- Neurocognitive stimulation platform for patients undergoing mechanical ventilation: feasibility of innovation in Health Care (FIPSE), mentoring (MIT-Boston/Idea2Global) and business model (Inveniam).
- Effects of an early neurocognitive intervention on patient-ventilator interaction and stress/heart rate variability in patients receiving mechanical ventilation (Collaboration CIBERES-SEPAR-CIBERBBN).
- EU Projects: THALEA I / II “Telemonitoring and Telemedicine for Hospitals Assisted by ICT for Life saving co-morbid patients in Europe as part of a Patient personalized care program of the EU “.
- Anticoagulant treatment in experimental acute lung injury: Nebulized heparin reduces pulmonary coagulopathy and inflammation without producing systemic hemorrhage. Antithrombin III reduces inflammation in an cell culture in vitro model (Grifols).
- Multicenter clinical trials: ventilator-associated pneumonia, ARDS / ALI and strategies for mechanical ventilation.
- Weaning of mechanical ventilation: Prevention of the risk of reintubation in patients with low and high risk by the application of a high oxygen flow nasal cannula.
- Better Care® Middleware Platform (PCT / EP2008 / 052458) and Better Care Spin-off.
- Clinical guidelines (Reports of the Working Group of the World Federation of Societies of Intensive and Critical Medicine): Triage for ICU admission, 2) critical care specialists and 3) Criteria for the initiation of invasive ventilation in septic shock.

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PROGRAMMES

Infectious Respiratory Diseases

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Main lines of research

- Serious lower respiratory tract infection.
- Infection caused by bacteremia and catheter-related infection.
- Infection in immunocompromised patients and transplant patients.
- Hospital-acquired systemic mycoses.
- *C. difficile*
- Tuberculosis and diseases caused by mycobacteria.

Most relevant scientific articles

- Perez-Lago L., Izco S., Herranz M., Tudo G., Carcelen M., Comas I. et al. A novel strategy based on genomics and specific PCR reveals how a multidrug-resistant Mycobacterium tuberculosis strain became prevalent in Equatorial Guinea 15 years after its emergence. Clinical Microbiology and Infection. 2016.
- Cunha BA, Burillo A, Bouza E. Legionnaires' disease.Lancet (London, England). 2016;387(10016):376-85.
- Burillo A., Marin M., Cercenado E., Ruiz-Carrascoso G., Perez-Granda M.J., Oteo J. et al. Evaluation of the xpert carba-R (cepheid) assay using contrived bronchial specimens from patients with suspicion of ventilator-associated pneumonia for the detection of prevalent carbapenemases. PLoS ONE. 2016;11(12).
- Navarro Y, Romero B, Bouza E, Domínguez L, Juan Ld, García-de-Viedma D. Detailed chronological analysis of microevolution events in herds infected persistently by Mycobacterium bovis.Veterinary microbiology. 2016; 183:97-102.
- Munoz P., Bouza E., Alonso R., Anaya F., Banares R., Bustinza A. et al. The current treatment landscape: The need for antifungal stewardship programmes. Journal of Antimicrobial Chemotherapy. 2016;71: ii5-ii12.

Highlights

The etiologic diagnosis of Pneumonia, remains one of the more important challenges for physicians and researches. Only, after a proper etiologic diagnosis and antimicrobial susceptibility it is possible to apply a proper antimicrobial treatment and to convey an antimicrobial stewardship.
Our lines of research are mainly oriented to the end of providing rapid and adequate orientation for treatment of pneumonia in more patients and more rapidly. Our definition for rapid etiologic diagnosis is to provide etiology and antimicrobial treatment orientation within 8 hours after the reception of the clinical samples in the microbiology department.
Our achievements during 2016 with this orientation were the following:

- PNA-FISH in Lower Respiratory Tract Infections: This is a one hour rapid procedure (1 hour) using a beacon-based fluorescent in situ hybridisation (bbFISH) method to identify the major pathogens causing in LRT samples.
- The utility of assessing S. aureus colonization in patients admitted to a Major Heart Surgery Intensive Care Unit (MHS.ICU). We evaluated the nasal carriage of S. aureus upon admission to a MHS-ICU, comparing the yield of conventional cultures versus rapid molecular test. / The rapid method can be provided in less than 2 hours.
- Rapid identification of microbial pathogens and antimicrobial susceptibility using mass spectrometry (MALDI-TOF). We have been able to use this technique to improve de rapid diagnosis of bloodstream infections, pulmonary mycosis, urinary tract infections and other.
- The spectrum of disease caused by Respiratory Sincitial Virus in adults. We have been evaluating all adults presenting with "Influenza like syndrome" in a prospective way.
- Rapid detection of Carbapenemases directly from Lower Respiratory Tract Samples. We evaluated a rapid molecular test able to identify 5 different carbapenemases in less than 2 hours.
- A miscellany of other topics different than the former lines have been also studied.

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PROGRAMMES

Infectious Respiratory Diseases

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Main lines of research

- Development and evaluation of new experimental animal models in tuberculosis.
- New approaches to the nature, diagnosis and treatment of latent tuberculosis.
- New vaccines against tuberculosis.
- Antituberculosis drugs: resistance, action and evaluation of new drugs.
- New diagnostic methods and molecular epidemiology of tuberculosis.
- New molecular approaches to epidemiological, pathogenic and diagnostic of the respiratory infections caused by respiratory virus, *Haemophilus influenzae* and *Mycoplasma pneumonia.*
- Characterization of intracellular life stage of Staphylococcus aureus. Involvement in treatment and outcome of staphylococcal infections.
- Design and evaluation of a novel inpedimetric immunosensor for diagnosis of sepsis of respiratory origin.
- Improving the diagnosis of bloodstream Infections: PCR coupled with mass spectrometry.
- Multiplexed determination of pathogenic bacteria in sepsis by novel magneto-nanohollows immunoassays.

Most relevant scientific articles

- Zumla A., Rao M., Wallis R.S., Kaufmann S.H.E., Rustomjee R., Mwaba P. et al. Host-directed therapies for infectious diseases: Current status, recent progress, and future prospects. The Lancet Infectious Diseases. 2016;16(4): e47-e63.
- Boeck L., Soriano J.B., Brusse-Keizer M., Blasi F., Kostikas K., Boersma W. et al. Prognostic assessment in COPD without lung function: The B-AE-D indices. European Respiratory Journal. 2016;47(6):1635-1644.
- Rodrigo T., Casals M., Caminero J.A., Garcia-Garcia J.M., Jimenez-Fuentes M.A., Medina J.F. et al. Factors associated with fatality during the intensive phase of anti-tuberculosis treatment. PLoS ONE. 2016;11(8).
- Cardona P.-J., Prats C. The small breathing amplitude at the upper lobes favors the attraction of polymorphonuclear neutrophils to Mycobacterium tuberculosis lesions and helps to understand the evolution toward active disease in an individual-based model. Frontiers in Microbiology. 2016;7(MAR).
- Cardona P.-J.. The progress of therapeutic vaccination with regard to tuberculosis. Frontiers in Microbiology. 2016;7(SEP).

Highlights

During 2016 all the objectives have been fulfilled:

- New experimental models of active tuberculosis have been developed, with or without comorbidity presence (obesity and Multiple infection), and have been used to evaluate prophylactic and therapeutic strategies (WP2.2. and WP4.2.).
- One clinical trial (WP3.1.: NCT02715271) and two clinical trials (WP4.2, NCT02781909 and NCT02897180) have been started.
- Collaboration with IntraCIBER groups (S. Samper and JA Aínsa (CB06 / 06/0020), A. Torres (CB06 / 06/0028), JM Marín (CB07 / 06/2008), JJ Soler-Cataluña (CB06 / 06/0021), J. Ruiz-Cabello (CB06 / 06/1090) and M.Miravitlles (CB06 / 06/0030) and InterCIBER (CIBEREHD, CB06 / 04/0033, Dr. MR Sarrias, CIBERESP, CB06 CIBERESP, CB06 / 02/0050, Dr. Iñaki Comas, CIBER-BBN: M. Arruebo (CB06-01-0026), R. Eritja (CB06 / 01/0019), L MP Maroco (CB06 / 01/0036), M. Royo (CB06 / 01/0074), J. Santamaria (CB06 / 01 / 01/0026), and R. Villa (CB06 / 01/0049).
- Research Initiation grant by CIBERES (Ayudas a la Iniciación a la Investigación) to Albert Despuig has been achieved.
- The group has participated in 5 European / international projects funded by H2020 (TBVC2020 and EMI-TB), Innovative Medicines Initiative (IMI), EDCTP (Europe-Africa Collaboration) and FP7 (IRSES: TB prognosis).
- Four projects linked to the CIBERES network (SEPAR16 / 0023; PI16 / 01511), FIS INNOVA4TB (PI16 / 01912); and a MINECO project (SAF2015-67476-R).
- The IGTP and CIBERES spin-off, Manremyc SL, created to develop the NR® product, has signed a strategic alliance with the companies “Tablets India Limited” and “SRS life sciences” to distribute the nutraceutical to the African and Asian market.

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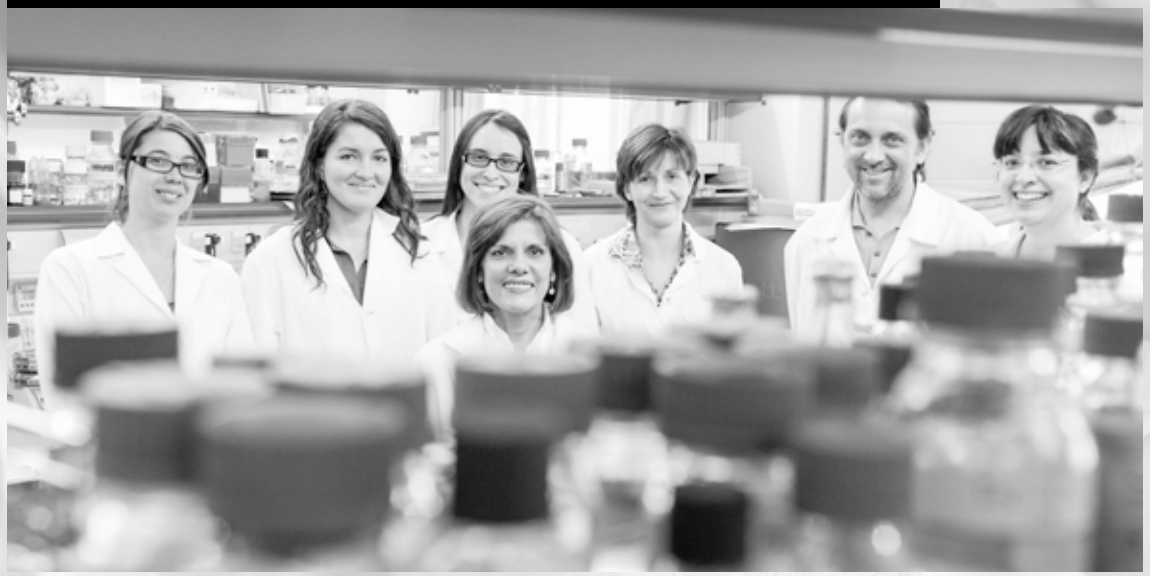
PROGRAMMES

Infectious Respiratory Diseases



GROUP MEMBERS

Staff members: Cañadas Benito, Olga | García-Fojeda García-Valdecasas, María Belén

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Main lines of research

The respiratory epithelium has evolved to produce a complicated network of extracellular membranes, called lung surfactant, that are essential for breathing and, ultimately, survival. Lung surfactant not only protects the lung against alveolar collapse during the breathing cycle but is involved in host defense. The manner in which surfactant components might participate in successful elimination of microorganisms without triggering excessive inflammatory response in the alveolus is still poorly understood. How biophysical surfactant properties and host defense mechanisms can be interdependent is also unknown. The focus of our group is to understand how surfactant lipids and proteins exert their action. We study:

1. Pulmonary surfactant:
   a) Evaluation of the mechanisms of surfactant membranes resistance to alteration/inactivation. b) Characterization of compositional and functional changes in pulmonary surfactant during respiratory disfunction.
2. Alveolar defense mechanisms against infection and inflammation:
   a) Study of the molecular mechanisms through which pulmonary collectins SP-A and SP-D modulate the inflammatory response of alveolar macrophages to pro- and anti-inflammatory stimuli. b) Determination of the mechanism through which SP-A acts in synergy with antimicrobial peptides to combat infection and modulate inflammation elicited by respiratory pathogens. c) Analysis of the molecular mechanisms that underlie the action of the lipid component of pulmonary surfactant in

limiting infection and modulating immune activation of alveolar macrophages.

3. Lung Pathophysiology: Characterization and analysis of alveolar injury and therapeutic strategies in animal models of: a) Acute lung injury. b) Gram-negative bacterial infection, c) Allergic airway inflammation. d)Lung transplant and ischemia-reperfusion injury.
4. Drug and biomolecule encapsulation for inhalatory administration: a) Encapsulation of drug/biomolecules in nanoliposomes. b) Studies of amphipathic drug/membrane interaction. c) Nanoparticle stability evaluation. d) Characterization of the interaction of surfactant components with nanoparticles.

This research has direct relevance for the development of new therapies for inflammatory and infectious lung diseases.

Most relevant scientific articles

- Ruge C.A., Hillaireau H., Grabowski N., Beck-Broichsitter M., Canadas O., Tsapis N. et al. Pulmonary Surfactant Protein A-Mediated Enrichment of Surface-Decorated Polymeric Nanoparticles in Alveolar Macrophages. Molecular Pharmaceutics. 2016;13(12):4168-4178.
- Minutti C.M., Garca-Fojeda B., Saenz A., De Las Casas-Engel M., Guillamat-Prats R., De Lorenzo A. et al. Surfactant protein a prevents IFN-γ/IFN-γ receptor interaction and attenuates classical activation of human alveolar macrophages. Journal of Immunology. 2016;197(2):590-598.

Highlights

- Relevant research project: SAF2015-65307-R (2016-2018). Natural anti-infective factors of the lung as new therapeutic strategies against respiratory infections. Funded by the Spanish Ministry of Economy and Competitiveness. Principal Investigator: Cristina Casals.

RELEVANT RESULTS:

- Line 2: (i) SP-A inhibits [IFN-g+LPS]-induced classical activation of macrophages; (ii) binding of SP-A to IFN-g abrogates IFN-g effects on human macrophages; and (iii) SP-A amplifies IL-4-induced macrophage proliferation and alternative activation, revealing an important role of SP-A in respiratory diseases with high levels of IL-4, such as asthma or fibrosis. Additionally, (iv) SP-A exhibits an antimicrobial synergic action with both endogenous and exogenous antimicrobial peptides against different Gram-negative bacteria; (v) the formation of SP-A/antimicrobial peptide complexes is required for such synergistic activity; and (vi) the complexes cross the cell wall and translocate to the periplasmic space, where they interact with the cytoplasmic membrane.
- Line 3: In an animal model of HDM-induced allergic airway inflammation SP-A/surfactant lipid ratio is increased. Since SP-A potentiates IL-4 action on macrophages, but lipids inhibit them, the elevated SP-A/lipid ratio may increase IL-4 effects in the alveoli during allergic inflammation.
- Line 4: SP-A-coated mannosylated nanoparticles exhibit a greater internalization by alveolar macrophages than non-SP-A-coated nanoparticles. This suggests that this formulation could be useful as a vehicle of anti-tuberculosis drugs.

DOCTORAL THESIS:

19/12/2016. Carlos Muñoz Minutti. “Regulation of alveolar macrophage activation by the pulmonary surfactant protein SP-A”. Complutense University of Madrid. Doctoral Program: Biochemistry, Molecular Biology and Biomedicine (“Mention of Excellence” by the Ministry of Science and Education). Evaluation: Excellent “cum laude”. Director: Dr. Cristina Casals and Dr. Belén García-Fojeda.

INTERNATIONAL COLLABORATION:

1) Prof. Dr. Timothy Weaver, Cincinnati Children’s Hospital (Ohio, USA); 2) Prof. Dr. Judith E. Allen, University of Edinburgh (U.K.); 3) Prof. Dr. Henk P. Haagsman (Utrecht University, Netherlands); 4) Prof. Dr. Elias Fattal (University of Paris-Sud in Châtenay-Malabry, France).

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PROGRAMMES

Chronic Respiratory Diseases
Diffuse Respiratory Diseases

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Main lines of research

- Pathophysiology of sleep apnea and acute lung injury in patients and animal models.
- Tissue engineering and regenerative medicine in respiratory diseases.
- Nanotechnologies and lab-on-a-chip for the study and characterization of the mechanical behavior of cells and tissue systems.
- Instrumentation for diagnostic, therapeutic and monitoring of sleep apnea and acute lung injury.

Most relevant scientific articles

- Sunyer R., Conte V., Escribano J., Elosegui-Artola A., Labernadie A., Valon L. et al. Collective cell durotaxis emerges from long-range intercellular force transmission. Science. 2016;353(6304):1157-1161.
- Khalyfa A., Almendros I., Gileles-Hillel A., Akbarpour M., Trzepizur W., Mokhlesi B. et al. Circulating exosomes potentiate tumor malignant properties in a mouse model of chronic sleep fragmentation. Oncotarget. 2016;7(34):54676-54690.
- Uriarte J.J., Meirelles T., Del Blanco D.G., Nonaka P.N., Campillo N., Sarri E. et al. Early impairment of lung mechanics in a murine model of marfan syndrome. PLoS ONE. 2016;11(3).
- Isetta V., Montserrat J.M., Santano R., Wimms A.J., Ramanan D., Woehrle H. et al. Novel approach to simulate sleep apnea patients for evaluating positive pressure therapy devices. PLoS ONE. 2016;11(3).
- Campillo N., Jorba I., Schaedel L., Casals B., Gozal D., Farre R. et al. A novel chip for cyclic stretch and intermittent hypoxia cell exposures mimicking obstructive sleep apnea. Frontiers in Physiology. 2016;7(JUL).

Highlights

The group has focused its work on two of the programs of CIBERES, addressed to study obstructive sleep apnea (OSA) and acute lung injury (ALI). Part of the group research has been carried out in the framework of contracts with companies and of two funded joint-projects with CIBER-BBN groups. A first main outcome in the field of OSA has been the development and characterization of a novel chip system capable of realistically simulating the main OSA stimuli at cell level. The chip allows cell application of controlled fast patterns of intermittent hypoxia and cyclic stretch at breathing and heart frequencies. A prove of concept application study on bone marrow-derived stem cells was carried out. In another study, we found that circulating exosomes modulate cancer progression (proliferation, migration and extravasation) in a mouse model of sleep fragmentation mimicking OSA, potentially explaining the adverse cancer outcomes observed in OSA. Concerning OSA treatment, we developed a novel bench test setting to test automatic CPAP devices. The model allows simulating a patient's night including different breathing features in each sleep phase. In the ALI program, the group has focused on the studying the crosstalk between cells and extracellular matrix (ECM). On the one hand, we used a mouse Marfan model (mutation in ECM fibrillin) to document that alterations in the ECM may induce distinct the micro- and macro-mechanical mechanical changes in the lung. In addition, we have provided novel evidence of different mechanisms driving isolated and collective cells migration in the presence of non-homogeneous ECM stiffness (durotaxis). We found that collective durotaxis is far more efficient than single-cell durotaxis, appearing as a potential robust mechanism to direct cell migration in lung epithelial/endothelial repair in ALI.

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PROGRAMMES

Infectious Respiratory Diseases

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Main lines of research

It is noteworthy that 65–80% of chronic bacterial infections are caused by microbes growing in biofilms. The tolerance of these communities to antibiotic therapy is well known. Firm evidence also links biofilms both to chronic and acute lung infections, as exemplified by cystic fibrosis and ventilator-associated pneumonia, respectively. The nasopharynx and the lungs are involved in constant and essential chemical signaling among the local microbiota, and between this and both local and systemic tissues critical to human physiology. The healthy nasopharynx and lungs are colonized by different microorganisms that form mixed biofilms: 1) encapsulated pneumococci associate with non-typeable pneumococci (NTPn), strains of S. pseudopneumoniae and/or non-typeable H. influenzae in the nasopharynx; 2) bacteria belonging to the phyla Firmicutes (mainly Streptococcus), Proteobacteria, and Bacteroidetes in lungs. We are currently studying the requirements (microbiological and otherwise) for in vitro mixed biofilm formation between S. pneumoniae and other bacterial pathogens.

Pathogenic bacteria are becoming increasingly resistant to the classic antibiotics used with much success in recent decades. Among the few alternatives currently envisaged for treating this problem are phage endolysins (also called enzybiotics), which are modular enzymes that hydrolyze specific peptidoglycan bonds of susceptible bacteria. In the laboratory we test new endolysins mainly targeted against respiratory pathogens, obtained from phage origin or by construction of chimeras resulting from the fusion of different functional domains. These enzymes are very effective against either planktonic cultures or biofilms. Validation of in vitro

results is carried out using different mice models or in zebrafish embryos. In addition, we also study other compounds with antibacterial activity, such as bicyclic amine esters that behave like choline analogues, an amino alcohol essential for pneumococcal survival.
Another aspect of marked interest for our group, consists in the identification of S. pneumoniae proteins as possible virulence factors, analyzing the molecular mechanisms involved in evasion of the host immune response using human cell lines and murine models of infection. Moreover, our research team participates in the characterization of new pneumococcal proteins to be used as novel antigens in the development of protein vaccines in the future.

Most relevant scientific articles

- Diez-Martinez R., Garcia-Fernandez E., Manzano M., Martinez A., Domenech M., Vallet-Regi M. et al. Auranofin-loaded nanoparticles as a new therapeutic tool to fight streptococcal infections. Scientific Reports. 2016;6.
- Ramos-Sevillano E., Urzainqui A., de Andres B., Gonzalez-Tajuelo R., Domenech M., Gonzalez-Camacho F. et al. PSGL-1 on Leukocytes is a Critical Component of the Host Immune Response against Invasive Pneumococcal Disease. PLoS Pathogens. 2016;12(3).
- Blazquez B., Fresco-Taboada A., Iglesias-Bexiga M., Menendez M., Garcia P.. PL3 amidase, a tailor-made lysin constructed by domain shuffling with potent killing activity against pneumococci and related species. Frontiers in Microbiology. 2016;7(JUL).
- Domenech M., Pedrero-Vega E., Prieto A., Garcia E. Evidence of the presence of nucleic acids and β-glucan in the matrix of non-typeable Haemophilus influenzae in vitro biofilms. Scientific Reports. 2016;6.
- Corsini B., Aguinagalde L., Ruiz S., Domenech M., Antequera M.L., Fenoll A. et al. Immunization with LytB protein of Streptococcus pneumoniae activates complement-mediated phagocytosis and induces protection against pneumonia and sepsis. Vaccine. 2016;34(50):6148-6157.

Highlights

- The P-selectin glycoprotein ligand-1 (PSGL-1) on leukocytes is involved in the phagocytosis process of S. pneumoniae by targeting the capsule and the surface protein LytA playing a critical protective role against invasive pneumococcal disease.
- Auranofin-loaded poly(lactic-co-glycolic acid (PLGA) nanoparticles showed a strong bactericidal effect against multiresistant pneumococcal strains on planktonic cultures, biofilms and in a zebrafish embryo model. Auranofin PLGA nanocarriers showed enhanced bactericidal activity compared to the free drug.
- Immunization with the peptidoglycan hydrolase LytB elicits IgGs of different subclasses that activates complement-mediated phagocytosis. Vaccination with LytB increased bacterial clearance and induced protection in animal models.
- A novel chimeric N-acetylmuramoyl-L-alanine amidase (PL3) was constructed by fusing the catalytic domain of the Pal amidase to the CBD of the LytA autolysin. Low doses of PL3 practically sterilized the cultures of streptococci of the mitis group. PL3, remained active when stored at 37°C and after lyophilization, and showed full protection against pneumococci-infected zebrafish embryos.
- The relevance of the diiA gene in pneumococcal pathogenesis was investigated. Mutants lacking diiA were less efficient in nasopharyngeal colonization and dissemination from lungs, and suffered a severe impairment in blood proliferation. Purified DiiA bound to collagen and lactoferrin with high affinity.
- Non-typeable Haemophilus influenzae (NTHi) forms biofilms in vitro, producing an extracellular matrix composed of proteins, nucleic acids, and a ß-glucan. Extracellular nucleic acids are essential in biofilm formation and maintenance. The matrix polysaccharide contains residues of Glcp(1->4). N-acetyl-L-cysteine killed in vitro NTHi biofilms.
- In 2016, the patent entitled “Detection of Streptococcus pneumoniae through magneto-amperometric genosensors employing specific primers and probes for the lytA gene” was approved both in USA and in the EU.
- María Soledad Escolano and Roberto Vázquez received awards for their oral presentation and poster communication, respectively, in the Jornadas de Formación del CIBERES (2016).

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Infectious Respiratory Diseases

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Main lines of research

- **Genetic-molecular mechanisms of hypoxic signaling**
  Our activity focuses on trying to define hypoxic signaling mechanisms in a model of continuous sustained hypoxia (COPD) and in another of chronic intermittent hypoxia (sleep apnea), through the identification and functional characterization of gene targets of the hypoxia-inducible factor (HIF), as well as by studying gene variants (SNPs) which might affect the response to HIF.
- **Sleep apnea and comorbidities with high mortality and social impact**
  In this line, we are interested both in the characterization of the pathogenic pathways, in the development of simplified diagnostic systems and in the evaluation of the CPAP effect on the comorbidity associated with obstructive sleep apnea (OSA). For several years, our projects have focused on the cardiovascular comorbidity of OSA (hypertension, heart failure, ischemic heart disease, pulmonary hypertension and venous thromboembolic disease), although recently we are also addressing its metabolic repercussion (type 2 diabetes) and the association between apnea and cancer.

- **Pathogenic mechanisms of airflow limitation**
  - We intend to contribute to the characterization of clinical, pathophysiological and structural aspects of COPD, both in the stable phase and during the exacerbation. We also studied the systemic effects and polymorphism of COPD, focusing mainly on the repercussion of the disease on daily physical activity.
  - Evaluation of the allergic and environmental causes and mechanisms of bronchial inflammation and remodeling. Our activity focuses on the identification of different triggers, the characterization of the asthmatic reaction, the description of molecular mechanisms of eosinophil activation and the definition of the biochemical and genetic mechanisms responsible for occupational asthma.
- **Regulation of the innate immune system in chronic respiratory infections**
  We pretend to recognize the molecular mechanisms of cell signaling responsible for the development of endotoxin tolerance, mainly in patients with COPD, cystic fibrosis and non-CF bronchiectasis. We are also particularly interested in the identification of several immunosuppression pathways of macrophages, natural killer cells and T cells in these patient groups.

Most relevant scientific articles

- Torres-Capelli M., Marsboom G., Li Q.O.Y., Tello D., Rodriguez F.M., Alonso T. et al. Role of Hif2α Oxygen Sensing Pathway in Bronchial Epithelial Club Cell Proliferation. Scientific Reports. 2016;6.
- Martinez-Ceron E., Barquiel B., Bezos A.-M., Casitas R., Galera R., Garcia-Benito C. et al. Effect of continuous positive airway pressure on glycemic control in patients with obstructive sleep apnea and type 2 diabetes a randomized clinical trial. American Journal of Respiratory and Critical Care Medicine. 2016;194(4):476-485.
- Roche O., Deguiz M.L., Tiana M., Galiana-Ribote C., Martinez-Alcazar D., Rey-Serra C. et al. Identification of non-coding genetic variants in samples from hypoxemic respiratory disease patients that affect the transcriptional response to hypoxia. Nucleic Acids Research. 2016;44(19):9315-9330.
- Alonso-Fernandez A., Suquia A.G., de la Pena M., Casitas R., Pierola J., Barcelo A. et al. OSA Is a Risk Factor for Recurrent VTE. Chest. 2016;150(6):1291-1301.
- Bobolea I., Barranco P., Del Pozo V., Romero D., Sanz V., Lopez-Carrasco V. et al. Sputum periostin in patients with different severe asthma phenotypes. Allergy: European Journal of Allergy and Clinical Immunology. 2016;70(5):540-546.

Highlights

In the field of hypoxic signaling, we have described several gene targets of HIF in patients with COPD or sleep apnea, and we have started the functional characterization of their responses. Among other achievements until now, we have described the role of HIF2alpha in the sensing pathway in bronchial epithelial club cell proliferation.

One of the main results obtained in sleep apnea is its identification as a risk factor for the recurrence of embolic episodes in patients with venous thromboembolic disease, which raises interesting clinical implications about the suppression or continuity of anticoagulation in this group of patients. Above all, we have contributed to the review of pathogenic pathways for deregulation of carbohydrate metabolism in patients with OSA and we have demonstrated a mid-term effect of CPAP on glycemic control in patients with OSA and poorly controlled type 2 diabetes.

In airflow limitation, we have generated the first results of our participation in a European project for the identification of lung function alterations in smokers with ischemic heart disease and we have described new routes of allergic sensitization in the children and in occupational asthma. In turn, we have provided information about the development of alterations in the symptomatic perception of obese individuals, who could simulate asthma. In this line, members of the group have participated in the preparation of the Spanish Guide for Asthma Management (GEMA 4.0) and the European recommendations for bronchial provocation with food.

In the innate immune system, we have provided information on macrophages reprogramming mechanisms in the context of chronic infections and we have obtained an integrated project of excellence of the ISCIII about endotoxin tolerance, which is coordinated by a group member.

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Main lines of research

- **Muscle disorders in COPD and other lung diseases**
  Most of our work focuses on the study of muscle abnormalities secondary to the different circumstances and factors present in patients with COPD and other chronic diseases: sedentary lifestyle, hypoxia, hypercapnia, ventilatory loading, inflammation and oxidative stress. In this regard our group has described the specific effects of several of these factors both in respiratory and limb muscles, using patients' samples and animal models. In the last period, we are mostly devoted to the study of the probable defects in muscle repair present in the above mentioned diseases.
- **Phenotyping COPD patients**
  There are also several of our recent studies searching for new key molecules that can explain part of the pathophysiology of COPD, and eventually serve as biomarkers of some of the traits that characterize the different subtypes of COPD patients or even help on the search of new therapeutic targets. The most ambitious project is BIOMEPOC, a multicenter study investigating potential biomarkers using different 'omic' approaches. In addition, new therapeutic targets for COPD may eventually be identified.

- **Molecular links between COPD and Lung Cancer**
  Our group is interested in investigating the mechanistic relationships between COPD and the onset of lung cancer, using both patient samples and animal models reproducing both entities. Our results indicate a series of differential characteristics present in patients with COPD who develop lung cancer.
- **Pulmonary hypertension**
  Some researchers from our group are studying the risk and prognosis factors, as well as different pathophysiological characteristics (both at general and molecular levels) of primary pulmonary hypertension. However, we are also very interested in secondary pulmonary hypertension present in many COPD patients. Studies focusing on the development of exercise-induced pulmonary hypertension are a particular focus of our last studies.

Most relevant scientific articles

- Chacon-Cabrera A., Gea J., Barreiro E. Short- and Long-Term Hindlimb Immobilization and Reloading: Profile of Epigenetic Events in Gastrocnemius. Journal of Cellular Physiology. 2016
- Alvarez-Lerma F., Marin-Corral J., Vila C., Masclans J.R., Gonzalez de Molina F.J., Martin Loeches I. et al. Delay in diagnosis of influenza A (H1N1) pdm09 virus infection in critically ill patients and impact on clinical outcome. Critical Care. 2016;20
- Purificacion P.-T., Jose R.-P., Juan C.R.-R., Roca O., Zapatero A., Gea J. et al. Prospective validation of right ventricular role in primary graft dysfunction after lung transplantation. European Respiratory Journal. 2016;48(6):1732-1742.
- Cosio B.G., Shafiek H., Iglesias A., Yanez A., Cordova R., Palou A. et al. Oral Low-dose Theophylline on Top of Inhaled Fluticasone-Salmeterol Does Not Reduce Exacerbations in Patients With Severe COPD: A Pilot Clinical Trial. Chest. 2016;150(1):123-130.
- Klionsky DJ, Abdelmohsen K, Abe A, Abedin MJ, Abeliovich H, Acevedo Arozena A, Gea J et al. Guidelines for the use and interpretation of assays for monitoring autophagy (3rd edition). Autophagy. 2016;12(1):-. FI 9.108

Highlights

In 2016 our group has published numerous research papers, highlighting those belonging to its classical research lines (muscle abnormalities in COPD and other chronic diseases, relationships between COPD and lung cancer, and pulmonary hypertension). The incorporation of a senior researcher to our group has added a new line, focused in the study of several disorders present in critically ill patients. Furthermore, the first step of the 'omics' analysis from the CIBERES project BIOMEPOC has been carried out. This is one of the main studies of the program on Chronic Respiratory Diseases (COPD line), and has facilitated the extension of our collaborations to bioinformatic groups from other research institutions. There are also collaborations with groups of CIBER BBN, which are focused on the development of instruments to monitor respiratory muscle function. Regarding translational activities it should be mentioned that we currently have two patented instruments that are currently commercialized (Europe and America). On the other hand, in the past year we participated in the elaboration and publication of the SEPAR recommendations for the management of lung cancer patients, and in a guide for the study of autophagy. An important and recent addition to the group has been our second CIBER postdoctoral investigator, an action that will undoubtedly boost our future research actions. In terms of projects, two actions were submitted to the EC 2020 Horizon program and both have been positively evaluated in the initial thematic selection. One of them would eventually be coordinated by CIBERES. As for postgraduate teaching, 4 doctoral theses from our group have successfully been defended in 2016, and 5 more are ongoing.

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PROGRAMMES

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Main lines of research

- Sleep Disorders: Central SA and cardiac disease. Association between respiratory sleep disorders and cutaneous melanoma growth rate. Effect of CPAP treatment in women with Obstructive sleep apnea. Medium and long term ventilation efficacy Noninvasive therapy in Pickwick obesity hypoventilation syndrome.
- Cancer: Lung cancer screening cohort of more than 550 patients with emphysema and/or COPD. Epigenetic study of minimally invasive samples obtained by EBUS in lung cancer. Prospective SAIL and SAILS studies dedicated to the prevalence of sleep apnea in patients with lung cancer and high risk subjects enrolled in the lung cancer screening cohort. Retrospective and prospective IASLC cohort. Metabolomics study of patients at high risk for lung cancer.
- COPD: Transcriptomic study of genetic susceptibility to lung damage in animal models. Identification of the key biomarkers in the development and progression of the disease in the animal model and its clinical significance. Prospective cohorts of Early-COPD patients and severe COPD. Metabolomic analysis of the longitudinal cohort CHAIN-SEPAR with search of predictive biomarkers in the evolution of the disease. New therapeutic targets based on the use of growth factors in the experimental models of the disease.

Most relevant scientific articles

- Kacmarek R.M., Villar J., Sulemanji D., Montiel R., Ferrando C., Blanco J. et al. Open lung approach for the acute respiratory distress syndrome: A pilot, randomized controlled trial. Critical Care Medicine. 2016;44(1):32-42.
- Masa J.F., Corral J., Caballero C., Barrot E., Teran-Santos J., Alonso-alvarez M.L. et al. Non-invasive ventilation in obesity hypoventilation syndrome without severe obstructive sleep apnoea. Thorax. 2016.
- Santos A., Lucchetta L., Monge-Garcia M.I., Borges J.B., Tusman G., Hedenstierna G. et al. The Open Lung Approach Improves Pulmonary Vascular Mechanics in an Experimental Model of Acute Respiratory Distress Syndrome. Critical Care Medicine. 2016-.
- Seijo L.M., Flandes J., Somiedo M.V., Naya A., Manjon J., Alvarez S. et al. A Prospective Randomized Study Comparing Manual and Wall Suction in the Performance of Bronchoalveolar Lavage. Respiration. 2016;91(6):480-485.
- Cosio B.G., Shafiek H., Iglesias A., Yanez A., Cordova R., Palou A. et al. Oral Low-dose Theophylline on Top of Inhaled Fluticasone-Salmeterol Does Not Reduce Exacerbations in Patients With Severe COPD: A Pilot Clinical Trial. Chest. 2016;150(1):123-130.

Highlights

The Sleep disorders area has been working on multicenter projects in lines of great interest within the CIBERES program (ADVENT-HF Trial, Association between respiratory sleep disorders and cutaneous melanoma growth rate, Effect of CPAP treatment in women with Obstructive Sleep Apnea, et.). It has also collaborated in respiratory therapy guidelines (SEPAR). Direction of the First Master on Sleep Disorders. Leads the PTT study (CIBERES / SEPAR): Usefulness of PTT in the noninvasive measurement of blood pressure in a Multidisciplinary Sleep Unit.

The COPD area continues recruiting cases for the BIOMEPOC and Early COPD cohorts. It has reached an agreement with the CNIC to access the study database and validate spirometry. It has also received funding from the AES 16 call (PI16 / 01783) to detect predictive markers in the evolution of COPD in the CHAIN-SEPAR cohort. In the experimental laboratory, we are concluding the PI13 / 01909 with transcriptomics, which has detected 290 differentially expressed genes with the treatment of LGF growth factor.

The cancer area continues to be linked to the IASLC, and maintains the screening cohort, with 550 patients recruited and 10 diagnosed cancers. It collaborates in the prospective studies SAIL and SAILS (more than 300 subjects) of prevalence of OSAS in patients with lung cancer and in the screening cohort. We participated in the BIOMEPOC cohort and in the study of epigenetics in EBUS samples. We participated in the metabolomic study to detect the risk of lung cancer. We participated in the coordination and collaboration in the SEPAR guide for the diagnosis and treatment of pulmonary carcinoma.

The results of most of these initiatives will be reported this year and are the subject of multiple communications to SEPAR, ERS and ATS meetings in 2017.

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Main lines of research

- Acute Respiratory Distress Syndrome.
  Clinical studies. Experimental studies.
- Mechanical Ventilation.
  Epidemiology. Weaning.
- Selectic Digestive Descontamination.
  Clinical and experimental.

Most relevant scientific articles

- Bellani G., Laffey J.G., Pham T., Fan E., Brochard L., Esteban A. et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA - Journal of the American Medical Association. 2016;315(8):788-800.
- Hernandez G., Vaquero C., Gonzalez P., Subira C., Frutos-Vivar F., Rialp G. et al. Effect of postextubation high-flow nasal cannula vs conventional oxygen therapy on reintubation in low-risk patients: A randomized clinical trial. JAMA - Journal of the American Medical Association. 2016;315(13):1354-1361.
- Laffey J.G., Bellani G., Pham T., Fan E., Madotto F., Bajwa E.K. et al. Potentially modifiable factors contributing to outcome from acute respiratory distress syndrome: the LUNG SAFE study. Intensive Care Medicine. 2016;42(12):1865-1876.
- Pandolfi R., Barreira B., Moreno E., Lara-Acedo V., Morales-Cano D., Martinez-Ramas A. et al. Role of acid sphingomyelinase and IL-6 as mediators of endotoxin-induced pulmonary vascular dysfunction. Thorax. 2016.
- Thompson B.T., Guerin C., Esteban A. Should ARDS be renamed diffuse alveolar damage? Intensive Care Medicine. 2016;1-3.

Highlights

- Finalization of the 4th International Study on Mechanical Ventilation. This is a prospective, observational, international study on the use of mechanical ventilation worldwide (IP Dr. Peñuelas).
- International Clinical Practice Guidelines on the Liberation of Mechanical Ventilation. Co-author: Dr. Esteban.
- Up dating of the hospital Autopsy Database of patients that received mechanical ventilation (IP Dr. Tejerina).
- Design of a Database of patients in mechanical ventilation and pulmonary Aspergillosis with postmortem examination (IP Dr. Tejerina).
- International study of patients on mechanical ventilation and ICU acquired weakness (IP Dr. Esteban).
- International database of patients with acute respiratory failure (LUNG SAFE), sponsored by the European Society of Intensive Care Medicine (National Coordinator Dr. Lorente, member of the Steering Committee Dr. Esteban).
- Hospital Registry of patients under mechanical ventilation with brain injury (IP Dr. Tejerina).
- Clinical trial in patients receiving mechanical ventilation, with extensive burns, on the effectiveness of different strategies for central line routine changes. Funded by ISCiii FIS: PI 11/01121 (IP Dr. Peñuelas).
- On going study on the Identification of new biomarkers and therapeutic targets for the ARDS. Funded by ISCiii FIS 15/01942 (IP: Dr. José A. Lorente).
- On going study on Abnormalities in tight junction proteins in the alveolar epithelium and their role in the pathogenesis of ARDS. A clinical and experimental study. Funded by ISCiii FIS 15/00482. IP: Dr. Raquel Herrero.

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Main lines of research

The main research areas developed are:

- Respiratory infection
- Antimicrobial resistance

Within the "Respiratory infection" area, his research focuses on the study of *Streptococcus pneumoniae*, from a clinical and epidemiological approach. Also, serotyping techniques and the efficacy of the new conjugate vaccines in the prevention of pneumococcal infection are priority issues in their research. Pulmonary infections caused by species of the genus Nocardia are also of great interest in this area. Resistance in respiratory pathogens, especially in *S. pneumoniae*, *S. pyogenes* and *Nocardia*, stands out in the research area of antimicrobial resistance. Apart from the epidemiology of the resistance, his investigations are based on the detection of the mechanisms and determinants of resistance of the different respiratory pathogenic bacteria and the application of new rapid techniques for the detection of this resistance.

Most relevant scientific articles

- Ercibengoa M., Perez-Trallero E., Marimon J.M. Autochthonous Nocardia cerradoensis infection in humans, Spain, 2011 and 2014. Emerging Infectious Diseases. 2016;22(1):109-111.
- Marimon J.M., Ercibengoa M., Tamayo E., Alonso M., Perez-Trallero E. Long-term epidemiology of streptococcus pneumoniae serogroup 6 in a region of southern Europe with special reference to serotype 6E. PLoS ONE. 2016;11(2).
- Tamayo E., Montes M., Vicente D., Perez-Trallero E. Streptococcus pyogenes pneumonia in adults: Clinical presentation and molecular characterization of isolates 2006-2015. PLoS ONE. 2016;11(3).
- Garcia-Moreno J., Igartua Laraudogoitia J., Montes Ros M. Pneumocystis jirovecii Pneumonia in a Patient with Anti-N-Methyl D-Aspartate Receptor Postherpetic Encephalitis. Pediatric Infectious Disease Journal. 2016.
- Marimon J.M., Ercibengoa M., Santacatterina E., Alonso M., Perez-Trallero E. Single-step multiplex PCR assay for determining 92 pneumococcal serotypes. Journal of Clinical Microbiology. 2016;54(8):2197-2200.

Highlights

- Description of a new bacterial species: *Nocardia donostienesis*. Ercibengoa M, Bell M, Marimón JM, Humrighouse B, Klenk HP, Pötter G, Pérez-Trallero E. Nocardia donostiensis sp. Nov., Isolated from human respiratory specimens. Antonie Van Leeuwenhoek. 2016; 109:653-60.
- Inclusion as a collaborating group in a European project of the program Horizon 2020 (EU / 2015 / PILOTS): "Antimicrobial flexible polymers for their use in hospital environments (FlexPol)." Reference: 721062. Dates: 2016-2019. Group. funding awarded: € 449,087.

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PROGRAMMES

Infectious Respiratory Diseases

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Main lines of research

Our Research Group on Mycobacterial Genetics has been working since 1992 in three lines of research funded by European and national research grants, being recognized as a leading group at the international level. Our current research interests are:

- Construction of New Vaccines against Tuberculosis, focusing on genes implicated in the pathogenicity and virulence of M. tuberculosis. PI Carlos Martín.
- Molecular Epidemiology of Tuberculosis & Transposition and Latency of M. tuberculosis focusing on the study of risk factors of transmission, and differences between strains of major epidemiological importance and the mechanism of slow growth of the Koch bacillus.PI Sofía Samper.
- Molecular Bases of Drug Resistance in Mycobacteria, focusing on the contribution of efflux pumps to intrinsic drug resistance and in the discovery of novel antituberculosis compounds. PI José Antonio Ainsa

Altogether, our commitment is to study the complexity of M. tuberculosis by using a multidisciplinary approach and to work in coordination with other national and international research groups.

Active Projects:

Line 1: TBVAC H2020 643381 - H2020-PHC-2014 “Advancing novel and promising TB vaccine candidates from discovery to preclinical and early Clinical development” 2015-18 • BIO2014-52580-P “Innovando MTBVAC como vacuna contra la tuberculosis y nuevas aplicaciones terapéuticas en cáncer”. 2015-18. • INNPACTO: Ref. IPT-2012-

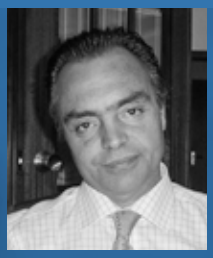
0327-090000 “Vacuna Inactivada contra tuberculosis en base a una cepa modificada genéticamente”. 2013-16.
Line 2: Polimorfismos genómicos y transcriptómicos en M. tuberculosis complex y su significado en clínica. IP: Sofía Samper. Número de investigadores: 10; FIS 12/1970, Instituto de Salud Carlos III. Jan 2013-Jul 2016. • Análisis de las diferencias de IS6110 entre los miembros del complejo Mycobacterium tuberculosis y el papel de su localización en el origen de replicación. IP: Sofía Samper. Número de investigadores: 8; FIS 15/0317, Instituto de Salud Carlos III. 2016-18. • European Reference Laboratory Network for Tuberculosis (ERLTB-Net). Sofía Samper es miembro de la Red. 2014-17.
Line 3: MM4TBMore Medicines for Tuberculosis. European Union FP7. 2011-16 • NAREB - Nanotherapeutics for antibiotic resistant emerging bacterial pathogens. European Union FP7. 2014-18 • SAF-2013-48971-C2-2-R. Aplicaciones biomédicas de AS-48, una proteína con amplio espectro de actividad antimicrobiana. 2014-17

Most relevant scientific articles

- Aguilo N., Alvarez-Arguedas S., Uranga S., Marinova D., Monzon M., Badiola J. et al. Pulmonary but not subcutaneous delivery of BCG vaccine confers protection to tuberculosis-susceptible mice by an interleukin 17-dependent mechanism. Journal of Infectious Diseases. 2016;212(11):831-839.
- Aguilo N., Uranga S., Marinova D., Monzon M., Badiola J., Martin C. MTBVAC vaccine is safe, immunogenic and confers protective efficacy against Mycobacterium tuberculosis in newborn mice. Tuberculosis. 2016; 96:71-74.
- Molina-Moya B., Kazdaglis G., Lacoma A., Prat C., Gomez A., Villar-Hernandez R. et al. Evaluation of GenoFlow DR-MTB array test for detection of rifampin and isoniazid resistance in mycobacterium tuberculosis. Journal of Clinical Microbiology. 2016;54(4):1160-1163.
- Sagasti S., Millan-Lou M.I., Soledad Jimenez M., Martin C., Samper S. In-depth analysis of the genome sequence of a clinical, extensively drug-resistant Mycobacterium bovis strain. Tuberculosis. 2016; 100:46-52.
- Scriba T.J., Kaufmann S.H.E., Lambert P.H., Sanicas M., Martin C., Neyrolles O.. Vaccination against tuberculosis with whole-cell mycobacterial vaccines. Journal of Infectious Diseases. 2016;214(5):659-664.

Highlights

In 2016 we have continued our participation in the European TBVAC2020 project “Advancing novel and promising TB vaccine candidates for preclinical and early clinical development”, in collaboration with 40 universities and research centers. The solid safety data and immunogenicity of the first clinical trial in humans with MTBVAC in Phase 1a in adults in Lausanne Switzerland were critical in initiating the Phase 1b safety study in newborns in South Africa, an endemic country with one of the highest incidences of tuberculosis in the world. The vaccination phase of the babies ended in September 2016 (ClinicalTrials.gov Identifier: NCT02933281) and immunity results are expected by the end of 2017.
In the line of TRANSPOSITION and MOLECULAR EPIDEMIOLOGY OF TUBERCULOSIS project FIS 12/1970 was closed, and FIS 15/0317 started. The characteristics of the isolates of the most relevant tuberculosis complex in our environment and the different polymorphisms in their genomes were determined. The study of Beijing strains of Community Canaria was started. The genome of a M. bovis isolate XDR “B” has been published. We started with transcriptome studies. A “SNaPShot” pyrosequencing technique was performed and an ampliTaq faster and easier to perform technique which, in turn offers the molecular resistance profile of the isolate, and its phylogeny is being designed.
In the line of MOLECULAR BASIS OF DRUG RESISTANCE IN MYCOBACTERIA, during 2016 works on European project MM4TB have finalized, and positive results have been achieved in the analysis of the role of efflux in the activity of several new families of antituberculosis compounds. Based on previous works that resulted in the identification of a polymorphism specific of Beijing strains in a gene encoding an efflux pump, we have worked for simplifying the protocol for detection, which may facilitate its implementation in the clinic. Concerning other series of antituberculosis compounds, we have continued with its characterisation, in particular we have worked on drugs under development combined with nanoparticles.



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Main lines of research

- Respiratory disorders and sleep apneas during sleep.
- Noninvasive ventilation treatment in acute and chronic settings.
- Lung cancer diagnosis and treatment.
- Telematic diagnosis in respiratory medicine.
- Tobacco quit and treatment.

Most relevant scientific articles

- Masa J.F., Corral J., Caballero C., Barrot E., Teran-Santos J., Alonso-alvarez M.L. et al. Non-invasive ventilation in obesity hypoventilation syndrome without severe obstructive sleep apnoea. Thorax. 2016.
- Khalyfa A., Kheirandish-Gozal L., Khalyfa A.A., Philby M.F., Alonso-Alvarez M.L., Mohammadi M. et al. Circulating plasma extracellular microvesicle MicroRNA cargo and endothelial dysfunction in children with obstructive sleep apnea. American Journal of Respiratory and Critical Care Medicine. 2016;194(9):1116-1126.
- Campos-Rodriguez F., Queipo-Corona C., Carmona-Berna C., Jurado-Gamez B., Cordero-Guevara J., Reyes-Nunez N. et al. Continuous positive airway pressure improves quality of life in women with obstructive sleep apnea a randomized controlled trial. American Journal of Respiratory and Critical Care Medicine. 2016;194(10):1286-1294.
- Kaditis AG, Alonso Alvarez ML, Boudewyns A, Alexopoulos EI, Ersu R, Joosten K et al. Obstructive sleep disordered breathing in 2- to 18-year-old children: diagnosis and management.The European respiratory journal. 2016;47(1):69-94.
- Masa JF, Corral J, Romero A, Caballero C, Terán-Santos J, Alonso-Álvarez ML et al. Protective cardiovascular effect of sleep apnea severity in obesity hypoventilation syndrome.Chest. 2016.

Highlights

PROJECTS

- "Eficacia de la VNI ajustada automáticamente en el SHO" " funded by FIS and Philips with 270,000€. Currently running.
- "iREST" "Improving obstructive sleep apnea therapy through a personalised telematic intervention" and "3DREST" 3 dimensional telematic intervention to improve obstructive sleep apnea therapy". Both projects were presented in April and in October Horizonte 2020 applications.
- Anticipate "A study comparing the current COPD intervention with a technology-assisted responsive and integrated approach to Prevent hospitalizations due to acute exacerbations" was presented in October Horizonte 2020 applications.

EVENTS

- V International Symposium "COPD and Tobacco": diagnostic-therapeutic update and future perspectives. Cáceres 10, 11 November 2016.

RESULTS

- From a multicentric, non-inferiority, cost-effectiveness, randomized controlled trial: Conventional polysomnography is not necessary in obstructive sleep apnea syndrome management. This finding could change established clinical practice, with a clear economic benefit. Presently in the second revision in Am J Respir Crit Care Med.
- From PICKWICK multicentric, randomized controlled trial: Echocardiographic changes with positive airway pressure modalities in obesity hypoventilation syndrome. Medium-term NIV therapy in patients with OHS is more effective than CPAP and lifestyle modification in improving pulmonary artery pressure and measures of LV hypertrophy. Presently the paper is ongoing.

GUIDELINES

- ERS Task Force on Technical Standards for the Scoring of Respiratory events using Type III devices for the diagnosis of Sleep Disordered Breathing. JF Masa is member of the writing committee.
- ATS guidelines: Obesity hypoventilation syndrome: Evidence-based guidelines for evaluation and management. JF Masa is the co-chairman.
- Sleep apnea and driving. Recommendations for the interpretation of Annex IV of the General Regulations of Drivers approved by R.D. 818/2009, as amended by the R.D. 1055/2015. JF Masa has been member (Arch Bronchoneumol in press).

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PROGRAMMES

Infectious Respiratory Diseases

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Main lines of research

- The group activity focuses on in-depth characterization of structure/function relationships in biomolecules and molecular recognition processes, with emphasis in
  I) bacterial virulent factors,
  II) host-pathogen interactions,
  III) search and characterization of new antimicrobials against respiratory pathogens, and
  IV) development of new designer's microarrays.

Most relevant scientific articles

- Kalograiaki I., Euba B., Proverbio D., Campanero-Rhodes M.A., Aastrup T., Garmendia J. et al. Combined Bacteria Microarray and Quartz Crystal Microbalance Approach for Exploring Glycosignatures of Nontypeable Haemophilus influenzae and Recognition by Host Lectins. Analytical Chemistry. 2016;88(11):5950-5957.
- Blazquez B., Fresco-Taboada A., Iglesias-Bexiga M., Menendez M., Garcia P. PL3 amidase, a tailor-made lysin constructed by domain shuffling with potent killing activity against pneumococci and related species. Frontiers in Microbiology. 2016;7(JUL).
- Kong N, Xie S, Zhou J, Menéndez M, Solís D, Park J et al. Catalyst-Free Cycloaddition Reaction for the Synthesis of Glyconanoparticles.ACS applied materials & interfaces. 2016;.
- Ruiz-Masó JA, Bordanaba-Ruiseco L, Sanz M, Menéndez M, Del Solar G. Metal-Induced Stabilization and Activation of Plasmid Replication Initiator RepB.Frontiers in molecular biosciences. 2016; 3:56.

Highlights

- The study of glycosylation patterns of Klebsiella pneumoniae clinical isolates exhibiting or not hypermucoviscous phenotypes has been initiated using lectins with different carbohydrate-binding specificities, in collaboration with Dr. C. Ardanuy (Group 19). The role of Haemophilus influenzae lipopolysaccharide as possible ligand for Viscum album and Ricinus communis agglutinins was also examined in collaboration with Dr. J. Garmendia (Group 19).
- Applicability of bacteria micorrays was extended to several streptococci, and behaviour of unfixed and fixed bacteria was compared. A comparative analysis of the binding of lectins of the innate immune system to the major respiratory pathogens has been started.
- A microarray study of the role diiA and pspA pneumococcal proteins in lactoferrin binding was initiated using diiA, pspA, or diiA plus pspA TIGR4 defective mutants, in collaboration with Dr. J.E. Yuste (Group 2).
- We have designed, produced, and tested in vitro and in vivo the PL3 chimera, the most potent amidase killing S. pneumoniae so far described. Several chimeric lysins with broader spectrum of susceptible bacteria have been also cloned and purified; testing of their bacteriolytic activities is in progress in collaboration with Dr. P. García (Group 2).
- We accomplished the structural and functional characterization of CW_7 cell-wall binding repeats, present in more than 300 proteins involved in cell wall synthesis or hydrolysis, several of them with proved antimicrobial activity.
- New compounds with bacteriostatic and/or bactericide activity against several respiratory pathogens were identified by screening of a non-commercial, chemical library. In vitro characterization of their activities has been initiated, in collaboration with Group 2.

ACTIVE PROJECTS

- 2011-2016. DYNANO (EU; FP7-ITN-GA:289003)
- 2012-2016. GLYCOPHARM (UE; FP7-PEOPLE-2012-ITN-317297)
- 2013-2016. Exploring exogenous and endogenous factors as tools for the control of infectious and immune processes (BFU2012-36825)
- 2016-2018. Search and development of new preventive and therapeutic approaches for fighting infections caused by Streptococcus pneumoniae (BFU2015-70052-R)

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PROGRAMMES

Chronic Respiratory Diseases
Diffuse Respiratory Diseases
Infectious Respiratory Diseases

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Main lines of research

- **Respiratory Respiratory Diseases Programme**
  In Lung Cancer, the group works on the clinical and molecular characterization in lung_cancer early stages. The Group coordinates two lung cancer cohorts (stage I / IIp), for which clinical and follow-up information is available and associated to blood, tumoral and non-tumor lung tissue samples, registered on the CIBERES Pulmonary Biobanc Consortium. The Group also investigates the identification of prognostic molecular markers in samples obtained by endoscopic approach.
  In COPD, the group participates in the creation and follow-up of a cohort of early diagnosis COPD (Early-COPD) and a second cohort of severe and fragile COPD patients due to frequent exacerbations. The group performs the analysis of bronchial inflammatory response and the study of bronchial microbiology to determines the Respiratory microbiome (culture-independent)
- **Infectious Respiratory Diseases Programme**
  The Group leads the research on non-ICU nosocomial pneumonia (NNPNV). The group coordinates a prospective multicenter study with therapeutic intervention on the incidence in hospitals in our area (NEUNOS14). In 2016, the Group assumed responsibility for coordinating research into the microbial causes of pneumonia in immunocompromised patients in the community and in the hospital, which has

incorporated the project "Pneumonia in non-neutropenic oncology (NONN) patients."
The Group maintains a study on clinical and molecular aspects of Legionellosis, including the prospective registry of new cases. In environmental health, the Group studies the disinfection effects and consequences of different measures applied on water supplies; evaluates the Legionella molecular typing techniques.

- **Singular Respiratory Diseases Programme**
  The Group participates in Pulmonary Hypertension, in the workpackage "Pulmonary Hypertension Associated with Respiratory Diseases and Hypoxia", which includes the central registry of the research line and its quality control. The Group has joined the Pulmonary Fibrosis line as a principal investigator in the study of the bacterial and viral microbiome and the inflammation and remodeling markers of the idiopathic pulmonary fibrosis cohort "FPI.cat Observatory" in 2016 and its relation with Progression of disease.

Most relevant scientific articles

- Gilabert-Porres J., Marti S., Calatayud L., Ramos V., Rosell A., Borros S. Design of a Nanostructured Active Surface against Gram-Positive and Gram-Negative Bacteria through Plasma Activation and in Situ Silver Reduction. ACS Applied Materials and Interfaces. 2016;8(1):64-73.
- Rosell A., Rodriguez N., Monso E., Taron M., Millares L., Ramirez J.L. et al. Aberrant gene methylation and bronchial dysplasia in high risk lung cancer patients. Lung Cancer. 2016; 94:102-107.
- Garcia-Nunez M., Quero S., Pedro-Botet M.L., Barrabeig I., Avarez J., Campoy I. et al. Characterization of unrelated clinical Legionella pneumophila isolates in Catalonia by monoclonal subgrouping and sequence-based typing. Future Microbiology. 2016;11(7):865-875.
- Abad J., Munoz-Ferrer A., Cervantes M.A., Esquinas C., Marin A., Martinez C. et al. Automatic video analysis for obstructive sleep apnea diagnosis. Sleep. 2016;39(8):1507-1515.
- Gallego M, Pomares X, Capilla S, Marcos MA, Suárez D, Monsó E et al. C-reactive protein in outpatients with acute exacerbation of COPD: its relationship with microbial etiology and severity. International journal of chronic obstructive pulmonary disease. 2016; 11:2633-2640.

Highlights

- The group has finalized the analysis of molecular markers of the an initial lung cancer cohort, and has objectified the relationship between stromal structure, tumor inflammation and disease survival.
- Organization of the workshop and international symposium "The Microbiome in Respiratory Medicine", on June 2 and 3 in Barcelona.
- Principal investigator and beginning of the project FIS 15/0167 "Respiratory Microbioma in COPD".
- Participant researcher and initiation of the FIS project 16/0977 "Prolonged global analysis with azithromycin in the microbiome and metabolome of patients with severe COPD and frequent exacerbations. Identification of systemic markers".
- In molecular typing the group has validated the SBT technique for the study of outbreaks of Legionellosis.
- Agreement with the Public Health Agency of Catalonia in which the Group is recognized as a reference center for the molecular typing Legionella.
- Principal investigator and beginning of the project FIS 16/01347 "New low cost products for disinfection in water systems: efficiency study on Legionella".
- Principal investigator and beginning of the project FIS 16/00216 "The pulmonary microbioma in idiopathic pulmonary fibrosis".

PATENTS

- Obtaining and licensing of PATENT P201531409 "Integrated filter holder and procedure for concentration and detection of microorganisms", licensed in 2016 by the company Waterologies.

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PROGRAMMES
Chronic Respiratory Diseases

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Main lines of research

- Apneas (OSA) and cancer. From 2011 there has developed a wide basic activity that can be considered to be seminal. Always based in 2 lines, the basic one co-working with the group of the Prof. Navajas and the clinic one with the Spanish Group of Sleep disorders (SEPAR) that have focused on the analysis of the melanoma. Actually, our group with the Profs. Navajas and Alcaraz (Urology Depar of the Hospital Clinic) has begun a new line of original investigation on the cancer and DARES. It is a question of analyzing the role of IT her DARES in the renal cancer. In this respect already there have been obtained very new publications (Vilaseca et to. J Urol. 2017).
- Our group has another important objective. Specifically and as the apneas are considered a systemic disease, our studies attempt to assess the effect of the OSA in other organs. Currently the group that works in the context of the Cyber-SAHS line explores the effect of the OSA in the CKD and the Microbiome instestinal already with initial results (Moreno-Indias Sleep 2016).
- The most important line that the group takes to out today is the telemedicine applied to the OSA. Both in monitoring, early works (Isetta et to the Thorax) as in the context of the creation of a virtual unit of sleep completely either ranging from diagnostic treatment and follow-up procedures using new information and communication technologies to work with primary. Those initial results were already presented (London ERS or SEPAR congresses) endorse this new form of work, very innovative, as good and cost effective.

Most relevant scientific articles

- Isetta V., Montserrat J.M., Santano R., Wimms A.J., Ramanan D., Woehrle H. et al. Novel approach to simulate sleep apnea patients for evaluating positive pressure therapy devices. PLoS ONE. 2016;11(3).
- Farre R., Navajas D., Montserrat J.M. Technology for noninvasive mechanical ventilation: Looking into the black box. ERS Monograph. 2016;2(1).
- Ambrosino N., Vitacca M., Dreher M., Isetta V., Montserrat J.M., Tonia T. et al. Tele-monitoring of ventilator-dependent patients: A European Respiratory Society Statement. European Respiratory Journal. 2016;48(3):648-663.
- Castro-Grattoni A.L., Alvarez-Buve R., Torres M., Farre R., Montserrat J.M., Dalmases M. et al. Intermittent Hypoxia-Induced Cardiovascular Remodeling Is Reversed by Normoxia in a Mouse Model of Sleep Apnea. Chest. 2016;149(6):1400-1408.

Highlights

National Investigation Lines. Respiratory sleep physiology, basic and clinical studies. Development of a virtual unit of sleep. Effects of sleep disorders of breathing on different tissues other than the cardiovascular system ones (CIBER, SEPAR, SES).
European Research Lines. Telemedicine and effects of sleep disorders of breathing in different tissues other than the cardiovascular system (ERS).
At present the CIBERES-Sleep Apnea area, has a new program. The group has also developed a new series of objectives whose initial scientific production is summarized below and represent the main challenges of the new task of the group. It is estimated that more results will come in the next years. According, to the new clinical needs, especially regards to the cost-effectiveness way of working the project will be divided in the three points.

1. Analysis of new information and communication technologies in clinical practice. More specifically analysis of the current technology like the devices as well as the clinical way of working with patients (web contacts or videoconferences) 1-3.
2. Closely linked to the previous point the different medical levels must work together as the best way to improve processes4. A basic schema has been proposed at the national level4. Finally,
3. Another aspect that we consider important is to assess the non-cardiovascular aspects of SAHS because the apnea is a systemic diseases and it is closely related in one or other aspect with among others as cancer, renal diseases or changes on the microbioma.

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PROGRAMMES

Host-Pathogen Interactions
Fibrosis
Pulmonary Hypertension

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Main lines of research

- COPD human and animal models: pharmacological modulation.
- Pulmonary fibrosis: human and animal models: pharmacological modulation.
- Pulmonary hypertension-associated pulmonary idiopathic fibrosis.
- In vitro models of corticoid-resistance on relevant to COPD.
- Animals and in vitro models of corticoid-resistance in Asthma.

Most relevant scientific articles

- Milara J, Morell A, Ballester B, Armengot M, Morcillo EJ, Cortijo J. MUC4 impairs the anti-inflammatory effects of corticosteroids in chronic rhinosinusitis with nasal polyps.The Journal of allergy and clinical immunology. 2016.
- Milara J., Escriva J., Ortiz J.L., Juan G., Artigues E., Morcillo E. et al. Vascular effects of sildenafil in patients with pulmonary fibrosis and pulmonary hypertension: An ex vivo/in vitro study. European Respiratory Journal. 2016;47(6):1737-1749.
- Morales-Cano D, Moreno L, Barreira B, Briones AM, Pandolfi R, Moral-Sanz J et al. Activation of PPARβ/δ prevents hyperglycaemia-induced impairment of Kv7 channels and cAMP-mediated relaxation in rat coronary arteries. Clinical science (London, England : 1979). 2016;130(20):1823-36.
- Gonzalez-Sanz R., Mata M., Bermejo-Martin J., Alvarez A., Cortijo J., Melero J.A. et al. ISG15 is upregulated in respiratory syncytial virus infection and reduces virus growth through protein ISGylation. Journal of Virology. 2016;90(7):3428-3438.
- Milara J, Cervera A, de Diego A, Sanz C, Juan G, Gavaldà A et al. Non-neuronal cholinergic system contributes to corticosteroid resistance in chronic obstructive pulmonary disease patients.Respiratory research. 2016;17(1):145.

Highlights

During 2016, three public funding projects have been continued. The first one, started in 2013 and whose researcher is Javier Milara, is entitled: Study of the Janus Kinasa 2 / STAT3 route as a pharmacological target in idiopathic pulmonary fibrosis and associated pulmonary hypertension: preclinical and translational analysis, financed project by Health Research Fund ISCIII. The second of them, whose investigator in charge is Julio Cortijo was initiated in 2015 and your title is: New anti-inflammatory drugs in COPD and asthma. Study in models of in vitro corticoresistencia financed by the Ministry of Economy and Competitiveness and finally the last one initiate also in 2015 and whose responsible investigator is Esteban Morcillo has as its title: Pharmacological modulation of signaling inflammation-remodeling by isoform-selective inhibitors of PDE4 and Comparators in relevant in vitro human models in COPD financed by the Ministry of Economy and Competitiveness.

On the other hand during this year also has participated in projects of private financing. The first one was based on the differential effects of Advanced Compound with comparators; panPDE4B inhibitor, selective PDE4B inhibitor, selective PDE4D inhibitor, roflumilast N-oxide and corticosteroids on leukocyte/endothelium interactions in in vitro models relevant to COPD financed by Grünenthal GmbH. In the second, the analysis of Mucociliary Clearance of test compounds using microCT-SPECT-Tc99m albumin nanocolloids in Guinea Pig. Project financed by Almirall. Finally, the study of effects of NOX4 inhibitors on primary fibroblasts from IPF patients; an in vitro study, a project financed by Glenmark Pharmaceuticals Limited company, is currently underway.

In addition to the projects mentioned, the group has participated in events of scientific diffusion among them in the congress of the European Respiratory Society and two doctoral theses have been presented as well as 4 end-of-degree / master's degrees.

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PROGRAMMES
Chronic Respiratory Diseases

GROUP MEMBERS

Staff members: Ojanguren Arranz, Íñigo

Associated members: Álvarez Fernández, Antonio | Bravo Masgoret, Carlos | Cruz Carmona, Mª Jesús | De Gracia Roldán, Javier | Ferrer Sancho, Jaime | Genover Llimona, Mª Teresa | Gómez Olles, Susana | Lloberes Canadell, Patricia | Martí Beltrán, Sergi | Monforte Torres, Víctor | Mravitilles Fernández, Marc | Orriols Martínez, Ramón | Roca Gas, Oriol | Rodríguez González, Esther | Román Broto, Antonio | Romero Santo Tomás, Odile | Ruano Burgos, Laura | Sampol Rubio, Gabriel | Untoria Corral, Mª Dolores | Venrell Belat, Montserrat

Main lines of research

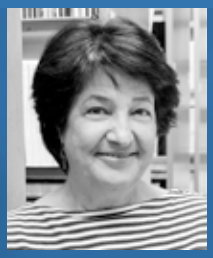
- The activity of basic and clinical research of the group focuses mainly in areas of inflammation and repair, respiratory failure and tissue hypoxia, and there is complementarity and interrelation of these areas for the study of diseases such as asthma, COPD, pulmonary fibrosis, infections, transplants, pulmonary hypertension and sleep-disordered breathing (SDB).
- Specifically, within the research in asthma the group is working in the MEGA project aimed at increasing knowledge about the molecular mechanisms of asthma as well as to study the parameters that can determine long-term changes in the patient's condition and treatments that can influence the progression of the disease. In short, the group aims to better understand the natural history of disease in order to reduce its incidence. We believe that the key to a better understanding of asthma is to carry out an integrated approach, in which immunological, genetic and environmental factors that define the relevant characteristics of the disease are analyzed.
- In the line of pulmonary fibrosis, our studies have shown that it is possible to determine the causes of this disease in half of the cases after the completion of a clinical study in depth. The group has shown that a major cause of idiopathic pulmonary fibrosis is exposure to minimal but persistent antigen quantities. Ultimately, it is the disease called hypersensitivity pneumonitis crónica. In this research the group has a murine model of hypersensitivity pneumonitis that will be significant in the near future to see the effect of different treatments as well as to study the pathophysiological pathways of this disease.
- Our center is currently one of the 7 hospitals in the country where lung transplants are performed and one of the most active in this field, which places it in one of the top European and world level. With the unique opportunity generated by the lung transplant program at our hospital, the group is actively working on the inclusion of samples in the CIBERES biobank.

Most relevant scientific articles

- Miravitlles M., Vogelmeier C., Roche N., Halpin D., Cardoso J., Chuchalin A.G. et al. A review of national guidelines for management of COPD in Europe. European Respiratory Journal. 2016;47(2):625-637.
- Quirce S., Vandenplas O., Campo P., Cruz M.J., de Blay F., Koschel D. et al. Occupational hypersensitivity pneumonitis: An EAACI position paper. Allergy: European Journal of Allergy and Clinical Immunology. 2016.
- Peghin M., Hirsch H.H., Len O., Codina G., Berastegui C., Saez B. et al. Epidemiology and Immediate Indirect Effects of Respiratory Viruses in Lung Transplant Recipients: A 5-Year Prospective Study. American Journal of Transplantation. 2016.
- Masa J.F., Corral J., Caballero C., Barrot E., Teran-Santos J., Alonso-alvarez M.L. et al. Non-invasive ventilation in obesity hypoventilation syndrome without severe obstructive sleep apnoea. Thorax. 2016.
- Aliberti S., Masefield S., Polverino E., De Soyza A., Loebinger M.R., Menendez R. et al. Research priorities in bronchiectasis: A consensus statement from the EMBARC Clinical Research Collaboration. European Respiratory Journal. 2016;48(3):632-647.

Highlights

During 2016, the group participated in the development of several clinical guidelines, such as the review of European regulations on the treatment of COPD (Eur Respir J 2016; 47: 625-637) or the POPE study (Int J Chron Obst Pulm Dis 2016; 11: 611-622). Dr. Sampol has also directed the clinical practice guide on the use of DAM in the treatment of OSAS, which has been completed in 2016 and is yet to be published. In the field of occupational / environmental pathology, the group has been involved in the development of the SEPAR asbestos disease normative and in the European Society of Allergy (EAACI) Task Force on hypersensitivity pneumonitis (Allergy. (6): 765-79). In the lung transplantation line, the group has participated in an international study that has demonstrated the relationship of air pollution with mortality and the occurrence of chronic graft dysfunction in patients with transplanted lung. The research has been published in the European Respiratory Journal. The Ciberes Asthma Program is carrying out a multi-center project (MEGA Project) for which it has funding from the Carlos III Health Institute. The group has published more than 60 articles during 2016, has several projects funded by the Instituto de Salud Carlos III, SEPAR, SOCAP, FUCAP etc. (See report) and has directed three doctoral theses.



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Group website

PROGRAMMES

Infectious Respiratory Diseases

GROUP MEMBERS

Staff members: Marcos Villar, Laura | Pazo Fernández, Alejandra

Associated members: Falcón Escalona, Ana | Melero Fontdevila, José Antonio

Main lines of research

- Mechanism of influenza virus interaction with the host cell.
- Mecahnisms of pathogeinicity of influenza virus.
- Study of human respiratory syncityal virus and metapneuomovirus glycoproteins.

Most relevant scientific articles

- Rodriguez-Frandsen A., De Lucas S., Perez-Gonzalez A., Perez-Cidoncha M., Roldan-Gomendio A., Pazo A. et al. HCLE/C14orf166, a cellular protein required for viral replication, is incorporated into influenza virus particles. Scientific Reports. 2016;6.
- Marcos-Villar L., Pazo A., Nieto A. Influenza virus and chromatin: Role of the CHD1 chromatin remodeler in the virus life cycle. Journal of Virology. 2016;90(7):3694-3707.
- Mas V., Rodriguez L., Olmedillas E., Cano O., Palomo C., Terron M.C. et al. Engineering, Structure and Immunogenicity of the Human Metapneumovirus F Protein in the Postfusion Conformation. PLoS Pathogens. 2016;12(9).
- Rodriguez P., Perez-Morgado M.I., Gonzalez V.M., Martin M.E., Nieto A. Inhibition of Influenza Virus Replication by DNA Aptamers Targeting a Cellular Component of Translation Initiation. Molecular Therapy - Nucleic Acids. 2016;5.
- Landeras-Bueno S., Fernandez Y., Falcon A., Oliveros J.C., Ortin J. Chemical genomics identifies the PERK-mediated unfolded protein stress response as a cellular target for influenza virus inhibition. mBio. 2016;7(2).

Highlights

During year 2016 we have studied the interactions between the influenza virus polymerase and the infected cell, modulation of viral replication by antiviral agents and the epigenetic changes induced by influenza virus infection. In addition, we have continued with the structural, antigenic and immunogenic characterization of *Pneumoviridae* fusion proteins with the aim of designing a universal vaccine for this family of viruses.

- **Cellular proteins that interact with influenza virus polymerase proteins**
  We have characterized the interaction of two transcription-related proteins with influenza virus polymerase. One is hCLE, a positive modulator of the RNAP II, and the other is CHD1, a chromatin remodeler. Both, positively modulate influenza virus replication and moreover, hCLE is incorporated into influenza virus particles.
- **Modulation of influenza virus replication by antiviral agents**
  We have used DNA aptamers that impair the interaction between influenza virus polymerase with components of the cellular translation machinery. Their use decreases viral replication and can be useful tools as potential antiviral compounds.
  We have shown that influenza virus downregulates the unfolded protein response mediated by the PERK sensor, while Montelukast, a drug used to treat asthma in humans, specifically stimulates this response and downregulates viral protein synthesis and multiplication. Hence, our studies suggest that modulation of the PERK-mediated unfolded protein response is a target for influenza virus inhibition.
- **Effect of influenza virus infection on chromatin remodelers and epigenetic changes induced in the infected cell.**
  We have studied the epigenetic changes of the cellular chromatin that take place during infection. DNA methylation is not modified, but histone modifications are altered. A general decrease in histone acetylation is observed and an increase in H3K79 methylation. Inhibiting the specific methylase of this residue we have observed that it controls the antiviral response and therefore influenza virus replication.
- **Generation and characterization of respiratory syncytial virus (RSV) and metapneumovirus (MPV) chimeric fusion proteins.**
  Based on previous structural studies of both RSV and MPV F glycoproteins, chimeric molecules were designed in which antigenic sites were swapped between the two molecules. Thus, soluble forms of postfusion MPV F with RSV antigenic site II and prefusion RSV F with MPV antigenic site IV were made and expressed from vaccinia recombinant viruses. The purified chimeric proteins showed the expected antigenic properties, as probed with monoclonal antibodies, and were capable of inducing cross-reactive and cross-neutralizing antibodies in mice. These results represent a proof of concept for a human Pneumoviridae universal vaccine.

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PROGRAMMES

Chronic Respiratory Diseases
Diffuse Respiratory Diseases

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Associated members: Agapito Serrano, María Teresa | Gallego Martín, Teresa | Gómez Niño, Ángela | Rigual Bonastre, Ricardo Jaime | Rocher Martín, Asunción | Yubero Benito, Sara

Main lines of research

- Obstructive sleep apnea and systemic effects: multifactor study in an animal model of Chronic Intermittent Hypoxia.
- Chronic intermittent hypoxia (OSA model) and spontaneous tumorigenesis in a murine model
- Animal model of pulmonary hypertension associated with sustained chronic hypoxia: vascular characterization.
- New role of carotid body arterial chemoreceptors in the pathophysiology: arterial hypertension and metabolic syndrome.

Most relevant scientific articles

- Quintero M., Olea E., Conde S.V., Obeso A., Gallego-Martin T., Gonzalez C. et al. Age protects from harmful effects produced by chronic intermittent hypoxia. Journal of Physiology. 2016;594(6):1773-1790.
- Masa J.F., Corral J., Romero A., Caballero C., Teran-Santos J., Alonso-Alvarez M.L. et al. The effect of supplemental oxygen in obesity hypoventilation syndrome. Journal of Clinical Sleep Medicine. 2016;12(10):1379-1388.
- Masa JF, Corral J, Romero A, Caballero C, Terán-Santos J, Alonso-Álvarez ML et al. Protective cardiovascular effect of sleep apnea severity in obesity hypoventilation syndrome.Chest. 2016.

Highlights

After the forced change of direction, our group has consolidated and matured with the following achievements:

- New IP, Ana Obeso.
- New funding: MINECO-FEDER project, BFU2015-70616R Pathophysiological implications of obstructive sleep apnea: arterial hypertension and tumorigénesis.
- Incorporation of new researchers: Dr. Jesús Prieto Lloret, postdoctoral contractor; Dr. Elvira González Obeso: specialist pathologist Hospital Universitario de Valladolid.
- Consolidation of collaborations with other intraCIBERES groups: Group 15, Group 12 and Group 28, with publications in common.
- Three doctoral theses have been defended, by Miguel Quintero, Elena Olea and Teresa Gallego (this one with international mention) directed by members of the group.
- We have been recognized as a Research Excellence Group (UIC) by the Junta de Castilla y León.

Our most relevant scientific achievements are summarized in the following points: Aging protects against the deleterious effects of chronic intermittent hypoxia on respiratory and cardiovascular function in a rat model. We demonstrate for the first time that chronic intermittent hypoxia is a risk factor promoting the spontaneous appearance of tumors in different tissues, and significantly in the lung, in a murine aging model. Sexual dimorphism is confirmed in the onset and progression of pulmonary hypertension associated with chronic hypoxia in a rat model. The role of carotid body (CB) in glucose homeostasis and in insulin sensitivity in rat adipose and hepatic tissue has been demonstrated.
The group has collaborated in activities organized by CIBERES, participating (Asuncion Rocher as a member of the CIBERES Teaching Commission) in the organization of the 9th CIBERES Training Days, Collaborative Projects with CIBERBNN, held in the Auditorium of the National Cardiovascular Research Center Carlos III (CNIC), Madrid 29-30 September. We have organized (Ricardo Rigual) and participated as guest speaker (Ana Obeso) with the lecture: “From carotid body oxygen sensing to chronic intermittent hypoxia, effects on spontaneous tumorigenesis” in the symposium entitled: “A new role for the carotid body in pathology” at the XXXVIII Congress of the Spanish Society of Physiological Sciences, Zaragoza 13-16 September 2016. We have participated as guest speaker in the International Symposium on Acute Pulmonary Injury Translational Research, INSPIRES, Organized by the Intensive Care Unit (with members of CIBERES) held at the University Hospital of Getafe on November 2 and 3, 2016 invited speaker Ana Obeso. Title of the presentation: “Cell response to hypoxia”.

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PROGRAMMES

Chronic Respiratory Diseases
Diffuse Respiratory Diseases
Infectious Respiratory Diseases

GROUP MEMBERS

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Associated members: Callejo Arranz, María | Cogolludo Torralba, Ángel Luis | Mondejar Parreño, Gema | Morales Cano, Daniel | Pandolfi, Rachele

Main lines of research

- Pulmonary hypertension is a condition characterized by increased pulmonary vascular resistance with a complex and not well characterized pathophysiology. Our interest is mainly focused on the mechanisms involved in pulmonary vasodilation and inhibition of cell proliferation in order to identify and design new drugs that are potentially useful in the treatment of pulmonary hypertension.
- Acute lung injury (ALI) or its more severe form, acute respiratory distress syndrome (ARDS) is characterized by pulmonary edema and alveolar collapse leading to severe arterial hypoxemia. Although the protective ventilatory support strategies have improved the prognosis of patients, the associated mortality remains unacceptably high. Our interest is to characterizie the pulmonary vascular inflammatory response associated with acute lung injury and the identification of therapeutic targets to improve prognosis in these patients.
- Our research work is focused in analyzing different signaling pathways involved in these pathologies: 1) Sphingolipids, components of the plasma membrane of all eukaryotic cells whose hydrolysis products (ceramides and sphingosine) play a key role in various signal transduction pathways. 2) Innate immunity receptors and danger-associated molecular patterns. 3) microRNAs

Most relevant scientific articles

- Pandolfi R., Barreira B., Moreno E., Lara-Acedo V., Morales-Cano D., Martinez-Ramas A. et al. Role of acid sphingomyelinase and IL-6 as mediators of endotoxin-induced pulmonary vascular dysfunction. Thorax. 2016.
- Morales-Cano D, Moreno L, Barreira B, Briones AM, Pandolfi R, Moral-Sanz J et al. Activation of PPARβ/δ prevents hyperglycaemia-induced impairment of Kv7 channels and cAMP-mediated relaxation in rat coronary arteries.Clinical science (London, England : 1979). 2016;130(20):1823-36.
- Chamorro V., Pandolfi R., Moreno L., Barreira B., Martinez-Ramas A., Morales-Cano D. et al. Effects of quercetin in a rat model of hemorrhagic traumatic shock and reperfusion. Molecules. 2016;21(12).
- Labrousse-Arias D., Castillo-Gonzalez R., Rogers N.M., Torres-Capelli M., Barreira B., Aragones J. et al. HIF-2α-mediated induction of pulmonary thrombospondin-1 contributes to hypoxia-driven vascular remodelling and vasoconstriction. Cardiovascular Research. 2016;109(1):115-130.
- Toral M., Romero M., Jimenez R., Robles-Vera I., Tamargo J., Martinez M.C. et al. Role of UCP2 in the protective effects of PPARβ/δ activation on lipopolysaccharide-induced endothelial dysfunction. Biochemical Pharmacology. 2016;110-111:25-36.

Highlights

PROJECTS

- SAF2016-77222-R - Vitamina D en la Hipertensión Pulmonar Plan Nacional. Convocatoria Retos. 30-12-16/29-12-19.
- PI15/01100 Potencial terapéutico de los exosomas derivados de las células mesenquimales y las células endoteliales progenitoras tardías en displasia broncopulmonar e hipertensión pulmonar. ISCIII. 01/01/2016-31/12/2018.
- SAF2014-55399-R MicroRnas implicados en disfunción vascular pulmonar: implicaciones fisiopatológicas y terapéuticas. Convocatoria Retos. 01/01/2015-31/12/2017.
- Beca Actelion 2016. Déficit de vitamina D en los pacientes con hipertensión pulmonar arterial y potencial valor terapéutico de la vitamina D como inhibidor de la proliferación de las células de músculo liso vascular arterial pulmonar. Fundación contra la Hipertensión pulmonar.
- European Consortium on BPD translational research (Spain; UK; Netherlands, Italy, Portugal).

THESIS

- Yeni Rojas Vega. Efecto de la descontaminación digestiva selectiva sobre el daño pulmonar inducido por la ventilación mecánica. JA Lorente/F Pérez Vizcaíno. Universidad Complutense de Madrid. 2016.
- Saskia Van Sterren. Oxygen homeostasis and oxidative stress in ductus arteriosus: studies in the chicken embryo model. Ángel Cogolludo Torralba / Eduardo Villamor. Universidad de Maastricht. 2016.
- Daniel Morales Cano. Vasodilatadores en la Hipertensión Pulmonar: Selectividad por el territorio vascular, por oxígeno y efectos antiproliferativos. F. Pérez Vizcaíno/Á. Cogolludo. 2016.
- Rob Moonen. Ethiopathogenesis of necrotizing enterocolitis. Universidad de Maastricht. 2016. LJ Zimmermann/F. Pérez Vizcaíno/BW Krammer/E Villamor

HUMAN RESOURCES

- Predoctoral felowship. María Callejo. Universidad Complutense de Madrid. 2016-2019.
- Contract “garantía juvenil” Comunidad de Madrid. Gema Mondejar. 2016-17.
- Research training grant: Beca iniciación a la investigación CIBERES. Sergio Esquivel 2016-17.
- Full professorship. Francisco Pérez Vizcaíno. Universidad Complutense. 2016.

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PROGRAMMES

Chronic Respiratory Diseases

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Main lines of research

- Mechanism underlying to genesis and evolution of asthma.
- Biomarkers and asthma phenotypes characterization:miRNAs.
- Characterization of asthma severity and identification of the factors that are involved in asthma severity.
- New therapies in asthma.
- Eosinophils.
- Exosomes and asthma.
- Occupational asthma.

Most relevant scientific articles

- Papi A., Price D., Sastre J., Kaiser K., Lomax M., McIver T. et al. Efficacy of fluticasone propionate/formoterol fumarate in the treatment of asthma: A pooled analysis. Respiratory Medicine. 2016;109(2):208-217.
- Bobolea I., Barranco P., Del Pozo V., Romero D., Sanz V., Lopez-Carrasco V. et al. Sputum periostin in patients with different severe asthma phenotypes. Allergy: European Journal of Allergy and Clinical Immunology. 2016;70(5):540-546.
- Yucesoy B., Kissling G.E., Johnson V.J., Lummus Z.L., Gautrin D., Cartier A. et al. N-Acetyltransferase 2 genotypes are associated with diisocyanate-induced asthma. Journal of Occupational and Environmental Medicine. 2016;57(12):1331-1336.
- Quirce S., Vandenplas O., Campo P., Cruz M.J., de Blay F., Koschel D. et al. Occupational hypersensitivity pneumonitis: An EAACI position paper. Allergy: European Journal of Allergy and Clinical Immunology. 2016.
- Uriarte S.A., Sastre J.. Clinical relevance of molecular diagnosis in pet allergy. Allergy: European Journal of Allergy and Clinical Immunology. 2016.

Highlights

During 2016 we have been working on the project “Exosomas and miRNAs in asthma: biomarkers of phenotypes and / or endotypes and possible therapeutic tools” describing a serum miRNA that possibly serves as a diagnosis for asthma. This miRNA is under study of patentability having aroused the interest of a biotech company. In addition, more than 200 patients have been registeres in the MEGA database of asthmatic patients, with corresponding storage of samples.

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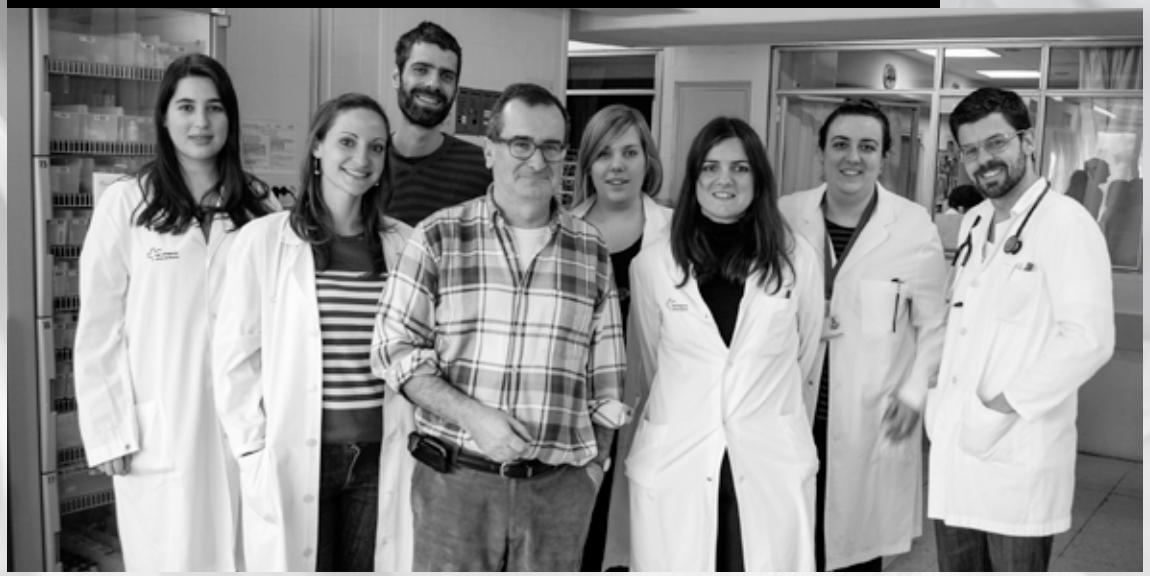
PROGRAMMES

Infectious Respiratory Diseases



GROUP MEMBERS

Staff members: Moyano Barbero, Silvia

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Contributors: Mazo Torre, Cristopher

Main lines of research

- Etiology, pathogenesis and treatment of pneumonia associated with mechanical ventilation.
- Eitology, pathogenesis and treatment of Chronic Obstructive Pulmonar Disease (COPD).
- Use of antimicrobials in Intensive Care Units.
- Serious community-acquired pneumonia: diagnosis, treatment and prevention.
- Non-invasive mechanical ventilation.
- Sepsis in the critical patient.
- Lung transplant.

Most relevant scientific articles

- Papazian L., Corley A., Hess D., Fraser J.F., Frat J.-P., Guitton C. et al. Use of high-flow nasal cannula oxygenation in ICU adults: a narrative review. Intensive Care Medicine. 2016;1-14.
- Martin-Loeches I, J Schultz M, Vincent JL, Alvarez-Lerma F, Bos LD, Solé-Violán J et al. Increased incidence of co-infection in critically ill patients with influenza.Intensive care medicine. 2016.
- Blot S.I., Rello J., Koulenti D. The value of polyurethane-cuffed endotracheal tubes to reduce microaspiration and intubation-related pneumonia: A systematic review of laboratory and clinical studies. Critical Care. 2016;20(1).
- Lujan M., Gallego M. Editorial Commentary: Pneumococcal Vaccination: Should We Kill the Enemy or Just Disarm It?. Clinical Infectious Diseases. 2016;62(2):148-149.
- Sole-Lleonart C., Roberts J.A., Chastre J., Poulakou G., Palmer L.B., Blot S. et al. Global survey on nebulization of antimicrobial agents in mechanically ventilated patients: A call for international guidelines. Clinical Microbiology and Infection. 2016;22(4):359-364.

Highlights

The group has reported two European Society Clinical Microbiology Infecdtious Diseases Position Papers on severe complications requiring ICU admission in travellers, generating tranfer of knowledge, endorsed by the European Society of Clinical Microbiology. A SR & MA on aerosolized antibiotics was concluded, with two seminal publications (Clin Microbiol Infect & Resp Care), in collaboration with Epidemiology CIBER & Cochrane Foundation being part of the PCI Pneumonia WP5. Collabaoration with IMI- Europena COmission Programme is part of the Internacionalization. We have been invited to lead an international task force for an institutional docuemnt on sepsis management. The International Journal of Infectious Disease Editor has requested a document to fix the “Research Agenda on Ventilator-associated pneumonia”
Some RCT on antibiotiocs have been performed and reported, enclosing a phase II RCT on a vaccine with nosocomial indication. This trial and the activity on personalized medicine had meda impact (enclosing CIBERES Web: http://www.ciberes.org/noticias/nueva-estrategia-para-prevenir-con-vacunas-las-infecciones-respiratorias-de-adquisicion-hospitalaria y http://www.ciberes.org/noticias/medicina-personalizada-en-pacientes-con-gripe). Three doctoral thesis were read and 8 are ongoing. One post-doct stage (J. Riera) has been done in Hannover (T Welte) to improve research skills on ECMO and Lung Transplant. We get a positive evaluation to get a post-doct from Marie Curie Programme re-incorporated to Spain. Eight additional thesis were ongoing (three with International Mention Doctor, with stages in University of Toronto, Liverpool, and Mexico). For second year, we directed a module of the VHIR translational Master.
Multicenter study of prevalence of asynchronies in chronic home ventilation, with a semiautomated diagnostic platform is ongoing. We requested a research grant to AGAUR from CIBERES. We get, with collaboration of a Rio Hortega fellow, a SEPAR grant, for an innovation of biomarkers in respiratory infections.

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Group website

PROGRAMMES

Chronic Respiratory Diseases
Diffuse Respiratory Diseases

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Main lines of research

The group is integrated in the Advanced Imaging Unit (AIU) that was established in the Spanish National Centre for Cardiovascular Imaging in early 2012. It is a multidisciplinary group focused in developing new imaging applications and molecular imaging developments that will expand the molecular and cellular knowledge of the different cardiovascular and pulmonary diseases. With this aim our research is focused on 1) Cardiovascular and Pulmonary Imaging 2) Nanomedicine and radiochemistry and 3) Metabolomics. The group offers the scientific community state of the art imaging technologies including five modalities: MRI, X-ray CT, nuclear imaging (PET), ultrasound (echocardiography) and optical (bi and tri-dimensional luminescence and fluorescence). In the field of Nanomedicine the group encompasses a nanotechnology and organic chemistry laboratory in which we develop new nanoparticles, molecular probes and biofunctionalization techniques for the diagnosis and treatment of different cardiovascular and pulmonary diseases. Currently our group produces multifunctional nanoparticles for all imaging techniques available at our institution, like Iron Oxide, liposomes, Up-converting Nanophosphors and Gold Nanoparticles, all of them functionalized with different cardiovascular and pulmonary biomarkers. Additionally, a new 68Ga (and from beginning of 2014) 89Zr radiochemistry laboratory is fully operative to provide specific

PET radiotracers for nuclear imaging. Finally, the group also has a long experience in the application of metabolic analysis to the study of different pathologies, by the use of Magnetic Resonance Spectroscopy and Mass Spectrometry and different statistical tools developed within the group. Our research projects range from technical developments and chemistry advances to in vitro studies and tracking biological processes in vivo.

Most relevant scientific articles

- Santos A., Rivas E., Rodriguez-Roisin R., Sanchez M., Ruiz-Cabello J., Arismendi E. et al. Lung Tissue Volume is Elevated in Obesity and Reduced by Bariatric Surgery. Obesity Surgery. 2016;1-8.
- Perez-Medina C., Abdel-Atti D., Tang J., Zhao Y., Fayad Z.A., Lewis J.S. et al. Nanoreporter PET predicts the efficacy of anti-cancer nanotherapy. Nature Communications. 2016;7.
- Latorre-Pellicer A., Moreno-Loshuertos R., Lechuga-Vieco A.V., Sanchez-Cabo F., Torroja C., Acin-Perez R. et al. Mitochondrial and nuclear DNA matching shapes metabolism and healthy ageing. Nature. 2016;535(7613):561-565.
- Bujak R., Mateo J., Blanco I., Izquierdo-Garcia J.L., Dudzik D., Markuszewski M.J. et al. New biochemical insights into the mechanisms of pulmonary arterial hypertension in humans. PLoS ONE. 2016;11(8).
- Chamorro V., Pandolfi R., Moreno L., Barreira B., Martinez-Ramas A., Morales-Cano D. et al. Effects of quercetin in a rat model of hemorrhagic traumatic shock and reperfusion. Molecules. 2016;21(12).

Highlights

The group participates in a project funded by the Foundation Against Pulmonary Hypertension “Beca Actelion” presented and obtained by Dr. Pérez Vizcaino as Principal Investigator. During this year 2016, we have obtained another initiative joint project with other members of Ciberes, such as the project awarded by the Department of Health of the Government of Navarra obtained from Dr. Junkal Garmendia García.
The different research members that constitutes the group 31 have obtained two more projects in 2016, funded respectively by the Carlos III Health Institute (PI-DTS-2016-0059) within the technological innovation program and another from the Ministry of Economy and Competitiveness (SAF2016- 79593-P).
We have presented different proposals to the H2020 framework, e.g. an ERA-NET (Euronanomed) as coordinators and to a ERC-Advanced program. Finally, in collaboration with the group of Dr. Germán Peces-Barba and a group from the Massachusetts General Hospital of Boston we have presented a joint initiative to the ROI call from the USA National Institutes of Health.
From the technological aspects of our research, we have filed for an European patent for methodology of erythrocyte labeling as a Positron Emission Tomography (PET)-based diagnostic tool with special relevance in the field of pulmonary hypertension and respiratory distress.

LEAD RESEARCHER

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Group website

PROGRAMMES

Chronic Respiratory Diseases

GROUP MEMBERS

Staff members: Aguilera Xiol, Elisabet | Fernández Barat, Laia | Li Bassi Li Bassi, Gianluigi | Motos Galera, Ana | Sancho Roset, Elisabeth

Associated members: Agustí García Navarro, Carlos | Almirall Pujol, Jorge | Badia Jobal, Juan Ramón | Bello Dronda, Salvador | Bodi Saera, María Amparo | Falguera Sacrest, Miquel | Ferrer Monreal, Miguel | Guerrero Molina, Laura | Huerta, Arturo | Martínez Olondris, Pilar | Menéndez Villanueva, Rosario | Ramírez Galleymore, Paula | Rodríguez Oviedo, Alejandro | Sellares Torres, Jacobo | Sirvent Calvera, José María | Soler Porcar, Néstor | Soy Muner, Dolores

Main lines of research

- Animal Model
- Community-acquired pneumonia (CAP)
- Bronchiectasis non-associated to Cystic Fibrosis (BQ-noFQ), Cystic Fibrosis (CF) and immune deficiencies
- Exacerbations of Chronic Obstructive Pulmonary Disease (COPD)
- Ventilator associated-pneumonia

Most relevant scientific articles

- Torres A., Ranzani O.T., Ferrer M. Pneumonia in 2016: towards better care. The Lancet Respiratory Medicine. 2016;4(12):949-951.
- Cilloniz C., Torres A., Niederman M., van der Eerden M., Chalmers J., Welte T. et al. Community-acquired pneumonia related to intracellular pathogens. Intensive Care Medicine. 2016;1-13.
- Torres A., Lee N., Cilloniz C., Vila J., Van Der Eerden M. Laboratory diagnosis of pneumonia in the molecular age. European Respiratory Journal. 2016;48(6):1764-1778.
- Amaro R., Liapikou A., Cilloniz C., Gabarrus A., Marco F., Sellares J. et al. Predictive and prognostic factors in patients with blood-culture-positive community-acquired pneumococcal pneumonia. European Respiratory Journal. 2016;48(3):797-807.
- Liapikou A., Cilloniz C., Gabarrus A., Amaro R., De La Bellacasa J.P., Mensa J. et al. Multilobar bilateral and unilateral chest radiograph involvement: Implications for prognosis in hospitalised communityacquired pneumonia. European Respiratory Journal. 2016;48(1):257-261.

Highlights

Following you will find the official projects and European Projects granted or existing in the year 2016:

- Proyecto FIS: Eficacia y caracterización de los efectos de los corticosteroides asociados a antibióticos en un modelo animal de neumonia grave por Streptococcus pneumoniae. PI15/00506. Período: 2015-2017. IP: Antoni Torres
- Proyecto FIS.: Incidencia de las agudizaciones de la EPOC y factores asociados al fenotipo agudizador. Estudio de base poblacional. PI15/01059. Periódo: 2015-2017. IP: Jordi Almirall
- Proyecto FIS: Biomarcadores inflamatorios y cardíacos como predictores de eventos cardiovasculares y mortalidad tras el alta en la neumonía adquirida en la comunidad" referencia PI13/00586. Periódo: 2013-2016. IP: Rosario Menéndez.
- Proyecto Europeo: Academic Partners of COMBACTE. IMI12_8TH_2STG_01.Periódo: 2013-2019 Categoría Partners. IP: Antoni Tores.
- Proyecto Europeo: Combatting Bacterial Resistance in Europe - Molecules Against Gram Negative Infections. (COMBACTE-MAGNET). CE_IMI13_11th_2stg. Periódo: 2015-2021. IP: Antoni Torres
- Proyecto Europeo: Antivirals for influenza-Like Illnes? An rCt of clinical and Cost effectiveness in primary CarE (ALIC'E) (PREPARE). Periódo: 2016-2018. IP: Antoni Torres

LEAD RESEARCHER

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Group website

PROGRAMMES

Diffuse Respiratory Diseases

GROUP MEMBERS

Staff members: García Laorden, María Isabel | Ramos Nuez, Ángela María

Associated members: Blanco Varela, Jesús | Corrales Moreno, Almudena | Del Pino Yanes, María del Mar | Flores Infante, Carlos Alberto | Pérez Méndez, Lina Inmaculada | Valladares Parrilla, Francisco

Main lines of research

- Epidemiology and Stratification of the Acute Respiratory Distress Syndrome (ARDS).
- Genetic Susceptibility to the Acute Respiratory Distress Syndrome.
- Ventilator-Induced Lung Injury (VILI).
- Cellular and Molecular Mechanisms of Lung Repair.
- Searching for common genetic activation and signalling pathways among ARDS, Asthma and Pulmonary Fibrosis.
- Genomic Medicine.

Most relevant scientific articles

- Villar J, Ambrós A, Soler JA, Martínez D, Ferrando C, Solano R et al. Age, PaO2/FIO2, and Plateau Pressure Score: A Proposal for a Simple Outcome Score in Patients With the Acute Respiratory Distress Syndrome.Critical care medicine. 2016;44(7):1361-9.
- Kacmarek R.M., Villar J., Sulemanji D., Montiel R., Ferrando C., Blanco J. et al. Open lung approach for the acute respiratory distress syndrome: A pilot, randomized controlled trial. Critical Care Medicine. 2016;44(1):32-42.
- Hernandez-Pacheco N., Flores C., Oh S.S., Burchard E.G., Pino-Yanes M. What Ancestry Can Tell Us About the Genetic Origins of Inter-Ethnic Differences in Asthma Expression. Current Allergy and Asthma Reports. 2016;16(8).
- Barreto-Luis A, Pino-Yanes M, Corrales A, Campo P, Callero A, Acosta-Herrera M et al. Genome-wide association study in Spanish identifies ADAM metallopeptidase with thrombospondin type 1 motif, 9 (ADAMTS9), as a novel asthma susceptibility gene.The Journal of allergy and clinical immunology. 2016.
- Slutsky A.S., Villar J., Pesenti A.. Happy 50th birthday ARDS! Intensive Care Medicine. 2016;1-3.

Highlights

PROJECTS

- PI13/0119: NAVA en pacientes con insuficiencia respiratoria. IP: Jesús Villar. / PI2012-FMM: Dexametasona en pacientes con ARDS. IP: Jesús Villar / REB11-024: Practice Variation in Discontinuing Mechanical Ventilation. Ministry of Research, Canada. Co-IP: Jesús Villar / PI14-00844: Susceptibilidad genética y microbioma en SDRA. IP: Carlos Flores. / AC15/00015: Systems pharmacology approach to difficult-to-treat pediatric asthma. Ministerio Economía-ISCIII. IP: Mª Mar Pino-Yanes. / ERACoSysMed 99: Systems pharmacology approach to difficult-to-treat pediatric asthma. ERA-Net ERACoSysMed, Horizon 2020. co-IP: Mª Mar Pino-Yanes. / PI16/0049: Descubriendo respuestas a tres cuestiones sin resolver en pacientes con SDRA: una iniciativa de medicina de precisión. IP: Jesús Villar. / 5P60MD006902-03: Genetics of Asthma and Obesity Using Admixture Mapping in Latinos. NIH. Co-IP: Mª Mar Pino-Yanes. / 1R01HL117004-01: Pharmacogenomics of Bronchodilator Response in Minority Children with Asthma. NIH. Co-IP: Mª Mar Pino-Yanes. / R01HL130796: Architectural Structure and Regulation of TOLLIP in IPF. NIH. Co-IP: Carlos Flores. / FDN143285: Mechanisms and Therapies of ARDS. Canadian Institutes Health Research. co-IP: Jesus Villar

RESEARCH PERSONNEL CONTRACTS

- FI12/00493: Predoctoral Training. / CD13/00304: Post- Doctoral Sara Borrel. / RYC-2015-17205: Ramón y Cajal contract. / FI16/00136: Predoctoral Training. / TESIS2015010057: Predoctoral training, Agencia Canaria de Investigación. / Expediente 11608852: Collaboration Grant, Ministry of Education. / Expediente: 13181420: Collaboration Grant, Ministry of Education.

PATENTS

- Invention Patent ES2408281 24/04/2014, P201131785 / Invention Patent ES2481990 29/09/2015, P201232075 / Patent application P201531475 “Methods to determine geographical ancestry”.

OTHERS:

- Jesus Villar: Peer-reviewer: New England Journal of Medicine, American Journal Respiratory and Critical Care Medicine, Critical Care Medicine, Intensive Care Medicine, Critical Care, Thorax
- Jesus Villar: Editorial Board: Intensive Care Monitor, Critical Care.
- Carlos Flores: Editorial Board: Pulmonology, Clinical Antiallergy antiinflamatory & Drugs
- Carlos Flores: Implementation of Genomics Division, Instituto Tecnológico y de Energías Renovables, Tenerife.

Linked group

José Luis López-Campos Bodineau

Lung Cancer and COPD Scientific programme

Hospital Virgen del Rocío, Sevilla

GROUP MEMBERS:

Emilia Barrot Cortés | Carmen Calero Acuña | Miriam Echevarría Irusta | Ana Montes Worboys | Nicolás Moreno Mata | Francisco Ortega Ruiz | Patricia Ortega Sáenz | Remedios Otero Candelera | Esther Quintana Gallego | Francisco Rodriguez Panadero | José Antonio Rodríguez Portal.

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