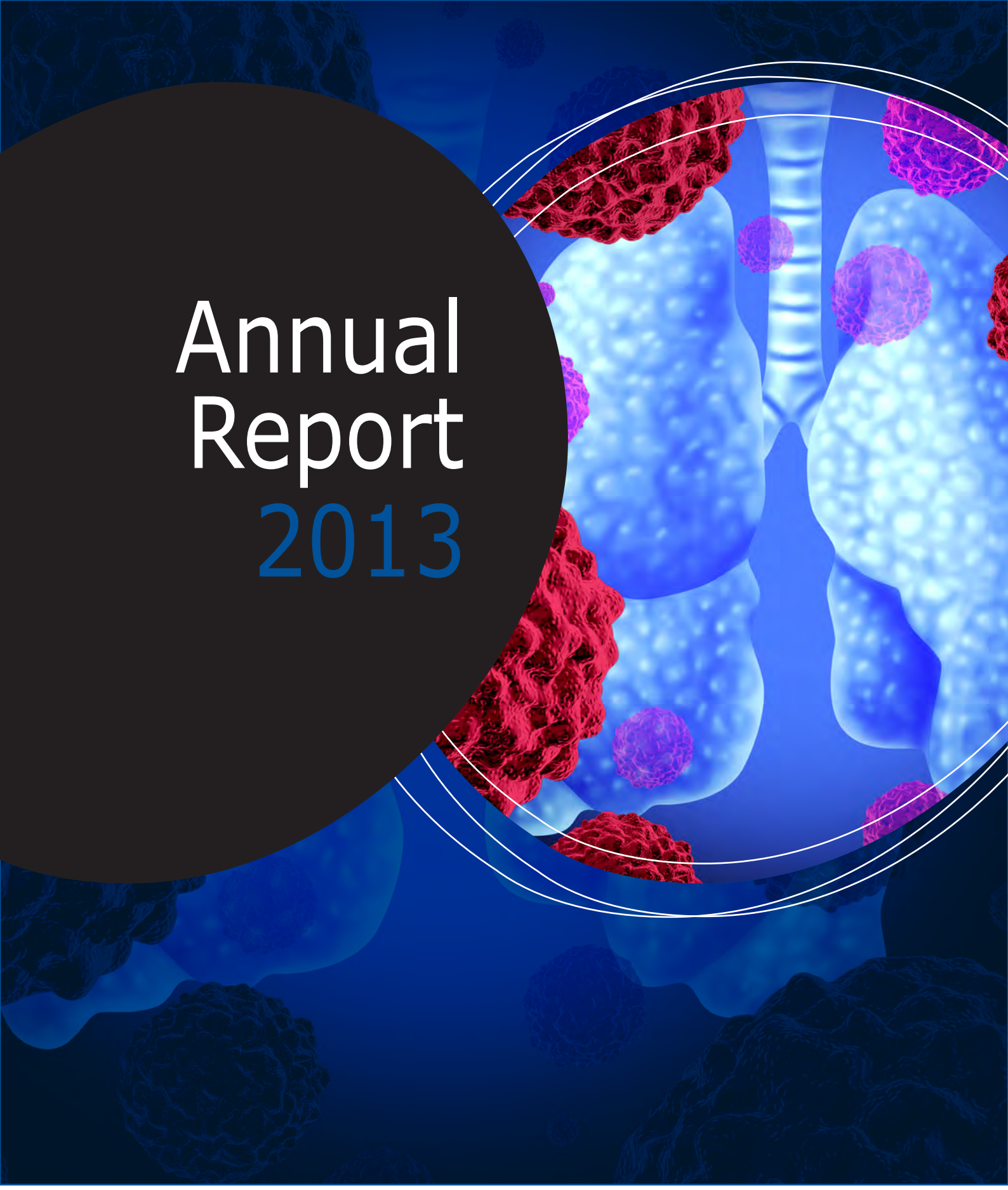


Annual Report 2013

ciberes

Centro de Investigación Biomédica en Red

Enfermedades Respiratorias

INDEX

1 Organization

Letter from the Scientific Director

It is my pleasure to present yet another year, making that eight, the Annual Report of the CIBER de Enfermedades Respiratorias (NBRC on Respiratory Diseases) corresponding to the year 2013, showing the lines of research and objectives of each of the strategic research programmes, the scientific activity carried out by the groups making up the centre, in addition to the actions and objectives of the transversal platforms for supporting research in said fiscal year.

The strategic projects started by the CIBERES corporate research programmes and favorably evaluated by an external committee were consolidated in 2013.

We are following our goal of continuing to be a competitive research centre in the field of respiratory diseases on both a national and international level. In fact, according to the 2013 Scimago Institution Ranking (SIR), CIBERES improved with respect to some of its primary scientific indicators, such as International Collaboration (scientific production of an institution produced in collaboration with foreign institutions) and High-Quality Publications (percentage of publications of an institution in journals in the first quartile of their category). We also maintained a Standardized Impact Factor above 2, specifically 2.15 in 2013, which means that CIBERES is mentioned 50% more than the worldwide average for institutions. I would also like to point out that, among other milestones, the CIBERES Pulmonary Biobank Platform was recognized as a member of the new national structure called "National Biobank Network Platform" in the 2013-2016 Strategic Action in Health call for proposals.

Finally, I would like to take this opportunity to thank you for your collaboration in carrying out our research activity and bid farewell to Scientific Management. After 8 years in charge, I feel the time has come for someone else to take over. I informed Management at the Instituto de Salud Carlos III (ISCiii), and they were sensitive to my request and appointed Dr. Ferran Barbé (Lérida) as the new director. Knowing Dr. Ferran like I do (after all, we worked together in Mallorca for 15 years), I am sure that he will make a wonderful director and with him, CIBERES will reach new levels of excellence in international respiratory science.

It has been a real privilege for me to be in charge of CIBERES for these eight years, and I want to thank you all for your collaboration, loyalty and daily work. At this point, however, I would like to especially thank those people I have worked with the most and without whom CIBERES would not have been the same. First, Paco Pozo, whose dedication, contribution, generosity and vision were absolutely essential. I would like to thank Paloma Vaquer, who I hope returns soon, for her brilliant work at the head of the CIBERES Office from the start. And of course I could not forget Javier Muñoz, an outstanding Scientific Manager; thanks Javier! Finally, Cristina Casals and Joaquin Gea (on behalf of all those who worked on the Steering Committee) thank you for your help, sincerity and spirit of collaboration. Like I said, it has been a real privilege and honor to lead this extraordinary enterprise. Nonetheless, I will continue working as an investigator in CIBERES, so you won't be getting rid of me that easily! Best wishes to everyone!

Àlvar Agustí García-Navarro
Scientific Director

Introduction

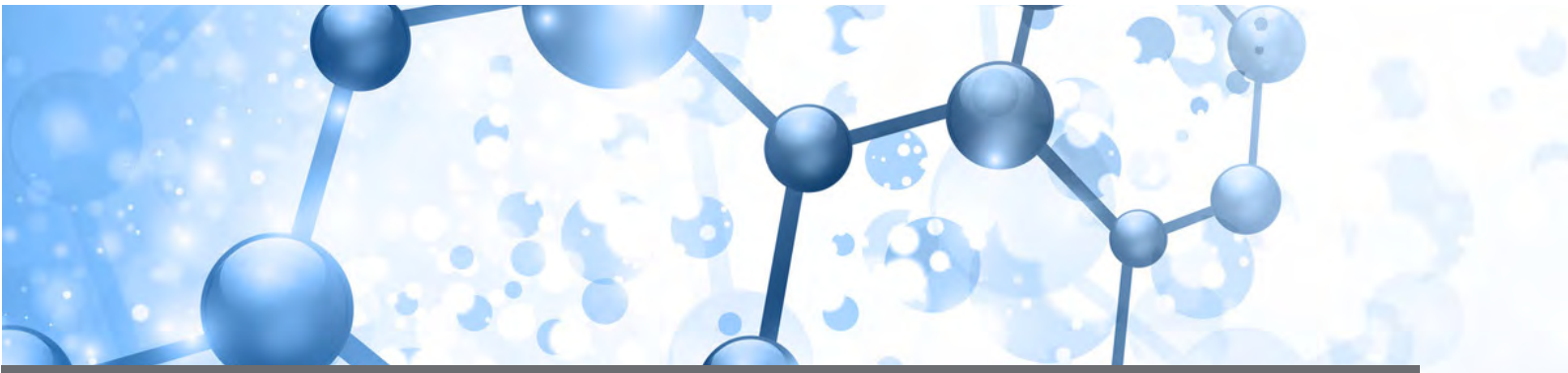
This purpose of this report is to present updated information about the structure and scientific activity of CIBERES in 2013, as well as the resources used and results obtained.

2013 entailed progress in the development of Corporate Research Programmes (CRPs) and transversal platforms, and it has made CIBERES a competitive research centre in the field of respiratory diseases on both national and international level.

CRPs have been focusing on specific respiratory pathologies with a high prevalence, morbi-mortality and high public health care cost and are the tools making up the backbone of the CIBERES's multicentre and multidisciplinary projects.

In 2013 the Strategic Projects (SPs) of the CRPs entered the developmental stage after having been evaluated by the Agencia Nacional de Evaluación y Prospectiva (National Agency of Evaluation and Planning- ANEP) and by the External Scientific Advisory Committee. The development of said SPs will focus on the work of the CIBERES until 2015 and will be evaluated every year by independent experts.

The work done and effort made by CIBERES staff, comprising almost 450 professionals with a multidisciplinary profile, who carried out clinical, basic and translational research, to face the challenge raised by respiratory diseases and to move forward in their research, is clearly reflected in this report.



List of Groups and Institutions

After the Resolution of July 28, 2006, whereby the ISCIII approved the initial list of applicants expressing interest (27 initial groups, 26 groups now resulting from the withdrawal of a group), and the Resolution of March 21, 2007 for incorporating new groups (7 groups), CIBERES was constituted in 2008 with 33 research groups. Subsequently, to execute the ISCIII call for proposals of March 12, 2008, in fiscal year 2009 a new research group joined CIBERES, which was then make up of a total of 34 research groups.

A clinical group joined in 2011 by means of an association agreement approved by the Board of Trustees in December 2011.

There was no increase or decrease in the number of groups forming the CIBERES in 2013.

Therefore, as of December 31, 2013 CIBERES is made up of 34 full member research groups incorporated through the official ISCIII call for proposals and 1 associated group.

Said groups bring together over 450 investigators, pneumolgists, technicians and other specialists from universities, health and research centres carrying out the clinical, basic and translational research of the networking centre.

These 34+1 groups are geographically distributed according to the information contained in the following table.

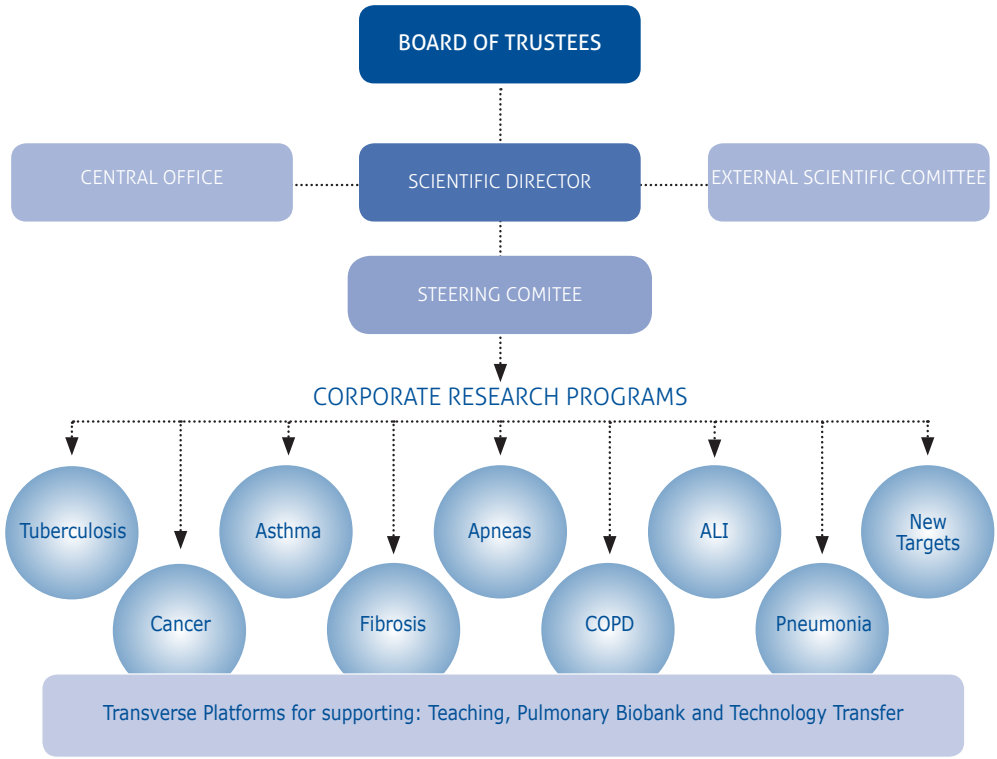
Autonomous Communities	Type of institution			TOTAL	%
	Research Centre	Hospital	University		
Aragon	-	-	1	1	2,9%
Balearic Islands	2	-	-	2	5,7%
Castile-Leon	-	-	1	1	2,9%
Catalonia	1	11	1	13	37,1%
Extremadura	-	1	-	1	2,9%
Gran Canaria	-	1	-	1	2,9%
Madrid	6	5	2	13	37,1%
Basque Country	-	1	-	1	2,9%
Valencia	-	-	1	1	2,9%
Andalusia	-	1	-	1	2,9%
TOTAL	9	20	6	34	100,0%

The following table shows the updated list of 34+1 groups forming CIBERES as of December 31, 2013:

Principal Investigator	Work Centre/Institution	Institution type	City / Auton. Community	Year
Casals Carro Cristina	Univ. Complutense de Madrid. School of Biology	University	Madrid/Madrid	2006
García López, Ernesto	Centro de Investigaciones Biológicas/CSIC	Research Cent.	Madrid/Madrid	2006
Gzlez. de la Campa, Adela	Centro Nacional de Microbiología/ISCIII	Research Cent.	Majadahonda/Madrid	2006
González Mangado, Nicolás	Fundación Jiménez Díaz-CAPIO. Respiratory Medicine Department/IISFJD	Hospital	Madrid/Madrid	2006
Picado Vallés, Cesar	Hospital Clinic i Provincial. Respiratory Medicine Dept.	Hospital	Barcelona/Catalonia	2006
Barberá Mir, Joan Albert	Hospital Clinic i Provincial. Respiratory Medicine Dept.	Hospital	Barcelona/Catalonia	2006
del Pozo Adejón, Mª Victoria	Fundación Jiménez Díaz-CAPIO. Immunology Dept./IISFJD	Hospital	Madrid/Madrid	2006
Regueiro Comesaña, Verónica	Fundació d'Investigació Sanitaria de les Illes Balears (FISIB)	Research Cent.	Buñol/Balearic Islands	2006
Martín Montañés, Carlos	Universidad de Zaragoza, School of Medicine.	University	Zaragoza/Aragon	2006
Agustí García-Navarro, Alvar	Hospital Clinic i Provincial	Hospital	Barcelona/Catalonia	2006
Monserrat Canal, Josep Mª	Hospital Clinic i Provincial	Hospital	Barcelona/Catalonia	2006
Navajas Navarro, Daniel	Universidad de Barcelona, School of Medicine	University	Barcelona/Catalonia	2006
Morcillo Sánchez, Esteban J.	Universidad de Valencia, School of Medicine	University	Valencia/Valencia	2006
Torres Martí, Antoni	Hospital Clinic i Provincial. Respiratory Medicine Dept.	Hospital	Barcelona/Catalonia	2006
Masa Jiménez, Juan F.	Hsp. San Pedro de Alcántara/ FUNDESALUD	Hospital	Cáceres/Extremadura	2006
Morell Botad, Ferran	Hsp. Gral. Vall d'Hebron/Inst. Catalá de Salut	Hospital	Barcelona/Catalonia	2006
Ausina Ruiz, Vicente	Hsp. Univ. Germans Trias i Pujol/FIIHGTP	Hospital	Barcelona/Catalonia	2006
Rello Condomines, Jordi	Hsp. Gral. Vall d'Hebron/Inst. Catalá de Salut	Hospital	Barcelona/Catalonia	2006
Liñares Louzao, Josefina	Hsp. Univ. de Bellvitge/Fundación IDIBELL	Hospital	L'Hospitalet de Llobregat/ Catalonia	2006
Álvarez Martinez, Carlos	Hospital Universitario 12 de Octubre/SERMAS	Hospital	Madrid/Madrid	2006
Gea Guiral, Joaquim	Hospital del Mar-IMIM/ Consorci Mar Parc de Salut de Barcelona	Hospital	Barcelona/Catalonia	2006
Esteban de la Torre, Andrés	Hospital Universitario of Getafe/SERMAS	Hospital	Getafe/Madrid	2006
González Martínez Constancio	Universidad de Valladolid. School of Medicine	University	Valladolid/Castile-Leon	2006
Melero Fontdevila, José Antonio	Unidad de Investigación/ISCIII	Research Cent.	Majadahonda/Madrid	2006
Pérez Trallero, Emilio	Hospital Donosti. Asoc. Instituto Biodonostia	Hospital	San Sebastian/Basque Country	2006
Bouza Santiago, Emilio	Hsp. Gral. Univ. Gregorio Marañón / SERMAS	Hospital	Madrid/Madrid	2007
Pérez Vizcaino, Francisco	Univ. Compl. de Madrid. School of Medicine	University	Madrid/Madrid	2007
Villar Hernández, Jesús	Hsp. Gral. de Grana Canaria Dr. Negrin/ Servicio Canario de Salud	Hospital	Las Palmas/Canary Islands	2007
Monsó Molas, Eduard	Hsp. Univ. Germans Trias i Pujol/FIIHGTP	Hospital	Barcelona/Catalonia	2007
Ruiz-Cabello Osuna, Jesus Mª	Centro Nacional de Investigaciones Cardiovasculares (CNIC)	Research Cent.	Madrid/Madrid	2007
Ortin Montón, Juan	Centro Nacional de Biotecnología/CSIC	University	Cantoblanco/Madrid	2007
Blanch Torra, Lluis	Inst. Univ. Fundación Parc Taulí. Hospital de Sabadell. Corporación Sanitaria Parc Taulí	Hospital	Sabadell/Catalonia	2007
Menéndez Fernández, Margarita	Instituto Química Física Rocasolano/CSIC	Research Cent.	Madrid/Madrid	2007
Barbé Illa, Ferrán E.	Hsp. Univ. Arnau de Vilanova/IRB Lleida	Research Cent.	Lerida/Catalonia	2007
López-Campos, José Luis	FISEVI – Hospital Virgen del Rocío	Hospital	Seville/Andalusia	Vinc. 2011

Organizational Structure

The CIBER de Enfermedades Respiratorias organized its governing, administration and management structure in 2013 according to the following flow chart:



The Board of Trustees, presided by the Instituto de Salud Carlos III (ISCIII), is the highest governing and administration body of the Consortium, and in 2013 it represented the institutions forming the consortium.

The Steering Committee, which is responsible for the executive management of the CIBERES, is formed by the following members, once the changes occurring in 2013 have been introduced:

STEERING COMMITTEE	
POSITION	**NAME**
Scientific Director	Dr. Alvar Agustí
Deputy Scientific Director (clinical field)	Dr. Joaquín Gea
Deputy Scientific Director (basic field)	Dr. Cristina Casals
Manager	Ms. Paloma Vaquer
Teaching Coord.	Dr. JA Barberà / Dra. Ana Obeso
Severe Asthma CRP Coord.	Dr. MªVictoria del Pozo
Cancer CRP Coord.	Dr. Eduard Monsó
Pulmonary Fibrosis CRP Coord.	Dr. María Molina
New Therapeutic Targets CRP Coord.	Dr. JA Bengoechea / Dra. J. Garmendia
Acute Lung Injury CRP Coord.	Dr. Andres Esteban
Tuberculosis CRP Coord.	Dr. Vicenç Ausina
Pneumonia CRP Coord.	Dr. Antoni Torres
Sleep Apnea CRP Coord.	Dr. JM Montserrat
COPD CRP Coord.	Dr. Borja García-Cosío
Pulmonary Biobank Plat. Coord.	Dr. Germán Peces-Barba
Technology Transfer Plat. Coord.	Dr. Lluis Blanch
Scientific Programme Manager	Javier Muñoz

In October 2013, the CIBERES Steering Committee approved the appointment of Dr. Ana Obeso as Teaching Coordinator to replace Dr. Barberá.

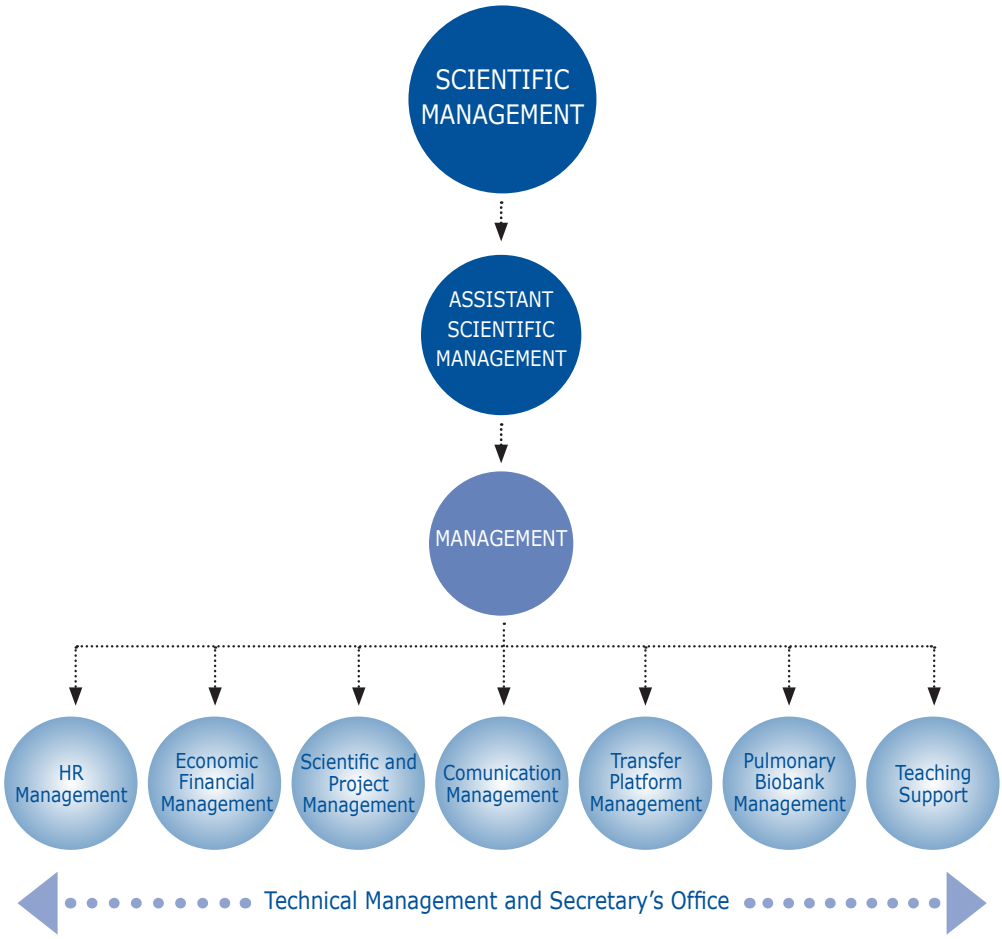
In December 2013, the CIBERES Steering Committee approved the appointment of the new coordinator of the New Therapeutic Targets CRP, Dr. Junkal Garmendia, CIBERES Group 8, Fundación de Investigación Sanitaria de las Islas Baleares (FISIB). Notification was sent to the Board of Trustees for final approval.

The External Scientific Advisory Committee (ESAC) is in charge of advising the Board of Trustees and the Steering Committee in the development of the research strategy.

The new setup of the External Scientific Advisory Committee was approved by the Board of Trustees in June 2012, and comprises top-level investigators covering all the scientific areas identified in CIBERES:

EXTERNAL SCIENTIFIC ADVISORY COMMITTEE		
AREA	**NAME**	**INSTITUTION**
COPD	Prof. B. Celli	Tufts University of Boston (EEUU)
Cancer	Prof. J.R. Jett	Mayo Clinic Rochester of Minnesota (USA)
New Therapeutic Targets	Prof. H. Klenk	Philipps-Universität Marburg (Germany)
Tuberculosis	Dr. J.C. Palomino	Univestity of Ghent (Belgium)
Fibrosis	Dra. A. Pardo	Univesidad Nacioinal Autónoma de México (México)
Sleep Apneas	Dr. J. Kimoff	McGill University of Montreal (Canada)
Pneumonia	Prof. S. Ewig	Evangelisches Krakenhaus Herne-EVK of Herne (Germany)
Acute Lung Injury	Dr. T. Thompson	Harvard Medical School, Hayward, California (USA)
Asthma	Prof. R. Polosa	Università Degli Studi di Catania (Italy)

The Central Office responsible for the proper running and management of the Entity was located in the Fundació de Investigación Sanitaria de les Illes Balears in 2013. The operating administration and management structure is as follows:



On January 23, 2012, CIBERES earned ISO 9001:2008 certification no. 108347-2011-AQ-IBE-ENAC, issued by ENAC (National Certification Entity), certifying the quality of the CIBER de Enfermedades Respiratorias management system. Said certification was renewed for fiscal year 2013.

2013 Budget

2013 BUDGET	
Total 2013 Revenues:	4.365.942,31
TOTAL resulting from previous fiscal years:	1.021.177,31
BALANCE LEFT OVER	1.021.177,31
TOTAL Revenues from public funding:	3.106.765,00
ISCIII registered funds	2.801.170,00
MICINN	18.900,00
ISCIII AES	36.695,00
European Projects	250.000,00
Other revenues	–
TOTAL Revenues from private funding:	220.000,00
Donations	–
Services	220.000,00
Agreements, awards, etc.	–
Other Revenues:	–
Revenues from bank interests	18.000,00
TOTAL 2013 Expenses:	4.415.577,21
Financial aid to other Entities	100.000,00
Staff expenses	2.702.964,80
Fungibles	320.230,10
Fixed assets	80.000,00
External collaborations	556.428,70
External services	536.077,14
Taxes	104.074,13
Other expenses	15.802,34

CIBERES staff

The average number of people hired per category in 2013 and 2012 is as follows:

Categories	Average 2013			Average 2012		
	Total	Men	Women	Total	Men	Women
Senior Investigators	17,34	3,54	13,80	18,08	5,08	13,00
Junior Investigators	24,33	7,12	17,21	28,81	6,97	21,84
Research Technicians	13,53	2,22	11,31	14,01	3,14	10,87
Support Staff	19,59	3,39	16,20	18,04	2,88	15,16
Grant Holders	4,64	0,02	4,62	5,11	0,98	4,14
Administrative Assistants	0,50	-	0,50	0,93	-	0,93
Technicians	1,98	1,00	0,98	1,95	1,00	0,95
Managers	5,00	1,00	4,00	5,27	1,46	3,81
Management	1,00	-	1,00	1,00	-	1,00
Average staff hired	87,91	18,29	69,62	93,21	21,51	71,69

The in house staff as of December 31, 2013 by group or centre of activity and category can be seen in the following table:

Fiscal year 2013					
Hired staff	Total	Men	Women	Indefinite Contract	Temporary Contract
Senior Investigator	18	5	13	8	10
Junior Investigator	28	9	19	8	20
Research Technicians	13	1	12	7	6
Support Staff	19	5	14	6	13
Grant Holders	5	-	5	-	5
Administrative Assistants	-	-	-	-	-
Technicians	2	1	1	1	1
Managers	5	1	4	4	1
Management	1	-	1	1	-
TOTAL	91	22	69	35	56

This staff as of fiscal year close includes 6 people (1 senior investigator, 2 research technicians, 2 managers and 1 technician) who left the CIBERES on December 31.

The average in house staff as of December 31, 2012 by group or centre of activity and category was the following:

Fiscal year 2012					
HIRED STAFF	**Total**	**Men**	**Women**	**Indefinite Contract**	**Temporary Contract**
Senior Investigator	17	4	13	8	9
Junior Investigator	32	8	24	7	25
Research Technicians	17	3	14	7	10
Support Staff	21	4	17	7	14
Grant Holders	4	1	3	-	4
Administrative Assistants	1	-	1	-	1
Technicians	2	1	1	1	1
Managers	5	1	4	4	1
Management	1	-	1	1	-
TOTAL	100	22	78	35	65

This staff as of fiscal year close included 11 people who left the CIBERES on December 31.

All the hired CIBERES staff is made up of non-civil service staff. The concept of civil service staff is not contemplated.

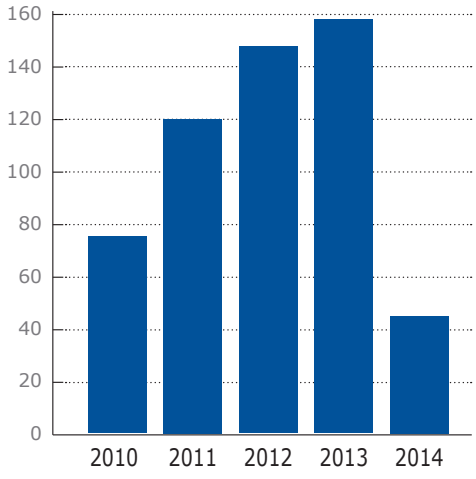
Additionally, as stated in the Bylaws, the Entity receives the support from affiliated research staff, i.e., staff from consortium institutions belonging to the CIBER, maintaining its rights and duties according to the laws that apply, and keeping the administrative and employment status they have in their institution of origin. As of December 31, 2013 there were 414 investigators affiliated with the Entity, whereas at the end of 2012 there were 399.

Scientific Production, Projects and Clinical Trials

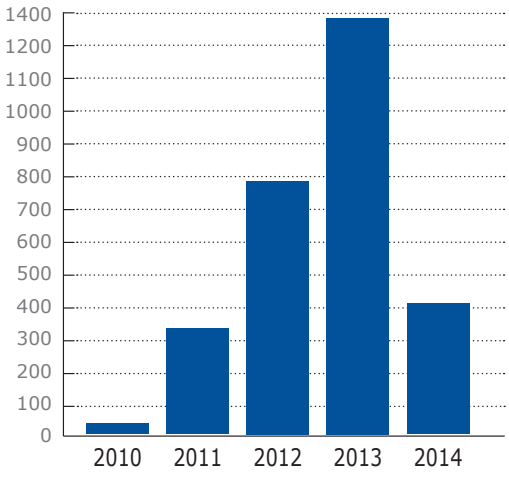
Publications

In 2013 CIBERES publication results, including only those in which CIBERES is mentioned in the author detail, remained positive and was on an upward trend. The progressive increase in publications in which reference is made to CIBERES as a centre continues, and citations thereof increase.

The graphical evolution of CIBERES publications and of their citations can be observed in the following graphs in which data from the year 2010 to May 2014 is analyzed (source Web of Science):



Publications by year



Citations by year

Both the number of citations and the h-index increased in 2013 as are summarized below:

Results found:	557
Sum of the Times Cited:	2966
Sum of Times Cited without self-citations:	2724
Citing Articles:	2577
Citing Articles without self-citations:	2429
Average Citations per Item:	5.32
h-index:	24

Taking into consideration the analysis of CIBERES publications from the time they are created up until May 2014, the distribution of the publications by subject matter, according to the Web of Science classification, is as follows:

Field: Research Areas	Record Count	% of 665
RESPIRATORY SYSTEM	176	26.466 %
GENERAL INTERNAL MEDICINE	116	17.444 %
IMMUNOLOGY	108	16.241 %
MICROBIOLOGY	96	14.436 %
ALLERGY	83	12.481 %
INFECTIOUS DISEASES	70	10.526 %
CARDIOVASCULAR SYSTEM CARDIOLOGY	35	5.263 %
SCIENCE TECHNOLOGY OTHER TOPICS	33	4.962 %
PHARMACOLOGY PHARMACY	31	4.662 %
BIOCHEMISTRY MOLECULAR BIOLOGY	28	4.211 %

It must be pointed out that according to the ICONO analysis: SCImago Institutions Ranking (SIR) (Spanish R&D&I Observatory), dependent on the Ministry of Economics and Competition, and published by the Fundación Española para la Ciencia y la Tecnología (Spanish Foundation for Science and Technology) (FECYT), in 2013 CIBERES continued in 2013 with a Standardized Impact Factor greater than 2, specifically 2.15, which means that CIBERES is mentioned above 50% more than the worldwide average for institutions. Furthermore, CIBERES improved in other indicators of this analysis, such as International Collaboration (scientific production of an institution produced in collaboration with foreign institutions) and High-Quality Publications (percentage of publications of an institution in journals in the first quartile of their category).

In summary, the CIBERES results as regards publications are very positive and on an upward trend.

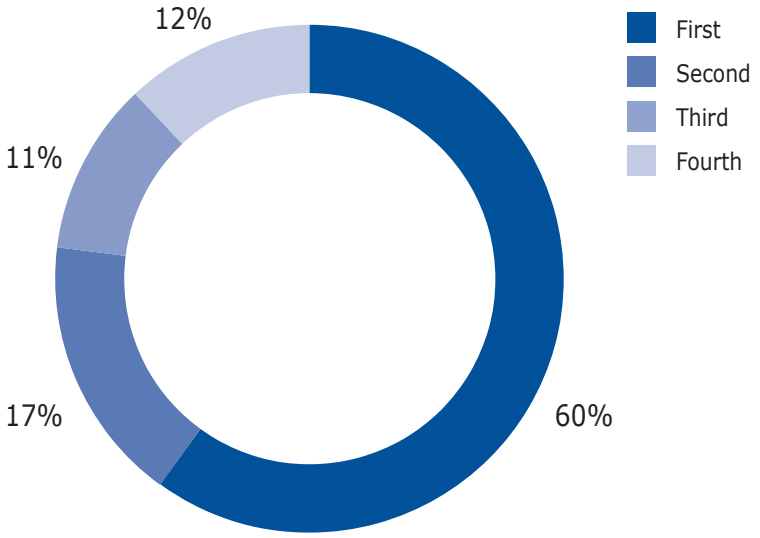
Analysis of publications by groups[1]

The scientific production reported by the groups in the CIBERES research areas during fiscal year 2013 was included in the publication of 569 articles in indexed journals with impact factor. These articles include those in which CIBERES is mentioned in the listing of authors and those in which the centre is not included in that category.

[1] The available data on the production of CIBERES groups are provisional and pending review and verification..

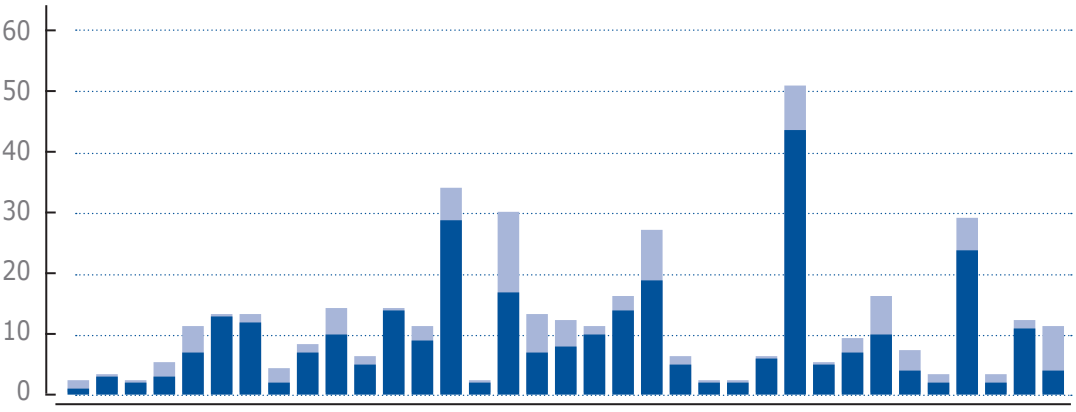
The following graph shows the percentage distribution in quartiles of all the publications, 60% of which are in the first quartile.

Publications according to quartile in 2013



The distribution of such publications in first and second quartile journals among the 34 CIBERES groups plus the associated group (V1) is as follows:

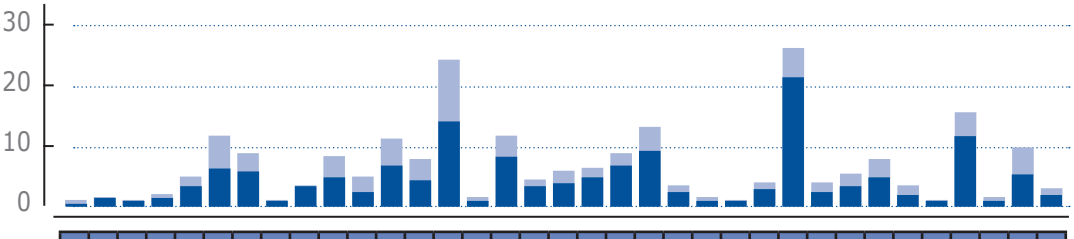
Publications by group in first and second quartile journals



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	V1
Q2	1	0	0	2	4	0	1	2	1	4	1	0	2	5	0	13	6	4	1	2	8	1	0	0	0	7	0	2	6	3	1	5	1	1	7
Q1	1	3	2	3	7	13	12	2	7	10	5	14	9	29	2	17	7	8	10	14	19	5	2	2	6	44	5	7	10	4	2	24	2	11	4

Furthermore, of the 322 publications in first quartile journals, a total of 155 (48%) are published in first decile journals and are distributed by groups as follows:

Publications by group in first decile journals between the total of first quartile journals



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	V1
D1	1	0	0	1	3	11	6	0	0	7	5	9	7	21	1	7	2	4	3	4	8	2	1	0	2	10	3	4	6	3	0	8	1	9	2
Q1	1	3	2	3	7	13	12	2	7	10	5	14	9	29	2	17	7	8	10	14	19	5	2	2	6	44	5	7	10	4	2	24	2	11	4

Projects

Analysis by CRP

The research activity of the 35 CIBERES member groups was very significant in 2013. It must be pointed out that all the groups participated in Corporate Research Programmes in force in 2013 and will participate in one or two of the 9 new CIBERES strategic projects, so a significant portion of their activity is collaborative.

In addition to the 9 massive strategic projects that started in 2013, the groups have kept 294 research projects funded by both public and private entities active.

The groups also participated in 76 other projects comprised in the 9 CIBERES Corporate Research Programmes (CRPs) according to the following distribution:

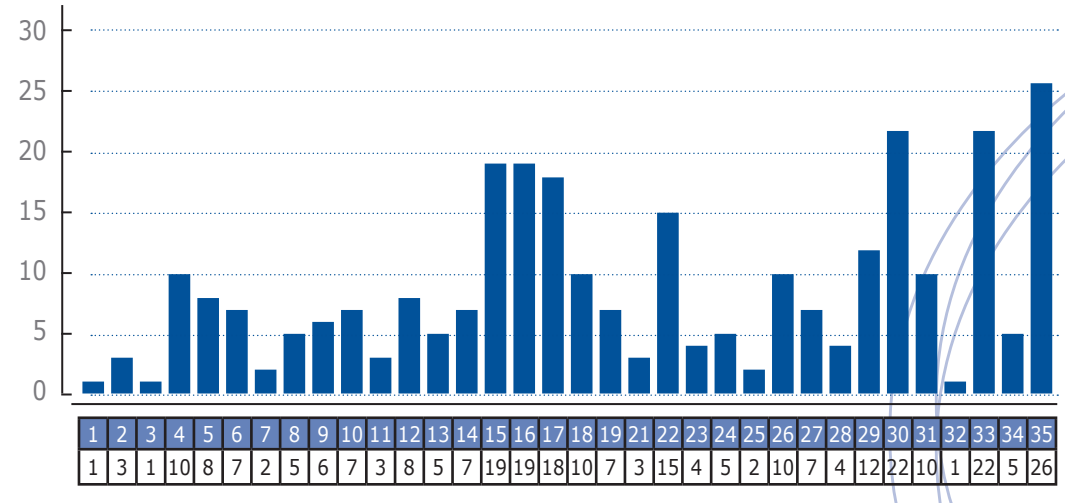
- Asthma CRP: 7 projects.
- Pulmonary Fibrosis CRP: 6 projects.
- Lung Cancer CRP: 8 projects.
- New Therapeutic Target CRP: 7 projects.
- Acute Lung Injury CRP: 8 projects.
- Tuberculosis CRP: 7 projects.
- Pneumonia CRP: 12 projects.
- Sleep Apnea CRP: 10 projects.
- Chronic Obstructive Pulmonary Disease CRP: 11 projects.

According to the internal evaluation of the CIBERES CRPs, the projects have been developed according to the expected timelines, achieving the scientific objectives and attaining the expected results.

Analysis by group

CIBERES groups kept 294 projects active in 2013. The distribution by groups is shown below:

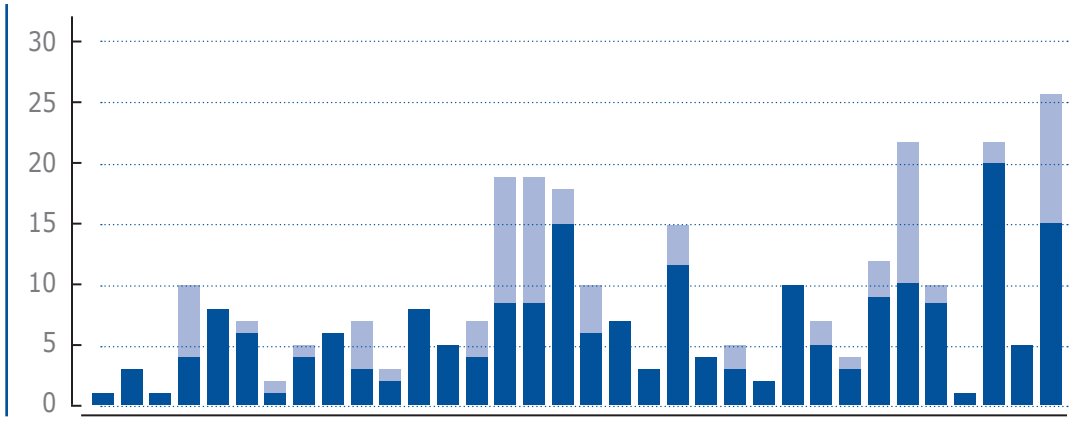
Active projects by group in 2013



The funding taken in to carry out the projects came from different spheres, such as public spheres on an international level, European level, national level, Autonomous Community level and local level, and funding has also come from the private sphere.

The following graph shows the distribution by group of projects according to their source of funding.

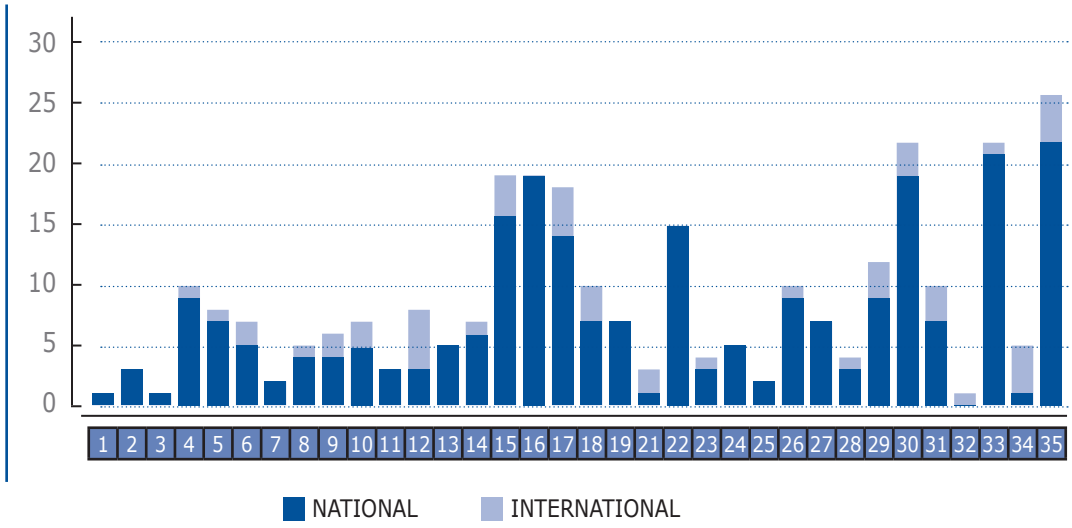
Projects with public and private funding by group



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
PRIV.	0	0	0	6	0	1	1	1	0	4	1	0	0	3	11	11	3	4	0	0	3	0	2	0	0	2	1	3	12	2	0	2	0	11
PÚB.	1	3	1	4	8	6	1	4	6	3	2	8	5	4	8	8	15	6	7	3	12	4	3	2	10	5	3	9	10	8	1	20	5	15

The participation of CIBERES groups is provided below, highlighting national projects (national, Autonomous Community and local) and international projects (European and international), and it can be seen that all the groups participate in more national projects than in international projects:

National and international projects by CIBERES groups in 2013

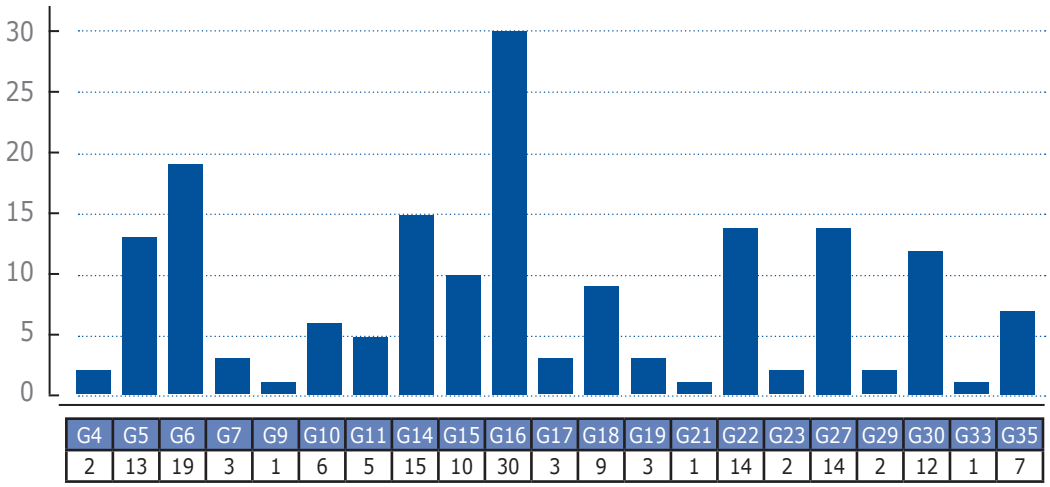


Clinical Trials

CIBERES groups participated in a total of 172 active clinical trials in 2013.

The distribution of these trials among participating groups is shown in the following graph:

Active clinical trials in 2013



G4	G5	G6	G7	G9	G10	G11	G14	G15	G16	G17	G18	G19	G21	G22	G23	G27	G29	G30	G33	G35
2	13	19	3	1	6	5	15	10	30	3	9	3	1	14	2	14	2	12	1	7

2 Corporate Research Programmes

Corporate Research Programmes (CRPs) are the corporate scientific work tool of CIBERES. Up until 2013, a CRP was defined as a collection of research PROJECTS grouped into LINES addressing a relevant health problem in the scope of respiratory diseases in a cooperative and comprehensive manner.

In 2012, under the guidance of the Scientific Council and with the support of the Centre's Scientific Management, the CRP committees made a fundamental change in the structure of CRPs and reorganized them around one strategic project per programme that started in 2013 after evaluation by ANEP and CCAE.

The strategic projects have been structured as work packets following the format of projects funded by the European Commission in the different framework research programmes and are clearly intended for transferring and translating results, therefore seeking the public investment to be returned to society as a whole.

As in previous years, for the 2013 fiscal year the CIBERES Steering Committee approved a budget item for each CRP. This budget item was managed by the Scientific Committee of each programme which has established the scientific priorities of each one. The amount assigned to each CRP was variable and was calculated based on the interest expressed by CIBERES investigators in participating in each of said programmes and on the external evaluations received:

Resource type	2013 Budget
Severe Asthma	88.541,49€
Pulmonary Fibrosis	34.339,31€
COPD	163.749,97€
Cancer	97.559,60€
Acute Lung Injury	251.275,66€
Sleep Apnea Syndrome	175.866,89€
Pneumonia	254.656,02€
Tuberculosis	89.832,71€
New Therapeutic Targets	247.178,32€
TOTAL	1.402.999,97€

At the same time work on strategic projects began, in 2013 CRPs continued working on projects taken on in previous years which were all set to end in 2014.

The projects developed and the main results obtained by the CRPs in 2013, as well as a brief introduction to each of the strategic projects and their objectives are shown schematically below.

Acute Lung Injury

Coordinator
Dr. Andrés Esteban

EARLY DIAGNOSIS AND NOVEL THERAPEUTIC STRATEGIES FOR ACUTE LUNG INJURY

Having a strong scientific interest, the present ALI CRP is endowed with a clear translational relevance, aiming at solving questions of great social impact. Indeed, most citizens will eventually require in their lifetime an intensive care unit (ICU) admission. About one third of them require mechanical ventilation, of which over two thirds have acute respiratory failure as the admitting diagnosis. Common causes of acute respiratory failure are the conditions termed acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). The social and economic impact of ALI and ARDS is documented by the high associated mortality rate -around 50%-, as well as the important sequelae of these patients, that often require prolonged rehabilitation treatment. This high mortality is comparable to the mortality of other conditions such as acute myocardial infarction, cancer or sepsis. However, funding from public or private agencies in this area is far from enough. This paradox implies a huge social and economic problem, given the severity of the disease, and the elevated cost of treatment, rehabilitation and work loss. The insufficient research in this field will not help solve these nationwide problems. Specifically, the present corporative research project (CRP) is designed to help solving the clinical and social problem of the early diagnosis and treatment of ALI.

Different groups of scientific excellence will participate in this research project, collaborating to accomplish a common objective: how to diagnose earlier and treat better patients with ALI and ARDS in order to decrease their high morbidity and mortality. Research questions include: (a) is there a specific diagnostic biomarker?; (b) which are the intracellular signalling pathways involved in the development and repair of ALI?; (c) which are the potential therapeutic targets based on involved pathways relevant to pathogenesis?; (d) can we define specific patient subgroups that could benefit from novel therapeutic approaches that will arise over the next 5 years?

The different research groups will collaborate with an integrated systems biology approach. Biological samples from participating patients with ALI and ARDS (i. e., serum, BAL fluid, etc.) will be collected for use in future investigations. These samples will be stored in and managed by the CIBERES' Biobank Platform.

The CRP is built on a limited number of WPs, defined to orchestrate in an efficient manner the different research areas, aiming at the common objective of diagnosis and treatment of ALI/ARDS.

Aims and objectives

1. **To identify genes/processes that are deregulated in preclinical models of ALI (assessed by functional genomics), or that constitute hits in genome-wide association studies being conducted.** To examine whether genetic variants of those genes are associated with acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS) development and outcome (mortality or protection). To find new enigmatic genes that can explain the diversity of clinical presentation of ALI/ARDS, the response to current medical treatment, and the individual's genetic predisposition.
2. **To discover biomarkers of ALI** among the three most relevant families of markers (i.e., inflammation-cytokine, endothelial related and epithelial derived markers). Determine the utility of MRS and MS as biomarkers of ALI. To validate volatile organic compounds in airway fluid and exhaled breath samples collected by non-invasive or minimally invasive as biomarkers of ALI/ARDS. To determine specific biomarkers for the early detection of alterations in CNS function in ALI/ARDS at the local brain level (alterations in tissue architecture, and mapping of biological markers related to neuronal activation of early genes, apoptosis and inflammation); and to define their correlation with systemic biomarkers.
3. **To demonstrate a key role of TLR/NLR receptor activation in the pathogenesis of ALI**. These effects will be studied in animal models of ALI and in serum from patients with ALI, as well as in different cell types and in isolated ventilated perfused lung model.
4. **To define the relationship of asynchronies to clinically relevant outcomes in patients with ALI**, in order to define therapeutic targets based on ventilatory management and to define ventilatory management strategies
5. **To explore lung repair mechanisms that are initiated immediately following the insult** leading to ALI/ARDS (i.e. sepsis, VILI). To study interactions between initiating factors, structural pulmonary elements, and signalling pathways that are involved in lung repair.

   To define biochemical factors determining changes in surfactant function and structure in a rat model of ALI. To define mechanisms of alveolar repair, by means of stem cells, in decellularized lung scaffolds and in a lung-on-a-chip model. To use of adult stem cells in treatment.
6. **To spread knowledge and evidence** providing new insights **and training on acute lung injury mechanisms and lung repair**.

Main results in 2013

Publications:

- Sun A, Ma SF, Wade MS, Acosta-Herrera M, Villar J, Pino-Yanes M, Zhou T, Lliu B, Belvitch P, Moitra J Functional promoter variants in sphingosina 1 fosfate receptor 3 associate with susceptibility to septis-associated acute respiratory distress syndrome. Am J Physiol Lung Cell Mol Physiolo 2013;305: L467-77.
- Thille A W, Esteban A, Fernández-Segoviano P, Rodríguez JM, Aramburu JA, Vargas-Errazuriz A, Martín-Pellicer A, Lorente JA, Frutos-Vivar F. Chronology of histological lesions in acute respiratory distress syndrome with diffuse alveolar damage: a protective cohort study of clinical autopsies. The Lancet Respiratory Medicine 2013; 1: 395-401.
- Puig F, Fuster G, Adda M, Blanch L, Farre R, Navajas D, Artigas A. Barrier-protective effects of activated protein C in human alveolar epithelial cells. Plos One 2013;8:e56965.
- Maria J Ribeiro, Joana F Sacramento, Constancio González, Maria P Guarino , Emilia C Monteiro and Silvia V Conde. Carotid body denervation prevents the development of insulin resistance and hypertension induced by hypercaloric diets. Diabetes 2013;62: 2905-2916.

Patent:

- Jesús Ruíz Cabello. Nano-partículas recubiertas de gelatina. Solicitud PCT/ES2013/070462. Fecha solicitud 3/7/2013.

Asthma

Coordinator
Dr. Mª Victoria Del Pozo

MECHANISMS UNDERLYING GENESIS AND EVOLUTION OF ASTHMA

Asthma represents a major health problem throughout the world. There has been an epidemic increase in global prevalence of asthma in the last decades with an estimated 300 million people affected worldwide. This is particularly relevant in the developed industrialized world, which has noted a tremendous increase in the prevalence of asthma over the last 50 years. Asthma currently affects 8-12% of the population in the developed world. Patients affected by this disease are recognized to have a poorer quality of life, reduced work productivity and school attendance and comorbidities associated. And, apart from individual suffering, because of their life-threatening of chronic course, these diseases present a high socioeconomic cost.

Asthma behaves as a spectrum of disorders initiated at different stages throughout life by a range of environmental factors interacting with a susceptible genetic background. At its simplest, asthma is divided into allergic (extrinsic) and no allergic (intrinsic) subtypes, but even within each of these 2 broad categories, there exists considerable heterogeneity with respect to underlying mechanisms, clinical and physiological manifestations, response to treatment, and natural history. The majority of asthma is associated with TH2-type T-lymphocyte-driven cell recruitment and mediator release involving mast cells, eosinophils, basophils, and macrophages that contribute to the chronic, subacute, and acute inflammatory responses.

During the last three decades an improved understanding of the pathophysiology underlying asthma, have led clinicians to shift their focus from managing acute attacks to achieving asthma control.

Severe asthma accounts for only 10% of patients with asthma, but it accounts for a considerable portion of the health care costs associated with the disease. Severe asthma patients are characterized by a poor quality of life, frequent hospitalisations and high risk of severe systemic side effects resulting from oral glucocorticoid therapy and/or high doses of inhaled glucocorticoids. All in all, these characteristics confer a relevant role to this group of patients when it comes to design a research programme aimed at achieving a better control of a disease that afflicts a progressively increasing number of patients.

Unmet needs in asthma are: The causes of the epidemic increase in asthma; Genetic susceptibility; The marginally understood interaction between environmental factors and immune system; Better subclassification of asthma: phenotypes; New agents acting on specific pathways in pathogenesis for the use as new therapeutic approaches; Better preclinical models for translation research; Better approaches in diagnosis and prediction of treatment responses and the monitoring of therapeutic effectiveness; Better tools to analysed complex data obtained; New and better biomarkers.

In our CRP project we will approach asthma as a trans-disciplinary research with expertise from clinical, epidemiological and biologist researchers to generate new therapeutic options based in a better diagnosis. **In our integrative approach we will approach immunological, genetic and environmental factors leading to complex asthma phenotypes in order to identify, describe and validate immunological and molecular networks involved in the genesis and evolution of asthma.** To achieve our aims we propose to study retrospectively and prospectively two well defined cohorts.

Aims and objectives

In our project we will focus our interests on the following problems:

- Mechanisms underlying genesis and evolution of asthma.
- Characterization of asthma phenotypes
- Characterization of asthma severity and identification of the factors that are involved in asthma severity
- New therapies for asthma
- To identify novel biomarkers and pathways that can be translated into targets for therapeutic strategies.
- To generate and disseminate expertise and knowledge obtained from the consortium to transfer information to scientific community and society.

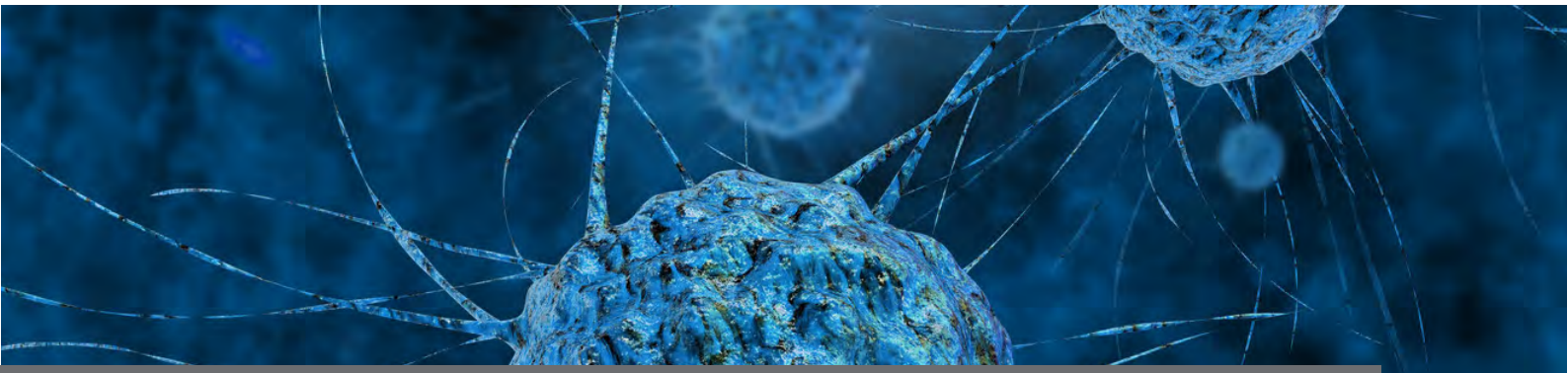
Main results in 2013

Publications:

- Castillo C, Lara B, Cruz MJ, Muñoz X. Protein identification of two allergens of Boletus edulis causing occupational asthma. Am J Respir Crit Care 2013;187(10):1146-8.
- Quirce S, Muñoz X, Urrutia I, Pérez-Camo I, Sabadell C, Domínguez-Ortega J, Barranco P, Plaza V. Changes in the asthma control test score with work-related asthma. J Investig Allergol Clin Immunol. 2013;23(4):284-5.
- de Llano LP, Vennera M del C, Álvarez FJ, Medina JF, Borderias L, Pellicer C, González H, Gullon JA, Martínez-Moragon E, Sabadell C, Zamarro Picado C, Muñoz X. Effects of omalizumab in non-atopic asthma: results from a spanish multicenter registry. J Asthma. 2013;50(3):296-301.
- Martínez-González I, Roca O, Masclans JR, Moreno R, Salcedo MT, Baekelandt V, Cruz MJ, Rello J, Aran JM. Human Mesenchymal Stem Cells Overexpressing the IL-33 Antagonist sST2 Attenuate Endotoxin-Induced Acute Lung injury. Respir Cell Mol Biol 2013;49(4):552-62.
- Bernstein DI, Kashon M, Lummus ZL, Johnson VJ, Fluharty K, Gautrin D, Malo JL, Cartier A, Boulet LP, Sastre J, Quirce S, Germolec D, Tarlo MJ, Muñoz X, Luster MI, Yucesoy B. CTNNA3 (alpha-catenin) gene variants are associated with diisocyanate asthma, a replication study in a Caucasian worker population. Toxicol Sci. 2013;131(1):242-6.

Clinical guidelines:

- van Kampen V, de Blay F, Folletti I, Kobierski P, Moscato G, Olivieri M, Quirce S, Sastre J, Walusiak-Skorupa J, Raulf-Heimsoth M. EAACI position paper: skin prick testing in the diagnosis of occupational type I allergies.Allergy. Mayo de 2013;68(5):580-4.
- Siracusa A, De Blay F, Folletti I, Moscato G, Olivieri M, Quirce S, Raulf-Heimsoth M, Sastre J, Tarlo SM, Walusiak-Skorupa J, Zock JP. Asthma and exposure to cleaning products - a European Academy of Allergy and Clinical Immunology task force consensus statement. Allergy. Diciembre de 2013;68(12):1532-45.
- Canonica GW, Ansotegui IJ, Pawankar R, Schmid-Grendelmeier P, van Hage M, Baena-Cagnani CE, Melioli G, Nunes C, Passalacqua G, Rosenwasser L, Sampson H, Sastre J, Bousquet J, Zuberbier T, Allen K, Asero R, Bohle B, Cox L, de Blay F, Ebisawa M, Maximiliano-Gómez R, González-Diaz S, Haahtela T, Holgate S, Jakob T, Larché M, Matricardi PM, Oppenheimer J, Poulsen LK, Renz HE, Rosário N, Rothenberg M, Sanchez-Borges M, Scala E, Valenta R. A WAO - ARIA - GA2LEN consensus document on molecular-based allergy diagnostics. World Allergy Organ J. 3 de octubre de 2013;6(1):17.



Lung Cancer

Coordinator
Dr. Eduard Monsó

CLINICAL AND MOLECULAR CHARACTERIZATION OF EARLY-STAGE LUNG CANCER (LC).

LC is an important disease on account of its high incidence and severity, and on the level of associated mortality. In contrast to the response obtained with other solid tumours and despite an enormous research effort, the prognosis for LC has improved only slightly in recent decades, with a 5-year survival less than 15%.

The typology of LC is defined by anatomo-pathological criteria that initially differentiate LC as small cell carcinoma and NSCLC, with the latter further classified as adenocarcinoma, squamous cell carcinoma and large cell carcinoma. In a proportion of NSCLC cases this differentiation is not possible, with the carcinoma remaining as undifferentiated. Immunohistochemical markers can be used to clarify in part the situation, but uncertainty in the estimation of prognosis and response to treatment is high. The incorporation of prognostic molecular markers, such as epidermal growth factor receptor (EGFR) in tumour cells, which modulates a different therapeutic response when a mutation is present, has led to significant changes in treatment regimens used in NSCLC, which have been incorporated into clinical guidelines.

Early identification of the disease favours the use of therapeutic interventions associated with prolonged survival. The TNM system of staging according to the degree of extension of the primary tumour (T), lymph nodes (N) and metastasis (M) has been and is important, but is imprecise in relation to the prognosis and treatment selection. The percentage variation in survival with the TNM model is only 30%, with each patient's prognosis depending on poorly known determinants. In fact, in patients considered to have early-stage LC, there has barely been any reduction over the last 30 years in mortality and relapse. In cases that have been resected and staged as Ip, without evidence of lymph node or systemic metastases at baseline, very high rates (35-50%) of mortality or relapse are seen during follow-up. Moreover, despite the benefits seen with the use of platinum-based adjuvant chemotherapy in cases of advanced stages, the available data do not support the use of such treatment in patients with stage IA cancer and show very questionable results in patients with stage IB cancer. **It seems clear that TNM staging based on tumour extension conceals in its apparent homogeneity a considerable level of biological heterogeneity of the tumour or tumour-host relationship, which is evidenced in terms of prognosis and prediction.**

The **inclusion of new predictive molecular variables to the staging of LC** could be a promising approach to improve establishment of the prognosis and prediction of treatment response, in addition and complementarily to the TNM; such an approach could be easily incorporated into clinical practice guidelines and could enable alternative therapies to be defined beyond those currently in use. Numerous studies have addressed this problem, with inconclusive or contradictory outcomes. The cause resides in complexity and

difficulty of the problem being studied, the methods used, studies with very specific scientific objectives, small case series, and results not validated in independent, external cohorts.

The SP-LC project within the CIBERES CRP aims to produce valid and useful knowledge from specific scientific objectives, avoiding the methodological problems that have placed in question the results of previous studies. The CRP also proposes, **in addition to using the GCCP-II-IASLC Cohort, to generate a CIBERES Cohort, a case series of patients diagnosed with LC of squamous or adenocarcinoma cell lineage, and staged post-resection as I/IIp**. Samples will include tumour tissue, non-tumorous pulmonary tissue, lymph nodes and peripheral blood, apart from the collection of clinico-pathological characteristics of the patient at the time of treatment and following the evolution of patients included in the prospective cohort at two and five years following treatment, with information about disease-free time and survival. This will involve only those hospitals with a thoracic surgery unit and associated with SEPAR (N = 53).

The CIBERES SP-LC aims to create a cohort of patients diagnosed with LC by screening with LR-CT. An Early COPD Cohort will be generated in the CIBERES Strategic Project on COPD. The objective of this work is to clinically and molecularly characterize patients with LC in this Cohort, to establish links between LC and COPD, and to verify molecular variables that differentiate cases identified by screening from cases diagnosed in clinical practice.

Aims and objectives

1. To identify a set of clinico-molecular variables that improve the prognostic and predictive capacity of the TNM staging in LC.

Analysis of biological and molecular variables that have prognostic and/or predictive value with respect the therapeutic response, independently of TNM staging, in tumour samples, pulmonary tissue, lymph nodes and peripheral blood will include:

- Epigenetics, according to the methylation pattern of chosen genes
- Immunohistochemistry, determining alterations of the stroma.
- Analysis of inflammation and oxidative stress, by measuring biomarker levels in tumour tissue and blood

2. To validate in a population of smokers with COPD screening techniques developed for the general population, and to validate in the former population prognostic and predictive clinic-molecular variables.

The specific aims for this population are:

- To create a high-performance cost-effective screening methodology for stage I/IIp LC.
- To identify biological and molecular variables with potential prognostic and/or predictive value independently of the pathological TNM, in samples of tumour tissue, non-tumour lung tissue, lymph nodes and peripheral blood from patients with squamous/adenocarcinoma-type NSCLC, identified by a screening programme.
- To identify biological variables associated with the early diagnosis of NSCLC by screening (Early-COPD Cohort), compared with the usual care clinical diagnosis (GCCP-II-IASLC and CIBERES Cohorts).
- To study the potential correlation between the activity of molecular variables for COPD and LC.

Main results in 2013

The Programme has successfully created a tumor tissue biobank containing tumor tissues from patients included in the International Association for the Study of Lung Cancer (IASLC) Cohort and in follow-up until 2016. It has over 250 samples available for the analysis of biological markers with potential prognostic capacity. Baseline clinical information of the patients included in this Cohort living in this territory was published by CIBERES investigators participating in the Programme (Sanchez de Cos J. Arch Bronconeumol [Barc] 2013) in 2013. In the line for identifying genetic, epigenetic and proteomic markers with potential prognostic capacity in early-stage lung cancer patients, CIBERES investigators participating in the Programme have validated, in biological samples from patients with risk factors for lung cancer and from patients suffering this disease, originating from clinical series, oxidative stress marker levels in bronchial secretions and peripheral blood using ELISA and immunoblotting.

Carbonylation, MDA protein adducts, antioxidants, TNF-α, interferon-γ, TGF-β and VEGF levels in bronchial secretions, and superoxide, damaged DNA, TNF-α, interferon-γ, TGF-β, VEGF and neutrophil levels in the blood were high in lung cancer patients. This justifies studying their prognostic significance in the disease (Barreiro E. Free Radical Biology and Medicine 2013). Investigators participating in the Programme have also examined the peripheral immune response in patients at risk of lung cancer due to smoking and COPD, focusing their attention on L-arginine catabolism and observing that circulating myeloid-derived suppressor cells (MDSCs) are activated in smokers and remain activated once the person stops smoking in COPD patients. This analysis has concluded that smoking modulates circulating MDSCs and that this alteration persists in COPD patients who quit smoking. It has allowed observing an effect of exposure to tobacco with potential clinical significance (Schrimini Resp Med 2013). As regards epigenetics, it has been observed that p16 methylation, which is observed in samples obtained non-invasively from mediastinal nodes, is a predictor of advanced diseases and therefore has prognostic value, with the advantage of being able to be examined in non-surgical samples (Millares, European Respiratory Society Congress).

Publications:

- Barreiro E, Fermoselle C, Mateu-Jiménez M, Sánchez-Font A, Pijuan L, Gea J, Curull V, Oxidative stress and inflammation in the normal air way sand blood of patients with lung cancer and COPD Free Radical Biology and Medicine 65(2013) 859–871.
- Scrimini S, Pons J, Agustí A, Soriano J, Cosio B, Torrecilla J, Núñez B, Córdova R, Iglesias A, Jahn A, Crespi C, Sauleda J Diferenteial effects of smoking and COPD upon circulating myeloid derived suppressor cells Respiratory Medicine – Diciembre de 2013 (Vol. 107, Número 12, Páginas 1895-1903, DOI: 10.1016/j.rmed.2013.08.002).
- J. Sánchez de Cos Escuín et al Registro del Grupo Cooperativo de Cáncer de Pulmón-II de la Sociedad Española de Neumología y Cirugía Torácica. Estudio descriptivo Arch Bronconeumol. 2013;49(11):462–467.

Chronic Obstructive Pulmonary Disease (COPD)

Coordinator
Dr. Borja G. Cosío

DEFINING BIOLOGIC ACTIVITY IN COPD: FROM THE FRAGILE PATIENT TO THE EARLY STAGE OF THE DISEASE

It is necessary to study patients with early COPD for the understanding of the natural history of the disease and for the design of therapeutic interventions with potential to modify its prognosis. COPD is a highly prevalent disease affecting about 44 million people in Europe. In contrast to other major causes of death, its prevalence has been increasing in the past three decades. However, the natural history of COPD is still poorly understood, which limits the targets for intervention. The heterogeneous nature of COPD has led to the proposal that there might be different natural histories with different pathogenetic mechanisms in COPD. Indeed, the ECLIPSE study has shown that this accelerated loss of lung function is not present in 40% of patients diagnosed and treated for COPD. There are many questions about the natural history of the disease unresolved, such as the effect of lung development during childhood and adolescence on the future risk of COPD, the progression or activity of the disease from early stages, the role of bronchial hyperresponsiveness, the role of infection, among others. The lack of a reliable animal model has contributed to maintain this problem. Also, little is known about the early stages of COPD because most patients are either never diagnosed or diagnosed at the age of sixty when they already have moderate to severe disease. Furthermore the diagnosis of COPD is associated with a poorer quality of life and to a greater use of health resources.

There is a need for biomarkers of disease progression even in animal models. A number of attempts have been made in the last decade to obtain suitable biomarkers of COPD and its different associated conditions. However, only a general approach to this objective, with no really wide clinical applicability, has been achieved. The fact that only a limited number of molecules have been explored so far, especially in the area of inflammatory activity, may account for such a shortcoming. Despite these considerations, there are still interesting new possibilities such as those concerning lung injury, and the structure and metabolism of vascular and muscular tissues, among others. It is therefore necessary to identify biological markers of progression and of upmost importance to define and validate the concept of disease activity in COPD.

The role of COPD exacerbations and airway infection on disease activity is unknown.

COPD exacerbations are intermittent events occurring in the course of this disease. They speed the progression of the disease, reduce health-related quality of life and are associated with significant mortality, which can all translate into disease activity. The role of treatment on disease activity is unknown. A recent European audit showed that delivery of care based on the differences of resources revealed a huge inequality of care throughout Europe. As a consequence the outcome of COPD in

terms of readmission rate and mortality within 90 days is alarming, and several factors have been identified. To study fragile patients cohorts in which these factors are present is required.

Infection and colonization of the tracheobronchial tree may be related to biological activity of the disease. Strong evidence implicates bacterial infection in the course and pathogenesis of COPD: (i) changes in the respiratory microbiome of COPD patients compared to healthy individuals have been reported; (ii) chronic and recurrent infection is associated to chronic bronchitis, to increased risk of exacerbation, and to accelerated loss of lung function, which may be translating into activity.; (iii) COPD infectious exacerbation is a frequent cause of death.

In this context, we hypothesize that COPD has different levels of activity that lead to different natural histories of the disease, ranging from the asymptomatic patient with preserved lung function along time with little or no exacerbations to the fragile symptomatic patient with accelerated loss of lung function and frequent exacerbations. The more fragile patients will show the most prominent markers of COPD activity that can be later applied to a cohort of early COPD patients in order to predict the type of progression. Markers of activity can be identified in the clinical, biopathology, microbiology and imaging domains.

Aims and objectives

The main aim of this project is to demonstrate and define properly the concept of biologic activity in COPD as the undergoing mechanism that leads to differential evolution of disease, ranging from the low activity with low impact and low progression of disease to the high activity with high impact and rapid progression. As starting point, it is assumed that the fragile patients with more severe disease are those in which the disease is-or has been-more active. For that reason, this project plans to explore the concept of activity in a fragile COPD population from the clinical, microbiologic and experimental point of view as a first step, and subsequently apply the information obtained from them into a population at early stages of disease. Mechanistic studies in animal models of fragile, early COPD and microbial infection will help to probe the hypothesis generated from the clinical studies. To achieve this general goal, the following specific objectives will be pursued:

1- To **validate frailty criteria in relation to prognosis and evaluate the impact** of different Health Care approaches to management on disease activity by generating a fragile COPD cohort.

2- To **analyse clinical, imaging and biological markers of activity** as determinants of disease progression and severity in fragile COPD patients.

3- To **identify microbiology patterns or changes** within the pathogen or the host associated to disease progression in Fragile COPD patients.

4- To **investigate potential markers of activity in animal models.**

5- To integrate the previously identified markers of activity in fragile patients into a cohort of early COPD patients in order to **identify the patients with more active disease and faster progression**.

Main results in 2013

Publications:

- Agustí A, Barberà JA, Wouters EF, Peinado VI, Jeffery PK. Lungs, bone marrow, and adipose tissue. A network approach to the pathobiology of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 15 de diciembre de 2013;188(12):1396-406.
- Agustí A, Hurd S, Jones P, Fabbri LM, Martinez F, Vogelmeier C, Vestbo J, Rodriguez-Roisin R. FAQs about the GOLD 2011 assessment proposal of COPD: a comparative analysis of four different cohorts. Eur Respir J. Noviembre de 2013;42(5):1391-401.
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Host-Pathogen Interaction

Coordinators
Dr. Juncal Garmendia &
Dr. José A. Melero

RESPIRATORY INFECTIONS: FROM MECHANISMS TO THERAPEUTICS

The main strategy for fighting infectious diseases has focused on targeting enzymes from pathogens with antibiotics. The rapid development of resistance shortens the life span of a therapeutic agent, leading to decreased interest of the industry to develop new agents because the costs are prohibitive compared to the economic potential of the drug. Moreover, there is an urgent need for specific antiviral therapies. Therefore, there is a need to develop effective therapeutics based on new targets/approaches and to develop efficient prophylactic measures. Importantly, the Spanish Research Plan and the next European research plan, Horizon 2020, consider respiratory infections and development of new therapies as a research priority.

The new project builds on the knowledge generated in the previous Research Programme. **It makes a major effort to analyse the transcriptome of alveolar macrophages infected with different pathogens.** Analysis of data is currently underway. Interesting results include the induction of antiviral responses by bacteria-infected macrophages and the activation of lipid metabolism in infected macrophages, independently of the pathogen used. These results open new avenues of research to fight infections. Collaborative efforts have also revealed new mechanisms of host-pathogen interaction and similarities between bacterial and viral strategies. Furthermore, the Programme has set up a microarray platform for the study of glycan-pathogen interactions that leads to the identification of some galectins interacting specifically with some pathogens. We also studied the lung surfactant modulation of the inflammatory response in airway epithelial cells infected by respiratory syncytial virus and other pathogens.

The project is divided into 6 work packages. Three of these are meant to pursue ambitious objectives at the forefront of research in infection biology. Importantly, one of these WPs aims to capitalize on the knowledge generated to develop new therapies. Therefore, the first pre-clinical studies have been planned.

Added value

Our project focuses on important respiratory pathogens with different infection strategies. We employ an alveolar macrophage cell line as a common denominator in all our investigations, and we focus on common cell targets (pattern recognition receptors-mediated recognition, inflammatory responses, and IFN-induced defence responses) in order to reveal common schemes and principal

differences of microbial infection strategies. These studies will allow the design of patient-customized therapeutic treatments. The project provides the required critical mass to carry out the research and developmental activities by joining leading scientists from important institutions in infection biology in Spain. Our work produces synergies based on:

- Distinct but complementary expertise of partners from the disciplines of microbiology, immunology, and cell biology.
- Common use of the established knock-out cells, reagents, and platforms.

The partners will work in a cooperative and supportive way. All WPs are set up in such a way that success is absolutely contingent on close interaction and collaboration.

Aims and objectives

In order to better understand how pathogens stimulate, inhibit, and manipulate host cell functions, we will analyse bacteria (K. pneumoniae, Haemophilus influenzae no tipable, S. pneumoniae, M. tuberculosis, S. aureus) and viruses (Influenza A viruses, paramyxoviruses, and respiratory syncytial virus) specified by various infection strategies. Analysis of pathways targeted by pathogens may reveal the strategies used to subvert immune responses and **lead to the identification of the various Achilles heels of host defence.** Although the immunomodulatory mechanisms used by viruses and bacteria may appear to be quite different, pathogens have to overcome the same host immune defences. Hence it is not surprising that there may be shared mechanisms. Consequently, the identification of a central core of systems implicated in host defence against several pathogens, which could be targeted for therapeutic manipulation, is an important goal of this project.

Our main hypothesis is that there is a common host response to infections associated with the clearance of the pathogen. In turn, pathogens try to counteract this response using conceptually similar but physically distinct processes. On the other hand, different signals (mediated by innate immune molecules and/or drugs) can tip the balance of this response, thereby affecting the outcome of the host-pathogen interaction.

The main objectives of our Programme are:

1. To **identify anti-immune strategies of different pathogens, focusing on their ability to modulate gene expression and hence cellular function via the manipulation of innate immune response.**
2. To **analyse the activation of pattern recognition receptors upon infection** with emphasis on these receptors launching IFN-dependent responses and controlling viral infections.
3. To **identify a set of IFN-dependent anti-infection determinants that might be common to viruses and bacteria.**
4. To **evaluate the impact of molecules of the innate immune system** (galectins and surfactant) on host-pathogen interactions.
5. To **uncover strategies to avoid intracellular killing**.

Main results in 2013

In vitro (including biofilms) and *in vivo* studies (using zebrafish embryos for the first time) have proven that modifications introduced in Cpl-7, a pneumococcal phage lysozyme, significantly increase its lethal activity and broaden its spectrum of action against other Gram-positive and Gram-negative bacteria.

- Díez-Martínez R. et al. Improving the letal effect of cpl-7, a pneumococcal phage lysozyme with broad bactericidal activity, by inverting the net charge of its cell wall-binding module. Antimicrob Agents Chemother. (2013) 57:5355-65.

Klebsiella pneumoniae subverts host inflammatory response by means of transactivating human EGFR receptor through capsular antigen recognition by TLR4.

- Frank CG et al., *Klebsiella pneumoniae* targets an EGF receptor-dependent pathway to subvert inflammation. Cell Microbiol. (2013) 15:1212-33.

Mycobacterium tuberculosis modulates cell apoptosis to its own benefit to significantly favor the spread of infection. This aspect is only observed in virulent strains and not in BCG or MTBVAC vaccine strains.

- Aguilo JI, et al. ESX-1-induced apoptosis is involved in cell-to-cell spread of *Mycobacterium tuberculosis*. Cell Microbiol. (2013) 15:1994-2005.

SP-BN and SP-A proteins present in alveolar fluid act synergistically against several bacterial lung pathogens *in vitro* and *in vivo*.

Both proteins have a therapeutic effect *in vivo* once infection by *Klebsiella pneumoniae* is established, suggesting the possible therapeutic use of recombinant forms.

Respiratory syncytial virus (RSV) modulates ubiquitination and ISGylation processes during infection and causes reduced expression of human glucocorticoid receptor GCa in differentiated bronchial epithelium, suggesting that said infection may favor the corticoid-resistance phenomenon.

Pneumonia

Coordinator
Dr. Antoni Torres

MULTIDISCIPLINARY TRANSLATIONAL RESEARCH IN RESPIRATORY TRACT INFECTIONS.

Severe acute respiratory infection (SARI) is the leading global cause of morbidity and mortality from infectious diseases. Under this term, **we include severe community-acquired pneumonia (sCAP) and other community-acquired infections requiring admission to intensive care unit**. Severe community-acquired pneumonia (sCAP) is a current major health concern. Despite the introduction of antibiotic agents (1950s), the outcome of sCAP has shown little improvement in the past 3 decades and remains between 25% and 40% in patients admitted to the intensive care unit (ICU).

Hospital-acquired pneumonia (HAP) is currently the second most common nosocomial infection, and is associated with high mortality and morbidity. The presence of HAP increases hospital stay by an average of 7 to 9 days per patient and has been reported to produce an excess cost of more than $40,000 per patient. Incidence increases by as much as 6- to 20-fold in mechanically ventilated patients, and in this case we call these Ventilator-associated respiratory infections (VARI) such as pneumonia, tracheobronchitis and other bronchopulmonary infections.

At present, the emphasis in the field of SARI and VARI should be on effective prevention measures, rapid diagnosis techniques and adequate clinical management tools and treatment. **Our group intends to perform activities that will allow us to better understand the current epidemiology, patterns of care and treatment, and patient outcomes**. Furthermore we plan to undertake studies to improve the diagnosis of SARI/VARI (focusing on rapid tests and using biomarkers as selective predictors of respiratory infection) and **in terms of treatment we will prioritize optimizing the dosage of currently used antibiotics for respiratory infections and investigating the value of biomarkers for enhancing therapy** in SARI/VARI as well as finding new targets for S. pneumoniae. As DNA topoisomerases and choline-binding proteins fulfil this requirement, they are attractive targets for the treatment of pneumococcal diseases. Furthermore, we have done an initial screening of the Prestwick Chemical Library **finding six hits (not including known antibiotics)** that appear to inhibit the growth of S. pneumoniae at submillimolar concentrations. If the antimicrobial activity of all these compounds is confirmed, these hits would be tested using in vitro (planktonic or biofilm) and in vivo (animal models of infection)

We also plan to **approach emerging pathogens causing severe respiratory infections** or those that seem to complicate existing respiratory co-morbidities, such as C. difficile.

Finally, since this is major problem, we want to place a major emphasis on prevention and patient safety by investigating care-bundles in VARI.

Aims and objectives

The principal aims of this programme are:

1. To study the **risk, and prognosis factors of severe acute community-acquired and ICU-acquired respiratory infections** in Spain, **including biomarkers and genetic factors.**
2. To study risk, and **prognosis of community-acquired and hospital acquired respiratory infections in patients not admitted to the ICU in Spain, also including biomarkers.**
3. To study in depth the microbial etiology and resistances of all the populations mentioned above. In this objective we will include the investigation of new rapid molecular techniques.
4. To study whether the **implementation of educational programmes** and bundles may decrease the incidence of hospital-acquired pneumonia inside and outside the ICU.
5. To investigate the **best way to treat multiresistant microorganisms.**
6. To investigate the **epidemiology, virulence, inflammatory response and clinical outcomes of serotypes of S. pneumoniae causing invasive disease before and after the introduction of the new vaccine PVC 13.**
7. To investigate new **mechanisms of virulence, resistance and treatment of S. pneumoniae.**
8. To use **our available animal models of severe pneumonia** (P. aeruginosa, MR S. aureus and S. pneumoniae) for translational research.
9. To develop **new clinical guidelines** for the management of community-acquired pneumonia, hospital-acquired pneumonia and ventilator-associated pneumonia.

Main results in 2013

Guidelines:

- Guía multidisciplinar para la valoración pronóstica, diagnóstico y tratamiento de la neumonía adquirida en la comunidad. Antoni Torres*, José Barberán, Miquel Falguera, Rosario Menéndez, Jesús Molina, Pedro Olaechea y Alejandro Rodríguez, en nombre del Grupo de la Guía Multidisciplinar para el Manejo de la Neumonía Adquirida en la Comunidad; 1,2 Med Clin (Barc). 2013;140(5):223.e1–223.e19.
- A care bundle approach for prevención of ventilator-associated pneumonia. Rello J, Afonso E, Lisboa T, Ricart M, Balsera B, Rovira A, Valles J, Díaz E; Investigadores del proyecto FADO. Clin Microbiol Infect. Abril de 2013; 19(4):363-9.

Publications:

- Intensive Care Med. Abril de 2013; 39(4):672-81. Potentially resistant microorganisms in intubated patients with hospital-acquired pneumonia: the interaction of ecology, shock and risk factors. Martin-Loeches I1, Deja M, Koulenti D, Dimopoulos G, Marsh B, Torres A, Niederman MS, Rello J; Investigadores del estudio EU-VAP.

- Rolo D, Fenoll A, Fontanals D, Larrosa N, Giménez M, Grau I, Pallarés R, Liñares J, Ardanuy C; Serotype 5 Study Group. Serotype 5 pneumococci causing invasive pneumococcal disease outbreaks in Barcelona, Spain (1997 to 2011). J Clin Microbiol. 2013;51:3585-90.
- Characterization of recombinant fluoroquinolone-resistant pneumococcus-like isolates. Balsalobre L, Ortega M, de la Campa AG. Antimicrob Agents Chemother. Enero de 2013; 57(1):254-60.
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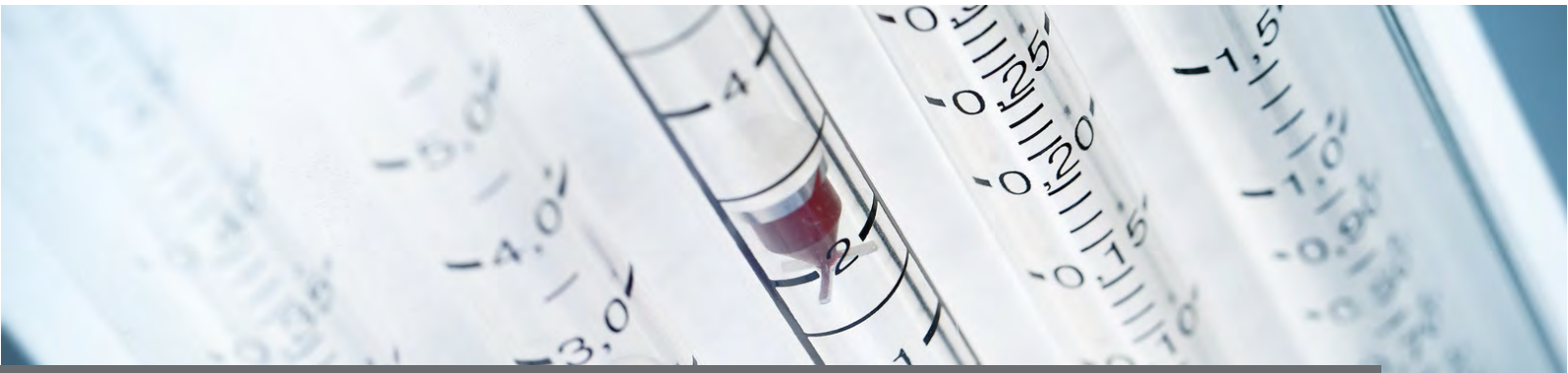


Pulmonary Fibrosis

Coordinator
Dra. María Molina

CELL PLASTICITY AND MICROENVIRONMENT IN LUNG FIBROSIS: LOOKING FOR ITS REGULATION AS A POTENTIAL TREATMENT

Idiopathic pulmonary Fibrosis (IPF) is the most lethal interstitial lung disease (ILD), with no effective treatment and a mean survival of 2-4 years from the diagnosis. The histological defined pattern is the usual interstitial pneumonia (UIP), characterized by the loss of epithelial structures, interstitial collagenized fibrosis, microscopic honeycombing, and focal areas of "fibroblast foci". The current pathogenic **hypothesis posited epithelial injury and impaired wound repair as the etiology of fibrosis.** The initial cause is unknown, but genetic factors have been found to be associated such as telomerase gene mutations, which imply an impaired cell turnover and aging. IPF is characterized by a reactive stroma surrounding the altered alveolar epithelial units that exhibits a spatial accumulation of fibroblasts and myofibroblasts. The imbalance between the increase of pro-fibrotic growth factors, such as transforming growth factor beta1 (TGF-β1), angiotensin-II (ANGII), or reactive oxygen species (ROS), and the decrease of anti-fibrotic mediators such as prostaglandin-E2 (PGE-2), enhance the perpetuation of the process. Despite advances in the knowledge of fibrotic pathogenesis, the complex and potentially therapeutically relevant relationship and interactions between the containing cells and ECM remain poorly understood.

Cell regenerating answer to tissue damage.

Pneumocyte loss is followed by attempted tissue regeneration and exaggerated release of molecular signals triggering fibroblast proliferation and migration. The increased activation of the Wnt-pathway signalling in IPF is directly related to abnormal myofibroblast activity and epithelial-mesenchymal transition (EMT). They have been a number of studies characterising population of stem cells in lung, as well as markers of EMT and MET and their implication in the fibrotic process. So far, though, LRSC's of whatever origin have not been characterized in human diseased lungs. On the other hand, in animal model, introduction of MSCs into the lungs ameliorates bleomycin injury since a BM-MSCs subpopulation provides protection from lung injury. These data **suggest that different MSCs subpopulations can significantly modulate the onset of a fibrogenic response.**

Interstitial hallmarks of the altered wound healing in IPF.

Progressive tissue distortion and hardening in fibrosis have been associated with abnormal wound healing. Thus, in normal physiological conditions our organism can repair epithelial injury by forming a provisional structure generated by ECM protein deposition, fibroblast proliferation and transient myofibroblast activation. Completion of injury repair is followed by degradation of the provisional ECM and apoptosis of

myofibroblasts. In pathologic conditions, some glycoprotein ECM components remain increased, collagen I and III are not degraded; myofibroblasts evade apoptosis and develop dysfunctional repair mechanisms. The contributions of the different environmental alterations during dysfunctional repair to tissue scar are likely to depend on the particular disease and organ, and overall remain poorly understood. Our group has recently demonstrated abnormally high levels of ECM components in IPF lungs that are implicated in tissue remodelling (cell adhesion, fibroblast migration). Myofibroblasts are interstitial key effector cells in pulmonary fibrosis that can be derived from resident fibroblasts undergoing fibroblast-to-myofibroblast transformation (FMT), alveolar epithelial-to-mesenchymal transition (EMT), mesenchymal stem cells (MSCs) or even endothelial cells (EnMT). FMT is characterized by a dramatic increase in wound ECM components including collagens and glycoproteins. Extracellular microenvironment can regulate FMT and EMT. Based on these observations **it is tempting to speculate that there is a positive feedback loop between cell and extracellular-dependent microenvironment**. Although EnMT has been less studied, it has been included as one of the different cellular process characteristics in the remodelling of pulmonary hypertension (PH)-associated IPF, together with endothelial dysfunction. PH in IPF portends a poor prognosis.

Advanced 3D cell culture model for the study of cell-ECM protein interactions.

Traditional approaches to study IPF include conventional 2D culture systems, which lack essential components of the original tissue, and animal models that contain the full complexity of the tissue but lack the irreversible behaviour of IPF. There is wide evidence that cells grown in 3D cultures with appropriate ECM components retain many of their phenotypic characteristics, thereby behaving more closely to their in vivo conditions. Our programme is working in a 3D culture model.

Aims and objectives

1. To **study glycoprotein effect on primary human lung alveolar and mesenchymal cells** (migration, metabolism and differentiation) and the regulation of its synthesis in fibro-myofibroblasts .
2. To **evaluate the differences in cell behaviour and experimental results depending on telomere length and telomerase gene mutations.**
3. To i**dentify, characterize and assess, in vitro, the functional status and the regenerative/reparative capacity of both hLRSC**, including lung-hMSCs and BM-hMSCs, from patients with IPF, compared to those obtained from subjects with normal lung function.
4. **Compare in these cells released factors related to signalling pathways** that induce proliferative and fibrogenic features of pulmonary target cells.
5. To **investigate the remodelling of those vascular structural cells from patients with PH complicating IPF**, and its possible regulation through some inhibitors.
6. To **study aquoporin system in lung fibrosis** and its modulation depending on the cell type and environmental growing conditions.

Main results in 2013

Publications:

- Almudéver P, Milara J, De Diego A, Serrano-Mollar A, Xaubet A, Pérez-Vizcaino F, Cogolludo A, Cortijo J. Role of tetrahidrobiopterin in pulmonary vascular remodelling associated with pulmonary fibrosis. Thorax. 2013;68(10):938-48.
- Uhal BD, Dang M, Dang V, Llatjos R, Cano E, Abdul-Hafez A, Markey J, Piasecki CC, Molina-Molina M. Eur Respir J. 2013;42(1):198-210.
- Gabasa M, Royo D, Molina-Molina M, Roca-Ferrer J, Pujols L, Picado C, Xaubet A, Pereda J. Lung myofibroblasts are characterized by down-regulated ciclooxygenase-2 and its main metabolite, prostaglandin-E2. PLoS One. 2013;8(6):e65445.

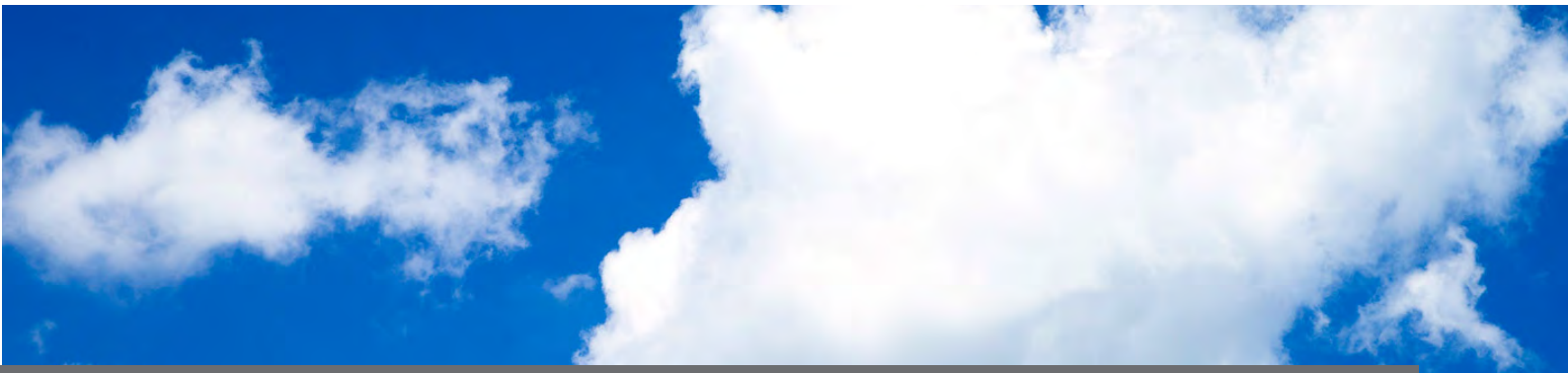
Clinical Guidelines (2013):

- Guía Española para el diagnostico y tratamiento de FPI:

  Xaubet A, Ancochea J, Bollo E, Fernández-Fabrellas E, Franquet T, Molina-Molina M, Montero MA, Serrano-Mollar A. Guidelines for the diagnosis and treatment of idiopathic pulmonary fibrosis. Sociedad Española de Neumología y Cirugía Torácica (SEPAR). Research Group on Diffuse Pulmonary Diseases. Arch Bronconeumol. Agosto de 2013; 49(8):343-53.

Innovation:

- Solicitud de patente europea; EP14382007.



Sleep Apnea

Coordinator
Dr. Josep M. Montserrat

SLEEP APNEA. NEW TARGET POPULATIONS

SAHS is a common condition affecting 4-6% of the adult population and 2% of infants, while over 50% of the elderly population experience more than 10 events per hour. Repetitive episodes of upper airway obstruction disrupt the sleep architecture, induce episodes of hypoxia normoxia, and activate the sympathetic system and trigger systemic inflammation and endothelial dysfunction. SAHS is typically associated with excessive daytime sleepiness, snoring, and witnessed apneas. It is considered a cardiovascular risk factor (hypertension) as it also induces metabolic deregulation. An incremental mortality has been described.

At this point in time the **whole research picture in Sleep Apneas is about to change in several very important ways.** In fact, some changes have occurred. Our data and those from other groups have now provided a good – or at least basic – guide to the management of most SAHS patients. Nevertheless, new works need to be done in a number of directions. Future research must embrace new mechanisms, clinical studies and technological approaches but also studies of transference to the health system to ensure cost-effective procedures, as well as transference to companies to ensure returns on research capital. Nowadays, a return on research capital is considered an essential component of a company's productivity and growth as well as Medicine 2 procedures are.

Furthermore, all the research to date has been performed on the adult population while other populations have been almost ignored. **The major aim of our new programme is to address this imbalance by investigating even more prevalent populations of SAHS, such as those associated with age (elderly or children), obesity such as the obesity hypoventilation syndrome, as well as other forms that have only recently come to light – such as cancer-related SAHS and acute coronary disease with SAHS.** All these topics could open up exciting new avenues of research.

The USA agency for Healthcare Research and Quality (AHRQ) (No. 12-EHC031-EF February 2012 published a list of recommendations with respect to future research needs. In our project we address many of these questions with some differences. **The research we have undertaken coincides with the recommendations of AHRQ especially those related to future research needs for the diagnosis and treatment of Obstructive Sleep Apnea** (OSA). These recommendations reflect very closely not only our past research but also our current research in progress as well as the one proposed. **This programme tries to combine basic and clinical research together with cost-effectiveness, translational, transference and technological aspects to be able to produce return on the research capital invested as well as to use Medicine2 procedures.**

Key Questions need to be addressed:

1. Diagnosis

- Different diagnostic tests, subgroups of population or patients with different characteristics.
- How is phased testing working in sleep apnea diagnosis?. Role of new technologies.
- Long-term consequences and impact in the clinical management
- Studies facing clinical and basic aspects for the better understanding and the better management.
- To develop networks in order to detect better the patients (family and physicians among others).

2. Treatment

- Comparative effects of different sleep apnea treatments, depending on different characteristics (patient's personal characteristics, different physiological variables (SaO2), among others).
- Pre-treatment characteristics of patients and compliance.
- Interventions to improve compliance in different treatments. Role of telemedicine.
- To develop networks to improve management and control of sleep apnea and follow-up (nurses, family, physicians….)
- Non CPAP treatment of sleep apnea.

Aims and objectives

The major aims are as follows:

1. Study the management and impact of sleep apnea in the new target populations mentioned above;

2. Develop new technologies to be applied in the diagnosis, treatment and follow up of patients with SAHS,

3. Work on transference protocols as well as a new cost-effective clinical protocols and

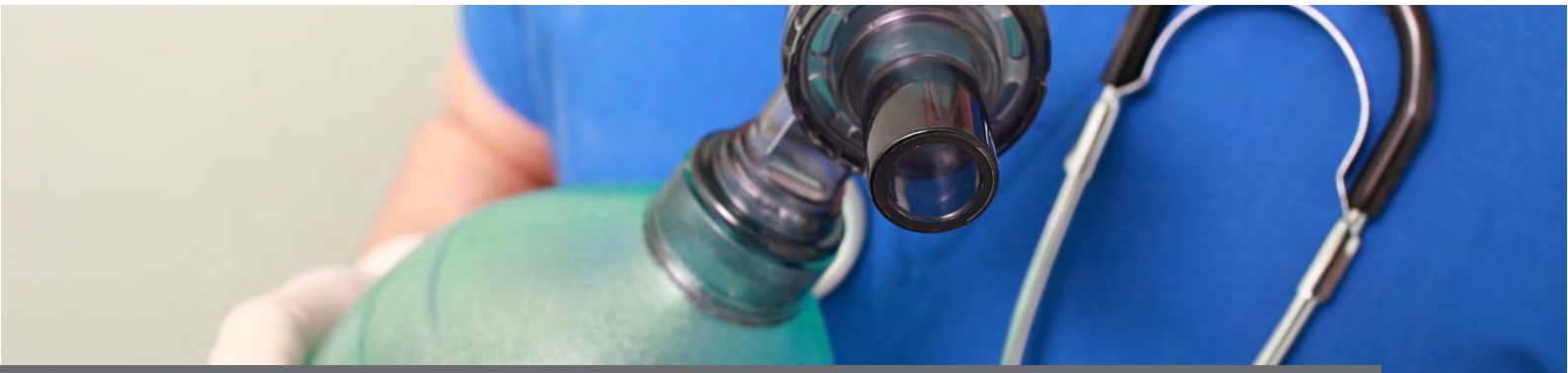
4. To start using the Medicine 2 system for working.

Main results in 2013

Publications:

- Esquinas et al. (2013). Rationale and Methodology of the Impact of Continuous Positive Airway Pressure on Patients With ACS and Nonsleepy OSA: The ISAACC Trial. Clinical cardiology, 36(9), OI:10,1002/clc.22166.
- Almendros I, Montserrat JM, Torres M, Dalmases M, Cabañas ML, Campos-Rodríguez F, Navajas D, Farré R. Intermittent hypoxia increases melanoma metastasis to the lung in a mouse model of sleep apnea. Respir Physiol Neurbiol, 186 (2013) 303– 307.

- Campos-Rodríguez F, Martínez-García MA, Martínez M, Durán-Cantolla J, de la Peña M, Masdeu MJ, González M, del Campo F, Gallego I, Marín JM, Barbe F, Montserrat JM, Farre R. Association between Obstructive Sleep Apnea and Cancer Incidence in a large multicenter Spanish Cohort. Am J Respir Crit Med, 2013; 187: 99-105.
- Almendros I, Wang Y, Becker L, Lennon FE, Zheng J, Coats BR, Schoenfelt KS, Carreras A, Hakim F, Zhang SX, Farré R, Gozal D. Intermittent hipoxia-induced changes in tumor associated macrophages and tumor malignancy in a murine sleep apnea model. Submitted. Am J Respir Crit Care Med. 2014; 189: 593-601.
- Isetta V, León C, Torres M, Embid C, Roca J, Navajas D, Farré R, Montserrat. JM. Telemedicine-based approach for obstructive sleep apnea management: building evidence. Interact J Med Res. 9 de febrero de 2014; 3(1):e6. doi: 10.2196/ijmr.3060.



Tuberculosis

Coordinator
Dr. Vicente Ausina

NEW RESEARCH AND INNOVATION ON TUBERCULOSIS: BASIC RESEARCH, PREVENTION, DRUG REGIMENS AND DIAGNOSIS.

Tuberculosis (TB) is a major global health problem. Each year, there are around nine million new cases of TB, and close to two million deaths. All countries are affected, but 85% of cases occur in Africa (30%) and Asia (55%), while India and China alone represent 35% . TB is closely connected with HIV. People living with HIV, represent over 10% of annual TB cases, and are up to 37 times more likely to develop TB than people who are HIV-negative.

Yet TB is, in most instances, a curable disease. More than 90% of people with drug-susceptible TB can be cured in six months using combinations of first-line drugs. Treatment of multidrug-resistant TB (MDR-TB) is more challenging, requiring the use of second-line drugs that are more costly, cause more severe side-effects, and must be taken for up two years. Cure rates for MDR-TB are lower, typically ranging from 50% to 70%

In 2006, the Stop TB Partnership launched the "Global Plan to Stop TB 2006-2015", a roadmap for scaling up prevention and treatment, for research and development, and for financing. By 2015, it is expected that we will have: point-of-care tests than can be used in health centres for diagnosing active TB, diagnosing latent TB infection and predicting the risk of progression to TB disease, and detecting drug resistance; a new, four-month TB treatment regimen for patients with drug-susceptible TB; at least one new drug on the marked for treatment of drug-resistant TB; a safer, higher-efficacy regimen for the treatment of latent TB infection; four new TB vaccine candidates in Phase III clinical trials for safety and efficacy. If no improvements in TB control are made, about 10 million people will die from TB by 2015.

This research programme is the result of evolution from previous versions of Corporate Research Programme on Tuberculosis since CIBERES consortium was established in 2006. **Some topics on the programme coincide with those listed in the "The Global Plan to Stop TB 2011-15".**

Aims and objectives

1. Basic research. New approaches to the nature of latent tuberculosis infection (LTBI) and its treatment in experimental models.

LTBI affects one third of humanity, with the lack of clinical symptoms, in which case it may go unnoticed. However, approximately 10% of these cases develop into active disease. **The main problem is lack of understanding of the underlying mechanisms of the infection and the evolution of the active dis-**

ease. In spite of the classic theory to explain the origin and progression of LTBI, the data obtained in recent years have generated scientific doubts. On the other hand, to date, and despite the existence of very useful animal models to evaluate the different characteristics of the new therapeutic candidates, **the presence of a model that is able to faithfully imitate the infection and disease in humans has not been established**. An exception is, perhaps, the model in pigs, established by Cardona et al. Thus, research based on the development of animal experimental models plays an ever more essential role in terms of its importance for translation.

In CIBERES researchers have been working in the field of basic research of latent tuberculosis infection since 1997. This work is essentially based on in an effort to determine its underlying mechanisms and novel **animal experimental models have been developed that can better imitate the infection and its progression into active disease** with the idea of being able to use them in the assessment of new drug or vaccine candidates developed by other research groups, with which stable collaboration networks can be established to facilitate the evolution of these candidates into clinical development.

2. Design and evaluation of new vaccine candidates against tuberculosis

The current BCG tuberculosis vaccine offers low protection against the respiratory forms of tuberculosis, among which are found the drug-resistant strains, as well as the high incidence of AIDS in third world countries and the difficulties in following treatment programmes, which makes a new, effective vaccine necessary to substitute the current BCG vaccine.

Since 1999, our efforts have been invested in creating a new, attenuated tuberculosis vaccine, studying the test concepts and developing this new attenuated live vaccine. An attenuated vaccine has been created based on the double deletion of the genes phoP and fadD the MTBVAC. The first vaccine based on attenuated M. tuberculosis satisfying the "Geneva consensus" safety criteria for entry of new TB vaccines into clinical trials. Taken together, GMP production of freeze-dried MTBVAC and rigorous preclinical characterization from mouse to non-human primates provide the bases for entry into first-in-human clinical trials.

3. Design and evaluation of new therapeutic strategies against tuberculosis (resistance, action and discovery of new drugs).

Anti-tuberculosis therapy constitutes one of the fundamental pillars in the battle against this disease. The success of the treatment can be compromised when the strains acquire resistance to any one of the drugs used in the treatment. Then the active drug arsenal against this disease is extremely limited. In addition various mechanisms of intrinsic drug resistance in *M. tuberculosis* could play a major role in favouring the acquisition of mutations that confer even greater levels of resistance.

Based on these facts, **discovering new, active drugs against *M. tuberculosis* is one of the main priorities of tuberculosis research at a world level.** Insights have been made in the usefulness of efflux inhibitors have companion drugs in the therapy of tuberculosis.

4. Design and evaluation of new diagnostic and molecular epidemiology methods in tuberculosis.

Effective control of TB is based on the rapid detection of M. tuberculosis, followed by the implementation of an adequate anti-tuberculosis therapy. As a result of several epidemiologic studies, new analytical challenges have been identified, for which a response must be given. Mainly, greater speed to obtain the genotypes, to identify the earliest transmission events, and thus facilitate the intervention is required. Likewise, the precision in identifying the transmission environment must be improved.

CIBERES researchers have made important contributions in the diagnosis of latent TB infection and TB disease. Molecular techniques are essential tools to improve the control of tuberculosis. These techniques allow the strains to be differentiated from different clonal origins with greater efficiency.

Main results in 2013

Publications:

- Construction, characterization and preclinical evaluation of MTBVAC, the first live-attenuated M. tuberculosis-based vaccine to enter clinical trials. Arbues A, Aguilo JI, Gonzalo-Asensio J, Marinova D, Uranga S, Puentes E, Fernández C, Parra A, Cardona PJ, Vilaplana C, Ausina V, Williams A, Clark S, Málaga W, Guilhot C, Gicquel B, Martín C. Vaccine. 1 de octubre de 2013. Volumen: 31 Número: 42 Páginas: 4867-73.
- Analysis of mutations in streptomycin-resistant strains reveals a simple and reliable genetic marker for identification of the Mycobacterium tuberculosis Beijing genotype. Villellas C, Aristimuño L, Vitoria MA, Prat C, Blanco S, García de Viedma D, Domínguez J, Samper S, Aínsa JA. Journal of clinical microbiology. Julio de 2013. Volumen: 51 Número: 7 Páginas: 2124-30.
- Ibuprofen therapy resulted in significantly decreased tissue bacillary loads and increased survival in a new murine experimental model of active tuberculosis. Vilaplana C, Marzo E, Tapia G, Diaz J, García V, Cardona PJ The Journal of infectious diseases. 15 de julio de 2013 Volumen: 208 Número: 2 Páginas: 199-202.

Spin-off:

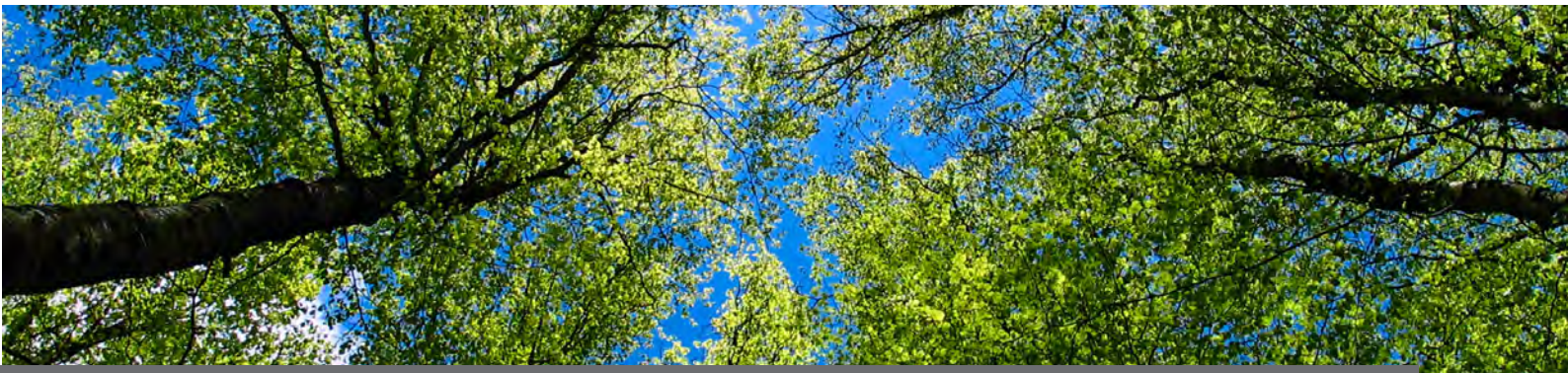
- Creación de una spin-off (MANREMYC. Manresana de Microbiologia SL) con vistas a la comercialización de un nuevo prebiótico que puede permitir acortar el tratamiento de la infección tuberculosa latente.

Fundraising:

- Fondos conseguidos en el 2013 por el PCI de la UE y de agencias nacionales han sido 1.741.391€

3

Internationalization of CIBERES Activity



Internationalization of Activity

One of the strategic objectives of CIBERES in 2013 was to continue promoting the process of internationalizing all aspects of its activity to enhance the quality of scientific and technological activities, employee training, the projection of the results and the creation of synergy in the international framework of cooperation.

In 2013 CIBERES continued with its commitment to internationalize its scientific activity considering that results of excellence can only be obtained in collaboration with the best international groups.

The 2010-2013 internationalization plan established the following objectives for 2013:

- Participation in and signing of collaboration agreements with international scientific institutions and companies.
- International certification of the Pulmonary Biobank Platform.
- Increase the no. of investigators who are part of the steering committees of the networks, consortiums and associations in which it is participating.
- Increase the no. of investigators who received international scientific awards and distinctions.
- Increase the no. of national investigators on editorial committees of international journals.
- Increase the no. of investigators evaluating international projects.

To achieve these objectives, CIBERES internationalization in 2013 can be seen in the following activities:

- Publishing articles and clinical guidelines in collaboration with international research groups.
- Developing projects in collaboration with international groups.
- Submitting and funding projects in international competitive calls for proposals.
- Entering into contracts with international industry.
- Coordinating with national and international agencies and offices, promoting the internationalization of research, among others:
  - Office of European Projects of Instituto de Salud Carlos III (OPE ISCiii).
  - Centro para el desarrollo tecnológico industrial (CDTI).
  - Innovative medicines initiative (IMI).
- Coordinating international projects.

- Promoting internationalization among CIBERES investigators.
- Training the CIBERES management staff in the area of internationalizing research.
- Other activities:
  - Conferences being given by CIBERES investigators in international forums.
  - Having CIBERES investigators on the editorial or scientific committee of international journals.
  - Having CIBERES investigators on the Scientific Committee of international scientific associations.
  - Further collaboration with international groups.
  - Hiring international staff.
  - Training its own staff abroad.
  - Evaluating international funding programmes.

Despite budget cutbacks in R&D&I and its internationalization, it can generally be said that CIBERES maintained internationalization results and activities in 2013 compared to previous years and achieved the objectives proposed for this period.

An example of this would be in relation to publications and projects where, as mentioned in the corresponding section, CIBERES improved its "International Collaboration" indicator in reference to the scientific production of an institution produced in collaboration with foreign institutions.

Actions of both Instituto de Salud Carlos III and of the Centro de desarrollo tecnológico industrial (CDTI) with the offices of international projects also continued. Joint actions were carried out with these entities intended for promoting topics of interest for CIBERES to include them in future calls for proposals of the Horizon Programme 2020.

In 2013, CIBERES managers participated, fundamentally online, in specific training in internationalization promoted by the European Commission through projects such as Fit To Health, or by other institutions such as the Innovative Medicines Initiative (IMI).

In 2013, CIBERES continued participating in and coordinating ongoing European projects in which it is a partner and/or coordinator, and several project proposals have been submitted for the final call for proposals for projects in the 7th Framework Programme. The objective of increasing participation in international projects was met, and this was done as project coordinators. CIBERES continued searching for and disseminating all those international calls for proposals that the research groups could submit a proposal to.

In the framework of planning the internationalization of CIBERES, which is an element having a transversal dimension, the internationalization activities performed by active Platforms, such as the Pulmonary Biobank Platform (PBC), the development of the European Initial Training Network Pulmonary Imaging Network (P-NET) project, Ref: 264864, of the FPVII-PEOPLE-2010-ITN, funded by the European Union and coordinated by CIBERES in the framework of the teaching programme, as well as communication and dissemination activities aimed at favoring internationalization of CIBERES activity which are described in each of the corresponding sections, must also be taken into account.

4

Transversal Platforms

for Supporting Research

Pulmonary Biobank Consortium

To help CIBERES groups in their research work, there are a number of transversal support platforms:

Scientific Director
Dr. Germán Peces-Barba

Manager
Dr. Cristina Villena

National Networking Biobank for Respiratory Diseases

The Pulmonary Biobank Consortium (PBC) was created in 2009 to promote research in respiratory pathologies and related diseases by means of supplying samples and data to any (national or international) investigator requesting them. This initiative is sponsored by the Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERES), in which there are 10 participating hospitals from 4 autonomous communities (Hospital U. 12 de Octubre, Hospital U. de Getafe, Fundación Jiménez Díaz-Capio, Hospital Clínic, Hospital U. Germans Trias i Pujol, Hospital U. de Bellvitge, Hospital del Mar, Hospital U. de Tarragona, Consorcio Hospital General U de Valencia and Hospital U. Son Espases), coordinating their activity in Hospital Universitario Son Espases (Balearic Islands).

Purpose

Providing well-characterized human biological samples to any investigator with a funded project to promote translational research in respiratory pathologies and related diseases.

Vision

The PBC's networking work is a result of the specific circumstances of the entity that creates it, strengthening multicentre collaborations and reinforcing participation in strategic initiatives to cover unmet and necessary needs in high-level national and international corporate networking projects.

Quality

The PBC's operation is certified as it meets the requirements of ISO standard 9001:2008, and its activity is registered in the ISCIII National Biobank Registry (B.0000471), passing its yearly external audits and evaluations.

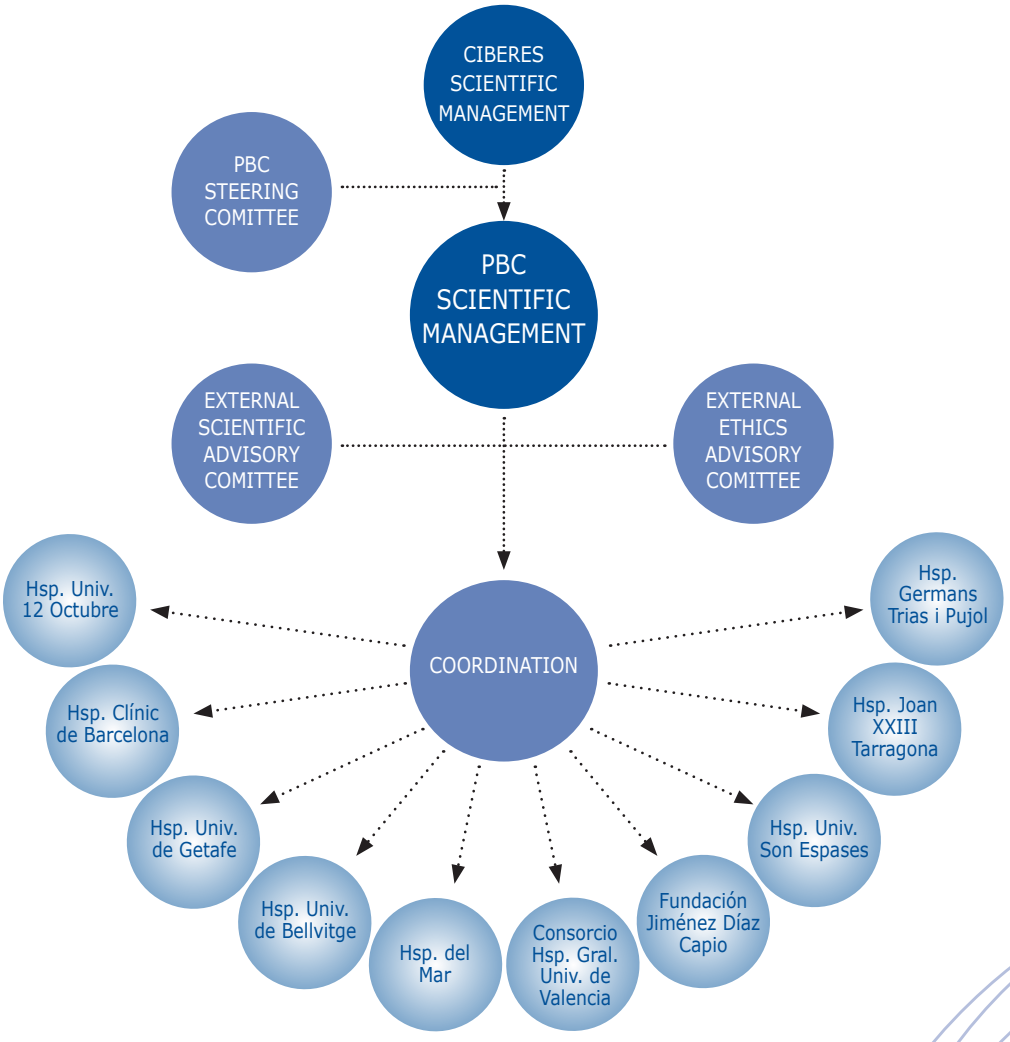
Structure

The PBC is organized like a consortium of hospital entities coordinated by the CIBERES for the organization, management and harmonization of clinically well-characterized samples. All this activity was agreed on and put into writing in collaboration agreements with the participating entities. Furthermore, the entire sample and clinical information collection system has been organized by means of creating

work groups in participating hospitals. These work groups consisting of leaders from the areas and departments involved to make sure the activity is performed correctly, and their commitments are also previously put into writing. A list of the institutions and people responsible for the activity can be found at http://biobancopulmonar.ciberes.org/index.php/es/redhospitales.

It has a coordination office consisting of 2 people, a Scientific Director, ten work groups with 57 affiliated people in the participating centres, a PBC Steering Committee, an External Ethics Advisory Committee and an External Scientific Advisory Committee.

Its organizational flow chart is as follows:



The **PBC Steering Committee** consists of delegated members of participating hospitals, CIBERES management, the Scientific Director and coordination of the PBC. Its function is to advise the Scientific Director, to handle planning and to make decisions affecting the PBC as a whole.

The **External Scientific Advisory Committee** is an independent, interdisciplinary advisory body whose basic functions consist of complying with scientific suitability and quality in using samples managed by the PBC. It consists of members who are experts in the fields involved and who are not associated with CIBERES.

Services

- Supplying tissue samples and blood derivatives complying with strict quality criteria (multicentre collections obtained and processed using the same standard operating procedures, the same requirements, recording tissue sample ischemia times) for related studies in respiratory pathologies.
- Supplying consensual and standardized clinical data for related studies in respiratory pathologies.
- Supplying images (CT scans) in original, anonymized DICOM files for related studies in respiratory pathologies.
- Centralized sample collection storage.
- National and international sample shipment management.
- Creating new collections in multicentre studies (management, coordination and training to obtain, handle, conserve and ship harmonized and standardized samples).
- Control, follow-up and audits on multicentre sample collections (both centralized and decentralized collections to assure the required quality requirements, compliance with the laws in force and customer satisfaction).
- Implementation of quality management systems.
- Standardized data recording platform.
- Counseling in ethical and legal aspects (creation, use and conservation of new sample collections or of retrospective samples collections under the laws in force).
- Scientific-technical counseling for the creation and use of new collections.
- Counseling in biobank management and creation.

Inventory

The number of cases recorded in the PBC amount to 1,618 donors (Table 1) from whom about 37,000 samples in total have been obtained (Table 2). Since the PBC was created, 25 patients were recruited on average per month, and most of them (about 90%) were recruited from lung cancer surgeries. However, in 2013 recruitment focused on obtaining healthy lungs and pathological lungs in the last stages of the disease. Ten healthy lungs from healthy patient organ donations and 36 explants (15 cases of severe COPD, 14 cases of Diffuse Interstitial Lung Disease, 6 cases of Pulmonary Hypertension and 1 case of Bronchiectasis) were included.

	Year						Total no. cases
Hospital Centre	**2009**	**2010**	**2011**	**2012**	**2013**	**2014***	
Fundación Jiménez Díaz-CAPIO	6	9	5	25	1		46
Hospital 12 de Octubre	33	89	77	67	25	11	302
Hospital Clínico de Barcelona	8	27	41	42	15	1	134
Hospital de Bellvitge	28	19					47
Hospital de Getafe	18	17	8	16	20	13	92
Hospital de Tarragona Joan XXIII			10	53	37	7	107
Hospital del Mar	19	29	19	39	30	9	145
Hospital General de Valencia	36	28	26	28			118
Hospital Germans Trias i Pujol				29	17	4	50
Hospital Son Espases	89	109	87	109	93	41	528
GRIPE Project			49				49
Total no. cases	237	327	322	408	238	86	1.618

*Table 1. Total number of cases recorded annually in the PBC in each of the participating hospitals. Some of the 58 recorded cases are in the process of being completed. *2014 is incomplete because it corresponds to data recorded at the time this report was being prepared.*

Thirty-seven percent of the patients who were recruited present an obstructive pattern, 13% present possible restrictive patterns and 27% present normal lung function. The rest (23%) are undetermined. In addition, 16% are non-smokers, 33% are regular smokers and 40% are former smokers who quit more than 6 months before the surgical intervention. The distribution by sex shows that the majorities of those who are affected are men (75%), Caucasians (98%), and people between the ages of 50-80 years old (88%). The diseases presenting the majority of co-morbidities are COPD (stages I and II), emphysema, asthma, bronchiectasis, and others with a history of tuberculosis and sleep apneas.

	Año						Total no. samples
Centro hospitalario	**2009**	**2010**	**2011**	**2012**	**2013**	**2014***	
Fundación Jiménez Díaz-Capio	168	257	157	1.016	57		1.655
Hospital 12 de Octubre	264	622	611	999	2.905	1.307	6.709
Hospital Clínico de Barcelona	120	385	795	950	352	4	2.606
Hospital de Bellvitge	525	372					897
Hospital de Getafe	458	422	198	370	622	287	2.357
Hospital de Tarragona Joan XXIII			162	1.360	854	113	2.491
Hospital del Mar	469	932	448	913	804	243	3.809
Hospital General de Valencia	296	219	223	306			1.044
Hospital Germans Trias i Pujol				860	474	106	1.440
Hospital Son Espases	2.019	2.659	1.946	2.635	2.704	1.700	13.663
Proyecto GRIPE			500				500
Nº Muestras Totales	4.319	5.868	5.040	9.409	8.772	3.760	37.171

*Table 2. Number of total samples recorded in the PBC every year in each of the participating hospitals. *2014 is incomplete because it corresponds to data recorded at the time this report was being prepared.*

The collected samples in the PBC are for the most part lung tissue (Tables 3-7) and peripheral blood derivatives (Tables 8-11), although the management and organization for collecting another type of samples demanded by the investigators (Table 12) was implemented at the end of 2013. In the following tables the total number of samples recorded annually according to type in each of the hospitals (Table 3-12), and described according to the type of preservation, in the case of lung tissue according to later applications (Table 3-7).

	Year						Nº samples (RNAlater)
Hospital Centre	**2009**	**2010**	**2011**	**2012**	**2013**	**2014***	
Fundación Jiménez Díaz-CAPIO	6	7	5	21	1		40
Hospital 12 de Octubre	34	87	76	66	28	11	302
Hospital Clínico de Barcelona	8	27	41	41	15	1	133
Hospital de Bellvitge	28	19					47
Hospital de Getafe	18	17	8	16	20	13	92
Hospital de Tarragona Joan XXIII			4	52	36	6	98
Hospital del Mar	19	29	18	37	29	9	141
Hospital General de Valencia	36	28	26	28			118
Hospital Germans Trias i Pujol				28	17	3	48
Hospital Son Espases	74	72	56	99	95	40	436
Total no. tissue samples (RNAlater)	223	286	234	388	241	83	1.455

*Table 3. Number of samples of lung tissue conserved in RNAlater recorded annually in the PBC in each of the participating hospitals. *2014 is incomplete because it corresponds to data recorded at the time this report was being prepared.*

Hospital Centre	Year						Nº Samples (Flash-frozen)
	2009	2010	2011	2012	2013	2014*	
Fundación Jiménez Díaz-CAPIO	6	8	5	21	1		41
Hospital 12 de Octubre	29	83	76	65	28	13	294
Hospital Clínico de Barcelona	8	27	41	41	15		132
Hospital de Bellvitge	28	19					47
Hospital de Getafe	18	16	8	15	18	13	88
Hospital de Tarragona Joan XXIII			9	46	26	3	84
Hospital del Mar	19	29	19	37	25	8	137
Hospital General de Valencia	29	17	21	24			91
Hospital Germans Trias i Pujol				28	17	3	48
Hospital Son Espases	71	72	56	99	81	34	413
Total no. tissue samples (Flash-frozen)	208	271	235	376	211	74	1.375

*Table 4. Number of samples of flash-frozen lung tissue recorded annually in the PBC in each of the participating hospitals. *2014 is incomplete because it corresponds to data recorded at the time this report was being prepared.*

Hospital Centre	Año						No. samples (Paraffin blocks)
	2009	2010	2011	2012	2013	2014*	
Fundación Jiménez Díaz-CAPIO	4	9	4	20	1		38
Hospital 12 de Octubre	33	85	65	66	26	11	286
Hospital Clínico de Barcelona	8	27	41	42	15	1	134
Hospital de Bellvitge	22	18					40
Hospital de Getafe	18	16	8	16	13	7	78
Hospital de Tarragona Joan XXIII			12	48	25		85
Hospital del Mar	18	29	19	34	20	8	128
Hospital General de Valencia	35	28	26	28			117
Hospital Germans Trias i Pujol				27	16	3	46
Hospital Son Espases	70	66	55	74	92	43	400
Total no. tissue samples (Paraffin blocks)	208	278	230	355	208	73	1.352

*Table 5. Number of samples of lung tissue fixed in formol and embedded in paraffin recorded annually in the PBC in each of the participating hospitals. *2014 is incomplete because it corresponds to data recorded at the time this report was being prepared.*

Hospital Centre	Año						No. samples (Parafor-OCT)
	2009	2010	2011	2012	2013	2014*	
Fundación Jiménez Díaz-CAPIO	6	6	5	21	1		39
Hospital 12 de Octubre	4		1	1	1		7
Hospital Clínico de Barcelona	8	27	41	41	15		132
Hospital de Bellvitge	21	16					37
Hospital de Getafe	18	17	8	16	20	13	92
Hospital del Mar	18	25	18	34	22	8	125
Hospital General de Valencia	27	15	21	25			88
Hospital Germans Trias i Pujol				26	15	3	44
Hospital Son Espases	69	60	46	75	79	32	361
Total no. tissue samples (Parafor-OCT)	171	166	140	239	153	56	925

*Table 6. Number of samples of lung tissue fixed in paraformaldehyde, frozen and embedded at Optimal Cutting Temperature (OCT) recorded annually in the PBC in each of the participating hospitals. *2014 is incomplete because it corresponds to data recorded at the time this report was being prepared.*

Hospital Centre	Year						No. samples (FF-OCT)
	2009	2010	2011	2012	2013	2014*	
Fundación Jiménez Díaz-CAPIO	5	9	5	21	1		41
Hospital 12 de Octubre	30	88	71	67	28	12	296
Hospital Clínico de Barcelona	7	27	40	41	15		130
Hospital de Bellvitge	22	16					38
Hospital de Getafe		1		1	2		4
Hospital de Tarragona Joan XXIII				37	2		39
Hospital del Mar		2					2
Hospital Germans Trias i Pujol				28	17	3	48
Hospital Son Espases	26	17	6	14	32	13	108
Total no. tissue samples (FF-OCT)	90	160	122	209	97	28	706

*Table 7. Number of samples of flash-frozen lung tissue embedded at Optimal Cutting Temperature (OCT) recorded annually in the PBC in each of the participating hospitals. *2014 is incomplete because it corresponds to data recorded at the time this report was being prepared.*

Hospital Centre	Year						Total no. blood samples
	2009	2010	2011	2012	2013	2014*	
Fundación Jiménez Díaz-CAPIO				24	1		25
Hospital de Tarragona Joan XXIII			1	51	35	7	94
Hospital del Mar		19		1	7		27
Hospital Germans Trias i Pujol				28	17	4	49
Hospital Son Espases	83	101	79	86	28	19	396
GRIPE Project-coordination			34				34
Total no. whole blood samples	83	120	114	190	88	30	625

*Table 8. Number of samples of total blood frozen less than 1 hour after venipuncture recorded annually in the PBC in each of the participating hospitals. *2014 is incomplete because it corresponds to data recorded at the time this report was being prepared.*

Hospital Centre	Year						Total no. serum samples
	2009	2010	2011	2012	2013	2014*	
Fundación Jiménez Díaz-CAPIO				24	1		25
Hospital de Tarragona Joan XXIII			10	52	37	7	106
Hospital del Mar		18		1	7		26
Hospital Germans Trias i Pujol				28	17	4	49
Hospital Son Espases	83	101	78	86	45	36	429
GRIPE Project-coordination			34				34
Total no. serum samples	83	119	122	191	107	47	669

*Table 9. Number of samples of serum frozen less than 1 hour after venipuncture recorded annually in the PBC in each of the participating hospitals. *2014 is incomplete because it corresponds to data recorded at the time this report was being prepared.*

Hospital Centre	Year						Total no. plasma samples
	2009	2010	2011	2012	2013	2014*	
Fundación Jiménez Díaz-CAPIO				24	1		25
Hospital de Tarragona Joan XXIII			7	51	35	7	100
Hospital del Mar		19		1	7		27
Hospital Germans Trias i Pujol				28	17	4	49
Hospital Son Espases	2	102	79	86	28	19	316
GRIPE Project-coordination			34				34
Total no. plasma samples	2	121	120	190	88	30	551

*Table 10. Number of samples of plasma frozen less than 1 hour after venipuncture recorded annually in the PBC in each of the participating hospitals. *2014 is incomplete because it corresponds to data recorded at the time this report was being prepared.*

Hospital Centre	2011	2012	Total no. leukocyte samples
Hospital de Tarragona Joan XXIII		12	12
GRIPE Project-coordination	49		49
Total no. leukocyte samples	49	12	61

Table 11. Number of samples of purified leukocyte concentrates recorded annually in the PBC.

Hospital Centre	2013	2014*	Total no. fatty tissue samples
Hospital Son Espases	1	10	11
Total no. leukocyte samples	1	10	11

*Table 12. Number of fatty tissue samples recorded annually in the PBC. *2014 is incomplete because it corresponds to data recorded at the time this report was being prepared.*

Participation in cooperative projects

Project	Funding entity / sponsor	Type of activity
MICINN research programme on pandemic flu strain A/H1N1	CIBERES-REIPI (Red Española de Investigación en Patología Infecciosa)-SEMICYUC (Sociedad Española de Medicine Intensiva, Crítica y Unidades Coronarias)	Counseling in sample methods, management and handling
OSIRIS Project (Pulmonary thromboembolism)	SEPAR (Sociedad Española de Neumología y Cirugía Torácica)	Creation of a multicentre collection of standard sample collection (pending signing the agreement)
Lung cancer staging project (strategic project of the Corporate Lung Cancer Programme)	SEPAR-FIS-CIBERES	Coordination, management and creation of a new network of hospitals for retrospective and prospective sample collection
From 2008–2012	ISBER	Committee participation: Marketing and Promotion
From 2011–present	ESBB	Participation in work group: Biospecimen Science
From 2012–present	National Biobank Network	Participation in LIBM work group

Multidisciplinary

Thoracic Surgery Dept., Anatomical Pathology Dept., Respiratory Medicine Dept., Intensive Medicine Dept., Transplant Coordination Teams with the National Organization Transplants, Nursing and Research of the participating hospitals all participate.

Cooperative structures PBC belongs to

The PBC is member of the new national structure called "National Biobank Network Platform" of the call for proposals of the 2013-2016 Strategic Action in Health coordinated by the former National Biobank Network. This new structure seeks to promote quality biobanks and give added value to the network, mainly by means of promoting collections having a strategic national value and improving harmonization and quality of the samples and the associated data.

PBC is also member of the following international scientific societies:

- International Society for Biological and Environmental Repositories (ISBER).
- European, Middle Eastern & African Society for Biopreservation & Biobanking (ESBB).

Activity

In 2013 8 requests for samples were received, sending samples that were available for 5 of them. As a result of providing samples on previous occasions, in 2013 several presentations were given in congresses, and several articles and theses were also written:

Congresses

- Sobradillo, P, et al. Role of NLRP3 in COPD. European Respiratory Society, Barcelona (2013).
- Faner, R, et al. Caspase-1 regulated cytokines in Chronic Obstructive Pulmonary Disease. XXXVII Congreso Nacional de la Sociedad Española de Inmunologia, Salamanca (2013).
- Catalina Balaguer, Amanda Iglesias, Mercedes Rodríguez, Ángel Carvajal, Ángel Ríos, Borja G Cosío, Carlos Río, María Antonia Durán, Àlvar Agustí, Ernest Sala. Expresión de la eritropoyetina y de su receptor (Epo-R) en tejido pulmonar de pacientes con EPOC. 46 Congreso Nacional SEPAR, Barcelona (2013).
- Faner, R, et al. The NLRP3 inflammasome in COPD. European Congres of Immunology. Glasgow (2012).

Articles

- Uhal BD, Dang M, Dang V, Llatos R, Cano E, Abdul-Hafez A, Markey J, Piasecki CC, Molina-Molina M. Cell cycle dependence of ACE-2 explains downregulation in idiopathic pulmonary fibrosis. Eur Respir J. 2013 Jul;42(1):198-210. (IF 6.355).
- R. Faner, P. Sobradillo, A Noguera, C. Gomez, T. Cruz, N. Gonzalez, E. Ballester, N. Soler, JI Arostegui, R. Rodriguez-Roisín, J. Yagüe, B Cosio, M. Juan, A. Agustí. Caspase-1 regulated inflammation in COPD patients during stability, exacerbations and recovery. Thorax, Submitted. (IF 6.840).
- Faner, R. Plos One, Submitted. (IF 3.730).
- Molina-Molina, M. BMC Pulmonary Medicine, Submitted (IF 2.760).

Thesis

- The detection and characterization of partial deletions of the human mitochondrial genome in lung tissue of patients with asthma and chronic obstructive pulmonary disease. Angela Steinmann, Honours thesis for the Bachelor of Biotechnology, University of Wollongong, Australia.
- Identification and characterization of large deletions of the mitochondrial genome in the lungs of asthmatics and sufferers of chronic obstructive pulmonary disease. Erin Treadwell, Honours thesis for the Bachelor of Science (Advanced), University of Wollongong, Australia.

Dissemination and teaching

Participation in national and international conferences and congresses:

- **European Respiratory Society Congress (Barcelona, 2013).**

  C Villena, P Giménez, F Pozo-Rodríguez, AP Gámez, JL Rodriguez-Peralto, A Maroto, AB Enguita, EM Arias, C Marrón, JC Meneses, JA Barberà, L Molins, J Ramírez, VI Peinado, A Esteban, L Jiménez, B de Olaiz, E Camarero, JA Aramburu, M Casares, I Sánchez, A Rosell, J Moya, E Condom, M Molina, S Estany, DR Montserrate, J Gea, J Minguella, L Pijuan, C Casadevall, R Pedreny, J Cortijo, R Guijarro, M Martorell, G Juan, J Lluch, G Peces-Barba, J Fernandez-Arias, M Escribano, J Zapatero, I Muguruza, M Fernández J, MJ Rodríguez-Nieto, E Monsó, P López de Castro, C Martínez, MT Fernández, A Marín, E Pedrosa, M García-Nuñez, JJ Sirvent, E Canalís, JF Garcia, MA Bodí, LL Gallart, A Carvajal, A Torrecilla, V Perna, O Gigirey, C Gómez, J Sauleda, B Cosio, A Agusti, on behalf of Pulmonary Biobank Consortium. CIBERES Pulmonary Biobank Consortium.

- **3rd Conference of the European, Middle Eastern & African Society for Biopreservation & Biobanking. (Verona, 2013).**

  C Villena, P Giménez, F Pozo-Rodríguez, AP Gámez, JL Rodriguez-Peralto, A Maroto, AB Enguita, EM Arias, C Marrón, JC Meneses, JA Barberà, L Molins, J Ramírez, VI Peinado, A Esteban, L Jiménez, B de Olaiz, E Camarero, JA Aramburu, M Casares, I Sánchez, A Rosell, J Moya, E Condom, M Molina, S Estany, DR Montserrate, J Gea, J Minguella, L Pijuan, C Casadevall, R Pedreny, J Cortijo, R Guijarro, M Martorell, G Juan, J Lluch, G Peces-Barba, J Fernandez-Arias, M Escribano, J Zapatero, I Muguruza, M Fernández J, MJ Rodríguez-Nieto, E Monsó, P López de Castro, C Martínez, MT Fernández, A Marín, E Pedrosa, M García-Nuñez, JJ Sirvent, E Canalís, JF Garcia, MA Bodí, LL Gallart, A Carvajal, A Torrecilla, V Perna, O Gigirey, C Gómez, J Sauleda, B Cosio, A Agusti, on behalf of Pulmonary Biobank Consortium. Quality management system on a multicenter biobank: challenges and opportunities.

- **4th Congress of the National Biobank Network (Madrid, 2013).**

  C Villena, P Giménez, F Pozo-Rodríguez, AP Gámez, JL Rodriguez-Peralto, A Maroto, AB Enguita, EM Arias, C Marrón, JC Meneses, JA Barberà, L Molins, J Ramírez, VI Peinado, A Esteban, L Jiménez, B de Olaiz, E Camarero, JA Aramburu, M Casares, I Sánchez, A Rosell, J Moya, E Condom, M Molina, S Estany, DR Montserrate, J Gea, J Minguella, L Pijuan, C Casadevall, R Pedreny, J Cortijo, R Guijarro, M Martorell, G Juan, J Lluch, G Peces-Barba, J Fernandez-Arias, M Escribano, J Zapatero, I Muguruza, M Fernández J, MJ Rodríguez-Nieto, E Monsó, P López de Castro, C Martínez, MT Fernández, A Marín, E Pedrosa, M García-Nuñez,

JJ Sirvent, E Canalís, JF Garcia, MA Bodí, LL Gallart, A Carvajal, A Torrecilla, V Perna, O Gigirey, C Gómez, J Sauleda, B Cosio, A Agusti, on behalf of Pulmonary Biobank Consortium. Implantación de un sistema de gestión de la calidad en un biobanco multicéntrico.

- **CIBERES Training Workshops (Buñola, 2013).**

  C Villena, P Giménez, F Pozo-Rodríguez, AP Gámez, JL Rodriguez-Peralto, A Maroto, AB Enguita, EM Arias, C Marrón, JC Meneses, JA Barberà, L Molins, J Ramírez, VI Peinado, A Esteban, L Jiménez, B de Olaiz, E Camarero, JA Aramburu, M Casares, I Sánchez, A Rosell, J Moya, E Condom, M Molina, S Estany, DR Montserrate, J Gea, J Minguella, L Pijuan, C Casadevall, R Pedreny, J Cortijo, R Guijarro, M Martorell, G Juan, J Lluch, G Peces-Barba, J Fernandez-Arias, M Escribano, J Zapatero, I Muguruza, M Fernández J, MJ Rodríguez-Nieto, E Monsó, P López de Castro, C Martínez, MT Fernández, A Marín, E Pedrosa, M García-Nuñez, JJ Sirvent, E Canalís, JF Garcia, MA Bodí, LL Gallart, A Carvajal, A Torrecilla, V Perna, O Gigirey, C Gómez, J Sauleda, B Cosio, A Agusti, on behalf of Pulmonary Biobank Consortium. CIBERES Pulmonary Biobank Consortium.

Dissemination with informative brochures, the web page, informative newsletters, being listed in the catalogs of international organizations and press notes:

- 02/28/2013 "The CIBERES Pulmonary Biobank Platform, the first biobank focusing on research on respiratory diseases registered in the National Registry"
- 12/9/2013 "The CIBERES Pulmonary Biobank Platform incorporates healthy lungs and dieseased lungs that are hard to come by for research".

Training provided by:

- University Master's degree in Biobanks (Universidad Católica de Valencia).
- University Master's degree in Translational Medicine (Universidad de Barcelona).
- University Master's degree in Health Law (Universitat de les Illes Balears).

Technology Transfer Platform

Coordinator
Dr. Lluís Blanch

Manager
Dr. Cristina Broceño

The Technology Development and Transfer Platform (PDTT-CIBERES) is a transversal instrument of CIBERES the primary purpose of which is to boost the technological research and development activity of our groups in the field of respiratory medicine and to focus the results on clinical translation and corporate transfer to companies. The PDTT is a unified path for channeling technology transfer and innovation offers and demands for CIBERES.

The objectives of the PDTT are:

- To promote innovation and transfer in CIBERES.
- To increase the projection and exposure of the technological activities of CIBERES.
- To ensure an operative, fast and effective response of the entire transfer process to investigators and to CIBERES.
- To protect the Intellectual Property Rights of CIBERES and its investigators.
- To achieve good coordination and communication between the different CIBERES transfer/innovation agents.

2013 PDTT action summary

Within its capabilities, the PDTT, carries out all the actions necessary for promoting innovation and transfer of CIBERES results. The actions are grouped by lines of action. The following has been done throughout 2013:

1. Promoting innovation in CIBERES

- **Promoting innovation among investigators. B**y means of individual interviews and in presentations of the PDTT on innovation at Scientific Workshop (round table with 6 innovative CIBERES investigators and discussion concerning questions about innovation) and the annual CIBERES Training Workshop.
- **Continuous counseling in relation to intellectual property and transfer for hired and associated investigators.**
- **Managing the 2012 joint CIBERES-BBN-SEPAR multidisciplinary projects.**
- **Managing CIBERES intellectual property.**

Assessment of ideas.

In 2013 the PDTT evaluated 6 ideas. For 3 of them, the PDTT led the assessment by means of evaluating the state of the art and the market. The other 3 were led by majority co-owning institutions. For all 6, interest was evaluated and the information and protection procedure was managed together patent co-owners, inventors and agents.

The following table shows the ideas at CIBERES that are currently in a protection and/or company search phase:

CIBERES Group	Title of the Invention	Ownership	Transfer leader	Status
17	Method of genotyping bacterial clones by IS	IGTP: 50% / CIBERES: 50%	CIBERES	Seeking company
23	miRNA Biomarkers set for Diffuse Alveolar Damage	CIBERES: 66,7% /FIB Hospital Universitario de Getafe: 33,3%	CIBERES	In collaboration agreement with a company
35	miRNA Biomarkers for Assessment of CPAP use in SAOS and RH patients	U. Lleida: 50% / 50%: CIBERES	IRB Lleida/ CIBERES	Evaluating market
29	VILI Early Diagnosis by Microparticles.	CIBERES: 66,6 % / Sistema Canario Salud: 33,3%	CIBERES	Seeking company

Patent management.

Throughout 2013 up until January 2014, 4 new patents listing CIBERES as a co-owner were filed, and all the steps required for the 11 patents were taken. These steps include: requesting and evaluating budgets, specifications, information, communication with co-owners, inventors and agents, filing patent extensions, performing timely follow-up and filing corrections and applications in a timely manner; drafting and managing specific agreements with inventors, and co-ownership, assignment, non-disclosure and collaboration agreements, and closing reports….

All the current patents in which CIBERES is listed as an owner are shown in the following table:

Date and Priority Application No.	Title of the invention	CIBERES group	Owners	Extensions	Transfer leader	Status
16/12/2009 P200931177	Detection of streptococcus pneumoniae through magneto-amperometric genosensors using lyta gene-specific primers and probes	2	CSIC: 50% UCM: 26% CIBERES: 24%	PCT/ ES2010/070836 19/12/10	CSIC	Active. licensed to Alphasip date: 12/19/2012
17/12/2009 P200931186	Use of seconeolitsine and n-methyl-seconeolitsine for the manufacture of medicaments	3	ISCIII: 50% U. Valencia: 40% CSIC: 5% CIBERES: 5%	PCT/ ES10/070808 03/12/2010	ISCIII	Spanish patent in force. PCT abandoned
29/07/2010 ES 201031183	Device for generating an obstruction of the upper airways in animals	12	UB: 33,3% IDIBAPS: 13,3% H. Clinic: 33,3% CIBERES: 20%		Univ. de Barcelona	Abandoned
28/12/2010 P201031978	Pyrimidine urea-derived compound for treating inflammatory diseases	29	CIBERES: 50% U.La Laguna: 25% Sistema Canario Salud: 25%	PCT/ ES2011/070822 25/11/2011	CIBERES	Spanish patent in force. PCT abandoned

08/11/2011 P201131785	Use of a chemical compound derived from a 1,2,3,5-tetrasubstituted pyrole in the preparation of a drug for use in treating inflammatory diseases involving processes of cellular apoptosis	29	CIBERES50%/U. La Laguna 25% / Sistema Canario Salud 25%	PCT/ ES2012/070767 31/10/2012	CIBERES	Abandoned
24/11/2011 EP11382362	Engineered stem cells and their therapeutic use	16	IDIBELL50% / FUVall de Hebron 37,5%/ CIBERES12,5%	PCT/ ES2012/070823 23/11/2012	IDIBELL	Active. Licensed to Histocell 12/4/2012
11/10/2012 EP 12382393.2,	Marker for assessing the risk of developing acute kidney injury	23	CIBERES 66,7%/ FIB Hospital Universitario de Getafe 33,3%		CIBERES	Abandoned
31/12/2012 P201232075	Cyclopentanone compounds, method for obtaining them and their use in the preparation of a drug used for treating inflammatory diseases associated with cellular fibrotic and apoptotic processes	29	CIBERES50%/U. La Laguna 16,67% /Sistema Canario Salud 16,67%/ CSIC 16,67%	PCT/ ES2013/070909 20/12/ 2013	CIBERES	Active
15/06/2012 P201200640	Inactivated mycobacteria for oral use in the prevention of tuberculosis	17	Institut germansTries i Pujol (IGTP) 66,7%/ CIBERES 33,3%	PCT/ ES2013/000145 13/06/2013	IGTP	Active. Licensed to Manremyc.
28/05/2013 P201330777	Improved bactericidal enzybiotics against pneumococcus and other bacteria	34	CSIC 90%/ CIBERES10%	PCT. Mayo 2014	CSIC	Active
10/01/2014 EP14382007	Methods and systems for providing oxygen to a patient	5/ 30	IDIBELL57,5%/ UAB 37,5%/ CIBERES 5%		IDIBELL	Active
17/03/2014 EP14382093	Micellar nanoparticles containing antitumoralglycosides	31	CNIC 40%/CSIC 40%/CIBERES 20%		CNIC	Active

Managing the transfer to a company.

The PDTT, in collaboration with Parc Tauli, Innovation Unit has conducted 3 new market studies on CIBERES ideas, and usefull in the search for companies and to present the product to them.

To improve exposure of our technology offer the transfer section on our web page has been updated, and a new section dedicated to the CIBERES technology offer has been created. This section currently presents 10 technology offers from CIBERES ideas (these documents were drafted by the PDTT for the CIBERES web page and sent to companies and include proposals that are co-owned by CIBERES as well as patents belonging to CIBERES groups). Specific documents in relation to these offers have also been prepared so they can be disseminated in the Europe Enterprise Network (EEN).

This documentation has been necessary in order to present the technology to specific companies in the area. Companies have been actively sought and contacted as regards the product being presented. At least 10 companies have been contacted for each technology transfer patent managed by CIBERES PDTT.

For the purpose of assuring an operative response in the protection and transfer process, the PDTT has also been responsible for drafting and/or revising and managing non-disclosure agreements, collaboration agreements and licensing agreements, among others.

2. Promotion of CIBERES innovation outside CIBERES

Besides disseminating the CIBERES technology offer directly to companies, the PDTT works to promote the ideas and the capabilities of our work programmes and of our investigators and groups. Some of the work done throughout 2013 includes:

- **CIBERES requesting to be and being accepted as a collaborator in the ITEMAS Platform.** Participation in the ITEMAS Assessment Work Group.
- **Drafting and preparing CIBERES documentation to present at meetings, to companies and to entities.** PDTT posters, CIBERES PDTT dossiers, technology offer and objectives of the Corporate Programmes.
- **Sending notifications relating to company/innovation to the CIBERES web page.**
- **"Network CIBERES".** Presenting CIBERES, its offer and its capabilities (co-owned by CIBERES or CIBERES groups) in Forums, to companies, to entities that support innovation, to networks, at informative meetings and in specific training courses.

3. Establishing systematic procedures in innovation and transfer in CIBERES.

To constantly improve the transparency of procedures in the transfer/innovation area at CIBERES, and to therefore generate trust and a feeling of proximity to these subjects among CIBERES investigators and the consortium entities, the PDTT established certain processes for 2013 which include:

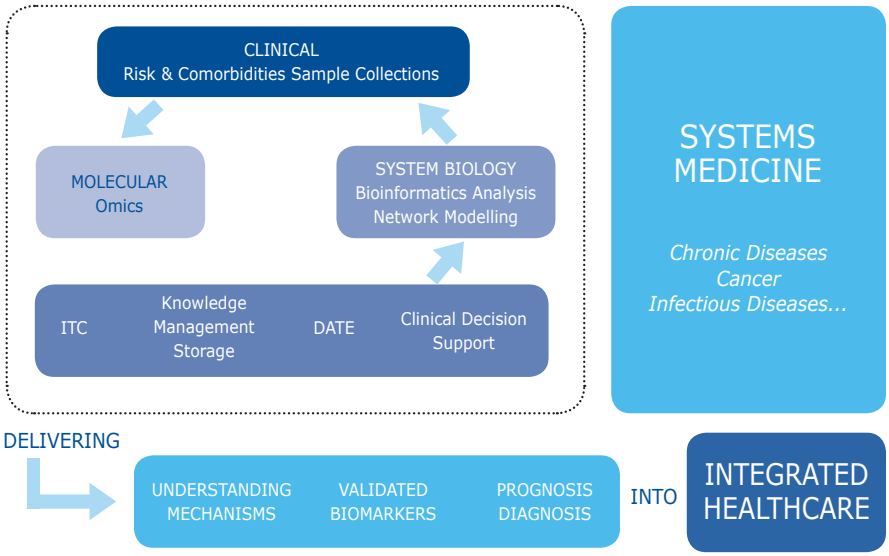
- **Annual Meeting and timely consultation with the CIBERES Innovation Committee.** To discuss topics relating to innovation and transfer in CIBERES, to advise the Scientific Management and establish processes.
- Under the collaboration agreement signed at the end of 2011 with the Innovation Unit of the Corporació Sanitaria Parc Taulí, PDTT has been working on the **systematization of procedures in innovation and in the valorization and transfer of ideas.**
- **A document describing the CIBERES Intellectual Property Guidelines, agreed on by the different CIBERES Consortium Institutions, was submitted to ISCIII.** This document establishes the basis for the rights and duties of CIBERES, of its investigators and of the Consortium Institutions as regards IP.
- **Drafting, delivering and correcting model documents** to enforce legal compliance in the framework of the CIBERES. Non-disclosure agreements, inventor agreements, co-ownership agreements, collaboration agreements with companies, consortium agreements, assignment agreements, licensing agreements....
- **Assistance in the CIBER unification process for CIBERES transfer.** In addition to drafting patent **specifications and PDTT action plans,** PDTT presentations, executive summaries, minutes, etc.

Systems Biomedicine Unit

Systems Biology is a new approach to biomedical research that seeks to integrate relevant information on several levels (omic, clinical and socio-environmental). Its impact on the diagnosis, classification and treatment of diseases can be quite significant. This transfer is expected to lead to the so-called "P4 Medicine" (Predictive, Preventive, Personalized and Participatory).

It is a transversal subject with a huge potential and future that globally integrates genomic, proteomic and metabolomic information through bioinformatic tools.

CIBERES therefore promotes the organization of a Systems Biomedicine Unit in collaboration with other institutions which allows starting up such research approach.



This initiative has been implemented simultaneously with the following actions:

- Identifying areas and projects that allow developing "Success Stories".
- Promoting alliances and collaborations with other institutions and industry. Collaboration with Harvard University (Prof. Al Barabasi) and the Institute for Systems Biology (Seattle, USA).
- Assessing the possibility of including this field in the training plan.
- Promoting the signing of agreements providing CIBERES with bioinformatic services.

5 Teaching Programme

Teaching Programme

Coordinators
Dr. Joan A. Barberà
and Dr. Ana Obeso

The primary objectives of the training and teaching programme are:

- To promote the acquisition of integrated clinical-basic knowledge among CIBERES investigators to provide a translational approach to the scientific objectives.
- To boost interest for research in respiratory diseases among younger people undergoing training within the field of Biomedicine so that they can nurture future CIBERES research teams, as well as attract those who are the most talented.
- To facilitate interaction and mobility of staff between the teams integrated in CIBERES to improve their technical abilities and scientific capacity.

Three action programmes were established to achieve these objectives, and their activity in 2013 included:

Training programme for research staff

Research Initiation Grants (BII).

This programme was considerably successful in CIBERES because of the interest in the call for proposals and because of the results obtained. The grants can be used as aid to young investigators to begin their training. For 1 year, they are a part of a research project funded by official bodies comprised within one of the research groups forming part of CIBERES. The intention is that in that year, the grant holders can access an official research staff training programme (FPI) and be linked to the CIBERES group. 66% of the grant money is provided by the CIBERES training and teaching programme and 33% of it is provided by the group actually receiving the grant holder.

Like in previous years, according to available budget, 5 grant agreements for grants awarded at the end of 2012 were developed in 2013. 5 grants were offered again in the last quarter of 2013 (BII 7th call for proposals), and those grants were awarded in December 2013.

Mechanisms for the evaluation of the results of this programme by both the CIBERES training committee and by the grant holders themselves were implemented in 2010 according to the recommendations of the External Scientific Committee. These mechanisms of evaluation were maintained in 2013.

Implementation of the Initial Training Network Pulmonary Imaging Network (P-NET), Ref: 264864, of the FPVII-PEOPLE-2010-ITN, funded by the European Union and coordinated by CIBERES.

The π-net ITN project, which started in October 2010, brings together the efforts of different European Research Teams to contribute to the pulmonary functional field in MRI (Magnetic Resonance Imaging). π-net proposes research and training activities that are complementary to and highly interconnected with these functional studies. The objective of the main line of research is to apply the MRI technique for diagnosis (human and preclinical activities) and treatment (only preclinical), to coordinate lung diseases (COPD, lung cancer, cystic fibrosis, asthma) without excluding the possibility of other optical techniques (nuclear, CT and optical imaging) and molecular studies (including molecular optics and metabolomic analysis) that may be of use. π-net proposes a training programme to provide new, educational, multidisciplinary, technical ESR subject matter with a high scientific level for animal study, MRI and other optical techniques, and translational aspects of research.

The project network is formed by 10 groups, located in 5 countries (Spain, France, United Kingdom, Germany and Sweden). The centres have investigators with prior networking experience and investigators with a high and qualitative percentage of scientific production and with experience in physics, therapy, clinical and physiopathological applications of MRI and the molecular aspects of respiratory diseases.

CIBERES set aside in their budget to hire two Early-Stage Researchers or ESRs (juniors investigators) to carry out the proposed activities in the work programme submitted to the European Union. The contract has a 3-year term. The following two ESRs were hired in 2011 after the relevant call for proposals:

Name	Country of Origin	Work centre	CIBERES group	Investigator in charge CIBERES	First date of employment	End date
Hugo Groult	France	CNIC	31	Jesús Ruíz-Cabello	24/03/2011	23/03/2014
Pablo Cardinal	Uruguay	Hospital de Getafe	23	Andrés Esteban	20/05/2011	19/05/2014

* 2012 training activities

Two training activities (webinars) and the Mid-term Review Meeting, held in Mallorca with a very satisfactory result, were conducted in fiscal year 2012:

Meeting	Activity	Dates	Organizer	Location
1	*New PINET Website*	31 Mayo 2012	CIBERES	Virtual (Webinar)
2	*Introduction to patents*	17 Julio 2012	CIBERES	Virtual (Webinar)
3	*Mid-term Review Meeting*	September 28-29, 2012	CIBERES	Virtual (Webinar)

Improvement and Mobility Programme

There are currently 3 lines of action:

- **Co-funding registration fees** (generally for 3rd cycle university courses). Modules of up to 500 Euros/module.
- **Travel expenses** for attending training courses or activities outside of one's place of residence. Modules of up to 500 Euros/module.
- **Co-funding stays** in another city for learning techniques. Modules of up to 1200 Euros. A total of 16 aid packages is envisaged.

Nineteen requests were submitted in 2013, and they were all provided with funding. The following table shows the request for 2013 and the resolutions handed down in the framework of this programme:

Call for proposals for improvement and mobility. 2013 resolutions

Resolution	Name	Group	Type of request		
				Travel Expenses	Stays
25ª	Laura Chimenti	33 (Lluís Blanch)	√	---	---
	Ester Puig	22 (Joaquim Gea)	√	---	---
	Mercè Mateu	22 (Joaquim Gea)	√	---	---
	Marina Benito	31 (Jesús Ruiz.-Cabello)	---	√	---
	David Moranta	08 (José A. Bengoechea)	√	---	---
	Manuel Sánchez	35 (Ferran Barbé)	---	---	√
	Sara Yubero	24 (Constancio González)	---	---	√
	Raquel Herrero	23 (Andrés Esteban)	√	---	---
26ª	Andrea Martínez	28 (F.Pérez-Vizcaíno)	√	---	---
	Arnau Domenech	19 (Josefina Liñares)	---	√	---
	Bianca Barreira	28 (F.Pérez-Vizcaíno)	√	---	---
	Daniel Morales	28 (F.Pérez-Vizcaíno)	√	---	---
	Ioanna Kalograiaki	34 (Margarita Menéndez)	---	---	√
	Izaskun Bilbao	31 (Jesús Ruiz-Cabello)	---	√	---
	Laura Millares	30 (Eduard Monsó)	---	√	---
	Nuria Coll	06 (Joan Albert Barberà)	---	---	√
	Nuria Esther Cabrera	29 (Jesús Villar)	---	---	√
	Palma Rico	34 (Margarita Menéndez)	---	---	√
	Rachele Pandolfi	28 (F.Pérez-Vizcaíno)	√	---	---

According to the recommendations of the External Scientific Committee, more restrictive criteria are applied to receive a grant after fiscal year 2010. Close follow-up of the grant holder's actions is conducted, and internships in foreign centres and investigator exchanges between CIBERES groups in particular are promoted.

Programme to Promote interest in the Respiratory Research

Research staff training conference

As occurred from the start, the fourth conference was held in Mallorca on October 17 and 18, 2013, with the participation of over 70 investigators and a very successful discussion and interaction transpired between them. 36 posters and 10 oral communications were presented by the younger investigators (recent predoctoral and postdoctoral investigators) and 6 wonderful lectures were given by 6 consolidated CIBERES investigators.

In 2013 the organizational logistics of the Conference was handled by CIBERES Central Office, continuing with its aim to reduce conference cost.

This conference is held every year, so the seventh installment of said conference is expected to be held in Valladolid in the fall of 2014.

Agreement with the Universitat de Barcelona and the Universitat Pompeu Fabra to develop the Respiratory Medicine Masters Programme.

By means of this agreement, CIBERES assigns a budget item intended for co-funding up to 30% of the amount of the registration for students belonging to any of the CIBERES groups. Registration co-funding is expected to be maintained. For next year, the Masters Programme will fundamentally be virtual, so this will make it easier for students located in different Spanish cities to attend. At the end of the course how the Masters Programme activities are developed will be assessed with a view to continuing with co-funding.

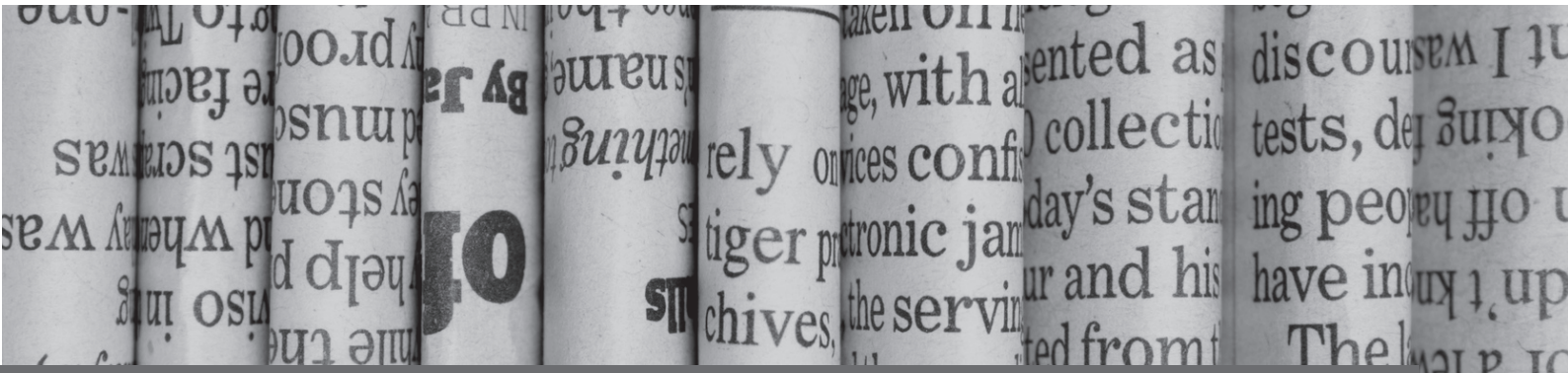
The following aid was granted in the 2012-2013 course:

Student	Group	PI
Alejandro Robles Pérez	Group 5	César picado
Anna Rodó Pin	Group 22	Joaquim Gea
Mercè Mateu Jiménez	Group 22	Joaquim Gea
Roberto Chalela Rengifo	Group 22	Joaquim Gea
Xavier Alsina Restoy	Group 6	Joan Albert Barberà

2012-2013 actions for improvement

- Align actions of the training plan with the training needs of the CIBERES Corporate Research Programmes (CRPs).
- Expand training actions intended to promote internationalization of CIBERES. Inclusion of a presentation about internationalization of scientific research at the CIBERES teaching conference held in October 2013.
- Promote the "culture" of innovation and transfer of research results.
- Increase scientific collaboration with other organizations working in the field of respiratory diseases.
- Implement the action recommendations resulting from the CIBERES training needs study performed in 2011, proposing a draft for a system for evaluating the impact results of the training activities.

5 Scientific Communication



Scientific Communication

The communication activities of the CIBER de Enfermedades Respiratorias from 2012 continued on into 2013.

Social networks such as Twitter were therefore used, and the daily news service for the respiratory sector was consolidated through the CIBERES web page. The newsletter listing calls for proposals, awards, courses and other relevant events considered to be of interest for investigators, particularly for our CIBER, as well as the CIBERES: TITULARES newsletter, which includes the Centre's most relevant news, were also sent out monthly.

Like in previous years, communication supported coordination of the 7th Communication Conference of CIBERES, held in June at the Escuela Nacional de Sanidad de Madrid, and of the 6th Training Conference for Predoctroal and Postdoctoral Investigators, held in October in Mallorca.

External Communication provided CIBERES and the scientific publications holding the highest social interest with exposure by handling press notes, media outlets and digital encounters in the press.

As regards cooperation between CIBER Communication Departments, the events held during 2013 Science Week must be pointed out. A round table was held in Barcelona in November at the CIBEK centre, where the 9 CIBERs participated and put forth 9 practical cases of translational research serving the patient. 9 mini interactive scientific CIBER workshops were given in Madrid at Instituto de Salud Carlos III to 200 students in the last few years of secondary school.

Finally, the participation of CIBERES in 2013 in the European Communication project, CommHERE, which started in October 2011 and funded with 2M Euros, must be highlighted. CommHERE is led by the Karolinska Institute of Sweden, and CIBERES participates in the project as a Third Party associated with the Instituto de Salud Carlos III, an official partner of the project. It primary objective is to improve the communication and management of knowledge of the results obtained in European projects in the area of health to the mass media, to the general public and to another target public, including the European Commission, within the European Union.

6
Research Groups

PROGRAMME:
COPD / Fibrosis

Group 10

Group Members

STAFF MEMBERS

Iglesias Coma, Amanda
Sunyer Dequiogiovanni, Gemma

ASSOCIATED MEMBERS

Barceló Martín, Bernardino
Faner Canet, María Rosa
Ferrer Balaguer, Joana Maria
García-Cosío Piqueras, Fco. de Borja
González Sánchez, Nuria
López Zamora, Meritxell
Molins López-Rodo, Laureano
Noguera Bennaser, Francisca Ana
Pons de Ves, Jaime
Ríos Olivencia, Angel
Sala Llinas, Ernest
Sauleda Roig, Jaume
Sibila Vidal, Oriol
Soler Cataluña, Juan José
Togores Solivellas, Bernat
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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 polimorbility " 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

- Polkey MI, Spruit MA, Edwards LD, Watkins ML, Pinto-Plata V, Vestbo J et al.. Six-minute-walk test in chronic obstructive pulmonary disease: minimal clinically important difference for death or hospitalization.Am J Respir Crit Care Med. 2013 Feb 15;187(4):382-6.
- Rennard SI, Vestbo J, Agustí A. What is chronic obstructive pulmonary disease anyway?: Continua, categories, cut points, and moving beyond spirometry.Am J Respir Crit Care Med. 2013 May 15;187(10):1036-7.
- Roche N, Reddel HK, Agusti A, Bateman ED, Krishnan JA, Martín RJ et al.. Integrating real-life studies in the global therapeutic research framework.Lancet Respir Med. 2013 Dec;1(10):e29-30.
- Müllerova H, Agusti A, Erqou S, Mapel DW. Cardiovascular comorbidity in COPD: systematic literature review.Chest. 2013 Oct;144(4):1163-78.
- Faner R, Cruz T, Agusti A. Immune response in chronic obstructive pulmonary disease.Expert Rev Clin Immunol. 2013 Sep;9(9):821-33.

Highlights

PROJECTS:

- Instituto Carlos III- Project –PI12/01117: "Capacidad regenerativa pulmonar en pacientes con EPOC: análisis integrado de la funcionalidad de las células madre y el micro-ambiente inflamatorio". Duration 3 years (2013-2015). IP: Alvar Agustí.
- "Envelliment pulmonar prematur i MPOC". Duration 2 years.(Obra Social de la Caixa) RecerCaixa. 2012-2013. Barcelona. IP: Alvar Agusti.
- Research project: "Riboleucograma en la Enfermedad Pulmonar Obstructiva Crónica". Fundación Mutua Madrileña. Duración: Duration:1 year (2013). IP: Alvar Agusti.
- PI192/2012: Detección y correlación de células madre pulmonares y micro-ambiente inflamatorio en pacientes con EPOC.Entidad financiadora: SEPAR. Duration:2 years 2013-2014 IP: Maria Rosa Faner Canet.
- Title: Detección y correlación de células madre pulmonares y micro-ambiente inflamatorio en pacientes con EPOC. Entidad financiadora: FUCAP. FUNDACIÓ CATALANA DE PNEUMOLOGIA. Duration: 2013-2014.IP: Maria Rosa Faner Canet.
- Project 065. " Epigenética e Inflamación Sistémica persistente en la EPOC" Becas Separ 2013. Duration 2 years 2014-2015.

COURSES OR EDUCATIONAL:

- Scientific coordinatoro. IX International Symposium of Pulmonolgy Siglo XXI. Welcome session and presentation. Summary and closing. Madrid 15/16 February 2013
- "Ens serveix d'alguna cosa el GOLD ABCD?" Scientific Sessions of Pulmonology and respiratory allergy. Hospital Clinic i Provincial de Barcelona. 22 January 2013
- Hacia la Medicina Personalizada en EPOC. VII Scientific Conferences of CIBERES. Madrid 20-21 June 2013
- Medicina Personalizada y Enfermedades Crónicas. UIMP Barcelona. Centre Ernest Lluch. La Atención a la cronicidad entre la mejora y la transformación. 10-11 July 2013. Barcelona
- Academics opening 2013/2014. "Magistral Conference". Universidad de Vic/ Complejo Hospitalario de Vic. 3 October de 2013

PROGRAMME:
COPD/Lung Cancer/ Pulmonary Hypertension

Group 21

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Main lines of research

Consolidated research lines:

- COPD: clinical evolution, comorbidity, clinical management model, Mortality and Readmissions.
- Lung Cancer: Diagnosis, clinical staging, clinical developments, clinical management model, Mortality and Recurrences.
- Pulmonary hypertension: clinical and biological characterization of the disease, clinical developments, clinical management model, Mortality and Readmissions.

Other developed thematic:

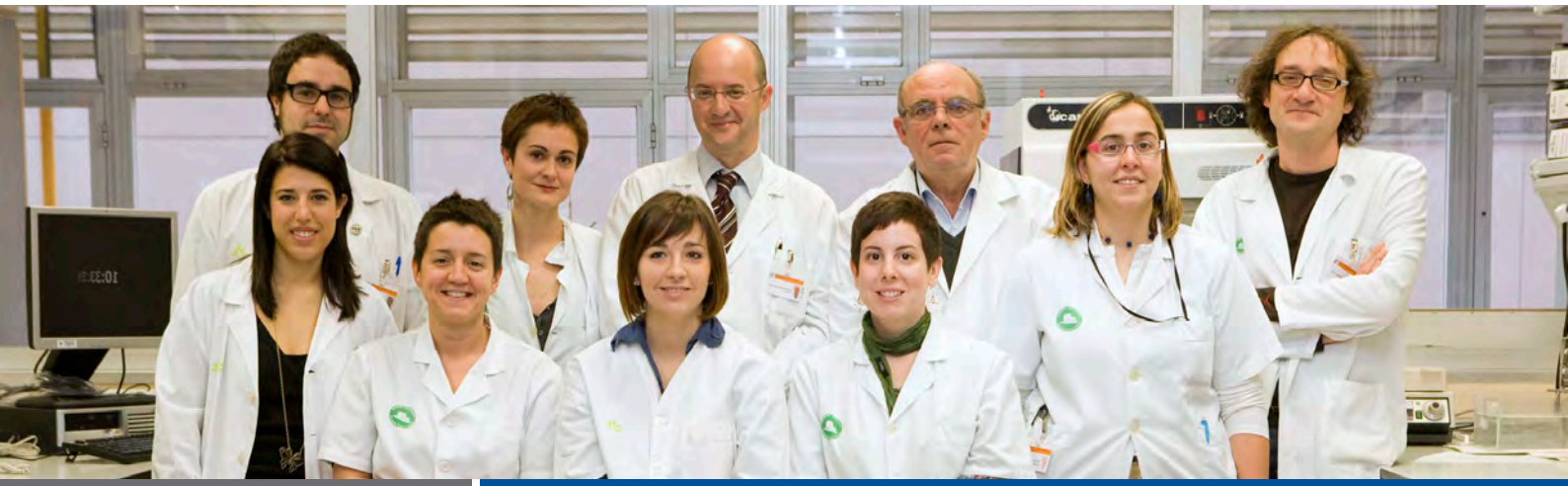
- Asthma.
- Pulmonary Fibrosis.
- Apnea, hypoventilation and Sleep.
- Lung Transplant.

Most relevant scientific articles

- López-Campos JL, Hartl S, Pozo-Rodríguez F, Roberts CM, European COPD Audit team. European COPD Audit: design, organisation of work and methodology.Eur Respir J. 2013 Feb;41(2):270-6.
- Roberts CM, Lopez-Campos JL, Pozo-Rodríguez F, Hartl S, European COPD Audit team. European hospital adherence to GOLD recommendations for chronic obstructive pulmonary disease (COPD) exacerbation admissions.Thorax. 2013 Dec;68(12):1169-71.
- Martínez-García MA, Capote F, Campos-Rodríguez F, Lloberes P, Díaz de Atauri MJ, Somoza M, Masa JF, González M, Sacristan L, et al.. Effect of CPAP on blood pressure in patients with obstructive sleep apnea and resistant hypertension: the HIPARCO randomized clinical trial.JAMA-J AM MED ASSOC. 2013;(310):2407-15.
- Osarogiagbon RU, Rami-Porta R. Early stage non-small-cell lung cancer: surgical implications of the new adenocarcinoma classification.J Thorac Oncol. 2013 May;8(5):e45-6.
- Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A. Updated clinical classification of pulmonary hypertension.J Am Coll Cardiol. 2013 Dec 24;62(25 Suppl):D34-41.

Highlights

1. Participation in the construction of Strategic Research Projects of the PCI to 3 years in the thematic areas of COPD, cancer and pulmonary hypertension:
   - Corporate Research Programme in Chronic Obstructive Pulmonary Disease (COPD).
   - Corporate Research Programme Lung Cancer: Molecular staging of lung cancer stage I / IIp .
   - Corporate Research Programme CIBERES Pulmonary Hypertension.
2. Consolidation of a hospital in COPD research network with the participation of all the Spanish regions (CCAA):
   - DELICATO Project: Design and Local Implementation of clinical audits in differents types of old (fragile COPD)
   - Advanced Spanish cohort of COPD (CEPA).
     - CEPA, Subproject 1: Annual incidence and spatial distribution of mortality. Longitudinal study of a cohort of patients with Severe COPD.
     - CEPA, Subproject 2: Phenotypic characterization and clinical evolution to three years .
     - CEPA, Subproject 3: inflammasome comorbidity and clinical course.
   - European ERS COPD AUDIT.
   - Project AUDIPOC Spain.
3. Coordination and analysis of the data from the first European audit of COPD exacerbations (European ERS COPD Audit) : Members of the Steering Group and Data Analysis Team.
4. Contribution to 2016 TNM Spanish record and the tissues samples repository: Retrospective cohort of lung cancer (GCCP-II/IASLC).
5. Contribution to the Spanish Registry of Pulmonary Hypertension: REHAP.
6. Coordination of SEPAR normatives: Spirometry and Nonspecific bronchial hyperresponsiveness in Asthma.
7. Coordination of the SEPAR normative for management of solitary pulmonary nodules.



PROGRAMME:
Tuberculosis* / New Therapeutic Targets*

Group 17

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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.

* Strategic project 2013-2015: New research and innovation on tuberculosis: basic research, prevention, drug regimens and diagnosis.

** Strategic project 2013-2015: Respiratory infections: form mechanisms to therapeutics

Most relevant scientific articles

- Aabye MG, Latorre I, Diaz J, Maldonado J, Mialdea I, Eugen-Olsen J. Dried plasma spots in the diagnosis of tuberculosis: IP-10 release assay on filter paper.Eur Respir J. 2013 Aug;42(2):495-503.
- Vilaplana C, Marzo E, Tapia G, Diaz J, García V, Cardona PJ. Ibuprofen therapy resulted in significantly decreased tissue bacillary loads and increased survival in a new murine experimental model of active tuberculosis.J Infect Dis. 2013 Jul 15;208(2):199-202.
- Ausina Ruiz V, Fernández-Rivas G, Vilaplana Messeguer C. Selected culture and drug-susceptibility testing methods for drug-resistant Mycobacterium tuberculosis screening in resource-constrained settings.Expert Rev Mol Diagn. 2013 Apr;13(3):247-9.
- Villellas C, Aristimuño L, Vitoria MA, Prat C, Blanco S, García de Viedma D. Analysis of mutations in streptomycin-resistant strains reveals a simple and reliable genetic marker for identification of the Mycobacterium tuberculosis Beijing genotype.J Clin Microbiol. 2013 Jul;51(7):2124-30.
- Arbues A, Aguilo JI, Gonzalo-Asensio J, Marinova D, Uranga S, Puentes E. Construction, characterization and preclinical evaluation of MTBVAC, the first live-attenuated M. tuberculosis-based vaccine to enter clinical trials.Vaccine. 2013 Oct 1;31(42):4867-73.

Highlights

Following the WHO priorities stated in the "Global Plan to Stop TB 2006-2015", over the last few years researchers belonging to group 17 within CIBERES have generated considerable scientific knowledge, with an emphasis on joint publications involving groups form different Programs and collaborations with other national and international groups in the context of the pathogenesis, prevention, diagnosis and treatment of tuberculosis. The researchers of this group have continued investigating new prophylactic and therapeutic vaccines against tuberculosis, and have also developed new experimental animal models that better reproduce infection and disease in humans. Studies have also been carried out that provide new insights into the resistance of *M. tuberculosis* and multi-drug resistant TB. New procedures have been developed and evaluated for the molecular typing of *M. tuberculosis* for epidemiological purposes. New immunological techniques to diagnose latent tuberculosis infection have also been evaluated. As a result of this work, the researchers have actively participated in the development of clinical guidelines for the use of new diagnostic tests (interferon-gamma release assays-IGRAs) for latent tuberculosis infection.

Group 17 members have also developed several research projects related to other respiratory pathogens: S. aureus, M. pneumoniae, S. pneumoniae, H. influenzae and respiratory viruses. One line of research in which the group has been active in recent years is the assessment of the importance of the inflammatory response in respiratory tract infections. The main objective is to identify and describe pathogen and host factors that modulate clinical outcome.

Researchers belonging to group 17 are currently involved in five projects funded by the EU in the FP7 framework, and in several research projects funded by national agencies (FIS, Ministry of Economy and Competitiveness and others), the industry and the Administration. We have also developed scientific collaboration with other CIBER (CIBER-BBN, CIBEResp, and others).

The research activities of the group have recently generated six new patents and created a spin-off with the aim of commercializing a new probiotic that may allow treatment shortening in latent tuberculosis infections.

PROGRAMME:
Sleep Apnea

Group 35

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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

- Martínez-García MA, Capote F, Campos-Rodríguez F, Lloberes P, Díaz de Atauri MJ, Somoza M, Masa JF, González M, Sacristan L, et al.. Effect of CPAP on blood pressure in patients with obstructive sleep apnea and resistant hypertension: the HIPARCO randomized clinical trial.JAMA-J AM MED ASSOC. 2013;(310):2407-15.
- Sánchez-de-la-Torre M, Campos-Rodríguez F, Barbé F. Obstructive sleep apnoea and cardiovascular disease.Lancet Respir Med. 2013 Mar;1(1):61-72.
- Campos-Rodríguez F, Martínez-García MA, Martínez M, Duran-Cantolla J, Peña Mde L, Masdeu MJ. Association between obstructive sleep apnea and cancer incidence in a large multicenter Spanish cohort.Am J Respir Crit Care Med. 2013 Jan 1;187(1):99-105.
- Muniesa MJ, Huerva V, Sánchez-de-la-Torre M, Martínez M, Jurjo C, Barbé F. The relationship between floppy eyelid syndrome and obstructive sleep apnoea.Br J Ophthalmol. 2013 Nov;97(11):1387-90.
- Barceló A, Esquinas C, Piérola J, de la Peña M, Sánchez-de-la-Torre M, Montserrat JM. Vitamin D status and parathyroid hormone levels in patients with obstructive sleep apnea.Respiration. 2013;86(4):295-301.

Highlights

The group 35 of the Biomedical Research Networking Center Consortium for Respiratory Diseases (CIBERES) has participated during 2013 in major national and international forums of respiratory medicine (SEPAR, ATS, ERS, Sleep & Breathing) both invited lectures and presentation of the results of ongoing projects. Currently continues one of the projects that is international referencie in the study of the impact of sleep apnea syndrome in the development of acute coronary syndrome (ISAACC Study, NCT NCT01335087). During the same year the group has produced more than 20 original publications, 5 review articles and has a total of 20 ongoing research projects.

PROGRAMME:
Lung Cancer / COPD

Group 6

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Main lines of research

- Pulmonary Hypertension
  - Biopathology, role of progenitor cells in the injury and repair
  - Identification of new biomarkers and therapeutic targets. Experimental models.
- COPD:
  - Physical activity, cellular biogenetic and systemic effects.
  - Gas exchange abnormalities.
  - Biopathology of pulmonary vascular changes.
- Healthcare continuity and information technology and communication in chronic respiratory diseases:
  - Quality control model of forced spirometry supported by information and comunication technologies (ICT)
  - Early detection of sleep breathing disorders with ICT support

Most relevant scientific articles

- Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, Anzueto A et al.. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary.Am J Respir Crit Care Med. 2013 Feb 15;187(4):347-65.
- Seeger W, Adir Y, Barberà JA, Champion H, Coghlan JG, Cottin V et al.. Pulmonary hypertension in chronic lung diseases.J Am Coll Cardiol. 2013 Dec 24;62(25 Suppl):D109-16.
- Freixa X, Portillo K, Paré C, García-Aymerich J, Gómez FP, Benet M et al.. Echocardiographic abnormalities in patients with COPD at their first hospital admission.Eur Respir J. 2013 Apr;41(4):784-91.
- Blanco I, Santos S, Gea J, Güell R, Torres F, Gimeno-Santos E et al.. Sildenafil to improve respiratory rehabilitation outcomes in COPD: a controlled trial.Eur Respir J. 2013 Oct;42(4):982-92.
- Peinado VI, Gómez FP, Barberà JA, Roman A, Angels Montero M, Ramírez J et al.. Pulmonary vascular abnormalities in chronic obstructive pulmonary disease undergoing lung transplant.J Heart Lung Transplant. 2013 Dec;32(12):1262-9.

Highlights

Submission of the Expression of Interets to conform a Research Program on Pulmonary Hypertension.

PROJECTS STARTED IN 2013

- European Commission

  - Roca, J. Advancing Care Coordination & Telehealth Deployment (ACT). nº 20121209. 2013-2015. 117.053,29 € (Total EC Funding: 1,6 M Euros. Coordinator: Philips Healthcare Boeblingen).

- FIS

  - Barbera, JA. Biomarcadores endoteliales en la hipertensión arterial pulmonar: relación con la heterogeneidad clínica y la respuesta terapéutica. PI12/00510. 2013-2015. 183.315 €

  - Roca, J. PITES-ISA: Escalabilidad regional de los servicios de atención integrada y ayuda a la decisión clínica. PI12-01241. 2013-2015. 38.115 €

- FCHP

  - Barbera, JA. Marcadores biológicos de integridad y función endotelial en la evaluación y seguimiento de los pacientes con hipertensión arterial pulmonar. 2013-2014. 12.000 €

- SOCAP

  - Barbera, JA / Chamorro, N. Marcadors biològics d'integritat i funció endotelial en l'avaluació i seguiment dels pacients amb hipertensió arterial pulmonar. Juliol 2013-Juliol 2014. 12.000 €

TRASLATION. GUIDES.

- Vachiéry JL, Adir Y, Barberà JA et al. Pulmonary hypertension due to left heart diseases. J Am Coll Cardiol. 2013; 62: D100-108. PMID: 24355634.
- Seeger W, Adir Y, Barberà JA et al. Pulmonary hypertension in chronic lung diseases. J Am Coll Cardiol. 2013; 62: D109-116. PMID: 24355635.
- Vestbo J, Hurd SS, Agusti AG, Jones PW, Vogelmeier C, Anzueto A, Barnes PJ, Fabbri LM, Martínez FJ, Nishimura M, Stockley RA, Sin DD, Rodríguez-Roisin R. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease, GOLD Executive Summary. Am J Respir Crit Care Med. 2013; 187: 347-365. PMID: 22878278.
- García-Río F, Calle M, Burgos F, Casan P, Del Campo F, Galdiz JB, Giner J, González-Mangado N, Ortega F, Puente Maestu L. Espirometría. Arch Bronconeumol. 2013; 49: 388-401. PMID: 23726118.

PROGRAMME:
Acute Lung Injury / Pneumonia

Group 33

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Main lines of research

The main lines of research in our group are part of the two Corporate Research Programs in which we participate:

- Acute Lung Injury: Early Diagnosis and Novel Therapeutic Strategies for Acute Lung Injury (EDIT-ALI) Project
- Pneumonia: Multidisciplinary Translational Research Project in Respiratory Tract Infections (MARTIN)

LINES:

- Prevalence of asynchronies during mechanical ventilation in critically ill patients.
- Models of acute lung injury and specific treatment.
- Brain-lung interaction during mechanical ventilation in different experimental models.
- Acute lung injury (ali), acute respiratory distress syndrome (ards) and mechanical ventilation in critically ill patients.
- Epidemiology study of ventilator associated pneumonia (vap) and tracheobronchitis (vat).

Most relevant scientific articles

- Vallés J, Palomar M, Alvárez-Lerma F, Rello J, Blanco A, Garnacho-Montero J. Evolution over a 15-year period of clinical characteristics and outcomes of critically ill patients with community-acquired bacteremia. Crit Care Med. 2013 Jan;41(1):76-83.
- Puig F, Fuster G, Adda M, Blanch L, Farre R, Navajas D et al.. Barrier-protective effects of activated protein C in human alveolar epithelial cells. PLoS One. 2013;8(2):e56965.
- González-López A, López-Alonso I, Aguirre A, Amado-Rodríguez L, Batalla-Solís E, Astudillo A. Mechanical ventilation triggers hippocampal apoptosis by vagal and dopaminergic pathways. Am J Respir Crit Care Med. 2013 Sep 15;188(6):693-702.
- Fernández R, Gili G, Villagra A, Lopez-Aguilar J, Artigas A. Assessment of the inflammatory effect of low-dose oxygen in mechanically ventilated patients. Intensive Care Med. 2013 Apr;39(4):711-6.
- Martín-Loeches I, Deja M, Koulenti D, Dimopoulos G, Marsh B, Torres A. Potentially resistant microorganisms in intubated patients with hospital-acquired pneumonia: the interaction of ecology, shock and risk factors.Intensive Care Med. 2013 Apr;39(4):672-81.

Highlights

- We have developed and validated a monitoring system (spin-off Better-Care and patent US2010106825). We have registered more than 160 patients in 5 ICU's, during the whole ventilatory period. This study has revealed the high incidence of asynchronies and its association with the risk of ICU mortality (financed projects in this field PI13/02204, TSI-020302-2010-134).
- We have demonstrated that the PEEP modulates the inflammatory response and the neuronal activation and apoptosis in an ALI experimental model (PMID 23962032).
- We have demonstrated that tissue oxygenation monitoring is useful to determine the weaning outcome in ventilated patients (PMID 23314894).
- Tracheal ischemia could be prevented by manual or continuous control of cuff pressure (PMID 24572178).
- Efficacy of single-dose antibiotic prophylaxis at intubation to decrease the incidence of early pneumonia in comatose MV patients (PMID 23715136).
- We have finished the study analyzing the incidence of tracheobronchitis and VAP.
- We have assessed the inflammatory effect of oxygen in mechanically ventilated patients (PMID 23296630).
- We have applied non-invasive biological monitoring system to detect volatile organ compounds related to lipid peroxidation in exhaled breath of mechanically ventilated patients with ARDS.
- Cell Therapy in ARDS based in the transplant of neumocytes type II cells in a sustained ARDS experimental model in rats has demonstrated an improvement in lung remodelling (PI12/02548).
- We demonstrated the usefulness of anticoagulant treatment with activated protein C and heparin in alveolar primary cell cultures, improving and preventing cell damage and alveolar permeability (PMID 23451122)
- We have signed an agreement to study the effect of Antithrombin in an in vitro model of Acute Lung Injury (Grifols).
- Educational postgraduate activities: 18th International Symposium on Infections in Critically Ill Patients (Sevilla 2013), ATS PG Course "Cardio Respiratory Monitoring" (Philadelphia 2013), Respiratory Applied Physiology (Sabadell 2013), Master in Critical Care.

PROGRAMME:
Pneumonia

Group 27

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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

- Pérez Granda MJ, Barrio JM, Hortal J, Muñoz P, Rincón C, Bouza E. Routine aspiration of subglottic secretions after major heart surgery: impact on the incidence of ventilator-associated pneumonia. J Hosp Infect. 2013 Dec;85(4):312-5.
- Guinea J, Padilla C, Escribano P, Muñoz P, Padilla B, Gijón P. Evaluation of MycAssay™ Aspergillus for diagnosis of invasive pulmonary aspergillosis in patients without hematological cancer. PLoS One. 2013;8(4):e61545.
- Iñigo J, García de Viedma D, Arce A, Palenque E, Herranz M, Rodríguez E. Differential findings regarding molecular epidemiology of tuberculosis between two consecutive periods in the context of steady increase of immigration. Clin Microbiol Infect. 2013 Mar;19(3):292-7.
- Bouza E, Granda MJ, Hortal J, Barrio JM, Cercenado E, Muñoz P. Pre-emptive broad-spectrum treatment for ventilator-associated pneumonia in high-risk patients. Intensive Care Med. 2013 Sep;39(9):1547-55.
- Escribano P, Peláez T, Muñoz P, Bouza E, Guinea J. Is azole resistance in Aspergillus fumigatus a problem in Spain? Antimicrob Agents Chemother. 2013 Jun;57(6):2815-20.

Highlights

The CIBER group of the Hospital General Universitario Gregorio Marañón (HGUGM) in Madrid has had a very successful year in 2013, both in scientific research and in scientific production.

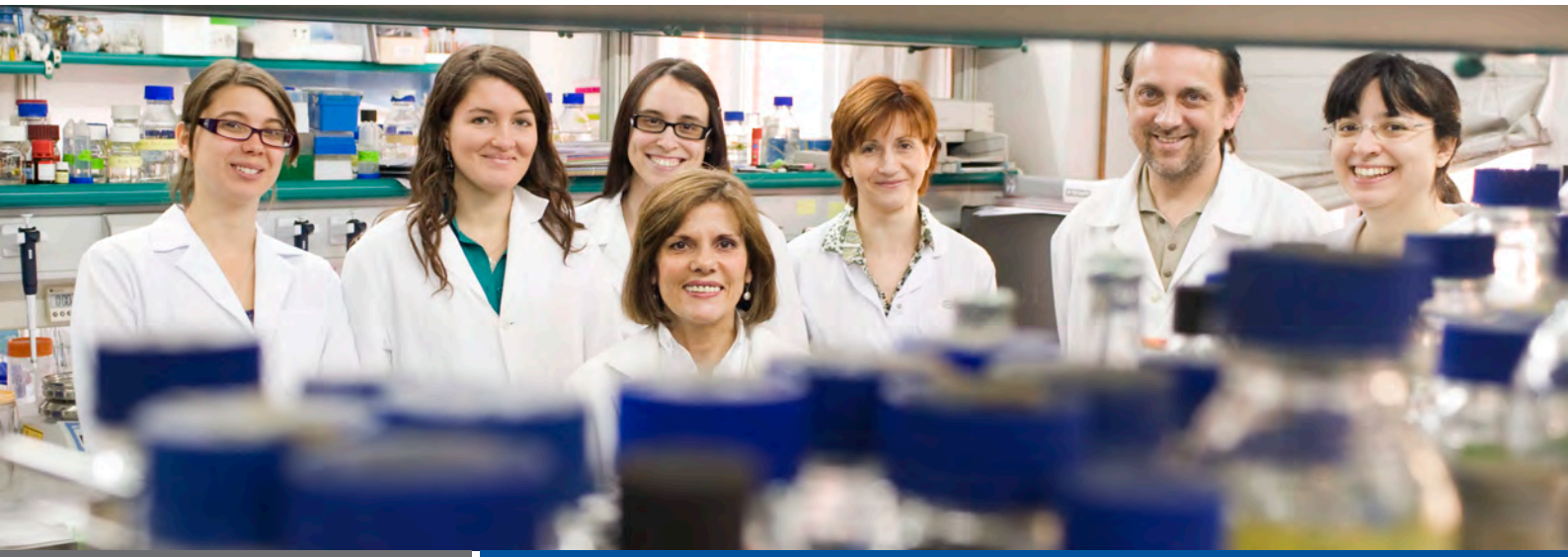
The list of publications of the group, that we include, reached the figure of 70, with a cumulative impact factor of more tha 240.

The scientific production has been good in the different study areas, the percentage of publications in the 1st decile and in the 1st quartile being 12 and 47 respectively.

In the area of ventilator-associated pneumonia, the study of the impact of routine aspiration of subglottic secretions after major heart surgery on the incidence of ventilator-associated pneumonia was finished. A second study on the use of pre-emptive broad-spectrum treatment to prevent ventilator-associated pneumonia in major heart surgery ICU patients proved to be effective in reducing its incidence and in delaying the onset of VAP. Still, an increase in the resistance of staphylococci to linezolid was observed in the entire institution. Thus, the ecological consequences have to be carefully evaluated in future trials, and different drugs should be tested.

The data on tuberculosis also show further progress in the study areas of the group. The scientific production has been in the following fields: development of new low cost techniques directed at Mycobacterium tuberculosis (MTB) genotyping in molecular epidemiology; development of rapid detection techniques of high-risk MTB strains; optimizing the detection of clonally complex MTB infections; population-based studies of complex infections (mixed infections and coinfections by clonal MTB variants); genotypic and phenotypic analysis of MTB variants emerging in microevolution events and assessment of their functional significance.

The group of respiratory mycosis has also had a high scientific production particularly in the fields of invasive aspergillosis, candidiasis and candidemia.



PROGRAMME:
New Therapeutic Targets/ Acute Lung Injury

Group 1

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Website: http://pendientedemigracion.ucm.es/info/respira/

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:

- L1 The molecular mechanisms by which surfactant components control unnecessary tissue inflammation, using cell culture models of inflammation and infection (CRP on Host-Pathogen Interactions).
- L2 The potential molecular interactions between surfactant protein A (SP-A) and antimicrobial peptides present in the alveolar fluid (SP-BN , LL37, and beta-defensins) that might facilitate (or block) antimicrobial actions (CRP on Host-Pathogen Interactions).
- L3 Surfactant membranes' mechanisms of resistance to inactivation by factors which increase in the alveolar fluid during infection and inflammation (CRP on Host-Pathogen Interactions).

- L4. Molecular interactions between alveolar protein SP-A and nanoparticles (CRP on New Therapies to Treat Respiratory Diseases).
- L5. The high-stretch ventilation impact in the alveolar space and in particular on the composition, structure, and functional activity of lung surfactant (CRP on Acute Lung Injury).
- L6. Benefits of intratracheal treatment of natural and synthetic surfactants as well as anti-inflammatory agents in acute lung injury induced by mechanical ventilation (CRP on Acute Lung Injury).

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

Most relevant scientific articles

- Monforte V, López-Sánchez A, Zurbano F, Ussetti P, Solé A, Casals C et al.. Prophylaxis with nebulized liposomal amphotericin B for Aspergillus infection in lung transplant patients does not cause changes in the lipid content of pulmonary surfactant.J Heart Lung Transplant. 2013 Mar;32(3):313-9.
- Cañadas O, Casals C. Differential scanning calorimetry of protein-lipid interactions. Methods Mol Biol. 2013;974:55-71.

Highlights

RELEVANT RESEARCH PROJECT: SAF2012-32728 (2013-2015) Lung surfactant as protector and modulator of lung infection and inflammation. Funded by Spanish Ministry of Economy and Competitiveness. Principal Investigator: Cristina Casals.

RELEVANT RESULTS:

- Line 1: We demonstrated that internalized lung surfactant vesicles containing human surfactant protein C affect the state of macrophage activation induced by bacterial lipopolysaccharide and inhibit expression of inflammatory mediators by human pneumocytes induced by respiratory syncytial virus.
- Line 2: We demonstrated that SP-A and SP-BN acted synergistically to kill capsulated K. pneumoniae (serotype K2) at neutral pH, where neither of these proteins had bactericidal activity. In addition, we found that i.t. administration of SP-A and SP-BN confers protection against K. pneumoniae K2 infection. Moreover, SP-A/SP-BN administration 6 or 24 h after pathogen inoculation (once K. pneumoniae infection was established) resulted in a 4-fold decrease of lung bacterial burden, thereby indicating its therapeutic effect.
- Line 5: We demonstrated that ventilator-induced lung injury (VILI) only occurred in animal models when surfactant was inactivated. There was a direct link between a pronounced proinflammatory response and surfactant inactivation. In addition, we showed that an attenuate inflammatory response together with increasing secretion of endogenous, fully active, surfactant, protected the lung against the hypoxia and the protein leakage.

DOCTORAL THESIS: 14/10/2014- Virginai Egido. "Lung response against ventilator induced lung injury: role of pulmonary surfactant". Complutense University of Madrid. Doctoral Program: Biochemistry, Molecular Biology and Biomedicine ("Mention towards Excellence" by the Ministry of Science and Education). Evaluation: Excellent "cum laude" Director: Dr. Cristina Casals.

INTERNATIONAL COLLABORATION: 1) Prof. Dr. Timothy Weaver, Cincinatti Children's Hospital (Ohio, USA), supervisor of Juan Manuel Coya during his predoctoral stay in USA-2013, granted by the Spanish Personnel Research Training Program; 2) Prof. Dr. Jan Johansson, Karolinska Institute, Stockholm Sweden (European Research Project submission in 2013 and 2014); 3) Collaboration agreement with Nycomed GmbH-Takeda in the biomed/biotech field.

PROGRAMME:
Asthma

Group 7

Group Members

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Main lines of research

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

Most relevant scientific articles

- Bernstein DI, Kashon M, Lummus ZL, Johnson VJ, Fluharty K, Gautrin D et al.. CTNNA3 (α-catenin) gene variants are associated with diisocyanate asthma: a replication study in a Caucasian worker population. Toxicol Sci. 2013 Jan;131(1):242-6.
- Sastre B, Fernández-Nieto M, Rodríguez-Nieto MJ, Aguado E, Sastre J, del Pozo V. Distinctive bronchial inflammation status in athletes: basophils, a new player. Eur J Appl Physiol. 2013 Mar;113(3):703-11.
- Siracusa A, de Blay F, Folletti I, Moscato G, Olivieri M, Quirce S et al.. Asthma and exposure to cleaning products - a European Academy of Allergy and Clinical Immunology task force consensus statement. Allergy. 2013 Dec;68(12):1532-45.
- van Kampen V, de Blay F, Folletti I, Kobierski P, Moscato G, Olivieri M et al.. Evaluation of commercial skin prick test solutions for selected occupational allergens. Allergy. 2013;68(5):651-8.
- Aguerri M, Calzada D, Montaner D, Mata M, Florido F, Quiralte J et al.. Differential gene-expression analysis defines a molecular pattern related to olive pollen allergy. J Biol Regul Homeost Agents. 2013 Apr-Jun;27(2):337-50.

Highlights

Bronchial asthma is defined as an inflammatory disease of the airways causing bronchial hyper response and/or airflow obstruction and manifests as symptoms such as cough, wheezing or breathlessness. Asthma has typically been considered a disease associated with atopy and/or allergic disease that starts during childhood and may or may not persist into adulthood. However, today it is considered a multifactorial heterogeneous disease that includes different phenotypes, each with its own natural history and different response to treatment. In this sense, in addition to allergic or extrinsic asthma and non-allergic or intrinsic asthma, other phenotypes have been defined over the last two decades based on clinical or physiological characteristics (seriousness, age of onset, degree of obstruction, resistance to treatment), asthma triggering factors (exercise, allergens, occupation, asthma induced by aspirin), or type of inflammation (eosinophilic, neutrophilic or paucicellular). These definitions are based on partial characteristics of the disease, and although they may be of help, they do not explain the complexity of asthma.

Therefore, today it is necessary to improve asthma phenotype classification, and there is a knowledge gap in many issues, such as what causes the increase in asthma, genetic susceptibility and interaction between environmental factors (microbes, contaminants, etc.) and the immune system, etc. All this means that the main focus of the asthma CRP is to achieve better asthma classification that allows new diagnostic and therapeutic approaches and better prediction of the response to treatment and therapeutic efficacy monitoring.

To do this, the asthma CRP consists of a primarily translational work group incorporating basic research and clinical knowledge as fundamental pillars. The asthma CRP aspires to be a national and international leader in understanding asthma, moving forward in learning about new diagnostic markers as well as possible therapeutic targets which, when monitored, allow evaluating patient recovery. The asthma CRP is therefore taking another step closer to personalized medicine for the treatment of asthma.

PROGRAMME:
Acute Lung Injury

Group 23

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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

- Peñuelas O, Melo E, Sánchez C, Sánchez I, Quinn K, Ferruelo A. Antioxidant effect of human adult adipose-derived stromal stem cells in alveolar epithelial cells undergoing stretch.Respir Physiol Neurobiol. 2013 Aug 1;188(1):1-8.
- Herrero R, Tanino M, Smith LS, Kajikawa O, Wong VA, Mongovin S. The Fas/FasL pathway impairs the alveolar fluid clearance in mouse lungs.Am J Physiol Lung Cell Mol Physiol. 2013 Sep;305(5):L377-88.
- Thille AW, Esteban A, Fernández-Segoviano P, Rodríguez JM, Aramburu JA, Peñuelas O. Comparison of the Berlin definition for acute respiratory distress syndrome with autopsy.Am J Respir Crit Care Med. 2013 Apr 1;187(7):761-7.
- Thille AW, Esteban A, Fernández-Segoviano P, Rodríguez JM, Aramburu JA, Vargas-Errázuriz P. Chronology of histological lesions in acute respiratory distress syndrome with diffuse alveolar damage: a prospective cohort study of clinical autopsies.Lancet Respir Med. 2013 Jul;1(5):395-401.
- Esteban A, Frutos-Vivar F, Muriel A, Ferguson ND, Peñuelas O, Abraira V. Evolution of mortality over time in patients receiving mechanical ventilation.Am J Respir Crit Care Med. 2013 Jul 15;188(2):220-30.

Highlights

Our group has continued to develop the main research lines started in recent years.

- The first one, which represents the core of our participation in the CRP on acute lung injury, is our research in the Acute Respiratory Distress Syndrome (ARDS). In 2013 we finalized the analysis of the clinico-pathological correlation of the so called Berlin Definition (Thille A, Esteban A,et al AJRCCM 2013;187:761-767) as well as on the chronological changes of the histological changes in ARDS (Thille A,Esteban A, et al The Lancet Respiratory Medicine 2013;1(5):395-401). We have also written a manuscript on the different clinical phenotypes hidden under the clinical diagnosis of ARDS (manuscript in preparation). In the area of biomarkers, we have identified a miRNA that is associated with diffuse alveolar damage (DAD) in rats undergoing mechanical ventilation-induced lung injury, and has good diagnostic characteristics in patients on mechanical ventilation when its expression is measured in the serum (FIS PI12/02898) (manuscript in preparation) (this project is also the thesis project of one of our fellows). (FIS PI12/02451).
- The second one is our research on mechanical ventilation. We have published the largest to date epidemiological study on the use of mechanical ventilation (Esteban A, Frutos-Vivar F , et al.AJRCCM 2013;188:220-30). We have also written two more manuscripts on the incidence, risk factors and time course of patients with ICU-acquired weakness (submitted), and on the effects of sedation of patients receiving noninvasive mechanical ventilation (submitted).
- The third one is our research on the prevention of respiratory infection in critically ill patients. We have finalized a study on the effects of selective digestive decontamination in the pulmonary response to mechanical ventilation in rats (manuscript in preparation) (this project is also the thesis project of one of our fellows). A study on the effect of central line replacement policy in critically ill burn patients on catheter related bacteremia is ongoing (FIS PI11/01121).

PROGRAMME:
Pneumonia / New Therapeutic Targets*

Group 2

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Main lines of research

The development of invasive pneumococcal disease is preceded by the establishment of the "carrier state", this is, the colonization of the human nasopharynx by *Streptococcus pneumoniae* (pneumococcus). Pneumococcal carriage takes place through the establishment of a still largely unknown, host-pathogen interplay as well as by interactions with other bacteria colonizing the same habitat, such as non-typeable pneumococci, other streptococci of the mitis group, or pathogens like Haemophilus influenzae. Most of these interactions involve bacterial surface proteins on one hand, and cellular receptors and host defense mechanisms on the other. Cell wall hydrolases (CWHs) are surface proteins produced by the pneumococcus that are directly involved in virulence. Thus, LytB and LytC are essential in nasopharyngeal colonization and help to avoid host immunity, while LytA triggers the release of other virulence factors, like the potent toxin pneumolysin and the neuraminidase and plays an important role in pathogenesis by releasing cell wall fragments that are markedly pro-inflammatory. All these CWHs are involved in biofilm formation. The role(s) in colonization of LytA and pneumolysin will be studied using biofilms (either mono or multispecies), cell

* 1) Multidisciplinary translational research in respiratory tract infections 2) Respiratory infections: from mechanisms to therapeutics

cultures, and a mouse model of nasopharyngeal colonization. Besides, the impact of risky behaviors like smoking that facilitates bacterial colonization of the lungs and that contributes to the acute exacerbations in patients with chronic obstructive pulmonary disease will also be examined. Finally, one of the main aims of the present project is to develop prophylactic and therapeutic approaches to fight pneumococcal colonization. This will be performed using CWHs (enzybiotics) like Cpl-7 (a phage-coded enzyme of great antibacterial potential), and novel drugs including several choline analogs and ceragenins. As for other objectives of this project, the efficacy of enzybiotics and novel drugs will be tested in vitro (planktonic as well as biofilm cultures) and in animal models of infection.

Most relevant scientific articles

- Domenech M, Ramos-Sevillano E, García E, Moscoso M, Yuste J. Biofilm formation avoids complement immunity and phagocytosis of Streptococcus pneumoniaeInfection and Immunity. 2013;81:2606-2615.
- Díez-Martínez R, de Paz H, Bustamante N, García E, Menéndez M, García P.. Improving the lethal effect of Cpl-7, a pneumococcal phage lysozyme with broad bactericidal activity, by inverting the net charge of its cell wall-binding moduleAntimicrobial Agents and Chemotherapy. 2013;57:5355-5365.
- Domenech M, García E, Prieto A, Moscoso M. Insight into the composition of the intercellular matrix of Streptococcus pneumoniae biofilmsEnvironmental Microbiology. 2013;15:502-516.

Highlights

In addition to that provided by CIBER, our research team is supported by grants from Plan Nacional de Investigación:

- Colonización neumocócica y estado de portador: bases moleculares, profilaxis y medidas terapéuticas. SAF2012-39444-C02-01 and -02. 2013-2015.
- Tecnología para cardiología y neumococo (NanoCardioCoco). IPT-2011-1337-010000. 2011-2014.

Besides, apart from the scientific publications indicated above, a PhD. thesis was developed in our laboratory and defended in 2013 that have been partially supported by CIBERES:

Elisa Ramos Sevillano. Enfermedad neumocócica invasiva: mecanismos moleculares de patogenicidad y protección. Universidad Complutense de Madrid. Facultad de Ciencias Biológicas. 2013. Sobresaliente *cum laude*.

http://eprints.ucm.es/22886/.

PROGRAMME:
COPD / Lung Cancer

Group 22

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Barreiro Portela, Esther
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Domínguez Álvarez, Marisol
Ferrer Monreal, Antonio
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Main lines of research

- Respiratory and limb muscle abnormalities in respiratory diseases
- Fenotyping in COPD
- Pulmonary abnormalities in COPD and lung cancer
- Pulmonary Hypertension

Most relevant scientific articles

- Donaire-Gonzalez D, Gimeno-Santos E, Balcells E, Rodríguez DA, Farrero E, de Batlle J et al.. Physical activity in COPD patients: patterns and bouts.Eur Respir J. 2013 Oct;42(4):993-1002.
- Bazan V, Grau N, Valles E, Felez M, Sanjuas C, Cainzos-Achirica M. Obstructive sleep apnea in patients with typical atrial flutter: prevalence and impact on arrhythmia control outcome.Chest. 2013 May;143(5):1277-83.
- Blanco I, Santos S, Gea J, Güell R, Torres F, Gimeno-Santos E et al.. Sildenafil to improve respiratory rehabilitation outcomes in COPD: a controlled trial.Eur Respir J. 2013 Oct;42(4):982-92.
- Barreiro E, Fermoselle C, Mateu-Jimenez M, Sánchez-Font A, Pijuan L, Gea J. Oxidative stress and inflammation in the normal airways and blood of patients with lung cancer and COPD.Free Radic Biol Med. 2013 Dec;65:859-71.
- Rubini Giménez M, Hoeller R, Reichlin T, Zellweger C, Twerenbold R, Reiter M. Rapid rule out of acute myocardial infarction using undetectable levels of high-sensitivity cardiac troponin.Int J Cardiol. 2013 Oct 9;168(4):3896-901.

Highlights

In 2013 our group has maintained its scientific outcomes, including original publications (20 Intl & 5 Ntl), reviews (4 Intl) and editorials (1 Intl & 3 Natl) in journals of the highest impact factor in our specialty. Group members also have editorial activities (editorship and editorial boards) from indexed journals (including Am J Respir Crit Care Med & J Appl Physiol), and reviewers of 8 of them (including N.Eng.J.Med). They are also reviewers of European projects (Horizon 2020) and French, Belgian, Dutch and Spanish agencies.

Education: In the group, 2 doctoral and 4 master theses were defended in 2013, and group members are actively engaged in teaching and management of undergraduate and graduate studies (eg. direction of a master) .

The most interesting scientific results of 2013 are related to the molecular and cellular events that occur in the muscles and bronchial airways of patients with COPD and/or lung cancer.

The group has continued or completed competitive projects from Plan Nacional, FIS, SEPAR and Maraton TV3, and 5 clinical trials. It has also obtained a FIS grant for intensification.

Members of the group have also registered a patent related to respiratory therapies (Controlizer©, nebulization), and participated in several clinical guidelines and regulations: Statement of the American Thoracic Society and European Respiratory Society on muscle dysfunction in COPD; Guide to diagnosis and treatment of lung cancer (SEPAR); Evaluation and clinical management of muscle dysfunction (SEPAR), whose documents will be published in high-class journals in 2014.

There are several active collaborations with international groups (Chicago, Basel, Maastricht) and participation in a working group of the National Institutes of Health. At the National level, the group belongs to 4 stable multi-institutional networks (plus CIBERES).

Finally, the group coordinator has been the Chair of the Annual Congress of the European Respiratory Society (Barcelona 2013).

PROGRAMME:
Pneumonia

Group 3

Group Members

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Main lines of research

- Molecular basis of antimicrobial action in pathogenic bacteria, mainly in *Streptococcus pneumoniaee*.
- Molecullar studies of the fluoroquinolone targets (DNA gyrase and DNA topoisomerase IV).
- Studies on the organization of the genome in supercoiling domains and their role in global transcription.
- Effect of fluoroquinolone treatment in the global transcription.
- Role of the S. pneumoniae small RNAs in gene expression.
- Characterization of new antimicrobial targets.
- DNA topoisomerase I as a new antibiotic target.
- Characterization of new virulence factors.

Most relevant scientific articles

- Balsalobre L, Ortega M, de la Campa AG. Characterization of recombinant fluoroquinolone-resistant pneumococcus-like isolates.Antimicrob Agents Chemother. 2013 Jan;57(1):254-60.
- Domenech A, Ardanuy C, Pallares R, Grau I, Santos S, de la Campa AG. Some pneumococcal serotypes are more frequently associated with relapses of acute exacerbations in COPD patients.PLoS One. 2013;8(3):e59027.

Highlights

CURRENT PROJECTS:

- "New antibacterial targets in streptococci: conserved protreins without assigned function. MICIN. CP10/00450. IP: Antonio Javier Martín Galiano. 2011-2014. 119.500,00 €
- "The control of the superencoiling level in Streptococcus pneumoniae as an antimicrobial target"MICIN. BIO2011-25343. IP: Adela González de la Campa. 2012-2014. 205.700,00 €
- "Papel de los RNAs no codificantes en la patogenicidad de *S. pneumoniae*". MICIN. PI11/00656. IP: Monica Amblar. 2012-2014. 198.714,67 €.

PROGRAMME:
COPD/ Sleep Apnea/ Lung Cancer

Group 4

Group Members

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Main lines of research

- CRP OF SLEEP APNEA: OSA as a risk factor for cardiovascular morbidity and mortality, OSA as a risk factor for cancer and SAHS in women.
- CRP OF CANCER: Early detection program in subjects at high risk for emphysema or lung function impairment. Risk of each individual as his smoking habit and personal and family history. Influence of associated diseases, especially chronic obstructive pulmonary disease (COPD) and emphysema over the risk of developing lung cancer and its prognosis. Genetic and molecular factors that determine the risk profile of each individual.
- CRP OF COPD: Susceptibility to the development of lung injury and its evolution up to present the well established disease in animal models. Identification of the key biomarkers in the development and progression of the disease and its translation to the clinic. Cohorts of COPD patients with early onset and with late-stage severe COPD. New therapeutic targets based on the utilization of growth factors in experimental models of disease and in endoscopic implantation in patients of spirals and valves for the treatment of emphysema .

Most relevant scientific articles

- Wise RA, Anzueto A, Cotton D, Dahl R, Devins T, Disse B. Tiotropium Respimat inhaler and the risk of death in COPD.N Engl J Med. 2013 Oct 17;369(16):1491-501.
- Suarez-Sipmann F, Borges JB. How we stretch the lung matters.Crit Care Med. 2013 Apr;41(4):1153-5.
- Pérez-Rial S, del Puerto-Nevado L, Terrón-Expósito R, Girón-Martínez Á, González-Mangado N, Peces-Barba G. Role of recently migrated monocytes in cigarette smoke-induced lung inflammation in different strain of mice.PLoS One. 2013;8(9):e72975.
- Ferrarini A, Rupérez FJ, Erazo M, Martínez MP, Villar-Álvarez F, Peces-Barba G et al.. Fingerprinting-based metabolomic approach with LC-MS to sleep apnea and hypopnea syndrome: a pilot study.Electrophoresis. 2013 Oct;34(19):2873-81.
- de-Torres JP, Blanco D, Alcaide AB, Seijo LM, Bastarrika G, Pajares MJ. Smokers with CT detected emphysema and no airway obstruction have decreased plasma levels of EGF, IL-15, IL-8 and IL-1ra.PLoS One. 2013;8(4):e60260.

Highlights

Our group coordinates the WP4 of the CRP of COPD on animal models of COPD, as translational support of WP 1 and 3 and has secured funding for it in the AES2013 call with a coordinated research project, under a PI belonging to our group with the participating of 5 CIBERES groups (PI13/01909). Within this WP4, we are studying in animal models the factors that determine the start of the development of COPD in response to the tobacco smoke and we described the contribution of monocytes in the beginning of disease.

Our participation in the CRP of OSA has featured as main result the ability to diagnose and stage the disease by metabolomic analysis of plasma patients.

Regarding participation in the CRP of cancer, initiated in 2013, we note that it has been approved the project for "Early detection of lung cancer" by using low dose CT in the high-risk population of patients with COPD.

Finally, we consider as relevant our participation the clinical guide of "Spirometry" pf SEPAR and the continued contribution to the recruitment of clinical cases of the coordinated projects of the three CRP.

PROGRAMME:
Acute Lung Injury/ Sleep Apnea

Group 24

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Main lines of research

- Oxygen sensing mechanisms in the carotid body arterial chemoreceptors.
- Mechanisms of the hypoxic damage: reactive oxygen species
- Animal models of intermittent and sustained hypoxia
- Biomarkers of the hypoxic damage
- Pulmonary hypertension.

Most relevant scientific articles

- Quintero M, Gonzalez-Martín Mdel C, Vega-Agapito V, Gonzalez C, Obeso A, Farré R et al.. The effects of intermittent hypoxia on redox status, NF-κB activation, and plasma lipid levels are dependent on the lowest oxygen saturation.Free Radic Biol Med. 2013 Dec;65:1143-54.
- Ribeiro MJ, Sacramento JF, Gonzalez C, Guarino MP, Monteiro EC, Conde SV. Carotid body denervation prevents the development of insulin resistance and hypertension induced by hypercaloric diets.Diabetes. 2013 Aug;62(8):2905-16.

Highlights

FINANCIAL SUPPORT OBTAINED IN 2013

- BFU2012-37459. Ministerio de Economía y Competitividad. DGICYT (2012-2014) Project title: Physiopathologicl mechanisms of the cardiovascular arterations encountered in the obstructive sleep apnea: foundations for therapeuctic designs. Budget: 222.300€. PI. Constancio Gonzalez.
- Asociación Española Contra el Cancer (A predoctoral Fellowship in Oncology) (2013-2015) Project title: Obstructive Sleep Apnoea Syndrome and Cancer. Budget: 56.000€. PI: Constancio Gonzalez. Fellowship recipient: Teresa Gallego Martín.

MOST RELEVANT FINDINGS IN 2013

We have found that a hypercaloric diet induces resistance to insulin and arterial hypertension, which are accompanied by a sensitization status of the carotid body arterial chemoreceptors. We also found that the carotid body sensitization is produced by the augmented insulin level. In turn, carotid body sensitization causes a sympathetic hyperactivity which is responsible for arterial hypertension and insulin resistance. A positive feed-back is generated that maintains and aggravates the cardiovascular and metabolic alterations present in obesity. The denervation of the carotid body eliminates hypercaloric diet induced insulin resistance and hypertension.

In another front, we have found that intermittent hypoxia mimicking obstructive sleep apnoea causes an oxidative damage characterized by a downregulation of the mitochondrial superoxide dismutase and activation of NFkB transcription factor. NFkB, in turn, upregulates the expression of inflammatory cytokines, which also generate oxidative damage. These alterations are proportional to the level of haemoglobin desaturation. Our findings provide an explanation to the oxidative and inflammatory status encountered in patients with obstructive sleep apnoea.

PROGRAMME:
Pneumonia / COPD

Group 19

Group Members

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Main lines of research

- Clinical and molecular epidemiology of invasive and non-invasive pneumococcal diseases
- Study of bacterial resistance mechanisms and mobile elements harboring resistance determinants
- Molecular typing and population dynamics of microorganisms causing respiratory infections(*Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Pseudomonas aeruginosa, Klebsiella pneumoniae, Streptococcus pyogenes, Staphylococcus aureus*).
- Bacterial diversity analysis of respiratory samples from patients with chronic obstructive pulmonary disease. Traditional culture-based vs culture-independent (microbiome) techniques.
- Biofilm formation by microorganisms causing respiratory tract infections. Bacterial genotypes persistence.

Most relevant scientific articles

- Puig C, Calatayud L, Martí S, Tubau F, García-Vidal C, Carratalà J, Liñares J, Ardanuy C. . Molecular epidemiology of nontypeable Haemophilus influenzae causing community-acquired pneumonia in adults.PLOS ONE. 2013;8(12):e82515.
- Domenech A, Puig C, Martí S, Santos S, Fernández A, Calatayud L. Infectious etiology of acute exacerbations in severe COPD patients.J Infect. 2013 Dec;67(6):516-23.
- Rolo D, Fenoll A, Fontanals D, Larrosa N, Giménez M, Grau I. Serotype 5 pneumococci causing invasive pneumococcal disease outbreaks in Barcelona, Spain (1997 to 2011).J Clin Microbiol. 2013 Nov;51(11):3585-90.
- Rolo D, S Simões A, Domenech A, Fenoll A, Liñares J, de Lencastre H. Disease isolates of Streptococcus pseudopneumoniae and non-typeable S. pneumoniae presumptively identified as atypical S. pneumoniae in Spain.PLoS One. 2013;8(2):e57047.
- Wyres KL, Lambertsen LM, Croucher NJ, McGee L, von Gottberg A, Liñares J. Pneumococcal capsular switching: a historical perspective.J Infect Dis. 2013 Feb 1;207(3):439-49.

Highlights

Throughout 2013 we have participated in two Corporative Research Programs (Pneumonia and COPD) of CIBERES. The following studies were funding by two Research Projects (PI11/0763 and PI09/01904).

- The study of fluorquinolone resistance rates and mechanisms of pneumococci in Spain in 2012 showed that resistance remained low and stable throughout the last decade. However, in 2012 a notably the expansion of a preexisting multi-drug-resistant clone, CC63, and the emergence of the CC156 clone expressing serotype 11A were observed. This paper has been published in 2014 (Domenech et al Antimicrob Agents Chemother 2014; 58:2393-2399).
- We have participated in an international study analyzing 426 world-wide isolated pneumococci dated from 1937 through 2007. The whole-genome sequencing showed that capsular switching has been a regular occurrence among pneumococcal populations throughout the past 7 decades. Recombination of large DNA fragments (>30 kb), sometimes including the capsular locus and penicillin-binding protein genes, predated both vaccine introduction and widespread antibiotic use. This type of recombination has likely been an intrinsic feature throughout the history of pneumococcal evolution.
- We have characterized the multidrug resistant serotype 8 pneumococci clone detected as causing invasive disease in Spain since 2004. It is the first world description of this multidrug-resistant recombinant clone. The new strain (serotype 8-ST63) was originated by recombination of capsular locus and flanking regions from a serotype 8-ST53-isolate (donor) to a ST63 pneumococci (receptor).
- We have characterized the genotypes and antimicrobial resistance of 95 NT-Haemophilus influenzae causing non-bacteremic pneumonia in adults. These strains had a high genetic diversity, and a high rate of reduced susceptibility to ampicillin due to PBP3 alterations. Finally, the analysis of treatment and outcomes in this group of patients demonstrated that NTHi strains with mutations in the PBP3 could be successfully treated with ceftriaxone or fluoroquinolones.

PROGRAMME:
Tuberculosis / New Therapeutic Targets

Group 9

Group Members

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Main lines of research

Our Research Group of Mycobacterial Genetics has been working since 1992 in four lines of research financed by European and national investigation funds and that has permitted it to acquire an internationally recognized prestige. These lines of research include:

1 - Construction of New Vaccines against Tuberculosis 2 - Molecular Epidemiology of Tuberculosis & Transposition and Latency of M. tuberculosis 3 - Molecular Bases of the Resistance of mycobacteria.

The objectives of our group are to study the complexity of M. tuberculosis in a multidisciplinary focus and our group is coordinated with other national and international groups. More concretely we focus our research in: 1 - Genes implicated in the pathogenicity and virulence of M. tuberculosis 2 - Molecular epidemiology of tuberculosis, risk factors of transmission, and differences between strains of major epidemiological importance and the mechanism of slow growth of the Koch bacillus 3 - Mechanisms of resistance. Projects:

- Line 1: NEW TBVAC 241745 FP7, ECDTP (TBTEA) FP7 TBTEA. 2011- 2013 BIO2011-23555 BIO2011-23555 MCyT/DGI/FEDER 2012-2014. INNPACTO: Ref. IPT-2012-0327-090000 Ministerio de Economía y Competitividad "BIOFABRI.
- Line 2: FIS, Instituto de Salud Carlos III. 2013- 2015.REFBIO. 2013- 2014 Network: European reference laboratory network for tuberculosis (ERLTB-Net) - to strengthen TB diagnosis, drug susceptibility testing and coordination at European Union.
- Line 3. Ref: GRANT/2013/003. ECDC. 2014. Line3 3: MM4TB More Medicines for Tuberculosis. European Union 2011-2014 NAREB - Nanotherapeutics for antibiotic resistant emerging bacterial pathogens European Union. 2014- 2018.

Most relevant scientific articles

- Arbues A, Aguilo JI, Gonzalo-Asensio J, Marinova D, Uranga S, Puentes E. Construction, characterization and preclinical evaluation of MTBVAC, the first live-attenuated M. tuberculosis-based vaccine to enter clinical trials.Vaccine. 2013 Oct 1;31(42):4867-73.
- Aguilo JI, Alonso H, Uranga S, Marinova D, Arbués A, de Martino A. ESX-1-induced apoptosis is involved in cell-to-cell spread of Mycobacterium tuberculosis.Cell Microbiol. 2013 Dec;15(12):1994-2005.
- Marinova D, Gonzalo-Asensio J, Aguilo N, Martín C. Recent developments in tuberculosis vaccines.Expert Rev Vaccines. 2013 Dec;12(12):1431-48.
- Rodrigues L, Villellas C, Bailo R, Viveiros M, Aínsa JA. Role of the Mmr efflux pump in drug resistance in Mycobacterium tuberculosis.Antimicrob Agents Chemother. 2013 Feb;57(2):751-7.
- Alonso H, Samper S, Martín C, Otal I. Mapping IS6110 in high-copy number Mycobacterium tuberculosis strains shows specific insertion points in the Beijing genotype. BMC Genomics. 2013 Jun 25;14:422.

Highlights

CLINICAL TRIAL VACCINE MTBVAC: MTBVAC is developed by the University of Zaragoza and produced by Biofabri in Spain. MTBVAC received approval by Swiss Rgulatory Authorities to enter first-in-human Phase 1a clinical trial for safety and immunogenicity in healthy adults in Lausanne, Switzerland (http://clinicaltrials.gov/ct2/show/NCT02013245).

INTERNATIONALIZATION EUROPEAN PROJECT. In the line Molecular Bases of the Resistance of mycobacteria Nareb - Nanotherapeutics for antibiotic resistant emerging bacterial pathogens for the application of nanotechnology for therapeutic purposes against emerging pathogens resistant to drugs.

RESULTS TRANSFER INTERNATIONAL. In the line Molecular Epidemiology of Tuberculosis & Transposition and Latency of M. tuberculosis. Our groups is collaborator of European Centre for Disease Prevention and Control (ECDC) and member of the European network of reference laboratories for tuberculosis since 2009. ERLN-TB and the new network ERLTB-Net (GRANT/2013/003)

RESULTS TRANSFER. In the line Construction of New Vaccines against Tuberculosis. Our group has the Spanish Biopharmaceutical BIOFABRI as partner of the University of Zaragoza for the production and development of vaccine against tuberculosis MTBVAC. Transfer agreements with Spanish company funded research funds in recent years have been: Vacuna Inactivada contra la tuberculosis en base a una cepa modificada genéticamente" INNPACTO IPT-2012-0327-090000 Ministerio de Economía y Competitividad. 2012-2015.

RESULTS TRANSFER. In the line Molecular Bases of the Resistance of mycobacteria, technological impact of its activity has resulted in a series of contracts with companies and institutions: GlaxoSmithKline (GSK) in the testing of new compounds with potential anti-tuberculosis activity.

PROGRAMME:
Sleep Apnea

Group 15

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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

- Martínez-García MA, Capote F, Campos-Rodríguez F, Lloberes P, Díaz de Atauri MJ, Somoza M, Masa JF, González M, Sacristan L, et al.. Effect of CPAP on blood pressure in patients with obstructive sleep apnea and resistant hypertension: the HIPARCO randomized clinical trial.JAMA-J AM MED ASSOC. 2013;(310):2407-15.
- Barbé F, Masa JF. Hypoglossal neurostimulation for obstructive sleep apnoea. Eur Respir J. 2013 Feb;41(2):257-8.
- Masa JF, Corral J, Pereira R, Durán-Cantolla J, Cabello M, Hernández-Blasco L, Monasterio C, Alonso-Fernández A, Chiner E, Vázquez-Polo FJ, Montserrat JM; Spanish Sleep Group.. Effectiveness of sequential automatic-manual home respiratory polygraphy scoring.EUR RESPIR J. 2013;41(4):879-87.

- Masa JF, Corral J, Gómez de Terreros J, Duran-Cantolla J, Cabello M, Hernández-Blasco L. Significance of including a surrogate arousal for sleep apnea-hypopnea syndrome diagnosis by respiratory polygraphy.Sleep. 2013 Feb 1;36(2):249-57.
- Masa JF, Corral J, Sanchez de Cos J, Duran-Cantolla J, Cabello M, Hernández-Blasco L. Effectiveness of three sleep apnea management alternatives.Sleep. 2013 Dec 1;36(12):1799-807.

Highlights

PROJECTS

- ESADA -European Sleep Apnea Database. Center: Cost Action European Union. From 2008 to 2018.
- The effects of adaptive servo ventilation on survival in patients with Heart Failure (HF) and SAS. The ADVENT -HF trial.
- Cost - Effectiveness of respiratory Polygraph (HRP). PRIS 11009; Separ. 048 / 201; Neumosur 16/2011; Air - liquide.
- Cost - effectiveness of an oversimplified system for SAS management in primary care. FIS 2013. PI13/02638.
- Association between SAS and the growth rate of cutaneous melanoma. FIS PI12/01363.
- Levels 2-3 tiroredoxina and indoleamine dioxigenas in patients with OSA and treatment response FIS 2010-2011-2013.
- Utility index thermometry actimetry and body position in the assessment of sleepiness in patients with OSA. FIS PII / 02642 (2011-2013).
- Impact of SAS in the development of acute coronary syndrome. Effect of intervention with CPAP. Fis, separ 2012-2014.
- Effectiveness medium and long term NIV in OHS (Pickwicks). PS FIS 09/ 00510, and Air Liquide separ.
- Effect of CPAP treatment in women with SAS. Fis PI13/00743.

HEALTH GUIDES

- Spanish COPD guidelines (GesEPOC). Prim Care Respir J. 2013 Mar, 22 (1):117-21
- Guidelines for the management of respiratory complications in patients with neuromuscular disease. Bronconeumol. 2013 Jul, 49 (7):306-13. doi: 10.1016/j.arbres.2012.12.003.

CONVENTIONS

- AirLiquide for Pickwikcs and HRP projects. € 280,000
- Vitalaire project "Dream -Burgos". € 26,000
- "Project polygraphy shirt.": 12,000 euros
- The University of Chicago "NANOS Project". 50,000 euros
- Income audiovisual entertainment system in sleep studies in children with SAS"

OTHER ACTIVITIES

- New ICT based health services:
  a) Spanish UCRI Patient Registry (REPUCRI).
  b) The telemedicine monitoring CPAP.
- Validation of equipment:
  a) improving maternal and child health through teleestetoscopía in Peru.
- Doctoral Thesis. Alternative CPAP titration.

PROGRAMME:
New Therapeutic Targets

Group 25

Group Members

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Main lines of research

Our group has been working for more than 30 years with respiratory viruses of human relevance such as respiratory syncytial virus (RSV), metapneumovirus (MPV) and influenza virus. One of the main aspects of our research has been the antigenic, immunogenic and structural characterization of some of the viral gene products, as well as the virus-host cells interactions.

On the one hand, we have presently focused our studies on the RSV and MNV fusion glicoproteins. These proteins are the main targets of the neutralizing and protective antibodies. Thus, we are carrying out an extensive and detailed analysis of the different conformations adopted by these proteins during the process of membrane fusion and the mechanisms by which neutralizing antibodies interfere with that process. These studies are essential for the development of safe and effective vaccines, which are currently lacking.

On the other hand, we are developing methods to uncover antigenic differences between hemagglutinins (HAs) from different influenza virus strains.

The new methods are allowing us to unveil antigenic differences that were undetected by traditional methods, such as the hemagglutination inhibition (HI) assay. In addition, amino acid changes associated to the noted antigenic differences could be identified. Thus, the new methods will allow a more detailed study of the antigenic evolution of human influenza virus.

Finally, we are also interested in the regulation of the intracellular signaling cascade associated to the antiviral response triggered in RSV infected cells. Fine modulation of these routes is essential not only to control virus replication but also to control the inflammatory response. The activity of many of the proteins participating in the signaling cascade is influenced by post-translational modifications, such as covalent linkage of ubiquitine or other tags (ISG15). Our results show that the expression of certain genes involved in the innate immune response, as well as RSV replication are regulated by these processes of ubiquitination and ISGylation.

Most relevant scientific articles

- Mata M, Martínez I, Melero JA, Tenor H, Cortijo J. Roflumilast inhibits respiratory syncytial virus infection in human differentiated bronchial epithelial cells.PLoS One. 2013;8(7):e69670.
- Melero JA, Moore ML. Influence of respiratory syncytial virus strain differences on pathogenesis and immunity.Curr Top Microbiol Immunol. 2013;372:59-82.
- Más V, Melero JA. Entry of enveloped viruses into host cells: membrane fusion.Subcell Biochem. 2013;68:467-87.
- Rodríguez A, Falcon A, Cuevas MT, Pozo F, Guerra S, García-Barreno B. Characterization in vitro and in vivo of a pandemic H1N1 influenza virus from a fatal case.PLoS One. 2013;8(1):e53515.

Highlights

Our group had two projects active in 2013, one of them funded by "Plan Nacional de I+D+i" and the other funded by FIS. The results derived from both projects were included in four international publications two of them done in collaboration with other groups of "CIBER de Enfermedades Respiratorias". Some of these results were also included in a national patent. We are currently under negotiations for exploitation of this patent. In addition, last year a license agreement was signed with Novartis Vaccine industry, for the non-exclusive exploitation of three monoclonal antibodies produced in our laboratory.

Several members of the group participated in the National Congress of Virology and in the XIII International Conference on Negative Strand Viruses. Additionally, we have participated in the evaluation of international (Germany) and national projects (ANEP, Fundación Andaluza Progreso y Salud). We have also participated in national and international (Institut Pasteur) courses and masters of Virology. The principal investigator was awarded last year Honoris Causa Doctorate by the "Universidad de la República Oriental del Uruguay".

PROGRAMME:
New Therapeutic Targets

Group 34

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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 bacterial virulent factors, enzyme-based antimicrobials, and host-pathogen interactions.

Most relevant scientific articles

- Díez-Martínez R, de Paz H, Bustamante N, García E, Menéndez M, García P.. Improving the lethal effect of Cpl-7, a pneumococcal phage lysozyme with broad bactericidal activity, by inverting the net charge of its cell wall-binding moduleAntimicrobial Agents and Chemotherapy. 2013;57:5355-5365.
- Ruiz FM, Fernández IS, López-Merino L, Lagartera L, Kaltner H, Menéndez M, André S, Solís D, Gabius H-J, Romero A. Fine-tuning of prototype chicken galectins: structure of CG-2 and structure–activity correlationsActa Crystallographica Section D, Biologycal Crystallography. 2013;D69(Pt 8):1655-1676.
- Carrero P, Ardá A, Alvarez M, Doyagüez EG, Rivero-Buceta E, Quesada E, Prieto A, Solís D, Camarasa MJ , Peréz-Pérez MJ, Jiménez-Barbero J, San-Félix A. Differential Recognition of Mannose-Based Polysaccharides by Tripodal Receptors Based on a Triethylbenzene Scaffold Substituted with Trihydroxybenzoyl MoietiesEuropean Journal of Organic Chemistry. 2013;1:65-76.
- Ermakova E, Miller MC, Nesmelova IV, López-Merino L, Berbís MA, Nesmelov Y, Tkachev YV, Lagartera L, Daragan VA, André S, Cañada FJ, Jiménez-Barbero J, Solís D, Gabius H-J, Mayo KH.. Lactose binding to human galectin-7 (p53-induced gene 1) induces long-range effects through the protein resulting in increased dimer stability and evidence for positive cooperativityGlycobiology. 2013;23 (5):508-523.

Highlights

After structurally and functionally characterizing the Cpl-7 endolysin from pneumococcal bacteriophage Cpl-7, we have engineered a protein variant with 15 amino acid substitutions and 18 negative charges less (Cpl-7S) whose exogenous killing activity against *Strepcotococcus pneumoniae*, *Streptococcus pyogenes* and other pathogens is significantly improved. Moreover, in the presence of 0.1% carvacrol, Cpl-7S also kills efficiently Gram-negative bacteria, an effect not described previously. Cpl-7S bacteriolytic activity was also validated in vivo using a new zebra-fish embryo model of infection. Cpl-7S and its modification strategy, extensible to other murolytic enzymes, have been patented.

Characterization of glycan-mediated host-pathogen interactions was also initiated. Thus, O-chain meditated binding of human galectins 3, 4, 8 and 9 to Klebsiella pneumoniae was demonstrated, while a similar study on nontypeable Haemophilus influenzae revealed a selective recognition of selected strains by human galectins 4, 8 and 9 whose biological implications are been investigated. Development of designer's bacterial microarrays has shown to be central to both studies. In parallel, structure/function relation-ships in human galectins 3 and 4 are being investigated using different protein variants.

Results have generated so far four publications in scientific journal, 10 communications to scientific congresses and specialized workshops, and one patent (Improved bactericidal antibiotics against Streptococus pneumoniae and other bacteria) in collaboration with Dr. E. Garcias's group of CIBERES.

ACTIVE PROJECTS:

- 2010-2012. Structural variability and substrate fine specificity of two families of biomedical relevant proteins. MICINN (BFU2009-10052)
- 2011-2013. Glycomics by High-throughput Integrated Technologies (UE; FP7-HEALTH-2010-260600)
- 2012-2015. Dynamic interactive nanosystems (EU; FP7-ITN-GA:289003)
- 2012-2015. Bioinformatics Integrative platform for structure-based drug discovery 2 (CAM; S2010/BMD-2457)
- 2012-2016 . The Sugar Code: from (bio)chemical concept to clinics (UE; FP7-PEOPLE-2012-ITN-317297)
- 2013-2015. Exploring exogenous and endogenous factors as tools for the control of infectious and immune processes (MINECO; BFU2012-36825)

PROGRAMME:
Lung Cancer/ COPD/Pneumonia

Group 30

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Main lines of research

- On Lung Cancer, the group coordinates the Strategic RCP on Lung Cancer (2013-2015). Three cohorts of lung early stage (I / IIp) cancer have been created, with obtaining clinical information and follow-up samples and tumor and non-tumor lung tissue and peripheral blood, registered in the CIBERES Pulmonar Biobank Consortium.
- On COPD, the Group participates in the RCP including patients in a cohort of iniatial COPD diagnosis (Early - Cohort COPD) and in a severe COPD cohort with fragility characteristics of frequent exacerbations. The group performs the analysis of bronchial inflammatory response and the study of bronchial microbiology.
- On Pneumonia, the Group is the partner of RCP participating in the register of invasive pneumococcal disease and the analysis of early mortality determinants in bacteremic pneumococcal pneumonia. The Group is leading a multicenter project focused on nosocomial pneumonia outside the Intensive Care Unit. 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, and acts as a reference center for Legionella molecular typing.

- As part of the actions of the Technology Transfer Platform, the Group has developed a signal synchronization platform to be applied to biomedical noninvasive ventilation that unifies and synchronizes the signal of respiratory mechanics with the consequences of pulmonary gas exchange and patient effort.

Most relevant scientific articles

- Luján M, Burgos J, Gallego M, Falcó V, Bermudo G, Planes A et al.. Effects of immunocompromise and comorbidities on pneumococcal serotypes causing invasive respiratory infection in adults: implications for vaccine strategies.Clin Infect Dis. 2013 Dec;57(12):1722-30.
- Sanz-Santos J, Cirauqui B, Sanchez E, Andreo F, Serra P, Monso E et al.. Endobronchial ultrasound-guided transbronchial needle aspiration in the diagnosis of intrathoracic lymph node metastases from extrathoracic malignancies.Clin Exp Metastasis. 2013 Apr;30(4):521-8.
- García-Nuñez M, Quero S, Catini S, Pedro-Botet ML, Mateu L, Sopena N et al.. Comparative molecular and antibody typing during the investigation of an outbreak of Legionnaires' disease.J Infect Chemother. 2013 Oct;19(5):896-901.
- Sogo A, Montanyà J, Monsó E, Blanch L, Pomares X, Luján M. Effect of dynamic random leaks on the monitoring accuracy of home mechanical ventilators: a bench study. BMC Pulm Med. 2013 Dec 10;13:75.
- Cubero N, Esteban J, Palenque E, Rosell A, García MJ. Evaluation of the detection of Mycobacterium tuberculosis with metabolic activity in culture-negative human clinical samples.Clin Microbiol Infect. 2013 Mar;19(3):273-8.

Highlights

On Lung Cancer, the Group maintains the line of diagnosis and noninvasive staging, and has consolidated the collaborative research network with SEPAR. The Group has established a biobank of tumor lung tissue of patients with stage I and II, and provided more than 200 samples. The program has partnered with the International Association for the Study of Lung Cancer to incorporate molecular staging variables, in collaboration with the Cancer RETIC. The Group has also started a line of endoscopic navigation generating a patent (publication number WO2013171356 A1) and the spin -off ADBRONCHUS SL.

On COPD, the Group has implemented the analysis of bronchial microbiome by metagenomic techniques, in collaboration with Genomics and Health Area of CSISP-FISABIO from the CIBERESP, and has demonstrated the segmentation of the bronchial microbial composition. This line used analyzed the variability of the respiratory microbiome in COPD, showing that the exacerbation in patients with chronic colonization is attributable to different pathogens from colonizers.

On Pneumonia, the Group is leading a multicenter study on invasive pneumococcal disease, and has designed an intervention project to determine the incidence of nosocomial pneumonia outside the ICU. The Group collaborates with the National Microelectronics Centre for biosensors development for Legionella detection, and environmental health studies about the effects of disinfection measures applied in water supplies, acting as a center of molecular typing of the Catalan Agency for Public Health. Additionally, the group maintains the spin –off AQUALAB SL, since 2003.

On technological innovation, the Group has developed a signal synchronization platform to be applied to biomedical noninvasive ventilation that unifies and synchronizes the signal mechanical respiratory signal with the consequences of gas exchange in collaboration with Bettercare, a spin -off of Ciberes.

PROGRAMME:
Síndrome de apneas del Sueño

Group 11

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Main lines of research

- Respiratory Sleep disorders, apnoea and cancer. Since 2011 the group was working group in this area that has been seminal with two lines of research clinical and basic. There are a number of published clinical and basic work .
- Sleep disorders and aging. For the group this aspect is considered essential because in the near future the elderly will be 20 % of the population and the number of apneas of them is usually much higher. Perhaps the diagnostic and therapeutic procedures in this patients would be different and more cost-efective procedures are neded. This studies are performed in human and in murine
- The group has another important goal. Specifically and as apneas are considered a systemic disease attempts to assess the effect of apnea in other organs. A first study already published in JAMA assesses the relationship between apnea and high blood pressure. Currently another line has already finished part (murine model) and is the effect of apneas on fertility. Now, will begin the human studies. In the future other organs such as liver, aspects of intestinal flora, etc. will be studied.
- Telemedicine and very specifically in the development of a virtual laboratory where all sleep studies and patient care will be performed outside of the hospital. In addition programs with nurses are on going to improve CPAP compliance.
- Finally mechanical ventilation in the direction of the appropriate titration and monitoring are priorities. Also in this context, the group works with companies to assess various devices.

Most relevant scientific articles

- Martínez-García MA, Capote F, Campos-Rodríguez F, Lloberes P, Díaz de Atauri MJ, Somoza M, Masa JF, González M, Sacristan L, et al.. Effect of CPAP on blood pressure in patients with obstructive sleep apnea and resistant hypertension: the HIPARCO randomized clinical trial.JAMA-J AM MED ASSOC. 2013;(310):2407-15.
- Almendros I, Montserrat JM, Torres M, Dalmases M, Cabañas ML, Campos-Rodríguez F. Intermittent hypoxia increases melanoma metastasis to the lung in a mouse model of sleep apnea.Respir Physiol Neurobiol. 2013 May 1;186(3):303-7.
- Masa JF, Corral J, Sanchez de Cos J, Duran-Cantolla J, Cabello M, Hernández-Blasco L. Effectiveness of three sleep apnea management alternatives.Sleep. 2013 Dec 1;36(12):1799-807.
- Masa JF, Corral J, Gómez de Terreros J, Duran-Cantolla J, Cabello M, Hernández-Blasco L. Significance of including a surrogate arousal for sleep apnea-hypopnea syndrome diagnosis by respiratory polygraphy.Sleep. 2013 Feb 1;36(2):249-57.
- Chamorro N, Sellarés J, Millán G, Cano E, Soler N, Embid C. An integrated model involving sleep units and primary care for the diagnosis of sleep apnoea.Eur Respir J. 2013 Oct;42(4):1151-4.

Highlights

CANCER AND SLEEP APNEA. This has probably been one of the most important points in the group's production. Not only has made the original and initial work in murine but also has been recently published the first clinical (multicenter study). Especially important is the Almendos, I. et al paper published in ERJ in murine where demonstrate the relationship between cancer and apneas. Campos et al (AJRCCM) demonstrated an increased incidence of cancer in patients with apnea.

TELEMEDICINA. Several studies have confirmed its value in sleep disorders. One of the first study was of the Isetta, V. et al also recently published (INTERACTIVE JOURNAL OF MEDICAL RESEARCH 2014. In addition and regarding within the information technology are two points to note. One, the group participation in European Chromed program as a member of the group led by Dr. Farre and finally the introduction of the participation of patients themselves in managing their disease through information technologies. This has been possible with the development of APP among other systems currently used.

CURRENT PROJECTS:

- SAHS and elderly supported by FIS. JM Montserrat Dr IP.
- SAHS and Melanoma. Supported FIS. IP Dr MA Martinez.
- Telemedicine and its application to sleep apnea syndrome compliance. supported by Esteve- Teijin. Dr JM Montserrat IP.
- APNEA during sleep and family physicians - Supported by FIS. IP: Dr Masa.
- Analysis of new devices (Respironics). IP: Dr Embid.
- Parabiotico Mouse Models in collaboration with the group of Dr Rojas (USA). IP: Dr Marta Torres.

PROGRAMME:
New Therapeutic Targets/ Fibrosis Pulmonar

Group 13

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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.

Most relevant scientific articles

- Rius C, Company C, Piqueras L, Cerdá-Nicolás JM, González C, Servera E. Critical role of fractalkine (CX3CL1) in cigarette smoke-induced mononuclear cell adhesion to the arterial endothelium.Thorax. 2013 Feb;68(2):177-86.
- Almudéver P, Milara J, de Diego A, Serrano-Mollar A, Xaubet A, Pérez-Vizcaino F. Role of tetrahydrobiopterin in pulmonary vascular remodelling associated with pulmonary fibrosis.Thorax. 2013 Oct;68(10):938-48.
- Milara J, Peiró T, Serrano A, Cortijo J. Epithelial to mesenchymal transition is increased in patients with COPD and induced by cigarette smoke.Thorax. 2013 May;68(5):410-20.
- Milara J, Peiró T, Serrano A, Cortijo J. Authors' response to: epithelial mesenchymal transition (EMT) in small airways of COPD patient.Thorax. 2013 Aug;68(8):784.
- Milara J, Serrano A, Peiró T, Artigues E, Gavaldà A, Miralpeix M. Aclidinium inhibits cigarette smoke-induced lung fibroblast-to-myofibroblast transition.Eur Respir J. 2013 Jun;41(6):1264-74.

Highlights

RELEVANT PUBLIC PROJECTS

- Cigarette smoke-induced remodeling and COPD in human and animal models: pharmacological modulation CP11/00293. (MIGUEL SERVET ISCIII)
- Pharmacological modification of cigarette smoke-induced COPD and remodeling: insights in human and animal models (SAF2011- 26443)
- Nuevas dianas farmacológicas para el tratamiento de la EPOC y sus comorbilidades vasculares. (Ayudas programa Prometeo para grupos de investigación de excelencia-prometeo/2013-fase II/ Generalitat Valenciana)

RELEVANT PRIVATE PROJECTS

- Effects of phosphodiesterase 5 system in pulmonary hypertension-associated pulmonary idiopathic fibrosis: an in vitro study (PFIZER)
- Effects of Roflumilast N-oxide, a PDE4 inhibitor on selected functions of polarized human bronchial epithelial cells in presence or absence of a long acting ß2-agonist (LABA), a long acting muscarinic antagonist (LAMA), a glucocorticoid, a PDE5 inhibitor or a statin (NYCOMED Pharma S.A)
- Anti-inflammatory activity of long-acting muscarinic receptor antagonists (LAMA) in those situations of corticoid-resistance on in vitro models relevant to COPD. (ALMIRALL PRODESFARMA S.A.)
- Characterization of differential effects of roflumilast N-oxide versus corticosteroids and long-acting ß2-adrenergic agonist (LABA) on neutrophils from healthy and COPD patients: Mechanistic studies. (FOREST RESEARCH INSTITUTE)
- Analysis of the additive/synergistic anti-inflammatory effects of combinations of aclidinium bromide, corticosteroids and long-acting ß2-adrenergic agonist (LABA) on neutrophils from healthy and COPD patients. (ALMIRALL PRODESFARMA S.A)
- Analysis of the additive/synergistic anti-inflammatory effects of combinations of MABA and corticosteroids on neutrophils from healthy and COPD patients. (ALMIRALL PRODESFARMA S.A.)

PROGRAMME:
Asthma

Group 16

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Main lines of research

The PCI on asthma has started the MEGA project (Mechanism underlying to genesis and evolution of asthma) with the aim to examine the mechanism underlying to genesis and evolution of asthma in a well defined cohort. Using an integrate approximation, MEGA will identify, describe and validate immunological and molecular networks involved in the genesis and evolution of asthma. This project will devise, operate and exploit a carefully integrated network of collaborative studies designed to understand the mechanism underlying to the asthma genesis and evolution. The knowledge generated by this project will be translated into therapeutic strategies designed to address the current epidemic of asthma in the world.

The Group is also working in the evolution of occupational asthma in order to know if cessation of exposure really improve prognosis (paper submitted):

Muñoz X, Viladrich M, Manso L, del Pozo V, Quirce S, Cruz MJ, Carmona F, Sánchez-Pla A, Sastre J. Evolution of occupational asthma: does cessation of exposure really improve prognosis?. Under Review

However, the group has published in 2013 more than 50 scientific articles which more than half are collaborative. This is because, the clinical and basic research activity of the group 16 is mainly focused on areas of inflammation and repair, respiratory failure and tissue hypoxia, and there is complementarily and interrelatedness of these areas for the study of diseases such as asthma COPD, pulmonary fibrosis, infections, transplant, pulmonary hypertension and sleep-disordered breathing. For this reason, the Group is also collaborating with other Corporate Research Programs such us COPD, Sleep Disorders and others (see publications of the Group).

Most relevant scientific articles

- Freixa X, Portillo K, Paré C, García-Aymerich J, Gómez FP, Benet M et al.. Echocardiographic abnormalities in patients with COPD at their first hospital admission.Eur Respir J. 2013 Apr;41(4):784-91.
- Martínez-García MA, Capote F, Campos-Rodríguez F, Lloberes P, Díaz de Atauri MJ, Somoza M, Masa JF, González M, Sacristan L, et al.. Effect of CPAP on blood pressure in patients with obstructive sleep apnea and resistant hypertension: the HIPARCO randomized clinical trial.JAMA-J AM MED ASSOC. 2013;(310):2407-15.
- Peinado VI, Gómez FP, Barberà JA, Roman A, Angels Montero M, Ramírez J et al.. Pulmonary vascular abnormalities in chronic obstructive pulmonary disease undergoing lung transplant.J Heart Lung Transplant. 2013 Dec;32(12):1262-9.
- Bernstein DI, Kashon M, Lummus ZL, Johnson VJ, Fluharty K, Gautrin D et al.. CTNNA3 (α-catenin) gene variants are associated with diisocyanate asthma: a replication study in a Caucasian worker population.Toxicol Sci. 2013 Jan;131(1):242-6.
- Monforte V, López-Sánchez A, Zurbano F, Ussetti P, Solé A, Casals C et al.. Prophylaxis with nebulized liposomal amphotericin B for Aspergillus infection in lung transplant patients does not cause changes in the lipid content of pulmonary surfactant.J Heart Lung Transplant. 2013 Mar;32(3):313-9.

Highlights

The Group has published in 2013 a paper entitled "Human mesenchymal stem cells overexpressing the IL-33 antagonist sST2 attenuate endotoxin-induced acute lung injury" which resulted in a patent. This study has served us to establish new collaborations with other groups like the group of Human Molecular Genetics from IDIBELL, with whom we have signed a license agreement with the Basque company Histocell for the use of our patent for the treatment of acute lung diseases with mesenchymal stem cells. These cells, administered intravenously, have the ability to go directly to the damaged lungs, which act as a "smart drug".

In the same line, the group has submitted a new publication for the use of these cells in the treatment of asthma that is under review.

We are currently working with the Department of Molecular Physiology and channelopathies from the Universitat Pompeu Fabra for the study of the impact of overexpression of the gene ORMDL3 on the susceptibility to develop occupational asthma .

At present the group is part of a project funded by NIOSH / CDC and led by Dr. David Bernstein, Division of Immunology, Allergy and Rheumatology, University of Cincinnati College of Medicine, Cincinnati, Ohio, for the study of the genetic susceptibility to occupational asthma. This project has resulted in sevaral papers published in journals of first quartile and has now begun a second phase of the study. One of these paper has been published this year and includes two of the groups of the asthma PCI (see publications).

PROGRAMME:
Sleep Apnea / Acute Lung Injury

Group 12

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Main lines of research

- Pathophysiology of sleep apnea and acute lung injury in patients and in animal models.
- Cell and Tissue Mechanobiology in respiratory diseases.
- Instrumentation and diagnostic, therapeutic and monitoring methodologies for sleep apnea and acute lung injury.
- Nanotechnologies and lab-on-a–chip devices for the study and characterization of the mechanical behavior of cells and tissues.

Most relevant scientific articles

- Campos-Rodríguez F, Martínez-García MA, Martínez M, Duran-Cantolla J, Peña Mde L, Masdeu MJ. Association between obstructive sleep apnea and cancer incidence in a large multicenter Spanish cohort.Am J Respir Crit Care Med. 2013 Jan 1;187(1):99-105.
- Franquesa M, Hoogduijn MJ, Reinders ME, Eggenhofer E, Engela AU, Mensah FK. Mesenchymal Stem Cells in Solid Organ Transplantation (MiSOT) Fourth Meeting: lessons learned from first clinical trials.Transplantation. 2013 Aug 15;96(3):234-8.
- Kim JH, Serra-Picamal X, Tambe DT, Zhou EH, Park CY, Sadati M. Propulsion and navigation within the advancing monolayer sheet.Nat Mater. 2013 Sep;12(9):856-63.
- Luque T, Melo E, Garreta E, Cortiella J, Nichols J, Farré R. Local micromechanical properties of decellularized lung scaffolds measured with atomic force microscopy.Acta Biomater. 2013 Jun;9(6):6852-9.
- Li Bassi G, Ranzani OT, Marti JD, Giunta V, Luque N, Isetta V. An in vitro study to assess determinant features associated with fluid sealing in the design of endotracheal tube cuffs and exerted tracheal pressures.Crit Care Med. 2013 Feb;41(2):518-26.

Highlights

The group belongs to the CIBER of Respiratory Diseases and is an associated group of CIBER of Bioengineering, Biomaterials, and Nanomedicine. In CiberES our research is currently focused on the Corporate Programs on Acute Lung Injury Program (ALI) and Sleep Apnea - Hypopnea Syndrome (SAHS). In CiberBBN we participate in the project Multimodal Diagnosis by Signal Interpretation of the Respiratory System oriented to Pulmonary Diseases and Sleep Disorders (MUDIRES-2PSD). Our research is interdisciplinary and is developed in collaboration with other groups of the CIBER. We transfer technology by means of contracts with companies of respiratory medical devices.

In SAHS program our group is active in the study of the pathophysiology and consequences of the disease. Members of the group have led two publications in 2013 based on a mouse model of melanoma and intermittent hypoxia, showing for the first time that intermittent hypoxia similar to OSA increases tumor growth - probably via overexpression of vascular endothelial growth factor – and promotes tumor metastasis to the lung. We have also published two studies in patients revealing a significant incidence/mortality of cancer in patients with SAHS. The group leads a Work Package of the European project CHROMED on home monitoring in patients with chronic respiratory diseases. We have also developed a platform for telematics control of CPAP treatment in patients with sleep apnea at home.

Within the ALI program and in order to understand the mechanisms that govern the cell-matrix interplay in lung repair/regeneration we have characterized the mechanical properties of the lung extracellular matrix by means of nanotechnologies. This work has revealed for the first time the mechanical heterogeneity of the cell niche in different lung structures. In addition, we have evaluated the effect of different decellularization procedures on the nanomechanics of lung matrix. Moreover, the mechanical forces governing collective migration involved in the tissue repair mechanisms have been identified. We have also developed a lab-on-a-chip device to study the cellular response to cyclic deformation.

PROGRAMME:
New Therapeutic Targets

Group 32

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Main lines of research

- Structure-function studies on the influenza virus RNA polymerase.
- Virus counteraction to the interferon response after infection.
- Mechanism of influenza virus interaction with the host cell.

Most relevant scientific articles

- Rodríguez A, Falcon A, Cuevas MT, Pozo F, Guerra S, García-Barreno B. Characterization in vitro and in vivo of a pandemic H1N1 influenza virus from a fatal case.PLoS One. 2013;8(1):e53515.
- Alfonso, R., Rodríguez, A., Rodríguez, P., Lutz, T., Nieto A . CHD6, a cellular repressor of influenza virus replication, is degraded in human alveolar epithelial cells and mice lungs during infection.Journal of Virology. 2013;.
- Martín-Benito, J., Ortin, J.. Influenza Virus Transcription and ReplicationAdv Virus Research. 2013;.
- Yángüez E, García-Culebras A, Frau A, Llompart C, Knobeloch KP, Gutierrez-Erlandsson S, García-Sastre A, Esteban M, Nieto A, Guerra S. ISG15 regulates peritoneal macrophages functionality against viral infection.Plos Pathogen.;.

Highlights

CHARACTERISATION OF THE H1N1 PANDEMIC VIRUS PATHOGENICITY.

Along 2013 we have analysed the pathogenicity of various pandemic H1N1 influenza virus Straits. We studied two different virus isolates, one derived from a mild influenza case and the other obtained from a fatal human case. The analysis in cultured cells indicated that the virus obtained from the fatal case was clearly more pathogenic. Full genome sequencing of either virus showed that the high pathogenicity was associated to 3 mutations detected in the polymerase and haemagglutinin genes. In addition, the study of the genetic background of the patients showed that the deceased patient was homozygous for a deletion in the CCR5 chemokine receptor, that leads to an inactive protein, a fact the probably contributed to the disease development.

ANALYSIS OF THE INTERACTIONS OF INFLUENZA VIRUS WITH THE INFECTED CELL.

The expression of the influenza virus genome is very much dependent on the cellular transcription machinery. The cellular transcription is modulated by the chromatin dynamics and therefore the virus gene expression is dependent on chromatin changes. The virus infection fires a proteolytic mechanism that leads to degradation of cellular RNA polymerase II, once virus transcription is completed and no further cellular transcription is required. We have shown that not only RNA polymerase II, but also chromatin remodeller CHD6 is degraded along infection. These events occur in infected tissue cultured cells and also in the lungs of infected mice, reinforcing the importance of the chromatin structure for influenza virus gene expression.

PROGRAMME:
Pneumonia

Group 26

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Main lines of research

RESPIRATORY INFECTION:

Main objective: to study the epidemiology of respiratory infections.

- *Streptococcus pneumoniae* infection.
  - Pneumococcal invasive infection in paediatric and adult populations: incidence, serotypes and genotypes.
  - Non-invasive pneumococcal infection: otitis media and conjunctivitis. Serotypes and genotypes. Antibiotic resistance.
  - Studies on vaccines. Impact of the 13 -valent conjugate vaccine. Comparison with the 7-valent vaccine. Influence of childhood vaccination with the new 13-valent vaccine on invasive infection and nasopharyngeal carriage in the first years of life.
  - Design of new pneumococcal typing techniques.
  - Determine the evolution of S. pneumoniae antibiotic resistance over time: new serotypes causing infection and genetic resistance determinants; influence of antibiotic consumption in resistance; spread of multi-resistant clones after the introduction of conjugate vaccines.
  - To confirm the replacement of the "resistant serotypes" as a result of the commercialization of 13-valent conjugate vaccine in 2010.
  - Influence of childhood vaccination on antibiotic resistance in adults.
- *Streptococcus pyogenes* infection.
  - Incidence and characterization of strains causing invasive disease.

- Incidence and characterization of S. pyogenes strains causing non-invasive disease: otitis, pharyngitis, and other skin and soft tissue infections.
- *S. pyogenes* pneumonia. Clinical and epidemiological aspects.
- Phenotypic and genotypic characterization of *S. pyogenes isolates*.
- Study of antibiotic susceptibility. *S. pyogenes* mechanisms of resistance to macrolides, tetracyclines and fluoroquinolones.

• Respiratory infection caused by virus.

- Influenza-virus infections. Genetic characterizations of seasonal strains.
- Microbiological characterization of emerging respiratory viruses: influenza pandemic H1N1 and H3N2 virus, human metapneumovirus, bocavirus. Diagnosis and epidemiology of their infections.
- Epidemiology of non- influenza viruses causing ILI. Seasonality, hospitalization and incidence distributed by age groups.
- Value or significance of viral infections in exacerbations of COPD.
- Characteristics of mixed infections by two or more respiratory virus and between viruses and bacteria in pneumonia.

Most relevant scientific articles

- Marimon JM, Ercibengoa M, García-Arenzana JM, Alonso M, Pérez-Trallero E. Streptococcus pneumoniae ocular infections, prominent role of unencapsulated isolates in conjunctivitis.Clin Microbiol Infect. 2013 Jul;19(7):E298-305.
- Alonso M, Marimon JM, Ercibengoa M, Pérez-Yarza EG, Pérez-Trallero E. Dynamics of Streptococcus pneumoniae serotypes causing acute otitis media isolated from children with spontaneous middle-ear drainage over a 12-year period (1999-2010) in a region of northern Spain.PLoS One. 2013;8(1):e54333.
- Montes M, Tamayo E, Oñate E, Pérez-Yarza EG, Pérez-Trallero E. Outbreak of Streptococcus pyogenes infection in healthcare workers in a paediatric intensive care unit: transmission from a single patient.Epidemiol Infect. 2013 Feb;141(2):341-3.
- Picazo JJ, González-Romo F, García Rojas A, Peréz-Trallero E, Gil Gregorio P, de la Cámara R. [Consensus document on pneumococcal vaccination in adults with risk underlying clinical conditions].Rev Esp Quimioter. 2013 Sep;26(3):232-52.
- Montes M, Artieda J, Piñeiro LD, Gastesi M, Diez-Nieves I, Cilla G. Hand, foot, and mouth disease outbreak and coxsackievirus A6, northern Spain, 2011.Emerg Infect Dis. 2013 Apr;19(4).

Highlights

The recognition of our group by the Basque Government as a "research group of excellence", with funding for the next 6 years, and three FIS projects achieved by the group (two health research projects and a staff substitution to intensify the research work) are the most important facts of the group concerning funded projects (resources) in 2013.

Regarding Congresses, two works of the Coordinated Project "Pneumonia" were accepted for oral presentations at two international conferences: the ECCMID, held in Berlin, Germany in April and the ICAAC, held in Denver, Colorado, USA in September. In these conferences, 8 other communications were also presented as posters.

In educational training, it is noteworthy to underscore the two Doctoral Theses directed by the Head of the Group, both evaluated as "Apto cum laude" (best qualification).

As for publications, highlight that more than half of those published during 2013 (15 indexed publications) have been done in collaboration with other research groups.

PROGRAMME:
Acute Lung Injury

Group 28

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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.

Most relevant scientific articles

- Almudéver P, Milara J, de Diego A, Serrano-Mollar A, Xaubet A, Pérez-Vizcaino F. Role of tetrahydrobiopterin in pulmonary vascular remodelling associated with pulmonary fibrosis.Thorax. 2013 Oct;68(10):938-48.
- Reboredo M, Chang HC, Barbero R, Rodríguez-Ortigosa CM, Pérez-Vizcaíno F, Morán A. Zolmitriptan: a novel portal hypotensive agent which synergizes with propranolol in lowering portal pressure.PLoS One. 2013;8(1):e52683.
- Menendez C, Martínez-Caro L, Moreno L, Nin N, Moral-Sanz J, Morales D. Pulmonary vascular dysfunction induced by high tidal volume mechanical ventilation.Crit Care Med. 2013 Aug;41(8):e149-55.
- Zarzuelo MJ, Gómez-Guzmán M, Jiménez R, Quintela AM, Romero M, Sánchez M. Effects of peroxisome proliferator-activated receptor-β activation in endothelin-dependent hypertension.Cardiovasc Res. 2013 Sep 1;99(4):622-31.
- Moreno L, Gatheral T. Therapeutic targeting of NOD1 receptors.Br J Pharmacol. 2013 Oct;170(3):475-85.

Highlights

ONGOING PROJECTS 2013:

- Micropartículas: vasoconstricción pulmonar y vías de señalización. SEPAR 142/2011. 01/06/2012-31/06/2013. PI: F. Perez-Vizcaino.
- New vasodilators for pulmonary hypertension. CICYT (SAF2011- 28150) 01/01/2012 -31/12/2014. PI: F. Perez-Vizcaino.
- Prevención de la mortalidad y el daño pulmonar agudo asociada a shock hemorrágico traumático por el flavonoide quercetina, por imipramina y otros inhibidores de la esfingomielinasa ácida. Fundación Mutua Madrileña. 01/09/2012-31/12/2013. PIs: JL. Álvarez-Sala and F. Perez-Vizcaino.
- Papel de los receptores de inmunidad innata en las alteraciones vasculares asociadas a daño pulmonar agudo e hipertensión pulmonar. Implicación de patrones moleculares endógenos asociados a peligro. MSC, ISCIII. 01/01/2013-31/12/2015. PI: Laura Moreno.
- Efectos cardiovasculares de agonistas de los receptores activados por proliferador de peroxisomas (PPAR)?/? en modelos de diabetes experimental. CICYT Proyecto coordinado (SAF2010-22066-C02-02). 01/01/2011-31/12/2013. PI: A. Cogolludo.
- Determinación de los cambios en los marcadores de inflamación y daño pulmonar en modelos experimentales y pacientes prematuros con hipertensión pulmonar asociada a displasia broncopulmonar tras la administración de células mesenquimales. Fundación contra la hipertensión pulmonar. 2013-14. PI: Laura Moreno.
- ENPATHY: Crowdfunding initiative promoted by the Fundación Contra la Hipertensión Pulmonar. (http://www.fchp.es).

MILESTONES:

Incorporation of a Miguel Servet Researcher (Dr Laura Moreno).

Doctorate Extraordinary Prize. Javier Moral-Sanz.

International Research Prize. Mars Prize on Flavonoid Research. 2013. F. Pérez Vizcaíno.

Visiting Investigators 2013: Camila Bedo (Univ. Paraguay), Virginia Chamorro (Granada, Spain) Jean Baptiste Carvés (Univ Descartes, France), Eduardo Villamor (Univ Maastricht, Holand), Vera Francisco (Univ Coimbra, Portugal).

Coordinator of the PhD Academic Program Comission (School of Medicine, UCM).

PROGRAMME:
Asthma

Group 5

Group Members

STAFF MEMBERS

Martín Robles, Irene Carla
Torres Blanch, Rosa
Vennera Trunzo, Mª del Carmen

ASSOCIATED MEMBERS

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Guilemany Toste, José María
Martínez Antón, María Asunción
Molina Molina, María
Mullol Miret, Joaquim
Muñoz Cano, Rosa
Pérez González, María
Pujols Tarres, Laura
Roca Ferrer, Jordi
Serrano Mollar, Ana María
Torres Blanch, Rosa
Valero Santiago, Antonio
Xaubet Mir, Antonio

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Picado Vallés, César

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Main lines of research

- Study of the links between upper airway diseases (rhinitis, rhinosinusitis and nasal polyps) and lower airway diseases (asthma, chronic obstructive pulmonary disease and bronchiectasis). Relationship between chronic rhinosinusitis and asthma severity.
- Study of the alterations in the regulation of glucocorticoid receptor in the reduced response to glucocorticoids (glucocorticoid resistance) in inflammatory airway diseases (chronic rhinosinusitis, nasal polyposis and asthma).
- Study of the role of the cyclooxygenase pathaway of arachidonic acid metabolism in the pathophysiology of airway inflammation (chronic rhinosinusitis, asthma), and in the airways remodelling and lung fibrosis.
- Study of the mechanisms involved in non-steroidal antiinflammatory drugs intolerance in asthma.
- Severe asthma: study of the efficacy of the new biologic therapies (omalizumab).
- New therapies: 6.1 In asthma (agonists of EP2 receptor of prostaglandin E2). 6.2 Transplantation of type II alveolar cells in the treatment of lung fibrosis

Most relevant scientific articles

- Fernández-Bertolín L, Mullol J, Fuentes-Prado M, Alobid I, Roca-Ferrer J, Picado C et al.. Deficient glucocorticoid induction of anti-inflammatory genes in nasal polyp fibroblasts of asthmatic patients with and without aspirin intolerance. J Allergy Clin Immunol. 2013 Nov;132(5):1243-1246.e12.
- Torres R, Herrerias A, Serra-Pagès M, Marco A, Plaza J, Costa-Farré C et al.. Locally administered prostaglandin E2 prevents aeroallergen-induced airway sensitization in mice through immunomodulatory mechanisms. Pharmacol Res. 2013 Apr;70(1):50-9.
- Gabasa M, Royo D, Molina-Molina M, Roca-Ferrer J, Pujols L, Picado C et al.. Lung myofibroblasts are characterized by down-regulated cyclooxygenase-2 and its main metabolite, prostaglandin E2. PLoS One. 2013;8(6):e65445.
- Liu T, Ullenbruch M, Young Choi Y, Yu H, Ding L, Xaubet A et al.. Telomerase and telomere length in pulmonary fibrosis. Am J Respir Cell Mol Biol. 2013 Aug;49(2):260-8.
- Almudéver P, Milara J, de Diego A, Serrano-Mollar A, Xaubet A, Pérez-Vizcaino F. Role of tetrahydrobiopterin in pulmonary vascular remodelling associated with pulmonary fibrosis. Thorax. 2013 Oct;68(10):938-48.

Highlights

Five active competitive research projects (Instituto Carlos III) whose principal investigators are members of the group. Five active clinical assays in asthma and two in idiopathic lung fibrosis. Twenty four publications in indexed journals, nine of them published in journals of the first quartile. Members of the group have participated as authors in three international clinical guides (ARIA/rhinitis and asthma, EPOS/chronic rhinosinusitis and nasal polyposis, and EACCI-aspirin intolerant asthma), and in two national guides (Gema/asma; SEPAR/Idiopathic Lug Fibrosis). The studies of the group have produced two patents: a) transplantation of type II alveolar cells in the treatment of idiopathic lung fibrosis. 2. Synergistic combination of an anti-IgE and EP2 receptor agonist in asthma.

PROGRAMME:
New Therapeutic Targets

Group 8

Group Members

STAFF MEMBERS

Euba Rementería, Begoña
Martínez Moliner, Veronica

ASSOCIATED MEMBERS

Cano García, Victoria
Garmendia García, Juncal
González Nicolau, María del Mar
Llobet Brossa, Enrique
Martín Lliteras, Juan Pablo
Moranta Mesquida, David

Lead Researcher

Regueiro Comesaña, Verónica

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Main lines of research

The main goal of our group is to study the immune response of hosts to face pathogenic microorganisms, and decipher the molecular mechanisms that regulate the interaction between host and pathogen. Thus, we study host response mechanisms, resistance and evasion systems developed by pathogens.

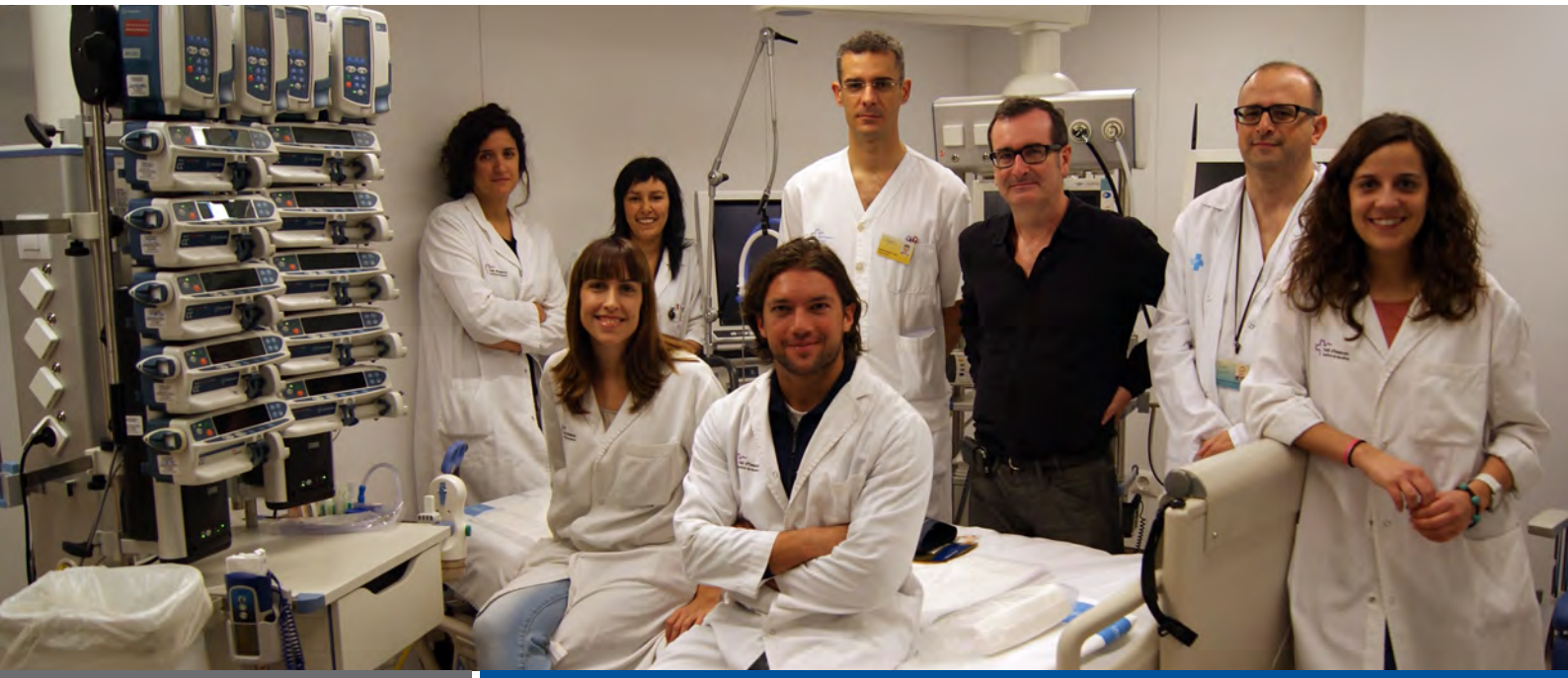
- Molecular dissection of host cellular systems involved in the immune response to front pathogens.
- Analysis of *Klebsiella pneumoniae* adaptations to survive in the lung.
- Analysis of antimicrobial peptide resistance mechanisms.
- Molecular mechanisms of bacterial infection associated to COPD exacerbation.
- Identification and preclinical evaluation of novel host-directed therapies to treat respiratory infection by the bacterial pathogen nontypable *Haemophilus influenzae*.
- Molecular evolution and human host adaptation of the bacterial pathogen nontypable *Haemophilus influenzae*.

Most relevant scientific articles

- Morey P, Viadas C, Euba B, Hood DW, Barberán M, Gil C, Grilló MJ, Bengoechea JA, Garmendia J. Relative contributions of lipooligosaccharide inner and outer core modifications to nontypeable Haemophilus influenzae pathogenesisInfection and Immunity. 2013;81(11):4100-11.
- Insua JL, Llobet E, Moranta D, Pérez-Gutiérrez C, Tomás A, Garmendia J, Bengoechea JA. Modeling Klebsiella pneumoniae pathogenesis by infection of the wax moth Galleria mellonellaInfection and Immunity. 2013;8(10):3552-3565.
- Frank CG, Regueiro V, Rother M, Moranta D, Maeurer AP, Garmendia J, Meyer TF, Bengoechea JA. Klebsiella pneumoniae targets an EGF receptor-dependent pathway to subvert inflammationCellular Microbiology. 2013;15(7):1212-33.
- March C, Cano V, Moranta D, Llobet E, Pérez-Gutiérrez C, Tomás JM, Suárez T, Garmendia J, Bengoechea JA. Role of bacterial surface structures on the interaction of Klebsiella pneumoniae with phagocytesPLOS ONE. 2013;8(2):e56847.

Highlights

- Molecular dissection of the relative contribution of the lipooligosaccharide molecule to nontypable Haemophilus influenzae pathogenesis.
- Identification of resistance to killing mediated by antimicrobial peptides as a strategy employed by nontypable Haemophilus influenzae to adapt and chronically infect the human respiratory tract.
- Human alveolar epithelial transcriptome-based indentification of novel therapeutic targets to treat infection by the bacterial pathogen nontypable Haemophilus influenzae.
- Identification of a novel EGF receptor-dependent pathway exploited by Klebsiella pneumoniae to subvert inflammation.
- Characterization of the wax moth Galleria mellonella infection by Klebsiella pneumoniae as a new model to test pathogenesis
- Characterization of Klebsiella pneumoniae surface structures role and its interaction with phagocytes.



PROGRAMME:
COPD / Pneumonia

Group 18

Group Members

STAFF MEMBERS

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Senna, Andrea

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Canalis Arrayas, Emilio
Díaz Santos, Emilio
Gallego Díaz, Miguel
Luján Torné, Manel
Masclans Enviz, Joan Ramon
Mendoza Asensi, Diego
Palomar Martínez, Mercedes
Pobo Peris, Angel
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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.
- Sepsis in the critical patient.
- Lung transplant.

Most relevant scientific articles

- Rello J, Chastre J. Update in pulmonary infections 2012.Am J Respir Crit Care Med. 2013 May 15;187(10):1061-6.
- Luján M, Burgos J, Gallego M, Falcó V, Bermudo G, Planes A et al.. Effects of immunocompromise and comorbidities on pneumococcal serotypes causing invasive respiratory infection in adults: implications for vaccine strategies.Clin Infect Dis. 2013 Dec;57(12):1722-30.
- Gattarello S, Borgatta B, Solé-Violán J, Vallés J, Vidaur L, Zaragoza R, Torres A, Rello J, CAPUCI II study investigators. Decrease in Mortality in Severe Community-Acquired Pneumococcal Pneumonia: Impact of Improving Antibiotic Strategies (2000-2013). Chest. 2013;.
- García-Laorden MI, Rodríguez de Castro F, Solé-Violán J, Payeras A, Briones ML, Borderías L. The role of mannose-binding lectin in pneumococcal infection.Eur Respir J. 2013 Jan;41(1):131-9.
- Rello J, Molano D, Villabon M, Reina R, Rita-Quispe R, Previgliano I. Differences in hospital- and ventilator-associated pneumonia due to Staphylococcus aureus (methicillin-susceptible and methicillin-resistant) between Europe and Latin America: a comparison of the EUVAP and LATINVAP study cohorts.Med Intensiva. 2013 May;37(4):241-7.

Highlights

During the year 2013, the most important scientific issues of our group were the following:

- Publications with an acumulated Impact Factor of 115.5 points.
- Development of a clinical trial of Pseudomonas pneumonia, currently under analysis.
- Highlight the publications derived from cooperative projects EUVAP and CAPUCI 2 and also projects of cooperative database pneumococcal, noted for its involvement and vaccine development, as well as the article on cooperative interaction of the pneumococcus and the H1N1 pandemic.
- About projects, the most important, titled Acute Respiratory Failure (primary graft dysfunction and rejection vs pneumonia) in postoperative lung transplant in ICU (ICU - TRASP), awarded by the Institute of Health Carlos III (FIS project) which refers to the study of biomarkers related complications associated with lung transplantation. The recruitment planned has been completed and now the study is in phase of analysing the results.
- The publication on the first two articles of the pharmacokinetics DALI in CID and IJAC.
- Turning to technology transfer, reference that the members of the group are involved in numerous projects, including the committee that updated guidelines of nosocomial pneumonia in SEPAR, the 2013 update of the Surviving Sepsis Campaign...
- Finally, every year the group organize some training courses (Ventilung and ICASIS) promoted in cooperation with other nodes Ciberes, where we have the pleasure to receive physicians of all autonomous communities.

PROGRAMME:
COPD

Group 31

Group Members

STAFF MEMBERS

Groult, Hugo
Pérez Medina, Carlos
Pérez Sánchez, José Manuel
Salinas Rodríguez, Beatriz

ASSOCIATED MEMBERS

Benito Vicente, Marina
Bilbao Luri, Izaskun
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Herranz Rabanal, Fernando
Pellico Saez, Juan
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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

- Vidorreta M, Wang Z, Rodríguez I, Pastor MA, Detre JA, Fernández-Seara MA. Comparison of 2D and 3D single-shot ASL perfusion fMRI sequences.Neuroimage. 2012 Nov 7;66C:662-671.
- Ferrarini A, Rupérez FJ, Erazo M, Martínez MP, Villar-Álvarez F, Peces-Barba G et al.. Fingerprinting-based metabolomic approach with LC-MS to sleep apnea and hypopnea syndrome: a pilot study.Electrophoresis. 2013 Oct;34(19):2873-81.
- Serrano-Ruiz D, Laurenti M, Ruiz-Cabello J, López-Cabarcos E, Rubio-Retama J. Hybrid microparticles for drug delivery and magnetic resonance imaging.J Biomed Mater Res B Appl Biomater. 2013 May;101(4):498-505.
- Ruiz A, Salas G, Calero M, Hernández Y, Villanueva A, Herranz F et al.. Short-chain PEG molecules strongly bound to magnetic nanoparticle for MRI long circulating agents. Acta Biomater. 2013 May;9(5):6421-30.
- Pérez-Medina C, Patel N, Robson M, Lythgoe MF, Arstad E. Synthesis and evaluation of a 125I-labeled iminodihydroquinoline-derived tracer for imaging of voltage-gated sodium channels.Bioorg Med Chem Lett. 2013 Sep 15;23(18):5170-3.

Highlights

The group has recently started a new path in the Spanish National Center for Cardiovascular Research (CNIC). We have just finished installing a smoke exposure chamber used for activities referred to the COPD PCI with mouse models. We have also commenced a collaborative study with Drs Peces Barba, Agustí and Cossio aimed to find early markers of COPD and its association with cardiovascular disease, for which purpose we will obtain image and omics data from the PESA-CNIC- Banco Santander study. For the ALI PCI, we have collaborated with the group of Dr. Esteban in metabolomic studies and with the group of Dr. Blanch in the brain-lung association of ALI pig model. An acquisition method for perfusion MRI has been scheduled for clinical team (see publication in Neuroimage). Several publications and thesis / dissertations will be obtained from both CIPs that have been funded by different projects, including the Pulmonary Imaging Network, of which we are coordinators, funded by the Seventh Framework Program. This work has enabled a better understanding of the relationship between the composition and the behavior and interaction of nanoparticles and plasma proteins . Additional funding has also been achieved in other competitive calls; an ITN within the same framework program (Cardionext) in which Jesus Ruiz -Cabello is one of the PI, and "La Marató" project in which we are partners. These projects allow us to advance in the application of molecular imaging techniques. Finally, in March 2013 our group organized an international course entitled "Translational Aspects of Cardiovascular and Pulmonary Imaging" involving pharmaceutical companies (AstraZeneca , Novartis, Boehringer Ingelheim) and representatives of hospitals and public research organizations from different countries. The course was a great succes allowing to reflect the role of imaging in the translational research chain.

PROGRAMME:
Pneumonia

Group 14

Group Members

STAFF MEMBERS

Fernández Barat, Laia
Li Bassi Li Bassi, Gianluigi
Martí Romeu, Joan Daniel
Sancho Roset, Elisabeth

ASSOCIATED MEMBERS

Agustí García-Navarro, Carlos
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Bello Dronda, Salvador
Cilloniz Campo, Catia
Falguera Sacrest, Miquel
Ferrer Monreal, Miguel
Li Bassi Li Bassi, Gianluigi
Marrades Sicart, Ramon Maria
Martínez Olondris, Pilar
Menéndez Villanueva, Rosario
Miravitlles Fernández, Marc
Polverino, Eva
Ramírez Galleymore, Paula
Sellares Torres, Jacobo
Sirvent Calvera, José María
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Soy Muner, Dolores

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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

- Sellares J, López-Giraldo A, Lucena C, Cilloniz C, Amaro R, Polverino E et al.. Influence of previous use of inhaled corticoids on the development of pleural effusion in community-acquired pneumonia.Am J Respir Crit Care Med. 2013 Jun 1;187(11):1241-8.
- Little P, Stuart B, Francis N, Douglas E, Tonkin-Crine S, Anthierens S et al.. Effects of internet-based training on antibiotic prescribing rates for acute respiratory-tract infections: a multinational, cluster, randomised, factorial, controlled trial.Lancet. 2013 Oct 5;382(9899):1175-82.
- Esperatti M, Ferrer M, Giunta V, Ranzani OT, Saucedo LM, Li Bassi G et al.. Validation of predictors of adverse outcomes in hospital-acquired pneumonia in the ICU.Crit Care Med. 2013 Sep;41(9):2151-61.
- Polverino E, Torres A, Menendez R, Cillóniz C, Valles JM, Capelastegui A. Microbial aetiology of healthcare associated pneumonia in Spain: a prospective, multicentre, case-control study.Thorax. 2013 Nov;68(11):1007-14.
- Huerta A, Crisafulli E, Menéndez R, Martínez R, Soler N, Guerrero M et al.. Pneumonic and nonpneumonic exacerbations of COPD: inflammatory response and clinical characteristics.Chest. 2013 Oct;144(4):1134-42.

Highlights

In the 2013 it has been awared with the following grant:

Potential benefits of lateral Trendelenburg position in preventing pneumonia associated with mechanical ventilation

INSTITUTION: National Plan. Ministry of Economy and Competitiveness

REFERENCE: SAF2012-3374

PERIOD: 2013-2015

QUANTITY: 105,300 Euros

INVEST.PRAL. Dr. Antoni Torres

And it has been publised the following guideline:

- Torres A, Barberán J, Falguera M, Menéndez R, Molina J, Olaechea P, Rodríguez A; ; on behalf of the Multidisciplinary Guidelines for the Management of Community Acquired Pneumonia Multidisciplinary guidelines for the management of community-acquired pneumonia. Med Clin (Barc). 2013 Mar 2;140(5):223.e1-223.e19.

From 2013 Dr. Torres is associated editor of the Thorax review and ICM (Intensive Care Medicine)

He has received the "Excelencia" award from the COMB and the ICREA award from the UB.

Another member of his group, Dr. Li Bassi has received one of the Juan de la Cierva positions from the Ministry of economy and competitivity.

PROGRAMME:
Acute Lung Injury

Group 29

Group Members

STAFF MEMBERS

Cabrera Benítez, Nuria Esther
Ramos Nuez, Angela María

ASSOCIATED MEMBERS

Blanco Varela, Jesús
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Flores Infante, Carlos Alberto
Pérez Méndez, Lina Inmaculada
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Main lines of research

- Epidemiology 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 from common genetic activation and signalling pathways among ARDS, Asthma and Pulmonary Fibrosis..

Most relevant scientific articles

- Villar J, Pérez-Méndez L, Blanco J, Añón JM, Blanch L, Belda J. A universal definition of ARDS: the PaO2/FiO2 ratio under a standard ventilatory setting--a prospective, multicenter validation study.Intensive Care Med. 2013 Apr;39(4):583-92.
- Sun X, Ma SF, Wade MS, Acosta-Herrera M, Villar J, Pino-Yanes M. Functional promoter variants in sphingosine 1-phosphate receptor 3 associate with susceptibility to sepsis-associated acute respiratory distress syndrome.Am J Physiol Lung Cell Mol Physiol. 2013 Oct 1;305(7):L467-77.
- Fan E, Villar J, Slutsky AS. Novel approaches to minimize ventilator-induced lung injury.BMC Med. 2013 Mar 28;11:85.

- Zhang H, Villar J, Slutsky AS. Circulating histones: a novel target in acute respiratory distress syndrome?Am J Respir Crit Care Med. 2013 Jan 15;187(2):118-20.
- Noth I, Zhang Y, Ma SF, Flores C, Barber M, Huang Y. Genetic variants associated with idiopathic pulmonary fibrosis susceptibility and mortality: a genome-wide association study.Lancet Respir Med. 2013 Jun;1(4):309-17.

Highlights

PROJECTS:

- PI10/0393: Mechanisms of Pulmonary Fibrosis Induced by Mechanical Ventilation. ISCIII. IP: Jesus Villar.
- PI13/0119: Randomized Study of Neurally Adjusted Ventilation Assisted in patients with Acute Respiratory Failure. ISCIII. IP: Jesus Villar.
- PI2012 FMM: Randomized Study to evaluate the effectiveness of dexamethasone in patients with ARDS . Mutua Madrileña Foundation. IP: Jesus Villar
- REB11 -024: Practice Pattern Variation in Mechanical Ventilation in Critically discontinuing Ill. Ministry of Research, Canada. IP: Karen Burns & Jesus Villar
- PI11/0623: Genetic susceptibility to asthma. ISCIII. IP: Carlos Flores.
- REGPOT FP7- 2012 -2013- 1: IMBRAIN : Improvement of Biomedical Research and Innovation in the Canary Islands. CORDIS.
- Open Lung Approach in ARDS. MAQUET, Sweden. IP: Jesus Villar
- NAVA in patients with Acute Respiratory Failure. MAQUET. IP: Jesus Villar
- PI-0279-2012: Identification of genetic mechanisms and characterization of functional networks with Systems Biology in hypersensitivity reactions to non-steroid anti-inflammatories Junta de Andalucía. Co- IP: Carlos Flores.

NETWORKS COORDINATED BY JESÚS VILLAR:

- SIESTA: Spanish Initiative for Epidemiology, Stratification, and Therapy of the Acute Respiratory Distress Syndrome.
- GUARDS: Genetics to Unravel the Acute Respiratory Distress Syndrome.

CONTRACTS FOR RESEARCH PERSONNEL

- CD11/00104: Post- Doctoral Sara Borrel. ISCIII .
- FI11/00074: Predoctoral Training Health Research. ISCIII.
- FI12/00493: Predoctoral Training Health Research. ISCIII.

PATENTS:

- BOPI Publication Award Patent 16/05/2013 , P201031978.
- Title or Certificate of Invention Patent ES2385443 07/11/2013, P201031978.
- BOPI Publication Report of the state of the art 19/06/2013, P201131785
- BOPI Publication resumption general award patent procedure IET 19/06/2013, P201131785.

INTERNATIONAL COLLABORATIONS:

- Keenan Research Center for Biomedical Science at the Li Ka Shing Knowledge Institute, St. Michael 's Hospital, Toronto.
- Department of Respiratory Care, Massachusetts General Hospital, Boston.
- Department of Pulmonary & Critical Care Medicine, University of Chicago

OTHER CONSIDERATIONS:

- Jesús Villar: evaluador para New England Journal of Medicine, American Journal of Respiratory and Critical Care Medicine, Critical Care Medicine, Intensive Care Medicine, Critical Care.
- Jesus Villar: Member, Editorial Board of Intensive Care Monitor.
- Carlos Flores: Comité Editorial ISRN Pulmonology, Clinical Antiinflamatory & Antiallergy Drugs.

PROGRAMME:
COPD

Linked Group 1

Group Members

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Lead Researcher

López-Campos Bodinau, José L.

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Main lines of research

- COPD
- Interstitial lung disease
- Pulmonary circulation
- Cystic fibrosis
- Sleep respiratory disorders.

Most relevant scientific articles

- Roberts CM, Lopez-Campos JL, Pozo-Rodríguez F, Hartl S, European COPD Audit team. European hospital adherence to GOLD recommendations for chronic obstructive pulmonary disease (COPD) exacerbation admissions.Thorax. 2013 Dec;68(12):1169-71.
- López-Campos JL, Hartl S, Pozo-Rodríguez F, Roberts CM, European COPD Audit team. European COPD Audit: design, organisation of work and methodology. Eur Respir J. 2013 Feb;41(2):270-6.
- Muñoz-Manchado AB, Villadiego J, Suárez-Luna N, Bermejo-Navas A, Garrido-Gil P, Labandeira-García JL, Echevarría M, López-Barneo J, Toledo-Aral JJ. Neuroprotective and reparative effects of carotid body grafts in a chronic MPTP model of Parkinson's diseaseNeurobiol Aging. 2013;34(3):902-15.
- López-Campos JL, Soriano JB, Calle M, Encuesta de Espirometría en España (3E) Project. A comprehensive, national survey of spirometry in Spain: current bottlenecks and future directions in primary and secondary care.Chest. 2013 Aug;144(2):601-9.
- Ortega-Sáenz P, Pardal R, Levitsky K, Villadiego J, Muñoz-Manchado AB, Durán R, Bonilla-Henao V, Arias-Mayenco I, Sobrino V, Ordóñez A, Oliver M, Toledo-Aral JJ, López-Barneo J. Cellular properties and chemosensory responses of the human carotid bodyJ Physiol. 2013;591(Pt 24):6157-73.

Highlights

During 2013 the Group has continued to develop its strategies and publishing results of ongoing project. In COPD has completed the analysis of the evaluative line through European COPD Audit Audit Euroepan COPD who participated in the 13 countries with 16018 cases. WE have presented the results as well as the first international publications. In addition, the line of basic research in COPD continues to progress with the FIS obtained in 2012.

In interstitial pathology continues collaboration with the groups of this program of research and progress in corporate joint projects.

In the pulmonary circulation line, the group is actively involved in the creation of new corporate research program to actively participate in the creation of the work packages. He has also participated in the Spanish consensus of pulmonary embolism. Faithfully developed the longitudinal study to identify predictive criteria HIP post- thrombotic, Osiris study, which involved 30 centers. It is linked to the creation of a network of biobanks of patients with pulmonary embolism, with potential use platform CIBERES biobank.

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