

ANNUAL
QUALITY
REPORT
2018

ciber

Centro de Investigación Biomédica en Red

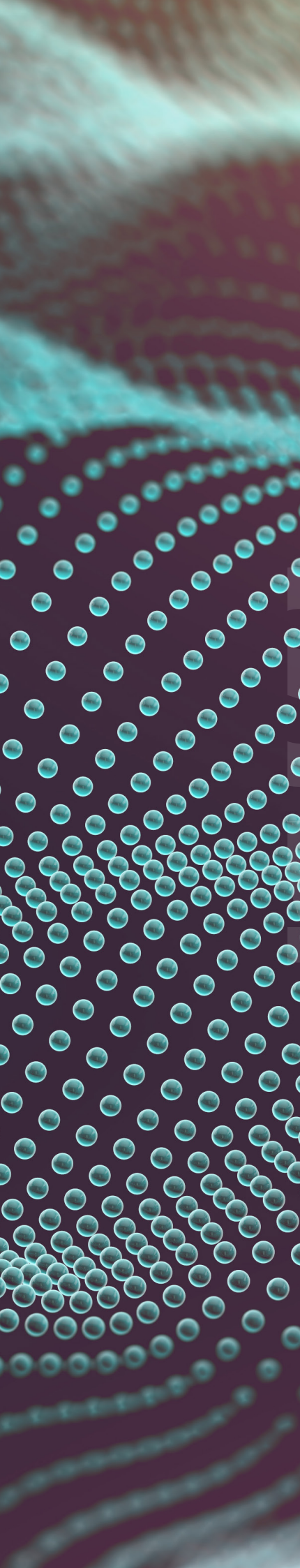
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PRES SENTATION CON



Presentation by the CIBER'S Managing Director

Manuel Sánchez Delgado

2018 was the year in which the consolidation of the three new CIBER areas which joined in the previous period was materialised. After having worked in the consortium for over two years, the over 100 groups in the CIBERCV, CIBERONC and CIBERFES have now adapted their processes and shored up their different research programmes. They have also furthered cooperation work in their own area and with the other thematic areas.

The task now facing the CIBER is to tackle the challenge of breaking through the limits of its thematic areas and encouraging its groups to work transversally, not only in their own areas but with groups from the whole consortium.

During the 2018 period the intention to encourage this type of cooperation work could be appreciated, for example in the directors' participation in several scientific events of other CIBER areas (CIBER-BBN Annual Conference and CIBERESP Symposia, to mention just a couple of these); or the Training Sessions of the CIBERES and the CIBERSAM Ideas Laboratory, events which yet another year stimulated dialogue and relations between the young researchers from the different areas of the CIBER.

We should also stress the cooperation of the ESP, OBN, CV and ONC areas in the *Encuentro para la Excelencia de la Investigación en Salud Pública*; or the cooperation in the organisation of the 52nd Annual Scientific Meeting of the European Society for Clinical Investigation (ESCI). The CIBEROBN

and CIBERCV took part in the organisation of this highly prestigious international event, in which CIBERFES and CIBEREHD were also involved. Several calls for projects promoting cooperation between different areas were also launched; as well as the already consolidated cooperation between the CIBER-BBN and the CIBERES, there was a call between groups in the CIBERONC and CIBER-BBN in 2018.

The Network Centre model fostered by the Instituto de Salud Carlos III, now consolidated and with a record of over 10 years' biomedical research, has around 7000 researchers (contracted and attached) in over 400 research groups of different kinds. The CIBER's budget for 2018 was over 45 million euros, as income from the transfer from the Instituto de Salud Carlos III, grants for projects, services provided and other funds.

The CIBER is today a strategic ally for applying for investigation projects, and a highly important partner in international calls requiring the cooperation of different groups. In 2018, the CIBER obtained funding of around 4 million € in competitive calls. 97 of the 129 projects under way during this period were national, 26 European and 6 from the U.S.A.

The scientific results obtained in this period continue along the lines of previous years. In 2018 over 6,700 publications came out, around 4000 of which were in the first quartile and more than 1700 in the first decile.

The growing interest shown by researchers in ensuring that society learns of their results is also remarkable.

This can be appreciated from the amount of informative content distributed: in 2018 more than 160 press releases were sent out to the media and over 10,000 appearances in these were recorded, both in general information newspapers and websites and those more specialised in health. 883 news items were furthermore distributed over the CIBER's own web pages, over 30 newsletters by CIBER and its areas and the work done on Twitter was kept up, reaching over 31,000 followers in the consortium's profiles.

The CIBER has likewise made an attempt to further the image of women in science, by joining the activities of 11 February and stressing the work done by our most relevant female researchers. Three of these outstanding women had the chance to present their work at the CIBER at the event in the Science Week, which is arranged by the centre every year, as one of the most successful scientific dissemination activities. In November 2018 "CienciaConPartitura" was held, at which we were proud to enjoy the participation of Susana Carmona (CIBERSAM), Malu M. Chantar

(CIBEREHD), Marina Pollán (CIBERESP) and Gemma Rojo (CIBERDEM) and an audience which every year displays increasing interest for the research work done by the CIBER.

As regards Technology Transfer, in 2018 23 new patent applications were submitted, with 1 registration of intellectual property, 1 trademark and 2 software registrations; 4 licence contracts and 1 licence option contract were signed.

I would also like to take this opportunity to congratulate the three CIBER researchers who in 2018 won the highly reputed Jaume I award: Dolores Corella, from the CIBEROBN, and María Vallet-Regí and Ramón Martínez-Mañez, from the CIBER-BBN. It says a lot for our researchers' quality that 3 of the 6 awards should have gone to CIBER researchers.

In short, we can say that 2018 has been a year with very good results for those of us forming the CIBER and yet another year it only remains for me to express my thanks for the hard work done by all the persons in the consortium.

Internal Organisation

The Centro de Investigación Biomédica en Red, a public research consortium set up by the Instituto de Salud Carlos III (ISCIII), furthers excellence research into Biomedicine and Health Sciences done in the National Health System and in the Science and Technology System.

The CIBER's scientific programme is based on the following thematic research areas:

- Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN)
- Diabetes and Associated Metabolic Diseases (CIBERDEM)
- Physiopathology of Obesity and Nutrition (CIBEROBN)
- Liver and Digestive Diseases (CIBEREHD)
- Rare Diseases (CIBERER)
- Respiratory Diseases (CIBERES)
- Epidemiology and Public Health (CIBERESP)
- Mental Health (CIBERSAM)
- Frailty and Healthy Ageing (CIBERFES)
- Cardiovascular Diseases (CIBERCV)
- Cancer (CIBERONC)

At the present time the CIBER has a staff of 913 persons and around 6000 attached researchers, forming part of over 400 research groups, working in separate locations, associated with 100 institutions in the consortium and belonging to administrations and public and private sector institutions of Spain's different regional "Autonomous Communities".

Its governing, management and administrative bodies are as follows:

Governing Board and Permanent Commission

The **Governing Board**, presided over by the Director of the ISCIII, is made up of three representatives of the ISCIII and an institutional representative of each of the institutions in the consortium, appointed by their senior authorities. It meets every six months.

The **Permanent Commission** is a delegated commission made up of the ISCIII and 8 members of the Governing Board, who can be renewed annually. Its operation and the support and assessment functions of the governing bodies are all established in the statutes of the CIBER.

Management Committee and Advisory Committees

In each CIBER area there is a **Management Committee** and an **External Advisory Scientific Committee**.

The Management Committee is made up of the Scientific Director of each Area, the programme coordinators and the Managing Director of the CIBER, as well as a representative of the Instituto de Salud Carlos III.

The External Advisory Scientific Committee is a body providing scientific assessment and support, made up of relevant personalities in the field of health sciences of great renown for their professional or scientific careers compatible with the objectives of the centre. This body is in charge of carrying out the annual assessment of the areas and their research groups.

Scientific Directors

The Scientific Directors of the CIBER represent each of the thematic areas and preside over the Management Committees. In 2018 the following persons held this office:

- Scientific Director of the CIBER-BBN:
Dr. Ramón Martínez Máñez
- Scientific Director of the CIBERCV:
Dr. Francisco Fernández-Avilés
- Scientific Director of the CIBERDEM:
Dr. Eduard Montanya Mías
- Scientific Director of the CIBEREHD:
Dr. Jordi Bruix Tudó
- Scientific Director of the CIBERER:
Dr. Pablo Lapunzina Badía
- Scientific Director of the CIBERES:
Dr. Ferran Barbé Illa
- Scientific Director of the CIBERESP:
Dr. Marina Pollán Santamaría
- Scientific Director of the CIBERFES:
Dr. Leocadio Rodríguez Mañas
- Scientific Director of the CIBEROBN:
Dr. Carlos Diéguez González
- Scientific Director of the CIBERONC:
Dr. Joaquín Arribas López
- Scientific Director of the CIBERSAM:
Dr. Eduard Vieta Pascual

Economic data

CIBER

Total resources

	ISCIII Transfer	Subsidies for projects	Provisions of services	Other income	TOTAL
INCOME 2018	26.303.330,00	7.113.467,94	1.904.617,58	2.583.367,69	37.904.783,21

Total expenses

PROJECT	Inventoriable sum applied	Supplies and other expenses for work	Personnel applied	TOTAL EXPENSE
Scientific Management. Scientific Secretariat. Communication	166.711,43	865.944,97	581.902,22	1.614.558,62
Groups	1.197.923,60	4.723.710,80	19.946.956,22	25.868.590,62
Training	-	315.980,94	1.656.939,55	1.972.920,49
Programmes	16.559,50	328.104,66	228.546,80	573.210,96
Platforms	42.459,92	211.420,24	488.658,54	742.538,70
Transfer	6.571,18	181.915,29	253.383,87	441.870,34
Third Party	-	1.540.984,39	-	1.540.984,39
Intramural Projects	93.453,34	433.667,29	158.175,52	685.296,15
External Projects	116.543,88	2.449.182,80	3.073.356,54	5.639.083,22
Economic resources Technical Unit (UT)	19.400,02	621.701,67	-	641.101,69
Human Resources UT	-	-	1.382.202,64	1.382.202,64
Prevention of Occupational Hazards UT	2.227,97	106.774,84	-	109.002,81
Communication UT	-	84.308,13	-	84.308,13
TOTAL FOR CIBER	1.661.850,84	11.863.696,02	27.770.121,90	41.295.668,76

(*) The difference between Expenditure and Income for the period is covered with Remainders from Previous Years

CIBER-BBN

Total resources

	<i>ISCIII Transfer</i>	<i>Subsidies for projects</i>	<i>Provisions of services</i>	<i>Other income</i>	<i>TOTAL</i>
<i>INCOME 2018</i>	3.960.160,00	2.233.955,71	287.775,34	206.781,21	6.688.672,26

Total expenses

<i>PROJECT</i>	<i>Inventoriable sum applied</i>	<i>Supplies and other expenses for work</i>	<i>Personnel applied</i>	<i>TOTAL EXPENSE</i>
<i>Scientific Management. Scientific Secretariat. Communication</i>	-	50.879,69	64.066,29	114.945,98
<i>Groups</i>	159.253,08	454.195,51	940.979,88	1.554.428,47
<i>Training-Capacity-building</i>	-	26.827,16	1.582.878,47	1.609.705,63
<i>Platforms</i>	37.625,16	82.725,84	83.829,29	204.180,29
<i>Transfer</i>	5.582,08	63.123,60	106.470,77	175.176,45
<i>Intramural Projects</i>	4.026,11	75.802,96	132.424,23	212.253,30
<i>External Projects</i>	32.093,04	1.530.543,45	547.575,56	2.110.212,05
<i>TOTAL FOR CIBER-BBN</i>	238.579,47	2.284.098,21	3.458.224,49	5.980.902,17

CIBERCV

Total resources

	<i>ISCIII Transfer</i>	<i>Subsidies for projects</i>	<i>Provisions of services</i>	<i>Other income</i>	<i>TOTAL</i>
<i>INCOME 2018</i>	-	125.911,00	-	8.000,00	133.911,00

Total expenses

<i>PROJECT</i>	<i>Inventoriable sum applied</i>	<i>Supplies and other expenses for work</i>	<i>Personnel applied</i>	<i>TOTAL EXPENSE</i>
<i>Scientific Management. Scientific Secretariat. Communication</i>	55.634,54	96.178,98	150.276,76	302.090,28
<i>Groups</i>	203.731,27	514.620,69	2.041.485,55	2.759.837,51
<i>Programmes</i>	2.613,98	20.976,63	-	23.590,61
<i>Transfer</i>	-	48.832,11	-	48.832,11
<i>External Projects</i>	-	9.167,29	11.793,45	20.960,74
<i>TOTAL FOR CIBERCV</i>	261.979,79	689.775,70	2.203.555,76	3.155.311,25

(*) The difference between Expenditure and Income for the period is covered with Remainders from Previous Years

CIBERDEM

Total resources

	<i>ISCIII Transfer</i>	<i>Subsidies for projects</i>	<i>Provisions of services</i>	<i>Other income</i>	<i>TOTAL</i>
<i>INCOME 2018</i>	2.796.280,00	73.205,00	34.000,00	-	2.903.485,00

Total expenses

<i>PROJECT</i>	<i>Inventoriable sum applied</i>	<i>Supplies and other expenses for work</i>	<i>Personnel applied</i>	<i>TOTAL EXPENSE</i>
<i>Scientific Management. Scientific Secretariat. Communication</i>	-	121.542,67	50.164,27	171.706,94
<i>Groups</i>	81.531,36	158.110,21	2.269.962,32	2.509.603,89
<i>Training</i>	-	37.184,75	-	37.184,75
<i>Platforms</i>	-	6.275,06	-	6.275,06
<i>Intramural Projects</i>	-	4.611,51	-	4.611,51
<i>External Projects</i>	-	160.361,37	54.433,95	214.795,32
<i>TOTAL FOR CIBERDEM</i>	81.531,36	488.085,57	2.374.560,54	2.944.177,47

(*) The difference between Expenditure and Income for the period is covered with Remainders from Previous Years

CIBEREHD

Total resources

	<i>ISCIII Transfer</i>	<i>Subsidies for projects</i>	<i>Provisions of services</i>	<i>Other income</i>	<i>TOTAL</i>
<i>INCOME 2018</i>	3.653.580,00	209.117,00	249.612,66	265.995,69	4.378.305,35

Total expenses

<i>PROJECT</i>	<i>Inventoriable sum applied</i>	<i>Supplies and other expenses for work</i>	<i>Personnel applied</i>	<i>TOTAL EXPENSE</i>
<i>Scientific Management. Scientific Secretariat. Communication</i>	-	117.051,50	-	117.051,50
<i>Group</i>	110.535,29	209.598,40	2.595.850,65	2.915.984,34
<i>Training</i>	-	22.081,46	-	22.081,46
<i>Platform</i>	-	2.862,50	88.745,56	91.608,06
<i>Transfer</i>	-	5.906,08	-	5.906,08
<i>Intramural Projects</i>	-	76.910,57	-	76.910,57
<i>External Projects</i>	10.627,07	183.894,55	479.092,03	673.613,65
<i>TOTAL FOR CIBEREHD</i>	121.162,36	618.305,06	3.163.688,24	3.903.155,66

CIBERER

Total resources

	<i>ISCIII Transfer</i>	<i>Subsidies for projects</i>	<i>Provisions of services</i>	<i>Other income</i>	<i>TOTAL</i>
<i>INCOME 2018</i>	4.905.860,00	552.870,44	554.503,22	134.901,88	6.148.135,54

Total expenses

<i>PROJECT</i>	<i>Inventoriable sum applied</i>	<i>Supplies and other expenses for work</i>	<i>Personnel applied</i>	<i>TOTAL EXPENSE</i>
<i>Scientific Management. Scientific Secretariat. Communication</i>	-	212.294,57	49.694,07	261.988,64
<i>Group</i>	40.448,69	386.448,64	3.395.334,12	3.822.231,45
<i>Training</i>	-	17.420,86	-	17.420,86
<i>Programmes</i>	-	34.009,47	82.831,65	116.841,12
<i>Platforms</i>	3.634,44	20.162,93	140.863,27	164.660,64
<i>Transfer-Translation</i>	989,10	50.016,79	50.035,42	101.041,31
<i>Intramural Projects</i>	3.360,90	11.450,23	-	14.811,13
<i>External Projects</i>	25.127,07	718.250,93	439.611,79	1.182.989,79
<i>Total CIBERER</i>	73.560,20	1.450.054,42	4.158.370,32	5.681.984,94

CIBERES

Total resources

	<i>ISCIII Transfer</i>	<i>Subsidies for projects</i>	<i>Provisions of services</i>	<i>Other income</i>	<i>TOTAL</i>
<i>INCOME 2018</i>	2.632.420,00	739.310,00	131.852,09	103.770,00	3.607.352,09

Total expenses

<i>PROJECT</i>	<i>Inventoriable sum applied</i>	<i>Supplies and other expenses for work</i>	<i>Personnel applied</i>	<i>TOTAL EXPENSE</i>
<i>Scientific Management. Scientific Secretariat. Communication</i>	-	24.341,82	54.341,03	78.682,85
<i>Groups</i>	132.464,22	406.415,20	1.460.516,17	1.999.395,59
<i>Training</i>	-	49.547,18	12.565,28	62.112,46
<i>Programmes</i>	-	4.013,23	-	4.013,23
<i>Platforms</i>	1.200,32	14.175,91	67.036,95	82.413,18
<i>Transfer</i>	-	14.036,71	96.877,68	110.914,39
<i>Intramural Projects</i>	31.255,21	118.655,56	-	149.910,77
<i>External Projects</i>	10.290,00	397.021,56	362.119,94	769.431,50
<i>TOTAL FOR CIBERES</i>	175.209,75	1.028.207,17	2.053.457,05	3.256.873,97

CIBERESP

Total resources

	ISCIII Transfer	Subsidies for projects	Provisions of services	Other income	TOTAL
INCOME 2018	2.916.660,00	228.347,97	14.950,00	37.923,10	3.197.881,07

Total expenses

PROJECT	Inventoriable sum applied	Supplies and other expenses for work	Personnel applied	TOTAL EXPENSE
Scientific Management. Scientific Secretariat. Communication	109.638,03	83.495,88	33.514,93	226.648,84
Group	12.826,62	689.200,47	1.628.367,24	2.330.394,33
Training	-	32.760,61	-	32.760,61
Programmes	4.343,08	171.618,58	145.715,15	321.676,81
External Projects	9.003,99	108.765,99	201.901,74	319.671,72
TOTAL FOR CIBERESP	135.811,72	1.085.841,53	2.009.499,06	3.231.152,31

(*) The difference between Expenditure and Income for the period is covered with Remainders from Previous Years

CIBERFES

Total resources

	ISCIII Transfer	Subsidies for projects	Provisions of services	Other income	TOTAL
INCOME 2018	-	1.899.247,08	34.800,00	-	1.934.047,08

Total expenses

PROJECT	Inventoriable sum applied	Supplies and other expenses for work	Personnel applied	TOTAL EXPENSE
Scientific Management. Scientific Secretariat. Communication	-	31.119,05	19.084,72	50.203,77
Groups	35.997,13	58.085,36	498.832,71	592.915,20
Platform	-	-	27.079,46	27.079,46
External Projects	-	210.200,00	-	210.200,00
Training	-	1.210,00	-	1.210,00
TOTAL FOR CIBERFES	35.997,13	300.614,41	544.996,89	881.608,43

CIBEROBN

Total resources

	<i>ISCIII Transfer</i>	<i>Subsidies for projects</i>	<i>Provisions of services</i>	<i>Other income</i>	<i>TOTAL</i>
<i>INCOME 2018</i>	2.887.230,00	208.663,22	103.148,42	11.330,63	3.210.372,27

Total expenses

<i>PROJECT</i>	<i>Inventoriable sum applied</i>	<i>Supplies and other expenses for work</i>	<i>Personnel applied</i>	<i>TOTAL EXPENSE</i>
<i>Scientific Management. Scientific Secretariat. Communication</i>	-	70.305,33	45.532,48	115.837,81
<i>Groups</i>	183.352,15	484.846,86	1.669.204,80	2.337.403,81
<i>Training</i>	-	29.451,93	-	29.451,93
<i>Programmes</i>	6.360,52	54.163,22	-	60.523,74
<i>Platforms</i>	-	26.201,88	81.104,01	107.305,89
<i>Intramural Projects</i>	53.521,78	92.290,21	-	145.811,99
<i>External Projects</i>	17.510,16	152.065,88	296.820,84	466.396,88
<i>TOTAL FOR CIBEROBN</i>	260.744,61	909.325,31	2.092.662,13	3.262.732,05

(*) The difference between Expenditure and Income for the period is covered with Remainders from Previous Years

CIBERONC

Total resources

	<i>ISCIII Transfer</i>	<i>Subsidies for projects</i>	<i>Provisions of services</i>	<i>Other income</i>	<i>TOTAL</i>
<i>INCOME 2018</i>	-	352.112,00	-	5.000,00	357.112,00

Total expenses

<i>PROJECT</i>	<i>Inventoriable sum applied</i>	<i>Supplies and other expenses for work</i>	<i>Personnel applied</i>	<i>TOTAL EXPENSE</i>
<i>Scientific Management. Scientific Secretariat. Communication</i>	225,00	33.563,76	58.222,23	92.010,99
<i>Groups</i>	149.283,68	824.745,12	2.108.128,56	3.082.157,36
<i>Training</i>	-	45.867,77	41.733,14	87.600,91
<i>Programmes</i>	-	28.214,09	-	28.214,09
<i>Intramural Projects</i>	-	1.780,94	-	1.780,94
<i>External Projects</i>	-	17.993,89	3.606,87	21.600,76
<i>TOTAL FOR CIBERONC</i>	149.508,68	952.165,57	2.211.690,80	3.313.365,05

(*) The difference between Expenditure and Income for the period is covered with Remainders from Previous Years

CIBERSAM

Total resources

	<i>ISCIII Transfer</i>	<i>Subsidies for projects</i>	<i>Provisions of services</i>	<i>Other income</i>	<i>TOTAL</i>
<i>INCOME 2018</i>	2.199.190,00	490.728,52	493.975,85	14.584,32	3.198.478,69

Total expenses

<i>PROJECT</i>	<i>Inventoriable sum applied</i>	<i>Supplies and other expenses for work</i>	<i>Personnel applied</i>	<i>TOTAL EXPENSE</i>
<i>Scientific Management. Scientific Secretariat. Communication</i>	1.213,86	25.171,72	57.005,44	83.391,02
<i>Groups</i>	88.500,11	537.444,34	1.338.294,22	1.964.238,67
<i>Training</i>	-	53.629,22	19.762,66	73.391,88
<i>Programmes</i>	3.241,92	15.109,44	-	18.351,36
<i>Platforms</i>	-	59.016,12	-	59.016,12
<i>Intramural Projects</i>	1.289,34	52.165,31	25.751,29	79.205,94
<i>External Projects</i>	11.892,55	501.902,28	676.400,37	1.190.195,20
<i>TOTAL FOR CIBERSAM</i>	106.137,78	1.244.438,43	2.117.213,98	3.467.790,19

(*) The difference between Expenditure and Income for the period is covered with Remainders from Previous Years

UT

Total resources

	<i>ISCIII Transfer</i>	<i>Subsidies for projects</i>	<i>Provisions of services</i>	<i>Other income</i>	<i>TOTAL</i>
<i>INCOME 2018</i>	351.950,00	-	-	1.795.080,86	2.147.030,86

Total expenses

<i>PROJECT</i>	<i>Inventoriable sum applied</i>	<i>Supplies and other expenses for work</i>	<i>Personnel applied</i>	<i>TOTAL EXPENSE</i>
<i>Economic resources</i>	19.400,02	621.701,67	-	641.101,69
<i>Human Resources</i>	-	-	1.382.202,64	1.382.202,64
<i>Prevention of Occupational Hazards</i>	2.227,97	106.774,84	-	109.002,81
<i>Communication</i>	-	84.308,13	-	84.308,13
<i>TOTAL UT</i>	21.627,99	812.784,64	1.382.202,64	2.216.615,27

(*) The difference between Expenditure and Income for the period is covered with Remainders from Previous Years

Personnel

Distribution of contracted personnel by areas, category and sex

	<i>MEN</i>	<i>WOMEN</i>	<i>OVERALL TOTAL</i>
<i>CIBER-BBN</i>	40	63	103
<i>Diploma holder</i>	-	1	1
<i>Doctor</i>	24	38	62
<i>Graduate</i>	14	17	31
<i>Technical staff</i>	2	7	9
<i>CIBERCV</i>	21	61	82
<i>Doctor</i>	10	18	28
<i>Graduate</i>	11	35	46
<i>Technical staff</i>	-	8	8
<i>CIBERDEM</i>	18	64	82
<i>Diploma holder</i>	-	2	2
<i>Doctor</i>	12	35	47
<i>Graduate</i>	3	16	19
<i>Technical staff</i>	3	11	14
<i>CIBEREHD</i>	30	66	96
<i>Diploma holder</i>	-	4	4
<i>Doctor</i>	16	22	38
<i>Graduate</i>	10	30	40
<i>Technical staff</i>	4	10	14
<i>CIBERER</i>	29	95	124
<i>Diploma holder</i>	-	1	1
<i>Doctor</i>	20	56	76
<i>Graduate</i>	8	23	31
<i>Technical staff</i>	1	15	16
<i>CIBERES</i>	14	56	70
<i>Diploma holder</i>	-	5	5
<i>Doctor</i>	4	23	27
<i>Graduate</i>	10	18	28
<i>Technical staff</i>	-	10	10

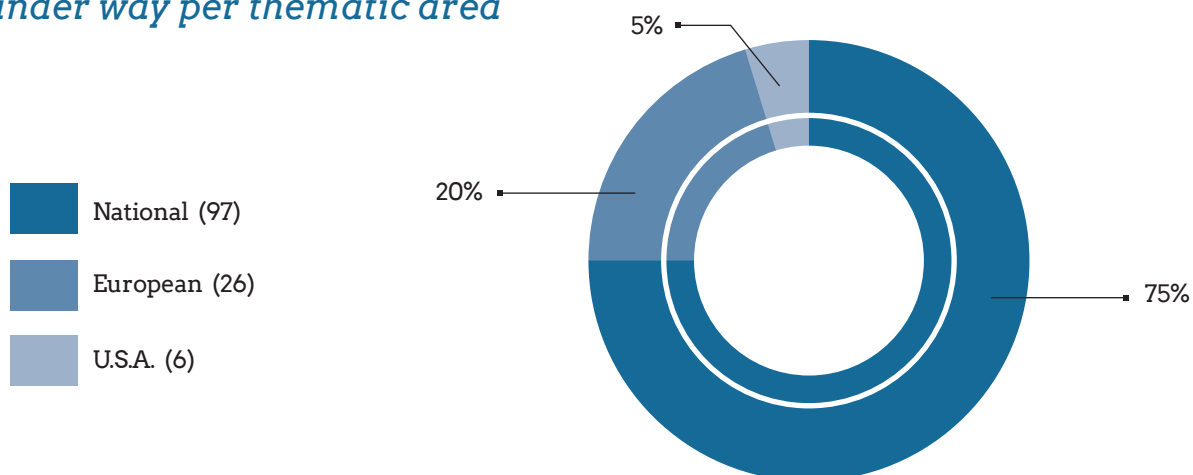
	MEN	WOMEN	OVERALL TOTAL
CIBERESP	15	52	67
<i>Diploma holder</i>	1	8	9
<i>Doctor</i>	4	14	18
<i>Graduate</i>	10	28	38
<i>Technical staff</i>	-	2	2
CIBERFES	7	8	15
<i>Doctor</i>	4	3	7
<i>Graduate</i>	3	5	8
CIBEROBN	19	52	71
<i>Diploma holder</i>	1	5	6
<i>Doctor</i>	6	11	17
<i>Graduate</i>	10	26	36
<i>Technical staff</i>	2	10	12
CIBERONC	18	69	87
<i>Doctor</i>	10	31	41
<i>Graduate</i>	8	26	34
<i>Technical staff</i>	-	12	12
CIBERSAM	18	61	79
<i>Diploma holder</i>	-	3	3
<i>Doctor</i>	9	15	24
<i>Graduate</i>	7	36	43
<i>Technical staff</i>	2	7	9
CIBERUT	10	27	37
<i>Doctor</i>	1	1	2
<i>Graduate</i>	9	22	31
<i>Technical staff</i>	-	4	4
Overall Total	239	674	913

Projects

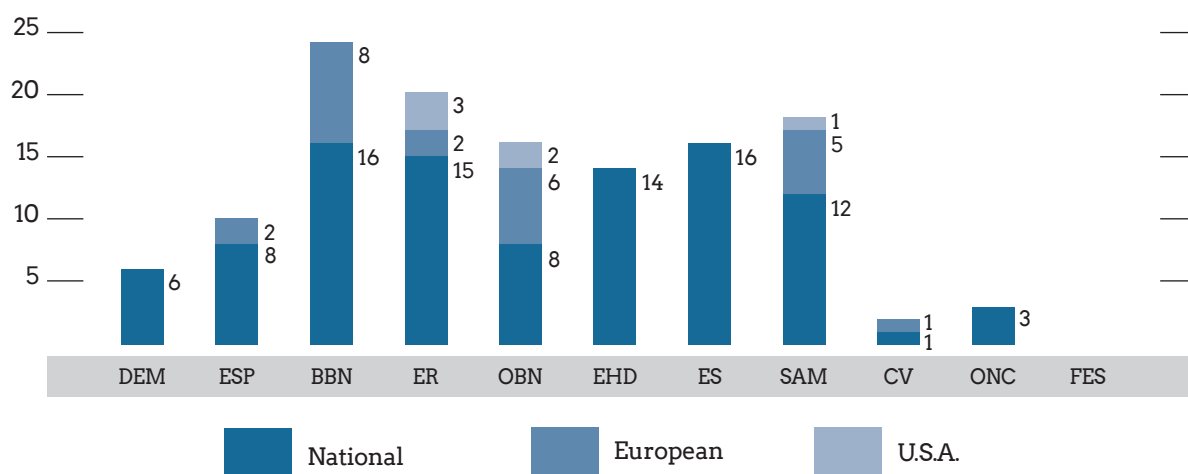
Number of projects under way in the 2018 period, as a result of competitive grants:

<i>Body / Grant</i>	<i>Subsidies applied in 2018</i>	<i>BBN</i>	<i>CV</i>	<i>DEM</i>	<i>EHD</i>	<i>ER</i>	<i>ES</i>	<i>ESP</i>	<i>FES</i>	<i>OBN</i>	<i>ONC</i>	<i>SAM</i>
<i>European</i>	26	8	1	-	-	2	-	2	-	8	-	5
<i>U.S.A.</i>	6	-	-	-	-	3	-	-	-	2	-	1
<i>National</i>	97	16	1	6	14	15	16	8	-	6	3	12
<i>ISCIII - FIS</i>	31	1	-	-	3	5	7	5	-	2	-	8
<i>ISCIII - Others</i>	18	3	-	2	3	1	4	2	-	2	-	1
<i>MECD Ministry</i>	1	-	-	-	-	-	-	-	-	-	1	-
<i>MINECO Ministry</i>	19	10	-	4	1	1	1	-	-	-	-	2
<i>Private foundations</i>	24	-	1	-	7	7	4	1	-	2	1	1
<i>Other public grants (Valencia, Aragon regional authorities)</i>	4	2	-	-	-	1	-	-	-	-	1	-

Competitive projects under way per thematic area



Competitive projects under way per thematic area



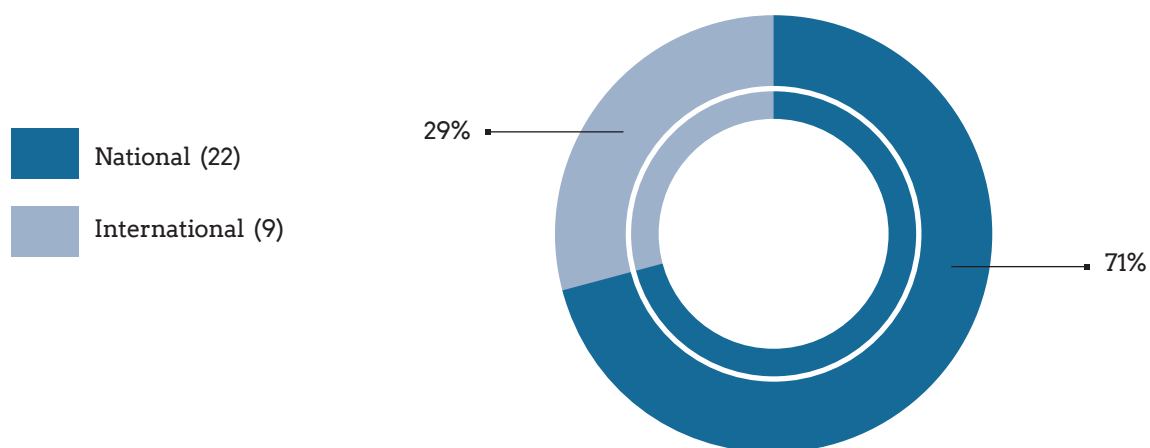
During the 2018 period, CIBER obtained the following grants from competitive calls.

<i>Date granted</i>	<i>Body</i>	<i>National/ international</i>	<i>Name of project</i>	<i>TOTAL GRANTED</i>
1/4/18	European Commission	International	GrapheneCore2	100.000,00 €
30/5/18	European Commission	International	INSPIRE-MED	250.904,88 €
13/6/18	European Commission	International	POSITION II	153.125,00 €
14/6/18	MINECO Ministry	Nacional	<i>La interacción entre microbiota y metabolismo del huésped regula la epigenética del huésped - bfu2017-87958-p</i>	205.700,00 €
15/6/18	Sociedad Española de Cardiología	Nacional	<i>El receptor nuclear NOR-1 en el remodelado cardiaco: análisis de mecanismos fisiopatológicos y validación de un modelo animal de utilidad preclínica</i>	15.000,00 €
18/6/18	European Commission	International	Innovation in Tuberculosis	61.648,00 €
30/6/18	MINECO Ministry	Nacional	<i>Gestión coordinada y promoción estratégica de NANBIOSIS</i>	89.700,00 €
27/7/18	Valencian Regional Authority	Nacional	<i>Ayuda Grupos Emergentes GVA_Gema Garcia</i>	16.000,00 €
27/7/18	Valencian Regional Authority	Nacional	<i>Ayuda Grupos Emergentes GVA_Mariam Ibáñez</i>	15.937,60 €
13/8/18	MECD Ministry	Nacional	<i>Ayuda de Movilidad José Castillejo-recipient Andrea Mayado</i>	17.976,00 €

<i>Date granted</i>	<i>Body</i>	<i>National/ international</i>	<i>Name of project</i>	<i>TOTAL GRANTED</i>
13/8/18	MECD ministry	National	Ayuda de Movilidad José Castillejo-recipient Laura Asín	11.620,00 €
11/10/18	European Commission	International	RD ACTION - Orphanet Network	82.494,84 €
23/10/18	Aragon Authority	National	Subvenciones para la reparación, mantenimiento y puesta a punto de equipamiento científico EQ/029/2018	2.800,00 €
26/10/18	European Commission	International	CARDIATEAM	655.500,00 €
7/11/18	Instituto de Salud Carlos III	National	MV18/00020	6.080,00 €
8/11/18	Instituto de Salud Carlos III	National	PI18/00266_Carlos Camps. <i>INMUNOGRAMA NO INVASIVO. Aproximación multidimensional para caracterizar y monitorizar el estatus inmune en cáncer de pulmón</i>	123.420,00 €
8/11/18	Instituto de Salud Carlos III	National	PI18/01020- Vanesa García Barberan_ <i>Papel de los exosomas como reguladores epigenéticos en el microambiente tumoral</i>	105.270,00 €
8/11/18	Instituto de Salud Carlos III	National	PI18/00825 - Eva M ^a Navarrete : <i>Dieta y actividad física en embarazo y tras el nacimiento y longitud del telómero en niños y adolescentes: Proyecto TeloDiPA</i>	75.020,00 €
8/11/18	Instituto de Salud Carlos III	National	PI18/00850 - Diana Gomez - <i>Mapas de riesgo de vectores y enfermedades emergentes o reemergentes en España. (MARVEEEE)</i>	26.620,00 €
8/11/18	Instituto de Salud Carlos III	National	PI18/00803 - Beatriz García: <i>Identificación de las vías de conexión entre calcificación vascular y mineralización ósea en diabetes mellitus tipo 2. Evaluación de su bloqueo como aproximación terapéutica.</i>	62.920,00 €
8/11/18	Instituto de Salud Carlos III	National	PI18/00449- Manuel Sánchez de la Torre: <i>Medicina de precisión en pacientes con apnea del sueño y síndrome coronario agudo: Modelo predictivo de respuesta al tratamiento</i>	87.120,00 €
8/11/18	Instituto de Salud Carlos III	National	PI18/00411- Irene Latorre: <i>Caracterización de nuevos marcadores celulares y estudio de anticuerpos glicosilados en el manejo de tuberculosis</i>	87.120,00 €
8/11/18	Instituto de Salud Carlos III	National	PI18/01165 - Eva García Escobar	117.370,00 €
19/11/18	MINECO	National	PTA2017-14443-I Paolo Saccardo	39.000,00 €
20/11/18	Instituto de Salud Carlos III	National	AC18/00107 Rafael López- EURONANOMED PANIPAC	169.702,50 €
20/11/18	Instituto de Salud Carlos III	National	AC18/00045- EURONANOMED METASTARG	169.884,00 €
26/11/18	Fundación La Caixa	National	CI18-00009-Hitshock - José Luis García	70.000,00 €

<i>Date granted</i>	<i>Body</i>	<i>National/ international</i>	<i>Name of project</i>	<i>TOTAL GRANTED</i>
3/12/18	Instituto de Salud Carlos III	National	Ayuda PFIS - Rosa Faner (FI18/00106)- Sandra Casas	82.400,00 €
3/12/18	European Commission	International	DIABFRAIL-LATAM	802.550,00 €
6/12/18	European Commission	International	Codification for Rare Diseases — RDCODE	54.966,63 €
17/12/18	European Commission	International	EJP-RD	61.853,00 €
TOTAL FUNDS IN COMPETITIVE GRANTS OBTAINED IN 2017				3.819.702,45 €

Competitive projects awarded in 2018



Applications for competitive grants submitted

The number of applications for competitive external financing projected in 2018 was 190 and the amount applied for came to 69,638.453 €.

Transfer

One of the CIBER'S main aims is the translation of the knowledge generated by its researchers, in such a way that the results of research are implemented in protocols, services and products for the improvement of clinical practice and the population's quality of life. To materialise this the Technology Transfer area of the CIBER works as a liaison between our researchers and companies, private organisations, public research centres and other innovation agents to put cooperation between them into practice and

make sure that the results of research can finally be applied.

In 2018 23 new applications for patents were submitted at the CIBER, with 1 intellectual property registration (CIBERSAM), 1 trademark (CIBERDEM) and 2 software (CIBERCV and CIBERBBN). 4 licence contracts and 1 licence option contract (CIBERES) were also signed.

<i>THEMATIC AREA</i>	<i>Priority patent applications</i>	<i>Other IPRs and software</i>	<i>Licences and licence options</i>
<i>CIBER-BBN</i>	8	1	3
<i>CIBERDEM</i>	2	1	-
<i>CIBEREHD</i>	1	-	-
<i>CIBERER</i>	6	-	1
<i>CIBERES</i>	3	-	1*
<i>CIBERESP</i>	-	-	-
<i>CIBEROBN</i>	2	-	-
<i>CIBERSAM</i>	1	1	-
<i>CIBERCV</i>	-	1	-
<i>CIBERONC</i>	-	-	-
<i>CIBERFES</i>	-	-	-

*Licence option

Two new orphan designations were also obtained for Fanconi anaemia, which means 8 orphan drugs sponsored by the CIBER until now (CIBERER area).

As an example of this, other measures concerning knowledge transfer and public-private cooperation that have been performed are:

- Dozens of CDAs and MTAs negotiated and signed.
- Assistance and participation in a large number of partnering and discussion forums, including: Biospain, BioEquity Europe, BioEurope, Workshop Kaertor, Transfiere Forum, as well as at other international, national and regional fairs and forums.

- Presentation of two business projects (of the CIBERER and CIBERES) for the “Mind the gap” forum of the Fundación Botín, reaching Phase II with both of these.
 - Obtaining a project at the Caixa Impulse 2018 call (CIBERER).
 - The continuing support for our spin-off (Epidisease S.L.) has also continued in both the application for proposals for projects and of presentation to investors.
 - Proposals have also been submitted at the Farma-Biotech Programme of Farmaindustria; the Caixaimpulse call and several open innovation programmes, such as that of the Fundación Kaertor.
 - The CIBERER area has arranged symposia for cooperation with industry, an important one of which was “Public/Private initiative for Advanced Therapies in Rare Diseases” organised at the ISCIII on 28 May 2018.
 - Along with the *Plataforma de Malalties Minoritàries* the CIBERER also arranged two new editions of the symposia on designation and development of orphan drugs, on 20 September at La Fe Hospital in Valencia and on 22 November 2018 at the Virgen del Rocío Hospital in Seville. The process of orphan drugs was explained at these events, from the preparation for obtaining this designation until these reach the patient.
-
- In the CIBERES area support for the HIPARCO has gone on. A new financing agreement was negotiated by the Fundación la Caixa (finally signed by the IRB Lleida) and other calls were applied for (MthG, FIPSE, AGAUR, etc.)
 - On 8 November 2018, the CIBER- BBN area arranged the 1 Forum for Emergence of new projects and “Tech transfer” along with Genesis Biomed at Barcelona’s Parc Científic.
 - In the CIBER-BBN area seven transfer projects were implemented in 2018 with the financial backing of seven companies. Six of these endeavours were got under way in 2018 and the seventh continued with the process previously started. A new call for this type of projects was issued, but none was awarded.
 - Also, at CIBER-BBN, the first call for valorisation projects was made in December 2018. 8 project proposals were submitted and 6 were financed. These projects have the main aim of helping to increase the TRL (Technology Readiness Level, the technology’s level of maturity) of their technologies in a step forward towards their exploitation and marketing (minimum TRL=3).

Communication

Press releases

In 2018 **163 press releases** were issued concerning the research results of the groups. These include press releases sent from the institutions in the consortium which were performed in cooperation with the CIBER.

CIBER AREA	Press releases 2018
CIBERCV	24
CIBEROBN	23
CIBERER	20
CIBERDEM	18
CIBERESP	15
CIBERES	13
CIBERONC	12
CIBERSAM	10
CIBER-BBN	7
CIBEREHD	7
CIBERFES	2
Colaboration. Several areas	11
CIBER	1
TOTAL	163

CIBER Newsletters

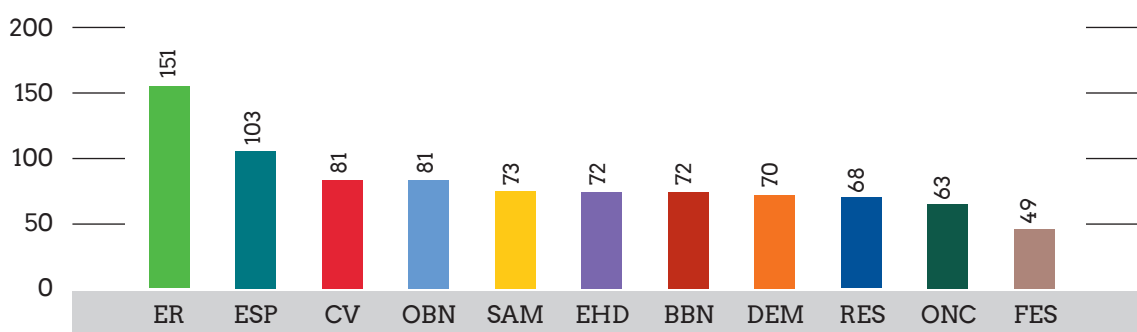
In 2018 **5 CIBER newsletters** and **70 newsletters from the thematic areas** were issued. The CIBERER also brought out **6 social newsletters**.

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

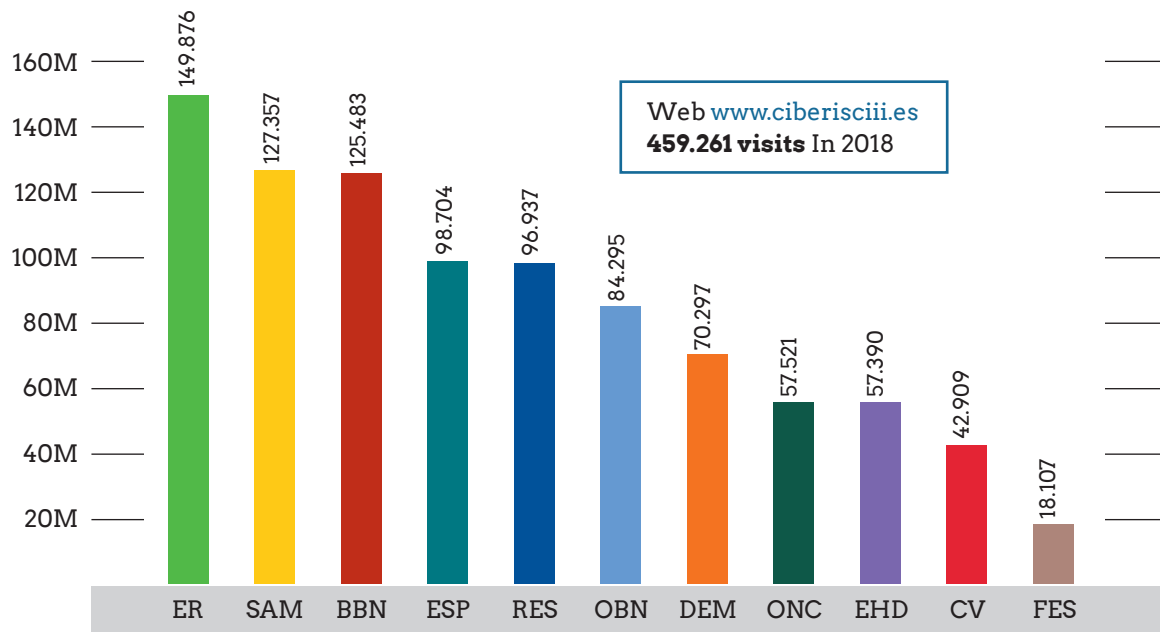
Web pages

886 news items and **791 agenda events** were announced on the areas' websites.

Web news 2018



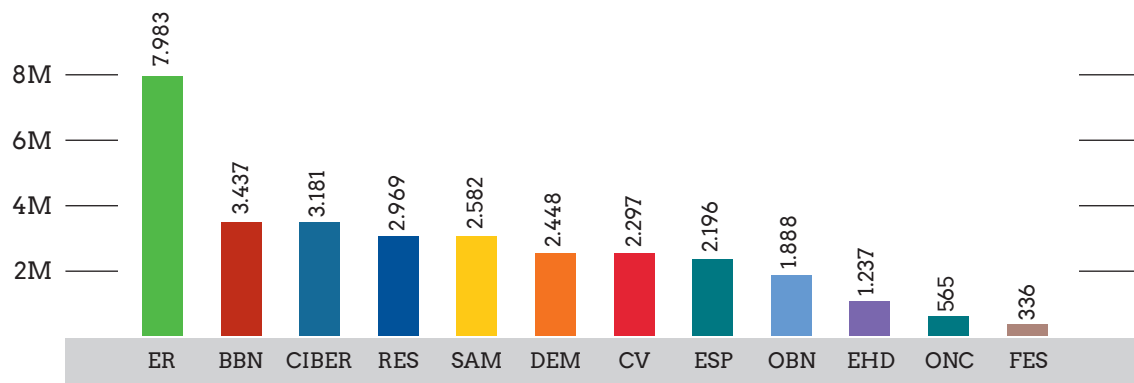
Visits to the web pages of the CIBER



Social networks

Followers on the different profiles of the CIBER
in Twitter

Followers 2018



CIBER activity at the Madrid Science Week and corporate video

In November the CienciaConPartitura [Science with sheet music] was held as part of the Madrid Science Week at the Fundación Giner de los Ríos in Madrid.

Four researchers submitted their work at the CIBER in the setting of their research area:

- Marina Pollán Santamaría, director of the CIBERESP, presented the results of the MCC project on breast cancer
- Malu Martínez Chantar, a CIBEREHD researcher, explained their work on the non-alcoholic fatty liver
- Susana Carmona Cañabate, al CIBERSAM researcher, talked about the changes in the woman's brain with maternity
- Gemma Rojo Martínez, a CIBERDEM researcher, explained the results of the di@bet.es study

The event, which was hosted by Luzma García, was livened up with four pieces of classical music. It was attended by over 180 persons.

[SEE VIDEO SUMMARY](#)





**Bioengineering,
Biomaterials
and Nanomedicine**



Scientific Director's Presentation

Ramón Martínez Máñez

I am pleased to present the annual report of CIBER-BBN, which covers the most significant parts of the work done by us in 2018 and is a good chance to look over and highlight what has been achieved this last year.

In the organisational sphere we have got under way the Strategic Plan 2018-2021, which has meant a new organisation pattern as regards the approach to our activity and the internal calls for projects.

As regards internationalisation and improvement of our external visibility, CIBER-BBN has been present at international events such as CLINAM or at the annual meeting of the ETPN. It has participated as a benchmark research centre by acting as "mentor" for the creation of an excellence centre in Cyprus as part of a European project. A major effort has been made in applying for ambitious projects in several H2020 calls, and in 2019 we took part in a project for the creation of major infrastructures facilitating the development of medical devices containing nanotechnology in compliance with European regulatory frameworks.

As for scientific activity, the traditional intramural projects have now become intramural cooperation schemes setting out to encourage collaborative research with all CIBER areas, taking advantage of the consortium's great potential. The permeability has been highly satisfactory, with almost half of the cooperation schemes incorporating research groups from other thematic areas.

The joint work under way covers a wide range of subject matters, which confirms our multidisciplinary nature and cooperation potential.

Another new initiative has been the early stage projects, led by contracted doctors and in which there has been a great response, with almost 30 projects under way.

As regards cooperation with other thematic areas, a joint call has been launched with CIBERONC with a very good response and in which three seed-stage projects are being funded. We should also stress the scientific sessions shared with CIBERER and CIBERFES researchers at the Annual Conference held in Valladolid.

In the framework of these sessions the prizes for the 1st Edition of CIBER- BBN awards for the best articles published in 2017 by young investigators were given. This is a new measure, aimed at encouraging our young researchers, which we hope to continue with in the future.

In 2018 we also launched the new valorisation projects, with which projects are funded so that a technology with a TRL of at least 3 can reach a more mature level of development. Five projects are being funded in the 2018 call. We also maintain the traditional call for transfer projects jointly funded by CIBER-BBN and by a company in which we have had seven projects active over the last year.

A Forum for Emergence of new projects and Tech Transfer has also been arranged for the purpose of identifying innovation projects with investment potential for creating spin-offs.

As for NANBIOSIS, its accreditation as a Singular Technical Scientific Structure has been revalidated and it has added BIONAND as an additional node to the two already existing ones.

Scientific production has increased slightly as compared with the previous year, while

maintaining the quality standards of publications in the first quartile and decile.

In all, one should consider the balance for 2018 as being highly positive. I would like to thank all the members of BBN for their work and daily endeavours, which are what ensure that the CIBER-BBN keeps its high scientific level.

Please read the rest of the report, which I hope will be of interest to you.

Scientific Programmes

Bioengineering and Medical Imaging

Coordinator: **Jordi Aguiló Llobet**

The Bioengineering programme was extremely active in 2018, with the presentation of 28 intramural cooperation proposals with a 4-year horizon. 18 of these proposals were submitted with groups from other thematic areas of the CIBER, mainly CIBERES, CIBERSAM, CIBERCV and CIBERNED, and 9 with external groups. The most frequently tackled pathologies were cardiovascular diseases (7 proposals) and neurological and mental ones (6 proposals), followed by respiratory diseases (5 proposals).

As for joint activities with groups from other thematic areas, we should stress the following projects:

- **ANS-RESP-WEANING:** Autonomic nervous system surrogates, cardiopulmonary coupling and respiratory parameters as predictors of successful weaning in mechanically ventilated patients, a collaborative project by the groups led by Pablo Laguna and Lluís Blanch (CIBERES) which continued to be developed in 2018.
- **NaTbiL:** PDT based on nanoconjugates triggered by biolight, presented by María de la Fuente Freire from the ONCOMET-CIBERONC group and José Miguel López Higuera at the 2018 call for CIBERONC-BBN projects. The project was the third most voted in the participative evaluation during the forum held and has already started to be implemented, going on until October 2019.

Apart from this 4 CIBER contracted staff members in groups of the Bioengineering, the call for Early Stage projects, presenting 2-year

long collaborative projects with other CIBER contracted staff. The Projects approved and their coordinators are:

- **CARDIOGRAFET II:** Disposable sensing platform based on graphene-SGFET to monitor biomarkers for cardiac diseases II, Elisabet Prats.
- **Nano-MEA:** Nanoparticle drug delivery systems for the improvement of the chronically implanted microelectrode-array viability, Cristina Soto.
- **NANORASI:** Optogenetic approach to visual rehabilitation using nanoparticle vectors, Lawrence Humphreys.
- **Lyfe4AD:** Comprehensive approach of non-adherent patients through an mHealth environment in people with endocrine diseases, Carmen Pérez Gandía.

On 8 May 2018 the I CIBER Forum on Emerging Technologies was held, at which the Bioengineering Programme was represented by Rosa Villa and Pablo Laguna, who took part in *the sessions on Nanotechnologies and on Omic Technologies and Big Data, respectively.*

At the session for young researchers during the Annual Symposia of CIBER-BBN, researcher Carolina Migliorelli from Raimon Jané's group was given the prize for the best article in the field of Bioengineering for her work entitled *Automated detection of epileptic ripples in MEG using beamformer-based virtual sensors.*

The Programme's activity in European initiatives was marked by the work done by Rosa Villa's team, a researcher in Jordi Aguiló's group, in the CORE 2 sub-project of the Graphene Flagship. One result of this work was the development of a graphene implant which overcomes the technical barriers for detecting cerebral activity at extremely low frequencies. The same group is also taking part along with Raquel Bailón's team from Pablo Laguna's group

in the IMI2 RADAR-CNS: *Remote Assessment of Disease and Relapse – Central Nervous System*, project which continued to be developed for a further year.

In 2018, the Bioengineering Programme welcomed two new group leaders: Elena

Hernando, who replaced Francisco del Pozo at the Universidad Politécnica de Madrid; and Xavier Setoain, who took over from Javier Pavía at the Universidad de Barcelona.

Biomaterials and Advanced Therapies

Coordinator:
Julio San Román del Barrio

32 proposals for intramural cooperation were submitted by the Biomaterials and Advanced Therapies Programme, 9 of which are with groups from other thematic areas of the CIBER, and 6 with external groups. Regenerative Medicine was the subject most frequently tackled (12 proposals) followed by Cancer (9 proposals) and Cardiovascular Diseases (5 proposals). In fact, the areas with greatest presence in intramural cooperation work are CIBERONC, CIBERCV and CIBERER.

9 projects coordinated by staff in groups from the Biomaterials and Advanced Therapies Programme were presented in the call for Early Stage projects. Their titles and coordinators are as follows:

- COAT-EBM: Bioactive coatings to promote osseointegration of personalized 3D porous titanium prostheses, Leonor Santos
- OCUSySTEM: Mesenchymal stem cells as a next generation drug delivery system for ocular surface diseases, Teresa Nieto Miguel
- SMEW: Therapeutic microparticles functionalized with stem cell secretome for chronic skin wound healing, Soledad Pérez-Amodio
- 3DHEPPEG: 3D bioprinting of novel heparin-PEG hydrogel for regenerative therapies, Miguel Ángel Mateos Timoneda
- HYDROREG: Engineering hydrogels to promote muscle regeneration, Patricia Rico

- tMELANO: Clinical validation of a novel temperature sensor based in bilayer organic material to help in melanoma diagnostic, Sara Oliván
- BONESCAFF: Improved ELRs scaffolds for bone regeneration, Alessandra Girotti
- MagTHor: Magnetic isolation of extracellular vesicles from genetically modified therapeutic human adipose mesenchymal stem cells for glioblastoma treatment, Oscar Meca Cortés
- CADHForce: Cell mechanosensing through cadherin complexes, Raimon Sunyer

At the session held for young researchers during the Annual Symposia of CIBER-BBN, researcher Alberto Cañibano from José Luis Pedraz's group was awarded the prize for the best article in the domain of Biomaterials for his work entitled "Alginate Microcapsules Incorporating Hyaluronic Acid Recreate Closer in Vivo Environment for Mesenchymal Stem Cells".

2018 was a prolific year for the Biomaterials and Advanced Therapies Programme as regards awards. María Vallet Regí, the head of the group at the Universidad Complutense de Madrid, was awarded the *Premio Rei Jaume I de Investigación Básica*. Julio San Román, head of the group at the Instituto de Ciencia y Tecnología de Polímeros of the CSIC and coordinator of the programme, received the George Winter 2018 award for research, at the 29th Conference of the European Society for Biomaterials held in Maastricht (Holland).

In the field of biomaterials, the project entitled POSITION II-ECSEL "A pilot line for the next generation of smart catheters and implants" led by researcher Jesús Ciriza from José Luis Pedraz's group has been active.

Nanomedicine

Coordinator: **M. Pilar Marco Colás**

In 2018 52 new intramural cooperation schemes were started up in the Nanomedicine Area, 25 of these for performance in cooperation with other thematic areas of the CIBER and 10 with groups outside this. As an innovation this year 14 Early Stage projects have been got under way in the Nanomedicine area led by CIBER contracted staff.

We should stress the efforts made by CIBER-BBN in the preparation of competitive proposals. Among these the researchers from the Nanomedicine Programme of CIBER-BBN have continued with internationally and nationally financed projects such as:

- European project SMART-4-FABRY “Smart multifunctional GLA-nanoformulation for Fabry Disease”, coordinated by CIBER (PI: Nora Ventosa).
- European project “Exploitation of extracellular vesicles for precision diagnostics of prostate cancer – PROSCANEXO” ERANET-TRANSCAN-2 (JTC2016) coordinated by CIBER (PI: Jesús Martínez de la Fuente).
- Continuation of Phase I of European project “Integrated Precision Medicine Research Center of Excellence – IPMT CoE”.
- European project “Monitoring of Acquired Brain Injury and recovery biomarkers by the combined label-free nanoSensing of multiple circulating molecules – ABISens” EURONANOMED-3 (JTC2018) coordinated by CIBER-BBN, (PI: Laura Lechuga).
- Participation of 15 CIBER-BBN groups in the COST-Action Nano2Clinics project “Cancer Nanomedicine - From bench to bedside”, contributing to the different work groups in the Action. The CIBER-BBN also forms part of the Management Committee for this measure.
- Health research project - AES2017 “Design of protein nanomedicines for treatments tackling cancer of the pancreas” led by contracted researcher José Luis Corchero.

- RETOS project NanoET-Leukemia, led by contracted researchers Anna Lagunas and Marina Inés Giannotti.

Apart from this, researchers from the Nanomedicine area have continued with the ERC obtained:

- ERC Advanced Grants (María Vallet-Regí and Jesús Santamaría with projects VERDI - polyValent mEsopoRous nanosystems for bone Diseases and CADENCE Catalytic Dual-Function Devices Against Cancer, respectively);
- ERC Consolidator: Manuel Arruebo with the project entitled “Nanohedonism and ERC Proof of Concept: HOTFLOW” by Jesús Martínez de la Fuente.

Luis M. Liz Marzán has furthermore obtained an ERC Advanced Grant this year for the project “4DBIOSERS Four-Dimensional Monitoring of Tumour Growth by Surface Enhanced Raman Scattering”.

The following events and congresses connected with the Nanomedicine Area were also attended:

- *XI Conferencia Anual de las Plataformas Tecnológicas de Investigación Biomédica*, 5 and 6 March 2018, Barcelona.
- CLINAM European Foundation for Clinical Nanomedicine, Basel 2-6 September 2018.
- Annual meeting of the ETPN (European Technology Platform of Nanomedicine). Berlin, 28–20 May 2018.
- Brokerage Event on Advanced Materials and Nanotechnology. Horizon 2020 NMBP Calls 2019. 3 July, IMDEA Madrid.

Researchers from the Nanomedicine Area Luis M. Liz Marzán and María Vallet-Regí appear on the list of **Highly Cited Researchers de Clarivate Analytics**, one of the most highly reputed classifications in the international academic and scientific community. The scientific director of CIBER-BBN, Ramón Martínez Máñez, was furthermore awarded the *Premio Rei Jaume I de Nuevas Tecnologías 2018*. Luis M. Liz Marzán was also given the National Research Award 2018 in the Chemical Science and Technology Area and Laura Lechuga was appointed associate editor by the Editorial Board of *Analyst* journal.

Training Programme

Coordinator: *Raimon Jané Campos*

The Training Programme of the CIBER-BBN sets out to increase the research skills of the staff forming part of the groups by improving the professional competence of the technical and research staff as a factor for change, by changing attitudes, knowledge and skills depending on the needs arising throughout development of their research work.

The main initiatives of the CIBER-BBN Training Programme are its grants for getting started in research and the mobility grants.

Unfortunately, administrative limitations have meant that in 2018 it has not been possible to arrange calls for grants for getting started in research, an endeavour which is very highly valued among CIBER-BBN groups since it enables young researchers still taking a master course to join the groups.

It was nonetheless possible to finance 5 contracts for traineeships lasting 6 months for young graduates with external funds from the donation collected from *Caja Ingenieros* every year.

The candidates were selected on the basis of the best project submitted.

Mobility grants

The aim of this training programme is to act as an incentive for short stays at other research groups in order to facilitate the transfer of experience and technology and to foster cooperation between the different groups in the CIBER-BBN. These stays have to be structured in priority strategic work lines for our thematic area.

In 2018 there were two mobility calls, in April and September, and a total number of 28 subsidies for stays at groups external to CIBER-BBN have been awarded.

Just one grant has been given as aid for mobility for research staff between CIBER-BBN groups, the call for these being permanent throughout the year.

Number of grants awarded

<i>Year</i>	<i>Intra-CIBER-BBN mobility grants</i>	<i>External mobility grants</i>	<i>Total nr. of mobility grants</i>
2011	6	10	16
2012	6	9	15
2013	1	20	21
2014	2	17	19
2015	3	18	21
2016	4	13	17
2017	3	18	21
2018	1	28	29

NANBIOSIS ICTS Platform

Coordinator: *Jaume Veciana Miró*

In 2018 NANBIOSIS renewed its accreditation as an "ICTS" (Singular Scientific and Technological Infrastructure). After the assessment of four years' work of the ICTS and their strategic plans, the Ministry of Science, Innovation and Universities passed the update of the National ICTS Map, including NANBIOSIS with the incorporation of a third node to the two founders (CIBER and CCMIJU). This third node is the Centro Andaluz de Nanomedicina y Biotecnología (BIONAND) in Malaga, which has brought Nanoimaging unit 28 into NANBIOSIS.

Furthermore, after the annual internal assessment of the NANBIOSIS units, one of these left the ICTS in 2018 and, going on with the process of incorporating new internal units, unit 29 for synthesis of oligonucleotides, located in the IQAC-CSIC, joined platform 1 for production of biomolecules.

The NANBIOSIS web page has been designed to directly promote *ground-breaking biomedical solutions*, by means of which researchers and companies are provided with the integrated expertise of the NANBIOSIS units. Some of these solutions are being structured and others are already under way, with some success cases. The most ambitious of these is the cascade characterisation of nanomedicines, which includes the services required to characterise the physical-chemical attributes and their in vitro and in vivo biological properties (immunology, toxicology and effectiveness), using suitable animal models. The video for dissemination of NANBIOSIS (https://www.youtube.com/watch?time_continue=3&v=vezgov-kc0g) specifically focuses on this biomedical solution.

The search for public or private external financing continues to be a priority. There has been a follow-up of cooperation schemes already started with companies and of national projects such as

BIOTAPES, from the RETOS-COLABORACIÓN programme, or European ones such as BERENICE (FP7) or DRIVE (H2020). In 2018 the European project known as SAFE-N-MEDTECH (H2020) was granted, with the aim of setting up an open-access platform based on online tools for companies and reference laboratories, to interconnect capacities, knowledge, networks and services for development, testing, assessment, scale improvement and exploitation of medical and diagnostic devices on the market, based on nanotechnology. The project is participated in by a further 27 partners apart from CIBER, and it will have wide-ranging participation of the NANBIOSIS units and of its organisational structure.

Funds has been obtained through the Pronanbiosis II project (Excellence Networks call) which enables taking on a person for daily management of NANBIOSIS as an ICTS and maintenance of the web page.

NANBIOSIS was presented at international bodies, national companies, foundations and public research organisations, and has been involved in partnering events for seeking associates such as Bio Europe (Berlin), Big Science Business Forum 2018 (Copenhagen), Brokerage event on Advanced Materials NMPB and the *XI Conferencia Anual de las Plataformas Tecnológicas de Investigación Biomédica*.

Among other activities we should stress the organisation by NANBIOSIS of a Forum in Drug delivery and targeting and a *Jornada de Nanotoxicidad* in cooperation with Materplat and NanomedSpain, as well as the participation of NANBIOSIS in the MATERPLAT.

The third meeting of the Scientific Advisory Committee of NANBIOSIS was held, coinciding with the CIBER-BBN Annual Conference.

Scientific Production

Publications

No. of publications in 2018

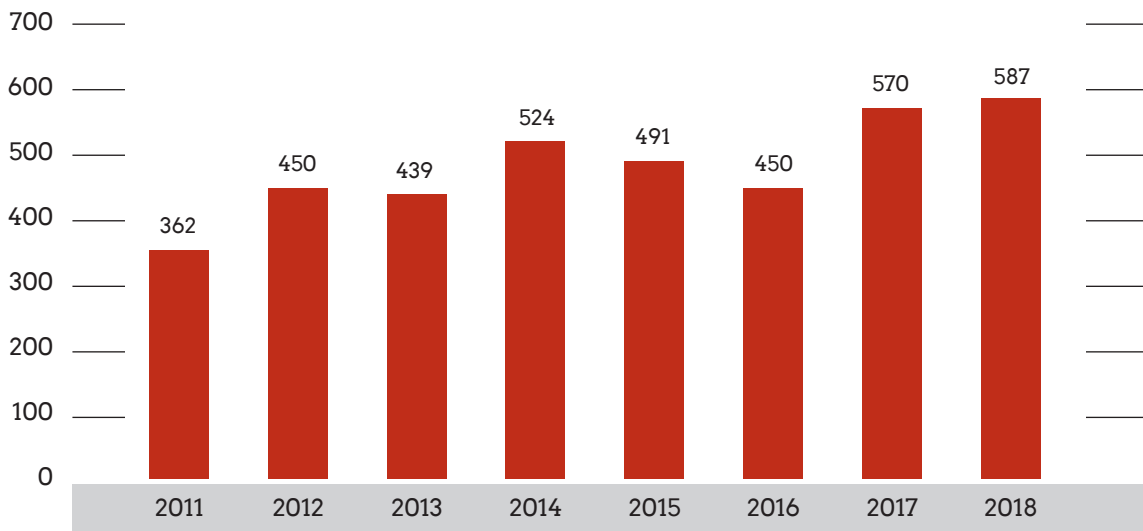
TOTALS	587
Q1	418
D1	178

Collaborative Publications

CIBER-BBN	68
CIBER*	89

*Over several thematic areas

Evolution of publications



10 most relevant publications of the CIBER-BBN in 2018 by impact factor

IF	Publication
51,941	PASTORIZA-SANTOS I., KINNEAR C., PEREZ-JUSTE J., MULVANEY P., LIZ-MARZAN L.M. <i>Plasmonic polymer nanocomposites. Nature Reviews Materials.</i> 2018;3(10):375-391.
41,577	LATORRE E., KALE S., CASARES L., GOMEZ-GONZALEZ M., UROZ M., VALON L. ET AL. <i>Active superelasticity in three-dimensional epithelia of controlled shape. Nature.</i> 2018;563(7730):203-208.
40,182	WU X., HAO C., KUMAR J., KUANG H., KOTOV N.A., LIZ-MARZAN L.M. ET AL. <i>Environmentally responsive plasmonic nanoassemblies for biosensing. Chemical Society Reviews.</i> 2018;47(13):4677-4696.
32,521	LIN L., WANG M., PENG X., LISSEK E.N., MAO Z., SCARABELLI L. ET AL. <i>Opto-thermoelectric nanotweezers. Nature Photonics.</i> 2018;12(4):195-201.
22,727	TREPAT X., SAHAI E. <i>Mesoscale physical principles of collective cell organization. Nature Physics.</i> 2018;14(7):671-682.
21,95	WANG M., KRASNOK A., ZHANG T., SCARABELLI L., LIU H., WU Z. ET AL. <i>Tunable Fano Resonance and Plasmon-Exciton Coupling in Single Au Nanotriangles on Monolayer WS2 at Room Temperature. Advanced Materials.</i> 2018;30(22):-.
21,95	HANSKE C., SANZ-ORTIZ M.N., LIZ-MARZAN L.M. <i>Silica-Coated Plasmonic Metal Nanoparticles in Action. Advanced Materials.</i> 2018;30(27):-.
20,955	MOSQUERA J., GARCIA I., LIZ-MARZAN L.M. <i>Cellular Uptake of Nanoparticles versus Small Molecules: A Matter of Size. Accounts of Chemical Research.</i> 2018;51(9):2305-2313.
19,064	UROZ M., WISTORF S., SERRA-PICAMAL X., CONTE V., SALES-PARDO M., ROCA-CUSACHS P. ET AL. <i>Regulation of cell cycle progression by cell-cell and cell-matrix forces. Nature Cell Biology.</i> 2018;20(6):646-654.
18,564	ELOSEGUI-ARTOLA A., TREPAT X., ROCA-CUSACHS P. <i>Control of Mechanotransduction by Molecular Clutch Dynamics. Trends in Cell Biology.</i> 2018;28(5):356-367.

Patents owned by CIBER



Applications

National

- Low energy X-Rays hybrid MC for fast dose computation (LEX-hMC) (Software).
- Device and method of continuous insulin infusion dose with a hybrid corrective and predictive PID monitoring.
- Multicomponent nanoparticles and use thereof.
- Self-associated functional acrylic copolymers and terpolymers and their use as vehicles for bioactive compounds.

- Injectable material for regenerating articular cartilage.
- Use of boron and its derivatives for the treatment of muscular dystrophies.
- Graphene transistor system for measuring electrophysiological signals..

Italian

- Cardiac activity measurement system and method thereof.

European

- Methods and systems for measuring a stress indicator, and for determining a level of stress in an individual.

PCT

- Porous material for detection of candida albicans, diagnosis method using this and method for preparing this.

- *Devices and methods for multiplexing liquid in biosensor micro-chambers.*
- *Photoisomerizable derivatives of dihydrofolate reductase inhibitors.*
- *Actively targeted polymeric micelles for drug and gene delivery.*

National phases

- *Microfluidic chip, microfluidic devices, procedures and associated uses (U.S.A. and Europe).*

Granted

National

- *Microfluidic chip, microfluidic devices, procedures and associated uses.*
- *Microfluidic devices and system for studying cell cultures.*

International

- *Methods and reagents for efficient and targeted delivery of therapeutic molecules to CXCR4 cells (Israel).*
- *Functionalised liposomes useful for delivering bioactive compounds (Japan, Europe).*

Clinical guidelines

- *Intensified recovery pathway in oesophago-gastric surgery.*
- *The Art of Hernia Surgery. A Step-by-Step Guide.*

- *Protocol for action with the adult patient with Potentially Severe Trauma (TPG) at the Emergency Service.*
- *SEOM clinical guideline in nasopharynx cancer.*
- *Paclitaxel unit a l'albumina: Tractament de primera línia del càncer de pàncrees metastàtic.*

CIBER-BBN Groups. Publications

Group leader	Publ.	Q1	D1	Institution / Centre	Province
 Aguiló Llobet, Jordi	15	10	4	Universidad Autónoma de Barcelona - Centro Nacional de Microelectrónica	Barcelona
 Albericio Palomera, Fernando	37	18	8	Universidad de Barcelona - Facultad de Química	Barcelona
 Arús Caralto, Carles	8	6	3	Universidad Autónoma de Barcelona	Barcelona
 Becerra Ratia, José	13	9	3	Universidad de Málaga - Facultad de Ciencias	Málaga
 Bellón Caneiro, Juan Manuel	11	4	1	Universidad de Alcalá - Facultad de Medicina	Madrid
 Calonge Cano, Margarita	13	9	3	Universidad de Valladolid - Instituto de Oftalmobiología Aplicada	Valladolid
 Corcoy Pla, Rosa	11	9	7	Instituto de Investigación del Hospital de la Santa Creu i Sant Pau	Barcelona

<i>Group leader</i>	<i>Publ.</i>	<i>Q1</i>	<i>D1</i>	<i>Institution / Centre</i>	<i>Province</i>
 Engel López, Elisabeth	4	4	2	Fundación Instituto de Bioingeniería de Cataluña	Barcelona
 Eritja Casadellà, Ramon	19	15	5	Agencia Estatal Consejo Superior de Investigaciones Científicas - Instituto de Química Avanzada de Cataluña	Barcelona
 Fernández Jover, Eduardo	10	8	2	Universidad Miguel Hernández de Elche - Instituto de Bioingeniería	Alicante
 Gómez Ramírez, Rafael	10	8	0	Universidad de Alcalá - Facultad de Farmacia	Madrid
 Gómez Ribelles, José Luis	13	7	1	Universidad Politécnica de Valencia - Centro de Biomateriales e Ingeniería Tisular	Valencia
 González Martín, María Luisa	3	3	0	Universidad de Extremadura - Facultad de Ciencias	Badajoz
 Gorostiza Langa, Pau	3	2	2	Fundación Instituto de Bioingeniería de Cataluña	Barcelona
 Hernando Pérez, María Elena ¹	17	11	1	Universidad Politécnica de Madrid - ETSI Telecomunicación	Madrid
 Jané Campos, Raimon	23	14	3	Fundación Instituto de Bioingeniería de Cataluña	Barcelona
 Laguna Lasasoa, Pablo	19	8	0	Universidad de Zaragoza.	Zaragoza
 Lechuga Gómez, Laura María	10	8	5	Agencia Estatal Consejo Superior de Investigaciones Científicas - Institut Català de Nanociència i Nanotecnologia	Barcelona
 Liz Marzán, Luis Manuel	33	31	18	CIC biomaGUNE	Guipúzcoa
 López Higuera, José Miguel	7	5	0	Universidad de Cantabria - Edificio I+D+I de ing. de Telecomunicación	Cantabria
 Mangues Bafalluy, Ramon	22	18	11	Instituto de Investigación del Hospital de la Santa Creu i Sant Pau	Barcelona
 Marco Colas, María Pilar	12	9	4	Agencia Estatal Consejo Superior de Investigaciones Científicas - Instituto de Química Avanzada de Cataluña	Barcelona
 Martínez Barca, Miguel Ángel	16	9	2	Universidad de Zaragoza	Zaragoza
 Martínez de la Fuente, Jesús	20	18	10	Agencia Estatal Consejo Superior de Investigaciones Científicas - Instituto de Ciencia de Materiales de Aragón	Zaragoza
 Martínez Máñez, Ramón	37	23	15	Universidad Politécnica de Valencia - Instituto Interuniversitario de Investigación de Reconocimiento Molecular y Desarrollo Tecnológico	Valencia
 Pedraz Muñoz, José Luis	28	17	5	Universidad del País Vasco - Facultad de Farmacia	Álava
 Peris Serra, José Luis	2	1	0	Asociación Instituto de Biomecánica de Valencia	Valencia
 Raya Chamorro, Ángel	9	7	2	Centro de Medicina Regenerativa de Barcelona	Barcelona
 Ritort Farran, Félix	7	6	2	Universidad de Barcelona - Facultad de Física	Barcelona

<i>Group leader</i>	<i>Publ.</i>	<i>Q1</i>	<i>D1</i>	<i>Institution / Centre</i>	<i>Province</i>
 Rodríguez Abreu, Carlos	12	7	3	Agencia Estatal Consejo Superior de Investigaciones Científicas - Instituto de Química Avanzada de Cataluña	Barcelona
 Rodríguez Cabello, José Carlos	9	8	4	Universidad de Valladolid	Valladolid
Rubio Vidal, Núria ²	3	1	1	Agencia Estatal Consejo Superior de Investigaciones Científicas - Instituto de Química Avanzada de Cataluña	Barcelona
 Ruiz Romero, Cristina	7	4	1	Servicio Gallego de Salud - Complejo Hospitalario Universitario A Coruña	A Coruña
 Samitier Martí, Josep	14	9	6	Fundación Instituto de Bioingeniería de Cataluña	Barcelona
 San Román del Barrio, Julio	6	6	1	Agencia Estatal Consejo Superior de Investigaciones Científicas - Instituto de Ciencia y Tecnología de Polímeros	Madrid
 Santamaría Ramiro, Jesús	33	24	11	Universidad de Zaragoza.	Zaragoza
 Santos Lleó, Andrés	9	8	4	Universidad Politécnica de Madrid - ETSI Telecomunicación	Madrid
 Schwartz Navarro, Simó	10	8	6	Fundación Hospital Universitario Vall d'Hebron - Institut de Recerca (VHIR) - Hospital Vall d'Hebron	Barcelona
 Setoain Peregó, Javier ³	20	15	6	Universidad de Barcelona - Hospital Clínic de Barcelona	Barcelona
 Trepát Guixer, Xavier	12	10	8	Fundación Instituto de Bioingeniería de Cataluña	Barcelona
 Vallet Regí, María	40	28	14	Universidad Complutense de Madrid - Facultad de Farmacia	Madrid
 Veciana Miró, Jaume	22	16	9	Agencia Estatal Consejo Superior de Investigaciones Científicas - Instituto de Ciencias de Materiales de Barcelona	Barcelona
 Vilaboa Díaz, Nuria	2	2	2	Servicio Madrileño de Salud - Hospital La Paz	Madrid
 Villaverde Corrales, Antonio	16	12	9	Universidad Autónoma de Barcelona - Instituto de Biotecnología y Biomedicina	Barcelona
 Farré Ventura, Ramón*	20	14	6	Universidad de Barcelona - Facultad de Medicina	Barcelona
 Muñoz Fernández, María Ángeles*	12	11	1	Servicio Madrileño de Salud - Hospital Gregorio Marañón	Madrid

1 Replaced Francisco del Pozo

2 Group deregistered in December 2018

3 Replaced Javier Pavía Segura

*CIBER-BBN Associated Groups



**Cardiovascular
Diseases**



Scientific Director's Presentation

Francisco Fernández-Avilés

Dear colleagues at the Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), I am writing again on behalf of the Management Committee and myself to thank you for the great efforts that you have made in 2018 and for your ongoing commitment. The second year in the development of our thematic area is unquestionably satisfactory, due both to the achievements made and to the great involvement of all the groups, which have managed to overcome a lot of difficulties.

In 2018 we passed the first assessment of the External Advisory Scientific Committee, which issued a clearly favourable report on our work and some very useful recommendations for improvement including: (1) the need to reinforce internationalisation and excellence; (2) to identify, recruit and retain young talent; (3) to commit to key areas, promoting the main technological capacities; (4) to foster and reward a multidisciplinary approach; and (5) to take advantage of and boost the enormous capacities of the national health system, specifically in the management of data and registers.

We are aware at the Management Committee that all the groups are making great efforts to ensure progress in these fields. This second year our CIBER has already managed to lead several joint schemes in European projects, both in the H2020 programme (Impact of Mediterranean Diet, Inflammation and Microbiome on plaque vulnerability and microvascular dysfunction after an Acute -JPI-HDHL-) and in the ERANET network and in the Innovative Medicines Initiative (CARDIA-TEAM- IMI2-2017-13-01).

What is more, in 2018 we managed to implement some of the main CIBERCV actions such as the competitive grants through intramural projects and through actions for identifying and encouraging talent by means of the Jordi Soler-Soler grants. Some of the major scientific achievements are different multi-centre studies led by CIBER researchers. Another great milestone in 2018 was signing a cooperation agreement with the *Agencia Española del Medicamento* for promoting and furthering research in the thematic area of cardiovascular diseases enabling us to go further in the integral management of data provided by the National Health System. Another great achievement was the coordination by the CIBERCV of the 52nd Annual Scientific Meeting of the European Society for Clinical Investigation, at which the main projects and scientific contributions made by the centre were presented.

We struggle from our economically weak position against the great bureaucratic difficulties found at the Central Administration. Our optimism nonetheless also makes us aware that science managers are also committed in this battle and we think that the Consortium which we have joined is an incomparable venue for excellence which guarantees us a stable budget, even though this is chronically low and seriously affected by today's political instability. All of this is enabling us to put Spanish cooperative cardiovascular research on the highest national and international rung of competitiveness. Thanks to you.

Scientific programmes

Myocardial damage and its consequences

Coordinators:
Francisco Fernandez-Avilés
Juan Cinca

In the second year's work done in programme 1, intended to understand and treat myocardial damage and its associated clinical consequences, some of the major targets set in the scientific management plan of CIBERCV have been achieved. This text attempts to give some examples of the accomplishments representing the entire work done by the programme:

In the line of structural and electrophysiological **remodelling and scar-formation**, it is important to stress the start of the "AdiFLAP Trial", financed by the *Instituto de Salud Carlos III* and in which the therapy of adipose graft transposition procedure (AGTP) will be validated to reduce the size of the post-infarction myocardial scar. This is a multi-centre project taking advantage of a structure like that of the CIBERCV to transfer a basic research study carried out by Dr Antoni Bayes-Genís' group to clinical practice.

In the line of **genetically caused myocardial damage** we should highlight the work entitled "Dilated Cardiomyopathy Due to BLC2-Associated Athanogene 3 (BAG3) Mutations", published in the *Journal of the American College of Cardiology*, in which over ten CIBERCV institutions have taken part. In this it was proven that dilated cardiomyopathy caused by mutations in gene BAG3 is characterised by a high penetration in carriers over 40 years of age and with a high risk of progressive heart failure, showing the importance of including this gene in the panels of genetic tests of hypertrophic cardiomyopathy.

In the line of research into **heart failure**, we should stress getting under way the prospective registry (Redinscor III) of patients with debut heart failure in which eleven CIBERCV groups are taking part and in which nearly 200 patients have been included in only three months from starting inclusion. This study involves taking a blood sample and clinical follow-up of all the patients for 3, 6 and 12 months and will be of vital importance to be able to reveal the causes and evolution of this major pathology. Some important steps forward in knowledge are being made thanks to prior registries Redicor I and II, such as for example the study entitled "Influence of sex and pregnancy on survival in patients admitted with heart failure: Data from a prospective multicenter registry" published in 2018 in the *Clinical Cardiology journal*.

Arterial Pathology, Myocardial Ischaemia and Structural Heart Pathology

Coordinators:

David García-Dorado
Alberto San Román

CIBERCV Programme 2 focussing on arterial diseases, myocardial ischaemia-reperfusion and structural cardiopathy has enjoyed a successful 2018 in which some important studies have been published as a result of the cooperation between different groups in the network, as well as getting under way some relevant projects.

In the line of **research into Myocardial Ischaemia and Reperfusion**, we should stress the study entitled “Ryanodine Receptor Glycation Favors Mitochondrial Damage in the Senescent Heart”, published in journal *Circulation* in which the cooperation between CIBERCV groups has shown that the mitochondria of senescent hearts develop a calcium overload as well as the part coming from the sarcoplasmic reticulum. The study has shown the mechanisms causing damage to the senescent myocardium, thus opening the way up to potential new therapeutic targets. The type of mechanistic studies led to patents and contracts for developing new therapies such as the inhibition of calpain in ventricular remodelling. In order to increase the strength and speed of translation of knowledge to patients and society, we have set up a platform for preclinical studies in lesions caused by ischaemia-reperfusion, the CIBERCLAP platform, in which the groups taking part share standardised experimental biochemical, molecular and morphological

Cardiovascular Epidemiology and Risk Factors

Coordinator:

Jaume Marrugat

studies and imaging methods with centralised randomisation installations and central laboratories. With regard to clinical studies, some ambitious randomised and multi-centre assays have been carried out on patients with acute myocardial infarctions, such as the COMBAT-MI tests (including 360 patients) and REBOOT (> 500 patients already included), in which many hundreds of patients have already been included, as well as major registries in acute coronary syndrome in cooperation with Programme 4, such as ATHOS.

The line of research focussing on **diseases of the aortic valve** includes mechanical cooperation studies to find out the molecular pathways leading to aortic dilation, the analysis of advanced images (a prominent one being CMR 4D, wall tension) of mechanical factors promoting dilation, and studies of genetic factors modulating dilation in genetics and acquired aortic diseases. Secondly, some large-scale cooperative multi-centre registries have been set up and academic clinical tests for studying the evolution of aortic stenosis (> 1400 patients), the ones determining the appearance and result of acute aortic syndrome (RESA III study, > 600 patients included), or the utility of atorvastatin for preventing aortic dilation in patients with bicuspid aortic valve (BICATOR, 220 patients included).

In the line of research focussing on **valve disease and congenital heart disease**, the main multi-centre studies under way include population studies on the prevalence of adults with congenital heart disease (ACHD) and on mortality and sudden death in ACHD, and a registry of patients with ACHD and synchronisation therapy (RETRACCA), as well as studies on N-glycosylation in congenital heart diseases (CARDIoG) and re-ervation after an atrial switch operation.

The purpose of the Programme on Cardiovascular Epidemiology and Risk Factors is to investigate the mechanism linking cardiovascular risk factors with the serious illnesses entailed by these such as ischaemic cardiopathy and cerebrovascular disease, for example. Programme 3 of the CIBERCV consists of two research lines.

Within the line of **Epidemiology, cohorts,**

risk factors and cardiovascular risk functions, progress has been made in several important projects in 2018. In the evaluation of the *magnitude of the problem of cardiovascular disease*, data has been obtained on the population incidence of acute myocardial infarction in the population >35 years on the prevalence of obesity in Spain. At present data on over 3 million people is being analysed.

Regarding the *risk factors associated with the development of cardiovascular diseases*, several risk factors connected with ischaemic cardiopathy have been identified, helping to improve predictive capacity. An analysis has been made of the importance of sleep and adherence to healthy lifestyles in cardiovascular risk.

Increasing knowledge in the *clinical epidemiology of acute myocardial infarction and coronary syndromes* in Spain is a very relevant part of the programme. In 2018, several hospital registers (SPARTA and ATHOS) in which 15 CIBERCV centres take part analysed anti-platelet treatment at 18 months in patients with ACS, the variability in treatment between centres and the prognosis of these patients. It is being analysed whether the generic information may help to identify patients with a worse prognosis.

The CORDELIA project has also been got under way, including 30 INTER-CIBER groups in this collaborative study of cohorts, with over 170,000 participants and biological samples of around 100,000. The nucleic

database is expected to be ready during summer 2019. This database will constitute the greatest *biobank of the general population and of patients with Myocardial Infarction* existing to date in this country.

As regards *knowledge transfer*, an adaptation of the REGICOR function for patients with HIV is being validated, analysing whether this population has a greater prevalence of factors of cardiovascular risk than the general population.

Furthermore, in the approach covering **genetics and mechanisms of arteriosclerosis**, progress has been made in 2018 with identifying genetic variants connected with *ictus, coronary disease, high blood pressure, familial hyperlipidaemia and other cardiovascular phenotypes*. An analysis has been made of the epigenetics of cardiovascular disease by means of a study of the methylation of DNA and miRNA. The findings were published in *Nature Genetics, Nature Communications, Circulation, Stroke, ATVB, Atherosclerosis*.

More specifically, we have used genetic information as an instrumental variable to analyse the causal relationship between soluble receptor LRP1 and characteristics of HDL, and heart disease. It has been shown that genetic biomarkers help to improve the prediction of classic risk functions and an online platform is being designed to facilitate access to the results of genomic studies in cardiovascular disease.

Molecular and imaging biomarkers and precision CV medicine

Coordinator:
Javier Díez

CIBERCV Programme 4 is intended for the identification, validation and translation to the National Health System of molecular and imaging biomarkers, enabling early and accurate diagnosis of cardiovascular

pathologies, for their personalised and effective treatment.

The line of research focussing on the **evaluation of known biomarkers**, coordinated by Dr Antoni Bayés-Genís, has made some major progress. In the field of heart failure, we should stress the validation of sST2 as a biomarker of clinical utility. IL-1b has also been identified as a prognostic biomarker in the setting of acute heart failure. With regard to the guide for treatment, the clinical utility of CA125 has been proven. Lastly, a recently identified molecule in a Line 2 project, IGFBP2, has been validated as a prognostic biomarker. In the field of heart disease, we should stress

biomarker ApoJGly, in a transfer process by means of a spin-off. The clinical utility of other biomarkers such as a panel of miRNAs and sTWEAK is being validated in Line 1.

Line 2 of Programme 4 focussing on the **identification of new biomarkers**, coordinated by Dr Jesús Vázquez, concentrates on the identification and small-scale validation of biomarkers in heart failure, ischaemic vascular disease, atrial fibrillation, valve diseases, myocardopathies and cardiovascular ageing. The projects have an interdisciplinary approach with omic methodologies and imaging and clinical and basic groups. In this line we should highlight the generation of new methodologies of heart imaging, systemic identification of biomarkers reflecting myocardial or coronary alterations, such as circulating RNAs and proteomic studies on extensive low-risk populations to identify early biomarkers. A representative example of the work done is the study entitled "Prognostic Value of Strain by Tissue Tracking Cardiac Magnetic Resonance After ST-Segment Elevation Myocardial Infarction", published in the *Journal of the American College of*

Cardiology Cardiovascular Interventions, where it is proven that monitoring tissue in the magnetic resonance technique was able to provide prognostic information shortly after a myocardial infarction, although this did not substantially improve the reclassification of the risk.

Lastly, the biomarkers programme has, with the cooperation of Dr Domingo Pascual, got under way the Platform for Precision Cardiovascular Medicine - PMPCV.net. This platform gives information on cohorts of patients and molecular tools, offered to the scientific community by the different groups of the CIBERCV, to facilitate translational research in biomarkers by combining forces. The platform has 63 collections of patients and 21 of animal models, in all over 19,000 samples, covering multiple cardiovascular pathologies. **PMPCV.net** has intellectual protection and is fully operative, having given rise to an internal call for projects.

Training Programme

Coordinator: *Borja Ibáñez*

The CIBERCV Training Programme sets out to train young people to become the cardiovascular researchers of the future in order to improve society's cardiovascular health through the "Jordi Soler Soler" programme. In the CIBERCV this programme remains the main training endeavour and certain modifications have been brought in to foster training even further in the framework of collaborative research. This programme is ultimately intended to foster quality translational and collaborative research in the cardiovascular field at the CIBERCV groups through a range of training meant for young people with a research vocation.

The specific objectives of this programme are:

- To structure a procedure for granting subsidies for contracting professionals taking a training plan in translational cardiovascular research in a multidisciplinary setting.
- The contract in research has the aim of promoting capacity-building in research in a cooperative framework between at least two groups tackling the same problem from different angles. At least one clinical research group and another non-clinical (basic, epidemiological/technological group will take part.

- These contracts are meant for any young research professional in the post-doctoral stage or equivalent (medical doctors after completing their MIR residency training, for example).

This first year's call has been granted to three researchers who are going to perform their research projects in at least two research centres.

- A study of the gut microbiota and/or bacterial metabolites in the stratification of risks and prognosis of patients diagnosed with heart failure.

- Pulmonary vascular remodelling in heart failure.
- Optimisation of Multi-point Stimulation by mean of Fusion-Optimised Intervals (FOI) and Validation of Electrocardiographic Imaging (ECGI) in Cardiac Resynchronisation Therapy.

As well as these grants, the Training Programme also funds research stays for CIBERCV staff at other groups inside the CIBERCV or at internationally relevant centres where the knowledge and capacities of the programme can be increased.

Scientific Production

Publications

No. of publications in 2018

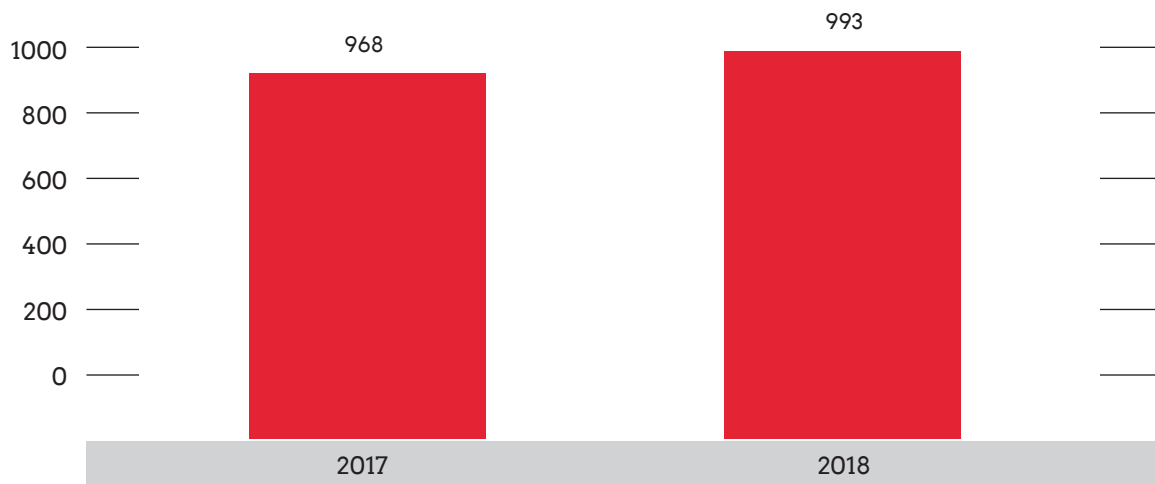
TOTALS	993
Q1	554
D1	251

Collaborative Publications

CIBERCV	208
CIBER*	331

*Over several thematic areas

Evolution of publications



10 most relevant publications of the CIBERCY in 2018 by impact factor

IF	Publication
79,258	<i>Relationship between clinic and ambulatory blood-pressure measurements and mortality</i> (Pubmed ID 29669232)
79,258	<i>Preventive therapies for chronic migraine</i> (Pubmed ID 29469552)
79,258	<i>Ambulatory Blood Pressure and Mortality</i> (Pubmed ID 30257163)
53,254	<i>Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial</i> (Pubmed ID 30158069)
53,254	<i>Radial versus femoral access and bivalirudin versus unfractionated heparin in invasively managed patients with acute coronary syndrome (MATRIX): final 1-year results of a multicentre, randomised controlled trial</i> (Pubmed ID 30153988)
53,254	<i>mHealth and the legacy of John Snow</i> (Pubmed ID 29676275)
53,254	<i>Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial.</i> (Pubmed ID 30291013)
53,254	<i>Dabigatran in patients with myocardial injury after non-cardiac surgery (MANAGE): an international, randomised, placebo-controlled trial.</i> (Pubmed ID 29900874)
53,254	<i>Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial.</i> (Pubmed ID 30166073)
41,577	<i>The tornadoes of sudden cardiac arrest.</i> (Pubmed ID 29595799)

Clinical guidelines

- *Practical guidelines for rigor and reproducibility in preclinical and clinical studies on cardioprotection.*
- *2018 Joint European consensus document on the management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous cardiovascular interventions.*
- *2018 ESC/ESH Guidelines for the management of arterial hypertension.*
- *"Spanish Cardiovascular Imaging Registry. First Official Report of the Spanish Society of Cardiology Working Group on Cardiovascular Imaging (2017)."*
- *"Spanish Catheter Ablation Registry. 17th Official Report of the Spanish Society of Cardiology Working Group on Electrophysiology and Arrhythmias (2017)"*
- *Libro blanco de la investigación en enfermedades cardiovasculares en España: retos y necesidades de futuro.*
- *Spanish Heart Transplant Registry. 29th Official Report of the Spanish Society of Cardiology Working Group on Heart Failure.*
- *ESC Guidelines on SVT Task Force Meeting European position paper on the management of patients with patent foramen ovale. General approach and left circulation thromboembolism.*
- *Fourth universal definition of myocardial infarction (2018).*

- 2018 ESC/EACTS Guidelines on myocardial revascularization.
- 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy.
- 2018 ESC/ESH Guidelines for the management of arterial hypertension.
- 2018 ESC Guidelines for the diagnosis and management of syncope.

CIBERCV Groups. Publications

<i>Group leader</i>	<i>Total</i>	<i>Q1</i>	<i>D1</i>	<i>Institution. Centre</i>	<i>Province</i>
 Andrés García, Vicente	11	9	5	Fundación Centro Nacional de Investigaciones Cardiovasculares	Madrid
 Badimon Maestro, Lina	31	25	14	Instituto de Investigación del Hospital de la Santa Creu i Sant Pau	Barcelona
 Bayés Genis, Antonio	81	44	22	Fundación Instituto de Investigación Germans Trias i Pujol - Hospital Germans Trias i Pujol	Barcelona
 Blanco Colio, Luis Miguel	10	9	3	Instituto de Investigación Sanitaria Fundación Jiménez Díaz	Madrid
 Bosca Gomar, Lisardo	8	6	1	Agencia Estatal Consejo Superior de Investigaciones Científicas - Instituto de investigaciones biomédicas Alberto Sols	Madrid
 Brugada Terradellas, Ramon	22	11	3	Fundación Instituto de Investigación Biomédica de Girona - Hospital Josep Trueta	Girona
 Chorro Gasco, Francisco Javier	18	4	2	Fundación para la Investigación del Hospital Clínico de la Comunidad Valenciana (Fundación INCLIVA) - Instituto de investigación sanitaria INCLIVA	Valencia
Cinca Cuscollola, Juan María	58	34	17	Instituto de Investigación del Hospital de la Santa Creu i Sant Pau	Barcelona
 Civeira Murillo, Fernando	27	22	5	Fundación Instituto de Investigación Sanitaria Aragón	Zaragoza
 Crespo Leiro, María Generosa	44	16	12	Servicio Gallego de Salud - Complejo Hospitalario Universitario A Coruña	A Coruña
 Delgado Jiménez, Juan Francisco	51	31	17	Servicio Madrileño de Salud - Hospital Universitario 12 Octubre	Madrid
 Díez Martínez, Domingo Francisco Javier	16	12	11	Fundación para la Investigación Médica Aplicada	Navarra
 Elosua Llanos, Roberto	20	10	3	Consorci Mar Parc Salut de Barcelona	Barcelona
 Fernández-Avilés Díaz, Francisco	69	32	13	Servicio Madrileño de Salud - Hospital Gregorio Marañón	Madrid
 García Pavía, Pablo	34	20	13	Servicio Madrileño de Salud - Hospital Universitario Puerta de Hierro	Madrid
 García-Dorado García, Antonio David	63	33	16	Fundación Hospital Universitario Vall d'Hebron - Institut de Recerca (VHIR) - Hospital Vall d'Hebron	Barcelona
 González Juanatey, José Ramón	64	29	10	Servicio Gallego de Salud - Complejo Hospitalario Universitario Santiago	A Coruña

<i>Group leader</i>	<i>Total</i>	<i>Q1</i>	<i>D1</i>	<i>Institution. Centre</i>	<i>Province</i>
 Jiménez Navarro, Manuel Francisco	34	19	11	Fundación Pública Andaluza para la Investigación de Málaga en Biomedicina y Salud (FIMABIS) - Hospital Universitario Virgen de la Victoria	Málaga
 Ibáñez Cabeza, Borja	69	37	16	Instituto de Investigación Sanitaria Fundación Jiménez Díaz	Madrid
 López-Sendon Hentschel, José Luis	1	1	1	Servicio Madrileño de Salud - Hospital La Paz	Madrid
 Marín Ortuño, Francisco	68	34	17	Fundación para la Formación e Investigación Sanitarias de la Región de Murcia (FFIS) - Hospital Universitario Virgen de la Arrixaca	Murcia
 Marrugat de la Iglesia, Jaume	35	17	7	ConSORCI MAR Parc Salut de Barcelona	Barcelona
 Martínez González, José	9	8	3	Agencia Estatal Consejo Superior de Investigaciones Científicas - Instituto de Investigaciones Biomédicas de Barcelona	Barcelona
 Mayor Menéndez, Federico	2	2	1	Universidad Autónoma de Madrid - Centro de Biología Molecular Severo Ochoa	Madrid
 Mont Girbau, Josep Lluís	70	34	11	Instituto de Investigaciones Biomédicas August Pi i Sunyer	Barcelona
 Ordóñez Fernández, Antonio	11	8	2	Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla - Hospital Virgen del Rocío	Sevilla
 Páramo Fernández, José Antonio	7	4	1	Universidad de Navarra - Clínica Universitaria de Navarra	Navarra
 Pérez-Villacastín Domínguez, Julián	25	16	11	Servicio Madrileño de Salud - Hospital Clínico San Carlos	Madrid
 Pompa Mínguez, José Luis de la	12	12	5	Fundación Centro Nacional de Investigaciones Cardiovasculares	Madrid
 Redondo Moya, Juan Miguel	20	14	10	Fundación Centro Nacional de Investigaciones Cardiovasculares	Madrid
 Rivera Otero, José Miguel	9	1	0	Fundación para la Investigación del Hospital la Fe - Hospital Universitario de La Fe	Valencia
 Salaices Sánchez, Mercedes	15	12	4	Universidad Autónoma de Madrid	Madrid
 San Román Calvar, José Alberto	41	28	13	Hospital Clínico Universitario de Valladolid	Valladolid
 Sánchez Fernández, Pedro Luis	41	18	8	Fundación Instituto de Estudios de Ciencias de la salud de Castilla y León - Hospital Universitario de Salamanca	Salamanca
 Sánchez Madrid, Francisco	20	15	7	Universidad Autónoma de Madrid	Madrid
 Sánchez Margallo, Francisco Miguel	5	3	1	Fundación Centro de Cirugía de Mínima Invasión Jesús Usón	Cáceres
 Sanchís Fores, Juan	51	22	11	Fundación para la Investigación del Hospital Clínico de la Comunidad Valenciana (Fundación INCLIVA) - Instituto de investigación sanitaria INCLIVA	Valencia
 Tamargo Menéndez, Juan	14	6	4	Universidad Complutense de Madrid - Facultad de Medicina	Madrid
 Vázquez, Cobos Jesús María	29	25	13	Fundación Centro Nacional de Investigaciones Cardiovasculares	Madrid
Zamorano Gómez, José Luis	42	22	18	Servicio Madrileño de Salud - Hospital Ramón y Cajal	Madrid

A 3D anatomical model of the human endocrine system. The left side shows a semi-transparent, light blue/grey model of the internal organs, including the brain, pituitary gland, thyroid, and adrenal glands. The right side is a solid orange background with a faint, larger-scale version of the same anatomical model. The text is centered on the orange background.

Diabetes and Associated Metabolic Diseases



Scientific director's presentation

Eduard Montanya Mías

In 2018, CIBERDEM placed the priority on strategic actions based on consolidation and scientific leadership, with special concern for young people. One relevant aspect of the implementation of the Strategic Plan were the calls for CIBERDEM Intramural Projects for young researchers, and of Grants for preparatory work meetings for projects. Another particularly fruitful initiative was the underpinning of institutional contact with the German Center for Diabetes Research (DZD), which has enabled the presence of DZD at our Annual Meeting, the visit of CIBERDEM researchers to DZD and the attendance of young researchers at the DZD course entitled *6th Diabetes Research School* (Berlin). The person-to-person meeting with the External Advisory Scientific Meeting allowed us to analyse and make an in-depth review of the structure and operation of CIBERDEM.

In the framework of its research work, CIBERDEM has kept up the standard of its scientific production, with 294 annual publications of an excellent quality level (average impact factor 5.3). The CIBERDEM groups continue with their cooperative work on the national and international levels, with 75% and 40% collaborative publications respectively. Our web page shows details of each group's most relevant publications. Some of the specific achievements in 2018 that should be stressed are that CIBERDEM has established the incidence of diabetes in Spain, as being 11.58 cases per 1000 persons-year, which represents about 386,003 new cases a year. The results

were presented in Spain in the framework of the *XXIX Congreso Nacional de la Sociedad Española de Diabetes*. The analysis being made of the data generated by the di@betes study will enable determining the risk factors associated with the development of diabetes, as well as the incidence of associated comorbidities, vital information for designing healthcare policies that are specifically aimed at preventing diabetes. In the scope of knowledge transfer, CIBERDEM has continued to take part in the preparation of national and international guidelines and consensus documents, and has carried out several patentability studies, submitting two patent applications and one PCT.

Looking back at 2018, we should also stress the initiatives in the Training Programme as detailed in the Report. In the section on Communication and Dissemination to Society, CIBERDEM has kept up its commitment and participation as a member of EURADIA to define guidelines for research into diabetes in Europe. CIBERDEM was present at the *Congreso de la Sociedad Española de Diabetes* and that of the European Association for the Study of Diabetes, this involvement being institutionally consolidated with both scientific associations. CIBERDEM has taken part in activities for social dissemination such as the Science Week, Diabetes Experience Day and the World Diabetes Day, taking part in the Diabetes and Family event, in the Spanish Parliament's Health Commission, and keeps its links with patients' associations.

Scientific Programmes

Epidemiology, Genetics and Epigenetics of Diabetes Mellitus. Chronic complications and Comorbidities

Coordinator:
Ángela Martínez Valverde

Epidemiology of diabetes mellitus, its chronic complications and comorbidities

The incidence of diabetes in Spain has been established, at 11.58 cases per 1000 persons-year, which represents about 386,003 new cases each year in the adult population. In the framework of the di@bet.es study, financing from the ISCIII has been obtained for a project on regulation of VEGF-b by circulating microRNAs.

Genetics, epigenetics and environmental factors in the development of diabetes and its complications

We took part in the clinical trial known as Trial to Reduce Insulin-Dependent Diabetes mellitus in the Genetically at Risk, the biggest international study on primary prevention in type 1 diabetes carried out until now. This has established that exposure to intact casein during childhood does not play any role in the development of type 1 diabetes (Knip et al., *JAMA* 2018).

In 2018, we should also stress the finding that candidate gene for type 1 diabetes DEXI is involved in the regulation of inflammation of the pancreatic

beta cell (Dos Santos et al., *Diabetologia* 2018).

In the setting of the European Nutritional Phenotype Assessment and Data Sharing Initiative (ENPADASI), CIBERDEM has taken part in a joint analysis of observational nutritional studies for establishing a methodology enabling the creation of robust meta-databases (Pinart et al., *J Nutrition*, 2018). Nutrition based on the Mediterranean diet has been described as reducing adverse perinatal events of women with gestational Diabetes (Assaf-Balut et al., *BMJ Open Diab Res Care*, 2018).

A reduction of the macrophage reverse specific cholesterol transport was reported in patients with diseases associated with cardiovascular risk, familial hypercholesterolaemia and abdominal aortic aneurysm by means of measuring the cell flow of cholesterol (Martínez-López et al., *Arterioscl Throm Vas* 2018). Progress has been made in the implementation of NMR methodology for determining the profile of lipoproteins in early detection of cardiovascular risk (Barrilero et al., *Anal Chem* 2018) and this is being applied to diabetes by means of the complete characterisation of the di@betes study cohort. It has been described that circulating inflammatory markers as soluble receptor type II of TNF α , C-reactive protein and total leukocyte count, along with the presence of anti-islet autoantibodies directed against GAD can help to differentiate latent adult autoimmune diabetes from classic type 1 diabetes in adults and from type 2 diabetes (Castelblanco et al., *Diabetes Care*, 2018).

The importance of CXCR3-mediated inflammatory axis and its ligands in metabolic dysfunction and angiogenesis of the adipose tissue during resistance to insulin has been shown in humans (Hueso et al., *Int J Obes* 2018). High-fat diets have been found to alter the regulation of kinase protein PASK and its inhibition could slow down obesity (Pérez-García et al., *J Nutr Biochem* 2018).

Molecular mechanisms associated with the appearance and progression of chronic complications of diabetes: therapeutic strategies

In this line of research, a proteomic analysis on human retina has been made, explaining common pathways of neurodegeneration of the retina and brain (Sundstrom et al., *Invest Ophthalmol Vis Sci* 2018).

Gene therapy was successfully tried out with whole protein SOCS1 and the mimetic peptide

in renal and vascular complications of diabetes in murine models (López-Sanz et al., *Lab Invest* 2018).

We should lastly highlight the fact that a dual role of protein tyrosine phosphatase 1B has been discovered in non-alcoholic steatohepatitis due to the modulation of pro-inflammatory pathways in immune cells of the liver during its progression and modulation of the pathways for signalling the proliferation of oval liver cells during its reversion (González-Rodríguez et al., *Molecular Metabolism* 2018).

Molecular and Cellular determinants of the Function, Lesion and Protection of Pancreatic Islets. Regenerative Medicine and Advanced therapies

Coordinator:
Franz Martín Bermudo

Function and regulation of pancreatic islets: molecular and cellular bases and therapeutic targets

The chemical modulation of repressor mark H3K27me3 has been shown to allow modification of in vitro Neurogenin 3-mediated gene activation. This opens up options for generation of protocols for obtaining insulin-producing cells (Fontcuberta-PiSunyer et al., *BBA-Gene Regul Mech* 2018).

Another of the accomplishments worthy of mention is that it has been described that specific inactivation of GATA6 in the pancreatic islets of mice reduces their insulin content, alters insulin secretion, generates ultra-structural alterations and affects the expression of specific genes of the beta cell. The animals also undergo an alteration of glycaemia homeostasis, indicating the importance of GATA6 in the function of pancreatic beta cells (Villamayor et al., *Diabetes* 2018).

Preventive and therapeutic strategies in regenerative medicine, cell therapy and gene therapy

We have managed to develop a new model for experimental transplants of human islets to immunodeficient mice which enables reducing the number of islets and animals necessary for the transplant, increases animal comfort and optimises resources by reducing the workload of researchers and carers (Estil·les et al., *Cell Transplant* 2018).

It has also been possible to report the capacity of gene therapy with FGF21 to treat diabetes and its associated metabolic diseases. The use of adeno-associated viral vectors to genetically modify the liver, adipose tissue or the muscle so that they secrete FGF21 blocks the appearance of resistance to insulin and obesity in ob/ob mice, fed for long periods of time with high-fat diets. (Jimenez et al., *EMBO Molecular Medicine* 2018).

It has been described how microRNA miR-7 is expressed in a different way during the process of differentiating human embryo stem cells (hESCs) towards insulin-producing cells and that their modulation plays an important role in the appearance of beta pancreatic cells. This finding can be exploited to optimise differentiation protocols of hESCs towards insulin-producing cells (Lopez-Beas et al., *Mol Ther Nucleic Acids* 2018).

Application of new technologies to treatment of diabetes

Current artificial pancreas systems are mainly hybrid systems which require a statement of intake.

An algorithm for detection of intake has been developed from an estimator of disturbances based on a minimum model enabling progress towards totally automatic systems, releasing the

patient from the task of counting carbohydrates (Ramkissoon et al., *Sensors* 2018).

Cellular and Molecular Mechanisms involved in the Development and Progression of Type 2 Diabetes and Identification of New Therapeutic Targets

Coordinator:
Antonio Zorzano Olarte

Factors determining resistance to insulin: molecular mechanisms involved

It has been described that hepato-visceral adiposity and insulin resistance do not seem to be influenced by prepuberal alterations of liver volume (Malpique et al., *Int J Obes* 2018).

Bacterial diversity has also been shown to be lower in women as compared with men, and that diversity particularly drops in obese women with polycystic ovary syndrome. The indices of bacterial diversity and profusion of several bacterial genera are positively correlated with serum concentrations of androgens and negatively with those of estradiol (Insenser et al., *J Clin Endocr Metab* 2018).

Inflammation as a pathogenic process in diabetes mellitus: Role of the adipose tissue and interaction with other tissues or organs

A new mechanism for induction of adiposity based on repression of autophagic factor TP53INP2 has been identified. Protein TP53INP2 has been described as being a negative regulator of adipogenesis through an autophagic process of sequestering protein GSK3b in late endosomes (Romero et al., *Nat Cell Biol* 2018).

It should also be highlighted that it has been possible to identify a signature of DNA methylation in adipocyte precursor cells in obesity with a significant impact on the metabolic phenotype of mature adipocytes. TBX15 has furthermore been identified as one of the most hypomethylated genes in adipocyte precursor cells in obesity, and genetic experiments show that TBX15 is a regulator of the mitochondrial mass of obese adipocytes (Ejarque et al., *Int J Obes* 2018).

Identification of molecular mechanisms and new therapeutic targets for development of personalised early interventions in diabetes mellitus

The VLDL hepatic receptor has been reported to be negatively regulated by PPAR δ and by FGF21 (Zarei et al., *Mol Metab* 2018). The results describe new mechanisms by means of which PPAR δ and FGF21 regulate the levels of VLDL receptors and have an influence on the development of hepatic steatosis.

The human islet amyloid polypeptide (hIAPP), or amylin tends to aggregate in insoluble amyloid fibrils, a characteristic typical of islets of individuals with type 2 diabetes. The over-expression of hIAPP in beta-pancreatic cells INS1E promoted the hyperactivation of mTORC1, and the concomitant inhibition of mitophagy. The expression of hIAPP favours a mitochondrial damage scenario and greater susceptibility to apoptosis and malfunctions induced by ER stress (Hernández et al., *Cell Death Dis.* 2018).

Identification of biomarkers of risk of diabetes progression

Palmitoleic acid isomers have been identified in phagocytic cells, with considerable anti-inflammatory activity (Astudillo et al., *J. Lipid Res.* 2018), and potential as biomarkers of anti-inflammatory activity and as therapeutic targets.

We should lastly stress the development of a new metabolomic methodology or analysis of network topology based on the intermediate centrality

of metabolites, which has made it possible to identify the 20 most important metabolites which, if added to the databases on mass spectrometry, may facilitate the characterisation of the

human metabolome in the future. (Frainay et al., *Metabolites* 2018).

Training Programme

Coordinator: *Ángel Nadal Navajas*

As main innovation of the Training Programme for 2018, CIBERDEM has launched a call for intramural projects for young researchers. The call was a great success, with 12 projects being assessed. With the aim of fostering a cooperation environment between groups and facilitating the development of new collaborative projects, CIBERDEM has launched a Call for Grants for work meetings in preparation for new projects.

The Mobility Grants Programme has continued to finance stays for CIBERDEM researchers at CIBER groups and international groups, with a total number of 7 grants being issued.

Our 9th Annual CIBERDEM Meeting was held on 23-25 May, with the participation of 150 CIBERDEM researchers and with 75 papers presented. The participation of the groups was highly active in both the discussion after the presentations and at the poster sessions, granting prizes to the best posters. The meeting was also attended by three heads of the German Center for Diabetes Research (DZD), who presented the organisation and lines of research of the DZD.

In the setting of the different training activities arranged by CIBERDEM with the cooperation of MSD, this year the Annual Symposium entitled

“La diabetes a debate 2018: la diabetes en la frontera del conocimiento” had the central themes of the cardiovascular effects of new SGLT2 inhibitors and the artificial pancreas with an approach involving basic investigation and its clinical applicability.

In the framework of the *XXIX Congreso Nacional de la SED*, CIBERDEM arranged the first SED – CIBERDEM panel, focussing this year on research into the beta cell. The interest of this type of activities in the context of the SED has encouraged its continuity in coming congresses.

After the success of the first edition, with 193 persons registered, CIBERDEM has again organised the postgraduate course of the Universidad de Barcelona, for Experts in Chronic Complications of Diabetes.

CIBERDEM groups have been extremely busy arranging scientific activities, congresses, courses, symposia, seminars and debates both in Spain and abroad. We should underline their participation in the arrangement of the Advanced Course in Lipidology, which forms part of the training plan of the European Atherosclerosis Society, held in Reus from 13 - 14 April.

Scientific Production

Publications

No. of publications in 2018

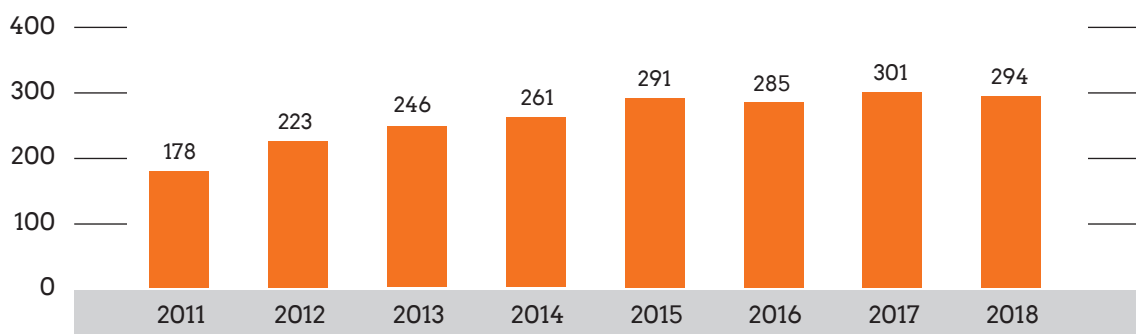
TOTALS	294
Q1	194
D1	65

Collaborative Publications

CIBERDEM	45
CIBER*	124

*Over several thematic areas

Evolution of publications



10 most relevant CIBERDEM publications in 2018 by impact factor

IF	Publication
47.661	KNIP M, ÅKERBLOM HK, AL TAJI E, BECKER D, BRUINING J, CASTANO L ET AL. <i>Effect of hydrolyzed infant formula vs conventional formula on risk of type 1 diabetes: the TRIGR randomized clinical trial. JAMA - Journal of the American Medical Association.</i> 2018;319(1):38-48.
26.919	GRÜNING B, DALE R, SJÖDIN A, CHAPMAN BA, ROWE J, TOMKINS-TINCH CH ET AL. <i>Bioconda: Sustainable and comprehensive software distribution for the life sciences. Nature Methods.</i> 2018;15(7):475-476.

20.773	HUAMAN JW, MEGO M, MANICHANH C, CAÑELLAS N, CAÑUETO D, SEGUROLA H ET AL. <i>Effects of prebiotics vs a diet low in FODMAPs in patients with functional gut disorders. Gastroenterology.</i> 2018;155(4):1004-1007.
20.265	ESCOBAR-MORREALE HF. <i>Polycystic ovary syndrome: Definition, aetiology, diagnosis and treatment Nature Reviews Endocrinology.</i> 2018;14(5):270-284
19.313	CERIELLO A, MONNIER L, OWENS D. <i>Glycaemic variability in diabetes: clinical and therapeutic implications. The Lancet. Diabetes and Endocrinology</i> doi: 10.1016/S2213-8587(18)30136-0. Epub 2018 Aug 13.
19.064	ROMERO M, SABATÉ-PÉREZ A, FRANCIS VA, CASTRILLÓN-RODRÍGUEZ I, DÍAZ-RAMOS Á, SÁNCHEZ-FEUTRIE M ET AL. <i>TP53INP2 regulates adiposity by activating β-catenin through autophagy-dependent sequestration of GSK3β. Nature Cell Biology</i> 2018;20(4):443-454.
19.064	SILVA J, AIVIO S, KNOBEL PA, BAILEY LJ, CASALI A, VINAIXA M ET AL. <i>EXD2 governs germ stem cell homeostasis and lifespan by promoting mitoribosome integrity and translation. Nature Cell Biology.</i> 2018;20(2):162-174.
18.964	CUADRADO A, MANDA G, HASSAN A, ALCARAZ MJ, BARBAS C, DAIBER A ET AL. <i>Transcription factor NRF2 as a therapeutic target for chronic diseases: A systems medicine approach. Pharmacological Reviews.</i> 2018;70(2):348-383.
16.834	CEDÓ L, PLANA N, METSO J, LEE-RUECKERT M, SANCHEZ-QUESADA JL, KOVANEN PT ET AL. <i>Altered HDL Remodeling and Functionality in Familial Hypercholesterolemia. Journal of the American College of Cardiology</i> 2018;71(4):466-468.
13.397	CASTELBLANCO E, HERNÁNDEZ M, CASTELBLANCO A, GRATACÒS M, ESQUERDA A, MOLLÓ À ET AL. <i>Low-grade inflammatory marker profile may help to differentiate patients with LADA, classic adult-onset type 1 diabetes, and type 2 diabetes. Diabetes Care.</i> 2018;41(4):862-868.

Patents owned by CIBER

Applied for

- Targeted interventions directed at reducing the levels of circulating succinate in a subject, and kits and method for determining effectiveness of said interventions
- Método de predicción de respuesta a tratamientos con cirugía bariátrica en diabetes mellitus tipo 2

PCTs presented

- Mejora de la eficacia del trasplante autólogo de células madre derivadas de tejido adiposo en pacientes con enfermedad de Crohn.

Clinical guidelines and consensus documents

- Scientific evidence on the links between periodontal diseases and diabetes: Consensus report and guidelines of the joint workshop on periodontal diseases and diabetes by the International Diabetes Federation and the European Federation of Periodontology. Sanz M, Ceriello A, Buysschaert M, Chapple I, Demmer RT, et al. *J Clin Periodontol.* 2018 45:138-149.
- Guía rápida ISCI (Infusión Subcutánea Continua de Insulina). Grupo de Trabajo de Tecnologías Aplicadas a la Diabetes, Sociedad Española de Diabetes 2018.
- Documento de abordaje integral de la diabetes tipo 2. Grupo de trabajo de Diabetes de la Sociedad Española de Endocrinología y Nutrición (SEEN) 2018.

CIBERDEM Groups. Publications

<i>Group leader</i>	<i>Publ.</i>	<i>Q1</i>	<i>D1</i>	<i>Institution / Centre</i>	<i>Province</i>
 Álvarez Escola, Carmen	4	4	3	Universidad Complutense de Madrid - Facultad de Farmacia	Madrid
 Álvarez García, Elvira	4	4	0	Universidad Complutense de Madrid - Facultad de Medicina	Madrid
 Balsinde Rodríguez, Jesús	4	3	0	Agencia Estatal Consejo Superior de Investigaciones Científicas - Instituto de Biología y Genética Molecular	Valladolid
 Benito de las Heras, Manuel Román	4	2	0	Universidad Complutense de Madrid - Facultad de Farmacia	Madrid
 Blanco Vaca, Francisco	15	9	3	Instituto de Investigación del Hospital de la Santa Creu i Sant Pau	Barcelona
 Bondía Company, Jorge	10	4	1	Universidad Politécnica de Valencia - Instituto Universitario de Automática e Informática Industrial	Valencia
 Bosch Tubert, Fátima	3	3	2	Universidad Autónoma de Barcelona - Centro de Biotecnología animal y Terapia Genética	Barcelona
 Burks, Deborah	3	3	2	Fundación Centro de Investigación Príncipe Felipe	Valencia
 Calle Pascual, Alfonso Luis	5	2	1	Servicio Madrileño de Salud - Hospital Clínico San Carlos	Madrid
 Castaño González, Luis	20	8	2	Asociación Instituto de Investigación Sanitaria de Biocruces - Hospital Universitario Cruces	Vizcaya
 Correig Blanchart, Francesc Xavier	20	16	6	Fundación Instituto de Investigación Sanitaria Pere Virgili - Universidad Rovira i Virgili	Tarragona
 Egido de los Ríos, Jesús	14	14	3	Instituto de Investigación Sanitaria Fundación Jiménez Díaz	Madrid
 Escobar Morreale, Héctor Francisco	12	5	2	Servicio Madrileño de Salud - Hospital Ramón y Cajal	Madrid
 Ferrer Marrades, Jorge	3	3	1	Fundación Centro de Regulación Genómica	Barcelona
 Guinovart Cirera, Joan Josep	3	2	0	Fundación privada Instituto de Recerca Biomédica (IRB-Barcelona)	Barcelona
 Ibáñez Toda, Lourdes	10	7	2	Fundación para la Investigación y Docencia Sant Joan de Deu - Hospital Sant Joan de Deu	Barcelona
 Martín Bermudo, Francisco	8	8	4	Universidad Pablo de Olavide - Centro Andaluz de Biología del Desarrollo	Sevilla
 Martínez Valverde, Ángela María	11	9	5	Agencia Estatal Consejo Superior de Investigaciones Científicas - Instituto de Investigaciones Biomédicas Alberto Sols	Madrid
 Masana Marín, Luis	19	16	3	Fundación Instituto de Investigación Sanitaria Pere Virgili - Universidad Rovira i Virgili	Tarragona

<i>Group leader</i>	<i>Publ.</i>	<i>Q1</i>	<i>D1</i>	<i>Institution / Centre</i>	<i>Province</i>
 Mauricio Puente, Diego	31	17	5	Instituto de Investigación del Hospital de la Santa Creu i Sant Pau	Barcelona
 Montanya Mías, Eduard	12	8	3	Fundación IDIBELL - Hospital Universitario de Bellvitge	Barcelona
 Nadal Navajas, Ángel	6	3	0	Universidad Miguel Hernández - Instituto de Bioingeniería	Alicante
 Novials Sardá, Anna María	30	17	6	Instituto de Investigaciones Biomédicas August Pi i Sunyer - Centro Esther Koplowitz	Barcelona
 Real Collado, José Tomás ¹	14	11	2	Fundación para la Investigación del Hospital Clínico de la Comunidad Valenciana (Fundación INCLIVA) - Instituto de Investigación Sanitaria INCLIVA	Valencia
 Rojo Martínez, Gemma	10	9	3	Fundación Pública Andaluza para la Investigación de Málaga en Biomedicina y Salud (FIMABIS) - Hospital Regional Universitario Carlos Haya	Málaga
 Simó Canonge, Rafael	25	14	5	Fundación Hospital Universitario Vall d'Hebron - Institut de Recerca (VHIR) - Hospital Vall d'Hebron	Barcelona
 Vallejo Fernández de la Reguera, Mario	1	1	1	Agencia Estatal Consejo Superior de Investigaciones Científicas - Instituto de Investigaciones Biomédicas Alberto Sols	Madrid
 Vázquez Carrera, Manuel	9	6	3	Universidad de Barcelona - Facultad de Farmacia	Barcelona
 Vendrell Ortega, Joan Josep	8	8	3	Fundación Instituto de Investigación Sanitaria Pere Virgili - Hospital Universitario Juan XXIII	Tarragona
 Vidal Cortada, Josep	18	15	5	Instituto de Investigaciones Biomédicas August Pi i Sunyer	Barcelona
 Zorzano Olarte, Antonio	9	9	6	Fundación privada Instituto de Recerca Biomédica (IRB-Barcelona)	Barcelona

¹Replaced Juan Francisco Ascaso in 2018

A microscopic view of various cells, including red blood cells and white blood cells, against a blue and purple background. The cells are shown in cross-section, revealing their internal structures. The background is a gradient of blue and purple, with a dark blue vertical strip on the left side. The text "Liver and Digestive Disease" is centered in the upper right quadrant.

Liver and Digestive Disease



Scientific Director's Presentation

Jordi Bruix Tudó

In 2018 the constant approach of high-level scientific activity continued with a large number of publications in journals with great impact. In many cases the results obtained had a direct impact on patients' health care. This translation displays the consolidation of the CIBEREHD as a forceful research structure with significant benefit for the community in terms of public health. All of this was done in spite of the budget difficulties and the limitations for hiring new researchers consolidating them.

The annual report sets forth the most relevant results in the different Programmes of the CIBEREHD and means one can appreciate the gradual increase in cooperative studies with international impact in all the programmes both in Spain and abroad. One interesting point is that international collaboration work is often led by researchers from the CIBEREHD, that translates in international recognition.

Research has been relevant in basic aspects but, as has been stressed, this was particularly significant in translation to patients affected by liver and digestive diseases. Different clinical

practice guides based on scientific evidence have been published as well as consensus documents in which the criteria and methods to be used in both basic and clinical research are defined.

Lastly, the CIBEREHD is backed by shared platforms which have played a relevant role on both the training level and as regards furthering extremely competitive research.

Scientific Management and the Management Committee as a whole continue to implement the four-year action plan, but a redesigning process is under way to tackle the evolutionary changes that are instrumental for the further expansion and success of the scientific activity. An increase in generation renewal and gender balancing has been attained on all levels. We continue to identify young researchers with scientific career ambitions in order to guarantee maintenance of research culture in Biomedicine. In this respect, three new high-level teams led by female researchers joined us in 2018, and their contribution has been significant right from the start.

Scientific Programmes

Liver injury mechanisms / evolution into advanced cirrhosis and transplantation

Coordinator:
Rafael Bañares Cañizares

The work done by Programme 1 in 2018 has gone on developing in the strategic approach set by the CIBEREHD. We should highlight the wide range of its research work covering practically all liver diseases, excluding liver cancer and viral hepatitis.

As part of the priority strategic lines we should stress the promotion of international relations; as occurred in earlier years, collaboration schemes with groups from other countries have been encouraged in the setting of different consortiums and European projects, which displays the programme's internationalisation capacity. With regard to this matter, some of the groups from the programme have led a proposal for a European project focussing on liver disease through fat accumulation. In the same fund-raising line, the groups in the programme were able to maintain their own lines for project financing and for recruiting human resources in competitive calls, which enables the critical mass of the programme to be maintained.

From the standpoint of cooperation between groups in the programme we have gone on in the traditional approach of carrying out cooperative studies in the clinical area. One significant measure has nevertheless been the generation of a network of basic

researchers through specific strategic actions of the CIBEREHD. To be more explicit, the development of a mouse model with humanised liver is enabling different experimental approaches based on that model; the network established for research into the role of extracellular vesicles has furthermore obtained some relevant scientific results which are likely to be published soon. It should similarly be highlighted that after creating a "map of interactions" as mentioned in previous reports, some relevant cooperation schemes are taking root between basic groups. Likewise, the frequent presence of collaborative studies between basic and clinical scientists has been kept up and, as occurred in previous years, some of the publications with greatest impact are precisely a result of these interactions.

As regards scientific results, production has continued to maintain a large proportion of publications in the first decile in this speciality, as well as the generation of clinical practice guidelines, as a final expression of the capacity for translation of research work to the patient. Without wishing to belittle the importance of all the scientific results of the programme at all, two major cooperative clinical studies on patients with cirrhosis complications should be stressed: one has enabled a more appropriate outline of the risk profile of patients with bleeding from esophageal varices with a view to urgent treatment with TIPS, and one characterising the prognostic impact of the presence of portosystemic shunts in patients with cirrhosis. In the field of transplantation it has been possible to establish the value of antiviral treatment of hepatitis C in the post-transplant stage and show that elastographic monitoring proves to be of great value. Once again, these studies reflect not only great scientific value but also the capacity for translation to clinical practice.

On the organisational level we should not fail to mention the application by the Management of the CIBEREHD of a strategic approach to redirect the scientific work of the groups more

Gastrointestinal physiopathology: inflammatory bowel disease and motility disorders

Coordinator:
Pere Clavé Civit

Clinical-scientific relevance of the subjects in the programme

This programme includes digestive diseases of great prevalence and impact on the public's health and quality of the life, structured in three overall lines: a) Oesophageal-gastroduodenal pathology; b) Inflammatory bowel syndrome; and c) Neuro-gastroenterology, alterations of digestive motility and functional disorders. Knowledge of the physiopathology, diagnosis, epidemiology, prevention and treatment of these diseases is furthered by means of cooperative and multidisciplinary research done by researchers in clinical, basic and epidemiological approaches. At the same time, a line of cooperation was created between basic researchers in the area by means of a strategic IntraCIBEREHD action which involves most of the groups. During 2018 the merger of two research groups was consolidated, one group joined, Group Leaders were renewed and one European H2020 (Cost-Action) measure was taken on with the leadership of the CIBEREHD and co-financed by the European Society for Swallowing Disorders.

a) Oesophageal-gastro-duodenal pathology.

The innovations in 2018 in this area focus on the development of pharmacological strategies, the publication of different guidelines and consensus on the strategies for eradicating infection by *helicobacter pylorii* in cases of resistance to first-line treatments. We

traditionally engaged in research into hepatitis C, taking into account the great effectiveness of antiviral therapy which has fortunately enabled most of the patients to be cured.

should also highlight the publications led by CIBEREHD researchers of the studies from the European Registry on the management of *Helicobacter pylori* infection (Hp-EuReg) enabling starting the implementation of a map of response to treatment and resistances with a European perspective. The study of the adverse effects of non-steroidal anti-inflammatory drugs on peptic disease and its complications continues to take a relevant place in this line of research, as well as new studies on oesophageal-gastric cancer.

b) Inflammatory Bowel Disease.

This continues to be the most productive line in this area and the one to which most human and material resources are allocated. Research is aimed at the primary causes of immune dysfunction and recognition of genetic and environmental determinants conditioning the phenotypic development of each IBD, the development and assessment of new diagnostic methods and for monitoring the disease, as well as developing new treatments. The results for 2018 are very relevant as regards the treatment of perianal Crohn's disease with stem cells, the publication of many studies and clinical trials comparing the effectiveness and safety of different immune-modulation treatments in different phases of the disease (active/remission) and the appearance of studies which evaluate the results of surgical treatment in refractory forms. One should also mention the evaluation of the role of different components of the innate immune system in the physiopathology and therapeutic potential of IBD. The usefulness of enterography by magnetic resonance has been appraised in different studies, the utility of calprotectin in IBD stools has been re-evaluated by means of a national consensus and different consensus have been reached in the evaluation of different optimum endpoints for clinical trials on these patients. This line also includes research projects connected with celiac disease and other high-prevalence diarrheic syndromes about which little is known such as the ones arising post-cholecystectomy.

c) Neuro-gastroenterology, alterations of digestive motility and functional digestive disorders.

2018 was a significant year for the study of disorders such as IBS, with a prevalence of 15% of the general public, or such as Oropharyngeal Dysphagia (OD), which affects 50% of the patients who have suffered from a stroke, neurodegenerative diseases and frail elderly persons. The 2018 studies include the assessment of the effect of different diet and nutrition elements in the oropharyngeal and gastrointestinal function, especially the biological and sensorial responses to intake, and the role of exclusion diets in IBS. Post-infection IBS and the role of probiotics occupied

a further significant group of studies, as well as the analysis of the epithelium dysfunction in IBS-D from a basic standpoint. Strategic action has continued to contribute to the dynamics of basic researchers in this area. As regards oropharyngeal motility, both clinical and basic studies address the development of active pharmacological treatments with oropharyngeal receptors TRPV1, TRPA1 and TRPM8 agonists, and of compensatory strategies known as "Minimal-Massive Intervention" for handling oropharyngeal dysphagia. Apart from this the prevalence, risk factors and clinical and economic impact of post-ictus dysphagia have been described.

Epidemiology, prevention and treatment of infection by the hepatitis virus

Coordinator:
Xavier Fornas Bernhardt

In 2018 the cooperation work done between groups in the programme was consolidated for the analysis of the repercussion of treatment with direct-acting antivirals in the natural history of hepatitis C.

This cooperation work is backed by the number and quality of the articles resulting from national and international multi-centre studies by members of the CIBEREHD. Some of these which deserve mention are: 1) International study for evaluating the effectiveness and safety of treatment with sofosbuvir and velpatasvir (with and without ribavirin) in patients with cirrhosis and genotype 3 (*Gastroenterology*. 2018; 155:1120-1127); 2) Prospective evaluation of the effectiveness and safety of oral regimens against HCV in patients with liver transplants co-infected with HIV (*Am J Transplant*. 2018; 18:2513-2522); 3) International studies for evaluating the effectiveness of different antiviral patterns in patients with liver or kidney transplants infected by HCV (*Hepatology*. 2018; 68:1298-1307, *J Hepatol* 2018;69:603-607); 4) impact of an antiviral treatment of HCV in patients with liver transplants from both the standpoint of the change in the composition in the waiting list (*J Hepatol*. 2018; 69:11-17) and in the natural history

of post-transplant recurrence (*Hepatology* 2018; 67:1683-1694); 5) the impact of antiviral treatment on the different comorbidities associated with infection by HCV (*J Hepatol*. 2018; 68:940-948) including cryoglobulinemia (*Gastroenterology* 2018; 155:311-315).

All these studies have been published in first decile journals and led by CIBEREHD researchers.

Other clinical areas in which there have been relevant progress and publications of interest are 1) Hepatitis A, with the description of outbreaks of this disease in the group of men who have sex with men (MSM), something which has become a public health problem in particular in certain European cities (*Liver Int*. 2018; 38:588-593); 2) Hepatitis B, where a European collaborative study has analysed the long-term impact with nucleos(t)ide analogue treatments in patients with "e minus" hepatitis B, proving that survival time in patients without cirrhosis is comparable to that of the general population (*J Hepatol*. 2018; 68:1129-113). An exhaustive analysis has been made of the natural history of the infection in "inactive carrier" or "grey zone" patients, coming to the conclusion that the great majority of these patients (if they are of Caucasian origin) could avoid indefinite treatment with antivirals; 3) in the field of fast diagnosis we should highlight the development and validation of a test for the diagnosis of hepatitis C which would be easy to apply in areas where a microbiology laboratory is not available (*Gut* 2018;67:2017-2024). This is of vital importance for the implementation of programmes for micro-elimination of the virus.

In translational research we must highlight our participation in an international consortium which has analysed the resistance patterns in

patients with hepatitis C treated with direct-acting antivirals (*Gastroenterology* 2018; 154:976-988). In this same line of work there has been an in vitro assessment of the resistance of certain strains of virus C to lethal mutagenesis. This could explain the persistence of the virus in complex clinical situations such as after diverse cycles of failed treatment (*Virology* 2018;523:100-109). Lastly, there has also been progress in the genomic characterisation of the delta virus, taking advantage of mass sequencing techniques (*Virus Res.* 2018 Jan 2; 243:52-59).

As done every year, it is important to underline the participation of researchers from the

programme in the preparation of Clinical Guidelines (Guidelines on treatment of hepatitis C virus infection. Spanish Association for the Study of the Liver, Gastroenterol Hepatol. 2018;41:597-608 and EASL Recommendations on Treatment of Hepatitis C 2018 <https://doi.org/10.1016/j.jhep.2018.03.026>) In the teaching field, different researchers from the programme have taken part in the postgraduate course of the *Asociación Española y Europea para el Estudio del Hígado* (2018) and have been organisers of international-scale events (International Hepatitis Meeting, Barcelona 2018).

Hepatic and Digestive Oncology

Coordinator:
Bruno Sangro Gómez-Acebo

Hepatobiliopancreatic and digestive system cancer is a frequent cause of death in the general population, represents a great care burden at hospitals and health centres, and very high healthcare and pharmaceutical costs. For this reason the CIBEREHD has a programme on this pathology. But tackling this goes beyond the programme itself and involves other CIBEREHD programmes in transversal lines of work focussing on partial aspects of the problem. Knowledge of this is contributed by molecular biology, genetics, immunology, epidemiology or clinical intervention.

Researchers from the Programme have taken part in drawing up the guidelines for handling for the management of hepatocellular carcinoma prepared at the request of the European Association for the Study of the Liver and the European Society for Medical Oncology. They have also taken part in defining a new international system for classifying the in-depth invasion of colorectal polyps.

In liver cancer they have helped to define how the risk of developing the more aggressive forms of hepatocellular carcinoma is temporarily increased in a percentage of patients after eradicating the infection by hepatitis virus C with direct-acting antivirals. The debate in this field has not been settled but the work done and the research lines undertaken from these clinical observations will enable progress in knowledge to be made.

From the therapeutic stance the first studies have been started in a line of work intended to identify the mechanisms of hepatocellular carcinoma's resistance to immunotherapy agents based on blocking checkpoints and developing combinations increasing their effectiveness. In this respect it has been shown in animal models that epigenetic modulators such as Belinostat can synergise with CTLA-4 and PD-1inhibitors; and the TGFbeta pathway has been identified as a probable fundamental aspect of resistance to these drugs. In large-scale international studies the groups from the Programme have furthermore contributed to defining the utility of new drugs in liver cancer.

In the field of bowel cancer progress has been made in learning the performance of hereditary risk markers for developing digestive cancer. These enable individuals at risk to be identified for them to participate in follow-up plans enabling the disease to be detected in early stages in which potentially curative treatment can be applied. The role of advanced dysplastic alterations in the risk of metachronous colon cancer has been reassessed in patients with small polyps.

Lastly, research work in cholangiocarcinoma has been consolidated, with the identification of circulating metabolites which could act as markers for the early diagnosis of the disease in patients with primary sclerosing cholangitis, a pre-cancerigenous entity, and for the distinction between the histology of cholangiocarcinoma or hepatocarcinoma in small-sized nodules of cirrhotic livers.

Training Programme

Coordinator: *Xavier Forns Bernhardt*

One of the CIBEREHD's aims is to promote the training of our researchers, (postdoctorate, predoctorate, nurses and technical staff) to raise the level of research and facilitate interaction between the different groups. These tasks are coordinated through the Training Plan as part of the Annual Action Plan.

The Training Plan of the CIBER for Liver and Digestive Diseases is implemented in the following measures:

- Training stays at CIBEREHD centres.
- Short training stays in Spain or abroad (maximum 8 weeks and exceptionally up to 3 months).
- Intramural visiting teacher programmes.
- Holding training courses or activities considered to be of interest for the CIBEREHD.
- Promoting scientific activities arranged by members of the CIBEREHD (sponsoring and financing seminars, symposia, courses for postgraduates), cooperating with activities for training scientific associations and virtual training activities given through the web.

In 2018, a total number of 28 grants were awarded to our researchers for different activities covered by the Training Plan Programme. The beneficiaries of these funds were 8 attached and 18 contracted members. The activities financed were 2 short stays abroad, 3 short stays in Spain for specific training and grants for attending 17 training courses in Spain and 6 courses abroad.

Some of these activities that could be highlighted are training stays at International and National Centres:

- Isabel Nerea from the group led by Dr. Francés received funding for a short stay at Dr. Jordi Gracia's laboratory (PI of the Dr. García Pagán group).
- Dr. Sopena, from Dr. Rafael Esteban's group, received a grant for a short stay at the Leipzig University Laboratory.

- Dr. Sofia Pérez del Pulgar from the group led by Dr. Xavier Forns received funding for a short stay at Dr Mala Maini's Laboratory at the University College of London.
- Dr. David Fernández Ramos and Dr. Marta María Varela Rey, from Dr. José María Mato's group, were given a grant for a short stay at the Pathology and Molecular and Cellular Therapy Department of the Instituto de Biomedicina de Valencia under Dr. Marta Casado.

We also co-financed or guaranteed the following Courses arranged by members of our Centre:

- *Jornadas de Otoño* of the AEEH 2018 – Malaga.
- *VI Curso de Gastroenterología y Hepatología* of Alicante General University Hospital.
- *Jornada de Disfagia* organised by Dr. Pere Clavé.
- Scientific course as part of the UEG WEEK organised by Dr. P Gisbert.
- 101st course of the Escuela de Patología Digestiva of the Hospital de Sant Pau.
- *The Jornada de Virología* organised by the Institut d'Estudis Catalans and the Societat Catalana de Biologia, with the participation of several speakers from the CIBER.
- *Congreso Nacional de Virología*.
- *Jornada de enfermedades hepáticas minoritarias*.

Special mention should be given to the Liver Seminars, an activity held under the auspices of and co-financed by the CIBEREHD, coordinated by Dr. R. Bañares Dr. and J. Gracia. This is a monthly lecture given by a speaker, usually foreign, of known prestige, given alternately at the centres of IDIBAPS (Barcelona) or the Hospital Gregorio Marañón (Madrid) simultaneously broadcasted to the other centre and open to the researchers. On the same day meetings of the expert with interested

researchers are also scheduled. This activity was started in September 2017 and, in view of its success in 2018, its financing was decided to be extended to 2019.

Strategic actions

In 2018 no strategic action was granted but a call was issued for new and emerging researchers. The researchers awarded these were:

New:

Execution period 2 years. The amount of the aid is 30,000 €, spread over two yearly payments.

Anabel Fernández Iglesias. Project: "Capillarization of the hepatic sinusoidal endothelium. Orchestration by miRNAs".

Jesús Cosín. Project: "Relevance of epithelial SUCRN1 in inflammatory bowel disease".

Through its Training Plan the CIBEREHD also sponsored the Postgraduate Course of the Asociación Española para el Estudio del Hígado (AEEH) and that of the Asociación Española de Gastroenterología (AEG), which are held coinciding with the annual congress of both associations.

Emerging:

Execution period 2 years. The amount of the grant is 40,000 €, spread over two yearly payments.

Marta Varela. Project: "Long Non-Coding RNAs signature as a clinically relevant diagnostic and prognostic tool in liver fibrosis".

Ana Blas. Project: "Identification of new pharmacological targets for hepatic fibrosis: regulation of signalling routes Jak-STAT1 and Jak-STAT3"

Platforms

Bioinformatics Platform

Coordinator:
Juanjo Lozano Salvatella

The Bioinformatics platform is taking an active part in the operation of this CIBER, as can be seen by the 15 publications issued as a result of its support during 2018. The most relevant publication is connected with the mechanism for action of immunosuppressants in the field of liver transplants, in which a project from the "Marató", led by our group, as part of an international collaboration scheme, was published:

- *Evidence of Chronic Allograft Injury in Liver Biopsies From Long-term Pediatric Recipients of Liver Transplants.* Feng S, Bucuvalas JC, Demetris AJ, Burrell BE, Spain KM, Kanaparthi S, Magee JC, Ikle D, Lesniak A, Lozano JJ, Alonso EM, Bray RA, Bridges NE, Doo E, Gebel HM, Gupta NA, Himes RW, Jackson AM, Lobritto SJ, Mazariegos GV, Ng VL, Rand EB, Sherker AH, Sundaram S, Turmelle YP, Sanchez-Fueyo. *Gastroenterology.* 2018 Dec;155(6):1.

Cooperation with groups from the CIBEREHD continues to generate some highly relevant publications.

Liver disease inflammation area:

- *Ductular reaction cells display an inflammatory profile and recruit*

neutrophils in alcoholic hepatitis. Aguilar-Bravo B, Rodrigo-Torres D, Ariño S, Coll M, Pose E, Blaya D, Graupera I, Perea L, Vallverdú J, Rubio-Tomás T, Dubuquoy L, Armengol C, Lo Nigro A, Stärkel P, Mathurin P, Bataller R, Caballería J, Lozano JJ, Ginès P, Sancho-Bru P. *Hepatology* 2018. doi: 10.1002/hep.30472.

- *Generation of Hepatic Stellate Cells from Human Pluripotent Stem Cells Enables In Vitro Modeling of Liver Fibrosis.* Coll

M, Perea L, Boon R, Leite SB, Vallverdú J, Mannaerts I, Smout A, El Taghdouini A, Blaya D, Rodrigo-Torres D, Graupera I, Aguilar-Bravo B, Chesne C, Najimi M, Sokal E, Lozano JJ, van Grunsven LA, Verfaillie CM, Sancho-Bru P. *Cell.Stem.Cell* 2018 Jul 5;23(1):101-113.

Our group continues to collaborate in new projects with great recognition for its work, since two new FIS were financed (PI18/00383, PI18/01125) this year with CIBER centres.

Chronic Hepatitis B platform. CIBERHEP

Coordinator:
David Tabernero Caellas

CIBERHEP chronic hepatitis B platform is a cooperation scheme between the CIBER and the Asociación Española para el Estudio del Hígado (AEEH). At the present time this is the main database for patients being treated for chronic hepatitis B in Spain, focussing mainly on the

follow-up of patients in antiviral treatment with entecavir (ETV) and tenofovir (TDF). 27 centres from 9 different autonomous communities (regional administrative areas) continue to take part in this and 1516 patients have been registered, with data from a total number of 15,056 visits available for analysis. In 2018 we continued with the review of patients already registered in the database, a process which was started in 2017, in which visits with incomplete or improperly compiled data were removed. This has entailed little activity this year. At the present time this platform's objectives are being reviewed to decide on its possible future reorientation.

e-CATCH

Coordinator:
Jordi Bruix Tudó

The e-CATCH platform has worked in two areas:

The service for advice on diagnosis and treatment of liver cancer was kept up with a limited number of consultations (average of 1 per month).

The growth in its activity was due to using the platform as an instrument for centralised assessment of images in the context of clinical trials promoted by the researchers.

This allows a blind evaluation of patients' evolution and a validation of what was reported in descriptive studies of cohorts in which a uniform reading is essential.

Hepa-C

Coordinator:
Xavier Forn Bernhardt

In 2018, as a result of the large amount of work done in previous years, Hepa-C multi-centre registry has included a much lower number of new patients. As was understandable, the

production resulting from this registry has dropped considerably. We should stress the article included below and two studies which will come out in 2019 and which appraise new guidelines for antivirals.

- Ampuero J, Jimeno C, Quiles R, Rosales JM, et al. *Impact of comorbidities on patient outcomes after interferon-free therapy-induced viral eradication in hepatitis C* *Hepatology*. 2018 May;68(5):940-948.

Registry of Vascular Liver Diseases. REHEVASC

Coordinator:
Juan Carlos García-Pagán

The REHEVASC platform has been running since 20 September 2011. This is a Registry of patients diagnosed with 4 vascular diseases of the liver in Spain of the type considered to be "Rare Diseases" with a prevalence under 5/10,000 inhabitants. It covers diseases with non-cirrhotic portal hypertension (NCPH):

- Non-cirrhotic non-tumoral portal thrombosis (PVT)
- Idiopathic portal hypertension (IPH)
- Budd-Chiari syndrome (BCS)
- Congenital hepatic fibrosis (CHF)

Its main aim is to provide a "uniform" diagnosis and treatment for these diseases as well as to improve this diagnosis and treatment of these diseases and be able to perform collaborative studies enabling furthering knowledge about these.

In 2018, the following proportions of new patients were diagnosed and registered:

- PVT: 25 patients, obtaining a final register of 340 patients in 2018.
- IPH: 19 patients, obtaining a final register of 143 patients in 2018.

- SBC: 8 patients, obtaining a final register of 88 patients in 2018.
- FHC: No new patients have been diagnosed, with a final register of 11 patients in 2018.

At the present time there are 20 reference hospitals nationwide involved in attempting to diagnose this type of patients:

- Hospital Universitario y Politécnico La Fe
- Hospital Virgen de la Salud, Toledo
- Hospital Universitario Puerta de Hierro
- Hospital Universitario Ramón y Cajal
- Clínica Universidad de Navarra
- Hospital Clínic de Barcelona
- Hospital Santa Creu i Sant Pau
- Hospital Universitario Gregorio Marañón
- Hospital Universitario Arnau de Vilanova
- Hospital Universitario Central de Asturias (HUCA)
- Hospital Universitario de Canarias
- Hospital Universitario Marqués de Valdecilla
- Hospital Universitario San Cecilio
- Hospital Universitario Son Espases
- Instituto universitario Dexeus
- Complejo Hospitalario Universitario de Albacete
- Hospital del Mar Hospital del Tajo, Aranjuez
- Hospital Germans Trias i Pujol
- Hospital Parc Taulí, Sabadell
- Hospital Broggi (cooperation with HCB, referrals of patients for registering)

Scientific Production

Publications

No. of publications in 2018

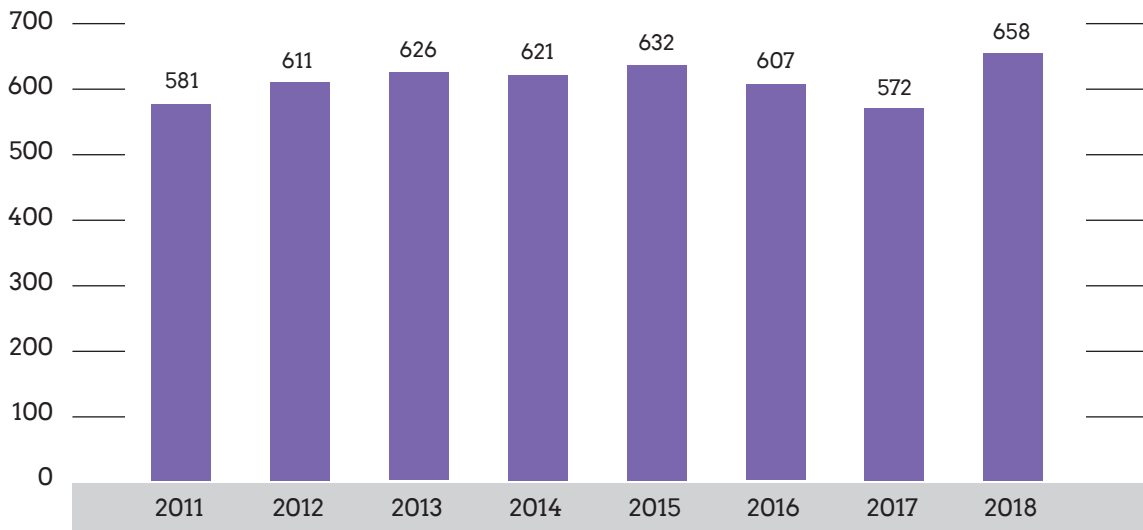
TOTALS	658
Q1	408
D1	194

Collaborative Publications

CIBEREHD	214
CIBER*	131

*Over several thematic areas

Evolution of publications



10 most relevant publications of the CIBEREHD in 2018 by impact factor

IF	Publication
32,6210	<i>Systemic messenger RNA as an etiological treatment for acute intermittent porphyria. Nat Med. 2018 Dec;24(12):1899-1909</i>
23,2900	<i>Generation of Hepatic Stellate Cells from Human Pluripotent Stem Cells Enables In Vitro Modelling of Liver Fibrosis. Cell Stem Cell. 2018 Jul 5;23(1):101-113.e7.</i>
20,7730	<i>Mechanisms of Damage to the Gastrointestinal Tract from Nonsteroidal Anti-Inflammatory Drugs. Gastroenterology. 2018 Feb;154(3):500-514.</i>
20,7730	<i>Long-term Efficacy and Safety of Stem Cell Therapy (Cx601) for Complex Perianal Fistulas in Patients with Crohn's Disease. Gastroenterology. 2018 Apr;154(5):1334-1342.e4.</i>
20,7730	<i>Female-Specific Association Between Variants on Chromosome 9 and Self-Reported Diagnosis of Irritable Bowel Syndrome. Gastroenterology. 2018 Jul;155(1):168-179.</i>
20,7730	<i>Fibrosis Severity as a Determinant of Cause-Specific Mortality in Patients with Advanced Non-alcoholic Fatty Liver Disease: A Multi-National Cohort Study. Gastroenterology. 2018 Aug;155(2):443-457.e17</i>
20,7730	<i>Effects of Prebiotics vs a Diet Low in FODMAPs in Patients with Functional Gut Disorders. Gastroenterology. 2018 Oct;155(4):1004-1007.</i>
20,7730	<i>Simvastatin Prevents Progression of Acute on Chronic Liver Failure in Rats with Cirrhosis and Portal Hypertension. Gastroenterology. 2018 Nov;155(5):1564-1577</i>
20,7730	<i>Efficacy and Safety of Budesonide, vs Mesalazine or Placebo, as Induction Therapy for Lymphocytic Colitis. Gastroenterology. 2018 Dec;155(6):1795-1804.e3</i>
17,0160	<i>Molecular predictors of prevention of recurrence in HCC with sorafenib as adjuvant treatment and prognostic factors in the phase 3 STORM trial. Gut. 2018 Aug 14. pii: gutjnl-2018-316408.</i>

Patents owned by CIBER

Applied for.

- *NUPR1 Inhibition for Treating Cancer.* EP18305672.0
- *Derivados de 4-fenildihidropiridina para el tratamiento y/o prevención de una infección o enfermedad causada por Helicobacter.* P201831019
- *Derivados de ácido ursodecoxílico para el tratamiento de enfermedades hepáticas poliquísticas.* PCT/ES2018/070840
- *Treatment of fibrosis and inhibition of fibrosis in non-alcoholic fatty liver disease patients.* US 16/182767
- *Methods for diagnosing and treating acute or chronic liver, kidney or lung disease.*

EP18382271.7

- *Method of Treating Colorectal Cancer.* US 16/022597
- *Method of Treating Advanced Colorectal Adenoma.* US 16/058940
- *Human Porphobilinogen Deaminase Derived Proteins and Polynucleotides And Uses Thereof.* WO2018/206125A1
- *Cepa de Bifidobacterium longum sub infantis y uso de la misma.* P201830961

Granted.

- *Predictive response biomarkers to corticosteroids.* EP17382246.1
- *In vitro method for identifying colorectal adenomas or colorectal cancer.* PCT/EP2017/080560
- *"Biomarkers for colorectal cancer".* EP17382267
- *Biomarkers for colorectal cancer.* EP 17382267.7

- *Use of ciclopirox as a modulator of the heme group biosynthesis and in the treatment of porphyrias and other diseases.* EP17382371.7
- *HepCom score.* RPI201799904462639
- *Computerized optical analysis methods of MR (magnetic resonance) images for quantifying or determining liver lesions.* JP2017-549070
- *Anti-CD5L antibody and uses thereof.* 300252564
- *A 3-protein signature to assess prognosis and therapeutic regimen in liver cancer.* 300257875
- *Human porphobilinogen deaminase derived proteins ad polynucleotides and uses thereof.* 2014030
- *Polynucleotides encoding prophobilinogen deaminase for the treatment of acute intermittent porphyria.* 2017005

Clinical guidelines

- *Asia-Pacific working group consensus on non-variceal upper gastrointestinal bleeding: an update 2018.*
- *Atenció a la disfàgia orofaríngia en els diversos àmbits del sistema de salut. Document de consens.*
- *Autologous haematopoietic stem cell transplantation (AHSCT) in severe Crohn's disease: A review on behalf of ECCO and EBMT*
- *Consensus document. Management of non-alcoholic fatty liver disease (NAFLD). Clinical practice guideline*
- *Document de posicionament diagnòstic i tractament de la síndrome de l'intestí irritable*
- *Documento de consenso. Manejo de la enfermedad hepática grasa no alcohólica (EHGNA). Guía de práctica clínica*
- *EASL Recommendations on Treatment of Hepatitis C 2018*
- *Executive summary of the 2018 KDIGO Hepatitis C in CKD Guideline: welcoming advances in evaluation and management*
- *GRADE CD Treatment Consensus Guidelines and Standards of Care in IBD*
- *Grupo de trabajo del Protocolo para el diagnóstico precoz de la enfermedad celíaca. Protocolo para el diagnóstico precoz de la enfermedad celíaca. Ministerio de Sanidad, Servicios Sociales e Igualdad. Servicio de Evaluación del Servicio Canario de la Salud (SESCS); 2018*
- *Guía AEEH-SEIMC de tratamiento de la infección por virus de la hepatitis C 2018*
- *Guidelines on treatment of hepatitis C virus infection. Spanish Association for the Study of the Liver (AEEH)*
- *Identification of Endpoints for Development of Antifibrosis Drugs for Treatment of Crohn's Disease*
- *International Liver Transplant Society Consensus Statement on immunosuppression in liver transplant recipients*
- *Management of acute liver failure. Clinical guideline from the Catalan Society of Digestology.*
- *Manejo de la anemia y ferropenia en la enfermedad inflamatoria intestinal*
- *Manejo de la insuficiencia hepática aguda grave. Guía Clínica*
- *Prevention and treatment of complications of selective internal radiation therapy: Expert guidance and systematic review*
- *Recomendaciones del Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa (GETECCU) sobre el uso de tiopurinas en la enfermedad inflamatoria intestinal.*
- *Recomendaciones del Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa (GETECCU) sobre la utilidad de la determinación de calprotectina fecal en la enfermedad inflamatoria intestinal*
- *Recomendaciones para la elaboración e interpretación de informes genéticos en enfermedad celíaca*
- *Recommendations for radioembolisation after liver surgery using yttrium-90 resin microspheres based on a survey of an international expert panel*
- *Recommendations for the treatment of hepatitis C virus infection in chronic kidney disease*
- *Recommendations of the Spanish Working Group in Crohn's Disease and Ulcerative Colitis (GETECCU) on the utility of the*





determination of faecal calprotectin in inflammatory bowel disease

- Recommendations of the Spanish Working Group on Crohn's Disease and Ulcerative Colitis (GETECCU) and the Association of Crohn's Disease and Ulcerative Colitis Patients (ACCU) in the management of psychological problems in Inflammatory Bowel Disease patients.
- Recommendations of the Spanish Working Group on Crohn's Disease and Ulcerative

Colitis (GETECCU) on the use of thiopurines in inflammatory bowel disease

- Recommendations of the Spanish Working Group on Crohn's Disease and Ulcerative Colitis (GETECCU) on the utility of the determination of faecal calprotectin in inflammatory bowel disease.
- Update on the management of *Helicobacter pylori* infection. Position paper from the Catalan Society of Digestology.

CIBEREHD Groups. Publications in 2018

Group leader	Publ.	Q1	D1	Institution / Centre	Province
 Martínez Albillos, Agustín	12	4	3	Universidad de Alcalá. Facultad de Medicina	Madrid
 Andrade Bellido, Raúl	15	8	7	Fund. Pública Andaluza para la Investigación de Málaga en Biomedicina y Salud (FIMABIS). Hospital Universitario Virgen de la Victoria	Málaga
 Armengol Niell, Carolina	16	10	5	Fundación Instituto de Investigación Germans Trias i Pujol. Hospital Germans Trias I Pujol	Barcelona
 Azpiroz Vidaur, Fernando	20	14	3	Fundación Hospital Universitario Vall d'Hebrón - Institut de Recerca (VHIR)	Barcelona
 Bañares Cañizares, Rafael	14	7	4	Servicio Madrileño de Salud. Hospital Gregorio Marañón	Madrid
 Berenguer Haym, Marina	25	18	9	Fundación para la Investigación del Hospital la Fe. Hospital Universitario de La Fe	Valencia
 Bruix Tudó, Jordi	29	22	14	Hospital Clínico y Provincial de Barcelona	Barcelona
 Bujanda Fdez. de Pierola, Luis	31	23	12	Asociación Instituto Biodonostia. Hospital Donostia	Guipúzcoa
 Calvet Calvo, Xavier	26	10	5	Corporación Sanitaria Parc Taulí	Barcelona
 Cascante Serratos, Marta	8	6	2	Universidad de Barcelona	Barcelona
 Castell Ripoll, Vicente	8	7	4	Fundación para la Investigación del Hospital la Fe	Valencia
 Castells Garangou, Antoni	42	30	14	Hospital Clínico y Provincial de Barcelona	Barcelona
 Clavé Civit, Pere	20	10	1	Fundación Privada Salud del Consorcio Sanitario del Maresme	Barcelona
 Domenech Morral, Eugeni	19	12	4	Fundación Instituto de Investigación Germans Trias i Pujol	Barcelona



<i>Group leader</i>	<i>Publ.</i>	<i>Q1</i>	<i>D1</i>	<i>Institution / Centre</i>	<i>Province</i>
 Esplugues Mota, Juan Vicente	14	14	8	Universidad de Valencia. Facultad de Medicina de Valencia	Valencia
 Esteban Mur, Juan Ignacio	24	10	2	Fundación Hospital Universitario Vall d'Hebrón - Institut de Recerca (VHIR)	Barcelona
 Esteban Mur, Rafael	26	13	7	Fundación Hospital Universitario Vall d'Hebrón - Institut de Recerca (VHIR)	Barcelona
 Esteve Comas, María	14	7	3	Fundación Mutua Terrassa	Barcelona
 Fabregat Romero, María Isabel	9	4	0	Fundación IDIBELL	Barcelona
 Fernández-Checa, José Carlos	21	15	9	Agencia Estatal Consejo Superior de Investigaciones Científicas. Instituto de Investigaciones Biomédicas de Barcelona	Barcelona
 Forns Bernhardt, Xavier	25	18	11	Hospital Clínico y Provincial de Barcelona	Barcelona
 Francés Guarinos, Rubén	16	8	6	Fund. para la Investigación Sanitaria y Biomédica de la Comunidad Valenciana (FISABIO). Hospital Gral .Univ. de Alicante	Alicante
 García-Marín, José Juan	11	7	2	Universidad de Salamanca	Salamanca
 García Pagán, Juan Carlos	25	16	14	Hospital Clínico y Provincial de Barcelona	Barcelona
 García-Samaniego Rey, Javier	6	4	2	Servicio Madrileño de Salud. Hospital La Paz	Madrid
 Genescà Ferrer, Joan	11	8	6	Fundación Hospital Universitario Vall d'Hebrón - Institut de Recerca (VHIR)	Barcelona
 Ginés Gibert, Pere	32	24	20	Hospital Clínico y Provincial de Barcelona	Barcelona
 Gómez Castilla, Jordi	7	3	0	Agencia Estatal Consejo Superior de Investigaciones Científicas. Instituto de Parasitología Y Biomedicina López Neyra	Granada
 González-Gallego, Javier	11	9	3	Universidad de León. Instituto Biomedicina de León	León
 Guarner Aguilar, Carlos	10	5	4	Instituto de Investigación del Hospital de la Santa Creu i Sant Pau	Barcelona
 Lanas Arbeola, Ángel	33	21	7	Instituto Aragonés de Ciencias de la Salud. Hospital Clínico Universitario Lozano Blesa	Zaragoza
 Martín Sanz, Paloma	5	4	0	Agencia Estatal Consejo Superior de Investigaciones Científicas. Instituto de Investigaciones Biomédicas Alberto Sols	Madrid
 Mata García, Manuel de la	19	11	7	Fundación para la Investigación Biomédica de Córdoba (FIBICO). Hospital Universitario Reina Sofía	Córdoba
 Mato de la Paz, José María	43	28	9	CIC BIOGUNE	Vizcaya
 Navasa Anadón, Miguel	33	18	9	Hospital Clínico y Provincial de Barcelona	Barcelona
 Panés Díaz, Julián	27	19	10	Hospital Clínico y Provincial de Barcelona	Barcelona

<i>Group leader</i>	<i>Publ.</i>	<i>Q1</i>	<i>D1</i>	<i>Institution / Centre</i>	<i>Province</i>
 Parés Darnaculleta, Albert	15	8	6	Hospital Clínico y Provincial de Barcelona	Barcelona
 Pastor Anglada, Marçal	3	3	1	Universidad de Barcelona Facultad de Biología. Universidad de Barcelona	Barcelona
 Pérez-Gisbert, Javier	36	20	10	Servicio Madrileño de Salud. Hospital Universitario La Princesa	Madrid
 Romero Gómez, Manuel	27	14	10	Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla. Hospital Virgen del Rocío	Sevilla
Salmerón, Francisco Javier (2)	5	4	2	Fundación para la Investigación Biosanitaria en Andalucía Oriental (FIBAO. Hospital Clínico San Cecilio	Granada
 Sánchez de Medina López Huertas, Fermín	20	17	6	Universidad de Granada. Facultad de Farmacia	Granada
 Sangro Gómez-Acebo, Bruno	20	13	8	Clínica Universidad de Navarra	Navarra

(1) PI replaced by Pedro Zapater Hernández

(2) Group deregistered in 2018

Associated clinical groups

<i>Group leader</i>	<i>Institution / Centre</i>	<i>Province</i>
 Beltrán Niclós, Ana Belén	Fundación para la Investigación del Hospital la Fe	Valencia
 Caballería Rovira, Llorenç	Universidad Autónoma de Barcelona	Barcelona
 Calleja Panero, Jose Luis	Universidad de Alcalá	Madrid
 Crespo García, Javier	Instituto de Investigación Marqués de Valdecilla	Cantabria
 Cubiella Fernández, Joaquín	Servicio Gallego de Salud	A Coruña
 García Monzón, Carmelo	Servicio Madrileño de Salud	Madrid
 Minguela Puras, Alfredo	Fundación para la Formación e Investigación Sanitarias de la Región de Murcia (FFIS)	Murcia
 Molina Infante, Javier	Fundación para la Formación y la Investigación de los Profesionales de la Salud (FUNDESALUD)	Cáceres
 Padillo Ruiz, Francisco Javier	Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla	Sevilla



**Rare
Diseases**



Scientific Director's Presentation

Pablo Lapunzina Badia

Dear friends,

This year we are again relying on our patients' involvement through the External Advisory Scientific Committee and the Patients' Advisory Board (CAP). This cooperation is unquestionably a great step forward which will enable us to improve our approach to research into rare diseases (RD), taking into account the needs of people affected and their families.

In 2018, CIBERER groups accomplished a large number of new results contributing to progress in the diagnosis of RD, the discovery of new genes, and treatment of RD with the development of orphan drugs and clinical trials in advanced therapies. Some aspects that are worthy of special mention are the Programme for Undiagnosed Rare Diseases (ENoD), and the 8 designations of orphan drugs for which the CIBERER acts as a sponsor (2 obtained this year). I would like to take this opportunity to stress the urgent need for getting the National Genomic Medicine Plan under way. This will mean that the results of our research can be directly passed on, implying an improvement in care, diagnosis and the search for therapies for rare diseases.

Apart from this the CIBERER has great international standing due to its participation in several European programmes and projects. The most important of these is undoubtedly the European Joint Programme on Rare Diseases (EJP-RD), the new European programme for improvement of research, use of data and

translation in rare disease. Special mention should also be given to the work done by the Orphanet España team, coordinated by CIBERER, an essential tool in the field of RD. We have furthermore worked on a complementary basis along with Orphanet to improve the access to information on RD continuing with the update of MAPER (RD research projects nationwide) and the incorporation of a map of research resources.

2018 is also a year of scientific restructuring. This year the new structure was approved, still being made up of 7 Research Programmes (PdI): the PdI on Genomic Medicine becomes Translational Genomic Medicine; the Mitochondrial Medicine PdI becomes part of the PdI on Inherited Metabolic and Mitochondrial Medicine; and the PdI of Neurological Diseases is created. All these changes have gone along with the relocation of some of the CIBERER'S research groups in them, consistent with the evolution in their lines of research. These changes have led to Pia Gallano and Cristina Fillat joining the Management Committee, respectively replacing Montserrat Milà and Francesc Palau.

I would lastly like to thank some of the precursors of this network centre for their work and dedication, as pioneers in their fields and great researchers, who have for personal or professional reasons ceased to lead some of the CIBERER units in 2018.

Scientific Programmes

Genetic Medicine

Coordinator:
Ángel Carracedo Álvarez

In 2018 the Genetic Medicine Programme continued to work on the implementation of genomic medicine and other omic applications for the diagnostic practice of hospitals. This will indeed be the last year in which the research programme will work under this name, changing to the new title of "Programme for Translational Genomic Medicine" now entirely focused on that objective and reduced to only 5 of the original 10 groups, with Miguel Ángel Medina's group from the Universidad de Málaga joining us to contribute all its experience in systems medicine.

2018 was also a prolific year for therapeutic research in this research programme. This is vouched for by some of the accomplishments made such as the designation of metformin as an orphan drug for treatment of Lafora disease by the FDA. The studies were undertaken by Pascual Sanz and José Serratosa's group. The CIBERER unit led by Luisa Botella at the Centro de Investigaciones Biológicas (CSIC) has obtained the designation of etamsylate as orphan drug for treatment of inherited haemorrhagic telangiectasia by the European Medicine Agency.

I should lastly highlight training activities such as the course on kidney pathology, organised on 29 October by the CIBERER led by María Teresa Caballero, and the II SCA36 International Symposium organised by Ángel Carracedo's group.

Inherited Metabolic Medicine

Coordinator:
Rafael Artuch Iriberry

The Research Programme (PdI) on Inherited Metabolic Medicine works on improving knowledge of inherited metabolic diseases and has achieved several relevant findings in 2018, such as:

- Obtaining promising results with the use of pharmacological chaperones for a type of methylmalonic aciduria, led by Belén Pérez.

doi.org/10.1016/j.bbadis.2017.11.024.

- Proof that LRR8 proteins are involved in Sertoli cell-only syndrome and megalencephalic leukoencephalopathy, led by Raúl Estévez. PMID:30076890.
- Description of a new pathogenic mechanism associated with phenylketonuria, led by Lourdes Ruiz Desviat. doi: 10.1371/journal.pgen.1007360.
- Description of the structural relationship of type IV collagen with Goodpasture's disease and Alport syndrome, led by Alberto Marina. doi.org/10.1107/S2052252518012459.
- Discovery of the implication of an amino acid transporter in age-related hearing loss, coordinated by Virginia Nunes and Manuel Palacín. doi.org/10.1073/pnas.1519959113.

- Starting up the National Registry of Mitochondrial Diseases, thanks to the donations of the Asociación de Enfermos de Patología Mitocondrial and the Fundación Ana Carolina Díez Mahou, led by Rafael Artuch and Miguel Ángel Martín Casanueva.

Some groups in the Pdl are taking part in the projects granted by the CIBERER in 2018 in the following calls:

- Translational Research Projects: highlighting the project on monitoring the treatment of patients with GLUT1 syndrome, which is coordinated by Luis González Gutiérrez-Solana and with the participation of several groups in the Pdl.
- Therapies: stressing the project on pharmacological chaperones for congenital glycosylation defect PMM2-CDG, coordinated by Belén Pérez with the participation of Vicente Rubio's group.

Lastly, the Pdl is prominent for its work in organising symposia and conferences in 2018. One example of this could be the Symposium on updating research into Rett's syndrome, arranged at the Hospital Sant Joan de Déu by Àngels García-Cazorla, Mar O'Callaghan, Judith Armstrong and Alfonso Oyarzábal. Another annual encounter organised by the Pdl is the symposium of the Group for Minority Diseases of the Adult coordinated by Rafael Artuch and Antònia Ribes, at which patients, researchers and healthcare staff from Barcelona met. The Pdl researchers also met those affected by CDG to present them with the results of their projects. Lastly, the multidisciplinary group for care for patients with mucopolysaccharidosis and other neurodegenerative diseases organised its event in Madrid, coordinated by Luis González Gutiérrez-Solana, with the participation of Mireia Del Toro and María Luz Couce.

Mitochondrial and Neuromuscular Medicine

Coordinator:
Francesc Palau Martínez

The 13 groups in the Programme have obtained some significant scientific results tackling mitochondrial diseases which affect the person's bioenergy balance. This was done through studying the genome-mitochondrial communication and the physiopathology and mechanisms of disease in cell models and iPSC, the promotion of translational research and therapeutic research from the development of animal models to the preclinical stage and biomarkers, especially in neuromuscular pathologies, such as:

- Review article on autoimmune encephalitis, inflammatory diseases of the brain which were completely unknown until 10 years ago, the authors being Josep Dalmau and Francesc Graus. Doi:10.1056/NEJMra1708712
- Different mitochondrial diseases converge in the same metabolic footprint: the oxidative damage of proteins, an article led

by José M. Cuezva with the participation of Ramón Martí and M.A. Martín. doi: 10.1016/j.freeradbiomed.2018.08.020.

- Identification of the muscular replacement by fat in a large group of those affected by oculopharyngeal muscular dystrophy, an article led by Jordi Díaz-Manera, from Isabel Illa's unit, in which researchers from the groups of Pía Gallano, M.A. Martín and Juan J. Vilchez have taken part. Doi: 10.1136/jnnp-2018-319578.

Some of the achievements in the therapeutic field that could be stressed are the participation of several groups from the programme in the Call for Therapies, and specifically 1 of the 4 financed projects being granted to the project for "Pharmacological screening and preclinical tests of Charcot-Marie-Tooth neuropathy due to mutations in *GDAP1*", coordinated by Francesc Palau and with the participation of the groups of José M. Cuezva, Jorguina Satrustegui and Juan Vilchez/ Teresa Sevilla.

As regards cooperation, special mention should go to the fact that in the Call for Work Groups issued this year, 3 of the 11 groups are coordinated by groups from the Pdl: "RedELA - Network for Research into Amyotrophic Lateral Sclerosis", "GRACIA - Genetic Research and Cerebral Integrative Action Circuits", and "Clinical

Registries in Rare Diseases”, and groups from the programme are participating in a further 5 groups.

The important work done by the groups in the Programme as regards Registries goes on: the Spanish Registry of Neuromuscular Diseases NMD-ES, Registry of Mitochondrial Diseases (in cooperation with AEPMI- Asociación de Enfermos de Patologías Mitocondriales and the Fundación Ana Carolina Díaz Mahou) and the McArdle Registry (EUROMAC).

In the field of transfer we should underline the fact that the EpiDisease spin-off, led by José Luis García, a researcher from Federico Pallardó’s group, has been considered as Best Bio Initiative

in Health by the BIOVAL Cluster. As well as this the HistShock project for a prognostic kit for sepsis and septic shock, also led by José Luis García, has been selected in the CaixaImpulse programme.

We should furthermore mention the fact that Francesc Palau has been appointed Chief Editor of the Orphanet Journal of Rare Diseases, the official journal of Orphanet, which is the benchmark European portal in rare diseases and orphan drugs, and that several CIBERER researchers (Francesc Cardellach, Joan-Lluís Vives Corrons and Rafael Artuch) are taking part on the editorial board of this journal.

Paediatric and Developmental Medicine

Coordinator:
Montserrat Milá Recasens

Fostering the development of genomic diagnosis tools for the diseases of interest for the programme:

- The transversal project for “Characterisation and contribution to genetic diagnosis of a cohort of patients with intellectual disabilities, autism and/or epilepsy” was completed in 2018. Three full research groups took part in this project (PIs: Susana Puig, Luis Pérez and Pablo Lapunzina) from this Pdl, along with a group from the Genetic Medicine Research Programme (PI: Joaquin Dopazo) and the four clinical groups linked with the Paediatric and Developmental Medicine Group (Group PIs: Encarna Guillén, Feliciano J. Ramos, Jordi Rosell and Maria Isabel Tejada). This project enabled developing a computer tool for registering clinical cases accessible via:

<http://ges.cipf.es/enod/login.aspx>. In fact, this project has meant that we already have this tool available as a means to compile cases from the Programme for Undiagnosed Rare Diseases (ENoD) and this is available for other projects to be able to benefit from it in its utility for collecting, keeping and discussing clinical information on line.

- Apart from this there are a large number of individual publications of the groups in this line, described in greater detail when each group is discussed.

Contributing to training of healthcare professionals and the general public.

The Course on Personalised Genomic Medicine was held on 5, 6 and 7 November 2018 at Campus del Mar - Universitat Pompeu Fabra, with the attendance of over 60 healthcare professionals and researchers. We should also mention different hospital sessions arranged under the auspices of this Pdl.

The training for patients was given in the setting of the second EURORDIS Summer School in Spanish, held at Castelldefels Barcelona from 11 to 15 June, with training on the diagnostic process on a dissemination level.

Sensorineural Pathology

Coordinator:
Lluís Montoliu José

In 2018 the 7 groups forming the Programme obtained some major scientific results in dissemination and cooperation with patients' associations, both independently, and in cooperation with other CIBERER groups.

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

In 2018 all the groups in the programme were taking part in intramural projects. In the Call for Work Groups, 2 of the 11 groups are coordinated by groups from the PdI entitled: "Genomic edition and gene therapy" and "Animal models of human diseases", and groups from the programme are taking part in a further 3 Work groups.

The NanoCrisprAlbino Therapy project illustrates the inter-area cooperation from the call for the Platform for Support for Internationalisation of the CIBER, coordinated by Lluís Montoliu with the participation of the group led by José Luis Pedraz (CIBER- BBN).

We should also stress the start of the project entitled RAREGenomics (Network for Research into Rare Diseases of Madrid Community), granted in the Biomedicine call of the CAM 2017, coordinated by Carmen Ayuso, in which a further 6 CIBERER groups are taking part, including Miguel Ángel Moreno, from this PDI. This project was awarded the FEDER Award for the best project in 2018 for fostering research by means of networking.

In the field of training, several courses and symposia have been arranged:

- Fundación Ramón Areces Symposium: "Applications of gene editing on research and therapy of human rare diseases", coordinated by Lluís Montoliu and José Carlos Segovia, held at the Fundación Ramón Areces on 25 and 26 January.
- 8th edition of the CNAG-CIBERER Symposium on "Medicina Genómica aplicada a Enfermedades Raras", coordinated by Carmen Ayuso, held on 5 July at the Fundación Jiménez Díaz.
- 9th Edition of the CIBERER Course for training in phenotyping, coordinated by Isabel Varela-Nieto, held from 28 to 30 November at the Colegio Oficial de Veterinarios de Madrid (with the cooperation of CIBERCV, CIBERONC and CIBERDEM).

There have been different appointments and awards granted to researchers from the programme: Isabel Varela-Nieto was appointed president of the International Committee of the Association for Research in Otolaryngology (ARO) and president-elect of the Sociedad Española de Bioquímica y Biología Molecular (SEBBM); Carmen Ayuso was given the Fenin Award for Technological Innovation 2018 and Lluís Montoliu obtained an award from the International Society for Transgenic Technologies (ISTT), the Asociación Española de Científicos (AEC), as well as SINC agency.

Another achievement as regards cooperation with patients' associations was the book entitled "¿Qué es el albinismo?", published by ALBA, co-sponsored by the CIBERER and written by Lluís Montoliu.

The PDI closed the year with its annual meeting, held at the Centro de Biología Molecular "Severo Ochoa" (CSIC-UAM) on 21 November, with the participation of Retina Madrid and Fundación Retina España, the Federación de Asociaciones de Retinosis Pigmentaria de España and Fundación Lucha Contra la Ceguera (FARPE-FUNDALUCE).

Endocrine Medicine

Coordinator:
Susan Webb

This research programme is made up of only three full research groups and a fourth associated

group, which is the reason for the importance of incorporating the additional strength of the Linked Clinical Groups. 2018 was the year for closing the project entitled: "Silent corticotroph adenomas: do these constitute a subtype of non-functioning pituitary adenomas with a more aggressive conduct?" Financed by the CIBERER, this project enabled combining the Linked Clinical Groups from the programme with the

full groups led by Susan Webb and Luis Castaño. The project enabled the joint study of collections of clinical cases of what were until now scattered groups to review the classification of this type of adenomas.

One important translation accomplishment deserving mention is the publication of the longitudinal study on growth 1995-2017. This has data for proper evaluation of growth during puberty, modifying clinical conduct, avoiding mistaken diagnoses and unnecessary treatment, preparing a bilingual website www.millennialsgrowth.com and an app for iOS and Android for the general public as well as an auxological programme for healthcare professionals.

Inherited Cancer, Haematological and Dermatological Diseases

Coordinator:
Juan Antonio Bueren Roncero

In 2018 the groups in this research programme went on working towards IRDIRC objectives. Several scientific events were promoted in this respect, such as the programme's own scientific meeting, which took place at the IMIBIC in Cordoba in November, the second meeting of the anaemia project of Blackfan Diamond (DBA) at the Hospital Gregorio Marañón, the support for the rare disease session of the 9th Biennial Congress of the Spanish Society for Gene and Cell Therapy and the organisation of the international symposium on telomeropathies at the Fundación Ramón Areces; here they brought up the lack of curative treatments currently available for telomeropathies, a group of rare diseases whose genetic basis is telomere shortening.

As for new discoveries with application in diagnosis, Jordi Surrallés's group from the Hospital Sant Pau, has discovered a new gene known as '*EDC4*' involved in familial

We should also stress the results attained with regard to possible treatments of rare endocrine diseases, such as for example the publication entitled: "A Sobetirome and its Amide Prodrug Sob-AM2 Exert Thyromimetic Actions in Mct8-Deficient Brain. *Thyroid*. 2018;28(9):1211-1220" by the group led by Ana Guadaño; or the description of the genetic causes of these pathologies and the publication of "Identification of an AR mutation-negative class of androgen insensitivity by determining endogenous AR activity". *Journal of Clinical Endocrinology and Metabolism*. 2016;101(11):4468-4477 by the group led by Antonio Carrascosa.

breast cancer. This gene encodes a protein which interacts with *BRCA1* and which plays a fundamental role in the repair of DNA by the homologous recombination mechanism. Researchers from the group led by Vicente Vicente at the Instituto Murciano de Biomedicina have studied the biochemical and cellular consequences of a mutation identified in a large family with antithrombin deficiency undergoing a large number of recurrent thromboses.

The group led by Javier Benítez at the CNIO has furthermore identified three new genes for susceptibility to testicular cancer (*PLEC*, *EXO5* and *DNAH7*) as potential candidates helping to explain the genetic bases of tumours of testicle germinal cells.

With regard to therapeutic developments, we can stress the designation of gefitinib and afatinib as orphan drugs for Fanconi anaemia. The studies coordinated by the team led by Jordi Surrallés have shown that this product, currently indicated for lung cancer, could work as a therapy for squamous tumours of the head and neck in patients with Fanconi anaemia. In this same pathology, Juan Bueren, head of the CIEMAT group, presented an anticipation of the results of the clinical trial in stage 1/2 of gene therapy in patients with Fanconi anaemia at the Congress of the American Gene and Cell Therapy Society held in Chicago.

Training Programme

Coordinator: *Luis Pérez Jurado*

The CIBERER Training Programme has carried out its main actions in 2018 in two overall lines:

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

The third customary line, the one for Predoctoral Grants, could not be implemented due to administrative limitations.

Courses: Organisation and calls for attendance grants

The CIBERER Training Programme organised a course directly, with its own additional call for attendance grants and two extra calls were offered for attending courses with teaching coordination by CIBERER researchers.

- Course on Personalised Genomic Medicine. Barcelona, 5-7 November.

Calls for grants for attending training courses and activities arranged by CIBERER and external groups

- Call for Grants: 2nd Edition of EURORDIS Summer School en Español Castelldefels from 11 to 15 June 2018. Two grants were given for attending this course.
- Call for Grants: Introduction to Research in Genetically Modified Animals, 9th Ed. CIBERER training courses in phenotyping, 28 to 30 November 2018. Fina grants for attending this course were given.

Mobility grants

In 2017, mobility grants continued to be open for internal and external, national and international mobility. The former were preferentially provided, with external mobility only being granted if this involved some transversal interest. Different researchers could thus benefit from this programme to extend their training and further the projects in which they were involved.

No. of mobility grants: eleven positive resolutions, representing two more in comparison with the nine granted in 2017. Seven of these were intramural, one national extramural and three internationals extramurals.

The following table covers the mobility operations performed in 2018:

Mobility operations carried out

<i>Beneficiary</i>	<i>Issuing Group</i>	<i>Receiving Group</i>
Tania Jareño Flores	PI: Isabel Varela	PI. Nunes Virginia
Belén Molla	PI: Pascual Sanz	CIBERBBN - grupo Ángel Raya
Jordi Minguillón	PI: Jordi Surrallés	PI: Juan Antonio Bueren
Ingrid González	PI: Francesc Cardellach	University of Helsinki
Verónica Palma Barqueros	PI: Vicente Vicente	PI: Juan Antonio Bueren
Jordi Minguillón	PI: Jordi Surrallés	PI: Juan Antonio Bueren
Noelia Fernández	PI: Daniel Grinberg	Goethe Universitat (Frankfurt)
Maria Isabel Álvarez	PI: Susana Puig	Radboud University (Nijmegen)
Nekane Ibarluzea	PI: María Isabel Tejada Mínguez	PI: Pablo Lapunzina
Dolors López	PI: Francesc Palau	PI: Jorgina Satrústegui
Jordi Minguillón	PI: Jordi Surrallés	PI: Juan Antonio Bueren

Platforms

Three support platforms have been set up to facilitate the research work done by the CIBER for Rare Diseases and the scientific community:

CIBERER Biobank, BIER, and MAPER. We will now highlight their main achievements in this last yearly period.

CIBERER Biobank

Coordinator:
Francesc Palau Martínez

The number of biological samples in the Biobank system continues to increase and this year the total number came to 1075, of 71 different pathologies (<http://www.ciberer-biobank.es>); as regards the number of biological samples assigned by the Biobank, this was 3, specifically to the company known as CASEBIA-THERAPEUTICS. In order to

improve the visibility of the Biobank and increase its activity, we should stress including information in the European catalogue coordinated by Eurobiobank and the changes that are being added to the web page of the CBK. As well as this, incorporating the service for immortalising fibroblasts has enabled increasing the number of services given by CBK this year by 25%.

The CBK continues to work in several cooperation schemes with Biobank networks. It is a member of the Red Valenciana de Biobancos (2010) and of the Eurobiobank (2017) and has cooperation agreements in force with IBSP-FISABIO Biobank and the Banco Nacional de ADN (2008). We also form part of two work groups of the

Plataforma Red Nacional de Biobancos of the ISCIII, specifically: Programme-3: Exploration of new types of samples, specifically of the “3.2-MicroRNA” and Programme-4: Plan for External Communication and Dissemination for patients’ associations, organisation of explanatory events and collaborative measures. As regards agreements with industry, two cooperation agreements have been signed with Epidisease: the first in the framework of a project entitled “TEST ScolioPro®” in which the CBK will process and store the samples for this study and the second for determining the telomerase activity of the lines of fibroblasts immortalised at the CBK.

The CBK has taken part in different media for disseminating its work such as: the European Night for researchers arranged at the Centro de Investigación Príncipe Felipe, the Congreso Nacional de Biobancos and it has taken part in a dissemination article on Biobanks in *Genética Médica News*.

In 2018 the CBK applied for a total number of 7 projects: i) Projects in the Call for Cooperative and Complementary Intramural Actions of the CIBERER. 3 of the 4 projects applied for have been granted; ii) Politécnico-FISABIO Project; iii) XIX Concurso Nacional de la Fundación Ramón Areces Project and iv) National Plan Project. This

year 5 of the 3 projects allowed were granted with the participation of the CBK with a financing of 13,500€.

Publications:

- *Circulating miRNAs as diagnostic biomarkers for adolescent idiopathic scoliosis*. JL. García-Giménez, PA. Rubio-Belmar, L. Peiró-Chova, D. Hervás, D. González, JS. Ibañez-Cabellos, P. Bas, S. Mena-Mollá, EM. García-López, FV. Pallardó and T. Bas. *Scientific Reports-Nature* 2018 Feb 8;8(1):2646.
- *Small RNA-seq analysis of circulating miRNAs to identify phenotypic variability in Friedreich’s ataxia patients*. M. Seco-Cervera, D. González-Rodríguez, JS. Ibañez-Cabellos, L. Peiró-Chova, FV. Pallardó and JL. García-Giménez. *Scientific Data-Nature* 2018 Mar 6;5:180021.
- *ANKK1 is found in myogenic precursors and muscle fibers subtypes with glycolytic Metabolism*. E. Rubio-Solsona, S. Martí, JJ. Vilchez, F. Palau and J. Hoenicka. *Plos One*. 2018 Jun 6; 13(6):e0198880.

BIER

Coordinator:
Joaquín Dopazo Blázquez

In 2018 the BiER continued with the work lines previously started, which include versioning and use in production of the MMP software (personalised medicine module), based on IVA partly developed with the ACCI- 2016-25. This software has been used for the two projects which have consumed most resources of the platform: the ENoD (cohort project), in which 188 exomes were analysed, and to a lesser extent (even while being of greater size), the NaGen, in which 254 whole genomes were analysed. As a result of the cooperation with the SAS, roughly 1554 samples were analysed at the MMP-SAS over the reported period, mainly clinical exomes designed at the SAS, but also exomes and genomes.

The BiER has gone on working on the server for genetic variation of the Spanish population

(CSVS: <http://www.ciberer.es/bier/csvs>), which has been opened to other projects outside the CIBERER in order to increase its volume, as few sequences come from the CIBERER (we do not know whether this is through low production or through low accession to contributing to the CSVS). At the present time this contains data of allelic frequencies of variants currently obtained mainly from exomes and some genomes of 2000 unrelated Spanish individuals. The CSVS is one of the Beacons of GA4GH (<https://beacon-network.org/>) and is one of the resources of ELIXIR-ES.

The BiER has furthermore been working for some time on different aspects of systems medicine and in particular on the development of mechanistic models to be applied in the study of disease mechanisms in RDs. We have recently been granted an ACCI project (PI María Peña) “Mathematical models of disease mechanisms for reformulation of medications in rare diseases” for its application to an eminently translational problem in RD: drug repositioning.

In this systems medicine field the BiER has given two courses on tools for handling mechanistic

models: one of these at the IMIBIC (Cordoba) on 13 April and the other at the Curie Institute in Paris, in the setting of the Disease Maps Community Meeting, on 22 June. The BiER has also arranged a course on the analysis of genomic data "From reads to disease variants" with the

renowned group of the MIT which developed the GATK, covering the processes ranging from obtaining the primary data of the sequencer to the prioritisation of variants (<http://courseswiki.clinbioinfospa.es/gatk2018/start>).

MAPER

In 2018 information for the MAPER database continued to be compiled. All the active clinical trials for rare diseases have been incorporated through cooperation with the Agencia Española de Medicamentos y Productos Sanitarios and other research and care resources of use for rare diseases and the future genomics plan.

The data on the validated research projects and clinical trials accessible over the MAPER web in

2018 is as follows::

- 879 biomedical research projects included and 514 clinical tests compiled.
- 120 financing agencies taking part in financing the research into RD.
- 515 Principal Investigators included in the database.
- 241 research centres included.
- Presentation of results at the annual CIBERER meeting for 2018 and updating the MAPER website to incorporate the test search engine.

Scientific Production

Publications

No. of publications in 2018

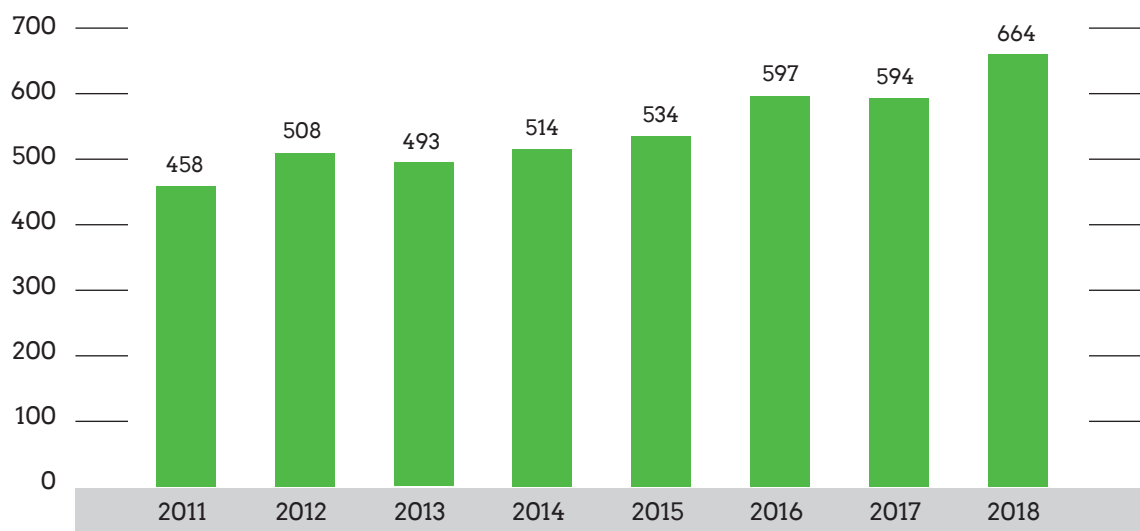
TOTALS	664
Q1	364
D1	168

Collaborations

CIBERER	69
CIBER*	93

*Over several thematic areas

Evolution of publications



10 most relevant CIBERER publications in 2018 by impact factor

IF	Publication
72,406	Oral Plasma Kallikrein Inhibitor for Prophylaxis in Hereditary Angioedema. <i>N Engl J Med</i> 07. 379(4):352-362

44,405	<i>Effect of Hydrolyzed Infant Formula vs Conventional Formula on Risk of Type 1 Diabetes: The TRIGR Randomized Clinical Trial.</i> JAMA01. 319(1):38-48
40,282	<i>Diagnosis and management of Cornelia de Lange syndrome: first international consensus statement.</i> Nat Rev GenetOct. 19(10):649-666
37,205	<i>Paternally inherited cis-regulatory structural variants are associated with autism.</i> Science04. 360(6386):327-331
37,205	<i>Analysis of shared heritability in common disorders of the brain.</i> Science06. 360(6395)
33,900	<i>MAGE-A3 immunotherapeutic as adjuvant therapy for patients with resected, MAGE-A3-positive, stage III melanoma (DERMA): a double-blind, randomised, placebo-controlled, phase 3 trial.</i> Lancet OncolJul. 19(7):916-929
33,900	<i>Sex as a predictor of response to cancer immunotherapy.</i> Lancet OncolAug. 19(8):e375
27,959	<i>Association analyses of more than 140,000 men identify 63 new prostate cancer susceptibility loci.</i> Nat GenetJul. 50(7):928-936
27,959	<i>A transcriptome-wide association study of 229,000 women identifies new candidate susceptibility genes for breast cancer.</i> Nat GenetJul. 50(7):968-978
27,959	<i>De novo variants in neurodevelopmental disorders with epilepsy.</i> Nat GenetJul. 50(7):1048-1053

Patents owned by CIBER

Applied for

- EP18382322.8. European Patent. *DNA damage repair disease therapies.* Grupo Jordi Surrallès.
- EP18382527.2. European Patent. *Therapeutic*

use of afatinib in cancer. Grupo Jordi Surrallès.

- 62/712,146. USA Patent. *Methods for Gene Modification of Hematopoietic Cells.* Grupo Juan Bueren.
- 62/573,037. USA Patent. *Lentiviral Vectors for Delivery of PKLR to Treat Protein Kinase Deficiency.* Grupo Juan Bueren.
- EP18382917.5. European Patent. *Treatment and prevention of glioblastoma.* Grupo Luisa Botella.

Clinical guidelines

- *Diagnosis and management of Cornelia de Lange syndrome: first international consensus statement.*
- *Diagnosis and follow-up of patients with Hunter syndrome in Spain: A Delphi consensus.*
- *Inborn Errors of Metabolism Overview:*

Pathophysiology, Manifestations, Evaluation, and Management.

- *Consensus document on the implementation of next generation sequencing in the genetic diagnosis of hereditary cancer.*
- *Management guidelines for disorders / different sex development (DSD).*
- *Consensus on insulin treatment in type 2 diabetes.*
- *Fragile X syndrome: An overview and update of the FMR1 gene.*

- *MelaNostrum: a consensus questionnaire of standardized epidemiologic and clinical variables for melanoma risk assessment by the melanostrum consortium.*
- *Management goals for type 1 Gaucher disease: An expert consensus document from the European working group on Gaucher disease.*
- *The view of experts on initiatives to be undertaken to promote equity in the access to orphan drugs and specialised care for rare diseases in Spain: A Delphi consensus.*
- *Guideline on cochlear implants.*

CIBERER Groups. Publications 2018




















Group leader	Publ.	Q1	1D	Institution / Centre	Province
 Antiñolo Gil, Guillermo	5	1	0	Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla. Hospital Virgen del Rocío	Sevilla
 Artuch Iriberry, Rafael	27	15	3	Fundación para la Investigación y Docencia Sant Joan de Deu. Hospital Sant Joan de Deu	Barcelona
 Ayuso García, Carmen	17	7	2	Instituto de Investigación Sanitaria Fundación Jiménez Díaz	Madrid
Bermejo Sánchez, Maria Eva (1)	6	2	1	Instituto de Salud Carlos III. Centro de Investigación de Anomalías Congénitas	Madrid
 Botella Cubells, Luisa María	7	4	1	Agencia Estatal Consejo Superior de Investigaciones Científicas. Centro de Investigaciones Biológicas	Madrid
 Bovolenta Nicolao, Paola	7	5	4	Agencia Estatal Consejo Superior de Investigaciones Científicas. Centro de Biología Molecular Severo Ochoa	Madrid
 Bueren Rocero, Juan Antonio	8	6	2	Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas (CIEMAT)	Madrid
 Caballero Molina, María Teresa	14	4	1	Servicio Madrileño de Salud. Hospital La Paz	Madrid
 Cardellach López, Francesc	15	10	4	Hospital Clínico y Provincial de Barcelona	Barcelona
 Carracedo Álvarez, Ángel	21	15	6	Universidad de Santiago de Compostela. Facultad de Medicina	A Coruña
 Carrascosa Lezcano, Antonio	16	2	0	Fundación Hospital Universitario Vall d'Hebron - Institut de Recerca (VHIR)	Barcelona
 Castaño González, Luis	11	3	1	Asoc. Instituto de Investigación Sanitaria de Biocruces. Hospital Universitario Cruces	Vizcaya
 Cuezva Marcos, José Manuel	8	7	2	Universidad Autónoma de Madrid. Centro de Biología Molecular Severo Ochoa	Madrid
 Dalmau Obrador, Josep	6	6	4	Instituto de Investigaciones Biomédicas August Pi i Sunyer	Barcelona
 Del Río Nechaevsky, Marcela	4	1	1	Universidad Carlos III	Madrid
 Dopazo Blázquez, Joaquín	5	5	3	Fundación Pública Andaluza Progreso y Salud. Hospital Virgen del Rocío	Sevilla

<i>Group leader</i>	<i>Publ.</i>	<i>Q1</i>	<i>ID</i>	<i>Institution / Centre</i>	<i>Province</i>
 Estévez Povedano, Raúl	5	1	0	Universidad de Barcelona. Facultad de Medicina	Barcelona
 Fernández Piqueras, José	4	1	0	Universidad Autónoma de Madrid	Madrid
 Fillat i Fonts, Cristina	13	11	3	Instituto de Investigaciones Biomédicas August Pi i Sunyer	Barcelona
 Gallano Petit, María Pía	9	4	1	Instituto de Investigación del Hospital de la Santa Creu i Sant Pau	Barcelona
 Garesse Alarcón, Rafael	4	1	1	Universidad Autónoma de Madrid. Madrid	Madrid
Giraldo Castellano, Pilar	9	1	0	Instituto Investigación Sanitaria Aragón (IIS Aragón)	Zaragoza
González Manchón, Consuelo	4	3	0	CSIC	Madrid
 Gratacos Solsona, Eduard	61	25	19	Hospital Clínico y Provincial de Barcelona. Instituto de investigaciones Biomédicas August Pi i Sunyer	Barcelona
 Grinberg Vaisman, Daniel	16	13	7	Universidad de Barcelona. Facultad de Biología.	Barcelona
 Guadaño Feraz, Ana Cristina	4	2	2	Agencia Estatal Consejo Superior de Investigaciones Científicas. Instituto de investigaciones Biomédicas Alberto Sols	Madrid
Illa Sendra, Isabel	28	19	8	Instituto de Investigación del Hospital de la Santa Creu i Sant Pau	Barcelona
Knecht, Erwin (1)	3	3	0	Fund. Centro de Investigación Príncipe Felipe. Centro de Investigación Príncipe Felipe	Valencia
 Lapunzina Badia, Pablo Daniel	29	15	7	Servicio Madrileño de Salud. Hospital La Paz	Madrid
 Marfany Nadal, Gemma	1	1	0	Univ. de Barcelona. Facultad de Biología.	Barcelona
 Martí Seves, Ramon	12	6	0	Fundación Hospital Universitario Vall d'Hebron - Institut de Recerca (VHIR)	Barcelona
 Martín Casanueva, Miguel Ángel	25	17	6	Servicio Madrileño de Salud. Hospital Universitario 12 de Octubre	Madrid
 Medina Torres, Miguel Ángel	9	7	4	Universidad de Málaga. Facultad de ciencias	Málaga
 Millán Salvador, José María	8	5	1	Fund. para la Investigación del Hospital la Fe	Valencia
 Montoliu José, Lluís	11	5	3	Agencia Estatal Consejo Superior de Investigaciones Científicas. Centro Nacional de Biotecnología	Madrid
 Montoya Villarroya, Julio	12	9	6	Universidad de Zaragoza. Facultad de Veterinaria	Zaragoza
 Moreno Pelayo, Miguel Ángel	6	5	3	Servicio Madrileño de Salud. Hospital Ramón y Cajal	Madrid
 Navas Lloret, Plácido	17	15	4	Universidad Pablo de Olavide. Centro Andaluz de Biología del Desarrollo	Sevilla
 Nunes Martínez, Virginia	3	3	2	Fundación IDIBELL. Hospital Duran i Reynals	Barcelona
 Palacín Prieto, Manuel	5	5	4	Fundación privada Instituto de Recerca Biomédica (IRB-Barcelona)	Barcelona

<i>Group leader</i>	<i>Publ.</i>	<i>Q1</i>	<i>ID</i>	<i>Institution / Centre</i>	<i>Province</i>
 Palau Martínez, Francesc	7	5	1	Fundación para la Investigación y Docencia Sant Joan de Deu. Hospital Sant Joan de Deu	Barcelona
 Pallardo Calatayud, Federico	5	4	0	Universidad de Valencia. Facultad de Medicina de Valencia	Valencia
 Pérez González, María Belén	15	3	1	Universidad Autónoma de Madrid. Centro de Biología Molecular Severo Ochoa	Madrid
 Pérez Jurado, Luis	13	6	3	Universidad Pompeu Fabra. Facultad de Ciencias Experimentales y de la Salud	Barcelona
 Perona Abellón, Rosario	3	2	0	Agencia Estatal Consejo Superior de Investigaciones Científicas. Instituto de investigaciones Biomédicas Alberto Sols	Madrid
 Posada de la Paz, Manuel	12	3	0	Instituto de Salud Carlos III. Instituto de Investigación en Enfermedades Raras	Madrid
 Puig Sardà, Susana	31	24	17	Hospital Clínico y Provincial de Barcelona.	Barcelona
 Pujol Onofre, Aurora	8	8	7	Fundación IDIBELL. Hospital Duran y Reynals	Barcelona
 Ribes Rubió, Antonia	7	4	0	Hospital Clínico y Provincial de Barcelona. Instituto de Bioquímica Clínica	Barcelona
 Robledo Batanero, Mercedes	30	24	13	Fundación Centro Nacional de Investigaciones Oncológicas	Madrid
 Rodríguez de Córdoba, Santiago	10	6	5	Agencia Estatal Consejo Superior de Investigaciones Científicas. Centro de Investigaciones Biológicas	Madrid
 Rubió Zamora, Vicente	4	3	1	Agencia Estatal Consejo Superior de Investigaciones Científicas. Instituto de Biomedicina de Valencia	Valencia
 Ruiz Pérez, Víctor Luis	4	2	1	Agencia Estatal Consejo Superior de Investigaciones Científicas. Instituto de Investigaciones Biomédicas Alberto Sols	Madrid
 Salido Ruiz, Eduardo	8	6	4	Fundación Canaria de Investigación Sanitaria (FUNCANIS). Hospital Univ. de Canarias	Santa Cruz de Tenerife
 Sanz Bigorra, Pascual	5	2	0	Agencia Estatal Consejo Superior de Investigaciones Científicas. Instituto de Biomedicina de Valencia	Valencia
 Satrústegui Gil Delgado, Jorgina (1)	1	1	1	Universidad Autónoma de Madrid. Centro de Biología Molecular Severo Ochoa	Madrid
 Serratosa Fernández, José	6	3	3	Instituto de Investigación Sanitaria Fundación Jiménez Díaz	Madrid
 Sevilla Mantecon, Maria Teresa	14	6	1	Instituto de Investigación Hospital UiP la Fe	Valencia
 Surrallés Calonge, Jordi	6	5	4	Universidad Autónoma de Barcelona. Facultad de Biociencias	Barcelona
 Varela Nieto, Isabel	13	6	4	Agencia Estatal Consejo Superior de Investigaciones Científicas. Instituto de investigaciones Biomédicas Alberto Sols	Madrid
 Vicente García, Vicente	24	9	5	Fundación para la Formación e Investigación Sanitarias de la Región de Murcia (FFIS). Hospital José María Morales Meseguer	Murcia
 Webb, Susan	12	2	0	Instituto de Investigación del Hospital de la Santa Creu i Sant Pau	Barcelona

(1) Group deregistered in 2018

Linked groups

<i>Group leader</i>	<i>Institution / Centre</i>	<i>Province</i>
<i>Research Programme on Paediatric and Developmental Medicine</i>		
 Encarna Guillén	Hospital Virgen de la Arrixaca	Murcia
 Feliciano J. Ramos	Hospital Lozano Blesa	Zaragoza
 Jordi Rosell	Hospital Son Espases	Illes Balears
 Isabel Tejada	Hospital Cruces	Bilbao
<i>Research Programme on Inherited Metabolic Medicine</i>		
 Luis Aldámiz- Echevarría Azuara	Hospital Cruces	Bilbao
 M ^a Luz Couce	Hospital Clínico de Santiago de Compostela	A Coruña
 Luis González Gutiérrez-Solana	Hospital Infantil Niño Jesús	Madrid
 Eduardo López Laso	Hospital Reina Sofía	Córdoba
 Guillem Pintos	Hospital Germans Trías i Pujol	Barcelona
 Mireia del Toro	Hospital Vall d'Hebrón	Barcelona
<i>Research Programme on Endocrine Medicine</i>		
 Irene Halperin	Hospital Clínic	Barcelona
 Antonio Picó	Hospital General de Alicante	Alicante
 Manuel Puig Domingo	Hospital Germans Trías i Pujol	Barcelona
 Alfonso Soto	Hospital Virgen del Rocío	Sevilla
<i>Research Programme on Inherited Cancer, Haematological and Dermatological Diseases</i>		
 Isabel Badell	Hospital de la Santa Creu i Sant Pau	Barcelona
 Cristina Beléndez	Hospital Gregorio Marañón	Madrid
 Albert Català	Hospital San Joan de Déu	Barcelona
 Julián Sevilla	Hospital Infantil Niño Jesús	Madrid
 Joan-Lluís Vives- Corrons	Hospital Clínic	Barcelona





Respiratory Diseases

PREVENTION



Scientific Director's Presentation

Ferran Barbé Illa.

Dear Friends,

Yet another year I have been given the chance to present the Annual Report of the CIBERES. This could well be one of the most gratifying tasks for me as scientific director, since it allows me to reflect on the present and future of the work done by CIBERES as a research area, based on the data which will be given below.

We continue to work, successfully I believe, on attaining the strategic objectives which we set ourselves in 2015. As part of our search for excellence we have submitted the work done in our lines of research from 2016-2018 for external assessment as well as the new projects for 2019-2021, with very good results in general. Our presence as CIBERES in proposals for international competitive projects has significantly increased over this last year with a more than acceptable success rate. We have very significantly improved our data on activities for awareness-raising and visibility of our scientific results and must continue to do so, and we have worked on the policy for collaboration schemes and alliances with some very positive cases in point, such as the Training Days arranged along with CIBERONC.

There is still work to be done, which we will attempt to complete over the next few months, including increasing the participation of patients' associations at our centre, giving them a chance to support, express opinions and have a positive influence on scientific strategy; obtaining an evaluation and advice on our work from the External Advisory Scientific Committee, as well as considering its

renovation and opening up new lines of research in accordance with our groups' scientific capabilities and with international trends in research into respiratory diseases and society's demands.

We have a thrilling year ahead of us in 2019 in which to go on undertaking our research work. I am sure that by working on our collaborative activity we will attain the aims that we have set ourselves and improve our results, thus feeding back into society the trust and resources that it provides us with.

Before finishing I would like to express my heartfelt remembrance of the three researchers who sadly left us in 2018: Dr. Antoni Xaubet, an active researcher in the diagnosis and treatment of diffuse interstitial diseases, especially in pulmonary fibrosis; Dr. Joaquín Terán Santos, coordinator of the Sleep Unit of the Hospital Universitario de Burgos, a pioneer in the study of sleep pathology in Spain and creative force behind what is now the Spanish Sleep Network, and Dr. José Antonio Melero, a researcher at the Centro Nacional de Microbiología of the Instituto de Salud Carlos III, a national and international benchmark in research into respiratory viruses. All three of them have handed down an example of dedication and excellence in work which should act as inspiration for our activity in the coming years.

I would like to close this text with my thanks to all the members of CIBERES, contracted and attached staff and collaborators, as well as the personnel of the CIBER Technical Office, for the excellent work done by them in 2018.

Scientific Programmes

Chronic Respiratory Diseases

Coordinator:
Juan Fernando Masa Jiménez

Asthma Line

- Researchers from La Paz, Fundación Jiménez Díaz and Hospital Vall d'Hebron have taken part in an international study on a cohort of 1167 patients on phenotypes connected with occupational asthma published in the journal *Allergy*.
- Two patents: "In vitro method for identifying stages of severity in patients with bronchial asthma" (P201730739) and "Differential biomarkers of asthma" (P201730947).
- The Hospital Clinic Barcelona has cooperated in an international study on the use of new technologies for the diagnosis, control and follow-up of rhinitis and asthma.

COPD Line

- A Clinical Research Collaboration has been set up with >33 European cohorts for the study of vital trajectories of lung function. <https://www.ersnet.org/research/cadset-chronic-airway-diseases-early-stratification>
- Factors in early age connected with the development of COPD. *Am J Respir Crit Care Med* 2018;198(7):973; *Lancet Respir Med* 2018;6(5):324-326 and *Lancet Respir Med* 2019.
- In the analysis of the respiratory microbiome in severe COPD we have objectified the microbiome in stable COPD according to the

severity of the obstruction, exacerbation and eosinophils.

Cancer Line

- An analysis has been made of the biology of systems of the retrospective cohort. Experience with biomarkers in this setting has partly been responsible for a paper in the *Journal of Thoracic Oncology* on biomarkers connected with the detection of lung cancer.
- Respiratory sleep disorders are highly prevalent in both a lung cancer cohort and in the early detection cohort.
- Nocturnal hypoxaemia (T90%) was significantly correlated with positive results in cancer detection.
- The analysis of a combined cohort of patients from the SAILS study and the SAIL study found a greater risk of lung cancer in patients with obstructive sleep apnoea and nocturnal hypoxaemia.

Sleep Line

- Studies from the Spanish Sleep Network showed that handling sleep apnoea in primary care is a cost-effective alternative to the usual treatment given by specialised units.
- Two studies show that in advanced age intermittent hypoxia does not cause the same alterations to the vascular wall, as well as in tumoral progression, as in younger individuals. This is presumably due to changes caused by age in the immune system.
- In patients with OSA there is an increase of PD-1 / PD-L1, through the induction of the inducible factor by intermittent hypoxia. This gives biological plausibility to the increase in the incidence and aggressiveness of the

cancer and the greater risk of infections reported.

- OSA is related to an increase in the aggressiveness of the cutaneous melanoma and a rise in high circulating levels of VCAM-1 which could indicate a contribution of OSA to tumorigenesis by means of the integrin-based adhesion pathway.
- Development of a simplified virtual sleep laboratory with integration of smart technology.
- A study with 70,469 patients treated with CPAP for sleep apnoea shows that the

treatment is associated with a reduction in mortality in men, but not in women.

- Prominent participation (chairman) in the preparation of an official clinical practice guide of the American Thoracic Society (ATS) (Evaluation and handling of the obesity-hypoventilation syndrome).

Infectious Respiratory Diseases

Coordinator:
Antoni Torres Martí

Pneumonia Line

The PNEUMOCOPER line ended in December 2018. A report on the three-years' life of the project was sent for evaluation by the ANECA, getting a mark of 12.5 out of 15. In the different sections valued the mark was always 4 or more points out of 5. Taking into account this very good evaluation we could say that the PNEUMOCOPER line was a considerable success. In 2018 two papers were published on two multi-centre clinical trials in the PNEUMOCOPER line: a) the REPROVE study published in *Lancet Infectious Diseases* (Torres A, et al. *Lancet Infect Dis.* 2018 Mar;18(3):285-295) and b) the CIGMA study, published in *Intensive Care Medicine* (Welte T, et al. *Intensive Care Med.* 2018 Apr;44(4):438-448). Lastly the new proposal for the pneumonia line entitled PREDITNEU was completed and delivered, its coordinators being: Carmen Ardanuy, Laia Fernández-Barat and Miquel Ferrer. The external valuation of the new line was 13 out of 15. This is a reflection of the scientific strength and networking of all the groups taking part in these lines.

Tuberculosis Line

In 2018 the work done by the research groups in the Line focussed on three main approaches to their action:

- Prevention: design, evaluation and development of: new candidates for vaccines (including MTBVAC), multivalent vaccines, hyper-attenuated vaccines for use in immune-suppressed patients. New prophylactic strategies for preventing infection by tuberculosis, active disease and the transmission of high-risk tuberculosis integrating the sequencing of whole genomes and specific PCRs of strains.
- Diagnosis: study of tuberculosis lesions obtained by surgery to seek biomarkers correlating with the pathology. Development and assessment of: new molecular and immune tests for latent tuberculosis infection, new point-of-care techniques for fast diagnosis intended for countries with low income and high rates of tuberculosis, and new tools in molecular epidemiology.
- Treatment: basic and clinical development of new antituberculosis drugs: evaluation of new therapeutic strategies intended for the host.

There were 32 publications in 2018.

Host-Pathogen Interaction Line.

Work has been done on three strategic lines: anti-virulence therapies, therapies addressing the host and systems of therapeutic administration. We have presented significant results in all three approaches:

- Pathoadaptive microbial evolution during chronic respiratory infection. We should stress the identification of patho-bacterial adaptation in the lung of COPD patients increasing their resistance to the bactericide effect of lipid inflammatory mediators.

- Subversion of respiratory immunity. We should underline the role of the SP-A protein of the pulmonary surface agent in the infection-immunity balance, a key aspect in limiting tissue damage after an infection.
- Preclinical valuation of antimicrobials. The immunogenic activity of chimeric fusion proteins inducing the production of cross-neutralising antibodies should be highlighted.

In 2018, the work done in this line has generated 18 scientific publications (7 additional works being reviewed), 1 patent, 30 (oral and poster presentations), 8 dissemination activities, and has led to the defence of 3 doctoral theses and 5 master theses.

Diffuse Respiratory Diseases

Coordinator:
Francisco Pérez Vizcaíno

- A paper on pulmonary hypertension associated with respiratory diseases of the 6th World Symposium on Pulmonary Hypertension (TASK FORCE 10, Nice 2018).
- Major increase in the number of donations to the Spanish Pulmonary Hypertension Biobank, which has reached a figure of 450 patients registered in the Spanish Pulmonary Hypertension Registry.
- Participation in the International Consortium for Genetic Studies in Pulmonary Arterial Hypertension (ICON-PAH).
- Holding the second Reunión de Investigación en Hipertensión Pulmonar CIBERES. Universidad Complutense de Madrid, February 2018.
- Demonstration that pulmonary hypertension affects the intestinal microbiome in an experimental mouse model.
- Demonstration of the implication of signalling pathway JAK2 in pulmonary vascular remodelling.
- Analysis of the role of microRNAs in

pulmonary vascular remodelling in patients with COPD.

- Analysis of the role of proteins of the human immunodeficiency virus in the pulmonary vascular function.
- Analysis of geographical variability of mortality over time of critical patients with a need for invasive mechanical ventilation.
- Analysis of the effect of driving pressure on the mortality of critical patients needing invasive mechanical ventilation with no criteria of the acute respiratory distress syndrome.
- Participation in the preparation of recommendations on Use of ECMO in ICU (Sociedad Española de Medicina Intensiva Crítica y Unidades Coronarias).
- Coordination and management of the Tercer Simposio Internacional de Investigación Traslacional en Lesión Pulmonar Aguda (INSPIRES) (Amsterdam, 2018).
- National coordination of the international study on disconnection of mechanical ventilation (WEAN-SAFE) in ICUs.
- Participation in the National Consensus and Recommendations on the use of non-invasive mechanical ventilation (NIV) in patients with respiratory failure of the SEMICYUC, SEPAR, SEMES, SEDAR and SECIP associations.
- Identification of miRNAs, as possible targets regulating the inflammatory process in

human alveolar epithelial cells, in animal models and in patients with ARDS.

- Identification of possible therapeutic targets (EGFR, IRAK1, FASL, FAS, Casp3) in acute lung damage.
- Identification of predictive factors and evaluation of the prognostic effect of telomere shortening in pulmonary fibrosis.
- Recruitment of new cases of patients with pulmonary fibrosis and telomere shortening by means of participation of new hospitals from the Spanish healthcare network.
- Participation in the scientific committee of the 20th International Colloquium on Lung and Airway Fibrosis (USA).
- Participation in the creation and coordination of a consortium in pulmonary fibrosis with European Union research groups in pulmonary fibrosis.
- Cooperation with international associations of patients with pulmonary fibrosis.

- Performance of multi-centre, international clinical trial (EC) MA39293-DIET (MADIET): EC phase IV, to evaluate the effect of the diet on adverse gastrointestinal events in patients with idiopathic pulmonary fibrosis treated with pirfenidone
- Design of a randomised test in patients with unclassifiable progressive interstitial fibrosis.
- Identification of MMP28 as a biomarker in differential diagnosis of idiopathic pulmonary fibrosis.
- Identification of AQP1 as a possible new therapeutic target in idiopathic pulmonary fibrosis.
- Identification of the combination of pirfenidone and rapamycin as new potential antifibrotic combination.

Training Programme

Coordinator: *Cristina Prat Aymerich*

In 2018, the funds of the CIBERES Teaching Programme enabled maintaining three of its four strategic actions.

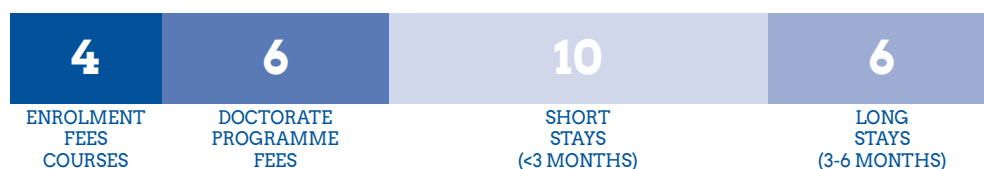
Improvement/mobility grants. Training grants.

In 2018, the results of this programme have taken a rising trend as compared with 2017, with a greater concession of grants for long stays. In all

26 training grants have been given, distributed between over 4 modalities: 4 applications for payment of fees for training activities or courses, 6 applications for payment of fees for Doctorate Programmes, 10 applications for short stays in another city (travel pools) and 6 applications for long stays in another city (3-6 months), four of which were international (Canada, USA and 2 in the United Kingdom).

CIBERES improvement/mobility grants 2017

Number of applications



Grants for recruiting external funding.

In 2018 the second call of this programme fostering internationalisation at CIBERES took place, with 3 grants being issued for cofinancing the expenses resulting from drafting, reviewing, discussing and preparing proposals for calls of European and international projects.

CIBERES-CIBERONC Training Days 2018

In 2018, the 11th CIBERES Training Days were held along with CIBERONC on 15 and 16 November at the Aula Magna Pittaluga of the Escuela Nacional de Sanidad in Madrid.

This year, just as in 2017, the Teaching Committee awarded a special “Constancio González” and three additional prizes for the best oral communication and three additional prizes for the best oral papers and posters which were selected from 20 oral communications and 38 posters presented. The work of three researchers who were given a mobility grant the previous year was also presented.

As one innovation, this year an agreement has been reached with SEPAR and Elsevier to proceed to publish the works presented in a supplement to the 11th CIBERES Training Days in the *Archivos de Bronconeumología* journal. We consider that this is a highly positive accomplishment for our young researchers as it will give them a chance to make their works visible in a quality publication.

Finally as a result of the cooperation emerging between the CIBERES-CIBERONC areas in the training days, and as was done the previous year with CIBERFES, it was proposed to launch a call for CIBERES-CIBERONC collaborative intramural projects for next year 2019, with the aim of presenting collaborative projects that could be proposed for coming European or international calls.

Grants for starting research

This initiative could regrettably not be cofinanced nor supported in 2018. It is intended to contract young researchers for one year in a research project of CIBERES groups. It is nevertheless hoped that calls can be taken up again in future years, going on attracting young talent to CIBERES groups.

Pulmonary Biobank Platform

Coordinator: *Cristina Villena Portella*

> Coordination of the Red Nacional de Biobancos-ISCIII (RNBB).

- Setting up a new office for coordination of the RNBB at the facilities of IdISBa, Majorca, and contracting two support staff.
- Planning and carrying out the action plan 2018.
- Co-organising the IX Congreso Nacional de Biobancos 2018.
- Co-organising the 1ª Jornada Comités de ética de Investigación y Biobancos.
- Starting contacts and first approaches for the RNBB to potentially join BBMRI-ERIC.
- Adapting the model of government of the RNBB.
- Creating and getting under way the Events Advisory Committee of the RNBB.
- Creating and getting under way the Ethical-Legal Advisory Committee of the RNBB.
- Support for coordination of the previous network for closing the PT13 project (AES2013).

> Member of the Red Nacional de Biobancos-ISCIII (RNBB) in the new stage, and closing the projects of the previous PT13. Some of the new projects deserving mention are:

- Participation in the line for improving data associated with samples, for starting up a data quality programme at Biobanks, from which the following has already been published:

Campaner MA, Gomez-Romano F, Esteva-Socias M, Sánchez-Navarro AL, Villena C, Somoza N, Torà M. *Propuesta de conjunto mínimo de datos clínicos de calidad enmarcado en la línea de trabajo del*

programa de la plataforma Red Nacional de Biobancos (PRNBB). Congreso Nacional de Biobancos, Oviedo, 2018. Comunicación Oral

- Participation in the EXOSOMAS work line.
- Performance of the project entitled Optimisation of tissue samples for developing and validating disease biomarkers: OPTIMARK project. OPTIMARK (FIS 2016) and participating in the R +D+i line in Biobanks in the human tissue area, from which 2 oral communications have been given at international congresses, and 4 poster format communications *.
- Start of cooperation with Luxembourg National Biobank (IBBL) for taking part in a common project on tissue quality biomarkers.

> Improving external visibility by participating in:

- Scientific events and meetings with experts
- Training activities (4 from the university and CIBERES 2018 Training Days).
- Management of the PBP social networks.

> Increase of collection of deficient samples (5911 new samples).

> Management and inclusion of the multi-centre ISAAC project collection, coordinated by the CIBERES Obstructive Sleep Apnoea line and SEPAR.

> Granting aid for technical staff of the PBP by the Regional Innovation Department of the Balearic Islands.

> Obtaining a quality certificate for new standard ISO 9001:2015 for the whole Quality Management System of the CIBERES Pulmonary Biobank Platform.

Scientific Production

Publications

No. of publications in 2018

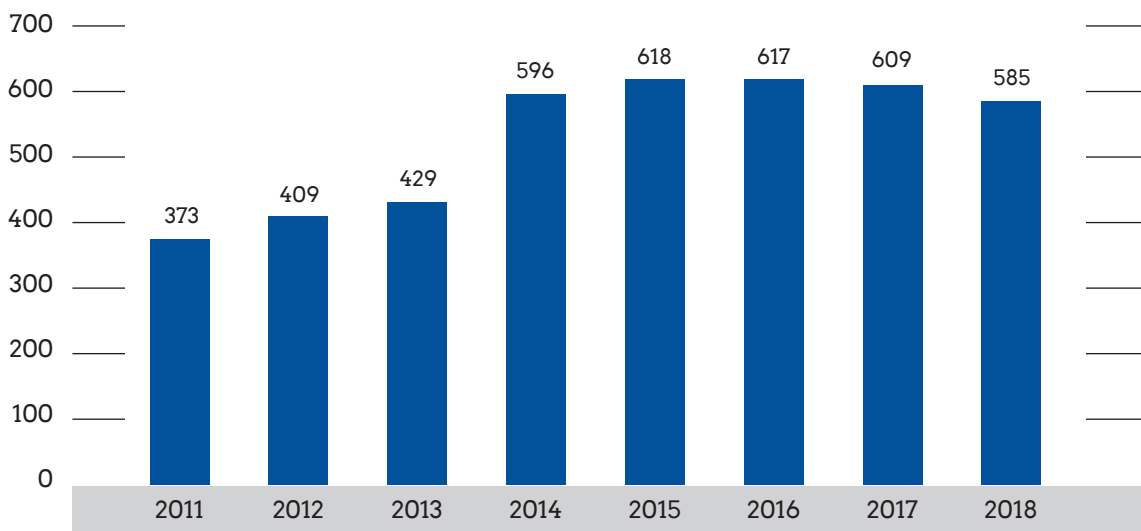
TOTALS	575
Q1	258
D1	114

Collaborations

CIBERES	143
CIBER*	102

*Over several thematic areas

Evolution of publications



10 most relevant CIBERES publications in 2018 by impact factor

IF	Publication
79,258	RABE K.F., NAIR P., BRUSSELLE G., MASPERO J.F., CASTRO M., SHER L. et al. <i>Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. New England Journal of Medicine.</i> 2018;378(26):2475-2485

79,258	CASTRO M., CORREN J., PAVORD I.D., MASPERO J., WENZEL S., RABE K.F. ET AL. <i>Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. New England Journal of Medicine.</i> 2018;378(26):2486-2496
53,254	PAVORD I.D., BEASLEY R., AGUSTI A., ANDERSON G.P., BEL E., BRUSSELLE G. ET AL. <i>After asthma: redefining airways diseases. The Lancet.</i> 2018;391(10118):350-400
53,254	Agusti A. <i>Filling the gaps in COPD: the TRIBUTE study. The Lancet.</i> 2018;391(10125):1004-1006
27,125	WAAGE J., STANDL M., CURTIN J.A., JESSEN L.E., THORSEN J., TIAN C. ET AL. <i>Genome-wide association and HLA fine-mapping studies identify risk loci and genetic pathways underlying allergic rhinitis. Nature Genetics.</i> 2018;50(8):1072-1080
25,148	TORRES A., ZHONG N., PACHL J., TIMSIT JF, KOLLEF M, CHEN Z ET AL. <i>Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, phase 3 non-inferiority trial. The Lancet. Infectious diseases.</i> 2018;18(3).
25,148	MAZUR N.I., HIGGINS D., NUNES M.C., MELERO J.A., LANGEDIJK A.C., HORSLEY N. ET AL. <i>The respiratory syncytial virus vaccine landscape: lessons from the graveyard and promising candidates. The Lancet Infectious Diseases.</i> 2018;18(10):e295-e311.
21,466	FERRANDO C., SORO M., UNZUETA C., SUAREZ-SIPMANN F., CANET J., LIBRERO J. ET AL. <i>Individualised perioperative open-lung approach versus standard protective ventilation in abdominal surgery (iPROVE): a randomised controlled trial. The Lancet Respiratory Medicine.</i> 2018;6(3):168-170.
21,466	AGUSTI A., FANER R. <i>COPD beyond smoking: new paradigm, novel opportunities. The Lancet Respiratory Medicine.</i> 2018;6(5):324-326.
21,466	AGUSTI A., FANER R., CELLI B., RODRIGUEZ-ROISIN R. <i>Precision medicine in COPD exacerbations. The Lancet Respiratory Medicine.</i> 2018;6(9):657-659.

Patents owned by CIBER

Applications

- Date: 13/2/2018 European patent EP18382080.2 "Method and apparatus for the cardiovascular assessment of a subject in need thereof".
- Date: 6/6/2018 European patent EP18382403.6 "In vitro method for the diagnosis or detection of non-tuberculous mycobacteria".

- Date: 18/6/2018 European patent EP18382437.4 "Identification of metabolomic signatures in urine samples for tuberculosis diagnosis".
- Date: 29/5/2018 PCT application PCT/ES2018/070390 "Método in vitro para identificar escalones de gravedad en pacientes con asma bronquial".

GRANTED

- Patent: "Micobacterias inactivadas para su uso por vía oral en la prevención de la tuberculosis" granted in China CN104582721 (B) Date 2018-01-26; and granted in Europe EP2865388 (B1) date: 2018-08-08.

Clinical Guides

- Guía de diagnóstico y tratamiento de la hipertensión pulmonar: resumen de recomendaciones.

- Recomendaciones sobre tratamiento no farmacológico en la enfermedad pulmonar obstructiva crónica de la Guía española de la EPOC (GesEPOC 2017).
- *Global strategy for the diagnosis, management and prevention of COPD, 2018 report.*

- *ARIA pharmacy 2018 "Allergic rhinitis care pathways for community pharmacy.*
- *MASK 2017: ARIA digitally-enabled, integrated, person-centred care for rhinitis and asthma multimorbidity using real-world-evidence.*
- *Diagnosis and management of NSAID-Exacerbated Respiratory Disease (N-ERD)-a EAACI position paper.*
- *Position paper on nasal obstruction: evaluation and treatment.*
- *Antibiotic selection in the treatment of acute invasive infections by Pseudomonas aeruginosa: Guidelines by the Spanish Society of Chemotherapy.*
- *Spanish Guidelines on the Evaluation and Diagnosis of Bronchiectasis in Adults.*
- *Spanish Guidelines on Treatment of Bronchiectasis in Adults.*
- *Russian guidelines for the management of COPD: algorithm of pharmacologic treatment.*
- *Vacunación frente a tuberculosis.*
- *Developing definitions for invasive fungal diseases in critically ill adult patients in intensive care units. Protocol of the FUNgal infections Definitions in ICU patients (FUNDICU) Project.*
- *Diagnóstico microbiológico de las infecciones causadas por el género Mycobacterium.*

CIBERES Groups. Publications 2018

Group leader	Total	Q1	D1	Institution / Centre	Province
 Agustí García Navarro, Álgvar	45	16	14	Hospital Clínic y Provincial de Barcelona	Barcelona
 Álgvarez Martínez, Carlos José	6	2	1	Servicio Madrileño de Salud. Hospital Universitario 12 de Octubre	Madrid
 Ardanuy Tisaire, María Carmen	20	6	1	Fundación IDIBELL. Hospital Universitario de Bellvitge	Barcelona
 Barbé Illa, Ferrán	40	18	5	Instituto de Investigación Biomédica de Lleida. Fundación Dr. Pifarre	Lleida
 Barberá Mir, Joan Albert	30	14	8	Hospital Clínic y Provincial de Barcelona	Barcelona
 Blanch Torra, Lluís	40	22	14	Corporación Sanitaria Parc Taulí	Barcelona
 Bouza Santiago, Emilio (1)	49	25	14	Servicio Madrileño de Salud. Hospital Gregorio Marañón	Madrid
 Cardona Iglesias, Pere Joan	17	9	3	Fundación Instituto de Investigación Germans Trias i Pujol. Hospital Germans Trias I Pujol	Barcelona
 Casals Carro, Cristina	2	2	0	Universidad Complutense de Madrid. Facultad de Biología	Madrid
 Del Pozo Abejón, María Victoria	15	6	4	Instituto de Investigación Sanitaria Fundación Jiménez Díaz	Madrid
 Farre Ventura, Ramón	20	14	6	Universidad de Barcelona. Facultad de Medicina	Barcelona
 García López, Ernesto	11	6	0	Agencia Estatal Consejo Superior de Investigaciones Científicas. Centro de Investigaciones Biológicas	Madrid
 García Río, Francisco José	31	9	4	Servicio Madrileño de Salud. Hospital La Paz	Madrid
 Gea Guiral, Joaquim	40	15	5	Consorci Mar Parc Salut de Barcelona. Hospital del Mar	Barcelona

<i>Group leader</i>	<i>Total</i>	<i>Q1</i>	<i>D1</i>	<i>Institution / Centre</i>	<i>Province</i>
 González Mangado, Nicolás (2)	14	5	2	Instituto de Investigación Sanitaria Fundación Jiménez Díaz	Madrid
 López-Campos Bodineau, José Luis	42	12	2	Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla. Hospital Virgen del Rocío	Sevilla
 Lorente Balanza, José Ángel	15	8	4	Servicio Madrileño de Salud. Hospital Universitario de Getafe	Madrid
 Marimón Ortiz de Zarate, José M ^a (3)	5	2	1	Asociación Instituto Biodonostia. Hospital Donostia	Guipúzcoa
 Martín Montañés, Carlos	13	9	4	Universidad de Zaragoza	Zaragoza
 Masa Jiménez, Juan Fernando	15	4	1	Fundación para la Formación y la Investigación de los Profesionales de la Salud (FUNDESALUD). Hospital San Pedro De Alcántara	Cáceres
 Menéndez Fernández, Margarita	6	4	2	Agencia Estatal Consejo Superior de Investigaciones Científicas. Instituto de Química Física Rocasolano	Madrid
 Monsó Molas, Eduard	15	8	2	Corporación Sanitaria Parc Taulí	Barcelona
 Montserrat Canal, Josep María	22	13	3	Hospital Clínico y Provincial de Barcelona	Barcelona
 Morcillo Sánchez, Esteban Jesús	5	2	1	Universidad de Valencia. Facultad de Medicina	Valencia
 Mullol Mirret, Joaquín	5	0	0	Hospital Clínico y Provincial de Barcelona. Instituto de Investigaciones Biomédicas August Pi i Sunyer	Barcelona
 Muñiz Albaiceta, Guillermo	6	4	1	Fundación para la Investigación e Innovación Biosanitaria en el Principado de Asturias (FINBA)	Asturias
 Muñoz Gall, Xavier	66	23	10	Fundación Hospital Universitario Vall d'Hebrón - Institut de Recerca (VHIR). Hospital Valle Hebrón	Barcelona
 Nieto Martín, Amelia	4	3	2	Agencia Estatal Consejo Superior de Investigaciones Científicas. Centro Nacional de Biotecnología	Madrid
 Obeso Cáceres, Ana (3)	4	2	0	Universidad de Valladolid. Facultad de Medicina	Valladolid
 Pérez Vizcaíno, Francisco	8	6	3	Universidad Complutense de Madrid. Facultad de Farmacia	Madrid
 Relló Condomines, Jordi	24	9	4	Fundación Hospital Universitario Vall d'Hebrón - Institut de Recerca (VHIR). Hospital Valle Hebrón	Barcelona
 Ruiz Cabello Osuna, Jesús	10	7	3	Universidad Complutense de Madrid. Facultad de Farmacia	Madrid
 Torres Martí, Antoni	53	23	11	Hospital Clínico y Provincial de Barcelona	Barcelona
 Villar Hernández, Jesús	20	12	4	Fundación Canaria de Investigación Sanitaria (FUNCANIS). Hospital Universitario de Gran Canaria Dr. Negrín	Las Palmas

(1) PI replaced by Patricia Muñoz

(2) PI replaced by Germán Peces-Barba

(3) Group deregistered in 2018



**Epidemiology and
Public Health**

PREVENTION
SENTINEL
ATTENTION



Scientific Director's Presentation

Marina Pollán Santamaría

In 2018 CIBERESP did a lot of hard research and collaboration work, with 1030 publications (58% in the first quartile and 29% in the first decile), including over 60 articles with an impact factor >10. We should underline the *New England* led by J.R. Banegas, (F. Rodríguez-Artalejo's group) "Relationship between clinic and ambulatory blood-pressure measurements and mortality".

CIBERESP has seven research programmes and one training programme. In Programme 1 "Epidemiology and Control of Chronic Diseases" we should stress the project granted by the AECC for the Gen-Risk proposal, the high scientific production of the MCC-Spain subprogramme and the new collaborative action with the Spanish Cancer Registries. In programme 2 "Communicable Disease Prevention, Surveillance and Control" this year we should stress the evaluation of the effectiveness of the anti-flu vaccination in the >65 and of the pertussis vaccination in pregnant women. From Programme 3 "Biological, Behavioural and Structural Determinants in the Contraction and Spread of Communicable Diseases in Vulnerable Populations" we should stress the cohort of immigrant families (PELFI), as well as the hard research work done in the field of HIV. In 2018 Programme 4 "Social Determinants of Health" started an action on Gender Violence, supported by a European project, and has studied the impact on health of the crisis. In Programme 5 "Epidemiology and Prevention in Environmental and Occupational Health" the scientific production of the INMA Project continues to deserve mention and is being extended with the creation of new cohorts. In Programme 6 "Evaluation of Health Services" the impact of the non-stable labour market on inability

to work has been quantified. This programme sustains the BiblioPRO platform, which has this year been internationalised with the creation of BiblioPRO-Europe. Programme 7 "Clinical Epidemiology" carried out a large amount of work in the assessment of clinical practice by means of °GRADE methodology, facilitating the dissemination of information and evaluation through several tools (MAPAC, GRAMA).

In 2018, we decided to change the structure of the Annual Meeting to give this a more scientific content and foster the participation of young researchers. At this meeting we invited the scientific directors of CIBERES (Dr. Ferrán Barbé), CIBERONC (Dr. Joaquín Arribas) and CIBERSAM (Dr. Eduard Vieta) to further the knowledge and cooperation between areas. The session had a round table on "Knowledge Transfer in Epidemiology and Public Health", at which we attempted to find out what this is and what the value of transfer is in our field.

In the Training Programme we should stress the cooperation of other CIBER areas in the *Encounter for Excellence in Public Health in Minorca*, the mobility actions and promotion of visibility of young people at the CIBERESP Scientific Symposium.

Lastly, CIBERESP works in close cooperation with the *Sociedad Española de Epidemiología* (SEE). This year, as well as the awards for the best communications of young epidemiologists, we organised a CIBERESP Spontaneous Round Table at the XXXVI SEE Scientific Meeting and 13th Meeting of the Portuguese Epidemiology Association in Lisbon.

Scientific Programmes

Programme for Epidemiology and Control of Chronic Diseases

Coordinator:
M^a José Sánchez Pérez

The programme has gone on with the scientific work of the MCC- Spain strategic subprogrammes (Multi-centre multi-case population-based study on cancer) and Gen-Risk (a subprogramme intended for genetic screening of the main chronic diseases, for preventive purposes), and a new subprogramme on Epidemiological Surveillance of Cancer has been got under way, in cooperation with the Spanish Network of Cancer Registries (REDECAN).

MCC-Spain

MCC-Spain is monitoring the cases of cancer to see how these evolve over time and to study their quality of life.

In 2018 21 scientific articles were published in indexed journals, the one with greatest impact (D1 and IF of 9.090) being a study providing the first evidence of an association between a pattern of western diet and chronic lymphatic leukaemia (CLL), which suggests that a proportion of the cases of CLL could be prevented by modifying eating habits: Solans M, Castelló A, Benavente Y, et al. 2018.

Another publication of MCC-Spain to be stressed due to its high media impact shows the importance of evaluating circadian rhythms in studies on diet and cancer. Leaving an interval of 2 hours between supper and bedtime could

reduce the risk of breast or prostate cancer by 20%: Kogevinas M, Espinosa A, Castelló A, et al. 2018.

Another result of MCC-Spain shows that maintaining high levels of vitamin D prevents the risk of developing breast cancer. This is the first study carried out in Spain providing information on the association between the levels of 25(OH)D in the blood and the different histological types of breast cancer.

Gen-Risk

The Fundación Científica de la Asociación Española contra el Cáncer (AECC) has given a 500,000€ grant for undertaking a project in the Gen-Risk sub-programme. The project, led by Victor Moreno, is to a large extent sustained on the MCC-Spain study. Its aim is to seek biomarkers which can be used for identifying which people have the greatest risk of developing one of the five cancers included in the study (bowel, breast, stomach, prostate and chronic lymphocytic leukaemia), in order to steer the prevention of these tumours more accurately, reducing both morbidity and the social and economic impact entailed by these.

Epidemiological Surveillance of Cancer

The Instituto de Salud Carlos III has financed the project entitled "Multi-level Population Study on Socio-economic Inequalities in the Geographical Distribution of the Incidence, the Mortality and the net Survival of Cancer in Spain" in the framework of the new sub-programme on Epidemiological Surveillance of Cancer, coordinated by Pablo Fernández and María José Sánchez. Its aim is to characterise socio-economic inequalities in the incidence, excess mortality, premature mortality and net

survival for three of the cancers with greatest incidence (lung, bowel and breast) in Spain, using the European Deprivation Index. This national population-based study will evaluate the impact of socio-economic inequalities,

Programme for Communicable Disease Prevention, Surveillance and Control (PREVICET)

Coordinator:
Pere Godoy García

Some of the most relevant projects in the CIBERESP PREVICET Programme are listed below:

The project entitled “Effectiveness of vaccine against pertussis in pregnant women in the third trimester” (PI: Pere Godoy PI15/01348) –which involves the groups led by **Àngela Domínguez**, Jesús Castilla, Cristina Rius and Carmen Muñoz– estimated the effectiveness of the (EV) vaccine to prevent cases in <1 year and <2 months. The EV adjusted to prevent whooping cough in <1 year was 78.9% (IC95%: 58.4- 89.3) and in <2 months 94.4% (IC95%: 66.3% -99.1%) (Articles under way). The doctoral thesis on “Effect of anti-influenza vaccination in patients admitted to hospital” was read (Itziar Casado, from the group whose PI is Jesús Castilla) with partial results of Research Project PI12/02005, PI: Àngela Domínguez.

The **group led by Amparo Larrauri** has taken part, along with other PREVICET groups, in the project on the effectiveness of the anti-flu vaccine in >64 years (Horizon2020, EU634446); also, in another European project on the effectiveness of the vaccine in <65 years (ECDC Call for tender) (one article in Eurosurveillance and two in I&ORV). The study entitled “Risk of complications in pregnant women admitted to hospital with serious flu infections” has been carried out (PlosOne). The groups led by Juan E. Echevarría, Jesús Castilla, Àngela Domínguez and the CIBER group on Respiratory Diseases led by José M. Marimón Ortiz took part in this. The research into the vaccine contributed to the reports for the selection of vaccine strains (GIVE 2018, WHO).

using ground-breaking epidemiological methods including spatial analysis, multi-level modelisation, net survival and the evaluation of economic impact.

Juan E. Echevarría has led collaborative projects – PIs: Amparo Larrauri, Jordi Figuerola and Carmen Muñoz – on diseases included in the triple viral vaccine (PI15CIII/00023), potentially emerging viral diseases associated with Iberian bats (SAF2017-89355-P), and by enteroviruses and parechoviruses causing serious pathologies in the child population (PI15CIII-00020) (7 publications). We should highlight a new proposal for molecular markers for the surveillance of parotitis, and the fact that the new Lleida lyssavirus is not appropriately neutralised by antibodies induced by the anti-rabies vaccine.

The **group led by Jordi Figuerola** and that of Juan E. Echevarría have assessed the effectiveness of two methods for detecting IgM antibodies against the Zika virus. The group led by Jordi Figuerola and Cristina Rius has studied two recent cases of Dirofilariosis in residents of the city of Barcelona. Lastly, the group led by Figuerola is involved in the Cost AIM action entitled Aedes Invasive Mosquitoes in Europe to improve the systems for surveillance of invasive mosquitos.

Carmen Muñoz and her team have taken part in two European studies on the impact of the PCV13 vaccine on the disease and serotypes (Thorax and Journal of Infection); also, in an international study on the performance of microbiological tests to determine causes of death (Scientific Reports) and on the diagnosis of Bordetella spp (J Clin Microbiol); also, in two studies on infection by cytomegalovirus, parvovirus and enterovirus in newborn babies and on the changes in the pneumococcal serotypes causing otitis (PlosOne).

The group led by **Cristina Rius** and Àngela Domínguez’s group have cooperated in the project for epidemiological characterisation of serious cases of flu. Rius’s group has also worked with Jordi Figuerola’s group on the detection of the first cases of autochthonous circulation of Dengue. Mosquitos with the Dengue virus were found near the house of one of the people affected, confirming the risk for public health.

DAPET Programme (Biological Behavioural and Structural Determinants in the Contraction and Spread of Communicable Diseases in Vulnerable Populations)

Coordinator:

Jordi Casabona Barbarà

- As part of the Subprogramme on Immigration and Health (SIS) cooperation with the group led by PI Fernando García Benavides (Programme 6) has continued, in particular analysing the information produced by the Platform of Longitudinal Studies on Immigrant Families (PELFI).
- Completion of the Communication Strategy of the SIS presented at the CIBERESP Scientific Symposium.
- The PREVICET Coordinator, Pere Godoy (Programme 2) was invited to the annual coordination meeting and a new Subprogramme for infections communicable by organic fluids in vulnerable populations was set up.
- A major participation at the Scientific Meeting of the Sociedad Española de Epidemiología, with different communications and spontaneous round table "Latin-American Network for Studies on HSH and Transsexual Women". The Network presentation was attended by the director of the Programa Nacional para a Infecção VIH, Sida de Portugal (Isabel Aldir).
- Three awards were given for the best paper in different categories (Ikram Benazizi, Andreu Bruguera and Cristina Agustí).
- Two intra CIBERESP mobility grants were obtained: Susana Ruiz and Laia Ferrer.

Participation in national and international projects:

- FIS: "Determinants and needs of sexual health in a multi-centre cohort of trans-gender women and men acting as sex workers in Barcelona - Sexcohort" (PI: J. Casabona).
- Gilead Sciences: "HepC-link-Pilot hepatitis C micro-elimination strategy in Pakistani immigrants in Catalonia through the implementation of a community intervention" (PI: E. Martró).

- Gilead Grants: "ReHCV - Molecular epidemiology study of HCV reinfection in the Catalan Penitentiary System" (PI: E. Martró).
- Ministry of Science, Innovation and Universities: "Genomics and evolution of bacteria resisting antibiotics: from molecular epidemiology to phylogenomics" (PI: F. González-Candelas).
- "Evaluation of the feasibility of a transcontinental study on mother-child microbial transmission in the autochthonous population of Latin-American countries" (PI: E. Calderón and A. Moya and J.C. Galán's groups).
- "ERANet-LAC-Recognition of the primary infection by Pneumocystis in infants: a silent threat to public health" (PIs: A Moya and E Calderón).
- "Sweetie- Study of the prevalence of the Human Papilloma Virus and other sexually-transmitted infections and study of their determinants in trans men and women sex workers"; (PI: S de Sanjosé and A Moya, J. Casabona, J.C. Galán's groups).
- "Study of new recombining forms of HIV in Sub-Saharan population"; (PIs: Á Holguín - J.C. Galán- and F. González-Candelas -A. Moya).
- "Analysis of plasmids associated with multi-resistance to antimicrobials in Enterobacteria; (PIs: F. González-Candelas -A. Moya- and Á. Sanmillán -J.C. Galán)
- "Evolution and genomic epidemiology of antibiotic-resistant enterobacteria" (PIs: T. Coque -J.C. Galán- and F. González-Candelas -A. Moya).
- "Genomic epidemiology of sexually transmitted bacteria" (PIs: F González- Candelas and J.C Galán).

Scientific production:

- 4 doctoral theses presented.
- Collaborative publications:
 - *Health Soc Care Community*. 2018 Jan;26(1):e64-e74.
 - *Int J Environ Res Public Health*. 2018 Nov 8;15(11). pii: E2488.
 - *Public Health*. 2018 Oct;163:27-34.
 - *Genome Biol Evol*. 2018; 10 (6): 1596-1606.
 - *PLoS One*. 2018; 13 (3): e0194186.
 - *J Viral Hepat*. 2018 Mar;25(3):236-244.
- Special issue of journal OBM-Genetics "Pneumocystis: A Model of Adaptive Coevolution". Editors: A. Moya, E. Calderón.

Programme for Social Determinants of Health

Coordinator:
M^a José López Medina

The programme has gone on with the scientific work resulting from the **subprogrammes on Impact of the crisis on health and Energy poverty and health**, and in 2018 a new subprogramme on **Gender Violence** started, which seeks to go further into a line of research which is covered by a competitive European project and others nationwide, all led by researchers from the programme.

Different groups from the programme have over the year published articles on the impact of the crisis on different health outcomes, such as mortality, reproductive health, drug-taking or perceived health, as well as a large number of articles connected with other fields connected with social determinants, published in first quartile international journals. One of these deserving mentions is the systematic review published in the British Medical Journal.

Furthermore, members of the different groups in the programme are leading workpackages on H2020 projects currently under way. These international projects cover different subjects such as child obesity, exposure to environmental tobacco smoke, gender violence or health technologies applied to the assessment of urban

interventions. In 2018 the European Union's Joint Action on Health Equity was also started. This was led by Giuseppe Costa (Italy) and one of the groups also takes part in this.

The different groups also lead projects financed by the Instituto de Salud Carlos III, which include subjects connected with gender violence, the impact on health of cooperative housing, factors associated with population ageing on the survival of acute lymphatic leukaemia.

In 2018 other projects were also obtained in competitive calls such as that of the National Plan for Drugs, and researchers were contracted in other competitive calls such as the Miguel Servet funding. The Programme also takes part in the Translational Coordinated Group (AECC): 'Genetic and metabolomics screening towards precision medicine in cancer prevention', for which financing was obtained in 2018.

We are also taking part in the PACE (Pregnancy And Childhood Epigenetics) consortium, made up of researchers from the National Institute of Environmental Health Science, USA (NIEHS) and from other worldwide institutions with the aim of examining the impact of environmental exposure in early stages of life on health throughout life, by analysing epigenetic biomarkers.

Lastly, a patent/licence for a patient safety questionnaire has been obtained (See <https://innovation.ox.ac.uk/outcome-measures/patient-reported-experiences-outcomes-safety-primary-care-preos-pc/>).

Programme for Epidemiology and Prevention in Environmental and Occupational Health

Coordinator:
Adonina Tardón García

In 2018 the INMA Project was carrying out cooperative research between 15 CIBERESP

groups (26% of all the groups) of 7 of Spain's 'autonomous communities' as reflected in joint publications, in the collaborative projects obtained and in mobility between the researchers in these groups. As well as being a multi-centre project including 7 birth cohorts distributed over 6 communities, we are examining the inclusion of new birth cohorts which are being started in other regions (GENEIDA, NELA, BiSC, Gijón), always maintaining a multi-disciplinary approach. We have also established contacts and cooperation with CIBER groups in other thematic areas, such as CIBERES, CIBERSAM and CIBEROBN, and are open to cooperation with other CIBERs. Lastly, the INMA project has a great track record in active cooperation with many international groups, bolstering the European network of birth cohorts

through cooperation in joint publications and projects, stressing the major role that this has in consolidation of the international network of birth cohorts (www.birthcohorts.net; www.lifecycle-project.eu). In line with the INMA policy of external collaboration, we have over 100 cooperation schemes under way with national and international groups. We have also carried out 8 mobility actions between CIBERESP groups or with other national or international groups.

We carry out research lines focussing directly on the main problems of child health affecting the Spanish population, such as obesity, asthma and respiratory health, nutrition, the effects of air contamination, exposure to persistent and non-persistent chemical compounds and exposure to electromagnetic fields, amongst others. In 2018 we carried out these research lines in the form of 42 national and international competitive projects currently in progress (2 of which were requested by the CIBERESP) granted to 25 researchers, 10 of them in their postdoctoral

or consolidation careers thanks to competitive contracts granted (Sara Borrell, Juan de la Cierva, Beatriu de Pinós, Miguel Servet type I and type II); 11 competitive predoctoral contracts (PFIS, iPFIS, FPU, FI-Agaur, etc.); 37 doctoral theses and 31 master theses leading to the publication of scientific articles of great impact in national and international journals. In 2018 we were granted 7 national research projects and 3 international ones (1 of which was applied for from the CIBERESP), 8 doctoral theses have been defended, 23 master theses; we have been granted 5 competitive predoctoral contracts (iPFIS, FPU, Rio Hortega, etc.), 3 competitive postdoctoral contracts (Juan de la Cierva, Beatriu de Pinós, Basque Government), and 1 contract for the consolidation of competitive researchers (Miguel Servet type II).

Programme for Evaluation of Healthcare Services

Coordinator:
Jordi Alonso Caballero

Subprogramme on "Estimation of the healthcare and social burden of chronic diseases based on the Continuous Cohort of Employment Records (MCVL)"

A growing employment market is connected with a lower risk of days' off through illness in young men (aOR: 0.21 [IC 95%: 0.04-0.96]). An association can be seen between the drop-in salary and risk of developing working leave patterns, in both young men and women. These results suggest that more stable labour markets reduce temporary incapacity episodes.

Subprogramme on Health Measurement - BiblioPRO.

The project continues to be in systematic review of the application of PRO instruments in Spain

and evidence-based recommendations. The platform has raised its number of users (16,108) currently providing information and access to 2026 questionnaires. There were two new developments in 2018 for internationalisation of the platform: new BiblioPRO-Europe website and online access for the valuation of the EMPRO tool.

Some of the **group's activities** deserving mention are the start of the project coordinated by Jordi Alonso "Suicide Risk Code", analysing a cohort of over 10,000 cases for predicting risk. Furthermore, in a systematic review of 148 prospective studies the specific pattern of side effects depending on the treatment is confirmed, proving that brachytherapy and active surveillance are alternatives to radical prostatectomy according to the results perceived by patients. Fernando G^a. Benavides's group used Kuznets' relative and Keppel's indices, in 20 Latin American countries, observing a lower occupation rate, greater unemployment and unreliability in women, young people and persons with a lower education level in most countries. A study was also made of general mortality between 15 and 60 years of age and the incidence of injuries due to occupational accidents. Victoria Serra's group cooperates in such international projects as Act on Scale and ICTUSnet, with significant scientific production and of clinical practice guidelines and reports, including the plan for evaluation of the impact of the Act on Dementia. We

should stress the article entitled “Identificación y priorización de prácticas clínicas de poco valor: los profesionales de atención primaria deciden”. Primary care. Antonio Serrano’s group has estimated the effectiveness of a non-pharmacological intervention on anti-depressives in tackling depression in Primary care, the effects of pharmaceutical co-payment on the non-

initiation of drugs prescribed in Primary Care. We have also taken part in the territorial diagnosis on Mental Health of 5 areas of Catalonia. The *XII edición del Curso de Evaluación Económica y Política Sociosanitaria* was held in Barcelona, along with the Universidad Loyola Andalucía, the King’s College of London and the London School of Economics and Political Science.

Clinical Epidemiology Programme

Coordinator:
José Ignacio Pijoán Zubizarreta

In 2018 the first cooperative publication of FIS PI15/00886 project “Study for adaptation of intermittent hormonal therapy in patients with prostate cancer” took place: Bonfill X. Intermittent androgen deprivation therapy: recommendations to improve the management of patients with prostate cancer following the GRADE approach. *Cancer Manag Res.* 2018; 10: 2357–2367. This presents a systematic review of the scientific evidence and establishes recommendations for use of intermittent antiandrogenic therapy in this pathology according to the GRADE approach, to be of use for evaluating the present use of participating institutions and autonomous communities.

A cooperative article has also been published for dissemination of a methodological web page for an efficient estimation of the sample size in clinical trials using compound variables as outcome variables: Marsal JR Bin-CE: A comprehensive web application to decide upon the best set of outcomes to be combined in a binary composite endpoint. *PLoS One.* 2018; 13(12): e0209000. Published online 2018 Dec 13. doi: 10.1371/journal.pone.0209000.

We commemorated the 25th anniversary of the creation of the Clinical Biostatistics Unit of the Hospital Universitario Ramón y Cajal with a scientific symposium with over 100 persons registered from different CIBERESP programmes and CIBER areas and other groups and research networks. The thematic axis was clinical research, and this was attended by reputed national

speakers, with the presence of professor Stuart Pocock, from the London School of Hygiene and Tropical Medicine.

In the area of transfer actions, the expansion of the **MAPAC** continues with the creation of further committees: Joint Committee of the Healthcare Organisations of the Hospital de Cruces and San Eloy Hospital in Bizkaia, with the preparation of the first report for transfer of recommendations on the use of SYSADOAs in arthrosis. This Committee is presided over by a researcher from the programme. A corporate MAPAC committee of Osakidetza/Basque Health Service was also set up, and similar committees are being created in all the organisations of Osakidetza, to work as a network. The programme also took part in the transfer round table organised at the CIBERESP scientific symposium with the talk on “What is transfer in Epidemiology and Public Health”. Vision of a rank and file epidemiologist.

The committees working in the Clinical Epidemiological Programme have produced over ten transfer reports which are being applied to the healthcare protocols of their centres. A digital platform (GRAMA) has been set up to support the joint work done by these committees and other similar ones that are being created in different autonomous communities. This platform enables using a common methodology, developed by several groups in the programme, and facilitates sharing resources and reports on adaptation and transfer of knowledge.

We should lastly stress the ERC grant of almost one and a half million euros obtained by Lucy A. Parker (PI Blanca Lumbreras) to research into the transfer and adaptation of guides produced in economically rich countries to environments with a lower degree of development, in the field of diabetes mellitus.

Training Programme

Coordinator: *Beatriz Pérez Gómez*

This year the Training Programme has maintained its two basic lines of action: mobility and improvement.

In 2018 the categories of mobility grants, created to encourage cooperation of CIBERESP researchers with each other and with other groups, have been maintained. These grants are intramural, meaning that they are intended exclusively for personnel contracted or attached to CIBERESP. On the national level, a total number of 12 grants for short stays at CIBERESP groups have been offered. International mobility has also been furthered, through grants for 3-month stays that CIBERESP traditionally calls to enable its doctorate students, including contracted, attached staff and contributors to get an international mention, four grants being issued this year.

Grants for improvement are extramural, open to researchers from outside the CIBERESP, and are intended to promote quality research into Public Health. They are also a good tool for furthering cooperation with other CIBER areas. In 2018 the existing agreement with CIBEROBN was extended to the CIBERONC and CIBERCV to cooperate in the Encounter for Excellence in Public Health which is traditionally arranged by CIBERESP at the Public Health Summer School in the Lazareto de Maó in Minorca. This encounter is intended to give young scientists

being trained in Epidemiology and Public Health the chance to directly debate and swap ideas on their doctoral thesis projects with scientists accredited in Public Health in an informal setting. Through this agreement, 8 of the total number of 11 grants offered were financed by CIBERESP, while the area of Obesity and Physiopathology of Nutrition (CIBEROBN) and that of Cardiovascular Diseases (CIBERCV) and Cancer (CIBERONC) each financed two attendance grants specifically intended for doctorands in their own fields. Once again, cooperation was highly positive, meaning that the agreement will be maintained in 2019.

Apart from this, CIBERESP also continues financing the Prize for the **10 best papers** presented by young research staff at the *SEE Scientific Annual Meeting*, which is held jointly with the Congress of the Portuguese Epidemiology Association, and the *Ibero-American Congress of Epidemiology and Public Health, SESPAS/SEE*. In its present format, this award includes a diploma and covers the cost of registering the prize winner at the meeting for the following year. The training programme also continues to promote training and scientific activities being done to establish special more favourable conditions for CIBERESP members.

Platforms

BIBLIOPRO

BiblioPRO is a virtual repository of Patient-Perceived Outcomes (PROs) with the task of promoting the measurement of PROs by obtaining

detailed information, as a result of systematic reviews of literature; scientific evaluations and specialised training.

The BiblioPRO Scientific Committee includes 18 researchers from 14 different institutions (including researchers from the CIBERESP, CIBERNED, CIBERSAM and REDISSEC).

Repository:

Registered users: 2962 new users (16,108 accumulated users: 23% increase as compared with the ones accumulated until 2017).

Monthly visits: an average of 9000 visits a month, maintaining annual visits at >100,000.

Sublicenses: 542 licences granted, similar to 2017.

New instruments: 331 new instruments included in the repository (2026 accumulated instruments: 20% increase as compared with the ones accumulated until 2017).

Systematic review:

- publications in 2016 – peer review of 2400 titles and 942 summaries, extraction of data from 738 articles.
- publications in 2017 – 1909 titles and summaries of 4695 articles identified have been reviewed.

BiblioPRO Europe:

Development of the new European website of BiblioPRO which will enable PROs to be distributed internationally.

An extension of the OPTUM agreement was signed, enabling the management of licences of the SF Health Surveys and other instruments and services of this company in Europe.

Other international distribution agreements being developed:

- Test on adhesion to inhalers (Chiesi, SEPAR), 13 languages
- Heridutart Angioedema -QoL for adults (FIBHULP-IdiPAZ): 19 languages.

Research:

Competitive research projects:

- “Application of PRO instruments in Spain: systematic review and evidence-based recommendations”, PI Olatz Garin and team with CIBERESP researchers and BiblioPRO Scientific Committee (PI16/00130-ISCIII/FEDER), 2017-2019.
- “Effectiveness of the treatment of massive injuries of the shoulder rotator cuff evaluated with relevant outcomes for the patient: mixed

methodology study”. co-PIs: Montserrat Ferrer and Carles Torrents, other researchers from the BiblioPRO team (PI18/00152-ISCIII/FEDER), 2019-2021.

- Cooperation in the BIBLIOINDICA project to design a library of healthcare indicators. Joint CIBERESP and REDISSEC initiative.

EMPRO Platform:

- New online platform of the EMPRO tool developed, measuring the metric characteristics of PROs. Allows the independent assessment by experts of PRO instruments, consensus and calculations of scores. The management of the new platform will be central by means of the new administrator (IMIM). Any interested researchers will receive the prepared user version.
- Presented at the two most important international congresses of PROs.

Publications:

- ZAROR C, MARTÍNEZ-ZAPATA MJ, ET AL. *Impact of traumatic dental injuries on quality of life in preschoolers and schoolchildren: A systematic review and meta-analysis. Community Dent Oral* 2018; 46(1): 88-101.
- VROTSOU K*, ÁVILA M, ET AL. *Constant-Murley Score: systematic review and standardized evaluation in different shoulder pathologies. Qual Life Res* 2018; 7(9): 2217-26.
- HERNÁNDEZ G, GARIN O, ET AL. *Validity of the EQ-5D new 5-level version and reference norms for the Spanish population. Qual Life Res* 2018; 27(9): 2337-48.
- MARTÍ-PASTOR M, PONT A, ET AL. *Head-to-head comparison between the EQ-5D-5L and the EQ-5D-3L in general population health surveys. Population Health Metrics* 2018, 16(1): 14.

Scientific Production

Publications

No. of publications in 2018

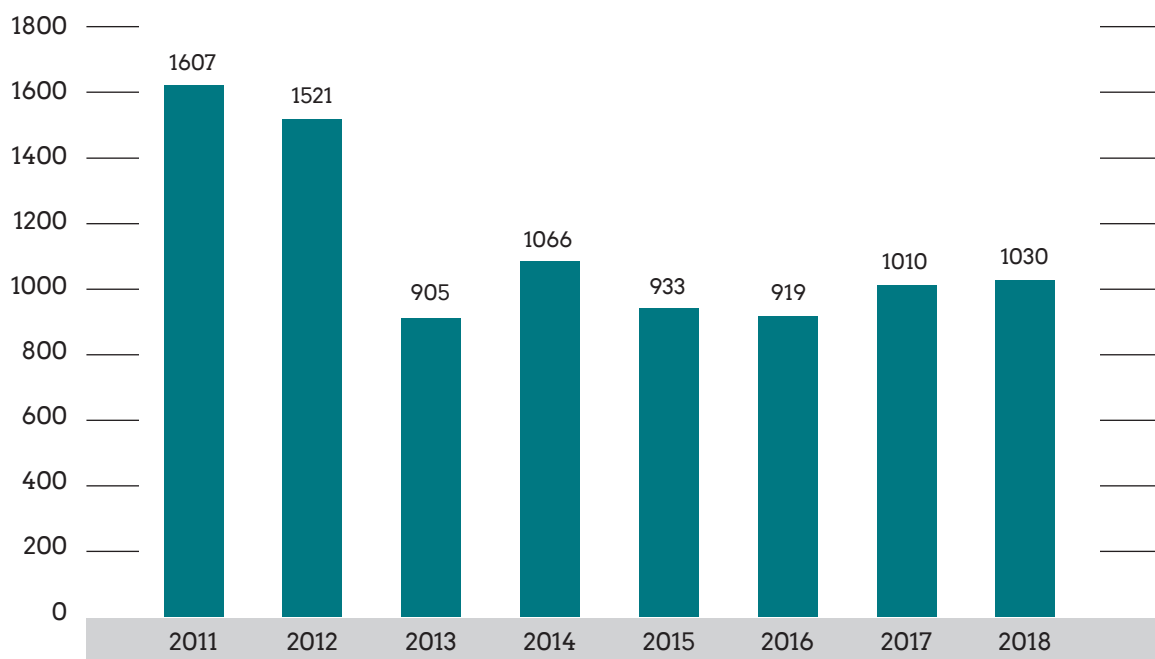
TOTALES	1030
Q1	594
D1	301

Collaborative Publications

CIBERESP	299
CIBER*	208

*Over several thematic areas

Evolution of publications



10 most relevant CIBERESP publications in 2018 by impact factor

In 2018, we cooperated in 17 articles published in journals with an impact factor >20. The 10 most relevant of these publications by impact factor are:

IF	Publication
79,2580	BANEGAS J.R., RUILOPE L.M., DE LA SIERRA A., VINYOLES E., GOROSTIDI M., DE LA CRUZ J.J. ET AL. <i>Relationship between clinic and ambulatory blood-pressure measurements and mortality. New England Journal of Medicine.</i> 2018;378(16):1509-1520.
13,9260	SANTOS C., SANZ-PAMPLONA R., SALAZAR R. <i>RET-fusions: A novel paradigm in colorectal cancer. Annals of Oncology.</i> 2018;29(6):1340-1343.
13,3970	LACLAUSTRA M., LOPEZ-GARCIA E., CIVEIRA F., GARCIA-ESQUINAS E., GRACIANI A., GUALLAR-CASTILLON P ET AL. <i>LDL Cholesterol Rises With BMI Only in Lean Individuals: Cross-sectional U.S. and Spanish Representative Data. Diabetes care.</i> 2018;41(10):-.
12,2420	HAVET A., ZERIMECH F., SANCHEZ M., SIROUX V., LE MOUAL N., BRUNEKREEF B. ET AL. <i>Outdoor air pollution, exhaled 8-isoprostane and current asthma in adults: The EGEA study. European Respiratory Journal.</i> 2018;51(4).
11,9820	GUXENS M., LUBCZYNSKA M.J., MUETZEL R.L., DALMAU-BUENO A., JADDOE V.W.V., HOEK G. ET AL. <i>Air Pollution Exposure During Fetal Life, Brain Morphology, and Cognitive Function in School-Age Children. Biological Psychiatry.</i> 2018;84(4):295-303.
11,7760	SAN MILLAN A. <i>Evolution of Plasmid-Mediated Antibiotic Resistance in the Clinical Context. Trends in Microbiology.</i> 2018;26(12):978-985.
11,6130	CORPAS R., GRIÑÁN-FERRÉ C., PALOMERA-ÁVALOS V., PORQUET D., GARCÍA DE FRUTOS P., FRANCISCATO COZZOLINO SM ET AL. <i>Melatonin induces mechanisms of brain resilience against neurodegeneration. Journal of pineal research.</i> 2018.
9,6550	LYTRAS T., KOGEVINAS M., KROMHOUT H., CARSIN AE, ANTÓ JM, BENTOUHAMI H ET AL. <i>Occupational exposures and 20-year incidence of COPD: the European Community Respiratory Health Survey. Thorax.</i> 2018;73(11).
9,0900	SOLANS M, CASTELLÓ A, BENAVENTE Y, MARCOS-GRAGERA R, AMIANO P, GRACIA-LAVEDAN E ET AL. <i>Adherence to the Western, Prudent, and Mediterranean dietary patterns and chronic lymphocytic leukemia in the MCC-Spain study. Haematologica.</i> 2018.
8,3600	BASAGANA X., PEDERSEN M., BARRERA-GOMEZ J., GEHRING U., GIORGIS-ALLEMAND L., HOEK G. ET AL. <i>Analysis of multicentre epidemiological studies: Contrasting fixed or random effects modelling and meta-analysis. International Journal of Epidemiology.</i> 2018;47(4):1343-1354.

CIBERESP Groups. Publications

Group leader	Total	Q1	D1	Institution. Centre	Province
 Alemany Vilches, M ^a Eulalia	33	22	11	Instituto Catalán de Oncología	Barcelona
 Alonso Caballero, Jordi	36	27	11	Consorci Mar Parc Salut de Barcelona	Barcelona
 Bolumar Montrull, Francisco	34	24	7	Universidad de Alcalá - Facultad de Medicina	Madrid
 Bonfill Cosp, Xavier	34	14	7	Instituto de Investigación del Hospital de la Santa Creu i Sant Pau	Barcelona

<i>Group leader</i>	<i>Total</i>	<i>Q1</i>	<i>D1</i>	<i>Institution. Centre</i>	<i>Province</i>
 Borrell Thio, Carme	49	18	5	Agencia de Salud Pública de Barcelona	Barcelona
 Bueno Cavanillas, Aurora	39	23	6	Universidad de Granada - Facultad de Medicina	Granada
 Calderón Sandubete, Enrique José	17	11	4	Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla - Hospital Virgen del Rocío	Sevilla
 Casabona Barbara, Jordi	23	9	4	Fundación Instituto de Investigación Germans Trias i Pujol - Centro de estudios epidemiológicos sobre las infecciones de transmisión sexual y sida de Cataluña	Barcelona
 Castilla Catalán, Jesús	84	66	27	Instituto de Salud Pública de Navarra	Navarra
 Chirlaque López, María Dolores	68	57	24	Fundación para la Formación e Investigación Sanitarias de la Región de Murcia (FFIS) - Dirección General de Salud Pública	Murcia
 Daponte Codina, Antonio	10	1	1	Escuela Andaluza de Salud Pública	Granada
 Delgado Rodríguez, Miguel	54	35	13	Universidad de Jaén - Facultad de Ciencias de la Salud	Jaén
 Domínguez García, Ángela	28	15	8	Universidad de Barcelona - Facultad de Medicina	Barcelona
 Echevarría Mayo, Juan Emilio	6	3	2	Instituto de Salud Carlos III - Centro Nacional de Epidemiología	Madrid
 Emparanza Knörr, José Ignacio	6	4	1	Asociación Instituto Biodonostia - Hospital Donostia	Guipúzcoa
 Ferreira González, Ignacio	10	3	2	Fundación Hospital Universitario Vall d'Hebron - Institut de Recerca (VHIR) - Hospital Vall d'Hebron	Barcelona
 Figueiras Guzmán, Adolfo	33	11	4	Universidad de Santiago de Compostela - Facultad de Medicina	A Coruña
 Figuerola Borrás, Jordi	24	14	11	Agencia Estatal Consejo Superior de Investigaciones Científicas - Estación Biológica de Doñana	Sevilla
 Fuente Hoz, Luis de la	16	9	2	Instituto de Salud Carlos III - Centro Nacional de Epidemiología	Madrid
 Galán Montemayor, Juan Carlos	22	12	8	Servicio Madrileño de Salud - Hospital Ramón y Cajal	Madrid
 García Benavides, Fernando	19	1	1	Universidad Pompeu Fabra - Centro de Investigación en Salud Laboral	Barcelona
 Gómez de la Cámara, Agustín	22	12	9	Servicio Madrileño de Salud - Hospital Universitario 12 de Octubre	Madrid
 Ibarluzea Maurologoitia, Jesús	76	63	30	Asociación Instituto Biodonostia - Subdirección de Salud Pública de Guipuzkoa	Guipúzcoa
 Iñiguez Hernández, Carmen	34	21	14	Fundación para la Investigación Sanitaria y Biomédica de la Comunidad Valenciana (FISABIO)	Valencia
 Kogevinas, Emmanouil	123	97	66	Fundación Privada Instituto de Salud Global Barcelona (ISGlobal) - Campus Mar	Barcelona
 Larrauri Cámara, Amparo	17	12	9	Instituto de Salud Carlos III - Centro Nacional de Epidemiología	Madrid
 López Medina, María José	20	7	4	Agencia de Salud Pública de Barcelona	Barcelona

<i>Group leader</i>	<i>Total</i>	<i>Q1</i>	<i>D1</i>	<i>Institution. Centre</i>	<i>Province</i>
 Lumbreras Lacarra, Blanca	12	5	3	Universidad Miguel Hernández	Alicante
 Marcos Dauder, Ricard	12	5	4	Universidad Autónoma de Barcelona	Barcelona
 Martí Puig, Eulalia	3	3	1	Universidad de Barcelona	Barcelona
 Menéndez Santos, Clara	22	15	3	Hospital Clínic de Barcelona	Barcelona
 Morales Suárez-Varela, María Manuela	27	12	4	Universidad de Valencia - Facultad de Medicina	Valencia
 Moreno Aguado, Víctor	31	26	9	Instituto Catalán de Oncología	Barcelona
 Moya Simarro, Andrés	40	25	11	Universidad de Valencia - Facultad de Medicina	Valencia
 Muñoz Almagro, María Carmen	22	7	2	Fundación para la Investigación y Docencia Sant Joan de Deu - Hospital Sant Joan de Deu	Barcelona
 Olea Serrano, Nicolás	17	12	7	Fundación para la Investigación Biosanitaria en Andalucía Oriental (FIBAO) - Hospital Clínic San Cecilio	Granada
 Pollán Santamaría, Marina	47	35	10	Instituto de Salud Carlos III - Centro Nacional de Epidemiología	Madrid
 Porta Serra, Miquel	17	12	8	ConSORCI Mar Parc Salut de Barcelona	Barcelona
 Rius Gibert, Cristina	31	16	7	Agencia de Salud Pública de Barcelona	Barcelona
 Rodríguez Artalejo, Fernando	9	5	1	Universidad Autónoma de Madrid	Madrid
 Rodríguez Farre, Eduard	46	33	17	Agencia Estatal Consejo Superior de Investigaciones Científicas - Instituto de Investigaciones Biomédicas de Barcelona	Barcelona
 Ruiz Pérez, Isabel	24	8	1	Escuela Andaluza de Salud Pública	Granada
 Sáez Zafra, Marc	24	17	3	Universidad de Girona	Girona
 Sánchez Pérez, María José	51	38	11	Escuela Andaluza de Salud Pública	Granada
 Schröder, Helmut	22	10	5	ConSORCI Mar Parc Salut de Barcelona	Barcelona
 Serra Sutton, Victoria	14	8	2	Agència de Qualitat i Avaluació Sanitàries de Catalunya (AQuAS)	Barcelona
 Serrano Blanco, Antonio	17	10	3	Fundación para la Investigación y Docencia Sant Joan de Deu - Parc Sanitari Sant Joan de Deu	Barcelona
 Sunyer Deu, Jordi	110	83	60	Fundación Privada Instituto de Salud Global Barcelona (ISGlobal) - Campus Mar	Barcelona
 Tardón García, Adonina	60	40	18	Universidad de Oviedo - Facultad de Medicina	Asturias
 Zamora Romero, Javier	26	13	9	Servicio Madrileño de Salud - Hospital Ramón y Cajal	Madrid

Associated CIBERESP Group:

Julia del Amo Valero, Instituto de Salud Carlos III - Centro Nacional de Epidemiología (Madrid)



Frailty and Healthy Ageing





Scientific Director's Presentation

Leocadio Rodríguez-Mañas

Over 2018 we consolidated our structure, completing the composition of the governing and advisory bodies and of our organisation. The CIBERFES has taken part in a joint call with CIBERES and is working on cooperation schemes with a further two areas (CIBEROBN and CIBER-BBN). Cooperation with groundbreaking groups has been consolidated (Johns Hopkins, University of Toulouse, INGER de Mexico, King's College, Aston University, Harvard University, amongst others) and other cooperative networks, such as the Canadian Frailty Network, and it continues to work with the WHO in its ageing programme and its rehabilitation programme.

Likewise, we have gone on signing research contracts with industry (Abbott), and industrial activities emerging from CIBERFES groups (GREMPAL, Universidad de Murcia, Hospital Universitario Reina Sofía de Córdoba) have been consolidated.

Some of the results worthy of mention are that genetic, epigenetic, omic and nutritional aspects have been established and the role of image and electroencephalographic biomarkers and of stem cells in frailty and in the ageing process itself has been evaluated, with special stress on the mitochondrial function. Animal models of frailty have been developed. There have also been findings in sarcopenia, osteoporosis, nutrition, dementia or physical activity and observational and interventional clinical studies have been carried out at these same organisations, as well as in heart and endocrine

pathology (diabetes), hip fracture or about its own function. It is important to mention the intervention study published in JAMA where the benefit of a short programme of exercise in very old patients admitted for acute pathology has been proven for the first time. It should also be highlighted that data on clinical and population cohorts exceeding 50,000 samples has been evaluated.

The CIBERFES has taken part in and led European calls in several programmes, in particular H2020, EIT-Health and DG-SANTE. We should underline the assignment of the DIABFRAIL-LATAM project, endowed with 4 million euros, coordinated by the CIBERFES and in which 4 groups from our CIBER are involved. We have again presented a cooperative project with the aim of establishing a clinical cohort between CIBERFES groups based on knowledge of the impact of frailty in clinical media, its modulators and potential interventions. Lastly, we continue to work on establishing institutional relations with international research and healthcare policy organisations.

As part of the Training Programme, in 2018 the draft of the Continuous Training Programme in Geriatrics and Gerontology was drawn up and we participated in the organisation of the Symposium on "Geroscience", co-organised by the National Institute of Ageing (NIA-NIH), to be held in Madrid next September 2019.

Scientific Programmes

Basic, clinical and environmental mechanisms associated with the development of frailty. Impact on Healthcare Systems.

Coordinator:
José Viña Ribes

Study of the mechanisms in the development of frailty.

The study of these mechanisms has this year focussed on the analysis of the mitochondria-healthy ageing link in models of mice with different genetic variants of mitochondrial DNA (Dr Enríquez and Dr Bolaños).

Research is being done to understand determinants of unhealthy ageing (Dr García).

Similarly, Dr Viña's group has published the theory of free radicals of frailty with data on both humans (Dr Viña, García and Rodríguez Mañas), and on mice (Dr Viña), with external cooperation (Dr de la Fuente and Dr Walston).

A volume in *Frontiers in Neuroscience* on experimental models for a study of brain ageing has been prepared (Dr García-Segura in cooperation with CIBERER and CIBEROBN).

Early signs of sarcopenia are being sought, studying mitochondrial alteration through the chronodisruption of clock genes in the muscle of several models of mice (Dr Acuña).

The study of the relationship between stem cells and frailty is being tackled, as well as its modulators, by means of the elimination of the Sox2 gene in mice (Dr Matheu).

Study of the mechanisms by means of which interventions may delay the appearance of frailty.

Among other programmes we have taken part (Dr Andres Lacueva) in the EU EITHealth project, INNOVATION BY DESIGN, COOK2Health entitled "Providing Personalized digital eating solution to motivate healthy dietary habits and prevent chronic disease". The same group has created software (MySQL) enabling inserting nutritional information of food questionnaires to estimate the nutrients and bioactive compounds by developing food composition tables complementary to those of USDA and Phenol Explorer.

In the original EXERNET cohort around 1000 people have been assessed. This is a valuable cohort because it was used to determine normative values in the Spanish population on physical condition, body composition and intervention, improving lifestyles (Dr Ara).

In the Chronobiology laboratory of the Universidad de Murcia, the Kronowizard online analysis platform has been developed. This will be used for detecting circadian frailty in the different projects granted in 2018 (Dr Madrid, cooperation with Dr Izquierdo, Viña and Rodríguez-Mañas).

A relevant clinical trial has been carried out to assess the effects of an innovative intervention for multi-component exercise in the functional state of elderly patients undergoing acute hospital care published in *JAMA* (Dr Izquierdo).

It has similarly been found that exercise delays the signs of frailty in models of sedentary and old mice (Dr Viña).

The FRAILCLINIC and MIDFRAIL studies (Dr Rodríguez-Mañas) have furnished relevant data on interventions on elderly people with frail and pre-frail diabetes. The association between osteoporosis and bone miRNA has been identified, as well as drafting a Clinical Practice Guide (Dr Muñoz Torres-other CIBER groups).

Tackling frailty. Detection, screening, diagnosis and treatment. Healthcare models.

Coordinator:
Adolfo Díez Pérez

Cohort studies.

The *Toledo study* on ageing has developed new tools for measuring frailty, has worked on interventions based on physical exercise and has extended its analysis of biological samples. The FRADEA study (Albacete) has developed a patented and validated precision tool for the walking test; it has published the confirmation that frailty goes before disability, presenting a new tool for evaluation of the functional continuum integrating frailty and disability to predict mortality. The Donostia cohort in AP works on studies of biomarkers and translational studies. The preparation of the project for a multi-centre prospective clinical cohort for analysing frailty courses and their progression factors has been completed, using a CIBERFES frailty scale, structuring the clinical groups in a central project and creating a biobank for basic/translational work.

Clinical studies.

Hospital Gregorio Marañón (PI Jose A. Serra Rexach) works on Geriatric Cardiology in heart failure and coronary syndrome and on incapacity through hospital admittance (prevention and rehabilitation with exercise and dietetics). The groups led by Manuel Muñoz

General analyses of data by using technologies applied to health.

We are carrying out an analysis of over 35,000 data of the European FRAILOMICS project led by Dr Rodríguez-Mañas. The first results of this analysis will be available in 2019 and in greater detail in 2020.

Torres in Granada and Jose M. Quesada Gómez in Cordoba are researching general-bone frailty, pain, biomarkers, falls (cooperation with INVESTEN PI Teresa Moreno), dysphagia, (coll. CIBEREHD) and circadian health (coll. Juan A. Madrid, Murcia). The Barcelona Nutrition Group (PI M. Cristina Andrés Lacueva) continues with studies on impact and intervention on nutrition and metabolomics. In chronobiological markers, the groups of Juan A. Madrid, Teresa Moreno (ISCIII) and Francisco José García (Toledo) have described a new algorithm identifying the degree of ageing based on human circadian analysis. The groups led by Teresa Moreno and Juan A. Madrid, along with external groups and thanks to European financing are developing a study for predictive model modulating ageing with European financing. The group led by Jose A. Serra Rexach is studying the risk of mortality in a cohort of ninety-year old persons with hip fractures. Tests on pharmacological and non-pharmacological intervention have also been made in MIDFRAIL, FACET, SPRINTT, exercise in hospital patients or with Bimagrumab. The IMIM group (PI Adolfo Díez Pérez) is taking part in studies on diagnosis and intervention in bone frailty.

Translational studies.

The group led by Adolfo Díez Pérez in the IMIM, in cooperation with GREMPAL (PI Daniel Prieto-Alhambra), the Cordoba group led by Jose M. Quesada Gómez and other CIBERER groups is working on the genomics and epigenetics of bone frailty and has discovered a new genetic variant in complications of bone treatments. It is also working on biomechanics and biomaterials. M. Quesada Gómez's group works on phenols and mesenchymal stromal cells and on regenerative medicine for treatment of skin ulcers.

Big Data Studies.

The GREMPAL Group, led by PI Daniel Prieto-Alhambra, studies developments and clinical profiles of frailty, on a predictive scale of osteoporotic fractures and a national fractures register (over 30 centres, cooperating with IMIM - PI Adolfo Díez Pérez). The group led by Jose A. Serra Rexach at Gregorio Marañón Hospital is analysing national data of the CMBD to study the variability in Spain of the incidence of hip fracture.

Dissemination.

Different CIBERFES groups have taken part in national and international clinical guides on frailty or specific aspects of this. The first intra-CIBERFES meeting of a transversal research group on care has been held. Two members of CIBERFES have formed part of the experts' commission on change. We are taking part in the organisation of national and international meetings and congresses in different areas of frailty and ageing.

All these aspects are reflected in a large number of publications with impact, many of them collaborative.

Training Programme

Coordinator: *Pedro Abizanda Soler*

CIBERFES is a unique opportunity not only for cooperation between groups with a common objective from different disciplines such as Frailty and Healthy Ageing, but for improvement in the quality of the groups' scientific production by means of interaction. The training programme facilitates these two aims, as well as being a platform for added value for displaying the scientific achievements.

The Training Programme should foster the quality of research and cooperation between CIBERFES groups and groups from other areas of the CIBER, but it should also prove appealing for other Spanish, European or private sphere research platforms to get involved in achieving the final aim of the programme.

CIBERFES acts in a transversal field affecting a large number of spheres in which a great many professionals are involved, mainly basic and clinical researchers, but also researchers into epidemiology, in the economics of health, nursing care, psycho-social or exercise fields amongst others. It furthermore works in a relatively new field of health. That is why training in this field should involve different professionals and provide innovative solutions to make the relevance of research into healthy

ageing and frailty visible in a gerontophobic world.

In 2018 we took on the following priorities and actions:

We have established a system for **open calls of mobility grants** for CIBERFES researchers to finance or co-finance national or international stays, preferably in the same area. Priority is given to the requests for stays at CIBERFES groups which are developing a (financed or intramural project) with the applicant's original CIBERFES group. This will enable not only encouraging cooperation between CIBERFES groups but also gaining knowledge and skills in different fields to the ones in which young researchers usually work. It is a priority for the different CIBERFES groups to be aware of the research that is being done at each of these to establish synergies and perform continuing training for their researchers. To this end different **training and dissemination meetings** have been held, such as for example the meeting of CIBERFES Groups at CAIXAFORUM Barcelona on 13 April 2018. CIBERFES cooperated in the 'III Congreso Nacional de Jóvenes Investigadores en Biomedicina: V Congreso de Biomedicina Predocs Valencia', which was held in that city

in November 2018. It took part in the forums with dissemination of the need to research into Ageing and Frailty for young researchers. At the Annual CIBER-BBN Symposia, held in Valladolid on 12 and 13 November 2018, CIBERFES participated with a clinical forum on Frailty and Healthy Ageing.

CIBERFES has taken an active part with several exhibitions at the 'INJOY Summer School EIT-HEALTH' held from 25 June to 4 July at the Universidad de Barcelona, a programme of 10 days' work intended for 30 professionals from all over the world interested in developing new business solutions for empowering citizens to modify their diet conducts and ensure healthy ageing. Research and innovation into Ageing and Frailty are basic foundations of the translation development in this field.

Lastly CIBERFES has taken part in other extramural training forums such as the '52nd ESCI Annual Scientific Meeting (ASM)' held from 30 May to 1 June 2018, at which Cristina Andrés Lacueva and Xavier Nogués Solán from CIBERFES took part in the Workshop entitled 'Precision nutrition' of 1 June and at the 'Reunión Advantage Joint Action' on 19 June 2018 in

Valencia, with the presentation in Spain of the ADVANTAGE Joint Action reports on frailty and the debate on the best way to confront frailty, in which José Viña Ribes, Pedro Abizanda Soler, Francisco José García García and Leocadio Rodríguez Mañas all took part.

In 2018 the *Programa acreditado de Formación Continuada en Fragilidad y Envejecimiento Saludable* started to be designed, It was directed by Professors José Viña, Leocadio Rodríguez Mañas and Pedro Abizanda, sponsored by CIBERFES and the Universidad de Valencia. The programme sets out to interrelate basic research with attended practical application and preferably addresses the medical professionals in Family and Community Medicine, but is also meant for doctors from other specialities and in general healthcare professionals devoting their work to the care of the elderly. It intends to provide tools and knowledge on basic Biogerontology and Clinical Geriatrics, to be able to perform a valuation of the elderly patient, thus promoting healthy ageing and delaying the appearance of frailty and its transition to dependence.

Scientific Production

Publications

No. of publications in 2018

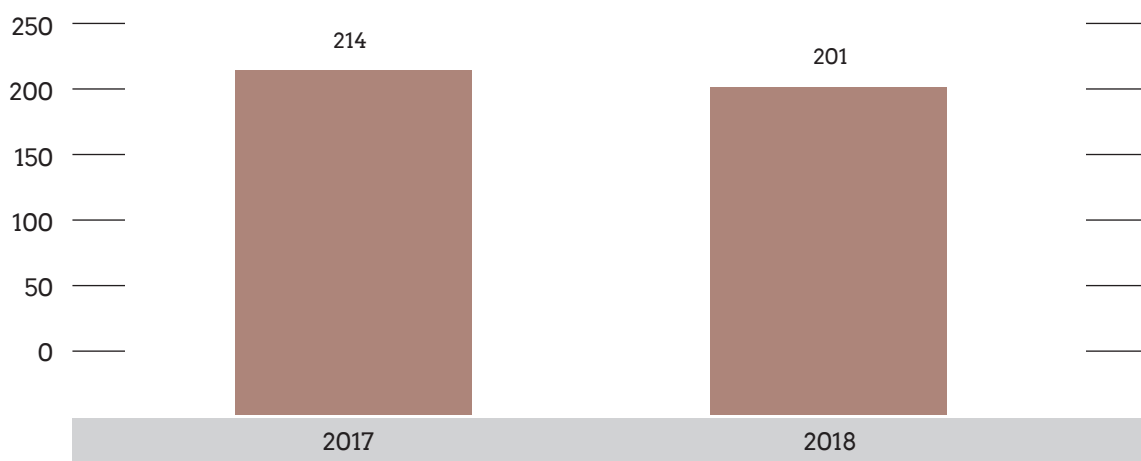
TOTALS	201
Q1	109
D1	44

Collaborative Publications

CIBERFES	34
CIBER*	65

*Over several thematic areas

Evolution of publications



10 most relevant CIBERFES publications in 2018 by impact factor

IF	Publication
79,2580	MARTÍNEZ-VELILLA N, CASAS-HERRERO A, ZAMBOM-FERRARESI F, LÓPEZ SÁEZ DE ASTEASU M, LUCIA A, GALBETE A ET AL. <i>Effect of Exercise Intervention on Functional Decline in Very Elderly Patients During Acute Hospitalization: A Randomized Clinical Trial. JAMA internal medicine.</i> 2018.

13,9260	ACIN-PEREZ R., LECHUGA-VIECO A.V., DEL MAR MUNOZ M., NIETO-ARELLANO R., TORROJA C., SANCHEZ-CABO F. ET AL. <i>Ablation of the stress protease OMA1 protects against heart failure in mice. Science Translational Medicine.</i> 2018;10(434).
13,3970	FIUZA-LUCES C, SANTOS-LOZANO A, JOYNER M, CARRERA-BASTOS P, PICAZO O, ZUGAZA JL ET AL. <i>Exercise benefits in cardiovascular disease: beyond attenuation of traditional risk factors. Nature reviews. Cardiology.</i> 2018.
12,2420	GIATTI S, GARCIA-SEGURA LM, BARRETO GE, MELCANGI RC. <i>Neuroactive steroids, neurosteroidogenesis and sex. Progress in neurobiology.</i> 2018.
11,9820	CACCIAGLIA R., MOLINUEVO J.L., FALCON C., BRUGULAT-SERRAT A., SANCHEZ-BENAVIDES G., GRAMUNT N. ET AL. <i>Effects of APOE-ε4 allele load on brain morphology in a cohort of middle-aged healthy individuals with enriched genetic risk for Alzheimer's disease. Alzheimer's and Dementia.</i> 2018;14(7):902-912.
11,7760	PAGANO A.F, BRIOCHE T., ARC-CHAGNAUD C., DEMANGEL R., CHOPARD A., PY G. <i>Short-term disuse promotes fatty acid infiltration into skeletal muscle. Journal of Cachexia, Sarcopenia and Muscle.</i> 2018;9(2):335-347.
11,6130	TORRALBA D., BAIXAULI F., VILLARROYA-BELTRI C., FERNANDEZ-DELGADO I., LATORRE-PELLICER A., ACIN-PEREZ R. ET AL. <i>Priming of dendritic cells by DNA-containing extracellular vesicles from activated T cells through antigen-driven contacts. Nature Communications.</i> 2018;9(1).
9,6550	QUINTANA-CABRERA R., QUIRIN C., GLYTSOU C., CORRADO M., URBANI A., PELLATTIERO A. ET AL. <i>The cristae modulator Optic atrophy 1 requires mitochondrial ATP synthase oligomers to safeguard mitochondrial function. Nature Communications.</i> 2018;9(1).
9,0900	ALONSO N, ESTRADA K, ALBAGHA OME, HERRERA L, REPPE S, OLSTAD OK ET AL. <i>Identification of a novel locus on chromosome 2q13, which predisposes to clinical vertebral fractures independently of bone density. Annals of the rheumatic diseases.</i> 2018;77(3).
8,3600	SHEN Y.-Q., GUERRA-LIBRERO A., FERNANDEZ-GIL B.I., FLORIDO J., GARCIA-LOPEZ S., MARTINEZ-RUIZ L. ET AL. <i>Combination of melatonin and rapamycin for head and neck cancer therapy: Suppression of AKT/mTOR pathway activation, and activation of mitophagy and apoptosis via mitochondrial function regulation. Journal of Pineal Research.</i> 2018;64(3).
9,5200	SERENA C, CEPERUELO-MALLAFRÉ V, KEIRAN N, QUEIPO-ORTUÑO MI, BERNAL R, GOMEZ-HUELGAS R ET AL. <i>Elevated circulating levels of succinate in human obesity are linked to specific gut microbiota. The ISME journal.</i> 2018.

CIBERFES Groups. Publications

Group leader	Total	Q1	D1	Institution. Centre	Province
 Abizanda Soler, Pedro	2	1	1	Servicio de Salud de Castilla La Mancha - Complejo Hospital General de Albacete	Albacete
 Acuña Castroviejo, Darío	6	3	2	Fundación para la Investigación Biosanitaria en Andalucía Oriental (FIBAO) - Hospital Clínico San Cecilio	Granada
 Andrés Lacueva, María Cristina	23	12	7	Universidad de Barcelona - Facultad de Farmacia	Barcelona
 Ara Royo, Ignacio	10	7	3	Universidad de Castilla la Mancha - Facultad de Ciencias del Deporte	Toledo

<i>Group leader</i>	<i>Total</i>	<i>Q1</i>	<i>D1</i>	<i>Institution. Centre</i>	<i>Province</i>
 Bolaños Hernández, Juan Pedro	4	3	2	Fundación Instituto de Estudios de Ciencias de la salud de Castilla y León - Instituto de Biología Funcional y Genómica	Salamanca
Díez Pérez, Adolfo	18	11	3	Consorti Mar Parc Salut de Barcelona - Hospital del Mar	Barcelona
 Enríquez Domínguez, José Antonio	6	6	4	Fundación Centro Nacional de Investigaciones Cardiovasculares	Madrid
 García Segura, Luis Miguel	10	7	1	Agencia Estatal Consejo Superior de Investigaciones Científicas - Instituto Cajal	Madrid
 García García, Francisco José	9	4	1	Fundación del Hospital Nacional de Parapléjicos	Toledo
 Izquierdo Redín, Miguel	36	17	10	Universidad Pública de Navarra	Navarra
 Madrid Pérez, Juan Antonio	6	1	0	Universidad de Murcia	Murcia
 Matheu Fernández, Ander	9	6	1	Asociación Instituto Biodonostia - Hospital Donostia	Guipúzcoa
 Molinuevo Guix, Jose Luis	8	5	2	Fundación Barcelonabeta Brain Research Center	Barcelona
 Moreno Casbas, Teresa	8	2	1	Instituto de Salud Carlos III - Unidad de Investigación en Cuidados de Salud	Madrid
 Muñoz Torres, Manuel	9	4	2	Fundación para la Investigación Biosanitaria en Andalucía Oriental (FIBAO) - Hospital Clínico San Cecilio	Granada
 Prieto Alhambra, Daniel	11	5	2	IDIAP Jordi Gol	Barcelona
 Quesada Gómez, José Manuel	11	6	3	Fundación para la Investigación Biomédica de Córdoba (FIBICO) - Hospital Universitario Reina Sofía	Córdoba
 Rodríguez Mañas, Leocadio	26	8	4	Servicio Madrileño de Salud - Hospital Universitario de Getafe	Madrid
 Serra Rexach, José Antonio	12	11	3	Servicio Madrileño de Salud - Hospital Gregorio Marañón	Madrid
 Viña Ribes, José	16	10	2	Fundación para la Investigación del Hospital Clínico de la Comunidad Valenciana (INCLIVA)	Valencia

A microscopic view of numerous cells, likely adipocytes, showing their characteristic large, clear lipid droplets. The image is split vertically: the left half is in warm orange and red tones, while the right half is in cool blue and cyan tones. The cells are densely packed and vary in focus, creating a sense of depth.

Physiopathology of Obesity and Nutrition



Scientific Director's Presentation

Carlos Diéguez González

It is a pleasure for me to be presenting the annual report of the work done by the CIBEROBN, representing the scientific area of Obesity and Nutrition of the public consortium known as CIBER. 2018 was a highly productive year in strategic terms with the development of its "Nutrition" and "Obesity" Programmes.

As regards the first programme I would like to highlight the hard work done by the members of the Executive Committee of PREDIMED to clear up different aspects connected with the work done these last few years. The work done has meant that the conclusions reached with PREDIMED are even more respected and accepted by practically all the scientific community, which is of special relevance in a field like human nutrition, in which discrepancies are fairly common.

Now more in the future sense, we should also stress not only that the PREDIMEDPLUS project has got up to cruising speed, as can be vouched for by the fact that there have already been several publications by this cohort, but also new cohorts have been got under way with the involvement of different CIBEROBN groups which will surely be a source of scientific joy in coming years. The Obesity Programme has continued to foster the development of joint prospective studies with a higher degree of cooperation between different CIBEROBN groups, which is generating new and greater opportunities.

What is more, to go on boosting this integration,

there has been a new call for intramural projects in which three projects have been financed, after the proper assessment: one of these focusses on obesity and abnormal behaviour through LIFESPAN; another involves the relationship of the microbiome and methylome before and after a weight loss treatment in liquid biopsy of patients with a liver disease connected with obesity for the identification of biomarkers of hepatic risk; and a third one for the validation of a fast lipidomic index to monitor the intake of omega-3 fatty acids in the body and its application in nutritional monitoring.

These measures are again part of the objectives of the Strategic Plan to foster research integration carried out by different groups in the CIBEROBN, and also the start of projects in new lines of research to go on underpinning our capacities. They have gone along with the launching of two new platforms (metagenomics and epigenetics) which along with the "Fatbank" have generated new bonds and projects.

The report submitted represents the work done by a total number of 33 groups in the CIBEROBN in 2018. I would like to stress the following points as regards its contents:

International projects. As well as continuing to be highly active in different country-wide calls, special emphasis has been placed on obtaining and developing projects financed by international sources. Six projects of this type have been implemented throughout 2018,

managed through the central office of the CIBEROBN, which are a mark of our groups' great ability to be awarded projects even in the most competitive settings.

Publications. An outstanding level of scientific production has been attained, with over 550 publications, over half of which are in journals with an impact factor of D1/ Q1. These bibliometric indices take on greater significance when they are seen in a comparative setting on the international scale. We are thus becoming consolidated as one of the European organisations with greatest scientific production in the scope of obesity and nutrition.

This busy research activity is vital for managing to convey the knowledge generated to the clinical environment and thus to the patient. In this context, researchers from our CIBEROBN have also participated in preparing Clinical Guides and consensus documents on both national and international scales.

Training. This is a field in which we have attempted to extend the number and type of activities. As well as the CIBEROBN Annual Meeting, this year training action has been carried out in cooperation with other CIBER areas such as the Meeting in Minorca arranged by CIBERSAM and the ones organised by researchers from our own CIBEROBN, including among these the meetings on "Nutrition and healthy lifestyles" in Palma de Mallorca, the FINUT meeting on "Progress in paediatric nutrition" or the ESCI Congress in Barcelona.

Awards. Considering the research work done by the different CIBEROBN researchers, it comes as no surprise that several of them should have got special recognition in the form of high-prestige awards. In this field I would like to stress the ones received in 2018 by Dolores Corella (*Premio Jaime I*), Luis Moreno (*Premio Estrategia NAOS*), Pablo Pérez (*Premio Jesús Serra*), Rosa Lamuela (*Instituto Danone*), Victoria Catalá and Miguel López (both prizes of the European Society for Clinical Investigation) and Rubén Nogueiras (*Premio Constantes y Vitales* for Biomedical Research).

Dissemination. We continue to be committed to the importance of the findings achieved by our researchers reaching the people, especially the ones that have a direct effect on positively influencing the healthy habits of the general public and in particular of patients with obesity. The efforts made in this sector are backed by the CIBEROBN yet again being one of the areas of the CIBER with greatest media impact. We should also stress our participation in the Campaign on "Prevention of Obesity, Lighten your life" which is promoted by the SEEDO and coordinated by two researchers (F. Casanueva and F. Tinahones) of the CIBEROBN.

In short, 2018 has been extremely satisfactory as regards obtaining the objectives set in the Strategic Plan. We are sure that in coming years we shall obtain even greater success that will be appreciated in an improvement in the care quality of our patients and in general of the population's quality of life.

Scientific Programmes

Nutrition Programme

Coordinator:
Jordi Salas Salvadó

The Nutrition Programme basically includes epidemiological research into obesity and nutrition through different types of epidemiological studies: transversal studies, cases and controls, cohorts and randomised trials. We are carrying out several of these studies with different aims and sample sizes, as well as with different degrees of national and international cooperation, and with both public and private funding. Some interesting results are being obtained in all of these, and have led to a large number of publications, collaboration, invitations to conferences and congresses, Doctoral Theses, National and International Awards and participations in meta-analyses and in applications for new projects.

Although all the studies are important, we should specifically stress the progress made in the PREDIMED and PREDIMED PLUS studies, as these are the largest randomised tests for valuing a nutritional intervention and are multi-centre studies. Most of the groups in the nutrition programme take part in these. We should also highlight the “Seguimiento Universidad de Navarra” (SUN) cohort for its design and results. The first results of the CORDIOPREV trial (on secondary prevention) and the WAHA study, the recently started MELIPOP study are being published. Neither should we fail to mention several recently started tests: MELIPOP, PREDI-DEP, PREDIMAR, as well as some cohort studies that have been got under way.

PREDIMED Study:

- In 2018 several important papers in the PREDIMED study (n=34) have continued to be published. These are from studies with different epidemiological designs focussing on different outcomes – cardiovascular events, osteoporosis, cataracts - and on other intermediate markers, as well as meta-analysis (*Circulation* 2018; *Atherosclerosis* 2018; *Nutrients*. 2018; *Am J Clin Nutr*. 2018; *Clin Chem* 2018; *Int J Cancer*. 2018; *Eur J Nutr*. 2018; *Eur J Public Health*. 2018; *Clin Nutr*. 2018, *y J Acad Nutr Diet*. 2018, amongst others) and a high-impact article was published in the *Annu Rev Food Sci Technol*. 2018.
- The republication of the reanalysis of the PREDIMED study in the *New Engl J Med*, 2018 and other corrections of related papers (*JAMA* 2018; *Diabetes Care* 2018 and others) should be mentioned in this respect.
- 9 high-impact papers have also been published at the boundaries of knowledge on metabolomics in the PREDIMED study (most in cooperation with the Harvard TH Chan School of Public Health) resulting from the three grants obtained from the NIH. These publications mean that the mechanisms by which the diet could modulate cardiovascular disease, diabetes and its phenotypes can be explained. Some of these papers to be highlighted are: metabolic networks of lipids connected with cardiovascular disease (*Int J Epidemiol*. 2018); lipidomic profile and the incidence of diabetes (*Diabetes Care*. 2018); TMAO and the risk of diabetes (*Am J Clin Nutr*. 2018); metabolic pathways of tryptophan and the risk of diabetes (*Clin Chem*. 2018); influence of ramified amino acids on the incidence of diabetes and its interaction with the PREDIMED intervention (*Diabetologia*. 2018); the associations between plasma lipids and cardiovascular disease (*Int J Cardiol*. 2018).
- The fourth International Symposium on

“Omics” in Nutrition has been organised by the University of Harvard and the PREDIMED groups from Navarre and Reus in May 2018 in Barcelona, as part of the Congress of the European Society of Clinical Investigation.

PREDIMED Plus:

- In late 2018 we had an average follow-up of three years of the over 6800 randomised participants in the clinical trial. Good weight loss results have been found after both one year and after two years, as well as a favourable evolution of the cardiovascular risk markers in the intensive intervention group. Results of PREDIMED and PREDIMED PLUS were disseminated at several national and international scientific meetings.
- The results of the pilot study made on the first 600 participants monitored over one year were published in the *Diabetes Care journal*, a description of the PREDIMED-Plus cohort in *Int J of Epidemiol* and the effects of the intervention on physical activity in *Int J Behav Nutr Phys Act*.
- 2018 was characterised by the publication of the first PREDIMED-PLUS studies (12 articles), most of these transversals with baseline data of the cohort. Some prominent ones of these were the one published in *J Clin Med* on polyamines, resistance to insulin and diabetes, and others on physical activity, sedentarism or sleep published in *Clin Nutr* or *Sleep*.
- In 2018 PREDIMED-Plus staff were trained (90 attendees) in Barcelona, with a meeting of PIs in Madrid and audits being made on all the PREDIMED-Plus centres.
- In November 2019 the meeting of the Data Safety Monitoring Board (DSMB) was held in Malaga, where a thorough assessment of the status of the project was performed. The members of the DSMB commended the course of the PREDIMED-PLUS project, the results obtained and the low abandonment rate.
- A European subproject was continued by several groups in the programme, entitled Effects of Nutrition and Lifestyle on Impulsive, Compulsive, and Externalizing behaviours: Eat2beNICE (H2020-SFS-2016-2).
- An NIH project (1R01HL137338 has been obtained, on the Effect of an Intensive Lifestyle Intervention on the Atrial Fibrillation Substrate; 2018–2022) on atrial fibrillation in cooperation between the universities of Emory, Navarre and 4 PREDIMED-Plus centres.

SUN COHORT (Universidad de Navarra):

The SUN cohort has celebrated the achievement of reaching its 200 scientific publications. Consisting of 23,000 participants and with an average follow-up over 10 years, it has a retention rate of over 91%. The most relevant of the 30 articles published by the SUN cohort in 2018 are that of the protective role of coffee consumption on total mortality (*Am J Clin Nutr*. 2018), and those which have found a major protective role against cardiovascular disease and total mortality for the combination of Mediterranean diet, physical activity and an appropriate lifestyle (*Am J Cardiol*. 2018; *Eur J Prev Cardiol*. 2018; *Prev Med*. 2018).

WAHA STUDY (Hospital Clínico de Barcelona): The WAHA study (WAlnuts and Healthy Aging) is being performed in cooperation with the Hospital Clínic de Barcelona and Loma Linda University. At present 90% of the participants (approximately 700 people) have completed the study. The first results on safety of the treatment and the effect on telomeres have been published in *Nutrients* and the first manuscripts are being prepared on the effect of the intervention on cognition, changes in the retina and lipidic metabolism.

CORDIOPREV (Universidad de Córdoba): The follow-up of the patients recruited in this secondary prevention study with Mediterranean diet went on, with several articles being published (With regard to Coenzyme Q10: *J Gerontol A Biol Sci Med Sci*; *Crit Rev Food Sci Nutr*; with regard to diabetes or prediabetes: *J Nutr Biochem*; *Mol Ther Nucleic Acids*, *Am J clin Nutr*).

MELIPOP PROJECT: Randomised and controlled multi-centre test with the Mediterranean diet and physical activity in children focussing on prevention of child obesity. The recruitment of participants for the pilot study has practically finished.

CORALS PROJECT: An agreement has been signed by the Instituto Danone España and CIBEROBN for a transversal study which should mean the start of a cohort of children with the participation of five CIBEROBN groups.

IMPACT STUDY – Improving mothers for a better Prenatal Care (Hospital Clínic de Barcelona): seeks to evaluate the effect of an intervention with Mediterranean diet and reduction of stress on foetal development and other secondary objectives in 1218 pregnant mothers with ultrasound data on the retardation of foetal growth.

MEDICAR STUDY: In cooperation with SEAT company a cohort study has been carried out on the 14,000 workers at the car factories in Martorell, El Prat de Llobregat and Barcelona Free Zone to appraise the relationship between lifestyle and health.

European project obtained:

STOP Project 2018-2022 (ID: 774548): "Science and Technology in Childhood Obesity Prevention". European study H2020 on policies for prevention and approaches to child obesity in Europe, in which several CIBEROBN take part.

SWEET Project 2018-2023 (ID: 774293): "Sweeteners and sweetness enhancers: Impact on health, obesity, safety and sustainability".

European Study H2020 in which epidemiological associations are analysed, the ULPGC will cooperate with data from Predimed-Plus Canarias.

Other studies, publications and collaboration:

We should stress the start of the PREDIMAR multi-centre study intended for secondary prevention of atrial fibrillation with a virgin-extra olive oil-rich diet (n=600), led by the Universidad de Navarra, and the PREDIDEP test on secondary prevention of depression with a Mediterranean diet led by the group from Las Palmas.

Obesity Programme

Coordinator:
Gema Frühbeck Martínez

The restructuring of the many programmes of the CIBEROBN carried out in the framework of the directives established in the Strategic Plan 2017-2019, in order to combine these into only two overall fields (Obesity and Nutrition) meant a radical change in 2018 and a challenge intended to avoid fragmentation in the search for common scientific objectives and obtaining a greater critical mass in companies of larger size and significance. The changes taking place in this respect will be seen more tangibly in the medium-long term, although they have already materialised in some ground-breaking publications in both the field of basic research with preclinical models and in some clinical-type works.

Some of the accomplishments deserving mention are the findings leading to the following publications: Leiva-Gea et al. *Diabetes Care* 2018;41:2385-2395; Seoane-Collazo et al. *Diabetes* 2018;67:2213-2226; Martos-Moreno GÁ et al. *EMBO Mol Med* 2018;10. pii: e9143; Cereijo R et al. *F. Cell Metab* 2018;28:750-763.e6.; Villarroya et al. *Cell Metab* 2018;27:954-961; Roa J et al. *Proc Natl Acad Sci USA* 2018;115:E10758-E10767; Quiñones M et al. *Nat Commun* 2018 4;9:3432; Vazquez MJ et al. *Nat Commun* 2018;9:4194.

Neurocognition subprogramme

This subprogramme deserves special mention since the groups' participation is proving excellent, in both the inter-group cooperation and in external collaboration with other CIBER areas (CIBERSAM, CIBERDEM and CIBERESP) and international groups (*Mol Psychiatry*, 23(5), 1169-1180. doi: 10.1038/mp.2017.88).

Synergies and dialogue between the groups have become constant features and the scientific production is extraordinary:

CIBEROBN and CIBERSAM:

Eur Eat Disord Rev., 26(6):629-637. Oct 15. doi: 10.1002/erv.2646; *Eur Psychiatry*, 54:109-116. doi: 10.1016/j.eurpsy.2018.08.001; *Front Psychiatry*, 16; 9:497.; *Gambl Stud.*, 34(1),209-223; *J Behav Addict.*, 7(3):770-780. doi: 10.1556/2006.7.2018.93; *J Behav Addict.*, 7(4):1112-1121. doi: 10.1556/2006.7.2018.132; *Addict Behav. Dec.*; 87:169-176. doi: 10.1016/j.addbeh.2018.07.006; *Curr Neuropsychopharmacol.*, 17. 16(8):1150-1163; *Eur Eat Disord Rev.*, 26(1):53-61. doi: 10.1002/erv.2570; *Addict Behav.* 2018 Jan 24; 80:124-129. doi: 10.1016/j.addbeh.2018.01.022; *Front. Psychiatry* 9:6. doi: 10.3389/fpsyt.2018.00006; *γ Front Psychiatry*, 25,9:208. doi: 10.3389/fpsyt.2018.00208. eCollection 2018.

CIBEROBN, CIBERDEM and CIBERSAM:

European Eating Disorders Review, 26 (6): 574-584; *Eur Eat Disord Rev.*, 26 (6), 645-656. doi: 10.1002/erv.2649; Intragrupo: *Front Psychol.*, 11; 9:934. doi: 10.3389/fpsyg.2018.00934.

eCollection 2018; *Nutrients*. 2018 Sep 21;10(10). pii: E1348. doi: 10.3390/nu10101348; Editoriales especiales: *Eur Eat Disord Rev.* Mar 26(2), 83-91; y *Eur Eat Disord Rev.*, 26(6):536-540. doi: 10.1002/erv.2645).

Another of the major milestones in the field of cooperation between the CIBER areas and the internationalisation achieved during the year was the organisation of the Obesity Workshop by the CIBEROBN at the 52nd Annual Scientific Meeting of the European Society for Clinical Investigation (ESCI), which took place from 30 May to 1 June 2018 in Barcelona. Gema Frühbeck and Lina Badimón were the Local Organisers of the ESCI and for the first time they managed to get the participation and cooperation of CIBEROBN, CIBERCV, CIBERFES and CIBEREHD in an international event of great prestige.

As well as this event several international meetings were held in 2018 with guest speakers:

- Prof. Astrid Müller (University Hannover, Germany), "New Perspectives in Behavioral Addictions" (9 March);
- Prof. Marc N. Potenza (Yale University School of Medicine, USA), "From Behavioral Addictions to Food Addiction: Neurobiological Perspective" (27 April);
- Gretchen Blycker, LMHC (University of Rhode Island, USA), "Sexual and Couples Therapy in Behavioral Addictions: A Neglected Topic" (27 April);
- Prof. Janet Treasure (King's College, London, UK), "The Role of Mothers and Fathers in Eating Disorders" (12 June);
- Prof. Alex Blaszczynski, PhD (University of Sydney), "Responsible Gambling: Research and Future Challenges" (21 September);
- Prof. Antonio Verdejo-García, PhD (Monash University, Melbourne, Australia), "Cervell i Adicció al Menjar" (1 October).

International interest was also attracted through the stays of foreign researchers: Prof. Georgios Paslakis, University of Hannover, Germany; Lilly Carlson, Predoc, University of Michigan, USA; Prof. Isabel Krug, School of Psychology, University of Melbourne, Australia) and some special issues on this matter were coordinated: Editor-in-Chief of three Special Issues:

- "Binge Eating Disorders" (K. Giel & F. Fernández-Aranda; 2018; *Nutrients*; https://www.mdpi.com/journal/nutrients/special_issues/binge_eating_disorder-IF4.196),
- "Food Addiction" (European Eating Disorders Review, 2018; Ed. Wiley)(Ed. F. Fernandez-Aranda, Janet Treasure & A. Karwautz). <https://onlinelibrary.wiley.com/toc/10990968/2018/26/6>
- "Endocrinology of Eating Disorders and weight control" (*Molecular and Cellular Endocrinology*; Ed. Elsevier), 2019.

As regards clinical trials, the active participation of CIBEROBN groups in the most relevant international multi-centre studies vouches for the proven quality of the care and research work done by our CIBER. This is shown by the analysis of the possible cardiovascular impact of two known anti-diabetic drugs which are displaying some promising results (Ludvik B et al. *Lancet Diabetes Endocrinol* 2018;6:370-381).

Another aspect of the hard-scientific work being done was the participation in drawing up Clinical Guides, as well as in Consensus and Positioning documents connected with obesity and clinical nutrition of Spanish and European Obesity Associations.

Training Programme

Coordinator: *Manuel Tena-Sempere*

The CIBEROBN Training Programme can be defined as a key tool for fostering continuous training, which is considered to be a vital element for sustaining the research work done by the groups in our centre. As in previous years, the basic point of the programme has been to focus on the younger members of our teams, with the aims of promoting training for researchers (especially for emerging and consolidating investigators) in obesity and nutrition, encouraging their mobility and helping to consolidate their professional careers as independent researchers in this thematic area. In this same line training activities have been undertaken in some cases with other CIBER thematic areas, intended to underpin the continuous training of members of our Area.

In line with the development of the programme, the main training measures have involved financing training stays of CIBEROBN members at other national and international research groups. To this end the programme has since its beginnings had an open dynamic system for applications which, after its evaluation by the scientific and managing team, enables granting economic aid for going on training stays at CIBEROBN groups (other than the ones located in the city where the applying group is located), at other CIBER groups and at national and international groups not forming part of the CIBER structure. In the experience we have built up, these stays are extremely fruitful for the development of our programmes, since young researchers are trained in specific techniques which they later immediately apply to studies of their CIBEROBN group.

More specifically, a total number of 10 applications for training stays of CIBEROBN researchers were financed during 2018, representing a 40% increase over the number of actions applied for in the previous year. Many of these actions lasted for around 3 months (the maximum time that the programme allows for financing) although others were for shorter stays, adapting to the specific needs of the applicants and the source groups. The total amount of funds allocated to financing mobility in 2018 was 21,000 €, which similarly means a 15% increase in respect of 2017. Another similarly

significant positive aspect of the programme was the high percentage of internationalisation, since 80% of all the stays financed were held at renowned foreign centres. This aspect reinforces not only the capacity for acquisition of new knowledge and ground-breaking techniques in the field, but for the establishment of scientific relations and cooperation on the top international level being carried out.

Apart from the mobility work mentioned above, the programme has continued with the dynamics already established in 2016 and 2017, addressing the organisation and support for complementary training activities. In this setting we should give particular emphasis to the support for the third consecutive year for the Encuentro de Doctorado de Excelencia, in Mahon, promoted by the CIBERESP, and the coordination of the organisation of the scientific programme of our CIBER area's annual meeting, which was this time called "OBESITY AND NUTRITION IN THE 21st CENTURY" held in Madrid on 21 and 22 November 2018.

Lastly, as well as facilitating the participation of a large number of speakers, from both our CIBER area and external ones, the Training Programme defrayed the attendance expenses of junior researchers (<35 years) of the CIBEROBN groups, of up to one for each node and financed the endowment of a total number of 8 awards, 4 for the best oral communications and a further 4 for the best posters presented at this Annual Meeting of the CIBEROBN 2018, with an endowment of 750 € each, which have to be used for the beneficiaries' training activities to be carried out in 2019.

Apart from this the CIBEROBN actively promoted and has contributed to part of the scientific programme of the congress of the ESCI (European Society for Clinical Investigation), held in Barcelona in May 2018. This set of activities enabled complementing the training components of the programme, extending its scope to practically all the groups in the CIBEROBN. The scientific management's strategy for the next year is to further this line and, apart from other initiatives, it already has under way the preparation of joint scientific symposia with the CIBERONC area on

metabolism and cancer, which will be held in 2019, and in which the Training Programme of our CIBER intends to finance the attendance of members of the groups and speakers, thus re-editing the joint CIBEROBN/CIBERDEM training action organised in 2017.

Lastly, and as a training element of the greatest importance, we should stress in this section that in 2018 a total number of 50 Doctoral theses (21 of which were international) were completed, which represents the consolidation of a growing trend in this major training activity.

The overall financing applied in this programme in 2018 came to 35,500€. In perspective, it may be considered that the CIBEROBN training and mobility programme is consolidated, and due to its flexibility, has become a valuable tool not only in the professional development of our researchers (especially the younger ones) but also in reinforcing international collaboration and connections of the groups forming part of our CIBER.

FatBank Platform

Coordinator: *José Manuel Fernández-Real*

ISO 9001:2015

The greatest achievement in 2018 is obtaining the ISO 9001:2015 standard by the IDIBGI Biobank, the coordinator of the platform.

This certificate is an internationally recognised standard to create, implement and maintain a Quality Management System and for this reason is recognised as the basis for any company to set up a system to guarantee the customer's satisfaction and trust, as well as the implementation of improvements.

These are the reasons why we are persuaded that this will help the entire Platform as regards the comprehensive management of the human samples kept there and all the associated data.

Web page

Since the FatBank's purpose is to facilitate biomedical research by providing high quality samples, one of its aims is to make the scientific community aware of the existence of those samples.

For this purpose the IDIBGI Biobank has set up a Web page in which this describes along with a great deal of other content all the collections that it houses, including the FatBank as one of the main collections, with information such as the purpose, collection points or types of donors and samples.

Link: <https://biobancidibgi.org/es/colecciones-principales/>

This year we would also like to stress the inclusion of a new (intraosseous) adipose tissue in the biobank, as well as the Symposium for celebrating the fifth anniversary of the Gerona Biobank in October 2018.

Scientific Production

Publications

No. of publications in 2018

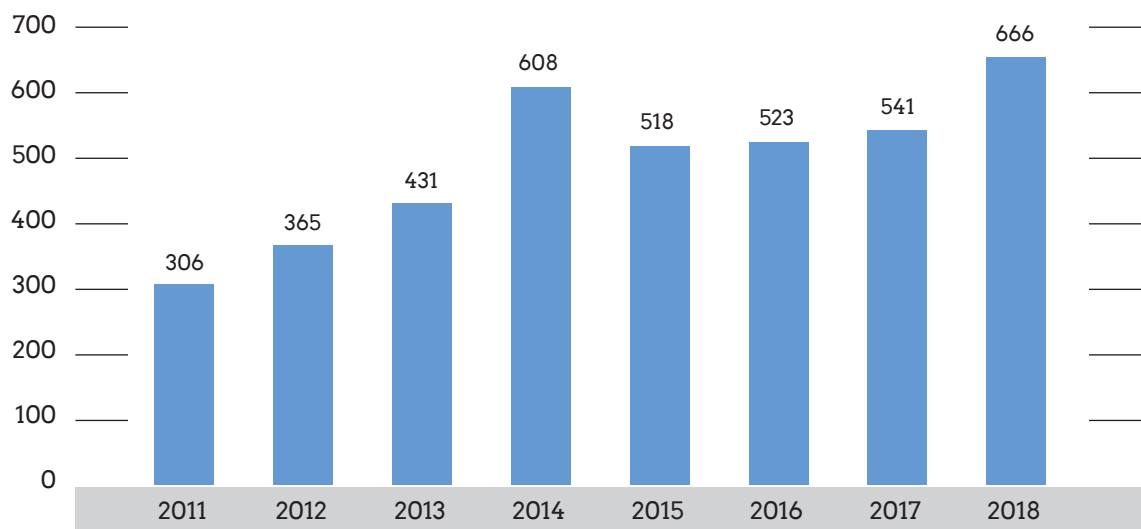
TOTALS	666
Q1	369
D1	123

Collaborative Publications

CIBEROBN	136
CIBER*	168

*Over several thematic areas

Evolution of publications



10 most relevant CIBEROBN publications in 2018 by impact factor

IF	Publication
23,259	<i>Food based dietary patterns and chronic disease prevention</i>
16,834	<i>Autosomal Recessive Hypercholesterolemia: Long-Term Cardiovascular Outcomes.</i>
19,313	<i>Precision medicine: diagnosis and management of obesity.</i>
19,064	<i>TP53INP2 regulates adiposity by activating β-catenin through autophagy-dependent sequestration of GSK3β</i>
19,313	<i>Dulaglutide as add-on therapy to SGLT2 inhibitors in patients with inadequately controlled type 2 diabetes (AWARD-10): a 24-week, randomised, double-blind, placebo-controlled trial</i>
20,565	<i>Toward an Understanding of How Immune Cells Control Brown and Beige Adipobiology</i>
79,258	<i>Primary prevention of cardiovascular disease with a mediterranean diet supplemented with extra-virgin olive oil or nuts</i>
32,621	<i>Molecular phenomics and metagenomics of hepatic steatosis in non-diabetic obese women</i>
16,834	<i>A Clinician's Guide for Trending Cardiovascular Nutrition Controversies: Part II</i>
32,621	<i>Genetic deficiency of indoleamine 2,3-dioxygenase promotes gut microbiota-mediated metabolic health</i>

Patents owned by CIBER

Applied for

- *Modelo predictivo para predecir el desarrollo de diabetes mellitus tipo 2 usando miARNs (FIBICO-17003) (National).*
- *Anti-leptin affinity reagents for use in the treatment of obesity and other leptin-resistance associated diseases (International).*

Clinical guides and consensus documents

National

- *Guía de la Alimentación Saludable para la Atención Primaria y Colectivos Ciudadanos.*
- *Guía práctica para el manejo de las dislipemias diabéticas.*
- *Documento de consenso sobre las dietas de exclusión en el síndrome del intestino irritable (SII).*
- *Guía de alimentación en el paciente oncológico.*
- *Guía de Prevención de los Trastornos de la Conducta Alimentaria en el Entorno Universitario.*
- *Utilizing nutritional genomics to tailor diets for the prevention of cardiovascular disease: a guide for upcoming studies and implementations.*

- *Perspectiva de género en investigación sobre ómicas en obesidad y fenotipos relacionados: Guía para su implementación.*
- *Guía de asesoramiento preconcepcional desde atención primaria.*
- *Grupo de Diabetes de la Sociedad Española de Arteriosclerosis. Consensus document of the Spanish Society of Arteriosclerosis (SEA) for the prevention and treatment of cardiovascular disease in type 2 diabetes mellitus.*
- *Guía del sueño saludable en el entorno universitario.*
- *Consensus on insulin treatment in type 2 diabetes.*
- *¿Por qué hay que apoyar al Ministerio de Sanidad en la implantación del etiquetado frontal de los alimentos nutri-score en nuestro país? Una excelente medida de Salud Pública.*
- *Document of recommendations of the SEA 2018. Lifestyle in cardiovascular prevention*
- *Spanish Diabetes Society (SED) recommendations for the pharmacologic treatment of hyperglycemia in type 2 diabetes: 2018 Update.*

International

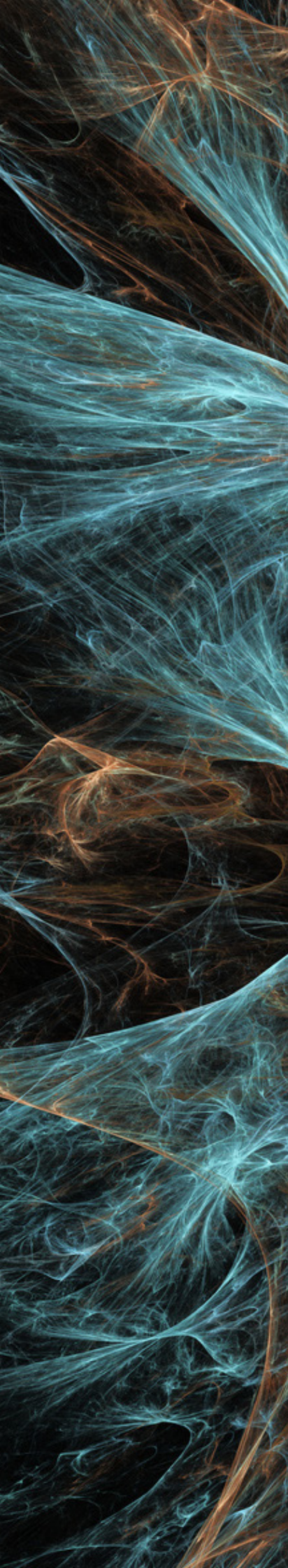
- *Embracing the Complexity of the Sex-Gender Perspective in Transcriptomic and Epigenomic Analyses for Precision Nutrition: A Guide to Closing the Gap in Nutrigenomics.*
- *COSMIC project: consensus on the objectives of the metabolic syndrome in clinic. Diabetes.*
- *Diagnosis and management of pseudohypoparathyroidism and related disorders: first international Consensus Statement.*
- *Obesity and cardiovascular risk: a call for action from the European Society of Hypertension Working Group of Obesity, Diabetes and the High-risk Patient and European Association for the Study of Obesity: part A: mechanisms of obesity induced hypertension, diabetes and dyslipidemia and practice guidelines for treatment.*
- *Obesity and cardiovascular risk: a call for action from the European Society of Hypertension Working Group of Obesity, Diabetes and the High-risk Patient and European Association for the Study of Obesity: part B: obesity-induced cardiovascular disease, early prevention strategies and future research directions.*

CIBEROBN Groups. Publications

Group leader	Total	Q1	D1	Institution. Centre	Province
 Argente Oliver, Jesús	29	10	5	Servicio Madrileño de Salud - Hospital Infantil Universitario Niño Jesús	Madrid
 Arós Borau, Fernando	19	15	6	Fundación Vasca de Innovación e Investigación Sanitarias - Hospital Universitario Araba. Sede Txagorritxu	Álava
 Baños Rivera, Rosa María	25	13	1	Universidad de Valencia - Facultad de Psicología	Valencia
 Casanueva Freijo, Felipe	20	6	0	Servicio Gallego de Salud - Complejo Hospitalario Universitario Santiago	A Coruña
 Corella Piquer, Dolores	41	26	12	Universidad de Valencia - Facultad de Medicina	Valencia
 Diéguez González, Carlos	28	19	8	Universidad de Santiago de Compostela - CIMUS	A Coruña

<i>Group leader</i>	<i>Total</i>	<i>Q1</i>	<i>D1</i>	<i>Institution. Centre</i>	<i>Province</i>
 Estruch Riba, Ramón	37	31	11	Hospital Clínic de Barcelona	Barcelona
 Fernández Aranda, Fernando	27	18	0	Fundación IDIBELL - Hospital Universitario de Bellvitge	Barcelona
 Fernández-Real Lemos, Jose Manuel	18	17	12	Fundación Instituto de Investigación Biomédica de Girona - Hospital Josep Trueta	Girona
 Fiol Sala, Miguel	27	22	6	Fundación Instituto de Investigación Sanitaria Illes Balears (IdISBa) - Hospital Universitario Son Espases	Illes Balears
 Fitó Colomer, Montserrat	46	37	14	Consorci Mar Parc Salut de Barcelona	Barcelona
 Frühbeck Martínez, Gema	27	14	4	Universidad de Navarra - Clínica Universitaria de Navarra	Navarra
 Gil Campos, María Mercedes	22	12	2	Fundación para la Investigación Biomédica de Córdoba (FIBICO) - Hospital Universitario Reina Sofía	Córdoba
 Lamuela-Raventos, Rosa María	12	10	4	Universidad de Barcelona - Facultad de Farmacia	Barcelona
 Lapetra-Peralta, Jose	22	17	6	Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla - Distrito Sanitario Atención Primaria de Sevilla	Sevilla
 Lasunción Ripa, Miguel Ángel	16	10	2	Servicio Madrileño de Salud - Hospital Ramón y Cajal	Madrid
 López Miranda, José	32	24	9	Fundación para la Investigación Biomédica de Córdoba (FIBICO) - Hospital Universitario Reina Sofía	Córdoba
 Lurbe Ferrer, Empar	17	12	2	Consorcio Hospital General Universitario Valencia - Fundación de Investigación del Hospital General Universitario de Valencia	Valencia
 Martínez González, Miguel Ángel	55	36	12	Universidad de Navarra	Navarra
 Martínez Hernández, Jose Alfredo	60	35	8	Universidad de Navarra	Navarra
 Moreno Aznar, Luis Alberto	43	19	2	Fundación Instituto de Investigación Sanitaria Aragón	Zaragoza
 Ortega Martínez de Victoria, Emilio	40	33	10	Hospital Clínic de Barcelona	Barcelona
 Osada García, Jesús de la	9	3	0	Universidad de Zaragoza	Zaragoza
 Palou Oliver, Andreu	15	11	7	Universidad de las Islas Baleares - Facultad de Ciencias de Mallorca	Illes Balears

<i>Group leader</i>	<i>Total</i>	<i>Q1</i>	<i>D1</i>	<i>Institution. Centre</i>	<i>Province</i>
 Pintó Sala, Xavier	24	16	3	Fundación IDIBELL - Hospital Universitario de Bellvitge	Barcelona
 Portillo Baqueda, María del Puy	18	10	4	Universidad del País Vasco - Facultad de Farmacia	Álava
 Remesar Betilloch, Xavier	9	5	0	Universidad de Barcelona - Facultad de Biología	Barcelona
 Salas Salvadó, Jordi	52	43	17	Fundación Instituto de Investigación Sanitaria Pere Virgili - Universidad Rovira i Virgili	Tarragona
 Serra Majem, Lluís	46	29	7	Universidad de las Palmas de Gran Canaria	Illes Balears
 Tena Sempere, Manuel	36	28	12	Universidad de Córdoba - Facultad de Medicina	Córdoba
 Tinahones Madueño, Francisco	49	34	12	Fundación Pública Andaluza para la Investigación de Málaga en Biomedicina y Salud (FIMABIS) - Hospital Regional Universitario Carlos Haya	Málaga
 Tur Mari, Josep Antoni	62	39	14	Universidad de las Islas Baleares - Facultad de Ciencias de Mallorca	Illes Balears
 Villarroya Gombau, Francesc	15	9	6	Universidad de Barcelona - Facultad de Biología	Barcelona



Cancer

PREVENTION



Scientific Director's Presentation

Joaquín Arribas López

After managing to integrate the research groups in the cooperative projects of the Programmes –thanks to the untiring work done by their respective Coordinators– CIBERONC has gone a step further during its second year, placing its efforts on fostering cooperation between the area's Research Programmes, as well as with other areas of the CIBER and with external organisations.

As one relevant accomplishment in the reinforcement of cooperation between the Programmes we should stress the formation of Work Modules, created as transversal research teams focussing on common fields of study between the CIBERONC groups: liquid biopsy and biomarkers, bioinformatics and omics of cancer, resistance to drugs and new therapies, immunoncology and experimental models. As well as helping the internal organisation to facilitate communication between CIBERONC members working on the same procedure, these Modules are also intended to help to promote young researchers' careers and to undertake transversal research projects which are eligible in external calls.

Through the creation of these Modules, the scientific work done by the CIBERONC is structured as a matrix with key aspects associated with Personalised Precision Medicine, such as bioinformatics or liquid biopsy, interconnected with scientific programmes studying the most prevalent pathologies, such as gastro-intestinal or breast cancer.

Apart from this, as one of the many endeavours carried out to foster cooperation between the areas, the organisation of the CIBERONC – CIBER-BBN forum proved to be of special relevance. A call for collaborative and co-financed seed projects was issued at this. One of the three winning projects led to setting up an international consortium linked to obtaining financing in a European call.

The Scientific Management has furthermore made an effort to start up cooperation schemes with external entities. One example to be stressed was the co-financing of one of the winning research projects in the call issued by the AECC Scientific Foundation in 2018.

These efforts have borne fruit in terms of scientific production, resulting in over 800 publications with CIBERONC affiliation and currently seven projects financed in external competitive calls.

As well as the progress made in scientific production, CIBERONC has gone on contributing to the training and promotion of young researchers through the measures taken in the Training and Mobility Programme, whose budget has increased in an attempt to extend the scope of its benefits to a larger number of groups.

For 2019 we hope that all these achievements will continue to proliferate as regards generating high-potential international collaborative projects and fostering the transfer of scientific results to society.

Scientific Programmes

Digestive Tract Tumour Programme

Coordinator:
Gabriel Capellá Munar

Co-coordinator:
Josep Taberneró Caturla

In 2018 the most relevant results of the Digestive Tract Tumour Programme include: (i) Starting the CIBERONC Registry for variants in genes of predisposition to gastrointestinal cancer coordinated by the ICO-IDIBELL Group and the Hospital Clínico San Carlos. This Registry in which CIBERONC groups are taking part in cooperation with other groups from Spain (the Autonomous Communities of Catalonia, Madrid and Valencia) has started with recording the variants of uncertain significance of repair genes which already

include 257 affected and 221 unique variants, 38 of which are recurrent. On a parallel basis, with the promotion of CIBERONC, the Spanish Registry of Familial Pancreatic Cancer has gradually grown, now including over 91 families. This year they will start to put all the variants identified in these families in the CIBERONC Registry. (ii) Under the leadership of Dr Eduard Batlle (IRB Barcelona) CIBERONC researchers have been provided with a biobank of murine colorectal tumour organoids which reproduce all the stages in neoplastic transformation; (iii) Dr Taberneró's team (VHIO) has got the Whole Exome Sequencing technology ready for studying circulating tumoral DNA displaying on a preliminary basis a close concordance with the biopsy, if the right depth of sequence readings is achieved. Over 2018 we have furthermore made substantial progress in the drafting of the new research Plan of the Programme which will focus on metastatic disease in bowel and pancreas cancer.

Breast Cancer Programme

Coordinator:
Atanasio Pandiella Atanasio

Co-coordinator:
Joan Albanell Mestres

In accordance with SAB recommendations, priority lines of research were redefined in 2018 as follows:

- HER2-positive tumours: mechanisms for resistance to antiHER2 therapy and new therapies.
- CDK4/6 inhibitors: new indications and biomarkers.
- Immunotherapy: preclinical models and analysis of TILs.

A nivel estratégico, se han establecido las bases. On a strategic level, the foundations of a formal cooperation agreement between our Programme and GEICAM have been established. This agreement, which should materialise in 2019, seeks to boost joint research between CIBERONC and GEICAM around the extensive biobank of

biological samples associated with patients in clinical trials, and the design of new clinical trials based on preclinical studies by CIBERONC. Mixed work groups have been set up around each of the strategic lines. In 2019 we should furthermore also consider cooperation with other cooperative groups such as SOLTI.

As regards scientific production, 59 articles with CIBERONC have been published, some in journals with a first decile impact index, such as NEJM, Science Translational Medicine, Nature Cell Biol, Annals of Oncology, Clinical Cancer Research, PNAS, Cancer Res, Lancet Oncol, etc. We should stress the following publications and achievements, by lines:

In HER2+ breast cancer one important accomplishment is the development of a p95HER2-T cell bispecific antibody for the subgroup of p95HER2+ breast cancers, with the participation of several groups from the Programme. This work is beginning a collaborative piece of research for developing ex vivo 3D cultures and humanised models on therapy with T cells in breast cancer. In 2018 a translational trial for seeking biomarkers of response / resistance to T-DM1 (GEICAM KATIA test) has been got under way. Tests have also been reported with new antiHER2 strategies and biomarker studies, both biological and of the immune system. As regards this last point, we

should stress the characterisation of a relevant association between NK, HLA cells and the efficiency of anti-HER2 antibodies. These results support the design of a clinical test on allogenic transplant of NK cells with the participation of PIs from the Breast Programme and other Programmes (I. Melero).

In the field of CDK4/6 inhibitors some relevant clinical trials have been reported in hormone receptor-positive disease and the characterisation of gene signatures associated with response. One valuable contribution was the description of the clinical behaviour of double positive breast cancers for hormonal receptors (oestrogen and progesterone) as compared with positive ones for a single marker. In luminal disease we should also stress our cooperation with other groups (R. Gomis) of the CIBERONC for establishing the role of MSK1 in the numbing of micrometastatic disease.

In triple negative breast cancer there has been cooperation in a new anti-stroma strategy which seems to fight chemo-resistance and modulate the plasticity of stem cells. Tests have also been published with PARP inhibitors, studies of response biomarkers, tests with selective inhibitors of active transcription of protein-coding genes in mutated and non-mutated BRCA breast cancer.

Respiratory Tract Tumours Programme

Coordinator:

Luis Montuenga Badía

Co-coordinator:

Luis Paz-Ares Rodríguez

In 2018, 117 articles with CIBERONC affiliation were published, some in journals with an outstanding impact index, such as NEJM, Cancer Discovery, Annals of Oncology, Clinical Cancer Research, Lancet Oncology, Lancet Respiratory Medicine, European Respiratory Journal, etc.

Objective 1. New therapeutic targets. We have published data on C5aR1 inhibition and its effect on bone metastases. This involved the groups led by Luis Montuenga (LM), Luis Paz-Ares LPA) and (Carlos Camps (CC). We have

studied FGFR1 signalling and its interactions with EGFR and N-cadherin, and the relevance of this interaction in anti-FGFR therapies (LPA and Amancio Carnero -AC-). We have characterised the amplification or over-expression of YES-1 as a possible driver in lung, head and neck carcinoma. (LM, CC, LPA, Juan Pablo Rodrigo- Tapia -JPR- and Xosé Bustelo, from the Molecular Mechanisms Programme).

Objective 2. Immune-oncology. One of our PIs, LPA, has this year made a significant contribution to clinical trials which are changing clinical practice: Durvalumab after chemotherapy in patients with non-microcytic lung carcinoma (NMLC); Pembrolizumab plus chemotherapy in squamous lung cancer; or Nivolumab plus Ipilimumab in NMLC with a high mutational level (TMB) (All published in the NEJM). The protocol for prospective collection of samples from the immune-oncology cohort IOR-CIBERONC (CC, LPA) was drafted and is now being evaluated by ethical committees. We are also collecting samples from a retrospective cohort of patients

treated with Immunotherapy, in order to reach 300 patients. We have started an exhaustive molecular and immune characterisation of the retrospective CIBERONC cohort, of surgical cases of NMLC (N>500). We are also studying two platforms for quantifying TMB (Illumina, ThermoFisher) comparing these with those of FoundationOne. We have fine-tuned and started to develop the VECTRA- POLARIS platform for multiplex analysis of the “immune landscape” in histological sections of human and mouse lung cancer. We have shown the effectiveness of combinations of inhibition of the complement and Immunotherapy (LM) in preclinical models.

Objective 3. Identification and analytical development of clinically relevant biomarkers in respiratory tract tumours.

A prospective study of an analysis of NGS in cfDNA has been carried out (Guardant 360) for molecular characterisation of advanced NMLC in plasma (LPA, CC). We have published

and patented two prognostic signatures for adenocarcinoma and squamous lung carcinoma (LM in cooperation with CIBERES). We have contributed to a mass analysis of EGFR mutations in liquid biopsy of NMLC patients (CC, LPA).

Other achievements: FIS project obtained through the CIBER: “Non-invasive immunogram: multidimensional approach for monitoring and characterization of immune status in lung cancer” PIs: CC and Eloisa Jantus. EURONANOMED III International Project: “Targeted multifunctional nanoemulsions to interrupt metastatic progression (METASTARG)” PI: María de la Fuente (cols: CC and Eloisa Jantus). Lastly, members of the programme have received a total number of 7 grants from the training and mobility programme.

Haematological Tumour Programme

Coordinator:
Dolors Colomer Pujol

Co-coordinator:
Marcos González Diaz

In 2018 117 articles were published and the experimental plan set in our Programme’s scientific project was followed up.

Different collaboration work was published, the most outstanding piece resulting in the publication of the epigenome of chronic lymphatic Leukaemia (CLL) (Beekman et al, *Nature Med*). The mutational profile of different entities has also been characterised by different mass sequencing studies (Ruiz-Heredia et al, *Haematologica*; Karube et al, *Leukemia*; Jimenez et al, *Ann Hematol*; Suárez-González et al, *Leukemia*), as well as the clinical impact of subclonal mutations on CLL (Nadeu et al, *Leukemia*). Different molecular signatures have been described for a better classification of different entities (Clot et al, *Blood*; Huet et al, *Lancet Oncol*; Arana et al, *Leukemia*; Manso et al, *Oncotarget*; Plos One; Ibañez et al, *Plos One*), as well as poor prognostic parameters (Criado et al, *Leukemia*; *Haematologica*; Matarraz

et al, *Mod, Pathol*; Parda et al, *Am J Hematol*; Montalban et al, *Br J Haematol*; Moreno et al, *Plos One*; Rodríguez-Otero et al, *Leukemia*; Martínez-Laperche et al, *Br J Haematol*; Labrador et al, *Leuk&Lymp*). We have also proposed that the over-expression of cyclin D1 induces a reduction of the overall transcription in LCM (Albero et al, *J Clin Invest*).

An analysis has been made of new epigenetic modifiers (Rabal et al, *J Med Chem*), inhibiting the regulation of intracellular pH (Celay et al, *Haematologica*), BET inhibitors (Esteve-Arenys et al, *Oncogene*) and mechanisms of resistance to sorafenib (Macias et al, *Oncotarget*) and bortezomib (Heine et al, *J Hematol Oncol*). Different studies connected with the immune system and transplantation have been completed (García-Guerrero et al, *Front Immunol*; Rodríguez-Barbosa et al, *MoAbs*; García-Barchino et al, *J Pathol*; Preciado et al, *Biol Blood Marrow Transplant*).

The results of different clinical trials in the I-II phase have been presented (Martínez-Cuadrón D, *Ann Hematol*; San Miguel et al, *Haematologica*), international tests (Mateos et al, *N Engl J Med*; Cuneo et al, *Haematologica*, Saussele et al, *Lancet Oncol*; Siegel et al, *J Clin Oncol*; Stauder et al, *Leukemia*) and of haematopoietic transplantation (Garderet, et al, Stiff et al, Stah et al, *Biol Blood Marrow Transplant*; Giannotti et al, *J Hematol Oncol*; Gayoso et al *Eur J Haematol*). An investigational clinical trial promoted with the ISCIII is being developed with an anti-CD19+

CART- 4-1BB-CD3z (ARI-0001) for resistant and refractory patients of CD19+leukaemias and lymphomas integrally generated in a CIBERONC group.

The members of the group have taken part in the preparation of recommendations and clinical guides (Caers et al, *J Hematol Oncol*; Ludwig et al, *Leukemia*; Mozas et al, *Blood Cancer J*; Mora et al, *Curr Opin Oncol*; Malcikova et al,

Leukemia; Gonzalez-Barca et al, *Oncotarget*; Romero et al, *Med.Clin*), in the standardisation of minimum residual disease in the MM (Holstein et al, *Biol Blood Marrow Transplant*) and in the preparation of reviews in high-impact journals (Puente et al, *Blood*; Garcia-Sanz et al, *Expert Opin Drug Saf*; Beekman et al, *Curr Opin Hematol*; Piris et al, *Semin Diagn Pathol*. Montore et al, *Curr Opin Oncol*).

Low prevalence tumour programme

Coordinator:
Enrique de Álava Casado

Co-Coordinator:
Ignacio Melero Bermejo

The challenge faced by our programme for 2018 was to implement two cooperative research programmes on two low-prevalence tumours, selected based on such a broad and heterogeneous group of organisations as the ones covered by the Programme.

The first half of 2018 was dedicated to generating data in the Programme's cooperation project on uveal melanoma; a neoplasm in which no translational project nationwide has been performed until now. For this project, the Programme had obtained additional financing through a prize awarded by the GETHI (Spanish Group of orphan and rare tumours) in 2017. The Programme specifically covered these two achievements:

- Evaluation and quantification of the levels of expression of Endoglin (EDG) / MMP14 and the HIPPO TAZ / YAP pathway effectors in 4 independent cohorts of samples of paired uveal melanoma samples.
- The generation of models of elimination of EDG, MMP14, TAZ and YAP by means of genomic edition using CRISPR- Cas9 technology, used for evaluating the functionality of these molecules in in vitro and in vivo models of uveal melanoma.

The generation of additional preliminary results of this first cooperative project of the Programme is continuing at the present time.

This action also gave rise to the organisation of the first collaborative event between GETHI and CIBERONC for the study of synergies in low-prevalence tumours. In this case the meeting focussed on uveal melanoma uveal and over 40 specialists in this area holistically analysed current needs in the research, diagnosis and treatment of this disease.

In the second half of 2018, the Programme drafted and got under way a second cooperative project, which covers the immune panorama of uterine tumours. Each group provided tools, samples and clinical data on this tumour, on which no cooperative translational research had been done in Spain until then. The project was got under way in September 2018 after being approved by the External Advisory Scientific Committee of the CIBERONC. The achievements until late December 2018 include:

- Compilation of the discovery cohort. A unique collection of paired samples has been compiled (primary / metastasis) of 50 patients with metastatic endometrial adenocarcinoma and 25 samples of leiomyosarcoma with a detailed follow-up of 4 different hospitals (PIs: Xavier Matías-Guío, Santiago Ramón y Cajal, Rosa Noguera, Enrique de Álava).
- The start of the pathological characterisation of the discovery cohort took place in November 2018.

The work done in this second cooperative project will go on until late 2020.

Tumour Progression Mechanisms Programme

Coordinator:
Xosé García Bustelo

Co-coordinator:
Anna Bigas Salvans

The scientific progress made includes the discovery of the tumour-suppression role of RAS oncoproteins found on the Golgi apparatus (*Nat Commun*, PMID 30185827; Piero Crespo and Xosé R. Bustelo), of a new signalling pathway involved in the generation of dormant metastases in breast cancer (*Nat Cell Biol*, PMID 29358704; Arkaitz Carracedo) and of a new therapeutic vulnerability of bowel cancer (*Nat Commun*, PMID 30065304; Anna Bigas). New diagnostic methods have furthermore been developed for diffuse gliomas (*Clin Cancer Res*, PMID 29615461; Joan Seoane), breast cancer (*Oncogene*, PMID 30087437; Xosé R. Bustelo) and thyroid cancer (*Annal Oncol*, PMID 29648575; Joan Seoane) using both diagnostic signatures and those of molecular taxonomy. Finally scientific reviews have been published in highly relevant journals in the field of molecular oncology such as *Curr Opin Cell Biol* (Anna Bigas, Xosé Bustelo; PMIDs 30287131, 30007125, 30006050), *Curr Opin Cell Genet* (Xosé R. Bustelo; PMID 29100209), *Nat Rev Cancer* (Arkaitz Carracedo; PMID 30194362), *Sci Sig* (Piero Crespo con Eugenio Santos; PMID 30377222), *Cell Stem Cell* (Anna Bigas, PMID 29727679) and *Trends Cancer* (Xosé R. Bustelo con Piero Crespo, PMID 30149880).

Tools for common use: an online tool has been developed allowing in silico analysis of different bases of genomic data of cancer by users with no bioinformatic knowledge (http://web.bioinformatics.cicbiogune.es/CANCER_TOOL/). This tool has also been published during this

period (*Cancer Res*, PMID 30232219; Arkaitz Carracedo, Xosé R. Bustelo, Carlos López-Otín).

Several members of the Programme have been involved in starting up different Work Modules of the CIBERONC, including the one for Bioinformatics (Xosé R. Bustelo, Arkaitz Carracedo, Carlos López-Otín, Javier Oliver, Jesús M. Paramio), Resistance and New Therapies (Jesús M. Paramio), Immune-Oncology (Anna Bigas), Liquid Biopsy (Joan Seoane) and Experimental Models (Xosé R. Bustelo, Arkaitz Carracedo, Alberto Muñoz).

Recruiting funds: the Programme goes on receiving financing through some highly competitive projects such as those of the AECC (Xosé R. Bustelo, Piero Crespo, Anna Bigas, Joan Seoane), the Fundación La Caixa (Arkaitz Carracedo) and EU programmes, including among the latter the ones corresponding to standard H2020 programmes (Anna Bigas), ERC-Consolidator (Arkaitz Carracedo) and ERC-Advanced (Carlos López-Otín).

Scientific dissemination: members of the Programme have organised three conferences of the European Association for Cancer Research (Arkaitz Carracedo, Joan Seoane), the 41st Congress of the European Thyroid Society (Pilar Santisteban) and two symposia for the international congresses of the Sociedad Española de Bioquímica y Biología Molecular (Xosé R. Bustelo) and of the Asociación Española contra el Cáncer (Carlos López-Otín). A course on Genomic Techniques was also organised (Jesús M. Paramio) for members of the CIBERONC.

Scientific leadership: members of our Programme have been appointed for office on the boards of directors of the EACR (Arkaitz Carracedo, Joan Seoane) and ESMO (Joan Seoane). Arkaitz Carracedo received awards for the best young scientist from the SEBBM and AstraZeneca. Roger R. Gomis (Arkaitz Carracedo's group) received the ASEICA Young Investigator Award.

Training and Mobility Programme

Coordinator:

Amparo Cano García

Co-coordinator:

Anna Bigas Salvans

The most prominent activities of the Programme, or “PFM”, were for the following Sub-programmes:

Promotion of young researchers

The I Encuentro de Jóvenes Investigadores (I EJI, held on 14 November 2018 at the Escuela Nacional de Sanidad, Madrid) was promoted. The organisation of the Encounter was handled by young CIBERONC researchers (predoctoral and junior postdoctoral). To this end an organising committee made up of 6 members was elected (one per CIBERONC research programme) which organised the scientific programme and the other activities at the Encounter. 6 scientific sessions were held (one per scientific programme) at which there were 2 oral communications per session (one predoctoral, one postdoctoral), selected by the PFM Coordination from a total number of 42 abstracts presented. One award per category was given to the best oral communications, chosen by votes cast by those attending. The scientific programme was completed with a plenary session and two round tables. The event had a large audience (limited to 60 participants by the possibilities of the venue) and was a great success with the young

researchers, who valued the experience as being of high training value, as was reflected in the satisfaction survey carried out, which obtained an overall valuation of 2.7 out of 3.

Getting started in research

We should highlight the programme of launching grants (co-financed by the Programme and the research groups). 5 contracts were financed for a period of 6 months for post-master students.

Mobility

14 short stays were financed at national groups and 7 international ones, out of a total number of 27 applications.

Training

The organisation of 3 courses by CIBERONC researchers was financed (Genomics of Cancer, Statistical Methods applied to studying the microbiota, Next Generation Sequencing applied to the diagnosis of haematological neoplasia) and attendance at external training courses outside CIBERONC by a total number of 18 researchers) (postdoctoral, predoctoral and technical) of a total number of 31 applications.

The work done by the PFM was assessed as being excellent by the external advisory committee, which led to an increase of 11% in the budget for the Programme for 2019.

Scientific Production

Publications

No. of publications in 2018

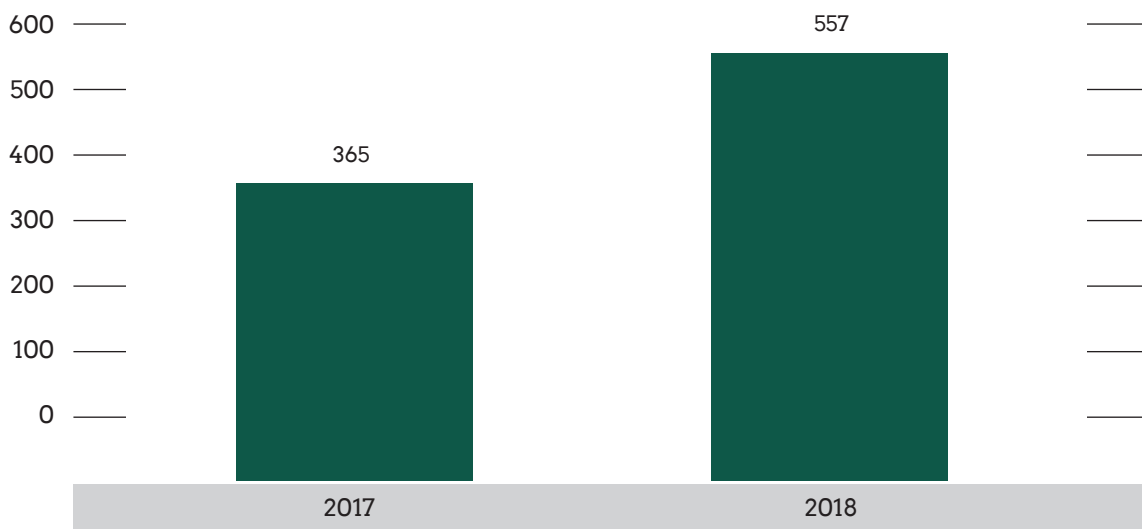
TOTALS	557
Q1	386
D1	222

Collaborative Publications

CIBERONC	128
CIBER*	133

*Over several thematic areas

Evolution of publications



10 most relevant CIBERONC publications in 2018 by impact factor

FI	Publication
79,2580	LITTON J.K., RUGO H.S., EITL J., HURVITZ S.A., GONCALVES A., LEE K.-H. ET AL. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. New England Journal of Medicine. 2018;379(8):753-763.

79,2580	DIMOPOULOS M.A., DYTFFELD D., GROSICKI S., MOREAU P, TAKEZAKO N., HORI M. ET AL. Elotuzumab plus Pomalidomide and Dexamethasone for Multiple Myeloma. <i>New England Journal of Medicine</i> . 2018;379(19):1811-1822.
79,2580	MORSCHHAUSER F, FOWLER NH, FEUGIER P, BOUABDALLAH R, TILLY H, PALOMBA ML ET AL. Rituximab plus Lenalidomide in Advanced Untreated Follicular Lymphoma. <i>The New England journal of medicine</i> . 2018;379(10):-.
50,1670	PASTOR F, BERRAONDO P, ETXEBERRIA I., FREDERICK J., SAHIN U., GILBOA E. ET AL. An rna toolbox for cancer immunotherapy. <i>Nature Reviews Drug Discovery</i> . 2018;17(10):751-767.
42,7840	KESHET R, SZLOSAREK P, CARRACEDO A, EREZ A, CARRACEDO PEREZ ARKAITZ. Rewiring urea cycle metabolism in cancer to support anabolism. <i>Nature reviews. Cancer</i> . 2018:-.
41,5770	COBO I, MARTINELLI P, FLANDEZ M., BAKIRI L., ZHANG M., CARRILLO-DE-SANTA-PAU E. ET AL. Transcriptional regulation by NR5A2 links differentiation and inflammation in the pancreas. <i>Nature</i> . 2018;554(7693):533-537
41,5770	TAURIELLO DVF, PALOMO-PONCE S, STORK D, BERENQUER-LLERGO A, BADIA-RAMENTOL J, IGLESIAS M ET AL. TGFβ drives immune evasion in genetically reconstituted colon cancer metastasis. <i>Nature</i> . 2018;554(7693):-.
36,4180	SAUSSELE S., RICHTER J., GUILHOT J., GRUBER F.X., HJORTH-HANSEN H., ALMEIDA A. ET AL. Discontinuation of tyrosine kinase inhibitor therapy in chronic myeloid leukaemia (EURO-SKI): a prespecified interim analysis of a prospective, multicentre, non-randomised, trial. <i>The Lancet Oncology</i> . 2018;19(6):747-757.
36,4180	HUET S., TESSON B., JAIS J.-P., FELDMAN A.L., MAGNANO L., THOMAS E. ET AL. A gene-expression profiling score for prediction of outcome in patients with follicular lymphoma: a retrospective training and validation analysis in three international cohorts. <i>The Lancet Oncology</i> . 2018;19(4):549-561.
36,4180	HURVITZ S.A., MARTIN M., SYMMANS W.F., JUNG K.H., HUANG C.-S., THOMPSON A.M. ET AL. Neoadjuvant trastuzumab, pertuzumab, and chemotherapy versus trastuzumab emtansine plus pertuzumab in patients with HER2-positive breast cancer (KRISTINE): a randomised, open-label, multicentre, phase 3 trial. <i>The Lancet Oncology</i> . 2018;19(1):115-126.

CIBERONC Groups. Publications in 2018

Group leader	Total	Q1	D1	Institution. Centre	Province
 Álava Casado Enrique de	11	9	5	Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla. Hospital Virgen del Rocío	Sevilla
 Albanell Mestres, Joan	18	14	7	Consorci Mar Parc Salut de Barcelona. Hospital del Mar	Barcelona
 Aranda Aguilar, Enrique	8	6	1	Fundación para la Investigación Biomédica de Córdoba (Fibico). Hospital Universitario Reina Sofía de Córdoba	Córdoba
 Arribas López, Joaquin	8	8	6	Fundación Privada Instituto de Investigación Oncológica Valle de Hebrón-VHIO	Barcelona
 Batlle Gómez, Eduard	1	1	1	Fundación Privada Instituto de Recerca Biomédica (IRB-Barcelona)	Barcelona
 Bigas Salvans, Anna	12	11	7	Consorci Mar Parc Salut de Barcelona. Hospital del Mar	Barcelona
 Bosch José Francesc, Xavier	5	2	1	Fundación Idibell Hospital. Universitario de Bellvitge	Barcelona

<i>Group leader</i>	<i>Total</i>	<i>Q1</i>	<i>D1</i>	<i>Institution. Centre</i>	<i>Province</i>
 Campo Guerri, Elías	24	22	18	Instituto de Investigaciones Biomédicas August Pi i Sunyer	Barcelona
 Camps Herrero, Carlos	14	7	2	Consortio Hospital General Universitario Valencia. Fundación de Investigación del Hospital General Universitario de Valencia	Valencia
 Cano García, Amparo	4	4	0	Universidad Autónoma de Madrid	Madrid
 Capella Munar, Gabriel	20	17	6	Fundación Idibell. Hospital Duran y Reynals	Barcelona
 Carnero Moya, Amancio	0	0	0	Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla. Hospital Virgen del Rocío	Sevilla
 Carracedo Pérez, Arkaitz	24	18	14	CIC Biogune	Vizcaya
 Carrato Mena, Alfredo	14	10	5	Servicio Madrileño de Salud. Hospital Ramón y Cajal	Madrid
 Cervantes Ruiperez, Andrés	17	13	11	Fundación para la Investigación del Hospital Clínico de la Comunidad Valenciana (Fundación Incliva)	Valencia
 Colomer Pujol, Dolors	19	18	13	Instituto de Investigaciones Biomédicas August Pi i Sunyer	Barcelona
 Crespo Baraja, Piero	6	5	4	Agencia Estatal Consejo Superior de Investigaciones Científicas. Instituto de Biomedicina y Biotecnología de Cantabria	Cantabria
 Díaz-Rubio García, Eduardo	24	19	6	Servicio Madrileño de Salud. Hospital Clínico San Carlos	Madrid
 Esteller Badosa, Manel	10	9	7	Fundación Idibell. Hospital Durán Reynals	Barcelona
 Feliu Batlle, Jaime	9	8	7	Servicio Madrileño de Salud. Hospital La Paz	Madrid
 García Bustelo, Xose Ramon	13	7	4	Fundación de Investigación del Cáncer de la Universidad de Salamanca. Centro de Investigación del Cancer	Salamanca
 González Díaz, Marcos	23	19	11	Fundación Instituto de Estudios de Ciencias de la Salud de Castilla y León. Hospital Universitario de Salamanca	Salamanca
 Lluch Hernández, Ana	11	5	3	Fundación Para la Investigación del Hospital Clínico de la Comunidad Valenciana (Fundación Incliva)	Valencia
 López López, Rafael	20	12	5	Servicio Gallego de Salud. Complejo Hospitalario Universitario Santiago	A Coruña
 López Otín, Carlos	16	13	10	Universidad de Oviedo. Facultad de Medicina	Asturias
 Malats Riera, Nuria	8	7	6	Fundación Centro Nacional de Investigaciones Oncológicas	Madrid
 Martín Jiménez, Miguel	24	14	12	Servicio Madrileño de Salud. Hospital Gregorio Marañón	Madrid
 Matías-Guiu Guía, Francisco Javier	15	5	1	Instituto de Investigación Biomédica de Lleida. Fundación Dr. Pifarre	Lleida
 Melero Bermejo, Ignacio	26	19	14	Universidad de Navarra. Clínica Universitaria de Navarra	Navarra
 Montuenga Badía, Luis	17	16	7	Fundación para la Investigación Médica Aplicada	Navarra
 Muñoz Terol, Alberto	5	5	1	Agencia Estatal Consejo Superior de Investigaciones Científicas. Instituto de Investigaciones Biomédicas Alberto Sols	Madrid

<i>Group leader</i>	<i>Total</i>	<i>Q1</i>	<i>D1</i>	<i>Institution. Centre</i>	<i>Province</i>
 Noguera Salva, Rosa	10	7	4	Fundación para la Investigación del Hospital Clínico de la Comunidad Valenciana (Fundación Incliva)	Valencia
 Oliver Pozo, Francisco Javier	3	3	1	Agencia Estatal Consejo Superior de Investigaciones Científicas. Instituto de Parasitología y Biomedicina López Neyra	Granada
 Orfao de Matos Correia e Vale, Jose Alberto	9	9	6	Fundación de Investigación del Cáncer de la Universidad de Salamanca. Centro de Investigación del Cáncer	Salamanca
 Palacios Calvo, José	0	0	0	Servicio Madrileño de Salud. Hospital Ramón y Cajal	Madrid
 Pandiella Alonso, Atanasio	9	6	2	Fundación de Investigación del Cáncer de la Universidad de Salamanca. Centro de Investigación del Cáncer	Salamanca
 Paramio González, Jesús María	17	9	7	Centro de Investigaciones Energéticas, Medioambientales Y Tecnológicas (CIEMAT)	Madrid
 Paz-Arés Rodríguez, Luis	25	17	9	Servicio Madrileño de Salud. Hospital Universitario 12 de Octubre	Madrid
 Pérez Simón, José Antonio	8	5	1	Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla. Hospital Virgen del Rocío	Sevilla
 Piris Pinilla, Miguel Ángel	8	4	2	Instituto de Investigación Sanitaria Fundación Jiménez Díaz	Madrid
 Prosper Cardoso, Felipe	12	10	8	Fundación para la Investigación Médica Aplicada	Navarra
 San Miguel Izquierdo, Jesús Fernando	24	23	20	Universidad de Navarra. Clínica Universitaria de Navarra	Navarra
 Santisteban Sanz, María del Pilar	6	4	3	Agencia Estatal Consejo Superior de Investigaciones Científicas. Instituto de Investigaciones Biomédicas Alberto Sols	Madrid
 Santos de Dios, Eugenio	5	3	2	Fundación de Investigación del Cáncer de la Universidad de Salamanca. Centro de Investigación del Cáncer	Salamanca
 Ramon y Cajal, Agüeras Santiago	18	12	8	Fundación Hospital Universitario Vall D'Hebrón - Institut De Recerca (VHIR). Hospital Valle Hebrón	Barcelona
 Real Arribas, Francisco Xavier	7	6	5	Fundación Centro Nacional de Investigaciones Oncológicas	Madrid
 Rodrigo Tapia, Juan Pablo	22	11	1	Fundación para el fomento en Asturias de la Investigación Científica Aplicada y la Tecnología. Hospital Universitario Central de Asturias	Asturias
 Sanz Alonso, Miguel Ángel	4	2	0	Universidad de Navarra. Clínica Universitaria de Navarra	Navarra
 Seoane Suárez, Joan	6	6	6	Fundación Privada Instituto de Investigación Oncológica Valle de Hébron-VHIO	Barcelona
 Taberbero Caturla, José María	18	16	13	Fundación Privada Instituto de Investigación Oncológica Valle de Hebrón-VHIO	Barcelona

The image features a microscopic view of neurons on the left side, with their cell bodies and branching processes visible. The right side of the image is dominated by a solid yellow background. Overlaid on this yellow background is the text 'Mental Health' in white, and the words 'PRESENTATION' in large, semi-transparent yellow letters.

Mental Health

PRESENTATION



Scientific Director's Presentation

Eduard Vieta Pascual

Two thousand and eighteen was a very significant year for CIBERSAM, as can be seen from this annual report, which shows the major scientific progress made by the Mental Health CIBER over the year recently ending. A year in which CIBERSAM published a record number of scientific articles (663, 21.56% of which were in the first decile for the speciality), new patents and guides for clinical practice, doctoral theses and international awards. This year, three CIBERSAM investigators appear on the list of the most influential ones in the world based on the number of citations of their articles. Figures nonetheless fail to portray the reality when the most relevant part is analysed: progress made in scientific knowledge.

In 2018, CIBERSAM has made a decisive contribution to discovering new action mechanisms for the development of fast-action anti-depressive drugs, has again taken part in the macro-project on the global burden of mental diseases (with two publications on the subject in the Lancet and one in JAMA in 2018) and has played a relevant role in international collaborative research published in journals of the very greatest prestige, such as Nature, Science and Cell, which have contributed to an understanding of the role of genetic variants involved in serious mental disorders. CIBERSAM has also disseminated the results of epidemiological studies on the clinical validity of ICD- 11 diagnostic criteria and on the relationship between anxiety and cognitive deterioration and has published some significant progress made in the neurobiology of the bipolar disorder, depression, obsessive-compulsive disorder, personality disorders or neurodevelopment disorders. The articles are the result of competitive projects, mainly international,

and in this line financing has been obtained for European Union projects, the Brain and Behavior Research Foundation in the United States and from the Canadian Government.

This year too CIBERSAM has continued to apply the strategic plan 2017-2019 which includes a greater focus on the patients' needs and participation. In this approach, in 2018 special stress was placed on the need to improve early attention in mental health and to identify risk factors of psychopathology in the vulnerable population. CIBERSAM has cooperated in drawing up the **First White Book in early intervention on psychosis in Spain** and has published a key article in the American Journal of Psychiatry highlighting the importance of early intervention in bipolar disorder. As in previous years, the CIBERSAM training programme has had the exclusive Inter-university Master course on Initiation to research into Mental Health, which this year has again completed the maximum number of applications for registration. The Neuroimaging platforms, the Library of Instruments in Mental Health and Disability and the DNA Collection, along with the external collection of the Brain Bank, have continued to collect samples to be used in intra- and inter-CIBER collaboration projects. Yet another year, CIBERSAM has been a privileged partner in taking part in major consortiums for research into genetics and neuroimaging. This report sums up, in a few pages, the efforts made by hundreds of researchers which have contributed to improving our understanding of mental diseases and their treatment. As scientific director, I am proud of my travelling companions and the social benefits entailed by the work done by them.

Scientific Programmes

Depression and Suicide Prevention

Coordinator:
Víctor Pérez Sola

In 2017 a change in the name of the programme was proposed, thus recognising the importance of suicide prevention in the CIBERSAM's objectives. Suicide is the main avoidable cause of death in the world and one of the main causes of death among young people, so its impact is devastating and very extensive, affecting families, communities and societies in general. Several groups have concentrated their research on the evaluation of risk factors of suicidal behaviour, working on the implementation of strategies for prevention and evaluation of its efficiency and participating in the creation of the future national strategy for prevention of suicide.

Researchers from the programme have cooperated in different epidemiological studies and international initiatives. Some prominent ones are the studies of clinical validity of ICD- 11 diagnostic criteria, as well as belonging to a world network of experts convened by the WHO, and the International Workers Organisation to assess the impact of working long hours and the incidence of depression. Another line of research is the evaluation of high-risk populations such as the elderly, children and the perinatal period, or of the social determinants such as the social-economic level, unemployment or loneliness in the etiopathogeny of the illness.

In the line of new therapeutic targets a new target was identified for a fast and more effective treatment of depression through inhibitory oligonucleotides addressing monoaminergic

neurons. Several basic groups have focussed their work on the action mechanisms of the drugs acting on the glutamatergic pathway in the treatment of depression. This is a new therapeutic strategy which will change current paradigms in the treatment of depression. Several clinical and basic groups lead research into the evaluation and study of the action mechanism of Deep Brain Stimulation and ECT in the treatment of resistant severe mental disorders. Lastly, the potential of cannabidiol and of ampakins as fast-action anti-depressants has been shown, evaluating their effects on the behavioural, neurochemical and molecular levels. Several collaborative projects have been started for the creation and validation of functional rehabilitation programmes in cognitive symptomatology. The factors most closely related with the therapeutic response have been described, analysing the barriers limiting the response to treatment or the implication of key symptoms such as circadian rhythms, pharmacogenetic studies or the Mediterranean diet in the evolution of the disorder and the therapeutic response. Studies have also been carried out on neuroimaging, genetic and neurohormonal biomarkers in different clinical phenotypes of depression.

As for the neurochemical bases of depression, studies confirm the involvement of the ventral cingulate cortex as a key cortical area in the physiopathology and treatment of depression, displaying the implication of glial glutamate transporters by means of siRNAs in animal models of depression. They also confirm the importance of inflammatory-immunological processes in the etiopathogeny of depression and the important role of the cannabinoid pathways in the physiopathology of the disease or suicide and their possible utility as a therapeutic target.

Schizophrenia

Coordinator:
Benedicto Crespo-Facorro

Some of the most notable results of the programme in 2018 are the number of 81 publications (25 of these (30%) with preferential CIBERSAM authorship) in journals indexed in the first decile according to the JCR in areas of psychiatry, neuroimaging, genetics, multidisciplinary sciences, neurology and neurosciences.

In connection with the programme in 2018: 2 projects of the Brain and Behavior Research Foundation, 1 project financed by NIMH, 3 H2020 projects and 3 projects financed by the Canadian government, as well as a COST-H2020 participation. In the Spanish area, a total number of 24 projects have obtained competitive financing in public calls of the AES 2017 and 2 in competitive private calls.

With regard to human resources contracts we should place great stress on the incorporation of a large number of researchers by obtaining 1 Marie Curie postdoctoral contract, 2 Ramón y

Cajal contracts, 2 Miguel Servet contracts, 2 Rio Hortega contracts, 2 Sara Borrell, 1 FTU and 2 PFIS.

Two patents have been published:

- *Synthetic I2 imidazoline receptor ligands for prevention or treatment of human brain disorders.* Authors: María Carmen Escolano, Mercé Pallás, Cristian G. Griñan, Sonia Ribas, L.F. Callado, Jesús García Sevilla. PCT/EP2018/085742;
- *An integrated system to predict response to ECT based upon brain functional connectivity patterns, as determined by FMRI.* Authors: Marta Moreno, Joan Prudic, Stefan Rowny y Daniel Javitt; CU17136 (presented in USA 30/03/2018).

Seven doctoral theses have been read in the CIBERSAM groups (one with an international mention) and two theses of CIBERSAM researchers received the extraordinary doctorate award this year.

As regards other merits, the members of the programme and their work have been recognised with different awards at meetings, congresses, national and international symposia and by relatives' associations.

Most outstanding scientific achievements in:

- Articles in Science and Nature.

Bipolar disorder

Coordinator:
Ana González-Pinto

Some of the most relevant results of the programme are the 36 articles in the first decile that have been published in journals of the highest repute such as World Psychiatry, British Journal of Psychiatry, Neuroscience and Biobehavioral Reviews, Molecular Psychiatry, JAMA Psychiatry, American Journal of Psychiatry, Lancet or Schizophrenia Bulletin.

The programme has a high rate of internationalisation and scientific productivity, stressing collaborative work between CIBERSAM groups and other CIBER areas and national and international cooperation.

In 2018 nine national and international projects with competitive financing have been obtained (FIS, ISCIII, Ministry of Science, Innovation and Universities, EU-HORIZON 2020, Generalitat de Catalunya).

Two private contracts have also been obtained:

- CB/07/09/0024 group contract with the company EVERIS. Title: "Smart Remote Treatment: personalised medicine for treatment of patients with bipolar disorder."
- Training Services Contract with the FINBA (Fundación para la Investigación Biosanitaria del Principado de Asturias) and Pfizer SLU. Title: "Clinical stay for training in the Programme for Giving Up Smoking in patients with schizophrenia or bipolar disorder".

The awards and other distinctions received by members of the programme were:

- Prize for the 2nd best article on an international scale in the Bioaraba Symposia for Research and Innovation "The complex association between the antioxidant defence system and clinical status in early psychosis".
- Third prize for the best article on an international scale at the Bioaraba Symposia for Research and Innovation "Can lithium salts prevent depressive episodes in the real world?".
- Prize at the National Psychiatry Congress 2018 "Use of benzodiazepines in patients with bipolar disorder".
- Eduard Vieta is among the most influential scientists in the world according to the list published by Clarivate Analytics. 2018 Highly Cited Researchers.
- Diego Hidalgo-Mazzei Award Hestia 2018 for Excellence in Socio-Healthcare Investigation and in Mental Health in the category of Best Project performed or Work published by the SIMPLe Project (Self-monitoring and psychoeducation in bipolar patients with a smartphone application).
- Prize for the doctoral thesis "Application of information and communication technologies (ICTs) in bipolar disorder" (Diego Hidalgo-Mazzei) directed by Eduard Vieta and Francesc Colom.
- Barraquer i Bordas Award for the doctoral thesis entitled "The bipolar disorder; changes

in the brain associated with the mood and cognitive deterioration" (Silvia Alonso) directed by Edith Pomarol-Clotet and Eduard Vieta.

Some of the most significant scientific achievements are:

- Doctoral thesis: "Self and Hetero-Aggression: Clinical Implications in Bipolar Disorder and Mixed States" (Norma Verdolini) directed by Eduard Vieta and Isabella Pachiarotti.
- Dr Vieta's participation in an international collaborative study published in Cell which genetically dissects bipolar disorder and schizophrenia and identifies different gene regions involved in the similarities and differences between both disorders.
- Rio Hortega Contract for 2018-2019 (Marina Garriga), with Eduard Vieta as the scientific director.
- Web www.bipogent.cat intended to provide information and recruit patients and controls for the study financed by ISCIII and CIBERSAM (groups led by: Peter J. Mckenna, Eduard Vieta and Elisabet Vilella).
- Participation of FIDMAG researchers in the ENIGMA international consortium.
- Clinical guide on "Coercion and mental health. Rules for clinical decisions". Manuel Gómez- Beneyto.

Therapeutic innovation

Coordinator:
Francesc Artigas Pérez

Some of the most relevant results (2018) to be highlighted are the publication of 12 clinical guides and 59 articles in D1, stressing the ones published in Nature (IF:41,577), Science (IF:41,058), Cell (IF:31,398), JAMA Psychiatry (IF:16,642), Nature Reviews Disease Primers (IF:16,071) and Lancet Psychiatry (IF:15,233).

In innovation we should stress 5 applications for patents (EP18382191.7, PCT/ES2018/070194, P201800272 and PCT/EP2018/085742; U.S.A./ Canada extension: P201500129).

As regards obtaining funds, 30 grants/projects for state public bodies have been obtained (MSSSI: PNSD2017/085; MINECO: SAF2017-86620-R, SAF2017-85888-R, SAF2017-83053-R; ISCIII: PI17/01766, PI17/00064, PI17/01066, PI17/00941, PI18/01691, PI18/00789, PI18/01001, PI18/00805, DTS17/00122, PT17/0017/0039 and PT17/0005/0001), regional authorities (GENCAT: 2017SGR717, PERIS- SLT006/17/00357; CAM: S2017/BMD-3867; Andalusia Authority: PI-0134-2018; GVA: INNVAL10/18/003), foundations (CEI-MAR: CEIJ-013; IDIVAL: INNVAL18/30; CaixaImpulse; CajaVital), international foundations/universities (ERAB: EA1819; UPENN: 1R01MH112070-01A1) and the European Union (H2020: GA754907, GA801091, Schizo-EPICOG 747487; EU18/08-VET PSYCH UP).

Awards and distinctions:

- Group with PI Eduard Vieta: Eduard Vieta was mentioned as being among the most influential scientists in the world, Clarivate Analytics; Hestia Award for Excellence in Social-Healthcare Research and in Mental Health, SIMPLe project and Extraordinary Medicine Doctorate Award from the UB (Diego Hidalgo-Mazzei).
- Group with PI José Javier Meana: Honorary mention for the best oral presentation 1st Meeting in Translational Pharmacology (G. Rivero, I. Brocos- Mosquera, J.J. Meana and L.F. Callado).
- Group with PI Juan Carlos Leza: 1st Prize for "Best piece of journalism in the healthcare field", awards for Albert Jovell (José Martínez López, Marisol Picón and Marina Díaz Marsá); group evaluated as "Excellent" by the AEI.
- Group with PI Manuel Desco: Santiago Reig Award CIBERSAM (Susana Carmona); best poster "X-Ray Imaging Technology", EMIM congress (A. Martínez, C. Martínez, M. Desco, M. Abella); 1st "Fundación Caja Rural" Prize for the best poster (L. de Sena, A. Arévalo, E. Bello, J. Ripoll, M. Desco, M.V. Gómez-Gaviro) and 2nd "Grupo CTO" Prize in the "Oral Presentation" category (A. Arévalo, E. Bello, J. Ripoll, M. Desco, M.V. Gómez-Gaviro), CEIBS congress.
- Group with PI Juan A. Micó: Mariano Marcos Bárcena Award for Transfer and Innovation for the best patent (Esther Berrocoso and Juan Antonio Micó); poster awarded 31st ECNP (Laura Pérez Caballero).
- Group with PI Francesc Artigas 2 posters

awarded, ECNP Workshop (Mireia Tarrés Gatus and Rubén Pavía Collado).

- Group with PI Benedicto Crespo: Extraordinary Doctorate Prize 2018 from the UC (Javier Vázquez Bourgon).

The following are some of the outstanding scientific achievements:

- Discovery of a key protein in the development of autism (CPEB4).
- Identification of a new therapeutic strategy in Parkinson's Disease based on conjugated inhibitory oligonucleotides.
- Study of the metabolic consequences of the electrode insertional effect in DBS by means of PET.
- Demonstration of noradrenergic mediation in the anti-depressant effect of Deep Brain Stimulation in the prefrontal cortex.
- Potential of cannabidiol and ampakins as fast-action anti-depressants: behavioural, neurochemical and molecular effects.
- Activation of BDNF receptors modifies the structural dynamics of presynaptic and postsynaptic elements in the neocortex.
- Genetic study for the differential diagnosis of the bipolar disorder and schizophrenia, with identification of different gene regions involved in the similarities and differences between both disorders.
- Consolidation as a reference in the diagnosis and early treatment of psychosis.
- Kynurenine metabolites alter excitatory transmission in an experimental model of depression.

Mental disorders of the Child and Adolescent

Coordinator:
Josefina Castro Fornieles

The programme for mental disorders of the child and adolescent is made up of six clinical and basic CIBERSAM groups. Its aim is to study the mental disorders of early childhood and adolescence, which constitute a high percentage of the set of

mental disorders with major impact throughout development. The main lines of research include psychotic disorders of early childhood and adolescence, bipolar disorder, the risk of psychosis, obsessive-compulsive disorder, autism spectrum disorder, child abuse, attention deficit disorder or early initiation depression. There are several European projects connected with the programme as well as collaborative projects with groups belonging to both the Child-Adolescent Psychiatry Programme and other groups belonging to the CIBERSAM.

Some of the most significant results of the programme deserving mention in 2018 are

publications mostly indexed in the first quartile according to the JCR, including the *American Journal of Psychiatry*, *Nature Neuroscience*, *Lancet Psychiatry*, *Journal of the American Academy of Child and Adolescent Psychiatry*, *Molecular Psychiatry*, or *JAMA Psychiatry*, amongst others. Some of the main findings are:

With regard to neuroimaging studies, alteration in the development of the thickness of the cerebral cortex has been found in autism, especially during adolescence. It has also been observed that gestation conditions the reduction of the volume of grey substance in regions connected with social cognition in new mothers, changes which predicted attachment behaviours.

In high-risk populations, in children of patients with bipolar disorder, the presence of any psychiatric diagnosis, the poor psychosocial functioning and the history of physical or sexual abuse condition the appearance of subclinical psychotic experiences. The children of patients with bipolar disorder and schizophrenia also have differences in such temperament aspects as adaptability, mood, flexibility or activity as compared with the children of controls, which are in turn associated with the risk of developing psychopathology.

Psychosomatic, Anxiety and Impulse Control Disorders

Coordinator:
José Manuel Menchón Magriña

The programme is aimed at clinical and basic epidemiological research into a large group of mental disorders and conditions with great impact on people's mental health and psychological wellbeing. It is made up of eight clinical and basic groups, whose main lines of research are personality disorders, ageing, neuroinflammation disorders, anxiety, obsessive-compulsive spectrum disorders, neurobiological and psychosocial aspects of pain, longitudinal epidemiological studies and risk factors in medical populations.

With regard to ageing, a study has found a greater

Several works have documented the importance of genetic alterations in neurodevelopment disorders. One study has found that the presence of gene EN2 is connected with alterations in neurodevelopment in the presence of structural encephalic alterations. A systematic review has documented the association between different genetic variants in scaffold proteins and the risk of schizophrenia or disorders of the autism spectrum and overlapping of the different characteristics linked with both. It has also been seen that the combination of techniques such as sequencing the exome and the analysis of binding may enable identifying new risk genes for neurodevelopment disorders such as TDAH. A new instrument has also been validated for measuring vital stress-inducing situations depending on aspects such as intensity or interpersonal relations, which are of central importance in this stage of development.

Members of the programme have, amongst others, been awarded the EPA Research Award 2018 (Child and Adolescent Psychiatry category) and the 4th Santiago Reig Award for young CIBERSAM investigators.

risk of hip fractures in males with slight cognitive deterioration as compared with women. We have also continued with the development of an instrument for establishing the needs for care required by patients with dementia. From the epidemiological standpoint, different studies have been carried out on large populations of old people, with greater survival being found in people with physical diseases who have good social support. Perceived stress also seems to be a risk factor for the development of cognitive deterioration. Different epidemiological studies of the group have related physical conditions with ageing and confirming that the concept of frailty has a neurocognitive component. Another study has found that age can play a role in reducing anxiety disorders mainly in people with low alcohol consumption.

Work has gone on in the studies of people with threshold personality disorder and an over-activation has been found in orbitofrontal regions during the processing of rewards. Apart from this it has been found that ayahuasca induces an improvement in emotional dysregulation in people with borderline personality traits, as well as an improvement in the 'acceptance' capacity.

In the line of research into impulse control disorders and specifically the study of suicide and related behaviours, the indicator of the relationship between suicide attempts and successful suicides has been put forward. Another study has found that neuropsychological deficits in adults with ADHD are not associated with emotional lability.

In the field of Obsessive-Compulsive Disorder (OCD), studies of the genetic and epigenetic mechanisms being performed by means of cultivating and reprogramming fibroblasts to obtain pluripotent stem cells and their later differentiation to neurons. In OCD work has furthermore gone on with studies of cerebral connectivity, finding an association between the amygdala and domains of emotional processing in these patients. Apart from this,

transdiagnostic relations have been established between OCD and major depression through the hypothalamic-pituitary-adrenal axis on finding common variations of the FKBP5 gene involved in this axis.

In the neuroinflammation area we should stress studies showing that proinflammatory cytokines due to a chronic slight stress alter the kynurenine pathway - an enzyme connected with the bioavailability of tryptophan - to synthesize serotonin - in the frontal cortex of rats. With regard to pain, the analgesic activity of tapentadol has been found to appear to be prevalently mediated through noradrenergic effects rather than its influence in opioid receptors.

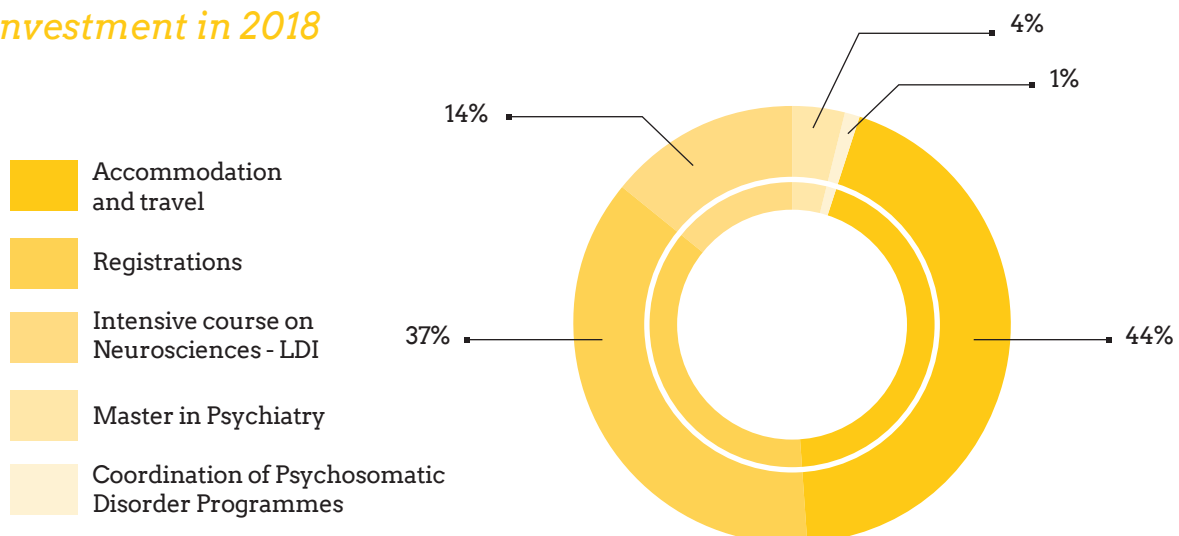
Training Programme

Coordinator: *Juan Antonio Micó Segura*

Last year the Training Programme financed a total number of 45 registrations for research courses and seminars coming to a sum of 18,432.34 €, which represents 37% of the budget and an inter-annual increase of 13 per cent. 59 mobility grants have also been defrayed, coming to a value of 22,362.73 €

(44%). In all, 113 applications were approved in 2018 as compared with 99 in 2017. This would reflect an increase in the investment in training by the groups in comparison with the previous year.

Investment in 2018



With regard to the Ideas Laboratory 2018 held in San Fernando – Cadiz, under the title of “Handling research data. Big Data”, 16 oral papers were presented, spread over 5 tables over the two days’ sessions with a total number of 26 scientific posters. The 4th Santiago Reig Award for the best research work published for young CIBERSAM investigators and the 1st Elsa Valdizán Award for the best Final Master Work (TFM) from the Master Course on Initiation to Research into Mental Health were also given. In all, around one hundred young researchers took part in the 6th edition of the Ideas Laboratory.

Again this year the Interuniversity Master on Research into Mental Health completed the number of registrations allowed. The total number of students registered in 2018 was 51. The number of students registered for type A stays was 39, with 38 going on type B stays. A total number of 30 TFM were also presented.

In the month of April CIBERSAM held the 26th Intensive Course for Introduction to Research into Neurosciences under the title of “Oxidative stress and inflammation in mental health: Cause or consequence?”. The course, given by the Biology Faculty of the Universidad de Barcelona, was attended by 143 persons including mental healthcare professionals, neuroscience researchers and students from different scientific disciplines.

In September the 9th Workshop of the Bank for Instruments in Mental Health and Disability of the CIBERSAM was held in the Teaching Area of the Parc Sanitari Sant Joan de Déu and had 19 participants and 4 speakers. This time, the course focussed on the standardisation of data on equivalent variables from different sources. The speakers were part of the researchers from the ATHLOS (Ageing Trajectories of Health: Longitudinal Opportunities and Synergies) project who have been working on the coordination of 18 longitudinal studies on ageing in the last two years. The session also involved a section for free presentations on the validation of instruments by healthcare professionals.

This encounter enabled an opportunity for training in the setting of research into healthcare sciences, encouraging the standardisation of procedures in disciplines making use of psychological evaluation to facilitate the comparison of results of different centres or research works, and also that of creating an opportunity for coordinating efforts and synergies in research in the area of psychiatry and mental health.

Platforms

Coordinator: *Javier Meana Martínez*

Throughout 2018, the three official CIBERSAM platforms (Library of Instruments in Mental Health and Disability, DNA Collection and Neuroimaging Platform) along with the external platform – Collections of brains – and the GRIDSAM platform of clinical data, currently in a coordination process, reached the operative targets set in the Strategic Plan.

Other measures have been taken in parallel, which can be summed up as follows:

- signing a new agreement with the Fundación Xenómica for maintenance of the repository for DNA collections;
- identification of DNA collections outside the CIBERSAM repository and which may be used in collaborative projects;
- adaptation of GRIDSAM to the new legislation on data protection;
- identification of intraCIBER and external groups which make use of the platforms;
- identification of problems in the indicators currently used and study of improvements for future strategic plans;
- identification of scientific and technological productivity generated by using the

- CIBERSAM platforms;
- making contact with the Network of Biobanks and Platforms of the ISCIII as well as participation in Symposia promoted by its members;
- promoting the creation of a Therapeutic Target platform;
- presentation of Platforms to the External Scientific Committee of the CIBERSAM.

	<i>Library of instruments</i>		<i>DNA collection</i>		<i>Neuroimaging</i>	
	<i>Target for 2018</i>	<i>Achieved in 2018</i>	<i>Target for 2018</i>	<i>Achieved in 2018</i>	<i>Target for 2018</i>	<i>Achieved in 2018</i>
<i>Existing instruments</i>	330	331				
<i>Added instruments</i>	5 new; 25 updated	6 new; 25 updated	-	-	-	-
<i>Enquiries or applications for use made</i>	13	4	-	-	18	19
<i>Publications financed</i>	65	81	-	-	-	-
<i>Training activities</i>	1	1				
<i>Images stored</i>	-	-	-	-	15.089	19.212
<i>Requests for use</i>	-	-	-	-	19	23
<i>Groups contributing</i>	-	-	7	7	11	12
<i>Groups of users</i>	-	-	6	2 consortium + 4 groups	7	11
<i>Questionnaires collected</i>	-	-	-	-	-	-
<i>Patients included</i>	-	-	+1.000	+1.733	-	-
<i>Requests for coordinated studies</i>	-	-	-	2	-	-

Number of **publications** which have used CIBERSAM platforms 24

Platforms used for the publications:

GRISDAM	12
DNA collections	3
Neuroimaging platform	4
Library of instruments	2
Brain collections	3

Number of **clinical trials** that have used CIBERSAM platforms 0

Number of **patents** that have used CIBERSAM platforms 0

Scientific Production

Publications

No of publications in 2018

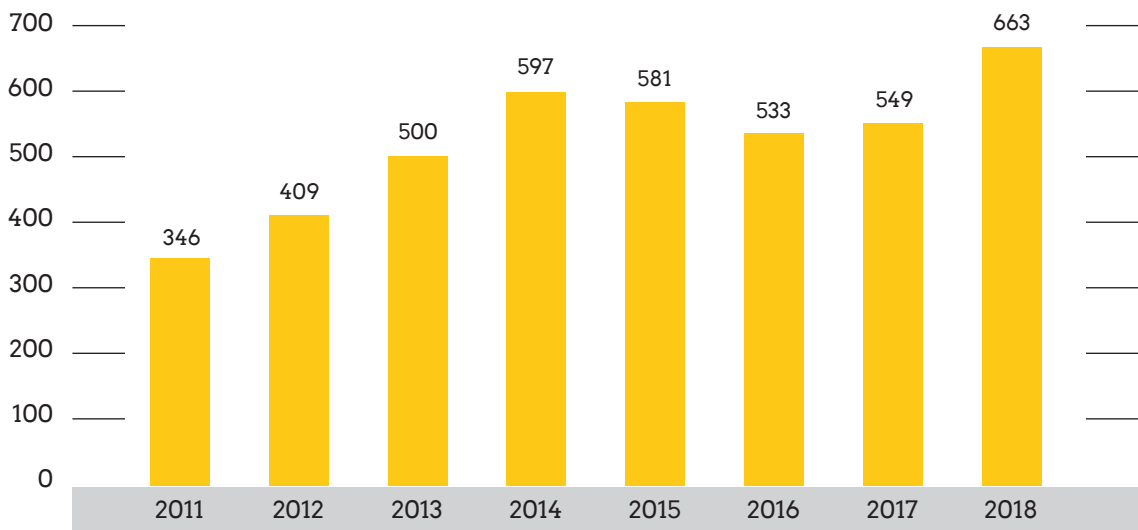
TOTAL	663
Q1	376
D1	143

Collaborative Publications

CIBERSAM	175
CIBER*	111

*Over several thematic areas

Evolution of publications



10 most relevant CIBERSAM publications in 2018 by impact factor

IF
53,2540

Publications

GRISWOLD MG, FULLMAN N, HAWLEY C, ARIAN N, ZIMSEN SRM, TYMESON HD, ET AL. *Alcohol use and burden for 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet.* 2018 Sep 22;392(10152):1015-1035.

53,2540	FULLMAN N, YEARWOOD J, ABAY SM, ABBAFATI C, ABD-ALLAH F, ABDELA J, ET AL. <i>Measuring performance on the Healthcare Access and Quality Index for 195 countries and territories and selected subnational locations: A systematic analysis from the Global Burden of Disease Study 2016</i> . <i>Lancet</i> . 2018 Jun 2;391(10136):2236-2271.
53,2540	DIELEMAN JL, HAAKENSTAD A, MICAH A, MOSES M, ABBAFATI C, ACHARYA P, ADHIKARI TB, ET AL. <i>Spending on health and HIV/AIDS: domestic health spending and development assistance in 188 countries, 1995-2015</i> . <i>Lancet</i> . 2018 May 5;391(10132):1799-1829.
53,2540	DIELEMAN JL, SADAT N, CHANG AY, FULLMAN N, ABBAFATI C, ET AL. <i>Trends in future health financing and coverage: future health spending and universal health coverage in 188 countries, 2016-40</i> . <i>Lancet</i> . 2018 May 5;391(10132):1783-1798.
47,6610	<i>Global Burden of Disease 2016 Injury Collaborators</i> , NAGHAVI M, MARCZAK LB, KUTZ M, SHACKELFORD KA, ARORA M, ET AL. <i>Global mortality from firearms, 1990-2016</i> . <i>JAMA</i> . 2018 Aug 28;320(8):792-814
41,5770	PARRAS A, ANTA H, SANTOS-GALINDO M, SWARUP V, ELORZA A, NIETO-GONZÁLEZ JL, ET AL. <i>Autism-like phenotype and risk gene mRNA deadenylation by CPEB4 mis-splicing</i> . <i>Nature</i> . 2018 Aug;560(7719):441-446.
41,0580	BRAINSTORM CONSORTIUM, ANTTILA V, BULIK-SULLIVAN B, FINUCANE HK, WALTERS RK, BRAS J, ET AL. <i>Analysis of shared heritability in common disorders of the brain</i> . <i>Science</i> . 2018 Jun 22;360(6395).
31,3980	RUDERFER DM, RIPKE S, MCQUILLIN A, BOOCCOCK J, STAHL EA, PAVLIDES JMW, ET AL. <i>Genomic Dissection of Bipolar Disorder and Schizophrenia, Including 28 Subphenotypes</i> . <i>Cell</i> . 2018 Jun 14;173(7):1705-1715.e16.
30,0000	REED GM, KEELEY JW, REBELLO TJ, FIRST MB, GUREJE O, AYUSO-MATEOS JL, ET AL. <i>Clinical utility of ICD-11 diagnostic guidelines for high-burden mental disorders: results from mental health settings in 13 countries</i> . <i>World Psychiatry</i> . 2018 Oct;17(3):306-315.
30,0000	DAVIES C, CIPRIANI A, IOANNIDIS JPA, RADUA J, STAHL D, PROVENZANI U, ET AL. <i>Lack of evidence to favor specific preventive interventions in psychosis: a network meta-analysis</i> . <i>World Psychiatry</i> . 2018 Jun;17(2):196-209.

Patents owned by CIBER

Applied for

- Application number EP18382191.7: *Composition for the treatment of schizophrenia and/or psychosis*.
- Application number P201800272: *Procedimiento para la elaboración de nanopartículas lipídicas, y nanopartículas lipídicas con los macrófagos cerebrales como células diana*.



Clinical Guides

- *Assessing and addressing cognitive impairment in bipolar disorder: The International Society for Bipolar Disorders Targeting Cognition Task Force recommendations for clinicians*.
- *Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder*.
- *Consenso Español sobre la Terapia Electroconvulsiva*.
- *Guía de Práctica Clínica sobre la Depresión Mayor en la Infancia y la Adolescencia. Actualización*.

- Guía de tratamiento del trastorno obsesivo-compulsivo en niños y adolescentes.
- Indicadores de calidad en el tratamiento de pacientes con depresión, trastorno bipolar o esquizofrenia. Estudio de consenso.
- *Joint BAP NAPICU evidence-based consensus guidelines for the clinical management of acute disturbance: De-escalation and rapid tranquillisation.*
- Lo que debo saber sobre Clozapina.
- *Quality indicators in the treatment of patients with depression, bipolar disorder or schizophrenia. Consensus study.*
- Ruta Asistencial Trastorno Mental Grave.
- *Guidelines for the Biological Treatment of Bipolar Disorders: Acute and long-term treatment of mixed states in bipolar disorder.*

CIBERSAM Groups. Publications

Group leader	Total	Q1	D1	Institution. Centre	Province
 Arango López, Celso	46	34	19	Servicio Madrileño de Salud. Hospital Gregorio Marañón	Madrid
 Artigas Pérez, Francesc	10	9	2	Agencia Estatal Consejo Superior de Investigaciones Científicas. Instituto de Investigaciones Biomédicas de Barcelona	Barcelona
 Ayuso Mateos, José Luis	33	18	4	Servicio Madrileño de Salud. Hospital Universitario La Princesa	Madrid
 Bernardo Arroyo, Miguel	50	33	16	Hospital Clínico y Provincial de Barcelona	Barcelona
 Bobes García, Julio	47	22	7	Universidad de Oviedo. Facultad de Medicina	Asturias
 Casas Brugué, Miguel	43	23	11	Fundación Hospital Universitario Vall d'Hebron – Institut de Recerca (VHIR). Hospital Vall d'Hebron	Barcelona
 Crespo Facorro, Benedicto	42	27	12	Instituto de Investigación Marqués de Valdecilla. Hospital Universitario Marqués de Valdecilla	Cantabria
 Descó Menéndez, Manuel	19	14	4	Servicio Madrileño de Salud. Hospital Gregorio Marañón	Madrid
 Fañanas Saura, Lourdes	36	22	4	Universidad de Barcelona. Facultad de Biología. Universidad de Barcelona	Barcelona
 González-Pinto Arrillaga, Ana	42	18	6	Fundación Vasca de Innovación e Investigación Sanitarias. Hospital Universitario de Álava – Sede Santiago	Álava
 Haro Abad, Josep María	119	70	24	Fundación para la Investigación y Docencia Sant Joan de Déu. Parc Sanitari Sant Joan de Déu	Barcelona
 Leza Cerro, Juan Carlos	15	10	5	Universidad Complutense de Madrid. Facultad de Medicina	Madrid
 Mckenna, Peter J.	53	38	20	Fundación para la Investigación y Docencia María Angustias Giménez (FIDMAG). Hospital Hermanas Hospitalarias Benito Menni	Barcelona

<i>Group leader</i>	<i>Total</i>	<i>Q1</i>	<i>D1</i>	<i>Institution. Centre</i>	<i>Province</i>
 Meana Martínez José Javier	27	16	5	Universidad del País Vasco. Facultad de Medicina y Odontología	Vizcaya
 Menchón Magriña, José Manuel	49	35	12	Fundación IDIBELL. Hospital Universitario de Bellvitge	Barcelona
 Micó Segura, Juan Antonio	10	7	2	Universidad de Cádiz. Facultad de Medicina	Cádiz
 Palomo Álvarez, Tomás	28	17	5	Universidad Complutense de Madrid. Facultad de Medicina	Madrid
 Pazos Carro, Ángel Armando	7	5	0	Universidad de Cantabria. Facultad de Medicina	Cantabria
 Pérez Sola, Víctor	78	42	17	Consorci Mar Parc Salut Barcelona	Barcelona
 Sáiz Ruiz, Jerónimo	31	15	6	Servicio Madrileño de Salud. Hospital Ramón y Cajal	Madrid
 Sanjuán Arias, Julio	21	12	9	Universidad de Valencia. Facultad de Medicina de Valencia	Valencia
 Tabarés-Seisdedos, Rafael	30	23	12	Universidad de Valencia. Facultad de Medicina de Valencia	Valencia
 Vieta Pascual, Eduard	81	62	22	Hospital Clínico y Provincial de Barcelona	Barcelona
Vilella Cuadrada, Elisabet	19	10	2	Fundación Instituto de Investigación Sanitaria Pere Virgili. Universidad Rovira y Virgili	Tarragona

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