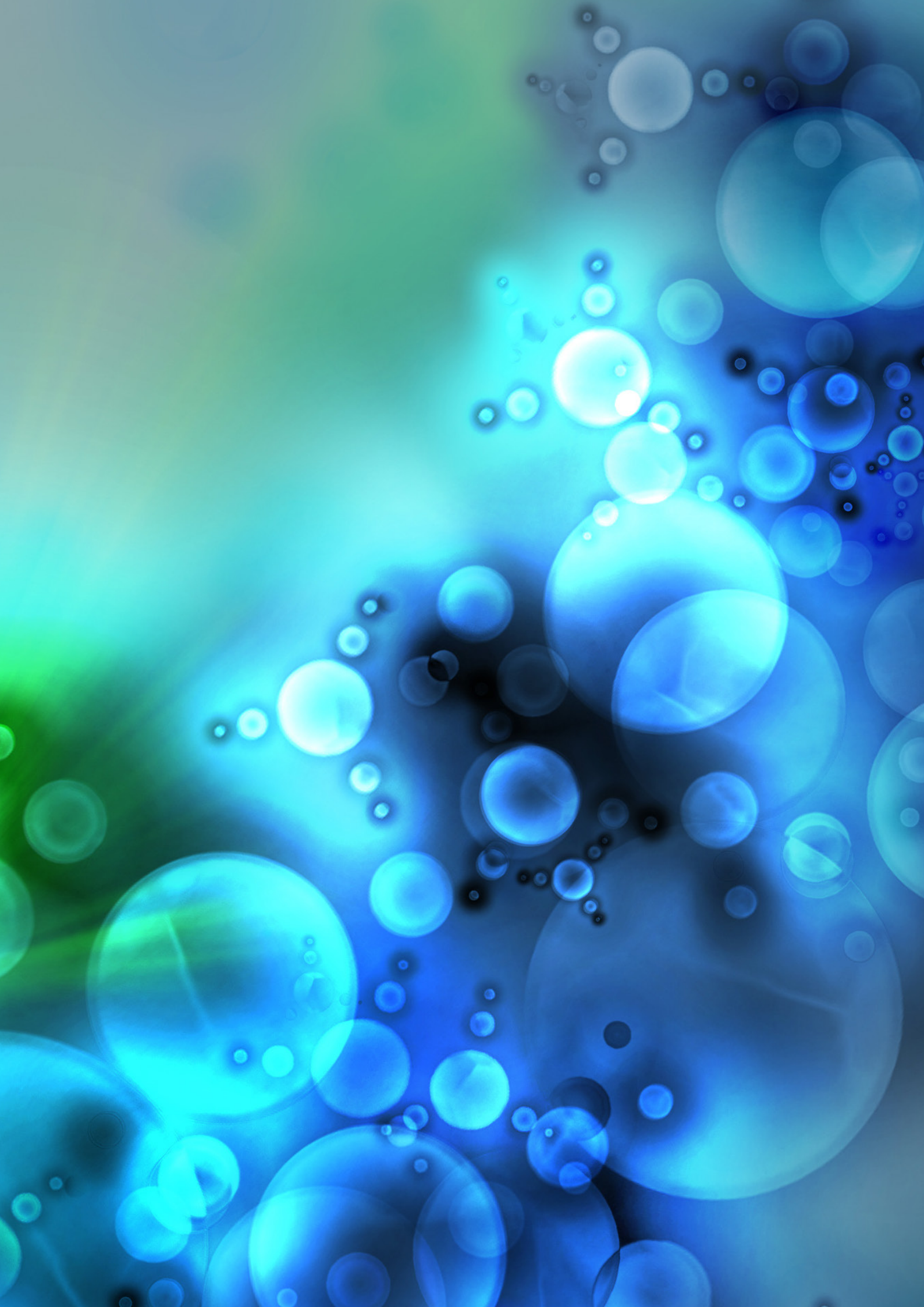


# ANNUAL REPORT 2019







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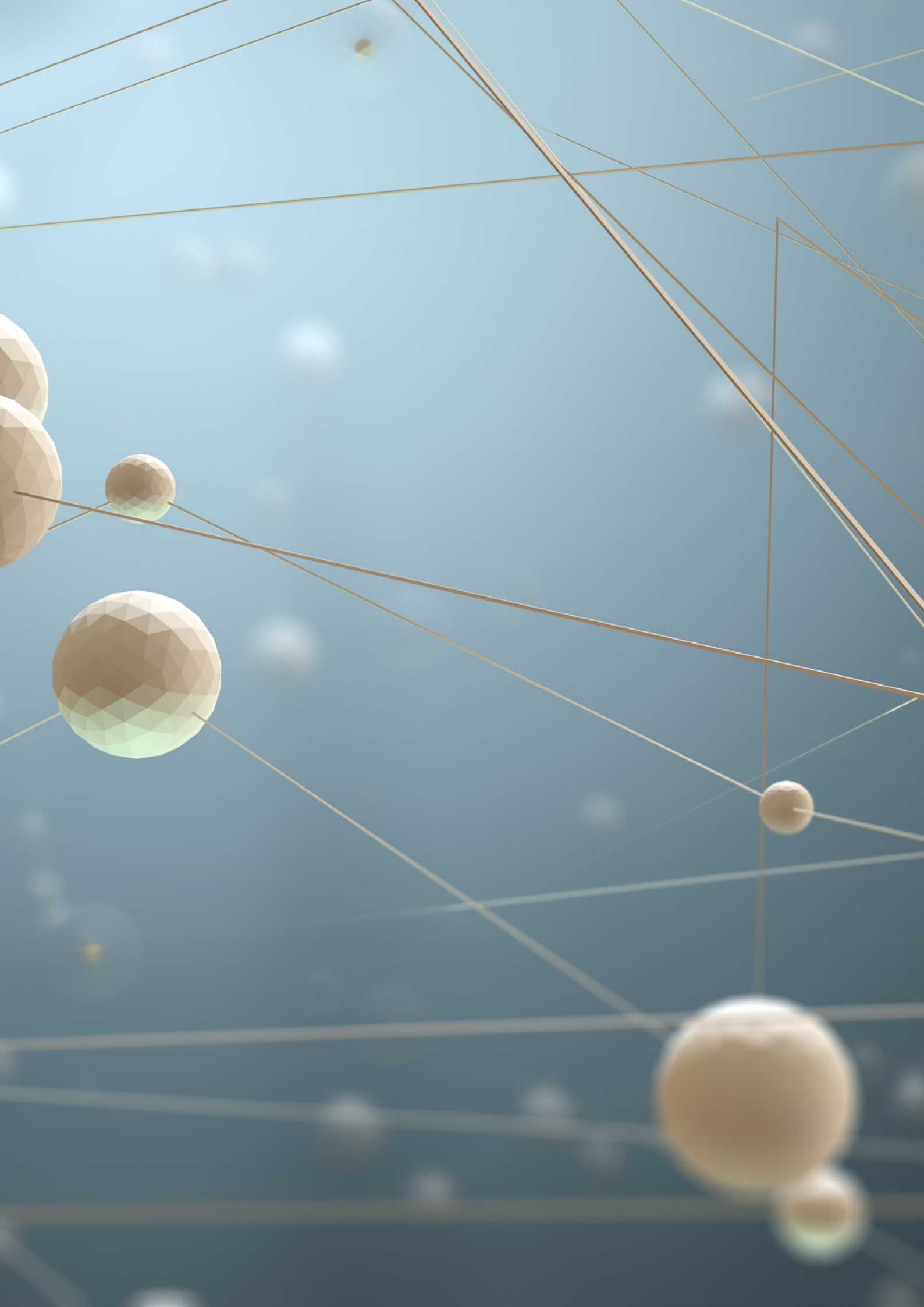
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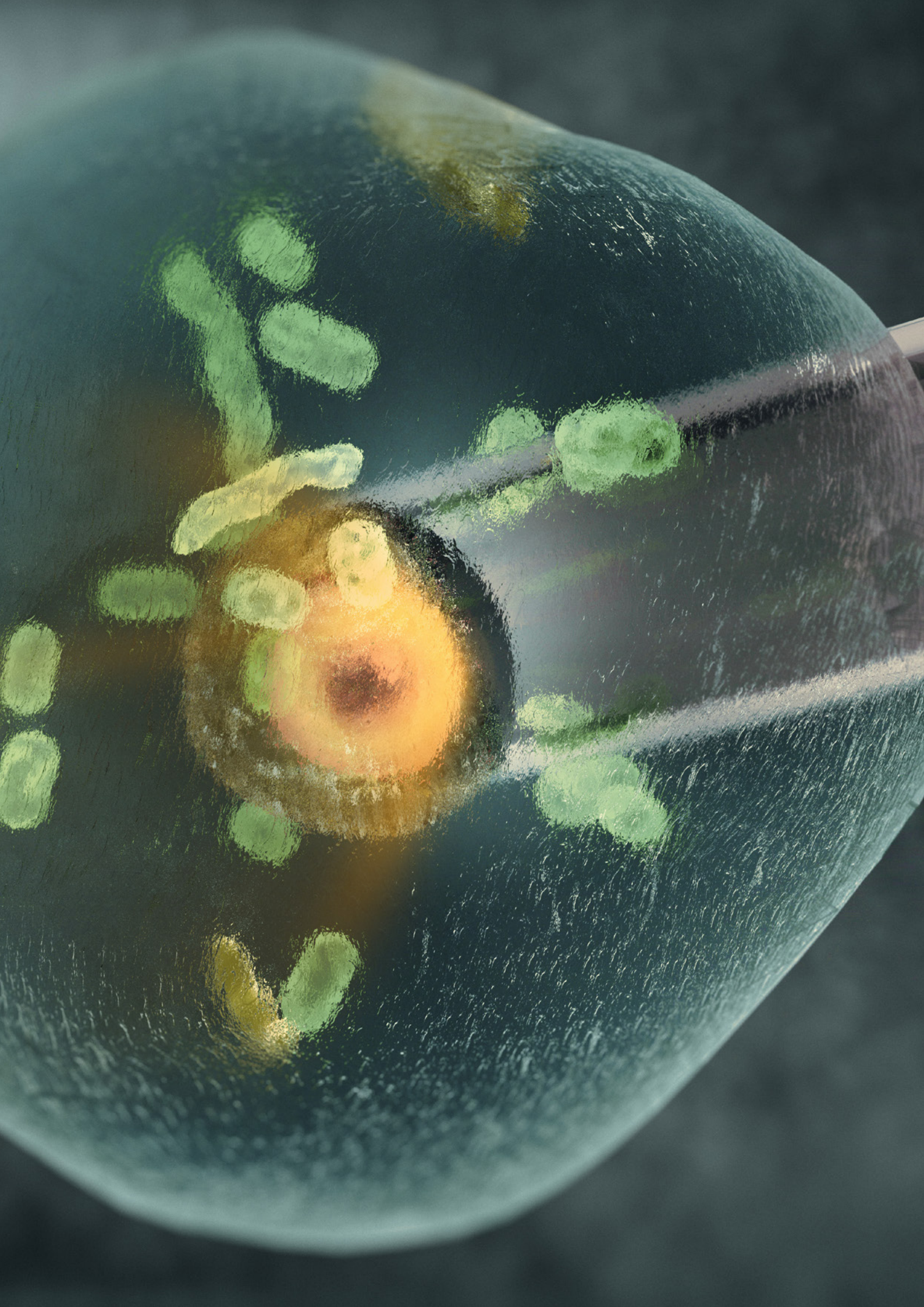




**Consorcio  
Centro de  
Investigación  
Biomédica en Red**

*ciber*







# Presentation by the CIBER's Managing Director

**Manuel Sánchez Delgado**



In 2019, the research groups that make up the CIBER Consortium in its eleven thematic areas have continued to work for the understanding, diagnosis and treatment of the multiple diseases studied in order to have an impact on the improvement of our National Health System and, ultimately, on the health of all citizens. In this period, eight new groups of excellence joined the Consortium in the areas of CIBERER, CIBER-BBN, CIBERES and CIBERSAM. Year after year, the research carried out by all the groups maintains this spirit of achieving the transfer to society and the transfer to the Industry, obtaining results of great value and contributing to the advancement of Science.

The collaboration and synergies between the thematic areas has continued to be strengthened during 2019 through the promotion of attendance and participation of different areas in conferences and events. For example, researchers from CIBERSAM and CIBEREHD participated in the CIBERESP conferences, and CIBERONC in turn participated in the CIBER-BBN sessions. In addition, the Meeting for Excellence in Public Health Research organised annually by CIBERESP invited groups from CIBEROBN, CIBERONC and CIBERCV to participate in its 2019 edition. In the same vein, the first CIBER Interdisciplinary Course on Immunotherapy, in which six CIBER areas participated, is also worth mentioning.

The CIBER network research model is unique in our country with around 7,000 researchers (contracted and attached) in more than 400 research groups of different kinds. An important part of the CIBER staff are women, although this proportion does not carry over to the number of group leaders. Thus, policies to promote equality are emerging, such as the introduction of the figure of CO-PI as a possible female replacement for group leaders which is already being implemented in some areas. The CIBER also participates in the celebration on February 11 of the International Day of Women and Girls in Science, trying to make visible the important role of female CIBER researchers. In addition, more and more initiatives are emerging to value the work of younger researchers as well. Some examples of these are the celebration in 2019 of the CIBERONC Young Researchers Meeting, CIBERDEM's Young Researchers Meeting, the CIBERES Teaching Days or CIBERSAM's Ideas Laboratory.

One of the milestones to highlight in 2019 is the signing of the first collective agreement for the staff of the Consortium, carried out between the Management and the CCOO Trade Union Section on June 26. The agreement aims to regulate and homogenise the working and remuneration conditions of the 879 workers who carry out their work in the consortium centres.

The scientific results obtained continue along the lines of previous years. In 2019, around 7,000 publications were made, of which close to 60% were in the first quartile and 27% in the first decile. It is important to note that more than 1,400 papers have been recorded as results in collaboration between various areas of the CIBER. In addition, in 2019, 16 new priority patent applications were submitted, 4 software were developed and 3 license agreements were signed. During this period, the CIBER obtained funding of nearly €3 million in competitive calls. Of the 113 projects under way during this period, 75 were national, 34 European and 4 from the U.S.A.

Finally, I'd like to underline the relevant role that the CIBER plays in promoting Scientific Culture, mainly in the dissemination of research results to society. In 2019, the CIBER Consortium joined the FECYT Network of Scientific Culture and Innovation Units (UCC + I) with the aim of further promoting institutional collaboration in science communication. Within the promotion of Scientific Culture, we must highlight the activity that takes place annually within the Science Week. In November 2019, with the collaboration of young researchers of the centre, the first CIBER Nano Challenge was held at the ISCIII, an immersive game which invited young students to become researchers.

Some examples of the highlights of 2019 have been referred to above and will be expanded upon in this Annual Report. All that remains for me to do now is to thank the CIBER staff for all of their efforts and congratulate them on yet another year of excellent results.



# Internal Organisation

The Centro de Investigación Biomédica en Red, M.P, CIBER, a public research consortium set up by the Instituto de Salud Carlos III (ISCIII), furthers excellence research in Biomedicine and Health Sciences carried out in the National Health System and 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 **879 persons** and around 6.000 attached researchers integrated in over **420 research groups** (7 outgoing groups and 8 incoming groups in 2019) working in separate locations, associated with **99 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 program 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 renowned for their professional or scientific careers compatible with the objectives of the center. 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 2019 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 Mias**
- 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: **Dra. 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 2019	33.803.330,00	3.894.238,35	1.738.994,62	2.350.702,31	<b>41.787.265,28</b>

### Total Expenses

PROJECT	Inventoriable sum applied	Supplies and other expenses for work	Provisions of services	TOTAL EXPENSE
Scientific Management, Scientific Secretariat, Communication	1.705,47	654.214,72	692.320,89	1.348.241,08
Groups	1.185.425,90	4.732.500,22	20.503.457,99	26.421.384,11
Training	-	247.264,42	1.758.820,78	2.006.085,20
Programmes	28.010,49	360.298,03	387.558,35	775.866,87
Platforms	100.508,09	227.876,39	419.629,43	748.013,91
Transfer	6.029,68	149.304,39	217.921,87	373.255,94
Intramural Projects	115.904,61	1.297.406,30	41.322,13	1.454.633,04
External Projects	149.579,06	2.825.199,87	2.290.273,51	5.265.052,44
Economic Resources Technical Unit (UT)	803,43	648.648,75	-	649.452,18
Human Resources UT	-	8.083,74	1.409.626,17	1.417.709,91
Prevention of Occupational Hazards UT	2.832,49	108.463,68	-	111.296,17
Communication UT	-	77.462,83	-	77.462,83
<b>TOTAL FOR CIBER</b>	<b>1.590.799,22</b>	<b>11.336.723,34</b>	<b>27.720.931,12</b>	<b>40.648.453,68</b>



## CIBER-BBN

### Total Resources

	ISCIII Transfer	Subsidies for projects	Provisions of services	Other income	TOTAL
INCOME 2019	3.922.660,00	1.233.075,30	183.056,23	52.652,73	<b>5.391.444,26</b>

### Total Expenses

PROJECT	Inventoriable sum applied	Supplies and other expenses for work	Provisions of services	TOTAL EXPENSE
Scientific Management, Scientific Secretariat, Communication	967,48	50.535,89	66.667,07	118.170,44
Groups	25.548,56	359.714,90	883.095,14	1.268.358,60
Training	-	22.780,03	1.574.264,47	1.597.044,50
Programmes	1.276,20	45.961,77	178.323,02	225.560,99
Platforms	98.452,30	34.041,80	50.558,33	183.052,43
Transfer	5.191,97	78.490,31	61.488,56	145.170,84
Intramural Projects	38.750,36	116.265,60	-	155.015,96
External Projects	38.223,87	338.525,18	584.306,09	961.055,14
<b>TOTAL FOR CIBER-BBN</b>	<b>208.410,74</b>	<b>1.046.315,48</b>	<b>3.398.702,68</b>	<b>4.653.428,90</b>

## CIBERCV

### Total Resources

	ISCIII Transfer	Subsidies for projects	Provisions of services	Other income	TOTAL
INCOME 2019	3.285.000,00	228.179,02	-	33.200,00	<b>3.546.379,02</b>

### Total Expenses

PROJECT	Inventoriable sum applied	Supplies and other expenses for work	Provisions of services	TOTAL EXPENSE
Scientific Management, Scientific Secretariat, Communication	-	46.601,77	178.565,43	225.167,20
Groups	166.006,83	662.987,18	2.180.617,40	3.009.611,41
Training	-	4.133,51	68.280,86	72.414,37
Programmes	276,46	1.564,16	-	1.840,62
Transfer	766,70	10.556,25	-	11.322,95
Intramural Projects	-	11.406,21	-	11.406,21
External Projects	-	15.406,85	77.014,38	92.421,23
<b>TOTAL FOR CIBERCV</b>	<b>167.049,99</b>	<b>752.655,93</b>	<b>2.504.478,07</b>	<b>3.424.183,99</b>

# CIBERDEM

## Total Resources

	ISCIII Transfer	Subsidies for projects	Provisions of services	Other income	TOTAL
INCOME 2019	2.796.280,00	68.365,00	46.249,83	-	<b>2.910.894,83</b>

## Total Expenses

PROJECT	Inventoriable sum applied	Supplies and other expenses for work	Provisions of services	TOTAL EXPENSE
Scientific Management, Scientific Secretariat, Communication	737,99	86.488,92	45.356,17	132.583,08
Groups	20.691,07	150.739,57	2.464.211,12	2.635.641,76
Training	-	15.261,82	-	15.261,82
Platforms	-	22.229,06	-	22.229,06
Intramural Projects	-	8.156,26	-	8.156,26
External Projects	-	154.561,02	7.152,28	161.713,30
<b>TOTAL FOR CIBERDEM</b>	<b>21.429,06</b>	<b>437.436,65</b>	<b>2.516.719,57</b>	<b>2.975.585,28</b>

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

# CIBEREHD

## Total Resources

	ISCIII Transfer	Subsidies for projects	Provisions of services	Other income	TOTAL
INCOME 2019	3.653.580,00	50.635,00	164.185,01	178.698,00	<b>4.047.098,01</b>

## Total Expenses

PROJECT	Inventoriable sum applied	Supplies and other expenses for work	Provisions of services	TOTAL EXPENSE
Scientific Management, Scientific Secretariat, Communication	-	123.499,96	-	123.499,96
Groups	156.729,91	362.787,78	2.524.461,85	3.043.979,54
Training	-	27.207,55	-	27.207,55
Platforms	-	2.398,83	89.587,90	91.986,73
Transfer	-	8.751,40	-	8.751,40
Intramural Projects	-	107.041,52	-	107.041,52
External Projects	2.592,50	103.297,38	332.708,39	438.598,27
<b>TOTAL FOR CIBEREHD</b>	<b>159.322,41</b>	<b>734.984,42</b>	<b>2.946.758,14</b>	<b>3.841.064,97</b>

# CIBERER

## Total Resources

	ISCIII Transfer	Subsidies for projects	Provisions of services	Other income	TOTAL
INCOME 2019	4.755.860,00	509.087,88	519.953,55	226.254,36	<b>6.011.155,79</b>

## Total Expenses

PROJECT	Inventoriable sum applied	Supplies and other expenses for work	Provisions of services	TOTAL EXPENSE
Scientific Management, Scientific Secretariat, Communication	-	158.168,50	123.583,25	281.751,75
Groups	-	111.837,34	3.409.578,86	3.521.416,20
Training	-	10.897,94	15.144,79	26.042,73
Programmes	-	27.070,21	-	27.070,21
Platforms	75,02	16.473,28	144.825,70	161.374,00
Transfer	-	27.345,12	57.138,55	84.483,67
Intramural Projects	42.150,45	654.318,01	41.322,13	737.790,59
External Projects	14.927,72	980.687,30	327.733,61	1.323.348,63
<b>Total FOR CIBERER</b>	<b>57.153,19</b>	<b>1.986.797,70</b>	<b>4.119.326,89</b>	<b>6.163.277,78</b>

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

# CIBERES

## Total Resources

	ISCIII Transfer	Subsidies for projects	Provisions of services	Other income	TOTAL
INCOME 2019	2.557.420,00	628.717,72	189.772,97	50.542,00	<b>3.426.452,69</b>

## Total Expenses

PROJECT	Inventoriable sum applied	Supplies and other expenses for work	Provisions of services	TOTAL EXPENSE
Scientific Management, Scientific Secretariat, Communication	-	9.682,22	35.010,92	44.693,14
Groups	158.116,23	342.437,72	1.389.697,08	1.890.251,03
Training	-	39.751,43	-	39.751,43
Programmes	-	5.101,81	-	5.101,81
Platforms	-	6.668,29	78.151,49	84.819,78
Transfer	71,01	21.325,73	99.294,76	120.691,50
Intramural Projects	11.329,66	88.315,74	-	99.645,40
External Projects	14.920,40	462.276,86	320.232,86	797.430,12
<b>TOTAL FOR CIBERES</b>	<b>184.437,30</b>	<b>975.559,80</b>	<b>1.922.387,11</b>	<b>3.082.384,21</b>



## CIBERESP

### Total Resources

	ISCIII Transfer	Subsidies for projects	Provisions of services	Other income	TOTAL
INCOME 2019	2.916.660,00	86.761,00	33.275,00	-	<b>3.036.696,00</b>

### Total Expenses

PROJECT	Inventoriable sum applied	Supplies and other expenses for work	Provisions of services	TOTAL EXPENSE
Scientific Management, Scientific Secretariat, Communication	-	39.600,34	34.487,84	74.088,18
Groups	117.848,34	577.983,96	1.697.030,62	2.392.862,92
Training	-	22.986,70	-	22.986,70
Programmes	9.860,14	200.980,69	151.779,13	362.619,96
External Projects	2.070,60	59.137,74	39.831,20	101.039,54
<b>TOTAL FOR CIBERESP</b>	<b>129.779,08</b>	<b>900.689,43</b>	<b>1.923.128,79</b>	<b>2.953.597,30</b>

## CIBERFES

### Total Resources

	ISCIII Transfer	Subsidies for projects	Provisions of services	Other income	TOTAL
INCOME 2019	780.000,00	7.260,00	5.600,00	-	<b>792.860,00</b>

### Total Expenses

PROJECT	Inventoriable sum applied	Supplies and other expenses for work	Provisions of services	TOTAL EXPENSE
Scientific Management, Scientific Secretariat, Communication	-	9.841,93	31.655,59	41.497,52
Groups	58.544,99	119.330,16	407.731,38	585.606,53
Programmes	-	219,80	55.169,44	55.389,24
Training	-	3.967,33	-	3.967,33
External Projects	51.199,00	5.487,30	954,51	57.640,81
<b>TOTAL FOR CIBERFES</b>	<b>109.743,99</b>	<b>138.846,52</b>	<b>495.510,92</b>	<b>744.101,43</b>

# CIBEROBN

## Total Resources

	ISCIII Transfer	Subsidies for projects	Provisions of services	Other income	TOTAL
INCOME 2019	2.887.230,00	463.049,01	499.574,28	10.100,00	<b>3.859.953,29</b>

## Total Expenses

PROJECT	Inventoriable sum applied	Supplies and other expenses for work	Provisions of services	TOTAL EXPENSE
Scientific Management, Scientific Secretariat, Communication	-	62.587,44	46.867,14	109.454,58
Groups	177.233,82	551.622,62	1.660.974,49	2.389.830,93
Training	-	15.116,54	-	15.116,54
Programmes	4.621,10	39.826,11	2.286,76	46.733,97
Platforms	-	75.253,10	46.963,32	122.216,42
Transfer	-	2.835,58	-	2.835,58
Intramural Projects	15.895,29	224.540,56	-	240.435,85
External Projects	10.428,29	181.793,63	278.524,07	470.745,99
<b>TOTAL FOR CIBEROBN</b>	<b>208.178,50</b>	<b>1.153.575,58</b>	<b>2.035.615,78</b>	<b>3.397.369,86</b>

# CIBERONC

## Total Resources

	ISCIII Transfer	Subsidies for projects	Provisions of services	Other income	TOTAL
INCOME 2019	3.735.000,00	174.993,60	1.210,00	9.000,00	<b>3.920.203,60</b>

## Total Expenses

PROJECT	Inventoriable sum applied	Supplies and other expenses for work	Provisions of services	TOTAL EXPENSE
Scientific Management, Scientific Secretariat, Communication	-	50.108,93	71.469,40	121.578,33
Groups	204.501,24	1.116.879,82	2.450.307,10	3.771.688,16
Training	-	58.871,22	53.706,87	112.578,09
Programmes	8.290,27	27.099,68	-	35.389,95
Intramural Projects	3.692,37	33.429,41	-	37.121,78
External Projects	-	73.943,15	-	73.943,15
<b>TOTAL FOR CIBERONC</b>	<b>216.483,88</b>	<b>1.360.332,21</b>	<b>2.575.483,37</b>	<b>4.152.299,46</b>

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

# CIBERSAM

## Total Resources

	ISCIII Transfer	Subsidies for projects	Provisions of services	Other income	TOTAL
INCOME 2019	2.161.690,00	444.114,82	74.463,35	1.950,00	<b>2.682.218,17</b>

## Total Expenses

PROJECT	Inventoriable sum applied	Supplies and other expenses for work	Provisions of services	TOTAL EXPENSE
Scientific Management, Scientific Secretariat, Communication	-	17.098,82	58.658,08	75.756,90
Groups	100.204,91	376.179,17	1.435.752,95	1.912.137,03
Training	-	26.290,35	47.423,79	73.714,14
Programmes	3.686,32	12.473,80	-	16.160,12
Platforms	1.980,77	70.812,03	9.542,69	82.335,49
Intramural Projects	4.086,48	53.932,99	-	58.019,47
External Projects	15.216,68	450.083,46	321.816,12	787.116,26
<b>TOTAL FOR CIBERSAM</b>	<b>125.175,16</b>	<b>1.006.870,62</b>	<b>1.873.193,63</b>	<b>3.005.239,41</b>

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

# UT

## Total Resources

	ISCIII Transfer	Subsidies for projects	Provisions of services	Other income	TOTAL
INCOME 2019	351.950,00	-	21.654,40	1.788.305,22	<b>2.161.909,62</b>

## Total Expenses

PROJECT	Inventoriable sum applied	Supplies and other expenses for work	Provisions of services	TOTAL EXPENSE
Economic Resources	803,43	648.648,75	-	649.452,18
Human Resources	-	8.083,74	1.409.626,17	1.417.709,91
Prevention of Occupational Hazards	2.832,49	108.463,68	-	111.296,17
Communication	-	77.462,83	-	77.462,83
<b>TOTAL FOR UT</b>	<b>3.635,92</b>	<b>842.659,00</b>	<b>1.409.626,17</b>	<b>2.255.921,09</b>

(\*) 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

	MEN	WOMEN	TOTAL
<b>CIBER-BBN</b>	40	69	109
Diploma holder	4	5	9
Doctor	23	39	62
Graduate	13	19	32
Technical staff	-	6	6
<b>CIBERCV</b>	23	66	89
Diploma holder	-	3	3
Doctor	11	22	33
Graduate	12	32	44
Technical staff	-	9	9
<b>CIBERDEM</b>	15	61	76
Diploma holder	-	2	2
Doctor	11	34	45
Graduate	1	15	16
Technical staff	3	10	13
<b>CIBEREHD</b>	27	69	96
Diploma holder	1	6	7
Doctor	14	25	39
Graduate	9	27	36
Technical staff	3	11	14

	MEN	WOMEN	TOTAL
<b>CIBERER</b>	28	78	106
Diploma holder	-	2	2
Doctor	21	49	70
Graduate	7	14	21
Technical staff	-	13	13
<b>CIBERES</b>	11	54	65
Diploma holder	-	5	5
Doctor	4	22	26
Graduate	7	19	26
Technical staff	-	8	8
<b>CIBERESP</b>	20	46	66
Diploma holder	3	6	9
Doctor	5	20	25
Graduate	11	19	30
Technical staff	1	1	2
<b>CIBERFES</b>	8	11	19
Doctor	5	4	9
Graduate	2	6	8
Technical staff	1	1	2



	MEN	WOMEN	TOTAL
<b>CIBEROBN</b>	16	61	77
Diploma holder	1	5	6
Doctor	5	17	22
Graduate	8	30	38
Technical staff	2	9	11
<b>CIBERONC</b>	17	58	75
Doctor	11	26	37
Graduate	6	23	29
Technical staff	-	9	9

	MEN	WOMEN	TOTAL
<b>CIBERSAM</b>	13	48	61
Diploma holder	-	3	3
Doctor	9	14	23
Graduate	4	26	30
Technical staff	-	5	5
<b>CIBERUT</b>	13	27	40
Doctor	1	1	2
Graduate	10	23	33
Technical staff	2	3	5
<b>Total general</b>	<b>231</b>	<b>648</b>	<b>879</b>

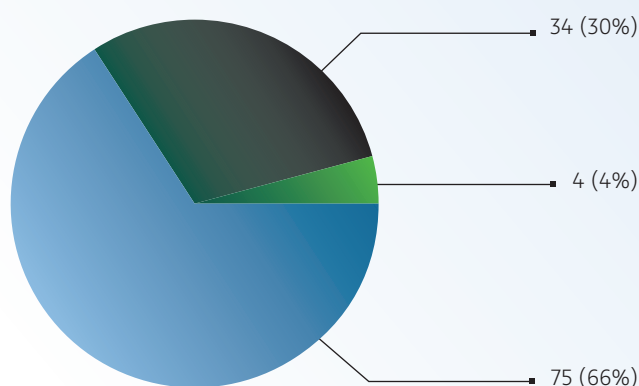
# Activity Highlights

## Projects

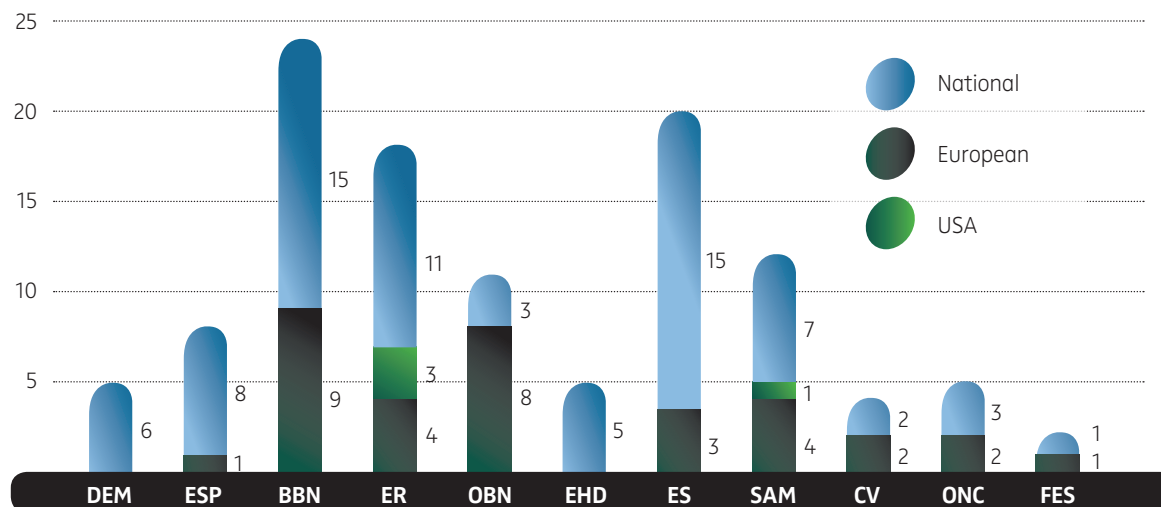
Number of projects under way in the 2019 period, resulting from competitive grants:

Body/Grant	Subsidies implemented 2019	BBN	CV	DEM	EHD	ER	ES	ESP	FES	OBN	ONC	SAM
European	26	8	1	-	-	2	-	2	-	8	-	5
U.S.A.	6	-	-	-	-	3	-	-	-	2	-	1
National	97	16	1	6	14	15	16	8	-	6	3	12
ISCIII - FIS	31	1	-	-	3	5	7	5	-	2	-	8
ISCIII - Others	18	3	-	2	3	1	4	2	-	2	-	1
MECD Ministry	1	-	-	-	-	-	-	-	-	-	1	-
MINECO Ministry	19	10	-	4	1	1	1	-	-	-	-	2
Private foundations	24	-	1	-	7	7	4	1	-	2	1	1
Other public grants (Valencia and Aragon regional authorities)	4	2	-	-	-	1	-	-	-	-	1	-

## Competitive projects per thematic area

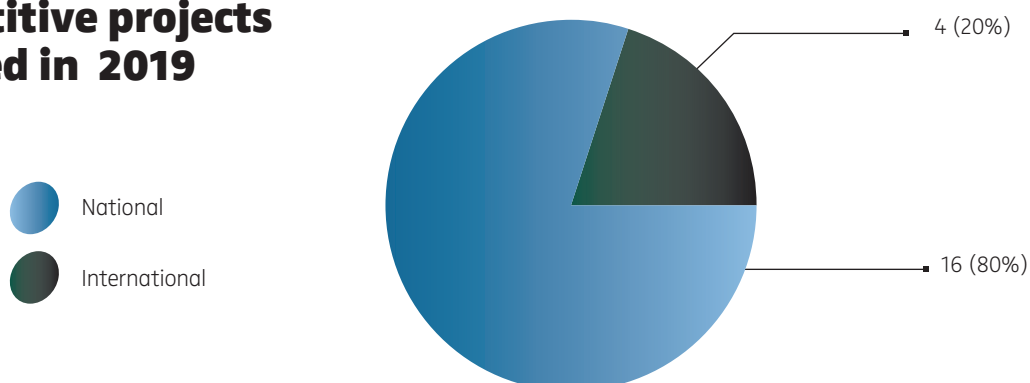


## Competitive projects under way as per origin of funds



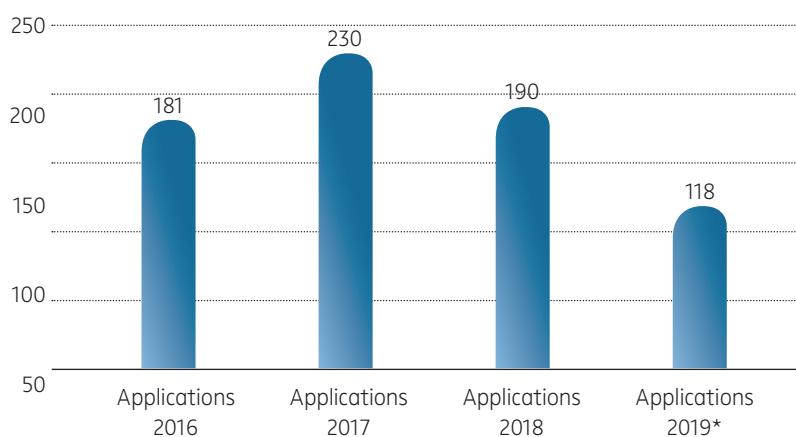
In 2019, CIBER obtained the following grants from competitive calls.

## Competitive projects awarded in 2019



The number of applications for competitive projects with external funding in 2019 has been 118.

## Applications for competitive grants submitted



(\*) The decrease in applications during this year is due to the impossibility of participating in certain calls and their not being collaborative projects.

# 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 quality of life of the population at large. To this end, the Technology Transfer area of the CIBER works as a liaison between our researchers and companies, private organisations, public research centers and other innovation agents to put the cooperation between them into practice, and ensure that the results of research can finally be applied.

In 2019, 16 new priority patent applications were submitted at the CIBER. In addition, 4 software were developed and 3 licence contracts were signed:

THEMATIC AREA	Priority patent applications	Other IPRs and software	Licences and licence options
CIBER-BBN	5	2	1
CIBERDEM	1	-	-
CIBEREHD	2	-	-
CIBERER	3	-	1
CIBERES	-	-	1
CIBERESP	-	-	-
CIBEROBN	3	2	-
CIBERSAM	1	-	-
CIBERCV	-	-	-
CIBERONC	1	-	-
CIBERFES	-	-	-

In addition, throughout 2019, the following activities and procedures were carried out, among others:

- Dozens of CDAs and MTAs were negotiated and signed.
- Support to the CIBER spin off (EpiDisease) in achieving a capital injection through a tax lease process from the company Kaudal.
- Various ongoing marketing and technology dissemination activities are maintained.
- A multitude of partnering congresses and fairs were attended such as: *BioEurope*, *Biotech Showcase*, *Pharmaforum*, *Medica*, *Biofit*, *ASEBIO investors Forum*, *World Orphan Drug Congress*, *Kaertor Foundation Meeting*, etc.
- Two projects were submitted to the Caixa Impulse call (CIBERES and CIBERER) with one reaching the second phase, though not chosen.
- The CIBERER area organised the two following meetings:
  - Research programs for drug discovery. (together with ASEBIO, December 4)
  - Designation and development of orphan drugs. (October 21, Bilbao).
- Calls for valorisation and transfer projects were launched from the CIBER-BBN area. Three valorisation projects were financed, with no transfer projects being awarded.
- Lastly, since June 2019, together with the AEMPS (Spanish Agency for Medicines and Health Products), the CIBER-BBN area participates in the *STARS-CSA project: Strengthening Training of Academia in Regulatory Science*.



## Communication

### Press releases

In 2019, 160 press releases were issued concerning the research results of the groups. These include press releases sent from the institutions in the consortium that were prepared in collaboration with the CIBER.

Throughout 2019, CIBER filed 16 new priority patent applications and 4 software were developed. In addition, 3 licence agreements have been signed.

CIBER AREA	Press releases 2019
CIBEROBN	25
CIBERSAM	18
CIBERER	17
CIBERCV	15
CIBERDEM	14
CIBEREHD	14
CIBERONC	13
CIBERESP	12
CIBERES	11
CIBER-BBN	9
VARIAS ÁREAS*	6
CIBERFES	4
CIBER	2
<b>TOTAL</b>	<b>160</b>

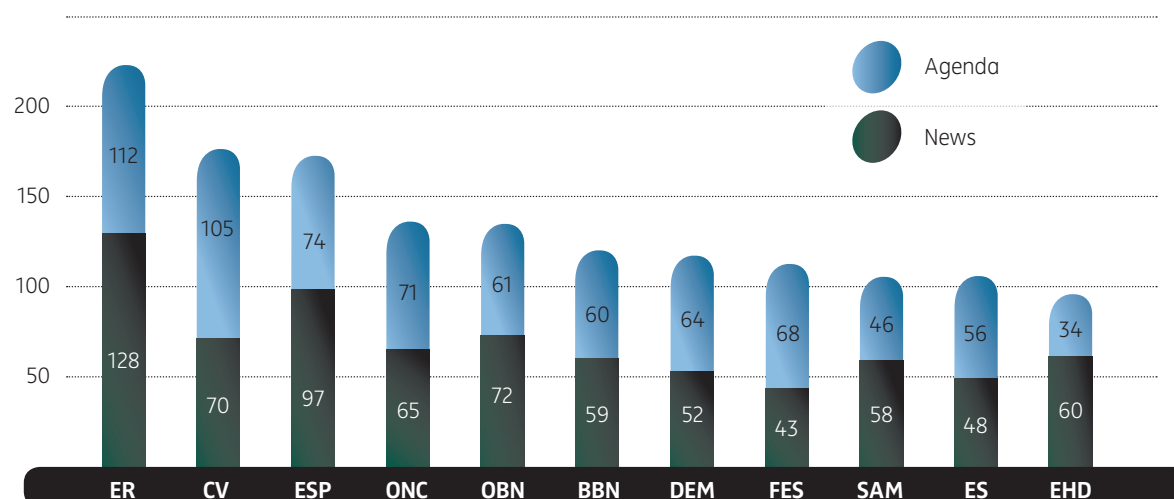
### Newsletters

In 2019, 5 CIBER newsletters and 40 newsletters from the thematic areas were issued. The CIBERER also brought out 6 social newsletters.

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

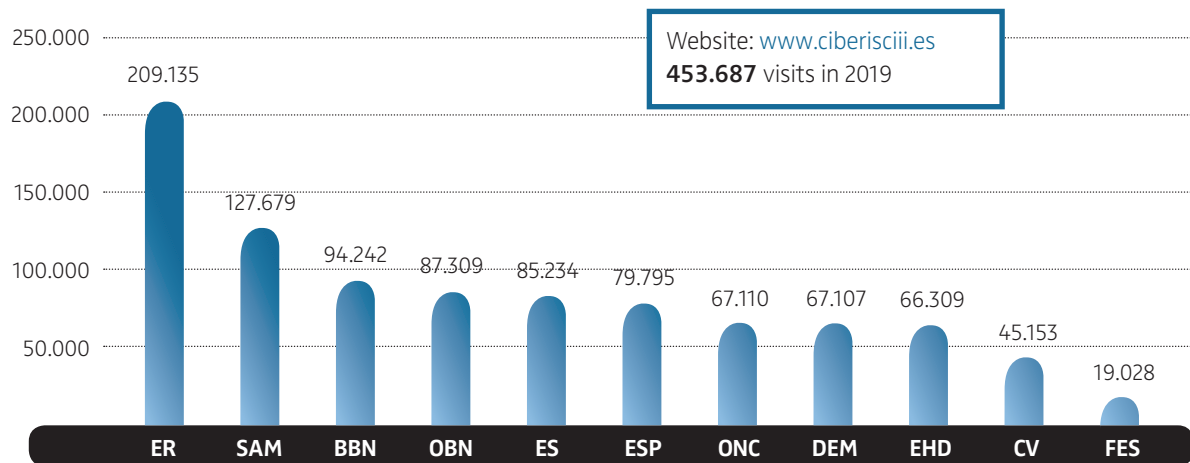
### Websites

752 news items and 751 agenda events were announced on the websites of the different areas.



## Visits to the CIBER web pages

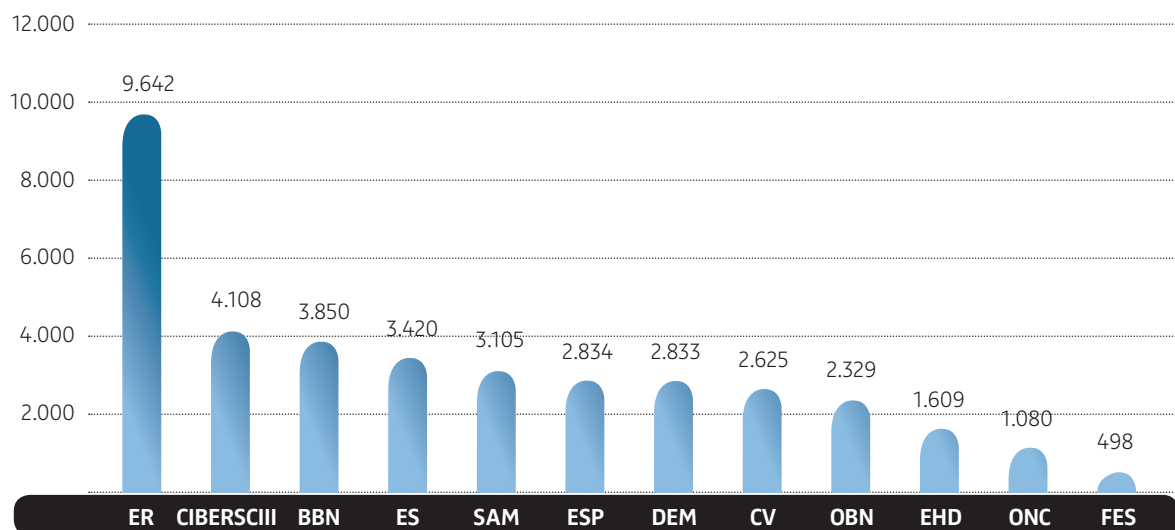
### Web Visits by areas



## Social Networks

Followers of the different profiles of the CIBER on Twitter

### Twitter: 31/12/2019



## Instagram

646 Followers on Instagram @ciber\_investiga

## CIBER Activity at the Madrid Science Week

On November 11-12, 2019, the CIBER Nanochallenge was held at the Salón de Actos Ernest Lluch of the Instituto de Salud Carlos III, within the programming of the Madrid Science Week. The activity consisted of an immersive game in which the participants had to resolve a series of tests to “cure the patient”.

Around 300 attendees from 7 schools/education centres in Madrid participated in the activity. Four workshops prepared by CIBER researchers were carried out within the activity:

- Elena Aznar and Jose Manuel Terrés, CIBER-BBN - Nanopharmaceuticals. La reina Luz y el rey Nano (“Queen Light and King Nano”)
- Almudena Fernández, CIBERER - Nanocrispr. Avatar mice.
- Susana Carregal, CIBERES - Nanotechnology. Multifunctional Nanoparticles.
- Sandra Diez, CIBERONC - Nanooncology. Metastarg. Stop metastasis.



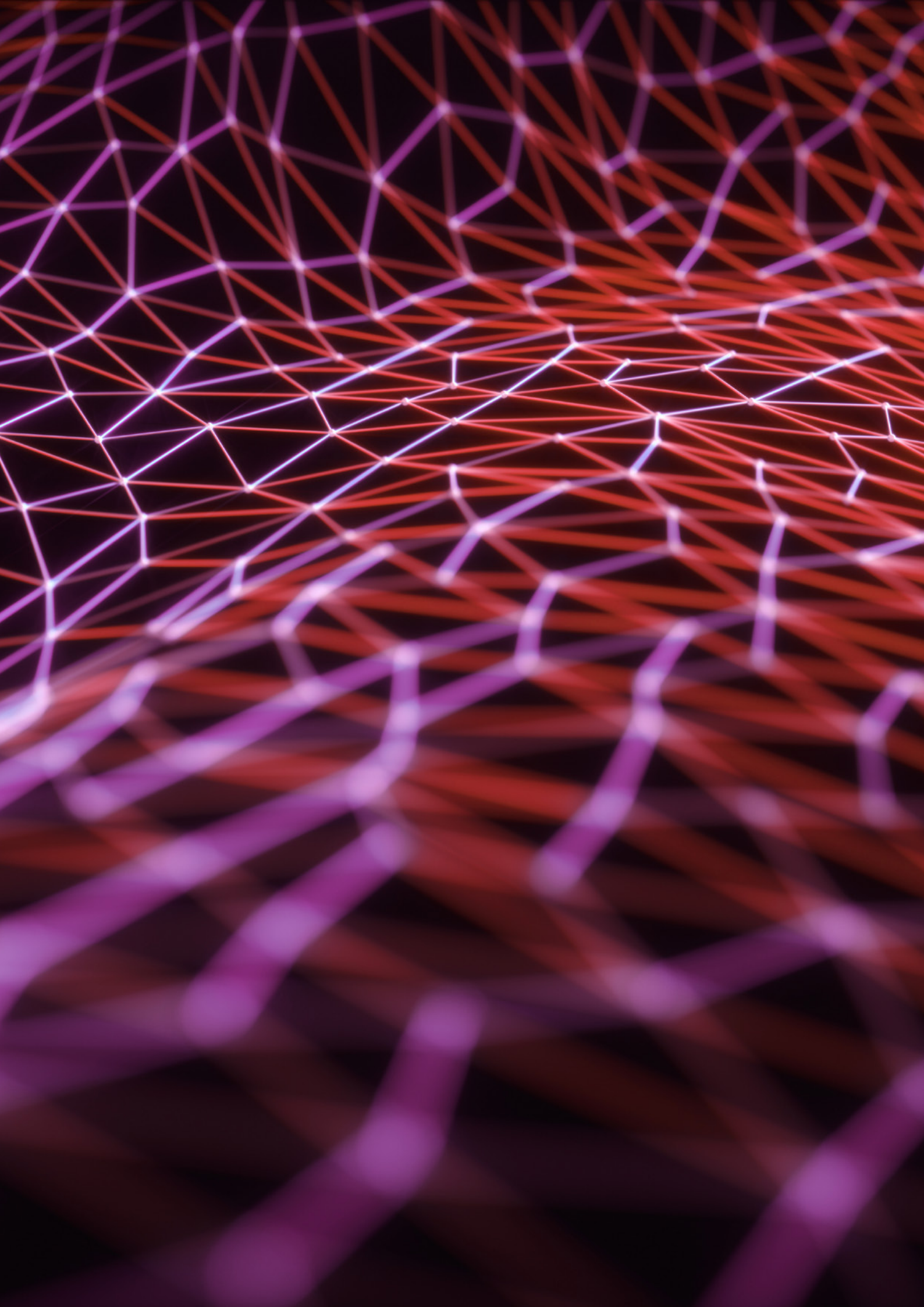
[Video](#)

[+Photos](#)

**Bioengineering,  
Biomaterials  
and Nanomedicine**

*ciber-bbn*







# Presentation by the Scientific Director

**Ramón Martínez Máñez**



Once again, I am pleased to review and highlight the activity carried out by CIBER-BBN during the previous year detailed in this annual report.

In 2019, we have continued the implementation of the 2018-2021 Strategic Plan, which involved a new way of organising our activity and our internal calls for projects.

At the international level, a project has started in which CIBER participates through our ICTS NANBIOSIS (Singular Scientific and Technological Infrastructures) to create large infrastructures that facilitate the development of medical devices containing nano-technology in compliance with European regulatory frameworks. Our presence in different international events has also been maintained to improve our external visibility.

In addition to the fact that our researchers have participated in various proposals for the European H2020 program, I would especially like to highlight the joint application, in coordination with all the thematic areas, to the COFUND program (Marie Skłodowska-Curie Actions), which includes the incorporation of 23 postdoctoral researchers to the CIBER, distributed among all the thematic areas. We are particularly satisfied with the proposal presented, which places CIBER in Europe as a highly attractive centre for foreign researchers in the field of biomedicine.

Regarding our scientific activity, 131 intramural collaborations have been active, in which groups from BBN and from all CIBER areas participate, which shows the multidisciplinary nature of our lines of work, as well as 30 Early Stage projects which are led by hired PhD researchers.

Within the framework of the Annual Conference, held in Tarragona with the presence of members of the External Scientific Advisory Committee, prizes were awarded to the best articles published in 2018 by young researchers, this being the 2nd Edition of the CIBER-BBN Awards.

In collaboration with other areas, the *seed projects* have been completed in collaboration with CIBERONC, as well as the joint projects with CIBERES and CIBERER.

Three new valorisation projects have also been launched in 2019, which receive funding to ensure that a technology with a minimum TRL of 3 can reach a more mature level of development. Several transfer projects from previous calls have also been maintained, jointly financed by CIBER-BBN and by a company.

As for NANBIOSIS, infrastructures of the Andalusian centre BIONAND have been integrated, making this institution a third additional node to the two existing ones, CIBER and Jesús Usón Minimally Invasive Surgery Centre. Also this year, the Nucleotide Synthesis Unit has been incorporated, which completes the Biomolecule Production Platform.

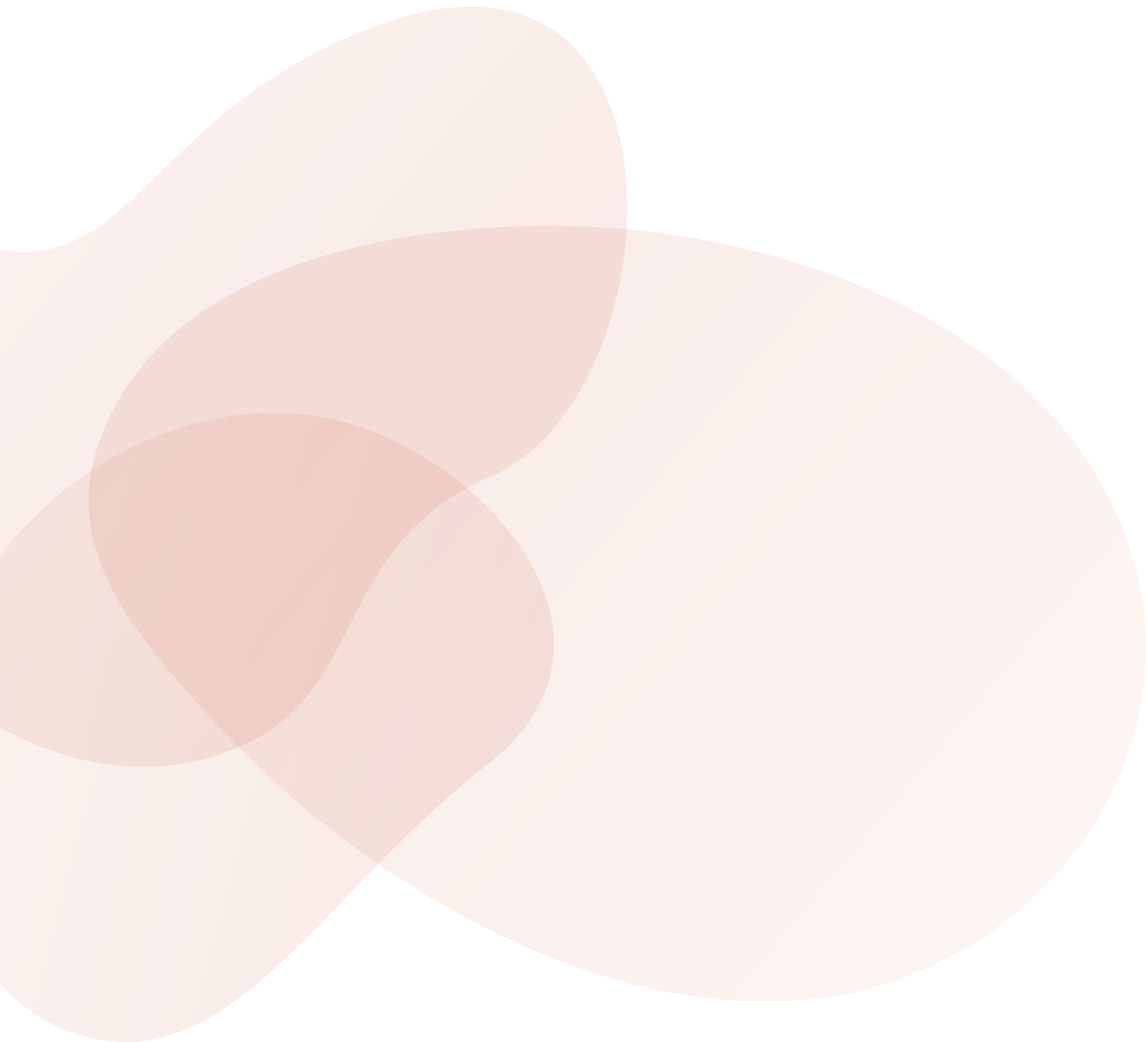
I would also like to note that CIBER-BBN has taken part, as have all areas, in the evaluation process promoted by the Instituto de Salud Carlos III to evaluate the CIBER programme for the 2015-2108 period.

The scientific production of this period has continued along the lines of the previous year, maintaining the quality standards for publications in the first quartile and decile.

2019 has been, in my opinion, very positive in terms of scientific activity, and on behalf of the Steering Committee and my own, I want to thank the researchers at CIBER-BBN for yet another year of continued effort and ongoing commitment.

In the following pages you will find a brief summary of the scientific activity developed by CIBER-BBN throughout 2019 which I hope will be of interest to you.

Best regards.



# Programmes

## Bioengineering and Medical Imaging

**Coordinator:** Jordi Aguiló Llobet

The Bioengineering Programme was very active in 2019, with the presentation of 8 intramural cooperation proposals with a 3-year horizon (2018-2021) to be added to the 28 that were presented in 2018 and which have been developed in the course of the year. Of these proposals, five were presented with groups of CIBERNED and other thematic areas of CIBER: CIBERER (1), CIBERSAM (1), CIBERFES (1) and CIBERNED (2). The proposals and their coordinators have been the following:

- *Artificial BioPancreas: Novel macro and micro encapsulation of pancreatic  $\beta$ -cells for diabetes type 1 therapy, coordinated by Rosa Villa.*
- *MR-based in vivo Biomarkers of immune system activity against Glioblastoma, coordinated by Carles Arús.*
- *New technologies at the service of prevention, assessment and early detection of cognitive impairment, coordinated by Fernando Maestú.*
- *Hyperspectral and OCT imaging of muscle for assessing muscle degeneration and dystrophy in Duchenne disease, coordinated by Olga Conde.*
- *Interactive platform for early detection of neurodegenerative diseases, coordinated by José M. López Higuera.*
- *Interactive tool for early detection of emotional impairments, coordinated by José M. López Higuera.*
- *Non-invasive sleep tracker using two complementary vibration technologies, coordinated by José M. López Higuera.*
- *Neurological mechanisms of resilience to Alzheimer's Disease, coordinated by Juan Domingo Gispert.*

The most frequently addressed pathologies have been neurological diseases with three proposals. The remaining proposals focus on chronic, rare, neuromuscular, mental, sleep-related and cancer diseases.

As for active projects with other thematic areas, these have been the following:

- *ANS-RESP-WEANING: Autonomic nervous system surrogates, cardiopulmonary coupling and respiratory parameters as predictors of successful weaning in mechanically ventilated patients, with the participation of the group led by Pablo Laguna and collaboration with CIBERES.*

- *NaTBil: PDT based on nanoconjugates triggered by biolight, with the participation of the group led by JM López-Hidalgo and collaboration with CIBERONC.*

In addition, during the year 2019, four ongoing Early Stage projects have continued being developed, corresponding to their second year of execution, led by CIBER contracted researchers:

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

In the session dedicated to young researchers during the CIBER-BBN Annual Conference, researcher David Hernando, from the group led by Pablo Laguna, received the award for the best article in the field of Bioengineering for his work entitled *Validation of Heart rate polar monitor RS800 for heart rate variability analysis during exercise*.

The activity of the Programme in European initiatives has been marked by the granting of the Graphene Flagship Core Project 3, whose applicant has been Rosa Villa, from the group led by J. Aguiló. In addition, seven new proposals currently pending resolution have been requested.

In the activity at the national level, we highlight the Juan de la Cierva grant received by the researcher in training Alba Martín Yebra from Pablo Laguna's group.

## Biomaterials and Advanced Therapies

**Coordinator:** Julio San Román del Barrio

From the Biomaterials and Advanced Therapies Programme, six intramural collaboration proposals were added in 2019, three of them with groups from other thematic areas of CIBER (CIBERER and CIBERONC). Cancer has been the most frequently addressed topic, followed by infectious diseases, neuromuscular diseases and sleep disorders. To these proposals we must add the 32 that were presented in 2018 and which have been developed throughout 2019.

During 2019, the nine Early Stage projects have been developed for the second year running, coordinated by CIBER staff in groups from the Biomaterials and Advanced Therapies Programme. 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.

2019 has been quite a prolific year for the Biomaterials and Advanced Therapies Programme in terms of awards. The researcher María Vallet-Regí received, among others, two highly prestigious international awards: the George Winter Award 2019 and the FEMS Materials Innovation Prize 2019.

The activity at the national level includes the concession in 2019 of the Research Challenges R + D + I Projects Modality B to researcher Patricia Rico, from the group led by José Luis Gómez Ribelles.

At the international level, an individual project has been submitted to the European Research Council (ERC) Consolidator Grants by the researcher Patricia Rico.

It is important to mention that, since June 2019, the CIBER-BBN participates as a *Stakeholder of the AEMPS (Spanish Agency for Medicines and Health Products) in the European project STARS-CSA: Strengthening Training of Academia in Regulatory Science*. <https://www.csa-stars.eu/index.html>. This project is developed by a consortium of 18 European regulatory agencies, including the AEMPS and the EMA (European Medicines Agency), with the objective being to analyse and improve the knowledge of regulatory science of the academic research groups that direct their research to the development of innovative drugs, including advanced therapies.

## Nanomedicine

**Coordinator:** M. Pilar Marco Colás

In 2019, seven new intramural collaborations were started in the Nanomedicine Programme, joining the 59 collaborations already started in 2018. In addition, the 14 Early Stage projects in the nanomedicine area have also been maintained, led by contracted CIBER staff.

The effort made by the CIBER-BBN in preparing competitive proposals for both European and national calls is worth mentioning. During the year 2019, the national project "Nanoplasmonic sensor platform for biomimetic analysis and without cell immunotherapy markings - SENSECELL", of the programme of the National Plan for the Generation of Knowledge 2018, led by Maria Soler (PI: Laura Lechuga), was started.

In addition, researchers from the CIBER-BBN Nanomedicine Programme have continued with the international and national financed projects already underway, highlighting among them:

- European project SMART-4 FABRY "*Smart functional GLA-nanoformulation for Fabry Disease*", coordinated by CIBER (PI: Nora Ventosa);
- European project PROSCANEXO "*Exploitation of extracellular vesicles for precision diagnostics of prostate*" ERANET-TRANSCAN-2 (JTC2016) led by Jesús Martínez de la Fuente;
- European project ABISens "*Monitoring of Acquired Brain Injury and recovery biomarkers by the combined label-free nanoSensing of multiple circulating molecules*" EURONANOMED-3 (JTC2018) coordinated by CIBER-BBN, PI: Laura Lechuga;
- National projects NanoET-Leukemia (RETOS R+D+i projects), and the project "*Design of protein nanomedicines for targeted treatments in pancreatic cancer*" AES 2017, led by CIBER researchers Anna Lagunas and Marina Inés Giannotti, and José Luis Corchero respectively;
- Worth highlighting are the ERC projects underway within the CIBER-BBN nanomedicine area such as (i) ERC Advanced Grants: María Vallet-Regí, Jesús Santamaría and Luis Liz-Marzán with the projects VERDI "*poly-Vanet mEsopoRous nanosystems for bone Diseases*", CADENCE "*Catalytic Dual-Function Devices Against Cancer*" and 4DBIOSERS "*Four-Dimensional Monitoring of Tumor Growth by Surface Enhanced Raman Scattering*" respectively, and the (ii) ERC Consolidator: Manuel Arruebo NANOLEDONISM project and (iii) ERC Proof of Concept: HOTFLOW project by Jesús Martínez de la Fuente Martínez.

As regards joint activities with groups from other thematic areas, we highlight the following projects:

- *NANOCRISPRALBINO: Preclinical development of CRISPR-based non-viral therapeutic approaches in existing cellular and animal models of albinism*, in collaboration with CIBERER and the participation of the group led by J.L. Pedraz.
- *ALYCIA: Artificial Lymph Nodes for Cancer ImmunoTherapy*, in collaboration with CIBERONC y and the participation of Judith Guasch (from the group led by J. Veciana).

CIBER-BBN nanomedicine researcher Luis M. Liz Marzán has once again been included in the list of Highly Cited Researchers by Clarivate Analytics, one of the most reputable classifications in the international academic and scientific community. We have participated in the following events related to the area of Nanomedicine: Nanomed Europe Conference, NME19 (Portugal), BioNanoNet Annual Meeting and Austrian Microfluidics Initiative (Salzburg, Austria) and 12th Annual Conference of Biomedical Research Technology Platforms (Madrid).





# Training Programme

The CIBER-BBN training programme aims to increase the research skills of the staff that make up the groups. It seeks to improve the professional competence of technical and research staff as a factor for change, transforming attitudes, knowledge and skills according to the needs that arise throughout the development of their research activity.

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

## Initiation to Research Grants

Unfortunately, administrative limitations have meant that in 2019 it has not been possible to arrange calls for the Initiation to Research Grants of 12 months' duration, an initiative which is very highly valued among CIBER-BBN groups as it enables young researchers still taking a master course to join the groups.

It was nonetheless possible to finance 6 contracts for trainees lasting 6 months for young graduates. 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 CIBER-BBN. These short stays must be structured within the priority strategic work lines of our thematic area.

In 2019, there were two mobility calls, in April and September, and a total number of 20 grants were awarded for stays at groups outside CIBER-BBN.

As regards mobility grants for research staff between CIBER-BBN groups, three grants were awarded. The call for these grants is permanent throughout the year.

# Platforms: NANBIOSIS ICTS

## Coordinator: Jaume Veciana Miró

After the update of the National ICTS (Singular Scientific and Technological Infrastructure) Map at the end of 2018 and the incorporation of BIONAND as a new node of NANBIOSIS, during 2019 we have worked on the integration of said node within the infrastructure. This includes the preparation of a new agreement between the three institutions to regulate, among other aspects, the operation of the ICTS, the incorporation of Nanoimaging Unit 28 and the change in the members of the Coordination Committee.

The promotion of groundbreaking biomedical solutions has been a priority for NANBIOSIS throughout this year. These solutions make available to researchers and companies the integrated expertise of the NANBIOSIS units. The cascade characterisation of nanomedicines and other cascades will be reinforced thanks to the launch of the European project SAFE-N-MEDTECH (H2020) whose objective is to create an open access platform based on online tools for companies and reference laboratories, to interconnect skills, knowledge, networks and services for the development, testing, evaluation, scaling, and exploitation of nanotechnology-based diagnostic and medical devices in the market. In the project, 27 other partners participate in addition to CIBER, and it also has a broad participation from the NANBIOSIS units and its organizational structure. In addition, projects already underway where NANBIOSIS units participate have also been continued, such as: the Biotapes project (Collaboration Challenges), the European DRIVE Project (H2020-NMBP) and the European POSITION-II project (H2020-ECSEL-2017).

In addition, NANBIOSIS is funded by the ProNanbiosis II project (Strategic promotion and Coordinated Management of Nanbiosis. SAF2017-90810-REDI) from the Dynamization Actions "Excellence Networks" call 2017, which allows hiring a person for the daily management of NANBIOSIS as an ICTS as well as for the updating of the website and communication via social networks. This year, 285 requests for the services of the CIBER-BBN platforms were handled (69% from external users, of which 11% were companies and the rest were research groups from public bodies). Additionally, this project has allowed to continue with the development of the actions foreseen in the NANBIOSIS Marketing Plan, such as dissemination through the website and social networks, as well as the organisation of a training and internal dissemination session especially aimed at the technical staff from the units. This was attended by more than 30 people with very positive results as reflected in the satisfaction surveys.

The participation of NANBIOSIS in international organisations and its collaboration with national companies, foundations and public research organizations continues to be important. We have participated in the following events: Nanomed Europe Conference, NME19 (Portugal), BioNanoNet Annual Meeting and Austrian Microfluidics initiative (Salzburg, Austria), and the 12th Annual Conference of Biomedical Research Technology Platforms (Madrid). Among other activities, the collaborative approach to other ICTS stands out, such as the Alba Synchrotron and the ICTS OmicsTech. In addition, NANBIOSIS actively participates in the MATERPLAT Platform as well as in actions that come from the NANOMED-SPAIN Nanomedicine Platform.

A session dedicated to related infrastructures was held at the CIBER-BBN 2019 Annual Conference and the fourth meeting of the Scientific Advisory Committee of NANBIOSIS also took place.

For more information please visit: <https://www.youtube.com/watch?v=vezgov-kc0g>

# Scientific Production

## Publications

### No. of publications in 2019

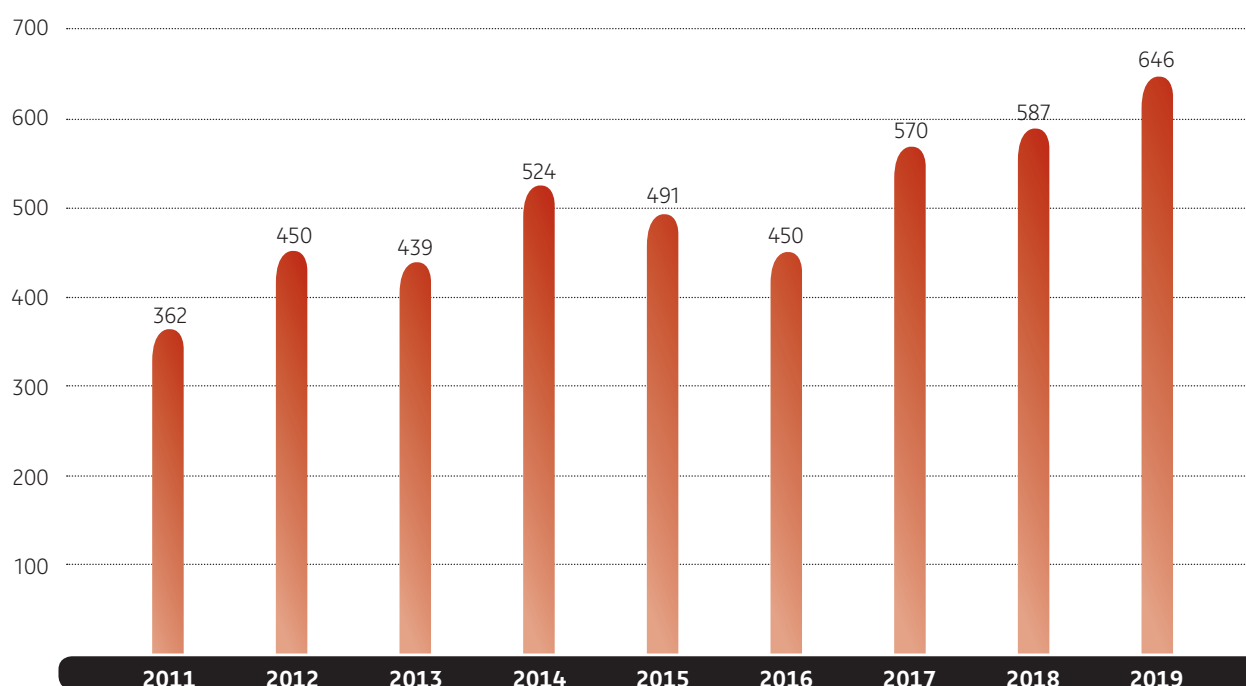
TOTALS	646
Q1	428
D1	156

### Collaborative publications

CIBER-BBN	59
CIBER*	65

\*Among several thematic areas

### Evolution of publications 2011-2019



## 10 most relevant publications by impact factor

IF	Publication
40,443	GRZELCZAK M., LIZ-MARZAN L.M., KLAJN R.. <i>Stimuli-responsive self-assembly of nanoparticles. Chemical Society Reviews</i> . 2019;48(5):1342-1361.
38,887	UROZ M., GARCIA-PUIG A., TEKELI I., ELOSEGUI-ARTOLA A., ABENZA J.F., MARIN-LLAURADO A. ET AL. <i>Traction forces at the cytokinetic ring regulate cell division and polyploidy in the migrating zebrafish epicardium. Nature Materials</i> . 2019.
38,887	PARK D., WERSHOF E., BOEING S., LABERNADIE A., JENKINS R.P., GEORGE S. ET AL. <i>Extracellular matrix anisotropy is determined by TFAP2C-dependent regulation of cell collisions. Nature Materials</i> . 2019.
38,887	MASVIDAL-CODINA E., ILLA X., DASILVA M., CALIA A.B., DRAGOJEVIC T., VIDAL-ROSAS E.E. ET AL. <i>High-resolution mapping of infraslow cortical brain activity enabled by graphene microtransistors. Nature Materials</i> . 2019;18(3):280-288.
38,887	GARRETA E., PRADO P., TARANTINO C., ORIA R., FANLO L., MARTI E. ET AL. <i>Fine tuning the extracellular environment accelerates the derivation of kidney organoids from human pluripotent stem cells. Nature Materials</i> . 2019;18(4):397-405.
25,809	CESPEDES M.V., CANO-GARRIDO O., ALAMO P., SALA R., GALLARDO A., SERNA N. ET AL. <i>Engineering Secretory Amyloids for Remote and Highly Selective Destruction of Metastatic Foci. Advanced Materials</i> . 2019.
24,646	CORCOY R.. <i>Glucose screening in pregnancy to predict future cardiovascular risk. Nature Reviews Endocrinology</i> . 2019.
20,113	PEREZ-GONZALEZ C., ALERT R., BLANCH-MERCADER C., GOMEZ-GONZALEZ M., KOLODZIEJ T., BAZELLIERES E. ET AL. <i>Active wetting of epithelial tissues. Nature Physics</i> . 2019;15(1):79-88.
20,113	CHEN T., CALLAN-JONES A., FEDOROV E., RAVASIO A., BRUGUES A., ONG H.T. ET AL. <i>Large-scale curvature sensing by directional actin flow drives cellular migration mode switching. Nature Physics</i> . 2019;15(4):393-402.
18,205	TERRAZAS M., GENNA V., PORTELLA G., VILLEGAS N., SANCHEZ D., ARNAN C. ET AL. <i>The Origins and the Biological Consequences of the Pur/Pyr DNA-RNA Asymmetry. Chem</i> . 2019;5(6):1619-1631.

## CIBER-BBN Groups. Publications in 2019

Group Leader	Publ.	Q1	D1	Institution / Centre	Province
 Aguiló Llobet, Jordi	14	10	4	Universitat Autònoma de Barcelona - Centro Nacional de Microelectrónica	Barcelona
 Albericio Palomera, Fernando	24	10	4	Universitat de Barcelona - Facultat de Química	Barcelona
 Arús Caralto, Carles	8	4	1	Universitat Autònoma de Barcelona	Barcelona
 Becerra Ratia, José	10	4	0	Universitat de Màlaga - Facultat de Ciències	Màlaga
 Bellón Caneiro, Juan Manuel	16	1	0	Universitat de Alcalá - Facultat de Medicina	Madrid
 Calonge Cano, Margarita	11	4	1	Universitat de Valladolid - Institut de Oftalmobiologia Aplicada	Valladolid
 Corcoy Pla, Rosa	10	6	4	Institut de Investigació del Hospital de la Santa Cruz y San Pablo	Barcelona
 Engel López, Elisabeth	8	6	2	Fundació Institut de Bioenginyeria de Catalunya	Barcelona
 Eritja Casadellà, Ramon	14	7	4	Agència Estatal Consejo Superior de Investigaciones Científicas - Institut de Química Avanzada de Catalunya	Barcelona



Group Leader	Publ.	Q1	D1	Institution / Centre	Province
 Fernández Jover, Eduardo	11	7	2	Universidad Miguel Hernández - Instituto de Bioingeniería	Alicante
 Gómez Ramírez, Rafael	21	17	3	Universidad de Alcalá - Facultad de Farmacia	Madrid
 Gómez Ribelles, José Luis	20	11	1	Universidad Politécnica de Valencia - Centro de Biomateriales e Ingeniería Tisular	Valencia
 González Martín, María Luisa	9	5	1	Universidad de Extremadura - Facultad de Ciencias	Badajoz
 Gorostiza Langa, Pau	8	7	6	Fundación Instituto de Bioingeniería de Cataluña	Barcelona
 Hernando Pérez, María Elena	27	18	4	Universidad Politécnica de Madrid - ETSI Telecomunicación	Madrid
 Jané Campos, Raimon	18	11	1	Fundación Instituto de Bioingeniería de Cataluña	Barcelona
 Laguna Lasasosa, Pablo	21	8	0	Universidad de Zaragoza - Instituto Universitario de Investigación en Ingeniería de Aragón	Zaragoza
 Lechuga Gómez, Laura María	12	9	4	Agencia Estatal Consejo Superior de Investigaciones Científicas - Institut Català de Nanociència i Nanotecnologia	Barcelona
 Liz Marzán, Luis Manuel	25	22	11	CIC biomaGUNE	Guipúzcoa
 López Higuera, José Miguel	13	11	0	Universidad de Cantabria - Edificio I+D+I de Ing. de Telecomunicación	Cantabria
 Mangues Bafalluy, Ramon	21	14	6	Instituto de Investigación del Hospital de la Santa Cruz y San Pablo	Barcelona
 Marco Colas, María Pilar	7	7	1	Agencia Estatal Consejo Superior de Investigaciones Científicas - Instituto de Química Avanzada de Cataluña	Barcelona
 Martínez Barca, Miguel Ángel	13	7	1	Universidad de Zaragoza - Instituto Universitario de Investigación en Ingeniería de Aragón	Zaragoza
 Martínez de la Fuente, Jesús	29	21	5	Agencia Estatal Consejo Superior de Investigaciones Científicas - Instituto de Ciencia de Materiales de Aragón	Zaragoza
 Martínez Máñez, Ramón	34	27	10	Universidad Politécnica de Valencia - Instituto Interuniversitario de Investigación de Reconocimiento Molecular y Desarrollo Tecnológico	Valencia
 Pedraz Muñoz, José Luis	34	30	16	Universidad del País Vasco - Facultad de Farmacia	Álava
 Peris Serra, José Luis	-	-	-	Asociación Instituto de Biomecánica de Valencia	Valencia
 Raya Chamorro, Ángel	12	12	6	Centro de Medicina Regenerativa de Barcelona**	Barcelona
 Rodríguez Abreu, Carlos	20	13	5	Agencia Estatal Consejo Superior de Investigaciones Científicas - Instituto de Química Avanzada de Cataluña	Barcelona
 Rodríguez Cabello, José Carlos	16	8	4	Universidad de Valladolid - Escuela de Ingenierías Industriales	Valladolid
 Ruiz Romero, Cristina	10	6	3	Servicio Gallego de Salud - Complejo Hospitalario Universitario A Coruña	A Coruña
 Samitier Martí, Josep	6	4	3	Fundación Instituto de Bioingeniería de Cataluña	Barcelona

Group Leader	Publ.	Q1	D1	Institution / Centre	Province
 San Román del Barrio, Julio	20	12	4	Agencia Estatal Consejo Superior de Investigaciones Científicas - Instituto de Ciencia y Tecnología de Polímeros	Madrid
 Santamaría Ramiro, Jesús	48	34	12	Universidad de Zaragoza - Instituto Universitario de Investigación en Nanociencia de Aragón	Zaragoza
 Santos Lleó, Andrés	14	10	4	Universidad Politécnica de Madrid - ETSI Telecomunicación	Madrid
 Schwartz Navarro, Simó	6	6	2	Fundación Hospital Universitario Vall d'Hebron - Institut de Recerca (VHIR) - Hospital Vall d'Hebron	Barcelona
 Setoain Peregró, Javier	25	15	5	Universidad de Barcelona - Hospital Clínic de Barcelona	Barcelona
 Trepas Guixar, Xavier	7	7	7	Fundación Instituto de Bioingeniería de Cataluña	Barcelona
 Vallet Regí, María	22	16	12	Universidad Complutense de Madrid - Facultad de Farmacia	Madrid
 Veciana Miró, Jaume	20	14	4	Agencia Estatal Consejo Superior de Investigaciones Científicas - Instituto de Ciencia de Materiales de Barcelona	Barcelona
 Vilaboa Díaz, Nuria	8	7	4	Servicio Madrileño de Salud - Hospital La Paz	Madrid
 Villaverde Corrales, Antonio	18	16	9	Universidad Autónoma de Barcelona - Instituto de Biotecnología y Biomedicina	Barcelona
 Farré Ventura, Ramón*	26	14	4	Universidad de Barcelona - Facultad de Medicina	Barcelona
 Muñoz Fernández, María Ángeles*	16	12	1	Servicio Madrileño de Salud - Hospital Gregorio Marañón	Madrid

\*CIBER-BBN Associated Groups

\*\*Currently Fundación Idibell

## Patents owned by CIBER

### National

- Method to produce enzymes
- Tools for the quantification of SPECT studies of the nigrostriatal dopamine system (tQUDOSY) (Software)
- Tools for statistical analysis of PET studies in refractory epilepsy (tSAPRE) (Software)

### European

- Therapeutic nanoconjugates and uses thereof
- Nanovesicles and its use for nucleic acid delivery
- Protein nano- or microparticles as artificial inclusion bodies
- Scaffold Proteins and Therapeutic Nanoconjugates based on Nidogen
- Self-associated functional acrylic copolymers and terpolymers and their use as vehicles for bioactive compounds.

### PCT

- Methods and Systems for Measuring a Stress Indicator, and for Determining a Level of Stress in an Individual
- Injectable material for the regeneration of articular cartilage
- Use of boron and its derivatives for the treatment of muscular dystrophies
- Graphene transistor system for measuring electrophysiological signals

**National Phases**

- Connecting device for microfluidic circuits (Europe).
- Graphene transfer and exfoliation procedure from a doped silicon carbide substrate to another substrate (Europe and USA)
- Nanostructured proteins and uses thereof (Europe, USA and China)
- Devices and methods for multiplexing liquid in biosensor micro-chambers (Europe)

**Granted Patents****National**

- Procedure for exfoliation and transfer of graphene from a doped silicon carbide substrate to another.
- Smart platform and method for monitoring body composition and assessing the nutritional and hydration status of a user.
- Injectable material for the regeneration of articular cartilage

**International**

- Bioreactor for cell co-culture (USA)
- Haptens and conjugates derived from pyocyanin, antibodies thereof, and immunochemical method for the detection of infections caused by pseudomonas aeruginosa (USA).
- Bioreactor for cell co-culture (USA)
- Use of an adrenomedullin inhibitor for the manufacture of a medicine useful in the prevention and treatment of diseases that reduce bone density (Europe)

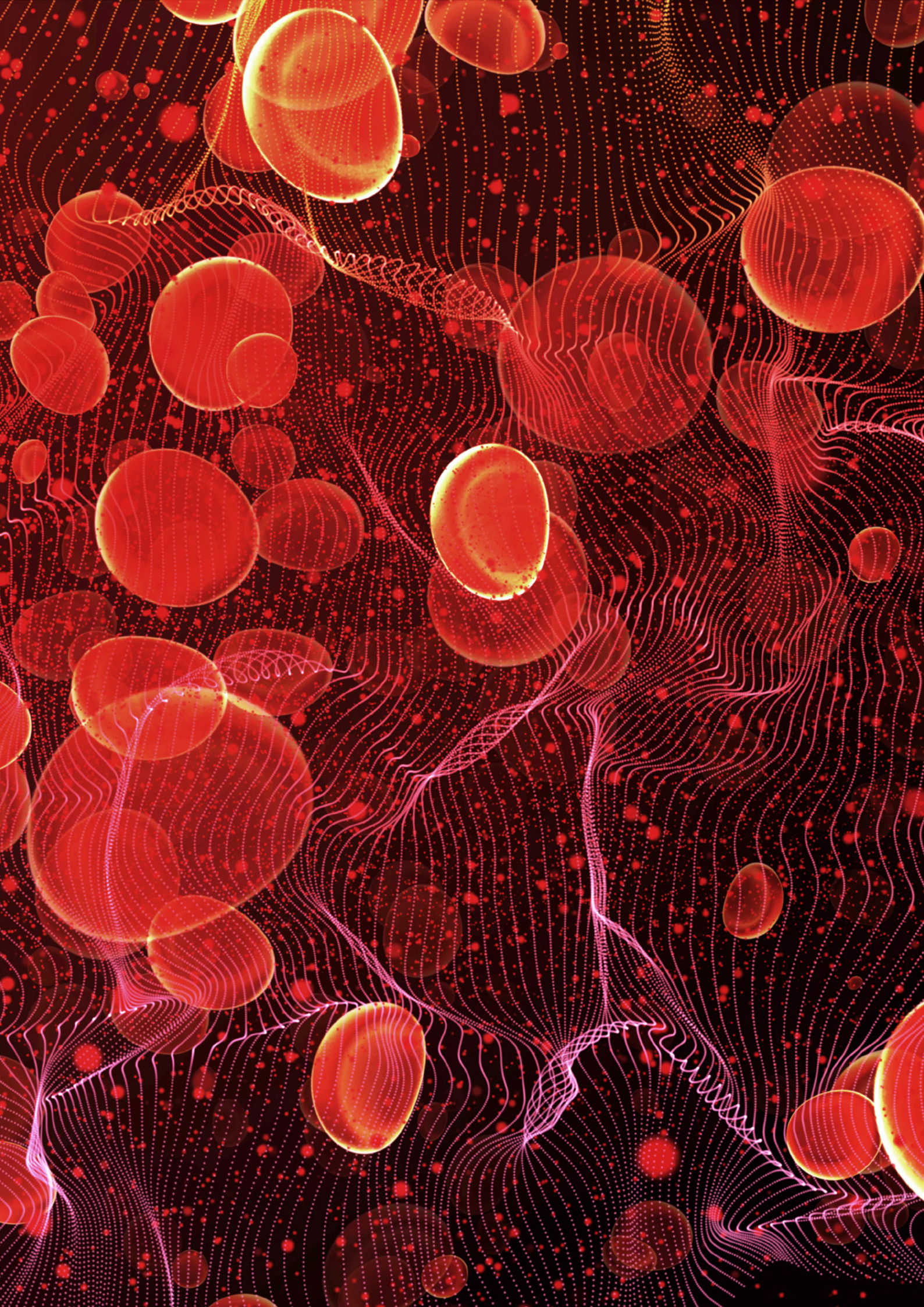




# **Cardiovascular Diseases**

*ciber cv*







# Presentation by the Scientific Director



## Francisco Fernández-Avilés

The third year in the development of the area of CIBERCV has been unquestionably satisfactory, both due to the achievements attained and to the great involvement of all the groups, which have managed to overcome a considerable amount of difficulties.

In 2019 we passed the second evaluation of the External Scientific Advisory Committee. In addition, we have managed to undertake a large part of the actions recommended by the Committee in its 2018 evaluation, striving for internationalisation and excellence, with actions to identify, attract and retain young talent, promoting and rewarding multidisciplinary and enhancing the management of data and registers in population cohorts.

The Management Committee is well aware that all the groups are making great efforts to ensure progress in these fields. In this third year, our CIBER has managed to participate in an IMI2 H2020 project with the participation of 4 CIBERCV groups for the early identification of myocardial damage in patients with Type 2 Diabetes Mellitus. In addition, the CIBERCLAP platform has been launched with the aim of establishing the first multicenter large animal research network to test different cardio-protection strategies, and the CORDELIA consortium, a compiler of 26 population cohorts (> 120,000 subjects) with up to 15 years of follow-up to identify clinical predictors and molecular events of cardiovascular events has been closed.

Furthermore, in 2019, the main actions of the CIBERCV have continued to be implemented, such as the competitive grants through intramural projects and through actions to identify and promote talent through the Jordi Soler-Soler grants. Among the important scientific achievements, several multicentre studies led by researchers from the CIBER stand out. Another important milestone of this 2019 has been the implementation of the agreement with the Spanish Medicines Agency for the creation of a National Registry of Ventricular Assist Devices and that will allow progress in the comprehensive management of data provided by the national health system.

Despite multiple difficulties, we are optimistic and are aware that science managers are also committed to overcoming the struggles we face. The Consortium that welcomes us is an unrivaled venue of excellence that ensures a stable budget. All this is allowing us to place Spanish cooperative cardiovascular research at the highest national and international level of competitiveness. Thanks to you all.

# Programmes

## P1: Myocardial damage and its consequences

**Coordinators:** Francisco Fernández-Avilés y Juan Delgado Jiménez

In the line of structural and electrophysiological remodelling and scar formation, a collaborative work led by the group of Dr. García-Dorado and Dr. Barrabés stands out in which the role of calpains in modulating isoproterenol-induced ventricular hypertrophy through modulation of GRK2 is described. In addition, in the context of this programme, CIBERCV participates in the European Project IMI2 aimed at studying cardiomyopathy of the diabetic patient through exhaustive image-based characterisation and biomarkers in a wide case-control cohort of patients with and without type 2 diabetes and with and without heart failure with a normal ejection fraction.

In the research line of genetically caused myocardial damage, the work aimed at studying the genetic variants associated with cardiomyopathy induced by chemotherapy treatment stands out. In a multicentre, clinical and preclinical multidisciplinary model study led by Dr. García Pavia's Group, the role of genetic susceptibility in chemotherapy damage has been established.

In the line of research in heart failure, it is important to highlight the launch of the FAISCA study "De novo atrial fibrillation in patients with heart failure: incidence, predictors and relevance", the result of the first intramural call for Research Projects of the Consortium, led by Dr. González-Juanatey. This is a collaborative initiative generated and funded in the context of CIBERCV in which advanced cardiac imaging techniques will be combined with implantable electrocardiographic monitoring to prospectively study the prevalence and implications of this arrhythmia in a large population of patients with HF.

## P2: Arterial Pathology, Myocardial Ischaemia and Structural Heart Pathology

**Coordinators:** Borja Ibáñez Cabeza y Alberto San Román Calvar

The CIBERCV programme 2 focusses on arterial disease, myocardial ischaemia-reperfusion and structural cardiopathy. The results in 2019 have been successful in attaining scientific achievements and the launch of important collaborative initiatives.

In the line of research into Myocardial Ischaemia and Reperfusion, to be highlighted is the completion of the inclusion of animals in the first blind, multicentre, randomized preclinical trial "CIBERCLAP". The objective of this initiative is to apply



the methodology of a clinical trial (randomisation, blinding, multicentre recruitment, centralised analysis) to an animal study aimed at analyzing the efficacy and mechanisms involved in ischaemic preconditioning strategies. The uniqueness of this initiative, led by Dr. Ibañez's group, lies in the rigor of the methodology to try to reduce the variability and the experimental biases that may justify the enormous variability in the results that have been described in the ischaemic preconditioning studies in large animal models.

In the aortic diseases research line, several collaborative multicentre studies have been completed to characterise the genetic and biomechanical bases of the bicuspid aortic valve and associated aortic dilatation. These studies, led by Dr. Evangelista, are an example of the potential of collaborative participation even in high prevalence diseases. Especially promising have been the results of the characterisation of aortic flow using phase contrast magnetic resonance imaging the basis of aortic dilation in bicuspid valve disease.

In the line of research focused on valve disease and congenital heart disease, the most important milestone of 2019 is the double initiative of the publication of a retrospective study aimed at analysing the prognostic implications of treatment with renin-angiotensin system inhibitors following transcatheter aortic valve replacement that was published in the Journal of the American College of Cardiology, led by Dr. San Román's group. In parallel, a pragmatic multicentre study was launched to analyse this same problem. This line of research will definitively clarify the potential of these drugs as a complementary treatment to valve replacement.

## P3: Cardiovascular Epidemiology and Risk Factors

**Coordinator:** Jaume Marrugat de la Iglesia

The purpose of the Programme on Cardiovascular Epidemiology and Risk Factors is to investigate the mechanism linking cardiovascular risk factors with the serious diseases they entail, such as ischaemic heart disease and cerebrovascular disease. Programme 3 of the CIBERCV is made up of two lines of research.

Within the line of Epidemiology, cohorts, risk factors and cardiovascular risk functions, progress has been made in several important projects in 2019. The group led by Dr. Sanchís has analysed in detail the impact of comorbidity and mortality due to revascularisation in patients with acute coronary syndrome without ST segment elevation.

Regarding the risk factors associated with the development of cardiovascular diseases, Dr. Marrugat's group has published a new study from the REGICOR cohort describing the usefulness of circulating microRNAs to reclassify healthy individuals and identify those with coronary artery disease.

## P4: Molecular and imaging biomarkers and precision CV medicine

**Coordinator:** Javier Díez Martínez

CIBERCV Programme 4 seeks the identification, validation, and transfer 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 research line focused on the evaluation of known biomarkers, coordinated by Dr. Antoni Bayés-Genís and Dr. Díez, has made important advances. In a major collaborative translational effort, the association between interleukin 1 $\beta$  axis activation and mortality in patients with decompensated acute heart failure has been established.

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, cardiomyopathies and cardiovascular ageing. To be highlighted in this line are the works led by Dr. Ibañez focused on the identification of new image-based biomarkers for the early detection of anthracycline cardiac damage, using a large animal model of cardiotoxicity.

# Training Programme

**Coordinator:** José Antonio Barrabés Riu

The CIBERCV Training Programme seeks 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 CIBERCV, this programme remains the main training initiative and some modifications have been introduced to further enhance training in the framework of collaborative research. This programme ultimately intends to foster quality and collaborative translational research in the cardiovascular area in the CIBERCV groups through a training offer for young people with a research vocation. The specific objectives of this programme are:

- To structure a procedure for granting subsidies for contracting professionals undergoing a training plan in cardiovascular translational research in a multidisciplinary setting.
- The research contract aims to promote capacity-building in research within a collaborative framework between at least two groups addressing the same problem from different perspectives. At least one clinical research group and another non-clinical 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 second call has been granted to a researcher who will carry out his research project led by Dr. Manuel Jiménez Navarro from the Cardiology Service of the Virgen de la Victoria Hospital in Málaga and Dr. Antonio Ordóñez, from the Cardiovascular Surgery Service of the Virgen del Rocío Hospital in Seville.

In addition to these grants, the Training Programme also funds research stays for CIBERCV staff at other groups within CIBERCV or at internationally relevant centres where the knowledge and capacities of the programme can be increased.

# Scientific Production

## Publications

### No. of publications in 2019

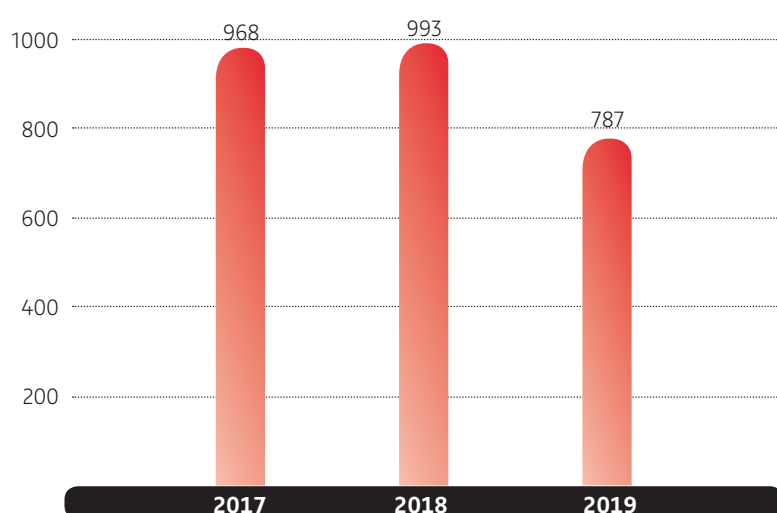
TOTALS	787
Q1	457
D1	182

### Collaborative Publications

CIBERCV	187
CIBER*	185

\*Among various thematic areas

### Evolution of publications 2017-2019



## 10 most relevant publications by impact factor

IF	Publication
70,67	<i>Efficacy and safety of low-dose colchicine after myocardial infarction</i> (Scopus ID: 85075950640; Pubmed ID: 31733140)
70,67	<i>Effects of serelaxin in patients with acute heart failure</i> (Scopus ID: 85071309086; Pubmed ID: 31433919)
59,102	<i>Effect of remote ischaemic conditioning on clinical outcomes in patients with acute myocardial infarction (CONDI-2/ERIC-PPCI): a single-blind randomised controlled trial</i> (Scopus ID: 85073227920; Pubmed ID: 31500849)
59,102	<i>Transcatheter edge-to-edge repair for reduction of tricuspid regurgitation: 6-month outcomes of the TRILUMINATE single-arm study</i> (Scopus ID: 85075510686; Pubmed ID: 31708188)
59,102	<i>Popeye's sign, heart disease, and amyloidosis</i> (Scopus ID: 85061788107; Pubmed ID: 30799016)
51,273	<i>Effect of a Strategy of Comprehensive Vasodilation vs Usual Care on Mortality and Heart Failure Rehospitalization among Patients with Acute Heart Failure: The GALACTIC Randomized Clinical Trial</i> (Scopus ID: 85076697113; Pubmed ID: 31846016)
44,019	<i>Dendritic cells in cancer immunology and immunotherapy</i> (Scopus ID: 85071950927; Pubmed ID: 31467405)
43,07	<i>Rising rural body-mass index is the main driver of the global obesity epidemic in adults</i> (Scopus ID: 85065577280; Pubmed ID: 31068725)
43,07	<i>p38γ is essential for cell cycle progression and liver tumorigenesis</i> (Scopus ID: 85064274373; Pubmed ID: 30971822)
23,239	<i>Proximal aorta longitudinal strain predicts aortic root dilation rate and aortic events in Marfan syndrome</i> (Scopus ID: 85069237607; Pubmed ID: 30977783)

## CIBERCV Groups. Publications in 2019

Group Leader	Publ.	Q1	D1	Institution / Centre	Province
 Andrés García, Vicente	9	4	4	Fundación Centro Nacional de Investigaciones Cardiovasculares	Madrid
 Badimon Maestro, Lina	18	15	9	Instituto de Investigación del Hospital de la Santa Cruz y San Pablo	Barcelona
 Barrabés Riu, Jose Antonio	64	41	13	Fundación Hospital Universitario Vall d'Hebron - Institut de Recerca (VHIR) - Hospital Vall d'Hebron	Barcelona
 Bayés Genis, Antonio	76	46	18	Fundación Instituto de Investigación Germans Trias i Pujol - Hospital Germans Trias i Pujol	Barcelona
 Blanco Colio, Luis Miguel	5	3	3	Instituto de Investigación Sanitaria Fundación Jiménez Díaz	Madrid
 Bosca Gomar, Lisardo	6	4	2	Agencia Estatal Consejo Superior de Investigaciones Científicas - Instituto de investigaciones biomédicas Alberto Sols	Madrid
 Brugada Terradellas, Ramon	18	8	4	Fundación Instituto de Investigación Biomédica de Girona - Hospital Josep Trueta	Girona
 Chorro Gasco, Francisco Javier	13	7	3	Fundación para la Investigación del Hospital Clínico de la Comunidad Valenciana (Fundación INCLIVA) - Instituto de investigación sanitaria INCLIVA	Valencia

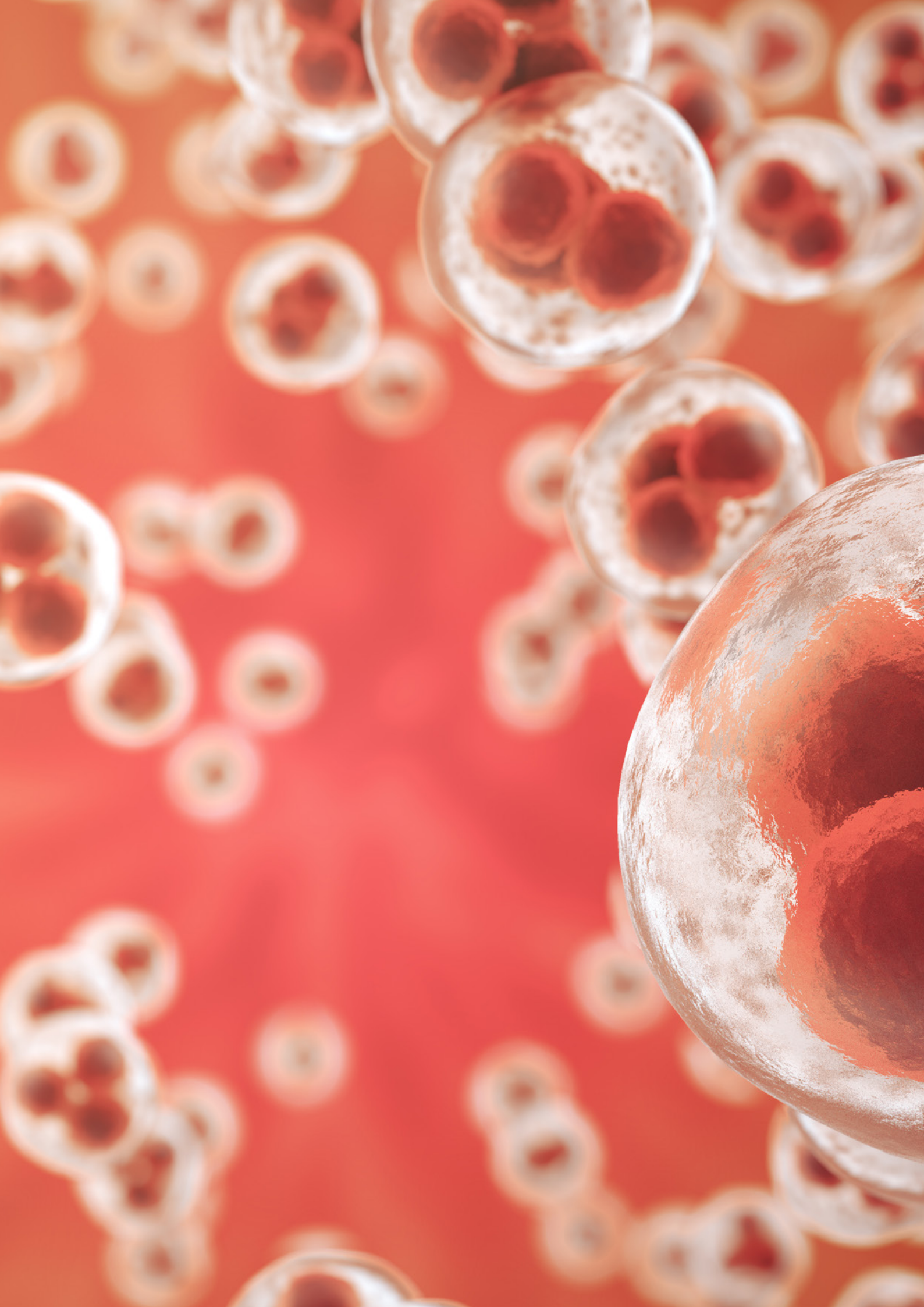
Group Leader	Publ.	Q1	D1	Institution / Centre	Province
 Civeira Murillo, Fernando	23	15	6	Fundación Instituto de Investigación Sanitaria Aragón	Zaragoza
 Crespo Leiro, María Generosa	31	17	7	Servicio Gallego de Salud - Complejo Hospitalario Universitario A Coruña	A Coruña
 Delgado Jiménez, Juan Francisco	46	24	14	Servicio Madrileño de Salud - Hospital Universitario 12 Octubre	Madrid
 Delpón Mosquera, Eva	17	12	9	Universidad Complutense de Madrid - Facultad de Medicina	Madrid
 Díez Martínez, Domingo Francisco Javier	16	13	6	Fundación para la Investigación Médica Aplicada	Navarra
 Elosua Llanos, Roberto	15	8	3	Consorti Mar Parc Salut de Barcelona	Barcelona
 Fernández-Avilés Díaz, Francisco	73	31	9	Servicio Madrileño de Salud - Hospital Gregorio Marañón	Madrid
 García Pavía, Pablo	34	15	9	Servicio Madrileño de Salud - Hospital Universitario Puerta de Hierro	Madrid
 González Juanatey, José Ramón	61	30	5	Servicio Gallego de Salud - Complejo Hospitalario Universitario Santiago	A Coruña
 Guerra Ramos, José María	31	14	6	Instituto de Investigación del Hospital de la Santa Cruz y San Pablo	Barcelona
 Ibáñez Cabeza, Borja	55	40	24	Instituto de Investigación Sanitaria Fundación Jiménez Díaz	Madrid
 Jiménez Navarro, Manuel Francisco	23	14	2	Fundación Pública Andaluza para la Investigación de Málaga en Biomedicina y Salud (FIMABIS) - Hospital Universitario Virgen de la Victoria	Málaga
 López-Sendon Hentschel, José Luis	1	0	0	Servicio Madrileño de Salud - Hospital La Paz	Madrid
 Marín Ortuño, Francisco	55	25	8	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	14	11	4	Consorti Mar Parc Salut de Barcelona	Barcelona
 Martínez Dolz, Luis	13	8	6	Fundación para la Investigación del Hospital la Fe - Hospital Universitario de La Fe	Valencia
 Martínez González, José	21	9	4	Agencia Estatal Consejo Superior de Investigaciones Científicas - Instituto de Investigaciones Biomédicas de Barcelona	Barcelona
 Mayor Menéndez, Federico	11	11	1	Universidad Autónoma de Madrid - Centro de Biología Molecular Severo Ochoa	Madrid
 Mont Gibrau, Josep Lluís	49	28	6	Instituto de Investigaciones Biomédicas August Pi i Sunyer	Barcelona
 Ordóñez Fernández, Antonio	5	3	0	Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla - Hospital Virgen del Rocío	Sevilla
 Páramo Fernández, José Antonio	9	2	0	Universidad de Navarra - Clínica Universitaria de Navarra	Navarra
 Pérez-Villacastín Domínguez, Julián	21	10	2	Servicio Madrileño de Salud - Hospital Clínico San Carlos	Madrid



Group Leader	Publ.	Q1	D1	Institution / Centre	Province
 Pompa Mínguez, José Luis de la	6	4	3	Fundación Centro Nacional de Investigaciones Cardiovasculares	Madrid
 Redondo Moya, Juan Miguel	9	7	5	Fundación Centro Nacional de Investigaciones Cardiovasculares	Madrid
 Salaices Sánchez, Mercedes	13	10	2	Universidad Autónoma de Madrid	Madrid
 San Román Calvar, José Alberto	28	18	8	Hospital Clínico Universitario de Valladolid	Valladolid
 Sánchez Fernández, Pedro Luis	26	14	5	Fundación Instituto de Estudios de Ciencias de la salud de Castilla y León - Hospital Universitario de Salamanca	Salamanca
 Sánchez Madrid, Francisco	15	10	4	Universidad Autónoma de Madrid	Madrid
 Sánchez Margallo, Francisco Miguel	7	6	1	Fundación Centro de Cirugía de Mínima Invasión Jesús Usón	Cáceres
 Sanchís Fores, Juan	43	21	10	Fundación para la Investigación del Hospital Clínico de la Comunidad Valenciana (Fundación INCLIVA) - Instituto de investigación sanitaria INCLIVA	Valencia
 Vázquez, Cobos Jesús María	22	15	6	Fundación Centro Nacional de Investigaciones Cardiovasculares	Madrid
 Zamorano Gómez, José Luis	21	12	1	Servicio Madrileño de Salud - Hospital Ramón y Cajal	Madrid

**Diabetes  
and Associated  
Metabolic  
Diseases**

*überdem*





# Presentation by the Scientific Director

**Eduard Montanya Mias**



In 2019, CIBERDEM has prioritised strategic actions based on enhancing the competitiveness and scientific leadership of young people and promoting a collaborative environment between groups, facilitating the development of new collaborative projects. A relevant aspect has been the concession of three intramural projects in which a total of 7 CIBERDEM groups participate. Another particularly fruitful initiative has been the holding, for the first time, of a Meeting of Young Researchers within the framework of the CIBERDEM Annual Meeting. The consolidation of institutional relationships with the German Centre for Diabetes Research (DZD) has made it easier for our young researchers to attend the DZD 7th Diabetes Research School (Barcelona).

In the field of research activity, CIBERDEM has increased its level of scientific production with 345 annual publications, as well as publications in the first decile and in the first quartile, representing 62% of the total. The CIBERDEM groups maintain their high collaborative activity at the national and international level, with 84% and 30% of collaborative publications, respectively. Our website shows in detail the most relevant publications of each group and the Annual Report details the main achievements of 2019. In the field of knowledge transfer, CIBERDEM has continued to participate in the preparation of national and international clinical guidelines and consensus documents and has carried out various patentability studies, and filed new patent applications. Looking back at 2019, the initiatives in the Training Programme also stand out, particularly those aimed at young researchers at CIBERDEM. In the area of Communication and Dissemination to Society, to be highlighted is the consolidation of CIBERDEM's participation in the congress of the Spanish Diabetes Society with a joint symposium and its presence at the congress of the European Association for the Study of Diabetes. CIBERDEM maintains its commitment to society, participating in social outreach activities such as the Meeting on unmet needs and variability in the management of diabetes, Diabetes Experience Day and World Diabetes Day, participating in the Diabetes and Family event, in the Spanish Parliament's Health Commission, and maintaining its ties with patient associations.

I invite all those interested in CIBERDEM's activity to review the Annual Report. For more detailed information please visit our website ([www.ciberdem.org](http://www.ciberdem.org)) and follow us on Twitter.

Kindest regards

# Programmes

## **PROGRAMME 1. Epidemiology, Genetics and epigenetics of diabetes mellitus. Chronic complications and comorbidities**

**Coordinator:** Ángela Martínez Valverde

### **Epidemiology of diabetes mellitus, its chronic complications and comorbidities**

In the framework of the diabetes study, the association between milk consumption and the presence of a better metabolic profile in the general population has been confirmed, as well as the increased risk of dysglycemia and insulin resistance in geographical areas with higher mean temperatures (Valdés et al., *Eur J Endocrinol.* 2019). The lipoprotein profile has been completed by means of NMR, glycosylated proteins and low molecular weight metabolites in the 5,072 samples of the cohort of the diabetes study, which has allowed to initiate an extensive phase of data analysis with the participation of several CIBERDEM groups.

CIBERDEM is participating in the International Study of Tertiary Prevention of type 1 diabetes in children and adolescents with intraganglionic GAD (glutamic acid decarboxylase) (DIAGNODE study). In this multicentre clinical trial, a CIBERDEM group coordinates the participation of the 10 clinical groups in Spain.

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

Atherosclerotic plaques in the carotid arteries of patients with type 1 diabetes have been characterised for the first time by ultrasound, with a higher frequency of plaques containing calcium found compared to people without diabetes (Castelblanco et al., *J Clin Med.* 2019). The study has been carried out in collaboration with CIBEROBN.

It has been reported that macrophage-specific reverse cholesterol transport (CRT) decreases in patients with type 2 diabetes and that, although overexpression of APOA1 improves this phenotype in a murine model of diabetes and obesity, it increases fatty liver and weight (Méndez-Lara et al., *Int J Mol Sci.* 2019). In collaboration with CIBERCV, the oxidation of certain amino acids of APOA1 has been characterised, which are key in the alteration of CRT and common to various diseases that carry great cardiovascular risk, such as abdominal aortic aneurysm (Martínez-López et al., *EBioMedicine.* 2019).



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

Treatment with the hypoglycemic drug empagliflozin has been reported to protect against macrovascular disease in ApoE-deficient mice regardless of glucose levels and blood pressure values (Ortega et al., *Arterioscler Thromb Vasc Biol.* 2019). The study has been carried out in collaboration between two CIBERDEM groups.

It has been described that the evaluation of retinal sensitivity in combination with ocular fixation parameters by means of microperimetry could be a reliable method to detect prodromal stages of dementia in the type 2 diabetic population (Ciudin et al., *J Clin Med.* 2019). This is the basis of a multidisciplinary project awarded by the EU-H2020 and coordinated by the CIBERDEM group. Topical administration of neuro-protective drugs has been shown to prevent progression of retinal neurodegeneration in patients with type 2 diabetes (Simó et al., *Diabetes* 2019).

The effects of the first-choice oral antidiabetic drug metformin hydrochloride have been compared with those of metformin glycinate in hepatocytes of mice and humans, with a greater effect of metformin glycinate in inhibiting hepatic gluconeogenesis, as well as a more sustained phosphorylation of hepatocytes suggesting that this chemical form is a more effective therapeutic alternative (Rada et al., *Food Chem Toxicol.* 2019). The work has been carried out in collaboration with Laboratorios Silanes S.A.

A simple method such as the ankle-brachial systolic pressure index has been described to identify patients with undiagnosed peripheral arterial disease (Nattero-Chavez et al., *J Clin Endocrinol Metab.* 2019). In patients with type 1 diabetes, both peripheral arterial stiffness and atherosclerosis are associated with autonomic cardiovascular neuropathy.

## **PROGRAMME 2. 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**

It has been described that the diabetogenic effect of the endocrine disruptor bisphenol A may be mediated by its action on the expression and function of the Na<sup>+</sup> and K<sup>+</sup> channels of pancreatic beta cells. This modulation occurs via activation of estrogen receptors typeβ (Martínez-Pinna et al., *Diabetologia* 2019).

The consumption of olive oil has been reported to regulate glucose homeostasis by improving insulin sensitivity and the function of pancreatic beta cells, in cases of type 2 diabetes (Jurado-Ruiz et al., *Sci Rep* 2019).

Cocoa consumption has been described as protecting against vascular structural alterations of diabetes. The Sirt-1, Nox2 and Nrf2 routes are implicated in this effect (Álvarez-Cilleros et al, *Mol Nutr Food Res*).

The absence of the proinflammatory cytokine TNFSF14 has been established to improve hepatic glucose tolerance and inflammation in hepatic steatosis (Herrero-Cervera et al., *Diabetologia* 2019).

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

It has been described that, during the development of type 1 diabetes, there is an increase in the renewal of pancreatic alpha cells, with the aim of maintaining their population or increasing the mass of beta cells, via transdifferentiation of these alpha cells. (Bru-Tari et al., *Sci Rep.* 2019).

The absence of the PTP-1B protein has been reported to increase the production of VEGF-A by pancreatic islets, improving their revascularization and increasing their survival after transplantation (Figueiredo et al., *Sci Transl Med.* 2019).

Knowledge of the three-dimensional architecture of the chromatin of the pancreatic islets is helping to understand the genetics of type 2 diabetes (Miguel-Escalada et al., *Nat Genet.* 2019).

The presence of ductal cells in pancreatic islet preparations has been established to be detrimental to the functionality of transplanted islets (Marín-Cañas et al., *PLoS One* 2019).

## **Application of new technologies to the treatment of diabetes**

Learning algorithms have been developed, which use data from the blood glucose of the patients to effectively prevent the appearance of postprandial hypoglycemia in insulinised patients (Oviedo et al., *Comput Methods Programs Biomed.* 2019).

# **PROGRAMME 3. Cellular and molecular mechanisms involved in the development and progression of type 2 diabetes and identification of new therapeutic targets.**

**Coordinator:** Antonio Zorzano Olarte

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

The succinate receptor SUCNR1 has been shown to control the anti-inflammatory programme in the macrophage by regulating the metabolic response to obesity (Keiran et al., *Nat Immunol.* 2019). Two CIBERDEM groups have collaborated in this study, as well as other CIBER areas. Various patents have been applied for (EP19382564.3, PCT / EP2019 / 051157).

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

The participation of the protein Mitofusin 2 in the development of chronic liver disease has been described through a mechanism that involves the transfer of phosphatidylserine from the endoplasmic reticulum to the mitochondria (Hernández-Álvarez et al., *Cell* 2019). This allows the development of insulin resistance and the development of non-alcoholic steatohepatitis to be related within the same pathological process. The study has been developed in collaboration with various CIBERDEM groups and other CIBER areas.

HRI activators (“heme-regulated eukaryotic translation initiation factor 2 $\alpha$  kinase”) have been shown to be a promising drug therapy for treating type 2 diabetes mellitus and non-alcoholic fatty liver disease due to their ability to increase FGF21 levels (Zarei et al., Br. J. Pharmacol. 2019).

The molecular mechanism has been described that implicates a new effector of inflammatory response, phospholipase A2 group IVC (or cytosolic phospholipase A2 c  $\gamma$ , cPLA2 $\gamma$ ), in the remodeling of membranes that occurs during cell activation in metabolic and cardiovascular diseases (Guijas et al., Cells 2019; Lebrero et al., Cells 2019).

## Identification of biomarkers of risk of diabetes progression

New biomarkers of diabetes remission have been described after bariatric surgery (Ceperuelo-Mallafre et al., Diabetes Care 2019), and of dysfunction of subcutaneous adipose tissue in women with polycystic ovary syndrome (PCOS) (Malpique et al., Pediatr Obes. 2019), of low-grade chronic inflammation in PCOS (Fuertes-Martín et al., J Proteome Res. 2019) and of ovulatory frequency and liver fat.

A new class of lipids with antidiabetic and anti-inflammatory properties has been described, which also have antiapoptotic properties, since their formation reduces intracellular concentrations of free hydroxy acids (Rodríguez et al., Cancers 2019).

A completely automated method of serum glycoprotein quantification using 1H-NMR has been developed, compatible with the Liposcale-TM test, previously developed, which is very useful for evaluating the degree of chronic inflammation in obesity and diabetes.

A nanostructured silicon substrate coated with gold nanoparticles has been designed, manufactured and validated, which allows to acquire metabolomic images by printing the tissues on it (Alexandra S, Advanced Functional Material 2019), and allows to acquire images at cellular resolution by Surface Enhanced Raman Spectroscopy.

A novel open source computational tool, CliqueMS, has been developed to annotate undirected metabolic data based on LC-MS. CliqueMS is able to correctly annotate more metabolites and adducts from a single spectrum than the tools available to date (Senan O, Bioinformatics 2019).

## Determinants of insulin resistance: molecular mechanisms involved

Insulin receptor isoform A has been reported to increase hepatic glucose uptake and improve hepatic steatosis under conditions of insulin resistance induced by a high fat diet (López-Pastor et al., Dis Model Mech. 2019).

# Training Programme

## Coordinator: Ángel Nadal Navajas

As the main novelty of the Training Programme in 2019, CIBERDEM has awarded three intramural projects for young researchers, in which seven CIBERDEM groups participate. It is noteworthy that, of the seven groups, six are led by young women researchers. The first Meeting of Young Researchers, organised by and for young people, took place within the framework of the Annual Meeting on November 6 and had the participation of 78 young researchers.

The Mobility Grants Programme has continued to finance stays in CIBER groups and international groups, with a total of seven grants awarded.

The 10th Annual CIBERDEM Meeting was held on November 7-8, in which more than 160 CIBERDEM researchers participated and 89 communications were presented. A symposium was held to present the results of the INFLAMES project (*Identification of novel modulators of chronic inflammation in prevalent diseases: unveiling divergent mechanisms of diseases*), which included the participation of researchers from CIBEROBN and CIBEREHD. The participation of the groups and discussion of results was very active, both in oral presentations and in poster sessions.

In the context of the various training activities that CIBERDEM organises in collaboration with Merck Sharp & Dohme España, this year the Annual Symposium "La diabetes a debate 2019: Diabetes in the Knowledge Frontier" had as its central themes the association between diabetes and cancer, and the implications of glycemic variability in type 2 diabetes.

Within the framework of the collaboration with the Spanish Diabetes Society (SED), CIBERDEM has organised for the second year the joint SED-CIBERDEM Symposium at the XXX SED National Congress. The Symposium focused on research on mitochondrial dynamics and metabolic disruption, on the role of long non-coding RNA in pancreatic beta cell destruction in type 1 diabetes and on hidden cardiovascular risk in patients with diabetes.

CIBERDEM has organised the second edition of the Expert Postgraduate Course at the University of Barcelona 2019-2020 "Chronic complications of Diabetes Mellitus," with 15 European ECTS credits, and 178 persons enrolled.

The CIBERDEM groups have been extremely active organising scientific activities, congresses, courses, symposia, seminars and debates, in Spain and abroad, and in collaboration with other CIBER areas. We highlight the participation in the Inter-CIBER Interdisciplinary Course: *Immunoterapia, más allá de la prescripción. Un reto para todos*. (April 5).

# Scientific Production

## Publications

### No. of publications in 2019

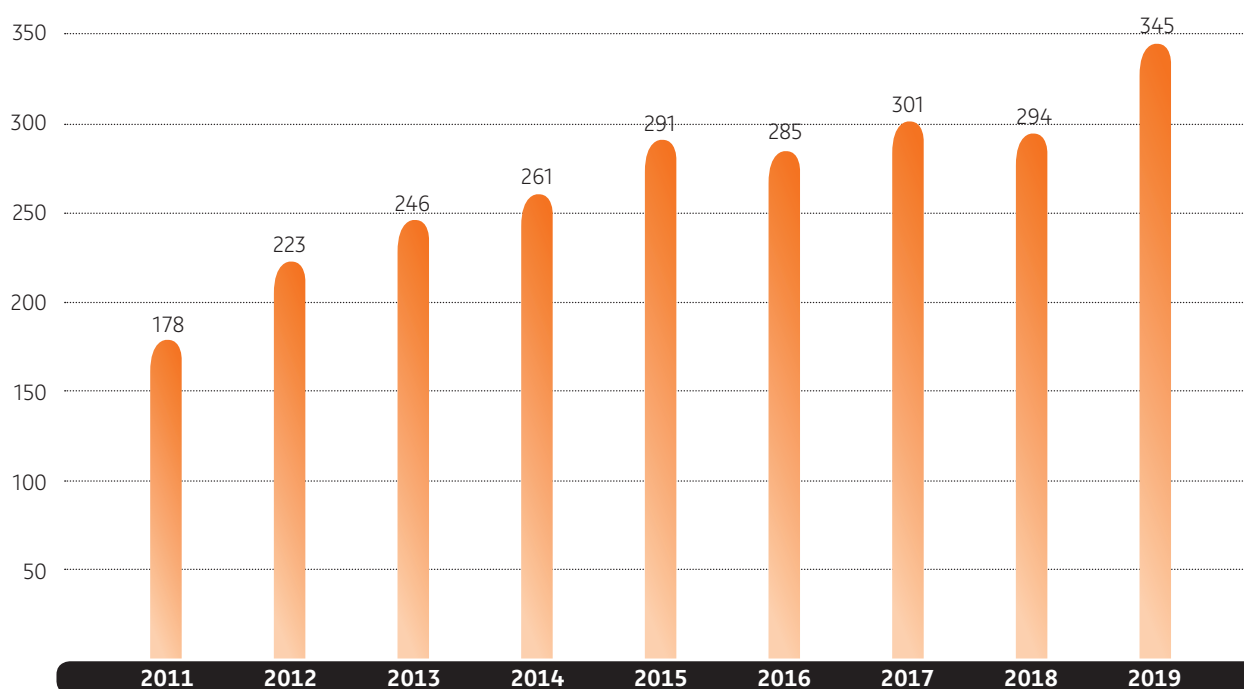
TOTALS	345
Q1	215
D1	87

### Collaborative Publications

CIBERDEM	51
CIBER*	146

\*Among various thematic areas

### Evolution of publications 2010-2019





## 10 most relevant publications by impact factor

IF	Publication
36,216	HERNANDEZ-ALVAREZ M.I., SEBASTIAN D., VIVES S., IVANOVA S., BARTOCCIONI P., KAKIMOTO P. ET AL. <i>Deficient Endoplasmic Reticulum-Mitochondrial Phosphatidylserine Transfer Causes Liver Disease</i> . <i>Cell</i> . 2019;177(4):881-895. e17.
25,455	MIGUEL-ESCALADA I., BONAS-GUARCH S., CEBOLA I., PONSÁ-COBAS J., MENDIETA-ESTEBAN J., ATLA G. ET AL. <i>Human pancreatic islet three-dimensional chromatin architecture provides insights into the genetics of type 2 diabetes</i> . <i>Nature Genetics</i> . 2019;51(7):1137-1148.
25,455	RAMOS-RODRIGUEZ M., RAURELL-VILA H., COLLI M.L., ALVELOS M.I., SUBIRANA-GRANES M., JUAN-MATEU J. ET AL. <i>The impact of proinflammatory cytokines on the <math>\beta</math>-cell regulatory landscape provides insights into the genetics of type 1 diabetes</i> . <i>Nature Genetics</i> . 2019;51(11):1588-1595.
24,54	IBANEZ L., DE ZEGHER F. <i>Exploring the use of metformin in pregnant women with polycystic ovary syndrome: new evidence, new wisdom</i> . <i>The Lancet Diabetes and Endocrinology</i> . 2019;7(4):242-243.
23,53	KEIRAN N., CEPERUELO-MALLAFRE V., CALVO E., HERNANDEZ-ALVAREZ M.I., EJARQUE M., NUNEZ-ROA C. ET AL. <i>SUCNR1 controls an anti-inflammatory program in macrophages to regulate the metabolic response to obesity</i> . <i>Nature Immunology</i> . 2019;20(5):581-592.
17,161	FIGUEIREDO H., FIGUEROA A.L.C., GARCIA A., FERNANDEZ-RUIZ R., BROCA C., WOJTUSCISZYN A. ET AL. <i>Targeting pancreatic islet PTP1B improves islet graft revascularization and transplant outcomes</i> . <i>Science Translational Medicine</i> . 2019;11(497): eaar6294.
15,621	IÁKAB S.A., RAFOLS P., GARCIA-ALTARES M., YANES O., CORREIG X. <i>Silicon-Based Laser Desorption Ionization Mass Spectrometry for the Analysis of Biomolecules: A Progress Report</i> . <i>Advanced Functional Materials</i> . 2019;29(45):1903609.
15,27	CERIELLO A., ROSSI M.C., DE COSMO S., LUCISANO G., PONTREMOLI R., FIORETTO P. ET AL. <i>Overall quality of care predicts the variability of key risk factors for complications in type 2 diabetes: An observational, longitudinal retrospective study</i> . <i>Diabetes Care</i> . 2019;42(4):514-519.
15,27	GUTIERREZ-CARRASQUILLA L., SANCHEZ E., BARBE F., DALMASES M., LOPEZ-CANO C., HERNANDEZ M. ET AL. <i>Effect of glucose improvement on spirometric maneuvers in patients with type 2 diabetes: The Sweet breath study</i> . <i>Diabetes Care</i> . 2019;42(4):617-624.
15,27	RODBARD HW, ROSENSTOCK J, CANANI LH, DEEROCHANAWONG C, GUMPRECHT J, LINDBERG SO, ET AL. <i>Oral semaglutide versus empagliflozin in patients with type 2 diabetes uncontrolled on metformin: The PIONEER 2 trial</i> . <i>Diabetes Care</i> . 2019;42(12):2272-2281.

## CIBERDEM Groups. Publications in 2019

Group Leader	Publ.	Q1	D1	Institution / Centre	Province
 Álvarez Escola, Carmen	7	6	1	Universidad Complutense de Madrid - Facultad de Farmacia	Madrid
Álvarez García, Elvira	0	0	0	Universidad Complutense de Madrid - Facultad de Medicina	Madrid
 Balsinde Rodríguez, Jesús	7	7	0	Agencia Estatal Consejo Superior de Investigaciones Científicas - Instituto de Biología y Genética Molecular	Valladolid
 Benito de las Heras, Manuel Román	2	1	0	Universidad Complutense de Madrid - Facultad de Farmacia	Madrid
 Blanco Vaca, Francisco	25	16	6	Instituto de Investigación del Hospital de la Santa Creu i Sant Pau	Barcelona
 Bondía Company, Jorge	12	5	1	Universidad Politécnica de Valencia - Instituto Universitario de Automática e Informática Industrial	Valencia
 Bosch Tubert, Fátima	4	4	1	Universidad Autónoma de Barcelona - Centro de Biotecnología animal y Terapia Genética	Barcelona
 Burks, Deborah	8	6	6	Fundación Centro de Investigación Príncipe Felipe	Valencia
 Calle Pascual, Alfonso Luis	11	7	2	Servicio Madrileño de Salud - Hospital Clínico San Carlos	Madrid
 Castaño González, Luis	11	8	1	Asociación Instituto de Investigación Sanitaria de Biocruces - Hospital Universitario Cruces	Vizcaya
 Correig Blanchart, Francesc Xavier	21	13	6	Fundación Instituto de Investigación Sanitaria Pere Virgili - Universidad Rovira i Virgili	Tarragona
 Egido de los Ríos, Jesús	14	9	4	Instituto de Investigación Sanitaria Fundación Jiménez Díaz	Madrid
 Escobar Morreale, Héctor Francisco	13	10	4	Servicio Madrileño de Salud - Hospital Ramón y Cajal	Madrid
 Ferrer Marrades, Jorge	1	1	1	Fundación Centro de Regulación Genómica	Barcelona
 Guinovart Cirera, Joan Josep	2	0	0	Fundación privada Instituto de Recerca Biomédica (IRB- Barcelona)	Barcelona
 Ibáñez Toda, Lourdes	14	11	5	Fundación para la Investigación y Docencia Sant Joan de Deu - Hospital Sant Joan de Deu	Barcelona
 Martín Bermudo, Francisco	15	7	2	Universidad Pablo de Olavide - Centro Andaluz de Biología del Desarrollo	Sevilla
 Martínez Valverde, Ángela María	8	6	2	Agencia Estatal Consejo Superior de Investigaciones Científicas - Instituto de Investigaciones Biomédicas Alberto Sols	Madrid
 Masana Marín, Luis	21	9	2	Fundación Instituto de Investigación Sanitaria Pere Virgili - Universidad Rovira i Virgili	Tarragona
 Mauricio Puente, Diego	29	16	7	Instituto de Investigación del Hospital de la Santa Creu i Sant Pau	Barcelona
 Montanya Mias, Eduard	13	8	2	Fundación IDIBELL - Hospital Universitario de Bellvitge	Barcelona
 Nadal Navajas, Ángel	9	6	1	Universidad Miguel Hernández - Instituto de Bioingeniería	Alicante
 Novials Sardá, Anna María	10	8	3	Instituto de Investigaciones Biomédicas August Pi i Sunyer - Centro Esther Koplowitz	Barcelona
 Real Collado, José Tomás	16	6	4	Fundación para la Investigación del Hospital Clínico de la Comunidad Valenciana (Fundación INCLIVA) - Instituto de Investigación Sanitaria INCLIVA	Valencia

Group Leader	Publ.	Q1	D1	Institution / Centre	Province
 Rojo Martínez, Gemma	19	7	2	Fundación Pública Andaluza para la Investigación de Málaga en Biomedicina y Salud (FIMABIS) - Hospital Regional Universitario Carlos Haya	Málaga
 Simó Canonge, Rafael	38	26	13	Fundación Hospital Universitario Vall d'Hebron - Institut de Recerca (VHIR) - Hospital Vall d'Hebron	Barcelona
 Vallejo Fernández de la Reguera, Mario	2	1	0	Agencia Estatal Consejo Superior de Investigaciones Científicas - Instituto de Investigaciones Biomédicas Alberto Sols	Madrid
 Vázquez Carrera, Manuel	7	6	4	Universidad de Barcelona - Facultad de Farmacia	Barcelona
 Vendrell Ortega, Joan Josep	13	9	4	Fundación Instituto de Investigación Sanitaria Pere Virgili - Hospital Universitario Juan XXIII	Tarragona
 Vidal Cortada, Josep	29	18	9	Instituto de Investigaciones Biomédicas August Pi i Sunyer	Barcelona
 Zorzano Olarte, Antonio	15	10	6	Fundación privada Instituto de Recerca Biomédica (IRB- Barcelona)	Barcelona

## Clinical guidelines and consensus documents

- Female Pattern Hair Loss and Androgen Excess: A Report from the Multidisciplinary Androgen Excess and PCOS Committee. Carmina E, Azziz R, Bergfeld W, Escobar-Morreale HF, Futterweit W et al., *J Clin Endocrinol Metab.* 2019; 104:2875–2891.
- Criterios de derivación para pacientes a las unidades de lípidos de la Sociedad Española de Arteriosclerosis. Sánchez-Chaparro MA., Pérez-Martínez P, Ibarretxe D, Suárez-Tembra M y Valdivielso P, en nombre del Grupo de Trabajo de las Unidades de Lípidos de la Sociedad Española de Diabetes. *Clin Investig Arterioscler.* 2019;31(1):26-30.
- Indicaciones de los inhibidores de PCSK9 en la práctica clínica. Recomendaciones de la Sociedad Española de Arteriosclerosis (SEA), 2019. Ascaso JF, Civeira F, Guizarro C, López Miranda J, Masana L, et al., *Clin Investig Arterioscler.* 2019;31(3):128-139.
- Estándares SEA 2019 para el control global del riesgo cardiovascular. Mostaza JA, Pintó X, Armario P, Masana L, Ascaso JF y Valdivielso P, en nombre de la Sociedad Española de Arteriosclerosis. *Clin Investig Arterioscler.* 2019;31(S1):1-43.
- Recomendaciones del grupo GARIN para el tratamiento dietético de los pacientes con enfermedad renal crónica. Alhambra Expósito MR, Molina Puerta MJ, Oliveira G, Arraiza Irigoyen C, Fernández Soto C et al., en representación del grupo GARIN (Grupo Andaluz de Revisión e Investigación en Nutrición, comisionado por Sociedad Andaluza de Nutrición y Dietética,). *Nutr Hop.* 2019;36(1):183-217.
- Documento de abordaje integral de la diabetes tipo 2. Grupo de trabajo de Diabetes de la Sociedad Española de Endocrinología y Nutrición, versión 2019.2. Reyes-García R, Moreno Pérez C, Tejera-Pérez C, Fernández-García JC, Bellido-Castañeda V, et al., en representación del Grupo de trabajo de Diabetes-SEEN.

## Patents owned by CIBER

### Patent applications:

- Succinate as a biomarker for selecting a bariatric surgical procedure and for predicting type 2 diabetes remission after bariatric surgery

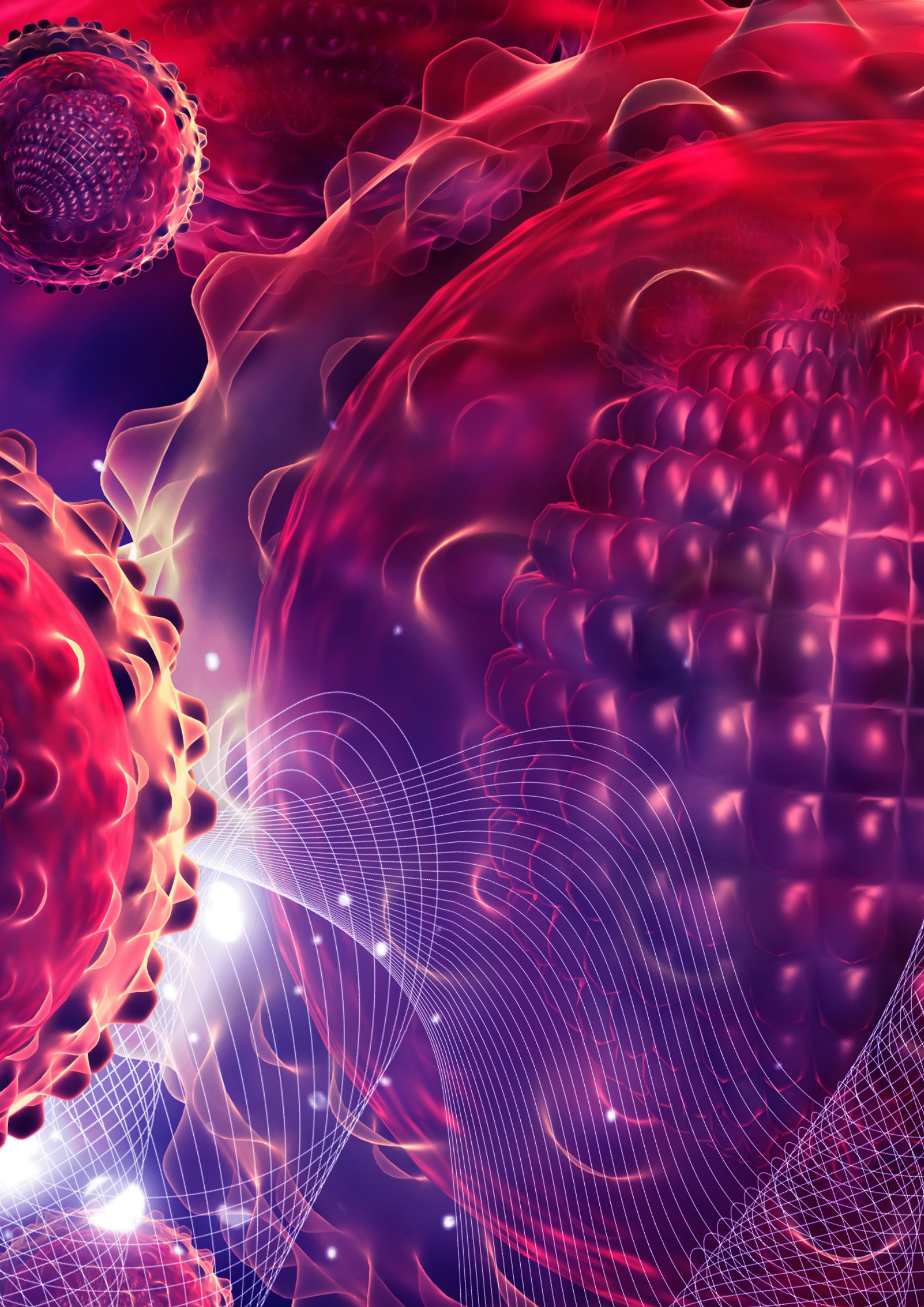
### PCT applications:

- 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

# **Liver and Digestive Diseases**

*čiberehd*







# Presentation by the Scientific Director

**Jordi Bruix Tudó**



In 2019, the constant approach of high-level scientific activity continued, with numerous publications in high-impact journals. In many cases, the results obtained have had a direct impact on patients' health care. This translation evidences the consolidation of the CIBEREHD as a powerful research structure with significant benefit for the community. All of this was accomplished despite budgetary difficulties and the limitations to make new hires.

The annual report sets forth the most relevant results in the various CIBEREHD Programmes where we are able to witness the progressive increase in collaborative studies with international impact in all the programmes both in Spain and abroad. Interestingly, international collaborations are frequently led by researchers from the CIBEREHD, bringing international recognition as a result.

Research has been relevant in basic aspects but, as has been highlighted, the most significant aspect has been in the translation to patients affected by liver and digestive diseases. Various clinical practice guidelines based on scientific evidence have been published, as well as consensus documents defining the criteria and methods that must be followed in both basic and clinical research.

Scientific Management and the Management Committee as a whole continue to implement the four-year action plan although the description of the activity has been redesigned based on collaborative projects. Generational renewal and genderbalancing has been ongoing on all levels. Moreover, we continue to identify young researchers with scientific career ambitions in order to guarantee maintenance of research culture in Biomedicine.

# Programmes

## **PROGRAMME 1. Liver injury mechanisms / evolution into advanced cirrhosis and transplantation**

**Coordinator:** Rafael Bañarés Cañizares

The activity of Programme 1 during 2019 has maintained its development within the strategic orientation of the CIBEREHD. Worth noting is the breadth of its research activity which covers practically all liver diseases (viral hepatitis, metabolic diseases, liver damage due to alcohol, complications of cirrhosis), excluding liver cancer.

Among the priority strategic lines, the promotion of international relations stands out; as in previous years, collaborations with groups from other countries have been strengthened in the setting of different European consortia and projects, evidencing the programme's internationalisation capacity. The groups of the programme have been able to maintain their own lines of project financing and recruitment of human resources in competitive calls, allowing the critical mass of the programme to be maintained.

From the standpoint of collaboration between groups in the programme, the development of cooperative studies in the clinical field has been ongoing. Nevertheless, the generation of a network of basic researchers, through specific strategic actions by the CIBEREHD, has been striking. Specifically, the development of a mouse model with humanized liver is enabling different experimental approaches based on that model; also, the network established for research into the role of extracellular vesicles has furthermore obtained some relevant scientific results of forthcoming publication. Similarly, the frequent presence of collaborative studies between basic and clinical scientists has been maintained and, as 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 specialty, 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 undermining the importance of all the scientific results of the programme, the large cooperative clinical studies in patients with complications of cirrhosis in the form of variceal bleeding or ascites decompensation should be highlighted. The National Hepatitis Plan has already ended, but the activity carried out continues to lead to generate publications describing how to refine the follow-up of patients with resolved infection. Interestingly, in patients with cirrhosis, it has been found that the risk of cancer does not disappear, making it necessary to maintain a structured follow-up. The presence of certain mutations in non-coding regions of the genome has been reported to be significantly more frequent in patients with severe forms of infection, such as fibrosing cholestatic hepatitis. Finally, we highlight the analysis of the mechanism that delta virus uses to escape the host's immune response.

The CIBEREHD Management has promoted a strategic analysis to assess the future of groups dedicated to hepatitis at a time when the cure of hepatitis C is feasible but still requiring research into the mechanisms of progression or regression of the liver disease once the virus has been eliminated.

## **PROGRAMME 2. Gastrointestinal Physiopathology: inflammatory bowel disease and motility disorders**

**Coordinator:** Pere Clavé Civit

This program includes digestive diseases of great prevalence and impact on the health and quality of life of the population, structured in 3 main lines: a) Oesophageal-gastroduodenal pathology; b) Inflammatory Bowel Disease; and c) Neuro-gastroenterology, alterations of digestive motility and functional disorders. Knowledge of the pathophysiology, diagnosis, epidemiology, prevention and treatment of these diseases is furthered through cooperative and multidisciplinary research among researchers in clinical, basic and epidemiological approaches.

- **Oesophageal-gastroduodenal pathology.**

The novelties of 2019 in this area focus on the development of pharmacological strategies and strategies for the eradication of helicobacter pylorii infection in cases of resistance to first-line treatments. Also noteworthy are the publications led by CIBEREHD researchers of the studies from the European Registry on the management of Helicobacter pylori infection (Hp-EuReg), which make it possible to start developing a map of response to treatment and resistances with a European perspective. The study of the adverse effects of non-steroidal anti-inflammatory drugs in peptic disease and its complications (mainly gastrointestinal bleeding) continues to occupy a relevant place, as well as new studies on the molecular basis of oesophageal-gastric cancer.

- **Inflammatory Bowel Disease.**

This continues to be the most productive line in this area. Research is aimed at the primary causes of immune dysfunction and recognition of the genetic and environmental determinants conditioning the phenotypic development of each IBD, the development and assessment of new diagnostic methods and methods for monitoring the disease, as well as the development of new treatments. The results for 2019 are very relevant, with the publication of multiple studies and clinical trials comparing the effectiveness and safety of different immune modulation treatments in different stages of the disease (active/) and the appearance of studies evaluating the results of surgical treatment in refractory forms. We also highlight the evaluation of the role of different components of the innate immune system in the pathophysiology and therapeutic potential of IBD. This line also includes research projects related to celiac disease and other diarrheic syndromes of high prevalence about which little is known, such as those arising post-cholecystectomy. Celiac disease has gained momentum with the incorporation of an expert group in this disease, and in 2020 a strategic action will be launched to establish epidemiological, diagnostic and follow-up aspects in collaboration with other CIBER areas

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

These disorders have a prevalence of 15% in the general population. Oropharyngeal Dysphagia (OD) affects 50% of patients who have suffered a stroke, neurodegenerative diseases and frail elderly persons. In 2019, the evaluation of the effect of different dietary and nutritional aspects on oropharyngeal and gastrointestinal function, especially biological and sensory responses to intake, and the role of exclusion

diets in IBS has been maintained. Post-infectious IBS and the role probiotics have occupied another significant group of studies, as well as the analysis of epithelial dysfunction in IBS-D from a basic standpoint. As regards oropharyngeal motility, the studies –both clinical and basic- are aimed at the development of active pharmacological treatments using oropharyngeal receptor agonists TRPV1, TRPA1 and TRPM8, and compensatory strategies called “Minimal-Massive Intervention” for the management of oropharyngeal dysphagia.

## PROGRAMME 3. Hepatic and Digestive Oncology

**Coordinator:** Bruno Sangro Gómez-Acebo

Hepatobiliopancreatic and digestive system cancer is a frequent cause of death in the general population, representing a high burden of care in hospitals and health centers, and very high healthcare and pharmaceutical costs. This has led CIBEREHD to include a programme dedicated to this pathology. Its approach goes beyond the programme itself, however, and involves various CIBEREHD groups in transversal lines of work focused on partial aspects of the problem, with knowledge being contributed from the fields of molecular biology, genetics, immunology, epidemiology or clinical intervention.

Studies in liver cancer have continued to analyse the incidence of cancer after viral cure, showing that oncogenic risk remains unchanged in patients with cirrhosis. Following the line investigating the potential association between treatment and the elimination of HCV and the recurrence of hepatocellular carcinoma, a collaborative study has been published that suggests that the presence of uncharacterized nodules in patients with HCV cirrhosis could represent a factor of risk for the development of hepatocellular carcinoma in the context of treatment.

CIBEREHD researchers have led studies with various immunomodulatory molecules for the treatment of hepatocellular carcinoma, and studies have been launched to understand the resistance to this option and identify predictors of favorable response. Unfortunately, no predictive parameter has been identified despite the various misleading suggestions that have been advertised in both specialized journals and the general media.

In the field of colorectal cancer, the level of output of quality publications has been maintained, both in relation to population screening programs as well as familial risk. This has been the result of clinical research associated with genetic analysis in collaboration with various CIBEREHD groups or from other areas.

Finally, the research activity in cholangiocarcinoma has been consolidated with the identification of circulating metabolites that could serve as markers for the early diagnosis of the disease in patients with primary sclerosing cholangitis, a pre-cancerous entity, and for the distinction between the histology of cholangiocarcinoma or hepatocellular carcinoma in small-sized nodules of cirrhotic livers.



# Training Programme

**Coordinator:** Xavier Forns Bernhardt

The basic philosophy of the CIBEREHD is to promote the training of young researchers facilitating the following:

- Short stays in other centres to acquire specific knowledge considered priority for the CIBEREHD.
- Attendance to meetings to improve their training and be able to interact with experts in their area of research.

As regards grants for CIBEREHD researchers to carry out short stays in national (CIBER) or foreign (European) centres, those between CIBER centres have been strengthened. Basically, they have focused on the following:

- Learning new techniques that represent an advance in a specific field.
- Training exchanges in the context of European projects in which CIBEREHD groups participate.
- Collaborative intra-CIBER works that require technological exchange, data analysis or study design.
- Training in a specific area for young researchers, which cannot be carried out at the requesting centre.

Regarding grants for young CIBEREHD researchers to attend meetings (in Spain or Europe) with a specific programme and clearly related to their area of research, priorities have been established, which are summarized as follows:

- Grants for basic researchers.
- The grants cover registration, accommodation and travel expenses with a maximum ceiling of €2,500 (ISCIII Tables must be complied with).
- No grants have been awarded for attendance to national or international conferences covering the entire specialty (AEEH, EASL, UEGF, AGA, AASLD.).

## Summary of training grants awarded in 2019. Groups which have benefited by programme.

### CIRRHOSIS

PI	Foreign	National	PI	Foreign	National
A. Albillos			J.M. Mato		● ●
P. Ginés	●		A. Pares		
R. Bañares			Juan Ignacio Esteban		
García Pagan			Rafael Esteban		
J. Genescà			Xavier Forns		
C. Guarner			Jordi Gómez		●
R. Andrade			Javier García-Samaniego		
R. Francés		● ●	Manuel Romero	●	
J. Castell			Juan Ignacio Esteban		●
Fdez-Checa			M. Navasa		
M. Navasa			M. de la Mata		
Glz-Gallego			M. Berenguer		
Martín Sanz			Juan Ignacio Esteban		

### GASTROENTEROLOGY

PI	Foreign	National
F. Azpiroz		
X. Calvet		
Domènech		
P. Clavé		
Esplugues		
A. Lanas		
Julià Panés		
Pérez-Gisb		●
Sanchez M.		
M. Esteve		

### ONCOLOGY

PI	Foreign	National
J. Bruix		
Bujanda		
Castells		
Garcia-M		
M. Pastor	●	
Sangro		
Fabregat		
Cascante		
C. Armengol		

# Platforms

## Bioinformatics Platform

**Coordinator:** Juanjo Lozano Salvatella

The Bioinformatics platform is actively collaborating in the operation of this CIBER, with 2019 being a successful year, as reflected in the 20 publications resulting from its support. The collaboration established with the colon cancer area has generated a very relevant publication related to the development of a genetic signature that increases the power to detect hemoglobin levels:

- *Identification and Validation of MicroRNA Profiles in Fecal Samples for Detection of Colorectal Cancer*. Duran-Sanchon S, Moreno L, Augé JM, Serra-Burriel M, Cuatrecasas M, Moreira L, ... Castells A. *Gastroenterology*. 2020 Mar;158(4):947-957.e4. doi: 10.1053/j.gastro.2019.10.005. Epub 2019 Oct 14

As part of a team of researchers from 24 institutions -including CIBEREHD- and organisations from nine European countries, coordinated and led from Barcelona by the European Foundation for the Study of Chronic Liver Failure (EF Clif), the blood metabolic signature - or "molecular signature" - of Acute on Chronic Liver Failure (ACLF) has been identified:

- *Blood metabolomics uncovers inflammation-associated mitochondrial dysfunction as a potential mechanism underlying ACLF*. Moreau R, Clària J, Aguilar F, Fenaille F, Lozano JJ, Junot C, ... V, Angeli P; j Hepatol. 2019 Nov 25. pii: S0168-8278(19)30696-8. doi: 10.1016/j.jhep.2019.11.009. [Epub ahead of print]

Collaboration with CIBEREHD groups and other national and international groups continues to generate highly relevant publications. In the area of inflammation in liver disease we have the following:

- *Defective HNF4 $\alpha$ -dependent gene expression as a driver of hepatocellular failure in alcoholic hepatitis*. Argemi J, Latasa MU, Atkinson SR, Blokhin IO, Massey V, Gue JP, ... Bataller R. *Nat Commun*. 2019 Jul 16;10(1):3126. doi: 10.1038/s41467-019-11004-3.

## e-CATCH

**Coordinator:** Jordi Bruix Tudó

During 2019, there was a lack of activity on the platform with no consultations regarding patients made.

The platform has been maintained as an instrument to share images and documentation of studies led by researchers from the Liver Cancer group and also involving the participation of other CIBER groups in other locations.

By becoming an instrument for research in liver cancer studies, the decision was taken to redefine the platform adding it as a research instrument of the Liver Cancer team and canceling the activity of providing second opinions and diagnostic / therapeutic advice.

## Hepa-C

**Coordinator:** Xavier Forns Bernhardt

In 2019, a significant number of patients continued to be registered, although given the high cure rate, the analysis to be carried out will require prolonged follow-up with publications being delayed. Currently, a cohort of more than 12,000 patients is available, which constitutes high-value epidemiological material.

## Registry of Vascular Liver Diseases. REHEVASC

**Coordinator:** Juan Carlos García Pagán

The REHEVASC platform has been running since September 20, 2011. It is a Registry of patients diagnosed with 4 Hepatic Vascular diseases 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-tumoural 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 their diagnosis and treatment and to be able to carry out collaborative studies that allow furthering our knowledge of these diseases.

In 2019, new patients were diagnosed and registered in the following proportions:

- PVT: 35 patients, obtaining a final register of 374 pacientes in 2019 .
- IPH: 10 patients, obtaining a final register of 153 patients in 2019.
- BCS: 5 patients, obtaining a final register of 93 patients in 2019.
- CHF: No new patients have been diagnosed with a final register of 11 patients in 2019.



There are currently 20 reference hospitals nationwide involved in attempting to diagnose this type of patients.

1. Hospital Universitario y Politécnico La Fe
2. Hospital Virgen de la Salud, Toledo
3. Hospital Universitario Puerta de Hierro
4. Hospital Universitario Ramón y Cajal
5. Clínica Universidad de Navarra
6. Hospital Clínic de Barcelona
7. Hospital Santa Creu i Sant Pau
8. Hospital Universitario Gregorio Marañón
9. Hospital Universitario Arnau de Vilanova
10. Hospital Universitario Central de Asturias (HUCA)
11. Hospital Universitario de Canarias
12. Hospital Universitario Marqués de Valdecilla
13. Hospital Universitario San Cecilio
14. Hospital Universitario Son Espases
15. Instituto universitario Dexeus
16. Complejo Hospitalario Universitario de Albacete
17. Hospital del Mar Hospital del Tajo, Aranjuez
18. Hospital Germans trias i Pujol
19. Hospital Parc Taulí, Sabadell
20. Hospital Broggi (colaboración con HCB, derivación pacientes para registro)

# Scientific Production

## Publications

### No. of publications in 2019

TOTALS	754
Q1	441
D1	244

### Collaborative Publications

CIBEREHD	188
CIBER*	146

\*Among various thematic areas

### Evolution of publications 2010-2019



## 10 most relevant publications by impact factor

IF	Publication
59,102	VILLANUEVA C., ALBILLOS A., GENESCA J., GARCIA-PAGAN J.C., CALLEJA J.L., ARACIL C. ET AL. <i>β blockers to prevent decompensation of cirrhosis in patients with clinically significant portal hypertension (PREDESCI): a randomised, double-blind, placebo-controlled, multicentre trial. The Lancet. 2019;393(10181):1597-1608.</i>
43,07	DUAN Y., LLORENTE C., LANG S., BRANDL K., CHU H., JIANG L. ET AL. <i>Bacteriophage targeting of gut bacterium attenuates alcoholic liver disease. Nature. 2019.</i>
32,274	ANDRADE R.J., CHALASANI N., BJORNSSON E.S., SUZUKI A., KULLAK-UBLIK G.A., WATKINS P.B. ET AL. <i>Drug-induced liver injury. Nature Reviews Disease Primers. 2019;5(1).</i>
25,455	HUYGHE J.R., BIEN S.A., HARRISON T.A., KANG H.M., CHEN S., SCHMIT S.L. ET AL. <i>Discovery of common and rare genetic risk variants for colorectal cancer. Nature Genetics. 2019;51(1):76-87.</i>
23,57	BANALES J.M., HUEBERT R.C., KARLSEN T., STRAZZABOSCO M., LARUSSO N.F., GORES G.J.. <i>Cholangiocyte pathobiology. Nature Reviews Gastroenterology and Hepatology. 2019.</i>
23,57	BRUIX J., DA FONSECA L.G., REIG M.. <i>Insights into the success and failure of systemic therapy for hepatocellular carcinoma. Nature Reviews Gastroenterology and Hepatology. 2019.</i>
23,57	GRACIA-SANCHO J, MARRONE G, FERNÁNDEZ-IGLESIAS A. <i>Hepatic microcirculation and mechanisms of portal hypertension. Nature reviews. Gastroenterology &amp; hepatology. 2019.</i>
23,57	BARKUN A.N., ALMADI M., KUIPERS E.J., LAINE L., SUNG J., TSE F. ET AL. <i>Management of nonvariceal upper gastrointestinal bleeding: Guideline recommendations from the international consensus group. Annals of Internal Medicine. 2019;171(11):805-822.</i>
19,233	PUIG I., LOPEZ-CERON M., ARNAU A., ROSINOL O., CUATRECASAS M., HERREROS-DE-TEJADA A. ET AL. <i>Accuracy of the Narrow-Band Imaging International Colorectal Endoscopic Classification System in Identification of Deep Invasion in Colorectal Polyps. Gastroenterology. 2019;156(1):75-87.</i>
19,233	KARIMZADEH H., KIRATHE M.M., OBERHARDT V., SALIMI ALIZEI E., BOCKMANN J., SCHULZE ZUR WIESCH J. ET AL. <i>Mutations in Hepatitis D Virus Allow It to Escape Detection by CD8 + T Cells and Evolve at the Population Level. Gastroenterology. 2019;156(6):1820-1833.</i>

## CIBEREHD Groups. Publications in 2019

Group Leader	Publ.	Q1	D1	Institution / Centre	Province
 Albillos Martínez, Agustín	28	15	12	Universidad de Alcalá	Madrid
 Andrade Bellido, Raúl	19	12	8	Fundación Pública Andaluza para la Investigación de Málaga en Biomedicina y Salud (FIMABIS)	Málaga
 Armengol Niell, Carolina	16	11	7	Fundación Instituto de Investigación Germans Trias i Pujol	Barcelona
 Azpiroz Vidaur, Fernando	18	9	2	Fundación Hospital Universitario Vall d'Hebron - Institut de Recerca (VHIR)	Barcelona
 Bañares Cañizares, Rafael	26	13	10	Servicio Madrileño de Salud	Madrid
 Berenguer Haym, Marina	21	6	6	Fundación para la Investigación del Hospital la Fe	Valencia
 Bruix Tudó, Jordi	20	15	12	Hospital Clínico y Provincial de Barcelona	Barcelona
 Bujanda Fernández de Pierola, Luis	58	41	26	Asociación Instituto Biodonostia	Guipuzcoa
 Calvet Calvo, Xavier	25	7	5	Corporación Sanitaria Parc Taulí	Barcelona

Group Leader	Publ.	Q1	D1	Institution / Centre	Province
 Cascante Serratosa, Marta	14	8	5	Universidad de Barcelona	Barcelona
 Castell Ripoll, José Vicente	9	8	4	Fundación para la Investigación del Hospital la Fe	Valencia
 Castells Garangou, Antoni	70	52	32	Hospital Clínico y Provincial de Barcelona	Barcelona
 Clave Civit, Pere	14	6	1	Fundación Privada Salud del Consorcio Sanitario del Maresme	Barcelona
 Domenech Morral, Eugeni	27	8	3	Fundación Instituto de Investigación Germans Trias i Pujol	Barcelona
 Esplugues Mota, Juan Vicente	19	13	5	Universidad de Valencia	Valencia
 Esteban Mur, Juan Ignacio	11	4	1	Fundación Hospital Universitario Vall d'Hebron - Institut de Recerca (VHIR)	Barcelona
 Esteban Mur, Rafael	19	12	8	Fundación Hospital Universitario Vall d'Hebron - Institut de Recerca (VHIR)	Barcelona
 Esteve Comas, María	19	8	5	Fundación Mutua Terrassa	Barcelona
 Fabregat Romero, María Isabel	5	4	1	Fundación IDIBELL	Barcelona
 Fernández-Checa Torres, José Carlos	21	16	11	Agencia Estatal Consejo Superior de Investigaciones Científicas	Barcelona
 Fondevila Campo, Constantino	30	17	11	Hospital Clínico y Provincial de Barcelona	Barcelona
 Forns Bernhardt, Xavier	21	10	6	Hospital Clínico y Provincial de Barcelona	Barcelona
 García Marín, José Juan	19	15	8	Universidad de Salamanca	Salamanca
 García Pagán, Juan Carlos	39	31	18	Hospital Clínico y Provincial de Barcelona	Barcelona
 García-Samaniego Rey, Javier	14	4	2	Servicio Madrileño de Salud	Madrid
 Genesca Ferrer, Joan	30	23	21	Fundación Hospital Universitario Vall d'Hebron - Institut de Recerca (VHIR)	Barcelona
 Gines Gibert, Pere	44	30	25	Hospital Clínico y Provincial de Barcelona	Barcelona
 Gómez Castilla, Jordi	11	6	0	Agencia Estatal Consejo Superior de Investigaciones Científicas	Granada
 González Gallego, Javier	11	7	3	Universidad de León	León
 Guarner Aguilar, Carlos	15	13	9	Instituto de Investigación del Hospital de Santa Cruz y San Pablo	Barcelona
 Lanas Arbeloa, Ángel	48	25	14	Fundación Instituto de Investigación Sanitaria Aragón	Zaragoza
 Martín Sanz, Paloma	1	1	1	Agencia Estatal Consejo Superior de Investigaciones Científicas	Madrid
 Mata García, Manuel de la Mata	17	8	3	Fundación para la Investigación Biomédica de Córdoba (FIBICO)	Córdoba
 Mato de la Paz, José María	45	32	15	CIC Biogune	Vizcaya
 Panés Díaz, Julian	22	11	10	Hospital Clínico y Provincial de Barcelona	Barcelona
 Pares Darnaculleta, Albert	22	16	9	Hospital Clínico y Provincial de Barcelona	Barcelona
 Pastor Anglada, Marçal	2	1	1	Universidad de Barcelona	Barcelona



Group Leader	Publ.	Q1	D1	Institution / Centre	Province
 Pérez Gisbert, Javier	53	17	11	Servicio Madrileño de Salud	Madrid
 Romero Gómez, Manuel	18	12	7	Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla	Sevilla
 Sánchez de Medina López Huertas, Fermín	15	10	5	Universidad de Granada	Granada
 Sangro Gómez-Acebo, Bruno Carlos	38	23	16	Universidad de Navarra	Navarra
 Zapater Hernández, Pedro	17	8	5	Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla	Alicante

## Associated clinical groups

Group Leader	Institution / Centre	Province
 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 Autónoma de Barcelona	Barcelona
 Crespo García, Javier	Instituto de Investigación Marques de Valdecilla	Cantabria
 Cubiella Fernández, Joaquim	Servicio Gallego de Salud	A Coruña
 García Monzón, Carmelo	Servicio Madrileño de Salud	Madrid
 Minguella 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)	Alicante
 Padillo Ruiz, Francisco Javier	Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla	Sevilla

## Patents owned by CIBER

### Patents granted

- *Bivalent reverse primer.*
- *Sistema y procedimiento para el diagnóstico mejorado de la Disfagia Orofaringea.*
- *Non-invasive method for the diagnosis or screening of colorectal cancer and/or pre-cancerous stage thereof.*
- *Biomarcadores no invasivos ccr.*
- *Methods for diagnosing and treating acute or chronic liver, kidney or lung disease.*
- *Method for predicting response to beta blocker.*
- *Lipid signatures for determining the outcome of embryo implantation during in vitro fertilization.*
- *Methods for diagnosing liver disease.*
- *Marcadores proteómicos de respuesta a fármacos anti-tnf en pacientes con enfermedad de Crohn.*

- *Nupr1 inhibition for treating cancer. Fecha: 31/05/2019.*
- *Compounds for the treatment of diseases caused by Helicobacter.*
- *Derivados de 4-fenildihidropiridina para el tratamiento y/o prevención de una infección o enfermedad causada por Helicobacter.*

## Patents applied for

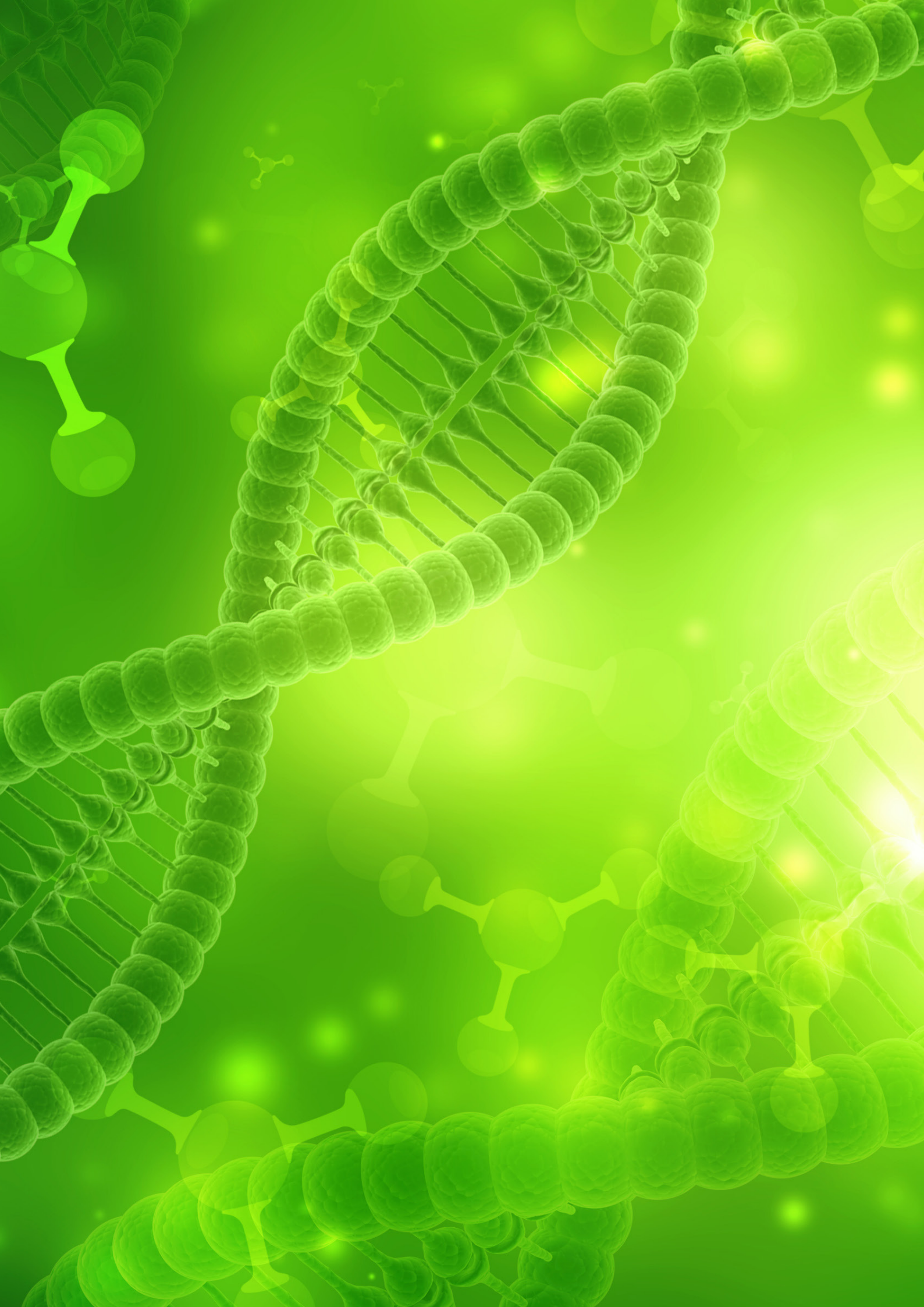
- *NUPR1 Inhibition for Treating Cancer.*
- *Derivados de ácido ursodecoxílico para el tratamiento de enfermedades hepáticas poliquísticas.*
- *Treatment of fibrosis and inhibition of fibrosis in non-alcoholic fatty liver disease patients.*
- *Methods for diagnosing and treating acute or chronic liver, kidney or lung disease.*
- *Method of treating colorectal cancer. Fecha:28/06/2018.*
- *Method of treating advanced colorectal adenoma.*
- *Human Porphobilinogen Deaminase Derived Proteins And Polynucleotides And Uses Thereof.*

## Clinical guidelines

- *Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C Virus infection in chronic kidney disease: Synopsis of the kidney disease: Improving global outcomes 2018 clinical practice guideline.*
- *Document de posicionament: Vies Clíniques Malalties Hepàtiques.*
- *Participation as an expert in the Darvadstrocel Evaluation report indicated for the treatment of complex perianal fistulas in patients with Crohn's disease.*
- *International Consensus on Diverticulosis and Diverticular Disease. Statements from the 3rd International Symposium on Diverticular Disease.*
- *Recommendations of the Spanish Working Group on Crohn's Disease and Ulcerative Colitis (GETECCU) on pouchitis in ulcerative colitis. Part 1: Epidemiology, diagnosis and prognosis.*
- *Alcohol-related liver disease. Clinical practice guidelines. Consensus document sponsored by AEEH.*
- *Elimination of hepatitis C. Positioning document of the Spanish Association for the Study of the Liver (AEEH).*
- *Recommendations for the detection, diagnosis and follow-up of patients with non-alcoholic fatty liver disease in primary and hospital care.*
- *Consensus document for the evaluation of donors with positive hepatitis c virus serology.*
- *Functional Constipation Guidelines Working Group. European Society of Neurogastroenterology and motility guidelines on functional constipation in adults.*

# **Rare Diseases**

*ciberer*





# Presentation by the Scientific Director

**Pablo Lapunzina**



Welcome to this new edition of the Scientific Annual Report, where we have the opportunity to present the results of the scientific and translational activity carried out by the research groups in the area of Rare Diseases (RD), whom I thank for their excellent work and dedication.

Once again, I want to highlight the essential role of patient associations as active partners who work on the front line to give support and make the voices of those affected heard, both through our Patient Advisory Board, as well as through our External Scientific Advisory Committee.

At CIBERER we actively work to achieve the IRDiRC objectives, specifically in achieving 1,000 treatments for RDs. Proof of this are the 10 orphan drug designations of which we act as a sponsor.

As regards progress in the diagnosis of RDs, I highlight the Programme for Undiagnosed Rare Diseases (ENoD). This is a transversal programme with a multidisciplinary and collaborative management model that currently collects clinical data from more than 400 patients with a diagnostic rate of 29%.

CIBERER participates in several strategic European programmes and projects in the field of RD: the European Joint Programme on Rare Diseases, on the one hand, which is the European program for the improvement of research, data use and translation in RD. Special mention should also be made of the work carried out by the Orphanet España team, coordinated by CIBERER and an essential tool in the field of RD at the international level.

Lastly, I would like to stress the urgency of implementing a National Plan for Genomic Medicine, and the recognition of the specialty of Clinical Genetics as both are essential steps for the results of our research to result in an improvement in the healthcare, diagnosis and search for therapies for those affected.

# Programmes

## Translational Genomic Medicine Programme

**Coordinator:** Ángel Carracedo Álvarez

In 2019, the Translational Genomic Medicine Programme was created with one of the main objectives being the implementation of the new genomic medicine and other omics applications to the diagnostic practice of hospitals. This group emerged from the former Genetic Medicine programme and has been reduced to only 5 of the original 10 groups. Among the main milestones in 2019, we highlight several relevant studies such as the one by Joaquín Dopazo, who has led a study published in Cancer Research on genomic big data in which 9,428 samples from 25 types of cancer have been analyzed to reveal metabolic modules whose individual or coordinated activity predicts the type of cancer and the evolution of the disease, also opening doors to new therapeutic opportunities. This same CIBERER group, together with the group led by Marcela del Río, has identified a common genetic signature in three rare skin diseases or genodermatosis (recessive dystrophic epidermolysis bullosa, Kindler syndrome and xeroderma pigmentosum).

Lastly, we highlight the Annual Scientific Meeting of the programme organised on March 13 in El Escorial, Madrid in which the coordinator Ángel Carracedo commented on the lines of work of this new area and the 1 million genomes initiative.

## Mitochondrial and Inherited Metabolic Medicine Programme

**Coordinator:** Rafael Artuch Iriberry

This programme works to improve knowledge of inherited metabolic diseases, and has achieved several relevant findings, such as:

- Identification of 5 molecules with the ability to reverse coenzyme Q deficiency thanks to a high-throughput screening method in a yeast model. DOI.org/10.1177/2472555219877185.
- Participation of CIBERER groups in the first liver transplant for the treatment of mitochondrial neurogastrointestinal encephalopathy (MNGIE) in Spain, carried out at the Vall d'Hebron Hospital in Barcelona.

- Demonstration of the potential of administered amino acid L-serine to improve neuronal function in a patient with a glutamate receptor mutation associated with atypical Rett syndrome with severe encephalopathy. DOI: 10.1126 / scisignal.aaw0936.
- Characterisation of the structure of one of the LAT family transporters. Mutations of these transporters are associated with diseases such as autism, cystinuria, etc. DOI: 10.1038 / s41467-019- 09837-z.
- Discovery of a new leukodystrophy, a childhood disease that leads to severe disability and death in some cases. DOI: 10.1172 / JCI123959.
- Description of the importance of a mitochondrial protease, the lack of which causes symptoms similar to Leigh's syndrome. DOI: 10.1073 / pnas.1811938116.

In 2019, the groups of this programme have obtained a multitude of projects both in Spain and abroad, but the projects promoted by patients as well as an internal collaborative project deserve special mention:

- The Spanish Federation of Rare Diseases has recognized, among others, a work led by M<sup>re</sup> Luz Couce on undiagnosed RDs.
- The Ramón Areces Foundation finances, among others, a project led by Cristina Fillat, in which Antonia Ribes also participates, for gene therapy to correct glutaric aciduria type I in murine models; and a project led by Juan Antonio García Ranea on systems medicine applied to the identification of new therapeutic targets in RD of genetic origin where programme groups like Belén Pérez's and Tomàs Pinós's participate.

The Research Programme (Pdl) stands out for its scientific-dissemination activity. As an example, we highlight the meeting on neurotransmitter diseases in collaboration with the De Neu Patient Association with Eduardo López-Laso and Àngels García-Cazorla, the GLUTIDS Congress which brought together the association of those affected and the researchers Belén Pérez, Rafael Artuch, Àngels Garcia Cazorla Alfons Macaya, M<sup>re</sup> Luz Couce, Luis González Gutiérrez-Solana and Eduardo López Laso. Another example is the meeting organised by the group led by Plácido Navas, which had the objective of agreeing on the reference values of Coenzyme Q10 levels (CoQ10) in fibroblast samples, with the participation of Rafael Artuch, Belén Pérez and Antonia Ribes, among others.

Finally, an informative video has been released to highlight how organisations of those affected collaborate with researchers in the search for a diagnosis of mitochondrial disorders. Miguel Ángel Martín has participated in this project.

## Neurological Disorders Programme

**Coordinator:** Pia Gallano Petit

This Research Programme, created in 2019, is made up of 7 groups from different fields, from clinical genetics, molecular genetics and molecular and cellular physiology, specialised in multiple rare neuromuscular and neurological pathologies, both of genetic and acquired origin.

The groups that make up the Programme have obtained important scientific, dissemination and collaboration results with patient associations.

Regarding the development of genomic diagnostic tools and the discovery of new genes, worth mentioning are the multiple funded research projects on the genomics of neuromuscular pathologies, such as Spinal Muscular Atrophy and Myopathies, developed by the group led by Pia Gallano. Also, the research projects on diagnostic biomarkers, highlighting the activity of the group led by Eduard Gallardo.

From a therapeutic point of view, for example, the publication in Experimental and Molecular Medicine, led by Pascual Sanz together with the group of José María Millán, in which metformin has been shown to relieve motor and neuropsychiatric symptoms of Huntington's disease in murine models stands out.

In this regard, the activity of the group led by José Serratosa also deserves mentioning. In the search for therapies for Lafora disease, together with Pascual Sanz and 3 other international groups, they participate in a project to search for a cure for Lafora disease financed with \$ 9.8 million by the National Institutes of Health (NIH). As part

of this project, they participated in the 5th International Meeting on Lafora disease, held from 9 to 11 September in Alcalá de Henares.

At the international level, we highlight the presence of Josep Dalmau on the list of the most cited scientists in the world in 2019 published by Clarivate Analytics, a former branch of the Thomson Reuters agency dedicated to intellectual property and science.

At the clinical level, the high level of activity of the groups led by Eduard Gallardo and Teresa Sevilla stands out. Their units belong to both the Centres, Services and Reference Units (CSUR) of the Spanish National Health System (SNS) and the European Reference Networks (ERN) of the European Union, being benchmarks in their field at the national and international level.

Also worth mentioning is the important activity of the groups of the Programme regarding Registries: Spanish Registry of Neuromuscular Diseases NMD-ES, Registry of Mitochondrial Diseases (in collaboration with AEPMI Association of Patients with Mitochondrial Pathologies and the Ana Carolina Díaz Mahou Foundation) and the McArdle Registry (EUROMAC).

In the area of transfer, it should be noted that the EpiDisease spin-off, led by José Luis García, researcher of Federico Pallardó's group, has been awarded the First Prize for Innovation at Eureka IIEC, an event promoted by innovation organisations and service providers between Australia and China.

This Research Programme stands out for its great rapport with patient associations, specifically with the Spanish Federation of Neuromuscular Diseases (ASEM Federation), with whom an agreement was signed in 2019. In addition, CIBERER was awarded the 2019 ASEM Prize, in recognition of its commitment to neuromuscular diseases.

## Paediatric and Developmental Medicine Programme

**Coordinator:** Cristina Fillat i Fonts

The main activities and results linked to the objectives defined in the 2019 Action Plan are summarized below.

Within the objective of promoting the development of genomic diagnostic tools for the diseases focussed on in the Programme:

- A study has been led that has identified genetic alterations involved in the development of large and giant congenital nevi based on data from the first series of Spanish patients characterized by massive sequencing and RNA-seq from the group coordinated by Susana Puig.
- A common genetic signature has been identified in three rare skin diseases prone to cancer from the group led by Marcela del Río in collaboration with the group of Joaquín Dopazo of the PoI of Genetic Medicine, which will make it possible, in the near future, to design effective and safe therapeutic approaches based on robust scientific evidence through a global analysis of gene expression.
- Genetic mutations in the muscle-specific exon of the FXR1 gene that cause a new congenital myopathy have been identified in an international study led by groups coordinated by Víctor Luis Ruiz-Pérez and Pablo Lapunzina.
- The genetic mutation causing lymphangiomatosis has been discovered, which opens the way for possible pharmacological treatments from the group led by Pablo Lapunzina and in which researchers from the group coordinated by Carmen Ayuso of the Sensorineural Pathology Research Programme have participated.



It has also been shown that an active substance present in green tea improves the cognitive functioning of people with fragile X syndrome in a collaborative study coordinated by the group led by Cristina Fillat with the participation of groups from other thematic areas of CIBER (CIBEROBN and CIBERSAM).

Furthermore, there are numerous individual publications of the groups within this line, described in more detail in the section of each group.

In addition, CIBERER has contributed to the training of health professionals and that of the general population through the organisation of various hospital sessions under the auspices of this Research Programme. It has also collaborated in training patients in the context of the second EURORDIS Summer School in Spanish, held in Castelldefels, Barcelona from June 10 to 16, with training on the diagnostic process at an informative level.

Also worth noting is the recognition by FEDER (Spanish Federation of Rare Diseases) of the networking carried out by the Paediatric Institute of Rare Diseases (IPER) of the Sant Joan de Déu Hospital in Barcelona, coordinated by Francesc Palau.

## Sensorineural Pathology Programme

**Coordinator:** Lluís Montoliu José

In 2019, the 7 groups that make up the Programme have obtained important scientific, dissemination and collaboration results with patient associations, both independently and in collaboration with other CIBERER groups.

At a scientific level, the development of new cell and animal models and RD therapies stand out with the publication in EMBO Molecular Medicine by Paola Bovolenta on a mouse model for the study of Bosch-Boonstra-Schaaf syndrome; José María Millán's publication in Experimental and Molecular Medicine, where they demonstrate that metformin alleviates the motor and neuropsychiatric symptoms of Huntington's disease in mice, and the publications of Isabel Varela-Nieto in FASEB Journal and ELife exploring the relationship between nutrition and hearing loss, or the role of DUSP1 phosphatase in hearing and aging, respectively.

Marta Cortón's research project, from the group led by Carmen Ayuso, applies diagnostic tools to the genetic characterisation of aniridia through genomic and experimental studies.

In 2019, all the groups in the programme participated in intramural projects and in five Working Groups (GdT), two of them coordinated by researchers from the Research Programme: "Genomic editing and gene therapy" led by Almudena Fernández, from Lluís Montoliu's group, and "Animal Models of human diseases" led by Silvia Murillo, from the laboratory of Isabel Varela-Nieto. The latter has published an informative video on the benefits of the responsible use of animals in research on rare diseases.

Events organised:

- II Practical Course on "Genomic Editing and Gene Therapy" July 1-2 at the National Centre for Biotechnology (CSIC), coordinated by Almudena Fernández, Óscar Quintana and Matías Morín.
- II Course on "Bioinformatic analysis of massive sequencing data applied to genetic diagnosis and translational research" held September 30 to October 9 at the Hospital Ramón y Cajal, coordinated by Miguel Ángel Moreno and Matías Morín.
- "III Conference on the Human Genome" organised by Miguel Ángel Moreno on November 13 at the Hospital Ramón y Cajal.

Isabel Varela-Nieto has been awarded the Morgagni Medal from the University of Padua (Italy) for her professional career in the study of hearing; Gemma Marfany has received the VI Distinction from the Faculty of Doctors and the Social Council of the University of Barcelona, for her activities in scientific dissemination; and Lluís Montoliu received the Scientific Dissemination Award from the Antama Foundation and the 12th ISTT Award from the International Society of Transgenic Technologies.

Lluís Montoliu published several popular science books in 2019: "Editando genes: recorta, pega y colorea" ("Editing genes: cut, paste and color"); (NextDoor Publishers), "¿Qué sabemos de...? El Albinismo" ("What do we know about ...? Albinism") (Catarata / CSIC) and the digital version of the book "What is albinism?"

Isabel Varela-Nieto has joined the European action COST 17103 Delivery of Antisense RNA Therapeutics, on therapies with antisense oligonucleotides.

The Annual Meeting of the Research Programme, organised by Gemma Marfany, took place at the Faculty of Biology of the University of Barcelona on December 3, which was attended by the President of Retina Asturias, Andrés Mayor.

## Endocrine Medicine Programme

**Coordinator:** Susan Webb Youdale

This Research Programme is made up of only three full-fledged research groups and a fourth associated group, hence the importance of incorporating the additional strength of the Linked Clinical Groups.

In 2019, among the publications of the groups associated with this Research Programme we highlight the work resulting from the collaboration between various groups of the programme within a translational medicine project financed by CIBERER in which different polymorphisms are described in the *POMC* gene in endocrine tumors "Why don't corticotroph tumors always produce Cushing's disease? Eur J Endocrinol. 2019 Sep; 181 (3): 351-361" by Webb y Picó.

This group also includes the review article focused on analysing the deficiencies in the care of people with diseases that alter normal development and sexual maturation "Addressing gaps in care of people with conditions affecting sex development and maturation. Nat Rev Endocrinol. 2019 Oct; 15 (10): 615-622" led by Dr. Moreno; the work done on Cushing's syndrome in both the quality of life of patients "Quality of Life in Patients With Cushing's Disease. Front Endocrinol (Lausanne). 2019 Dec 11; 10: 862 ", as well as on the results of the ERCUSYN registry focused on determining the causes of the highest mortality present in patients with Cushing syndrome "High mortality within 90 days of diagnosis in patients with Cushing's syndrome: results from the ERCUSYN registry . Eur J Endocrinol. 2019 Nov; 181 (5): 461-472" from Dr. Webb's group. Also, the work of the group led by Dr. Guadaño, focused on the development of a murine model for the study of human deficiency of *MCT8* "Adult Mice Lacking Mct8 and Dio2 Proteins Present Alterations in Peripheral Thyroid Hormone Levels and Severe Brain and Motor Skill Impairments. Thyroid. 2019 Nov; 29 (11): 1669-1682", the characterisation of the TRPM8 thermoreceptor in mouse brain thermoregulatory circuits "Expression of the cold thermoreceptor TRPM8 in rodent brain thermoregulatory circuits. J Comp Neurol. 2019 Apr 3" and the new entry route of thyroid hormones in the human fetal brain "Thyroid hormone availability in the human fetal brain: novel entry pathways and role of radial glia. Brain Struct Funct. 2019 Jul; 224 (6): 2103-2119." And finally, the description of a new mutation in the *AMRH2* gene related to persistent Müllerian duct syndrome from the group led by Dr. Moreno "A Novel Homozygous *AMRH2* Gene Mutation in a Patient with Persistent Müllerian Duct Syndrome. Sex Dev. 2019; 13 (2): 87-91".

In addition, we would like to highlight the award of the European Society of Endocrinology received by Dr. Webb. This prestigious award distinguishes clinical research in aspects of endocrinology at the forefront of clinical practice and is sponsored by the Clinical Endocrinology Trust.

# Inherited Cancer, Haematological and Dermatological Diseases Programme

**Coordinator:** Juan Antonio Bueren Roncero

In 2019, the groups of this research programme have continued working towards the IRDIRC objectives. In this sense, scientific events were promoted such as the scientific meeting of the programme, which took place at the IIB-Alberto Sols of the CSIC in Madrid in November, the 3rd forum of patients with red cell anemia due to pyruvate kinase deficiency organised in the Fundación Jiménez Díaz in Madrid on May 29, 2019, and the 17th European Meeting on Complement in Human Disease also organised in Madrid from September 14 to 17.

Regarding new discoveries applicable in diagnosis, the group led by Mercedes Robledo has identified a new gene involved in the development of a rare endocrine tumor. This new gene is involved in the Krebs cycle, *DLST*, which results in disease when mutated. We have also carried out an archeogenetics study led by researchers from the group led by Vicente Vicente where it has been discovered that a genetic alteration responsible for a rare disease, FXI deficiency, appeared 5,400 years ago and was distributed in different parts of Europe.

As regards therapeutic developments, this year has been quite prolific. We highlight the contributions made by Juan Bueren's group with the publication of the first results of the clinical trial on gene therapy in patients with Fanconi anemia in which the formation of blood cells of these patients from their own stem cells where the genetic defect has been previously corrected has been demonstrated for the first time; also, the results of preclinical research that has managed to correct the genetic defect in the blood stem cells of patients with Fanconi anemia through a novel way of editing the genome. We also highlight the results of the group led by Rosario Perona which has led a study that has discovered that a small 11 amino acid peptide (GSE4) attenuates the main pathological effects in cells of ataxia telangiectasia patients, and the demonstration by the team of Marcela del Río of the feasibility of a genomic editing strategy for recessive dystrophic epidermolysis bullosa (also known as butterfly skin) with the CRISPR / Cas9 tool in preclinical models of this disease.

# Training Programme

**Coordinator:** Luis Pérez Jurado

The CIBERER Training Programme has carried out its main actions in 2019 in three general lines:

- Courses: Organisation and calls for attendance grants.
- Organisation of training workshops held during the Annual Meeting.
- Mobility grants.

The third customary line, that of Predoctoral Grants, could not be implemented due to administrative limitations.

## Organisation of courses and calls for grants

The CIBERER Training Programme directly organised a course, with its own additional call for attendance grants. Three additional calls were made for attendance to courses with teaching coordination by CIBERER researchers and another for course attendance in collaboration with an association.

- II practical course on “Genomic editing and gene therapy”.

## Call for grants for course attendance

- EURORDIS SUMMER SCHOOL, 3rd Edition. One attendance grant was awarded.
- Bioinformatic analysis of massive sequencing data applied to genetic diagnosis and translational research. Four attendance grants were awarded.
- II Course on Personalised Genomic Medicine in clinical diagnosis. 7 attendance grants were awarded.
- Conference on Advances in Neonatal Screening. 2 attendance grants were awarded.

## Organisation of training workshops

The following training workshops were organised at the Annual Meeting:

- Project management workshop, focused on finding financing opportunities in competitive and non-competitive projects.
- Biobank workshop, focused on collection management.



## Mobility grants

In 2019, 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 was of transversal interest. Different researchers were thus able to benefit from this programme to extend their training and further the projects in which they were involved.

Number of mobilities: 3 positive resolutions, representing a decrease compared to the 11 granted in 2018. Of these, one was intramural, another international extramural and the third was awarded to a CIBER group from another thematic area. The following table shows the mobility operations carried out in 2019:

## Mobility operations carried out

Beneficiary	Issuing Group	Receiving Group
Verónica Palma Barqueros	IP: Vicente Vicente García	Molecular and Vascular Biology Centre (Leuven)
Carmen Grijota Martínez	IP: Ana Cristina Guadaño Ferraz	CIBERNED - Grupo: José Manuel García Verdugo
Verónica Palma Barqueros	IP: Vicente Vicente García	IP: Juan Antonio Bueren

# Platforms

## CIBERER Biobank

**Coordinator:** Federico Pallardó

The number of biological samples in the Biobank system continues to increase with a total this year of 1075 samples of 71 different pathologies (<http://www.ciberer-biobank.es>). During this year, the number of biological samples assigned has been a total of 107 (3 assignments). This clearly indicates that we have increasing visibility, partly because we are included in the European catalogue coordinated by Eurobiobank and also thanks to the Biobank website which was renewed in June, complying with the 7 recommendations of the National Biobank Network. We also focus on developing and offering new services for CIBERER researchers and this has meant that the number of services provided continues to increase annually. In 2019, 18 services were provided, 35% more than the previous year. A part of the assignments and services has been made to external groups and biotech companies, which brought in some revenue (€ 700).

We continue to maintain collaborations with Biobank networks. We are a member of the Valencian Network of Biobanks (since 2010) actively participating in different working groups. We were the Local Organizing Committee of the X National Congress of Biobanks held in October in Valencia and also of the Eurobiobank (since 2017), with a joint catalogue prepared in 2019. Collaboration agreements signed with Biobank IBSP-CV / FISABIO and Banco Nacional de ADN (DNA National Bank) have continued to be in force this year. Furthermore, we are part of a working group of the ISCIII National Biobank Network Platform, in the "PROCuRe" program".

Regarding agreements with the industry, two collaboration agreements are maintained with EpiDisease SL: the first within the framework of a "TEST ScoliPro®" project where the Biobank processes and stores the study samples and the second to determine the telomerase activity of lines of immortalized fibroblasts in the CBK. In addition, another collaboration with EpiDisease SL has also been initiated within the framework of a European project.

We have taken part in different media to disseminate our activity:

- European Researchers' Night organised at the CIPF.
- Participation in the World Day of Rare Diseases of the Autonomous Community of Valencia organised by la Alianza de Investigación Traslacional de Malalties Rares (Alliance for Translational Research of Rare Diseases) of the Autonomous Community of Valencia.
- XII Annual CIBERER Meeting.
- Workshop organised within the CIBERER Coordination Actions.
- X Congress of the National Network of Biobanks.
- Participation in an internal conference organised by FEDER-Valencia.

A total of 4 projects were applied for, of which only one has been resolved and awarded within the FIS Programme. Five 2018 projects have also been maintained: i) the ACCI-CIBERER Call, ii) the FEDER Funds 2018-2020 (Technological Innovation and Reinforcement of the Valencian Biobank Network- RVB) and iii) the National Plan project. These projects have secured a financing of € 69,000.

Publications:

- Phosphodiesterase Inhibitors Revert Axonal Dystrophy in Friedreich's Ataxia Mouse Model. Belén Mollá, Diana C. Muñoz-Lasso, Pablo Calap, Angel Fernandez-Vilata, María de la Iglesia-Vaya, Federico V. Pallardó, Maria-Dolores Moltó, Francesc Palau, Pilar Gonzalez-Cabo. *Neurotherapeutics*, 2019 Apr;16(2):432-449. doi: 10.1007/s13311-018-00706-z.

## BIER

**Coordinator:** Joaquín Dopazo Blázquez

During this year, the most relevant results have been the contribution to the EnoD project, in which, in addition to searching for potentially disease-causing SNVs, the search for structural variants has also been implemented. Furthermore, the database of genetic variability of the Spanish population (<http://csvs.babelomics.org/>) has grown to almost 2000 samples and has shown its usefulness for filtering local polymorphic variants in numerous studies, as well as bringing different researchers in contact, thus making the samples it contains discoverable. Furthermore, this "discoverability" has an international character since it is part of the GA4GH Beacon network (<https://beacon-network.org/>). It has also allowed the development of an imputation panel for the Spanish population. Lastly, the ACCI "Mathematical Models of Disease Mechanisms for Drug Reformulation in Rare Diseases" which uses mathematical models and artificial intelligence to semi-automatically propose drugs that are candidates for reuse constitutes a clear example of a paradigm shift in the research in rare diseases by proposing a mechanistic rather than a disease-based approach. Potential drugs have been proposed for Fanconi Anemia, Familial Melanoma, Retinitis Pigmentosa, Oculocutaneous Albinism, and Williams Syndrome. In the future this will expand to include more diseases.

## MAPER

In 2019, information for the MAPER database continued to be compiled, in addition to incorporating new specific data on research and healthcare resources useful for RDs and the future genomics plan. The data on research projects and clinical trials accessible through the MAPER website are as follows:

- 991 biomedical research projects included and 797 clinical trials compiled.
- 135 funding agencies participate in the financing of RD research.
- 630 Principal Investigators with at least 1 project or trial included in the database.
- Presentation of the results on February 28 at the Caixaforum in Madrid during the celebration of World Rare Diseases Day.

# Scientific Production

## Publications

### No. of publications in 2019

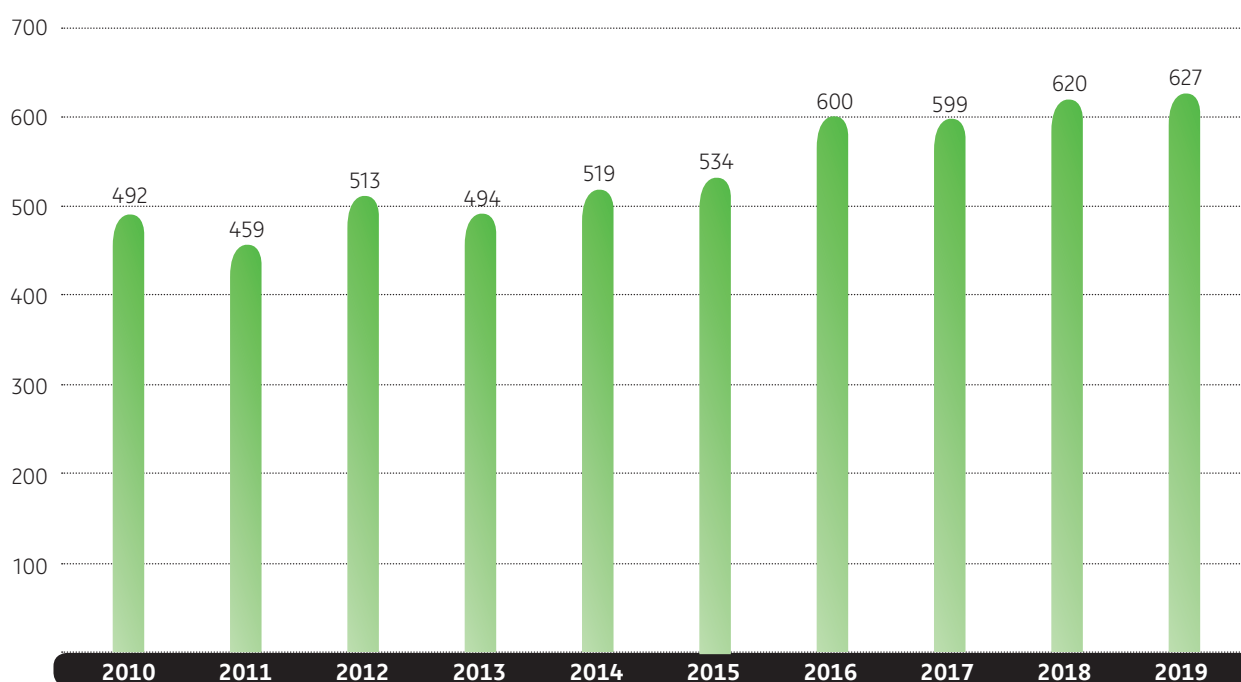
TOTALS	627
Q1	378
D1	164

### Collaborative Publications

CIBERER	108
CIBER*	12

\*Entre varias áreas temáticas

### Evolution of publications 2010-2019





## 10 most relevant publications by impact factor

IF	Publication
36,216	<i>Deficient Endoplasmic Reticulum-Mitochondrial Phosphatidylserine Transfer Causes Liver Disease.</i> 05. 177(4):881-895.e17. <i>Cell</i> .
28,349	<i>PROREPAIR-B: A Prospective Cohort Study of the Impact of Germline DNA Repair Mutations on the Outcomes of Patients With Metastatic Castration-Resistant Prostate Cancer.</i> 02. 37(6): 490-503. <i>J Clin Oncol</i> .
25,455	<i>Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder.</i> 01. 51(1): 63-75. <i>Nat Genet</i> .
25,455	<i>Association analyses of more than 140,000 men identify 63 new prostate cancer susceptibility loci.</i> 02. 51(2) :363 <i>Nat Genet</i> .
25,455	<i>Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Aβ, tau, immunity and lipid processing.</i> Sep. 51(9) :1423-1424. <i>Nat Genet</i> .
21,464	<i>Mapping the Global Chromatin Connectivity Network for Sox2 Function in Neural Stem Cell Maintenance.</i> 03. 24(3):462-476.e6. <i>Cell Stem Cell</i> 30849367 1875-9777 10.1016/j.stem.2019.02.004
21,464	<i>NHEJ-Mediated Repair of CRISPR-Cas9-Induced DNA Breaks Efficiently Corrects Mutations in HSPCs from Patients with Fanconi Anemia.</i> Nov. 25(5):607-621.e7. <i>Cell Stem Cell</i> . 31543367
21,126	<i>Elevated levels of Secreted-Frizzled-Related-Protein 1 contribute to Alzheimer's disease pathogenesis.</i> 08. 22(8): 1258-1268. <i>Nat Neurosci</i> .
17,943	<i>DYRK1A modulates c-MET in pancreatic ductal adenocarcinoma to drive tumour growth.</i> 08. 68(8):1465-1476.
17,943	<i>Systematic meta-analyses, field synopsis and global assessment of the evidence of genetic association studies in colorectal cancer.</i> Dec. <i>Epub. Gut</i> .

## CIBERER Groups. Publications in 2019

Group Leader	Publ.	Q1	D1	Institution / Centre	Province
 Antiñolo, Guillermo	5	1	0	Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla	Sevilla
 Artuch Iriberrí, Rafael	26	14	3	Fundación para la Investigación y Docencia Sant Joan de Deu	Barcelona
 Ayuso, Carmen	14	6	1	Instituto de Investigación Sanitaria Fundación Jiménez Díaz	Madrid
Bermejo Sánchez, María Eva (1)	6	2	1	Instituto de Salud Carlos III	Madrid
 Botella Cubells, Luisa María	6	4	1	Agencia Estatal Consejo Superior de Investigaciones Científicas	Madrid
 Bovolenta, Paola	6	5	4	Agencia Estatal Consejo Superior de Investigaciones Científicas	Madrid
 Bueren, Juan Antonio	8	6	2	Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas (CIEMAT)	Madrid
 Caballero Molina, María Teresa	13	4	1	Servicio Madrileño de Salud	Madrid
 Cardellach López, Francesc (2)	14	10	4	Hospital Clínico de Barcelona	Barcelona

Group Leader	Publ.	Q1	D1	Institution / Centre	Province
 Carracedo, Ángel	20	14	6	Universidad Santiago de Compostela	Santiago
 Castaño González, Luis	11	3	1	Asociación Instituto de Investigación Sanitaria de Biocruces	Vizcaya
 Cuezva, José Manuel	7	6	1	Universidad Autónoma de Madrid	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 Blazquez, Joaquin	4	4	2	Fundación Pública Andaluza Progreso y Salud	Sevilla
 Estévez Povedano, Raúl	5	1	0	Universidad de Barcelona	Barcelona
 Fillat, Cristina	11	9	2	Instituto de Investigaciones Biomédicas August Pi i Sunyer	Barcelona
 Gallano Petit, María Pia	8	3	0	Instituto de Investigación del Hospital de la Santa Cruz y San Pablo	Barcelona
 Garesse, Rafael	4	1	1	Universidad Autónoma de Madrid	Madrid
 Gratacos, Eduard	45	15	10	Hospital Clínico y Provincial de Barcelona	Barcelona
 Grinberg, Daniel	15	12	6	Universidad de Barcelona	Barcelona
 Guadaño Ferraz, Ana Cristina	4	2	2	Agencia Estatal Consejo Superior de Investigaciones Científicas	Madrid
 Illa Sendra, Isabel (3)	27	18	7	Instituto de Investigación del Hospital de la Santa Cruz y San Pablo	Barcelona
 Lapunzina Badía, Pablo Daniel	29	15	7	Servicio Madrileño de Salud	Madrid
 López Granados, Eduardo	1	1	0	Servicio Madrileño de Salud	Madrid
 Marfany Nadal, Gemma	1	1	0	Universidad de Barcelona	Barcelona
 Martí Seves, Ramon	12	6	0	Fundación Hospital Universitario Vall d'Hebron - Institut de Recerca (VHIR)	Barcelona
 Martín Casanueva, Miguel Ángel	24	17	6	Servicio Madrileño de Salud	Madrid
 Medina Torres, Miguel Ángel	8	6	3	Universidad de Málaga	Madrid
 Millán Salvador, José María	8	5	1	Fundación para la Investigación del Hospital la Fe	Valencia
 Montoliu Jose, Lluís	11	5	3	Agencia Estatal Consejo Superior de Investigaciones Científicas	Madrid
 Montoya Villarroya, Julio	12	9	6	Universidad de Zaragoza	Zaragoza
 Moreno Galdó, Antonio José	15	1	0	Fundación Hospital Universitario Vall d'Hebron - Institut de Recerca (VHIR)	Barcelona
 Moreno Pelayo, Miguel Ángel	5	4	2	Servicio Madrileño de Salud	Madrid
 Navas, Plácido	15	13	4	Universidad Pablo de Olavide	Sevilla
 Nunes, Virginia (4)	3	3	2	Fundación IDIBELL	Barcelona

Group Leader	Publ.	Q1	D1	Institution / Centre	Province
 Palacín, Manuel	5	5	4	Institut de Recerca Biomèdica de Barcelona (IRB-Barcelona)	Barcelona
 Palau Martínez, Francesc	7	5	1	Fundación para la Investigación y Docencia Sant Joan de Deu	Barcelona
 Pallardo Calatayud, Federico	5	4	0	Universidad de Valencia	Valencia
 Pérez González, María Belén	15	3	1	Universidad Autónoma de Madrid	Madrid
 Pérez Jurado, Luis	13	6	3	Universidad Pompeu Fabra	Barcelona
 Perona Abellón, Rosario	3	2	0	Agencia Estatal Consejo Superior de Investigaciones Científicas	Madrid
Posada de la Paz, Manuel	12	3	0	Instituto de Salud Carlos III	Madrid
 Puig Sardá, Susana	28	21	14	Servicio de Bioquímica y Genética Molecular del Hospital Clínico Barcelona	Barcelona
 Pujol Onofre, Aurora	7	7	6	Fundación IDIBELL	Barcelona
 Ribes, Antonia	6	4	0	Hospital Clínico y Provincial de Barcelona	Barcelona
 Robledo Batanero, Mercedes	28	22	12	Fundación Centro Nacional de Investigaciones Oncológicas	Madrid
 Rodríguez de Córdoba, Santiago	10	6	5	Agencia Estatal Consejo Superior de Investigaciones Científicas	Madrid
Rubio Zamora, Vicente (2)	4	3	1	Agencia Estatal Consejo Superior de Investigaciones Científicas	Valencia
 Ruiz Pérez, Víctor Luis	4	2	1	Agencia Estatal Consejo Superior de Investigaciones Científicas	Madrid
 Salido, Eduardo	8	6	4	Fundación Canaria de Investigación Sanitaria (FUNCANIS)	Tenerife
 Santos Hernández, Javier	3	0	0	Universidad Autónoma de Madrid	Madrid
 Sanz, Pascual	5	2	0	Agencia Estatal Consejo Superior de Investigaciones Científicas	Valencia
 Serratos, José	6	3	3	Instituto de Investigación Sanitaria Fundación Jiménez Díaz	Madrid
 Sevilla Mantecón, María Teresa	13	6	1	Instituto de Investigación Hospital UIP la Fe	Valencia
 Surrallés, Jordi	6	5	4	Universidad Autónoma de Barcelona	Barcelona
 Varela Nieto, Isabel	12	6	4	Agencia Estatal Consejo Superior de Investigaciones Científicas	Madrid
 Vicente García, Vicente	21	9	5	Fundación para la Formación e Investigación Sanitarias de la Región de Murcia (FFIS)	Murcia
 Webb, Susan	12	2	0	Instituto de Investigación del Hospital de la Santa Cruz y San Pablo	Barcelona

(1) Group decommissioned in 2019  
(2) PI replaced in 2020

(3) PI replaced in 2019  
(4) Group decommissioned in 2020

## Linked Clinical Groups

Group Leader	Institution / Centre	Province
Paediatric and Developmental Medicine Research Programme		
 Encarna Guillén	Hospital Virgen de la Arrixaca	Murcia
 Feliciano J. Ramos	Hospital Lozano Blesa	Zaragoza
 Jordi Rosell	Hospital Son Espases	Illes Balears
Isabel Tejada (1)	Hospital Cruces	Bilbao
Inherited Metabolic Medicine Research Programme		
 Luis Aldámiz-Echevarría Azuara	Hospital Cruces	Bilbao
 Ma 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
Endocrine Medicine Research Programme		
 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
Inherited Cancer, Haematologic and Dermatological Diseases Research Programme		
 Isabel Badell	Hospital de la Santa Creu i Sant Pau	Barcelona
 Cristina Beléndez	Hospital Gregorio Marañón	Madrid
 Albert Català	Hospital San Joan de Déu	Barcelona
 Julián Sevilla	Hospital Infantil Niño Jesús	Madrid
Joan-Lluís Vives-Corróns (1)	Hospital Clínic	Barcelona

(1) Group decommissioned in 2020

## Patents owned by CIBER

### Patents granted

- Granted in several countries. Peptides derived from GSE24.2 to treat diseases caused by oxidative stress and DNA damage.

### Patents applied for

- Compounds for treating Mcardle disease.
- Method of increasing mitochondrial DNA copy number.
- Ergothioneine, s-methyl-ergothioneine, and uses thereof.
- Addressing the diagnostic gaps in pyruvate kinase deficiency: Consensus recommendations on the diagnosis of pyruvate kinase deficiency.

## Clinical guidelines

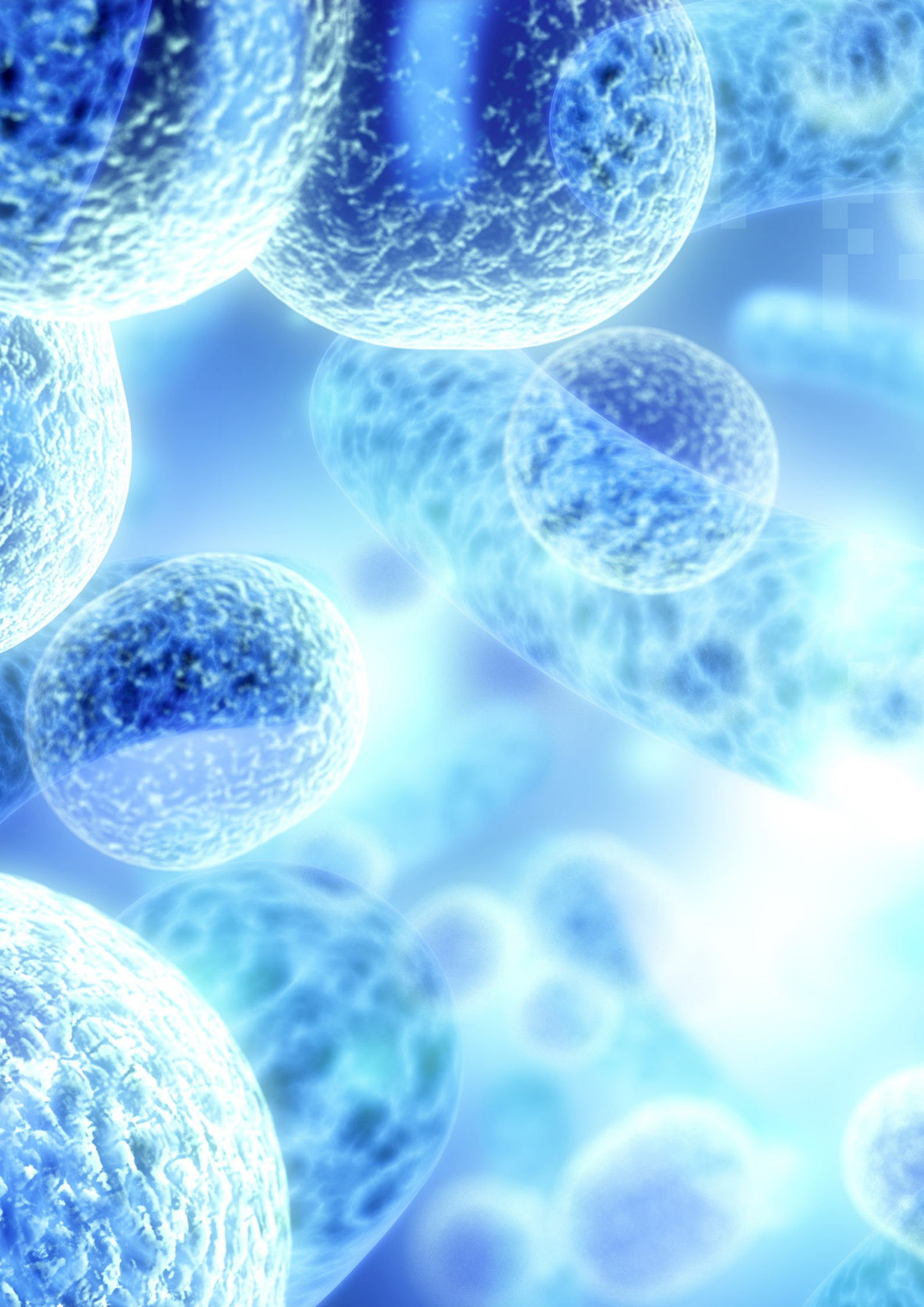
- *An overview of lipodystrophy and the role of the complement system.*
- *Consensus definition and essential reporting parameters of selective fetal growth restriction in twin pregnancy: a Delphi procedure .*
- *Consensus interpretation of the p.Met34Thr and p.Val37Ile variants in GJB2 by the ClinGen Hearing Loss Expert Panel.*
- *Consensus on the diagnosis, treatment and follow-up of patients with Duchenne muscular dystrophy.*
- *Diagnosis and treatment of basal cell carcinoma: European consensus-based interdisciplinary guidelines.*
- *Evidence-Based Consensus and Systematic Review on Reducing the Time to Diagnosis of Duchenne Muscular Dystrophy.*
- *Facial paralysis: Clinical practice guideline of the Spanish Society of Otolaryngology.*
- *International clinical guidelines for the management of phosphomannomutase 2-congenital disorders of glycosylation: Diagnosis, treatment and follow up.*
- *International Consensus on the Use of Genetics in the Management of Hereditary Angioedema.*
- *Management of Adult Patients with Primary Immune Thrombocytopenia (ITP) in Clinical Practice: A Consensus Approach of the Spanish ITP Expert Group.*
- *Nephritic Factors: An Overview of Classification, Diagnostic Tools and Clinical Associations.*
- *Newborn screening for homocystinurias: Recent recommendations versus current practice.*
- *Proposal for a simplified classification of IMD based on a pathophysiological approach: A practical guide for clinicians.*
- *Pulmonary exacerbations in patients with primary ciliary dyskinesia: an expert consensus definition for use in clinical trials.*
- *Suggested guidelines for the diagnosis and management of urea cycle disorders: first revision.*





# **Respiratory Diseases**

*ciberes*





# Presentation by the Scientific Director

**Ferran Barbé Illa**



Dear Friends:

I am pleased to present the CIBERES 2019 Annual Report.

As you will see on the following pages, CIBERES has continued to carry out an important scientific activity. As an example, our number of publications grew significantly with a good percentage of inter- and intra-CIBER collaborative publications, which shows that our goal of increasing collaborations between groups is being achieved.

We must continue working in this line of collaboration, perhaps the main mandate of the CIBER consortium, to allow researchers of excellence to work together and present results that can be transferred to society quickly and safely.

In 2019, we were unable to organise our Annual Scientific Conference. The Teaching Days, however, were successfully organised in which many of our young researchers were able to present their work and get to know the rest of the participants.

As a noteworthy result of the Teaching Days, I would like to point out the publication, for the second consecutive year, of the communications presented in the Archives of Bronchopneumology of Elsevier. The publication of an online supplement in the journal was possible thanks to an agreement of the CIBERES Teaching Commission with the Spanish Society of Pneumology and Thoracic Surgery SEPAR and Elsevier. It compiles 60 abstracts from both oral communications and posters and long-term mobility grant papers presented by researchers from CIBERES groups. [See communications.](#)

Another notable milestone in 2019 was the meeting held in May by the External Scientific Advisory Committee (ESAC) of CIBERES during the American Thoracic Society congress in Dallas (USA). At the meeting, not only was the progress and results of our Centre reported, but several young researchers were able to present their research to ESAC members as part of the award they received for presenting excellent work at the Teaching Days of 2018. After the meeting, the president of the ESAC, Dr. Gozal, issued a report of recommendations for CIBERES that was presented to the Governing Board.

It is complex to highlight some of the many news that were published on our website during 2019. This is that other important element on which we must continue working. Communication and dissemination of our work is essential. We must take advantage of the possibilities offered by our Communication Department of the Technical Office- press releases, web news, RSS- to make our activity known. It should be noted that, fortunately, our website receives increasingly more visits and is becoming a point of reference for respiratory diseases.

I want to end another year thanking you all for the excellent work you do and your commitment to science.

# Programmes

## Chronic Respiratory Diseases

**Coordinator:** Juan Fernando Masa Jiménez

### Asthma Line

- CIBERES ASTHMA cohort: ongoing studies derived from the cohort of patients created by the Line, currently consisting of 512 patients with a minimum follow-up of three years. Potentially useful biomarkers for the diagnosis, activity and classification of the disease and its relationship with phenotypic expression and response to treatment are validated.
- Participation in an international E-Phocas project with the aim of studying different asthmatic phenotypes from patients with occupational asthma

### COPD Line

- Active follow-up cohorts continue appropriately and closed ones are in the process of preparing publications.
- Biomarker evaluation; BIOMEPOC is in the process of writing up manuscripts. Finishing Blind analysis of clusters based on proteomic signatures is currently being completed.
- BIOEARLY COPD has all the samples in the PRBB-IMIM BIOBANK. Funds are being secured for their analysis.
- The therapeutic response evaluation project has begun field work with 12 centres nationwide.

### Cancer Line

- *Obstructive sleep apnea and nocturnal hypoxemia are associated with an increased risk of lung cancer.* Autores: Seijo LM, Pérez-Warnisher MT, Giraldo-Cadavid LF, Oliveros H, Cabezas E, Troncoso MF, Gómez T, Melchor R, Pinillos EJ, El Hachem A, Gotera C, Rodríguez P, González-Mangado N, Peces-Barba G. Journal: Sleep medicine. Publication date: 2019-11-01 DOI: 10.1016/j.sleep.2019.05.011.
- *Sleep disordered breathing and nocturnal hypoxemia are very prevalent in a lung cancer screening population and may condition lung cancer screening findings: results of the prospective Sleep Apnea In Lung Cancer Screening (SAILS) study.* Autores: Pérez-Warnisher MT, Cabezas E, Troncoso MF, Gómez T, Melchor R, Pinillos EJ, El Hachem A, Gotera C, Rodríguez P, Mahillo I, González-Mangado N, Peces-Barba G, Seijo LM. Journal: Sleep medicine. Publication date: 2019-02-01 DOI: 10.1016/j.sleep.2018.10.020.



- *Sleep Disordered Breathing Is Highly Prevalent in Patients with Lung Cancer: Results of the Sleep Apnea in Lung Cancer Study*. Autores: Cabezas E, Pérez-Warnisher MT, Troncoso MF, Gómez T, Melchor R, Pinillos EJ, ElHachem A, Gotera C, Rodríguez P, Mahillo Fernández I, Martínez-García MÁ, González-Mangado, Peces-Barba G, Seijo LM. *Journal: Respiration; international review of thoracic diseases* Publication date: 2019-01-01 DOI: 10.1159/000492273.

## Sleep Line

- Villanueva et al. *accuracy of one-night actigraphy for estimating sleep in patients with sleep apnea*. *Sleep Med*. 2019.
- Cabezas E, Pérez-Warnisher MT, Gómez T, Melchor R, Pinillos EJ, El Hachem A, Gotera C, Rodríguez P, Mahillo Fernández I, Martínez-García MÁ; González-Mangado, Peces-Barba G, Seijo LM. *Sleep Disordered Breathing Is Highly Prevalent in Patients with Lung Cancer: Results of the Sleep Apnea in Lung Cancer Study*. *Respiration* 2019; 97(2): 119 a 124. doi: 10.1159/000492273.
- *Experimental Approach to Examine Leptin Signaling in the Carotid Bodies and its Effects on Control of Breathing*. Shin MK, Kim LJ, Caballero-Eraso C, Polotsky VY. *J Vis Exp*. 2019 Oct 25;(152). doi: 10.3791/60298.
- Campos-Rodriguez F, Asensio-Cruz MI, Cordero-Guevara J, Jurado-Gamez B, Carmona-Bernal C, Gonzalez-Martinez M, Troncoso MF, Sanchez-Lopez V, Arellano-Orden E, Garcia-Sanchez MI, Martinez-Garcia MA; Spanish Sleep Network. *Effect of continuous positive airway pressure on inflammatory, antioxidant, and depression biomarkers in women with obstructive sleep apnea: a randomized controlled trial*. *Sleep*. 2019 Oct 9;42(10). pii: zsz145. doi: 10.1093/sleep/zsz145.

# Infectious Respiratory Diseases

**Coordinator:** Antoni Torres Martí

## Host-Pathogen Interaction Line

- Advances in the use of a bioinformatics tool that combines clinical-epidemiological data of patients and genetic characteristics of the pathogenic microorganism.
- Mutation S110L of H1N1 influenza virus hemagglutinin is a potent determinant of viral attenuation.
- Using *Streptococcus pneumoniae* capsular polysaccharide microarrays (CPSs), detection of anti-CPS IgGs in serum is possible using very small amounts of sample.
- Study of *Haemophilus* spp. reveals involvement of hemin uptake systems in *H. influenzae* infection, as well as importance of *H. parainfluenzae* as a multidrug-resistant opportunistic pathogen, supported by the description of the first capsular operon in this pathogen and publication of an optimization of the sensitivity to co-trimoxazole protocol.
- Two enzybiotics capable of hydrolyzing different peptidoglycan linkages have synergistic bactericidal activity against pneumococcus, esters of bicyclic amine are effective on mixed *S. pneumoniae*-*H. influenzae* biofilms, and the dual antimicrobial-immunomodulatory polyphenols and lipid component of lung surfactant have a protective effect against *H. influenzae*.

## Tuberculosis Line

Diagnosis. Algorithm for diagnosis of childhood TB developed, including incipient forms. Respiratory specimen transport and stabilization reagents reduce the sensitivity of cultures and GeneXpert. CD27- and CCR4 + cells are indicative of tuberculosis disease.

Prevention and immune response. Clinical phase of the new MTBVAC tuberculosis vaccine published in *Lancet Respiratory Medicine*.

Treatment. New project with GlaxoSmithKline to find inhibitors of PhoP action. Controlled release systems increase the bactericidal capacity of drugs against intracellular bacteria. Antituberculosis activity of bedaquiline increases when encapsulated in micelles. New project to validate the use of non-steroidal anti-inflammatory drugs and to develop a prognostic factor for TB patients.

Molecular epidemiology. Molecular analysis of MDR *M. tuberculosis* strains of the last 20 years in Spain. Characterisation by WGS of more transmissible strains. WGS couples with strain-specific PCR at certain locations (Almería, Panama, Peru, Argentina). Study of properties of more transmissible strains in infection models.

## Pneumonia Line

PREvention, Diagnosis and Treatment of pNEUmonia (PREDITNEU)

The existence of the Pneumonia Line enables the prevention, diagnosis and management of respiratory infections to be promoted through the analysis of microorganisms and biomarkers, optimising diagnostic tools and epidemiological evaluation.

Clinical epidemiology: The emerging lineage 11A-ST6521, arising after a capsular exchange, escapes the action of vaccines spreading in south-west Europe (Spain, France and Portugal).

The decrease in invasive pneumococcal infection after the introduction of the 13-valent vaccine in children has been offset by the increase in non-vaccine serotypes. The spread of antibiotic resistant lineages (11A and 24F) could jeopardize the treatment of severe pneumococcal diseases. Among them, the increase in serotype 11A has been related to the spread of a recombinant PMEN3 clone. The main 11A-PMEN3 lineage appeared after two recombination events between two main pneumococcal clones (11A-ST62 and NT-ST344). This project has produced two high impact publications: Clin Microbiol Infect. 2019 Nov 19. doi: 10.1016 / j. cmi.2019.10.034 [In press]; Eurosurveillance-D-19-00457R1 [In press, EMID: b6d3e5fb9571512b].

# Diffuse Respiratory Diseases

**Coordinator:** Francisco Pérez Vizcaino

## Pulmonary Hypertension Line

- Organisation and presentations at the *13th Pulmonary Vascular Research Institute Annual World Congress* (Barcelona 2019).
- Participation in the 1st Symposium of the International Consortium for Genetic Studies in PAH, February 2019.
- 3rd Research Meeting on Pulmonary Hypertension held. Hospital Clínic Barcelona, March 2019.
- Publication of results of combined therapy in patients with pulmonary arterial hypertension (*J Heart Lung Transplant*. 2019; 38 (12): 1286-1295; *Respir Res*. 2019; 20 (1): 208).
- Demonstration of involvement of Kv7 channels in pulmonary vasodilation induced by NO donors and riociguat (*Br J Pharmacol*. 2019; 176 (13): 2131-2145).
- Demonstration of usefulness of iron oxide nanoparticles in angiography and directed molecular imaging. (*ACS Omega*. 2019; 4 (2): 2719-2727.).
- Analysis of the impact of pulmonary artery denervation, physical exercise and rehabilitation on pulmonary hypertension (*Eur Respir J*. 2019; 53 (2). Pii: 1800332; *Basic Res Cardiol*. 2019; 114 (2): 5 ).
- Identification of FIGN as a modulator of low penetration in hereditary pulmonary arterial hypertension (*J Med Genet*. 2019; 56 (7): 481-490).

- Demonstration in an experimental model that type II diabetes is associated with the development of pulmonary hypertension (*PLoS One*. 2019; 14 (1): e0211281).
- Participation in position papers derived from the 6th World Symposium on Pulmonary Hypertension (*Eur Respir J*. 2019 Jan 24; 53 (1). Pii: 1801914) and the statement of the *European Respiratory Society* (ERS) on physical training and rehabilitation in pulmonary hypertension (*Eur Respir J*. 2019 Feb 28; 53 (2). pii: 1800332).

## Acute Lung Injury Line

- Desarrollo del Airtest Score para identificar complicaciones pulmonares post-operatorias.
- Identificación de nuevos miRNAs, como posibles dianas en pacientes con ARDS.
- Identificación del papel de PECAM1 y Wnt e al reparación y regeneración pulmonar.
- Desarrollo de una estrategia de mayor precisión para estratificar pacientes con SDRA para ensayos clínicos aleatorizados.
- Identificación del valor de la endotelina-1 circulante asociado a variables clínicas y ecocardiográficas para determinar el riesgo de broncodisplasia pulmonar.
- Papel de los purinoceptores pulmonares para desencadenar el daño cerebral inducido por la ventilación mecánica.
- Identificación de factores predictores de asincronías en la ventilación mecánica (Estudio EPISYNC).
- Análisis de las diferencias en el sexo en la susceptibilidad al daño inducido por ventilación mecánica.
- Identificación del perfil metabólico en SDRA de diferentes etiologías.

## Pulmonary Fibrosis Line

- Castillo D, Sánchez-Font A, Pajares V, Franquet T, Llatjós R, Sansano I et al. *A Multidisciplinary Proposal for a Diagnostic Algorithm in Idiopathic Pulmonary Fibrosis: The Role of Transbronchial Cryobiopsy*. Archivos de bronconeumología. 2019.
- Maher TM, Corte TJ, Fischer A, Kreuter M, Lederer DJ, Molina-Molina M et al. *Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: a double-blind, randomised, placebo-controlled, phase 2 trial*. *The Lancet. Respiratory medicine*. 2019.
- Planas-Cerezales L., Arias-Salgado E.G., Buendia-Roldan I., Montes-Worboys A., Lopez C.E., Vicens-Zygmunt V. et al. *Predictive factors and prognostic effect of telomere shortening in pulmonary fibrosis*. *Respirology*. 2019;24(2):146-153.

# Training Programme

**Coordinator:** Cristina Prat Aymerich

## Improvement/mobility grants

Four types of grants are available. The first three cover up to a maximum of €500. The fourth (long stays) cover up to a maximum of € 600 / month + 80% of travel tickets.

4	6	3	3
COURSE REGISTRATION FEES	DOCTORATE PROGRAMME FEES	SHORT STAYS (<3 MONTHS)	LONG STAYS (3-6 MONTHS)

## Fostering interest in respiratory research

Celebration of the CIBERES Training Days in Madrid on Friday, September 27, at the Escuela Nacional de Sanidad (National School of Health).

- Number of attendees: 85 people
- Number of communications received and evaluated: 60
- Number of selected oral communications: 30
- Number of awarded communications: 4

Publication of the Congress Supplement in the journal Archivos de Bronconeumología, recently promoted to the first quartile. All communications received are included, plus an abstract summary of five mobility grants for long stays carried out in 2018.

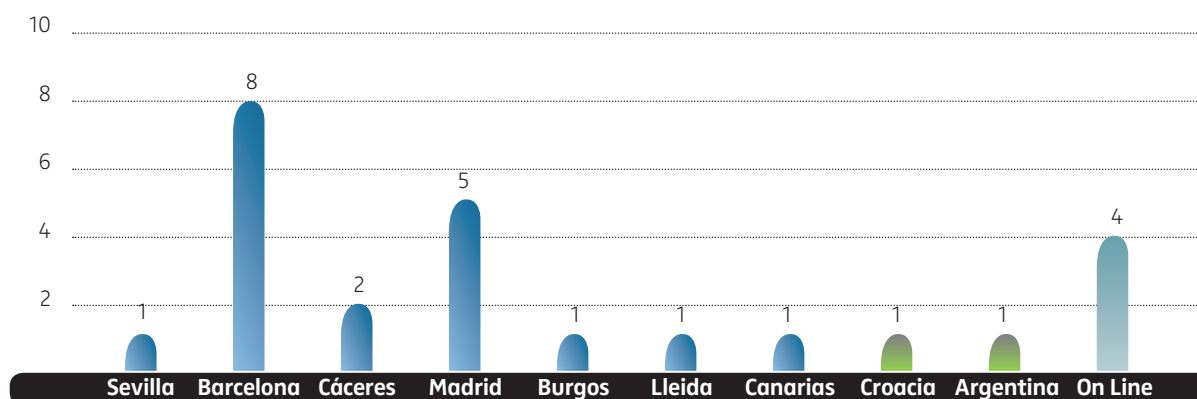
## CIBERES scientific endorsements

Courses, conferences, workshops, congresses or events of interest to the CIBERES research community are endorsed. Events are disseminated through the website, the Web Agenda and social networks to make them known to researchers for them to register.

- Events endorsed in 2019: 25



## CIBERES endorsements granted (2019)



# Pulmonary Biobank Platform

**Coordinator:** Cristina Villena Portella

Most relevant milestones of the Pulmonary Biobank Platform (PBP) in 2019:

- As part of the coordination of the Red Nacional de Biobancos-ISCIII (RNBB) (National Network of Biobanks):
  - Organization of the 1st RNBB Work Days at the CIEN Foundation (Madrid).
  - Planning and execution of the 2019 action plan.
  - Unification in a single file for the annual declaration of all the nodes to collect and process all the activity of the RNBB.
  - Publication of the first version of a unified catalogue of the samples immediately available in the RNBB (catalogue v1.0).
  - Update of the RNBB Website.
  - Co-organisation of the X National Congress of Biobanks 2019.
  - Involvement in the II Working Days of the RNBB (Valencia).
  - Publication of the main milestones achieved in 2019 by the RNBB.
  - Coordination of all activities, commissions, committees and programmes of the RNBB.
  - Interaction to establish synergies with TRANSBIONET, CSIC, innovation companies and biobanks in Middle Eastern countries.

- As a Member of the Red Nacional de Biobancos-ISCIII (RNBB):
  - Participation in the line of improvement of the data associated with the samples, for the implementation of a data quality program in the Biobanks.
  - Participation in the EXOSOMAS work line.
  - Execution and completion of the project Optimisation of tissue samples for the development and validation of disease biomarkers: OPTIMARK project. OPTIMARK (FIS 2016) and participating in the R & D + i line in Biobanks in the area of human tissues, from which an oral communication has been derived in an international congress, and two in national meetings, in addition to two publications:
  - Collaboration with the Integrated Biobank of Luxembourg (IBBL) for participation in a common project on tissue quality biomarkers.
- Improvement of external visibility through participation in:
  - Scientific events and meetings with experts.
  - Training activities (4 from the university and CIBERES 2019 Training Days).
  - Management of the PBP social networks.
- Increase in the collection of deficient samples (9,648 new samples).
- Management and inclusion of the multicenter ISAAC project collection, coordinated by the CIBERES Obstructive Sleep Apnoea line and SEPAR.
- IdISBa grant awarded for Margalida Esteva's stay at Integrated Biobank of Luxembourg during 2020.
- Maintenance of quality certificate of the new ISO 9001: 2015 standard for the entire Quality Management System of the CIBERES Pulmonary Biobank Platform.
- Development and configuration of a new PBP activity management software.

# Scientific Production

## Publications

### No. of publications in 2019

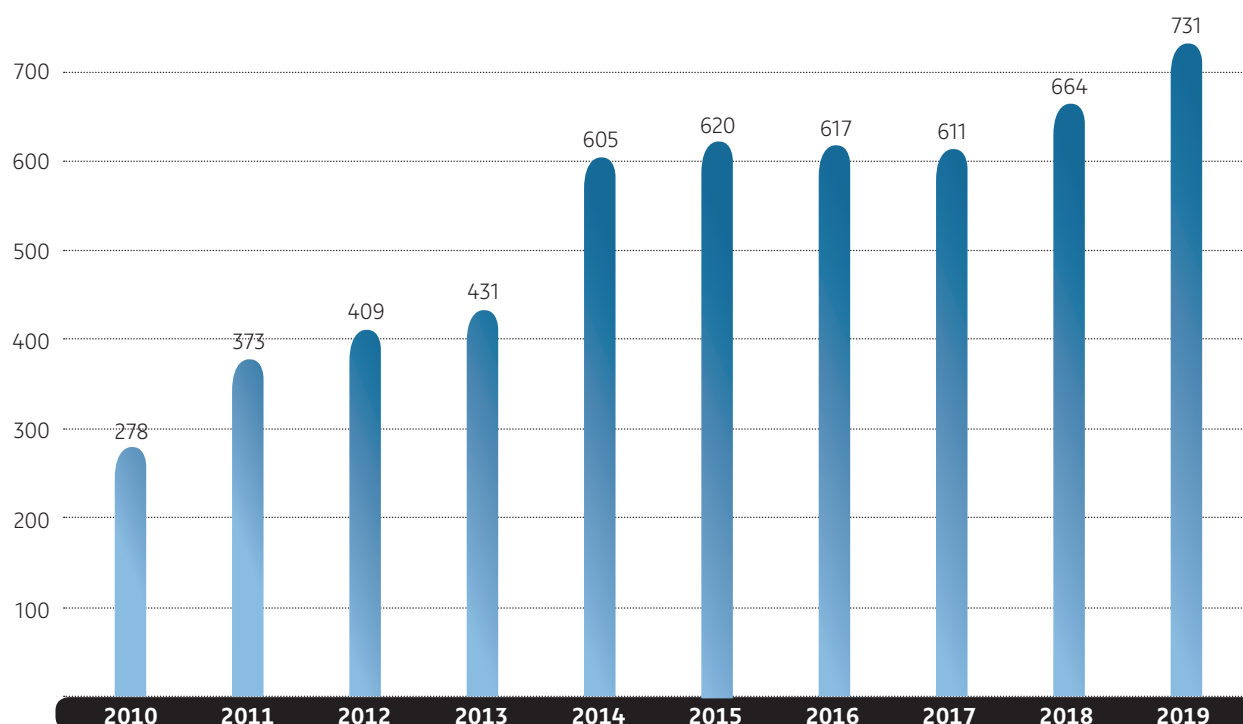
TOTALS	731
Q1	364
D1	134

### Collaborative publications

CIBERES	179
CIBER*	130

\*Among various thematic areas

### Evolution of publications 2010-2019



## 10 most relevant publications by impact factor

IF	Publication
70,67	SLUTSKY A.S., VILLAR J. <i>Early paralytic agents for ARDS? Yes, no, and sometimes. New England Journal of Medicine.</i> 2019;380(21):2061-2063.
70,67	AGUSTI A., HOGG J.C. <i>Update on the pathogenesis of chronic obstructive pulmonary disease. New England Journal of Medicine.</i> 2019;381(13):1248-1256.
27,516	RUBIO I., OSUCHOWSKI M.F., SHANKAR-HARI M., SKIRECKI T., WINKLER M.S., LACHMANN G. ET AL. <i>Current gaps in sepsis immunology: new opportunities for translational research. The Lancet Infectious Diseases.</i> 2019.
22,992	AGUSTI A., FANER R. <i>Lung function trajectories in health and disease. The Lancet Respiratory Medicine.</i> 2019;7(4):358-364.
22,992	MARTINEZ-GARCIA M.A., CAMPOS-RODRIGUEZ F., BARBE F., GOZAL D., AGUSTI A. <i>Precision medicine in obstructive sleep apnoea. The Lancet Respiratory Medicine.</i> 2019;7(5):456-464.
22,415	LATORRE-PELLICER A., LECHUGA-VIECO A.V., JOHNSTON I.G., HAMALAINEN R.H., PELLICO J., JUSTO-MENDEZ R. ET AL. <i>Regulation of Mother-to-Offspring Transmission of mtDNA Heteroplasmy. Cell Metabolism.</i> 2019;30(6):1120-1130.e5.
18,967	MARTIN-LOECHES I., ANTONELLI M., CUENCA-ESTRELLA M., DIMOPOULOS G., EINAV S., DE WAELE J.J. ET AL. <i>ESICM/ESCMID task force on practical management of invasive candidiasis in critically ill patients. Intensive Care Medicine.</i> 2019.
18,967	AQUINO ESPERANZA J., PELOSI P., BLANCH L. <i>What's new in intensive care: tracheostomy—what is known and what remains to be determined. Intensive Care Medicine.</i> 2019.
18,967	RELO J., CAMPOGIANI L., ESHWARA V.K. <i>Understanding resistance in enterococcal infections. Intensive Care Medicine.</i> 2019.
18,967	RELO J., ALP E., VANDANA K.E.. <i>Infectious diseases: the 10 common truths I never believed. Intensive Care Medicine.</i> 2019;45(2):243-245.

## CIBERES Groups. Publications in 2019

Group Leader	Publ.	Q1	D1	Institution / Centre	Province
 Agustí García Navarro, Àlvar	63	39	12	Hospital Clínico y Provincial de Barcelona	Barcelona
 Álvarez Martínez, Carlos José	6	4	1	Servicio Madrileño de Salud	Madrid
 Ardanuy Tisaire, María Carmen	29	11	4	Fundación IDIBELL	Barcelona
 Barbé Illa, Ferrán	58	24	8	Instituto de Investigacion Biomédica de Lleida. Fundación Dr. Pifarre	Lleida
 Barberà Mir, Joan Albert	35	21	9	Hospital Clínico y Provincial de Barcelona	Barcelona
 Blanch Torra, Lluís	29	16	7	Corporación Sanitaria Parc Taulí	Barcelona
 Cardona Iglesias, Pere Joan	15	9	4	Fundación Instituto de Investigacion Germans Trias i Pujol	Barcelona
 Casals Carro, Cristina	3	0	0	Universidad Complutense de Madrid	Madrid
 Farre Ventura, Ramon	26	14	4	Universidad de Barcelona	Barcelona

Group Leader	Publ.	Q1	D1	Institution / Centre	Province
 García González, Pedro	11	3	2	Agencia Estatal Consejo Superior de Investigaciones Científicas	Madrid
 García Río, Francisco José	46	26	6	Servicio Madrileño de Salud	Madrid
 Gea Guiral, Joaquim	37	26	5	Consorci Mar Parc Salut de Barcelona	Barcelona
 López-Campos Bodineau, José Luis	61	30	5	Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla	Sevilla
 Lorente Balanza, José Ángel	11	2	1	Servicio Madrileño de Salud	Madrid
 Martín Montañés, Carlos	17	13	7	Universidad de Zaragoza	Zaragoza
 Masa Jiménez, Juan Fernando	21	10	9	Fundación para la Formacion y la Investigación de los Profesionales de la Salud. FUNDESALUD	Cáceres
 Menéndez Fernández, Margarita	2	2	0	Agencia Estatal Consejo Superior de Investigaciones Científicas	Madrid
 Monsó Molas, Eduard	18	11	4	Corporación Sanitaria Parc Taulí	Barcelona
 Montserrat Canal, Josep Maria	23	9	4	Hospital Clínico y Provincial de Barcelona	Barcelona
 Morcillo Sánchez, Esteban Jesús	7	3	1	Universidad de Valencia	Valencia
 Mullol Miret, Joaquim	21	16	8	Hospital Clínico y Provincial de Barcelona	Barcelona
 Muñiz Albaiceta, Guillermo	6	2	1	Fundación para la Investigación e Innovación Biosanitaria en el Principado de Asturias. FINBA	Asturias
 Muñoz Gall, Xavier	54	28	5	Fundación Hospital Universitario Vall d'Hebron - Institut de Recerca. VHIR	Barcelona
 Muñoz García, Patricia	50	19	10	Servicio Madrileño de Salud	Madrid
 Nieto Martín, Amelia	4	2	1	Agencia Estatal Consejo Superior de Investigaciones Científicas	Madrid
 Peces Barba Romero, Germán	22	13	3	Instituto de Investigación Sanitaria Fundación Jiménez Díaz	Madrid
 Pérez Vizcaíno, Francisco	12	8	2	Universidad Complutense de Madrid	Madrid
 Pozo Abejón, María Victoria del	21	16	4	Instituto de Investigación Sanitaria Fundación Jiménez Díaz	Madrid
 Relló Condomines, Jordi	57	18	10	Fundación Hospital Universitario Vall d'Hebron - Institut de Recerca. VHIR	Barcelona
 Ruiz Cabello Osuna, Jesús	14	9	7	CIC biomaGUNE	Guipúzcoa
 Torres Martí, Antoni	72	34	14	Hospital Clínico y Provincial de Barcelona	Barcelona
 Villar Hernández, Jesús	35	13	7	Fundación Canaria Instituto de Investigación Sanitaria de Canarias	Las Palmas



## Patents owned by CIBER

### Patents granted

- Inactivated mycobacteria for oral use in the prevention of tuberculosis.

### Patent pre-grants

- *Method for predicting response to continuous positive air pressure treatment.*

### Patents applied for

#### PCT:

- *Method and apparatus for the cardiovascular assessment of a subject in need thereof.*
- *In vitro method for the diagnosis or detection of non-tuberculous mycobacteria.*
- *Identification of metabolomic signatures in urine samples for tuberculosis diagnosis.*

#### National Phases:

- In vitro method to identify severity stages in patients with bronchial asthma.

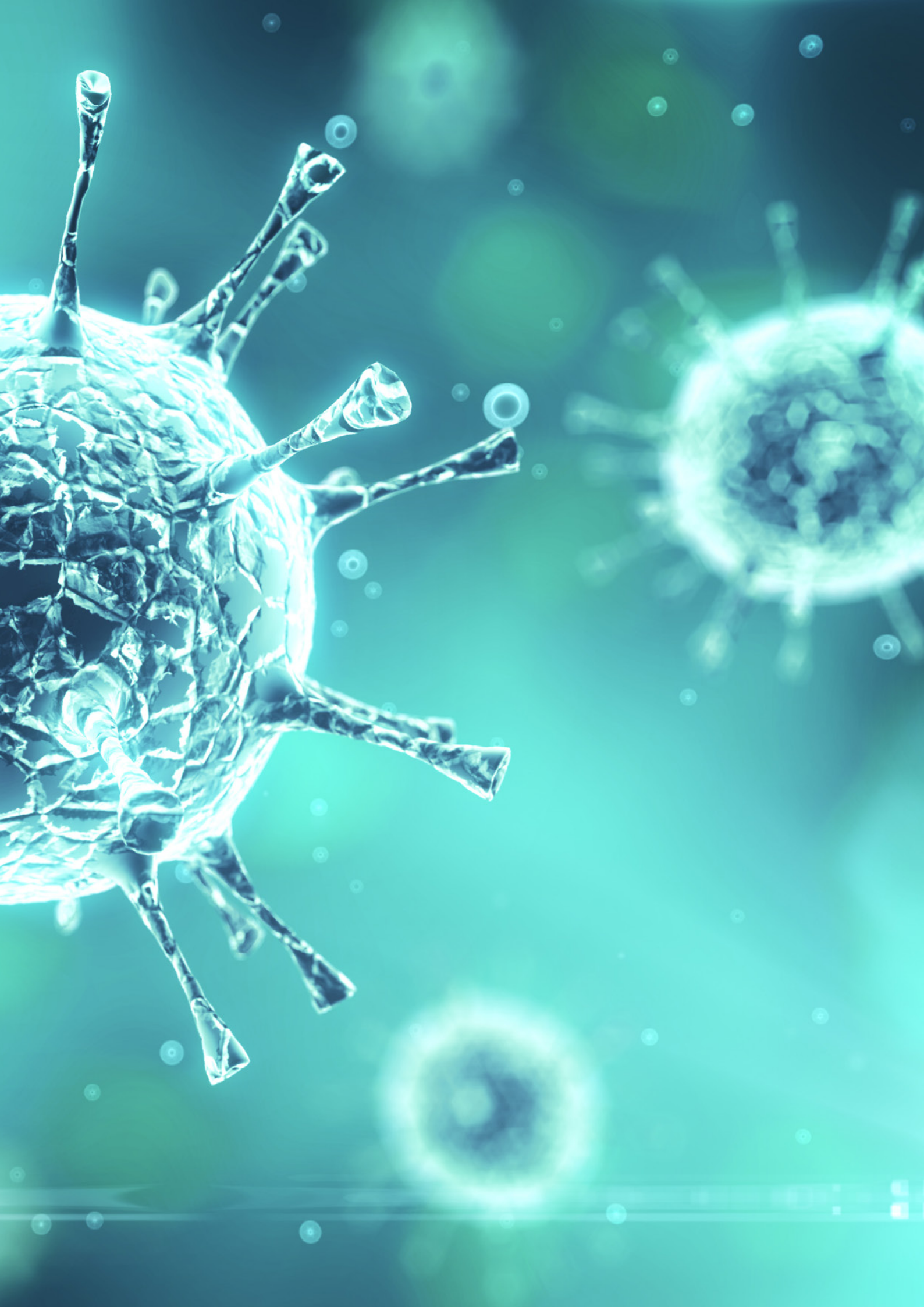
## Clinical Guides

- *Next-generation Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines for allergic rhinitis based on Grading of Recommendations Assessment, Development and Evaluation (GRADE) and real-world evidence.*
- *Next-generation ARIA care pathways for rhinitis and asthma: a model for multimorbid chronic diseases.*
- *ARIA masterclass 2018: From guidelines to real-life implementation.*
- *2019 ARIA Care pathways for allergen immunotherapy.*
- *Guidance to 2018 good practice: ARIA digitally-enabled, integrated, person-centred care for rhinitis and asthma.*
- *EPOS2020: development strategy and goals for the latest European Position Paper on Rhinosinusitis.*
- *Dilemmas and New Paradigms in Asthma Management.*
- *Practical Guide to the Identification and Diagnosis of Asthma-COPD Overlap (ACO).*
- *Patients with Chronic Obstructive Pulmonary Disease Exacerbations: Recommendations for Diagnosis, Treatment and Care.*
- *Evaluation and Management of Obesity Hypoventilation Syndrome. An Official American Thoracic Society Clinical Practice Guideline.*

The background is a solid teal color with several large, overlapping, organic shapes in lighter shades of teal and blue, creating a layered, wave-like effect.

# **Epidemiology and Public Health**

*cïberesp*





# Presentation by the Scientific Director

**Marina Pollán Santamaría**



In 2019, the groups included in CIBERESP continued to maintain the level of publications of previous years, which once again exceeded a thousand, with more than 50% of them in the first quartile and 30% in the first decile.

CIBERESP has seven research programmes and one training programme: Programme 1 “Epidemiology and Control of Chronic Diseases”, Programme 2 “Communicable Disease Prevention, Surveillance and Control”, Programme 3 “Biological, Behavioral and Structural Determinants in the Contraction and Spread of Communicable Diseases in Vulnerable Populations”, Programme 4 “Social Determinants of Health”, Programme 5 “Epidemiology and Prevention in Environmental and Occupational Health”, Programme 6 “Evaluation of Health Services” and Programme 7 “Clinical Epidemiology”. The main achievements of each of these programmes are reflected in the Annual Report.

At the end of the year, Angela Domínguez, Scientific Assistant Director of CIBERESP, Jordi Casabona, Coordinator of Programme 3 and Adonina Tardón, Coordinator of Programme 5, stepped down from the Steering Committee. On behalf of the entire CIBERESP family, I want to thank them for all the work and enthusiasm they have brought to our network. In place of the outgoing members, Jordi Alonso, from the Hospital del Mar Medical Research Institute, has stepped in as the Scientific Assistant Director, Juan Carlos Galán, researcher at the Ramón y Cajal Hospital in Madrid, joins as Coordinator of Programme 3, Marieta Fernández, from the University of Granada, is the new Coordinator of Programme 5 and Antonio Serrano, from the Parc Sanitari Sant Joan de Deu in Barcelona, has taken the lead of Programme 6.

In 2019, our External Scientific Advisory Committee (ESAC) was renewed, maintaining two of its previous members: Professors Henrique Barros from the University of Porto (Portugal) and Javier Nieto, from the University of Oregon (USA) and incorporating four prestigious researchers with complementary profiles: Prof. Jose María Valderas, from the University of Exeter (United Kingdom), Prof. Ana Navas, from Columbia University (USA); Dr. Teymur Noori from the European Center for Disease Control (ECDC, Sweden) and Dr. Ana Pilar Betrán, from the World Health Organization (Switzerland). In November we held a very productive joint meeting between the ESAC and the CIBERESP Steering Committee, which served to make the new members aware of the organisation and main results of CIBERESP and to reflect together on how to strengthen our research network and focus the activities that we develop in order to be more useful in facing the main national and international public health challenges. The main conclusions of this meeting were presented at the Annual CIBERESP Meeting where we maintained the scientific structure of 2018 which was very well received by our groups with presentations of a selection of communications and posters of the best work done by the groups of our area, promoting in this way the presence of young researchers. In this meeting, a summary of the first results of the opinion survey that we have carried out during this year among all the CIBERESP researchers was also presented, the analysis of which will be very useful for the Steering Committee.

We continue to maintain collaboration with the Spanish Society of Epidemiology. The CIBERESP Communications panel presented at the XXXVII Scientific Meeting in Oviedo was very well received by the attendees, from whom we have received numerous comments highlighting the quality of the presentations.

# Programmes

## P1: Epidemiology and control of chronic diseases

**Coordinator:** M<sup>a</sup> José Sánchez Pérez

The Programme has continued with the scientific activity of the three strategic subprogrammes.

### MCC-Spain

The MCC-Spain project, led by Manolis Kogevinas and Marina Pollán, is being used as a study of prognostic factors in patients with colorectal, breast or prostate cancer to find out what previous exposures, patient or tumor characteristics or the treatments received influence overall and disease-free survival. 4,837 cases of these cancers have been followed up. An article has been published describing the monitoring methodology and the characteristics of the 3 prospective cohorts (Alonso-Molero J, Molina AJ, Jiménez-Moleón JJ, et al, 2019).

In 2019, 15 scientific articles were published in indexed journals. One of the most impactful articles aimed to assess the correlation between pro-inflammatory and antioxidant dietary intake with the risk of developing colorectal and breast cancer (Obón-Santacana M, Romaguera D, Gracia-Lavedan E, et al), showing an association between the risk of colorectal cancer and the inflammatory potential of the diet, as well as the combination effect between the inflammatory potential of the diet and the total antioxidant capacity of the diet plan. However, there was no evidence of increased risk of breast cancer.

### Gen-Risk

The Gen-risk project, led by Víctor Moreno, is funded by the Fundación Científica de la Asociación Española contra el Cáncer (Scientific Foundation of the Spanish Association against Cancer-AECC), and is largely supported by the MCC-Spain study. Its objective is to improve cancer prevention through personalised strategies, looking for biomarkers that can be used to identify which people have the highest risk of developing one of the 5 cancers included in the study (colorectal, breast, stomach, prostate and Chronic lymphocytic leukemia), to better guide the prevention of these tumors, reducing both morbidity and the social and economic impact that they entail.

During the first year, 6,375 DNA samples were collected, with which an analysis of the complete genome will be carried out, to combine the data with another 2,463 samples for which this data is already available. The extraction of DNA from 402 blood and 65 saliva samples has been carried out, as well as the aliquoting of 562 DNA samples in the appropriate format to carry out the quantification and normalisation prior to genotyping.



## Epidemiological Surveillance of Cancer

The Epidemiological Surveillance of Cancer subprogramme, coordinated by Pablo Fernández and M<sup>a</sup> José Sánchez, has developed a remote GEO-CIBER application for the geocoding of 9,488 cases of breast, colon-rectum and lung cancer, included in the project “Multilevel Population Study of Socioeconomic Inequalities in the Geographical Distribution of Incidence, Mortality and Net Cancer Survival in Spain”, funded by the ISCIII, and which aims to characterise and evaluate the impact of socioeconomic inequalities on incidence, excess mortality, premature mortality and net survival for 3 of the cancers with greatest incidence in Spain.

We have worked with the European Deprivation Index and the new Deprivation Index in Spain (2011) by census section, prepared by the Group of Social Determinants of Health of the Spanish Society of Epidemiology.

In 2019, a collaboration/agreement was established with the AECC to evaluate the website of the AECC Cancer Observatory and a technical report was prepared with proposals for improvement. In addition, 4 scientific articles were produced that are in the process of peer review.

## P2. Communicable disease prevention, surveillance and control (PREVICET)

**Coordinator:** Pere Godoy García

The groups led by Àngela Domínguez and Carmen Muñoz have participated in the project on the evolution of invasive pneumococcal disease after the introduction of the 13-valent pneumococcal conjugate vaccine in the systematic schedule (PI: Juan José García PI17 / 00337).

The groups led by Àngela Domínguez and Cristina Rius have continued with the project to characterise severe cases of influenza (3 articles have been published). In addition, they have collaborated in the project for hospitalised patients with severe and mild flu for the 2017-18 season.

Funding has been obtained for the project “Effectiveness of influenza and pneumococcal vaccination to prevent hospitalisation in people under 65 who are at risk” (PI: Àngela Domínguez PI19 / 00354).

The group led by Amparo Larrauri, together with other PREVICET groups, has participated in the project on the effectiveness of the influenza vaccine (ECDC Call for tender) (two articles in Eurosurveillance). The study “Effectiveness of the influenza vaccine in pregnant women to prevent serious hospitalized cases in infants younger than six months of age” (groups 1, 11, 13, 32) and another on the impact of influenza vaccination programmes (an article in Eurosurveillance). Vaccine research contributed to reports for the selection of vaccine strains (GIVE 2019, WHO). The concern generated by the measles outbreaks in Europe has been addressed through articles and interviews.

The group led by Juan E. Echevarría, along with other PREVICET groups, has participated in 7 research projects on emerging diseases in Spain. They cover aspects related to the integration of surveillance, including the molecular characterisation of viruses, vaccine effectiveness, possible factors related to vaccine failure, as well as co-evolutionary factors of viruses and their related reservoir hosts (bats) related to the emergence of new zoonoses. The results of these projects have led to different collaborative publications as well as participation in articles and interviews in the media.

The group led by Jordi Figuerola, together with other PREVICET groups, have determined that the invasive mosquito *Aedes albopictus* is a competent vector for the Zika virus and may, therefore, lead to facilitating indigenous transmission cycles (Gutiérrez-López et al. 2019). Only 25% of pregnant women infected with Zika virus after traveling to countries at risk presented symptoms of disease and the three cases with problems in fetal development were associated with infections during the first trimester of pregnancy (Sulleiro et al. 2019). Also studied has been how the results of the Zika IgG and Zika IgA tests together with the date of onset of symptoms can help the diagnosis of these infections (Amaro et al. 2019), and the Zika virus infections imported into Spain after international travel have been characterised (Crespillo-Andujar et al. 2019). Finally, how the movement of seagulls can contribute to human exposure to Salmonella, Campylobacter and Chlamydia of zoonotic origin has been modeled (Navarro et al. 2019).

## P3. Biological behavioural and structural determinants in the contraction and spread of communicable diseases in vulnerable populations (DAPET Programme)

**Coordinator:** Juan Carlos Galán Montemayor\*

(\*Until November the coordinator was Dr. Jordi Casabona)

### Immigration and Health Subprogramme:

Projects:

- Gilead Sciences "HepC-link" Pilot hepatitis C micro-elimination strategy in Pakistani immigrants in Catalonia through the implementation of a community intervention" (PI: Dr. Casabona).
- FIS "Cost-effectiveness of a community intervention versus a strategy based on the healthcare system to promote the prevention, diagnosis and treatment of hepatitis B and C in immigrants in Catalonia" (PI: Dr. Casabona).
- Ibero-american Network of Pneumocystis in pregnant women and newborns (PI: Dr. Calderón).
- Project "ERANet-LAC: ELAC2014/HID0254 "Recognition of the primary infection by *Pneumocystis* in infants: a silent threat to public health". (PIs: Dr. Moya and Dr. Calderón).
- Project "Study of new recombinant forms of HIV in the sub-Saharan population" (PIs: Dr. Galán and Dr. Moya).

Publications:

- *Int. J. Environ. Res. Public Health* 2019, 16(11), 2027;
- *Int. J. Environ. Res. Public Health* 2019, 16(10), 1796;
- *Int. J. Environ. Res. Public Health* 2019, 16(7), 1288
- *Safety Science*, 2019 115, 36-41
- *Gac Sanit*, 2019 (in press).
- *Front Public Health*. 2019 Oct 15;7:292.
- *Front Public Health*. 2019 Oct 9;7:289.
- *Front Public Health*. 2019 Oct 4;7:275.
- *Clin Epidemiol*. 2019 Jul 22;11:615-624.
- *OBM Genetics volume 3, issue 1*. 10.21926/obm.genet.1901066

### Communicable infections through organic fluids Subprogramme:

Projects:

- "Determinants and needs of sexual health in a multicentre cohort of transgender men and women acting as sex workers in Barcelona and Madrid-Sexcohort" PI18/01481 (PIs: Dr. Casabona and Dr. Alemany).
- FIS Project "Selection of a panel of sera from patients with recent infection in the Hospital Ramón y Cajal for the comparison of the efficacy of early detection and/or quantification of HIV of various serological and molecular techniques currently available or under development" (PI: Dr. Galán).
- Gilead Grants "ReHCV - Molecular epidemiology study of HCV reinfection in the Catalan Penitentiary System" (PI: Dr. Casabona).
- Evaluation of the Xpert HCV Viral Load point-of-care assay from capillary blood in people who inject drugs (PI: Dr. Casabona).

- Ibero-american Network of studies on gay men, other men who have sex with men and transgender people (RIGHT Plus) (PI: Dr. Casabona).
- "Genomic Epidemiology of Sexually Transmitted Bacteria" Project (PIs: Dr. Moya and Dr. Alemany).
- Recognition of the primary infection by *Pneumocystis* in infants: a silent threat to public health. 2016-2018 ELAC2014 / HID0254. ERANET-LAC. (PIs: Dr. Calderón and Dr. Moya).
- Project "Hepatitis C virus: massive sequencing of complete genomes, resistances" (PIs: Dr. Moya and Dr. Casabona).

#### Publications:

- *Int J Drug Policy*. 2019 Dec;74:236-245
- *Environ. Microbiol.* 2019, 21(8): 3046-3062. 10.1111/1462-2920.14702
- *Forensic Sci. Int. Genet.* 2019, 42: 141-146. 10.1016/j.fsigen.2019.07.003
- *Euro Surveill.* 2019, 24(4) 1800005. 10.2807/1560-7917.ES.2019.24.4.1800005
- *Emerg Infect Dis.* 2019 Mar; 25(3): 507514. 10.3201/eid2503.181593
- *OBM Genetics volume 3, issue 1.* 10.21926/obm.genet.1901066
- *Enferm Infecc Microbiol Clin.* 2019 Oct;37(8):525-534. 10.1016/j.eimc.2019.01.014
- *Enferm Infecc Microbiol Clin.* 2019. 10.1016/j.eimc.2019.10.014

## P4. Social determinants of health

**Coordinator:** M<sup>a</sup> José López Medina

The programme has continued with the scientific activity resulting from the subprogrammes "Energy Poverty and Health" and "Gender Violence", and in 2019 a new subprogramme on Real World Data was started. This year, the Energy Poverty subprogramme has published several articles mainly related to the association of energy poverty and health, and to the evaluation of an intervention to reduce energy poverty in populations with the highest risk of vulnerability. In addition, the Gender Violence subprogramme has published throughout the year numerous articles related to the factors associated with gender violence, with the spatial analysis of femicides or with the evaluation of an intervention to reduce violence in adolescents, among other topics. The Real World Data subprogramme, aimed at providing statistical methods to establish and validate a population cohort of economic, social and environmental determinants of health, based on real-world data, has held its first meeting in which different study groups have been defined and work has been done on a new coordinated research project.

In addition to the scientific activity of the subprogrammes, the large number of articles published by researchers from the different groups, all related to the field of social determinants, is worth highlighting as well as the leadership and participation in research projects obtained in national and international competitive calls. These projects address very diverse topics, ranging from the study of masculinities and violence against women, to the evaluation of urban interventions, the evaluation of healthcare needs of people with chronic diseases according to social and environmental determinants through responsible data science or the health impact of cooperative housing. In 2019, the evaluation of an intervention to adapt schools to climate change was also launched, within the framework of the Urban Innovative Action of the European Union.

Beyond the scientific articles and the projects obtained in competitive calls, this year two highly relevant transfer and translation actions stand out in the Programme:

On the one hand, a session in the European Parliament in Brussels, in which the results of the European project TackSHS were presented regarding the impact of policies on exposure to environmental tobacco smoke, and data collected in more than 12 European countries through surveys and environmental measurements. The session aimed to make proposals to modify the laws based on the evidence generated in this project.

Furthermore, worth noting is the publication of the "Atlas of Social Determinants of Health in Spain. Evolution and Variability between the Autonomous Communities ", which aims to identify and develop indicators that serve to assess the impact that changes in the social and environmental context, including the most recent economic crisis,

have on health, its social determinants and inequalities in health in Spain and its Autonomous Communities. Both the indicator directory and the data will be periodically reviewed and updated. Thus, it becomes a highly useful tool for both public health professionals and the general public. The atlas can be consulted at the following website <https://www.osman.es/atlas/>

## P5. Epidemiology and prevention in environmental and occupational health

**Coordinator:** Mariana Fátima Fernández Cabrera\*

(\*Until November the coordinator was Dr. Adonina Tardón)

**Group led by Eulalia Martí Puig (PI):** detection of patterns of germline genetic variants in cancer patients (PanCancer Analysis of Whole Genomes study), and identification of variants with effect on susceptibility to disease (Nature, 578 (7793), 82-93 2020). Co-leadership of the P117 / 01935 project: Identification of molecular QTLs and their interactions with environmental factors in children: a study of molecular endophenotypes from the HELIX project. .

**Group led by Nicolás Olea Serrano (PI):** They have shown that: i) neonatal ICU medical devices involve exposure to Bisphenol A (BPA) and parabens in very low birth weight infants (Iribarne-Durán et al. EHP 2019; 127 (11): 117004); ii) general / occupational population exposed to BPA by thermal paper (Molina-Molina et al. Environ Res 2019; 170: 406-15); and iii) exposure to GAP and parabens in children's clothing <3 years (Freire et al. Environ Int 2019; 127: 592-600). INMA-Granada follow-up (15-17 years) and exposure to non-persistent pesticides in the entire INMA cohort. Leadership WP14 (Effect Biomarkers) within HBM4EU / H2020.

**Group led by Coral Sanfeliu Pujol (PI) and CIBERFES** demonstrate improvements in the memory of amateur rugby players (45-65 years old) compared to subjects with low physical activity, and identify biomarkers of the effect of chronic exercise in blood: i) decrease in lipid peroxidation (malondialdehyde), ii) adjustment of pro-cognitive factors (BDNF and Cathepsin B), iii) increased expression of rejuvenation and neuroprotection genes (SIRT1, SIRT3) and antioxidants (CAT, SOD1) and decrease of pro-inflammatory cytokines (IL1B) (de la Rosa et al., Sci Rep 2019; 9: 3337; Corpas et al., Front Aging Neurosci. 2019; 11: 352).

**Group led by Jordi Sunyer Deu (PI):** they have discovered that early exposure to air pollution is related to mild thyroid dysfunction during pregnancy and impairment of various cognitive functions, including working memory, attention function, memory, verbal and general cognition. Furthermore, prenatal exposure to air pollution is associated with a decrease in corpus callosum volume and, in turn, with an increased risk of hyperactivity problems.

**Group led by Adonina Tardón García (PI):** they assess the influence of genetic determinants on the incidence and evolution of lung cancer and the clinical utility of telomere length as a prognosis in non-small cells. INMA-Asturias (11 years): they have studied pre- and postnatal exposure to POPs with obesity and metabolic syndrome, evaluating RR and main adipokines.

**Group led by Carmen Iñiguez Hernández (PI):** participation and obtainment of projects: "Cervico-vaginal microbiota and human papillomavirus (HPVs) -related dysplasias in perimenopause: A pilot study" / IDEAS SEMI-LLA-AECC; "MercuryGenII-Genetic susceptibility to methylmercury"/Karolinska Institutet-Formas 2016-504; "Fine Particulate Matter, Fetal Growth & Neurodevelopment: Examining Critical Windows of Susceptibility" / NIEHS # 1R01ES028842-01A1. Relevant publications: Soler-Blasco et al. Environ Int 2019; 130: 104835; Costa et al. Environ Int 2019; 130: 104830.

**Group led by Francisco Bolumar Montrull (PI):** in INMA, high doses of folic acid in pregnancy are associated with an increased risk of low birth weight; and the consumption of sugary drinks, a higher intake of trans fatty acids and a lower adherence to the Mediterranean diet, with a higher risk of childhood obesity. In PREDIMED-PLUS, they observe that the Mediterranean low-calorie diet is associated with weight loss at the 1st and 2nd year of follow-up with favorable evolution of cardiovascular risk markers in those treated (18 publications -Diabetes Care and JAMA-).

**Group led by Ricardo Marcos Dauder (PI):** collaboration with the group led by Emmanouil Kogevinas evaluating genetic damage associated with exposure to DBPs in swimming pools (Environ Int, 131: 104988, 2019). They investigate genotoxicity markers as risk indicators in patients with bladder cancer (Environ Mol Mutagen, 60: 168-173, 2019)

and genetic determinants modulating the incidence of chronic kidney disease (Scientific Reports, 10: 144, 2020).

#### **INMA subprogramme:**

In 2019, fifteen CIBERESP groups (26% of the total number of groups) of 7 Autonomous Communities, carried out multidisciplinary and cooperative research reflected in joint publications, collaborative projects and researcher mobility. Collaborations with CIBERES, CIBERSAM, CIBERDEM, CIBEREHD and CIBEROBN, and with RedSAMID were established and international collaborations were strengthened: European network of birth cohorts (publications and joint projects), now consolidated in the consortium ([www.birthcohorts.net](http://www.birthcohorts.net); [www.lifecycle-project.eu](http://www.lifecycle-project.eu)). The inclusion of new birth cohorts from other Autonomous Communities (GENEIDA, NELA, BiSC, Gijón) was also initiated as well as the creation of joint databases, testing of old hypotheses, generation of new ones, and collaborative publications.

Main lines of research: 1) child health in the pre- and postnatal stage (obesity, asthma, neurodevelopment, nutrition, exposure to air pollution, persistent and non-persistent chemical compounds and electromagnetic fields, and (epi) genetics). 2) adolescent health (sexual development, sleep problems, stress, physical activity and sedentary lifestyle, obesity, cardio-metabolic health, inflammation markers, "exposome", microbiome, metabolomics and biomonitoring studies).

## **P6. Evaluation of healthcare services**

**Coordinator:** Antoni Serrano Blanco\*

(\*Until November the coordinator was Dr. Jordi Alonso)

**Group led by Jordi Alonso Caballero (PI):** Publication of a Universal Cohort Study, which concludes that the detection of mental disorders and the promotion of participation can reduce suicidal ideation among university students. Mood disorder (12 months) is the strongest risk factor for suicidal ideation at follow-up, while a sense of belonging to the university has a protective effect.

Source: Blasco MJ, Vilagut G, Alayoa I, Almenara J, Cebrià AN, Echeburúa E et al. *First-onset and persistence of suicidal ideation in university students: A one-year follow-up study. Journal of Affective Disorders* 2019; 256: 192-204.

**BIBLIOPRO:** The project of the systematic review of the application of PRO instruments in Spain and the evidence-based recommendations is ongoing. The platform has increased the number of users (19,316), currently providing information and access to 2,027 questionnaires. There were two new developments in 2019 for the internationalisation of the platform: the new BiblioPRO International website and online access for the evaluation of metric properties using the EMPRO tool.

**Group led by Victoria Serra Sutton (PI):** Publication of 26 articles and 9 technical reports that issued opinions or recommendations for decision-making in the clinical setting and for service planning. Three EIT-Health projects (*promoting innovation in health*) were awarded, in which group researchers participate with other institutions, along with private companies.

Collaboration began in a new project financed by the Fondo de Investigación Sanitaria (Health Research Fund) (PI19/00111) headed by the group led by Antoni Serrano Blanco.

The participation of group members in the Bioethics Committee of Catalonia, the Technical Commission in the field of clinical documentation and the Commission for the promotion of medical devices has been ongoing.

The projects *Act on Dementia Joint Action (Grant Agreement, GA No. 678481)* and *Act on Scale Joint Action (GA 709770)* have been completed.

**Group led by Fernando G. Benavides (PI):** Support guides for patients and professionals to promote the recognition of occupational diseases at the Instituto Nacional de la Seguridad Social.(National Institute of Social Security).

A research project is being carried out with the aim of making visible the burden of Occupational Diseases on the National Health System. In this project, financed by the Instituto de Salud Carlos III FIS (CEPS PI16 / 00061), 13 hospitals from all over Spain participate.



- Guide 1 - Su enfermedad tiene que ver con el trabajo (Your illness has to do with your job) ([https://www.upf.edu/documents/3192961/3207869/2018\\_11\\_29\\_GUIA+1+PROYECTO+CEPS.pdf/b696d3a3-ed88-a22b-2424-53bfbf43d86b](https://www.upf.edu/documents/3192961/3207869/2018_11_29_GUIA+1+PROYECTO+CEPS.pdf/b696d3a3-ed88-a22b-2424-53bfbf43d86b))
- Guide 2 - Hacer visible la enfermedad profesional (Making occupational disease visible) ([https://www.upf.edu/documents/3192961/3207869/2019\\_03\\_01\\_GUIA+2+CEPS.pdf/c9344130-3ab8-8418-99d8-883f3b5cc77c](https://www.upf.edu/documents/3192961/3207869/2019_03_01_GUIA+2+CEPS.pdf/c9344130-3ab8-8418-99d8-883f3b5cc77c))

Participation in the VI Meeting of the Expert Network on Working Conditions, Employment and Health Surveys (ECOTES Network) held on June 26-27, 2019 in Montevideo (Uruguay).

The Network has a website in Spanish, English and Portuguese <http://www.ecotes.una.ac.cr/> that will help further their objectives and which has been designed and financed financially by the Group.

**Group led by Antoni Serrano Blanco (PI):** Dr. Maria Rubio Valera obtained a Miguel Servet contract awarded by the ISCIII. The group has obtained two FIS projects focused on the study of adherence to antipsychotics and their derived costs and on the study of non-initiation of drugs in the pediatric population with mixed methodology.

Dr. Maria Iglesias González defended her doctoral thesis entitled "*Effectiveness and feasibility of watchful waiting for the management of major depression in primary care*" at the Universitat de Barcelona and obtained the qualification of cum laude.

## P7. Clinical epidemiology

**Coordinator:** José Ignacio Pijoán Zubizarreta

In 2019, several new financed competitive projects were obtained in the AES 2019 call: i) "Analysis of the prognostic value of biomarkers in sepsis. Series of Systematic Reviews and GRADE recommendations for clinical practice" with the participation of the programme groups of Javier Zamora (leader), José Ignacio Emparanza Knörr and Xavier Bonfill Cosp; ii) "Analysis and improvement of the adequacy of the chemotherapy prescription at the end of life" of the groups led by X. Bonfill and I. Emparanza, along with other groups.

We have continued making progress in carrying out actions to transfer the knowledge available in the scientific literature to clinical practice through the constitution of new MAPAC commissions to improve the adequacy of care in Spanish hospitals and the consolidation of existing ones. Some of the cooperative projects derived from the MAPAC initiative have yielded results published this year, such as: "Opiniones, barreras y facilitadores de los profesionales de la salud hacia las prácticas clínicas de poco valor en el ámbito hospitalario" ("Opinions, barriers and facilitators of health professionals towards clinical practices of little value in the hospital setting"), published in Gaceta Sanitaria by Ignacio Ferreira's group; or, in the field of rapid reviews: "*Rapid reviews of medical tests used many similar methods to systematic reviews but key items were rarely reported: a scoping review*", published in the *Journal of Clinical Epidemiology* by the groups led by X. Bonfill, I. Emparanza and J. Zamora.

The DIANASALUD platform has been updated with 178 new recommendations on low-value clinical practices.

Several Programme groups have led or participated in the preparation of Cochrane Reviews published in 2019, highlighting, for example: "*Plasma interleukin-6 concentration for the diagnosis of sepsis in critically ill adults*" and "*Buffered solutions versus 0.9% saline for resuscitation in critically ill adults and children*".

We have obtained the first results of the analysis of large population-based clinical and administrative databases for the study of therapeutic adherence and health results: "*Persistence with dual antiplatelet therapy after percutaneous coronary intervention for ST-segment elevation acute coronary syndrome: a population-based cohort study in Catalonia (Spain)*", published in BMJ Open by the groups led by I. Ferreira and I. Emparanza.

Other noteworthy milestones of the Programme are: obtaining the IV SHAM Award in recognition of the best projects in patient safety, quality of care, prevention and management of health risks carried out in Spain for the study "Evaluation of an evidence-based intervention to reduce central vascular catheter-associated bacteremia in very low birth weight infants. INBERBAC-Neo Project" by the groups of José Ignacio Emparanza Knörr (leader), Ignacio Ferreira González, Javier Zamora and Xavier Bonfill Cosp and the recognition of the Cochrane Centre of the community of Madrid (Javier Zamora's group) as a Cochrane associate center.

In 2019, the CIBERESP Scientific Conference of the Clinical Epidemiology programme on “Rapid Reviews in the healthcare setting” was organised. The meeting “The Cochrane Library in the framework of evidence-based health care” was also held. Presentation by Cochrane Madrid ” at the Spanish Ministry of Health, Consumer affairs and Social Welfare, in which the groups of X. Bonfill, J. Zamora, B. Lumberras Lacarra and J.I. Emparanza made presentations.

# Training Programme

**Coordinator:** Beatriz Pérez Gómez

The Training Programme has maintained its two basic lines of action: mobility actions, designed to facilitate contact and work with other national or international groups, and improvement actions, aimed at improving and rewarding the quality of scientific work or enhancing its dissemination in Public Health forums.

In 2019, the categories of **mobility grants**, created to promote the collaboration of CIBERESP researchers with each other and with other groups, have been maintained. These grants are intramural, meaning that they are intended exclusively for CIBERESP staff. At the national level, a total of 4 grants have been offered for short stays between CIBERESP groups. International mobility has also been enhanced with a total of 3 grants issued this year, through short three-month stays that CIBERESP calls annually to enable its doctoral students to obtain an international mention, aimed at contracted and assigned staff and contributors; as well as stays of up to 3 months in prestigious international centres aimed exclusively at contracted personnel from the thematic area.

The **extramural improvement grants** are open to researchers from outside the CIBERESP area and are a good tool to enhance collaboration with other CIBER areas. These aim to promote quality research in Public Health. In 2019, the existing agreement with CIBEROBN, CIBERONC and CIBERCV has been maintained to collaborate in the Encounter for Excellence in Public Health Research that CIBERESP traditionally organises at the Public Health Summer School in the Lazareto de Maó in Menorca. This meeting is intended to provide young CIBER scientists in training the opportunity to directly debate and exchange ideas about their doctoral thesis projects in an informal setting with accredited scientists in Epidemiology and Public Health. In the 2019 call, a total of 10 grants were offered, of which 7 were funded by CIBERESP, while the areas of Obesity and Physiopathology of Nutrition (CIBEROBN), and that of Cardiovascular Diseases (CIBERCV) and Cancer (CIBERONC) each financed an attendance grant for doctoral students in their own field. This collaboration is very positive and we hope that the agreement will continue in 2020.

Furthermore, CIBERESP collaborates with the Spanish Society of Epidemiology (SEE) with the financing of the Prizes for the 10 best communications presented by young research staff at the SEE Annual Scientific 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 current format, this award includes a diploma and covers the cost of registering the winner at the meeting the following year. The Training Programme also encourages that training or scientific activities carried out by other entities establish special more favourable conditions for CIBERESP members to participate.

# Platforms

## BiblioPRO

BiblioPRO is a virtual repository of Patient Reported Outcomes (PROs). Its mission is to promote the measurement of PROs through the preparation of detailed reports on each instrument through systematic literature reviews, scientific evaluations, and specialised training.

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

### Repository

- REGISTERED USERS: 3,208 new users (19,316 accumulated users: 26% increase compared to 2014-2018).
- NEW INSTRUMENTS: 23 new instruments (total of 2027 instruments; 1.1% compared to 2014-2018).
- MONTHLY VISITS: an average of 7,300 visits a month, (11% compared to 2014-2018).
- SUBLICENCES: 489 licenses granted, similar to the previous period.
- SYSTEMATIC REVIEW:
  - Publications in 2016 - peer review of 2,400 titles and 942 summaries; Data extraction from 738 articles, and 279 instruments identified.
  - Publications in 2017- 4,691 identified articles, 1604 for full text; information extraction of approximately 200.

### BiblioPRO International

- Although initially proposed as a new European website of BiblioPRO, it was finally decided that non-European countries would also be included, with the new BiblioPRO International website.
- The url [www.biblioprointernational.org](http://www.biblioprointernational.org) has been reserved and is waiting to be launched in 2020.
- Progress is being made in distribution agreements with:
  - SF Health Surveys (Optum-Insight): Europe and Latin America.
  - Test of adhesion to inhalers (Chiesi, SEPAR), 17 languages.
  - Hereditary angioedema-QoL questionnaire for adults (FIBHULP-IdiPAZ): 19 languages.

## Research

- Competitive research projects:
  - “Application of PRO instruments in Spain:”, PI Olatz Garin and team with CIBERESP researchers and BiblioPRO Scientific Committee (PI16 / 00130-ISCIII / FEDER), 2017-2019. Extended until 2021.
  - “Effectiveness of the treatment of massive injuries of the shoulder rotator cuff evaluated with relevant results for the patient:”. Co-PIs: Montserrat Ferrer and Carles Torrents, together with researchers from the BiblioPRO team (PI18 / 00152-ISCIII / FEDER), 2019-2021.
- Cooperation in the BIBLIOINDICA project to design a library of healthcare indicators. CIBERESP and REDISSEC joint initiative.

## EMPRO Platform

- The new online platform of the EMPRO tool has been developed, which measures the metric characteristics of PROs. The management of the platform will be centralized, through the administrator version (IMIM).
- A pilot test is being carried out in an international study on instruments for assessing oral health in older adults.
- Presented at the CIBERESP conference.

## IV Scientific Meeting

- IV BiblioPRO Scientific Conference (02/21/2019) at ENS, with the title “The role of PROs in the evaluation of health service providers”.
- 119 professionals participated, in addition to participants via streaming, with hundreds of views made. Reduced fee for CIBER researchers.
- The meeting had the institutional support of the IMIM Foundation, the ENS (National Security Scheme) and CIBERESP. Sponsored by CHIESI and MSD.

## Publications in 2019

- Zaror C, et al.. Assessing oral health-related quality of life in children and adolescents: a systematic review and standardized comparison of available instruments. Clin Oral Investig 2019;23(1):65-79.
- Hernández G et al.. EuroQol (EQ-5D-5L) Validity in Assessing the Quality of Life in Adults With Asthma: Cross-Sectional Study. J Med Internet Res 2019;21(1):e10178.
- Garcimartín P, et al. Cross-cultural adaptation to Spanish of the Patient empowerment in long-term conditions. Aten Primaria 2019;51(1):24-31.

# Scientific Production

## Publications

### No. of publications in 2019

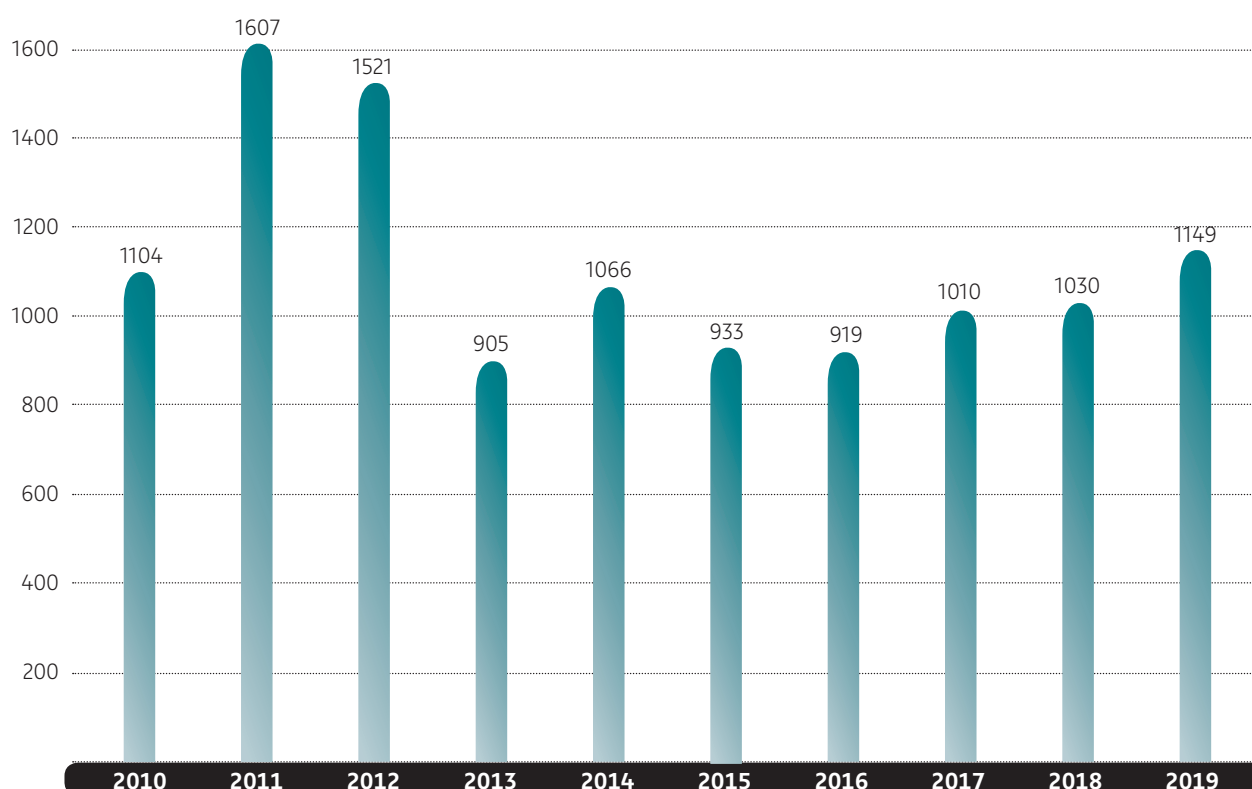
TOTALS	1149
Q1	623
D1	311

### Collaborative publications

CIBERESP	341
CIBER*	242

\*Among various thematic areas

### Evolution of publications 2010-2019





## 10 most relevant publications by impact factor

IF	Publication
9,055	DOBANO C., NHABOMBA A.J., MANACA M.N., BERTHOUD T., AGUILAR R., QUINTO L. ET AL. <i>A Balanced Proinflammatory and Regulatory Cytokine Signature in Young African Children Is Associated with Lower Risk of Clinical Malaria. Clinical Infectious Diseases.</i> 2019;69(5):820-828.
7,943	TAMAYO-URIA I., MAITRE L., THOMSEN C., NIEUWENHUIJSEN M.J., CHATZI L., SIROUX V. ET AL. <i>The early-life exposome: Description and patterns in six European countries. Environment International.</i> 2019;123:189-200.
7,943	FONT-RIBERA L., MARCO E., GRIMALT J.O., PASTOR S., MARCOS R., ABRAMSSON-ZETTERBERG L. ET AL. <i>Exposure to disinfection by-products in swimming pools and biomarkers of genotoxicity and respiratory damage – The PISCINA2 Study. Environment International.</i> 2019;131.
7,786	LEVIE D., KOREVAAR T.I.M., MULDER T.A., BATH S.C., DINEVA M., LOPEZ-ESPINOSA M.-J. ET AL. <i>Maternal thyroid function in early pregnancy and child attention-deficit hyperactivity disorder: An individual-participant meta-Analysis. Thyroid.</i> 2019;29(9):1316-1326.
7,339	JULVEZ J., FERNÁNDEZ-BARRÉS S., GIGNAC F., LÓPEZ-VICENTE M., BUSTAMANTE M., GARCIA-ESTEBAN R. ET AL. <i>Maternal seafood consumption during pregnancy and child attention outcomes: a cohort study with gene effect modification by PUFA-related genes. International Journal of Epidemiology.</i> 2019.
6,714	BUSTAMANTE M., HERNANDEZ-FERRER C., TEWARI A., SARRIA Y., HARRISON G.I., PUIGDECANET E. ET AL. <i>Dose and time effects of solar-simulated ultraviolet radiation on the in vivo human skin transcriptome. British Journal of Dermatology.</i> 2019.
6,68	MAYOR A., BASSAT Q.. <i>“Resistance” to diagnostics: A serious biological challenge for malaria control and elimination. EBioMedicine.</i> 2019;50:9-10.
6,529	CASTELLO A., URQUIA M., RODRIGUEZ-ARENAS M.A., BOLUMAR F.. <i>Missing girls among deliveries from Indian and Chinese mothers in Spain 2007–2015. European Journal of Epidemiology.</i> 2019.
6,402	CANO-IBÁÑEZ N., GEA A., RUIZ-CANELA M., CORELLA D., SALAS-SALVADO J., SCHRODER H. ET AL. <i>Diet quality and nutrient density in subjects with metabolic syndrome: Influence of socioeconomic status and lifestyle factors. A cross-sectional assessment in the PREDIMED-Plus study. Clinical Nutrition.</i> 2019.
6,402	CANO-IBÁÑEZ N., MARTÍNEZ-GALIANO JM, AMEZCUA-PRieto C, OLMEDO-REQUENA R, BUENO-CAVANILLAS A, DELGADO-RODRÍGUEZ M. <i>Maternal dietary diversity and risk of small for gestational age newborn: Findings from a case-control study. Clinical nutrition (Edinburgh, Scotland).</i> 2019.

## CIBERESP Groups. Publications in 2019

Group Leader	Publ.	Q1	D1	Institution/Centre	Province
 Alemany Vilches, M <sup>a</sup> Eulalia	18	10	2	Instituto Catalán de Oncología	Barcelona
 Alonso Caballero, Jordi	35	18	9	Consorci Mar Parc Salut de Barcelona	Barcelona
 Belza Egozcue, María José (1)	33	12	4	Instituto de Salud Carlos III - Centro Nacional de Epidemiología	Madrid
Bolumar Montrull, Francisco	48	38	19	Universidad de Alcalá - Facultad de Medicina	Madrid
 Bonfill Cosp, Xavier	49	22	16	Instituto de Investigación del Hospital de la Santa Creu i Sant Pau	Barcelona
 Borrell Thió, Carme	50	24	8	Agencia de Salud Pública de Barcelona	Barcelona
 Bueno Cavanillas, Aurora	43	28	7	Universidad de Granada - Facultad de Medicina	Granada

Group Leader	Publ.	Q1	D1	Institution/Centre	Province
 Calderón Sandubete, Enrique José	13	3	1	Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla - Hospital Virgen del Rocío	Sevilla
 Casabona Barbara, Jordi	15	4	2	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	67	42	15	Instituto de Salud Pública de Navarra	Navarra
 Chirlaque López, Ma Dolores	70	48	24	Fundación para la Formación e Investigación Sanitarias de la Región de Murcia (FFIS) - Dirección General de Salud Pública	Murcia
 Daponte Codina, Antonio	21	7	2	Escuela Andaluza de Salud Pública	Granada
 Delgado Rodríguez, Miguel	65	45	11	Universidad de Jaén - Facultad de Ciencias de la Salud	Jaén
 Domínguez García, Ángela	26	10	5	Universidad de Barcelona - Facultad de Medicina	Barcelona
 Echevarría Mayo, Juan Emilio	24	11	8	Instituto de Salud Carlos III - Centro Nacional de Epidemiología	Madrid
 Emparanza Knörr, José Ignacio	4	1	1	Asociación Instituto Biodonostia - Hospital Donostia	Guipúzcoa
 Ferreira González, Ignacio	17	5	3	Fundación Hospital Universitario Vall d'Hebron - Institut de Recerca (VHIR) - Hospital Vall d'Hebron	Barcelona
 Figueiras Guzmán, Adolfo	46	21	6	Universidad de Santiago de Compostela - Facultad de Medicina	A Coruña
 Figuerola Borrás, Jordi	18	13	9	Agencia Estatal Consejo Superior de Investigaciones Científicas - Estación Biológica de Doñana	Sevilla
 Galán Montemayor, Juan Carlos	17	10	3	Servicio Madrileño de Salud - Hospital Ramón y Cajal	Madrid
 García Benavides, Fernando	34	11	2	Universidad Pompeu Fabra - Centro de Investigación en Salud Laboral	Barcelona
 Gómez de la Cámara, Agustín	9	3	0	Servicio Madrileño de Salud - Hospital Universitario 12 de Octubre	Madrid
 Ibarluzea Mañolagoitia, Jesús	67	49	24	Asociación Instituto Biodonostia - Subdirección de Salud Pública de Guipuzkoa	Guipúzcoa
 Íñiguez Hernández, Carmen	44	31	22	Fundación para la Investigación Sanitaria y Biomédica de la Comunidad Valenciana (FISABIO)	Valencia
 Kogevinas, Emmanouil (3)	117	87	51	Fundación Privada Instituto de Salud Global Barcelona (ISGlobal) - Campus Mar	Barcelona
 Larrauri Cámara, Amparo	20	12	7	Instituto de Salud Carlos III - Centro Nacional de Epidemiología	Madrid
 López Medina, María José	19	7	1	Agencia de Salud Pública de Barcelona	Barcelona
 Lumbreras Lacarra, Blanca	14	4	0	Universidad Miguel Hernández	Alicante
 Marcos Dauder, Ricard	9	6	2	Universidad Autónoma de Barcelona	Barcelona
 Martí Puig, Eulalia	7	7	2	Universidad de Barcelona	Barcelona
 Menéndez Santos, Clara	16	10	7	Hospital Clínic de Barcelona	Barcelona

Group Leader	Publ.	Q1	D1	Institution/Centre	Province
 Morales Suárez-Varela, María Manuela	26	13	3	Universidad de Valencia - Facultad de Medicina	Valencia
 Moreno Aguado, Víctor	45	32	15	Instituto Catalán de Oncología	Barcelona
 Moya Simarro, Andrés	45	28	13	Universidad de Valencia - Facultad de Medicina	Valencia
 Muñoz Almagro, María Carmen	40	16	6	Fundación para la Investigación y Docencia Sant Joan de Deu - Hospital Sant Joan de Deu	Barcelona
 Olea Serrano, Nicolás	29	20	12	Fundación para la Investigación Biosanitaria en Andalucía Oriental (FIBAO) - Hospital Clínico San Cecilio	Granada
 Pollán Santamaría, Marina	52	39	13	Instituto de Salud Carlos III - Centro Nacional de Epidemiología	Madrid
 Porta Serra, Miquel	24	14	8	Consorci Mar Parc Salut de Barcelona	Barcelona
 Rius Gibert, Cristina	25	10	4	Agencia de Salud Pública de Barcelona	Barcelona
 Rodríguez Artalejo, Fernando	51	35	17	Universidad Autónoma de Madrid	Madrid
 Ruiz Pérez, Isabel	17	6	5	Escuela Andaluza de Salud Pública	Granada
 Sáez Zafra, Marc	32	16	3	Universidad de Girona	Girona
 Sánchez Pérez, María José	62	40	21	Escuela Andaluza de Salud Pública	Granada
 Sanfeliu Pujol, Coral (2)	5	3	0	Agencia Estatal Consejo Superior de Investigaciones Científicas - Instituto de Investigaciones Biomédicas de Barcelona	Barcelona
 Schröder, Helmut	28	19	13	Consorci Mar Parc Salut de Barcelona	Barcelona
 Serra Sutton, Victoria	23	11	6	Agència de Qualitat i Avaluació Sanitàries de Catalunya (AQuAS)	Barcelona
 Serrano Blanco, Antonio	8	4	1	Fundación para la Investigación y Docencia Sant Joan de Deu - Parc Sanitari Sant Joan de Deu	Barcelona
 Sunyer Deu, Jordi	129	92	58	Fundación Privada Instituto de Salud Global Barcelona (ISGlobal) - Campus Mar	Barcelona
 Tardón García, Adonina	60	47	24	Universidad de Oviedo - Facultad de Medicina	Asturias
 Zamora Romero, Javier	37	18	16	Servicio Madrileño de Salud - Hospital Ramón y Cajal	Madrid
 Amo Valero, Julia del*	-	-	-	Instituto de Salud Carlos III - Centro Nacional de Epidemiología	Madrid

(1) Luis de la Fuente Hoz up to 01/10/2019  
(2) Eduard Rodríguez Farré up to 29/11/2019  
(3) PI Replaced in 2020

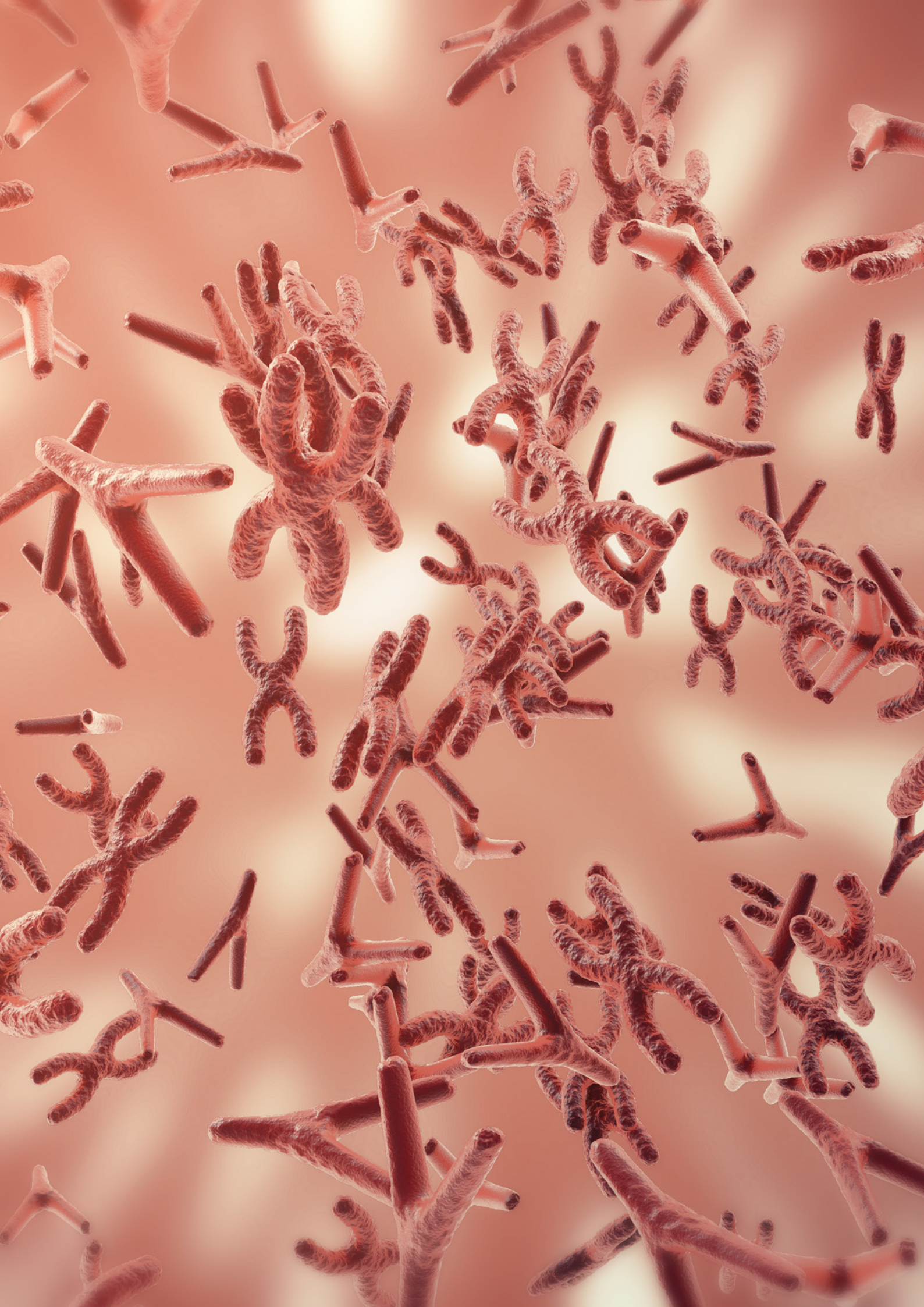
\* CIBERESP Associated Group



**Frailty  
and Healthy  
Ageing**

*cüberfes*







# Presentation by the Scientific Director

**Leocadio Rodríguez-Mañas**



Throughout 2019, CIBERFES has completed the composition of all its governing bodies, its Scientific Advisory Committee and has also joined senior citizen organisations. Collaborations with two other areas (CIBEROBN and CIBER-BBN) have also been furthered. In addition, cooperation schemes with leading groups have been consolidated (Johns Hopkins, University of Toulouse, INGER of Mexico, King's College, Aston University, Harvard University, University of Melbourne, Università Cattolica del Sacro Cuore-Roma, University of Milan, among others) and other cooperative networks, such as the Canadian Frailty Network. Collaboration with WHO continues, with its ageing programme through the *Clinical Consortium on Healthy Ageing-CCHA* and with its rehabilitation programme.

During this period, we have continued to sign research contracts with the industry (Abbott), and industrial activities emerging from CIBERFES groups (GREMPAL, University of Murcia, Reina Sofía University Hospital in Córdoba) have been consolidated.

Regarding scientific advances, genetic, epigenetic, omics and nutritional aspects have been established, the role of imaging and electroencephalographic biomarkers and stem cells in frailty and in the ageing process itself has been evaluated, with special emphasis on mitochondrial functioning, and animal models of frailty have been developed. There have also been findings in sarcopenia, osteoporosis, nutrition, dementia, and physical activity. Observational and interventional clinical studies have been carried out at these same organisations, as well as in cardiac and endocrine (diabetes) pathology, hip fracture or function. Accordingly, we have obtained funding through the regular call of the AES to launch a clinical frailty cohort (COHORFES), in which 9 CIBERFES groups participate, and an intervention study, in which 5 CIBERFES groups participate, to validate the strategy to tackle frailty recommended by the Ministry of Health and by the European Joint Action ADVANTAGE, which has been led by a group from our CIBER area. Data from clinical and population cohorts from various European countries exceeding 50,000 samples have continued to be evaluated.

In 2019, we have participated in and led European calls within various programmes, especially H2020 and EIT-Health. To be noted is the completion of the coordination of the European Joint Action ADVANTAGE and the start of the H2020 DIABFRAIL-LATAM project, endowed with 4 million euros, coordinated by CIBERFES and in which 4 groups from our CIBER participate. We are also leading the POSITIVE (EIT-HEALTH) project, in which two CIBERFES groups participate and which will evaluate the effectiveness of a technological platform in the detection, intervention and non-invasive home monitoring of frail elderly people or those at risk for frailty.

Lastly, we continue to work on establishing institutional relations with international research and healthcare policy organisations.

# Programmes

## **P1 - Basic, clinical and environmental mechanisms associated with the development of frailty. Impact on Healthcare Systems**

**Coordinator:** José Viña Ribes

Dr. Viña's group has worked on the search for biomarkers to determine Alzheimer's disease and the transition from minimal cognitive impairment to disease, in collaboration with CIBERNED (Dr. Jesus Ávila and Dr. Miguel Medina, Madrid). In addition, work has been carried out on the determination of oxidative stress parameters in diabetic patients and their relationship with frailty, in collaboration with Dr. Rodríguez Mañas and various CIBERFES groups (DIABLATAM project). Within the group, another milestone to highlight is the identification of a G6PD mouse as a vigorous mouse model.

Dr. Andres-Lacueva's group, within the framework of the EU JPIHDHL projects, "Joint Action Healthy Diet for a Healthy Life" has developed a metabolomics tool that allows the simultaneous quantification of more than 1000 metabolites of the Human Exposome enabling the robust characterisation of dietary intake, intestinal microbiome activity, exposure to contaminants and pesticides, as well as lifestyle biomarkers and metabotypes of risk for frailty syndrome. Dr. Andres-Lacueva organised the European summer school, INJOY with the collaboration of the groups led by Leocadio Rodríguez-Mañas and Pedro Abizanda, with funding from EIT Health and H2020.

The CronoLab group at the University of Murcia, thanks to its being part of CIBER, has been able to participate in a European DIABFRIL LATAM project led by CIBER itself, which began in early 2019, as well as a research contract from the CSIC Foundation (Project pilot for the establishment of a predictive model as a possible modulator of healthy ageing-ModulEn), in collaboration with the CIBERFES group led by Mayte Moreno. Collaborations have also been maintained with other areas of the CIBER, specifically with CIBERES through the CIBERES-FES2018-01 projects with the group led by Ramón Farré and CIBERES-FES2018-05 led by Olga Mediano San Andrés.

Dr. Mikel Izquierdo (Pamplona) has studied the effect of multi-component physical exercise programs in the prevention of frailty and risk of falls, with special interest in people admitted to the hospital setting, oncogeriatrics, acute units, COPD, diabetes and those who live in the community. They have developed systems for the screening for frailty and the analysis of muscle function using inertial measurement units. Dr. Izquierdo's group, together with Dr. Rodríguez Mañas and Dr. Viña, work on the European Diablatam project.

Dr. Enriquez and his group work on elucidating the molecular mechanisms that lead to ageing, using conplastic and heteroplasmic animal models. They study the bioenergetics in the strains of mice in relation to the variants of mitochondrial DNA, analyzing both cellular metabolites and ROS production, as second messengers that lead to the process of frailty and ageing.

Dr. Bolaños, in collaboration with Dr. Enríquez, has supported the study that explains mitochondrial segregation in different neural cells and, together with Dr. Matheu, they have studied the loss of neural precursors and their relationship with cognitive deterioration associated with ageing.

In addition, Dr. Bolaños's group has completed a work that will allow us to decipher a mechanism that explains cognitive and motor vulnerability due to an alteration in neuronal energy metabolism.

Dr. María Ángeles Arévalo's group studies microglial phagocytosis and the microglial response in the ageing brain that may contribute to sexual differences in the manifestation of neurodegenerative diseases.

Dr. Matheu, in addition to the collaborations mentioned above, is interested in centenarians and, together with Dr. Viña, scheduled a symposium on the role of centenarians as a model of healthy ageing.

Finally, Dr. Acuña and his group have evaluated the effect of melatonin in mice to enhance the oncostatic effect of other drugs

## **P2 - Tackling frailty. Detection, screening, diagnosis and treatment. Healthcare models.**

**Coordinator:** Adolfo Díez Pérez

The research of the group led by Dr. Xavier Nogués focuses mainly on the study of bone fragility as an underlying cause of deterioration in the quality of life in the elderly population. During 2019, the first data from the National Registry of Hip Fractures (RNFC), a multicentre, prospective and continuous Spanish registry that began in 2017, were published. 7,208 people from 54 hospitals were registered, with an average age of 86, 7 years (DE 5.6). The RNFC is the largest prospective database that provides data on the profile of patients hospitalized for hip fracture in Spain (Ojeda-Thies C, et al. *Osteoporos Int.* 2019). In another cohort study (SPARE-HIP) it has been confirmed that hip fracture produces a large decrease in the ability to perform activities of daily living and in health-related quality of life as reported by patients with only partial recovery among survivors 4 months after the fracture (Prieto-Alhambra D et al. *Arch Osteoporos.* 2019). Furthermore, individuals with T2DM have been found to be at increased risk of hip fracture and post-fracture mortality in the SIDIAP cohort (Tebé C et al. *Osteoporos Int.* 2019.).

Microindentation studies in men showed that BMSi discriminates prior fracture and parental hip fracture, which suggests that this parameter may be useful to identify men who are at higher risk of fracture (Rufus-Membere P et al. *Endocrinology.* 2019). In addition, *radiofrequency echographic multi spectrometry* (REMS) has been evaluated as another tool for estimating bone resistance, and thus for its use in the diagnosis of osteoporosis and prediction of fracture risk (Diez-Perez A et al. *Aging Clin Exp Res.* 2019).

In a study, within the ESCEO working group, a series of recommendations were established to improve adherence to antiosteoporotic treatments for implementation within clinical practice (Hilgsmann M et al. *Osteoporos Int.* 2019).

Along these same lines, in another study, we recommend using the serum PINP bone markers and the  $\beta$ CTX-I to control adherence to treatment with oral bisphosphonates (Lorentzon M et al. *Adv Ther.* 2019).

As cases needing special attention, we evaluated adherence to Aromatase inhibitors (AIs) in women with breast cancer (B-ABLE cohort) as these can considerably increase joint pain and loss of bone mass, thereby reducing health-related quality of life, mainly during the first year of treatment. Patients previously treated with tamoxifen experienced increased pain when they switched to AI therapy and showed a very high risk of discontinuing therapy for the first 12 months (Pineda-Moncusi M, et al. *Breast Cancer Res Treat.* 2019). In another population at risk, in this case HIV positive patients, we have published a study in which we observed a correlation between changes in bone quality and the inflammatory environment in individuals. Furthermore, among the underlying mechanisms, we highlight that the Wnt pathway has a significant role in the recovery of bone quality by means of antiretroviral treatment (Lerma-Chippirraz E, et al. *J Antimicrob Chemother.* 2019).

# Training Programme

**Coordinator:** Pedro Abizanda Soler

In 2019, CIBERFES has carried out the following training activities:

- We have maintained an open call system for mobility grants for CIBERFES researchers to finance or co-finance national or international stays, preferably within the same area. Priority is given to applications for stays in CIBERFES groups that are developing a project (financed or intramural) with the applicant's original CIBERFES group. This not only fosters collaboration between CIBERFES groups, but also the acquisition of knowledge and skills in fields different from those in which young researchers usually work.
- CIBERFES has actively participated with various exhibitions in the 'INJOY Summer School EIT-HEALTH' held from June 11-20, 2019 at the University of Barcelona, a 10-day work program for 30 professionals from all over the world interested in developing new business solutions to encourage citizens to modify their eating behaviors and ensure healthy ageing. This training initiative, aimed at interested entrepreneurs, students and researchers, aims to promote innovative business solutions aimed at empowering citizens to modify eating behaviors in favour of healthy ageing.
- Collaboration in consensus documents, such as that developed by Dr. María Teresa Vidán on the assessment of frailty in the elderly with heart disease, published in the Spanish Journal of Cardiology. The document highlights that frailty is associated with a worse prognosis in older patients with heart disease, and must therefore be systematically evaluated.
- During 2019, the 2020 scientific meetings were prepared, which have had to be postponed due to COVID-19.

CIBERFES has also participated in other extramural training forums which are worth mentioning:

- 'Final Meeting of the Advantage Joint Action' on September 12, 2019 in Toledo, with the presentation in Spain of the ADVANTAGE Joint Action reports on frailty and the debate on the most appropriate way to tackle frailty, in which José Viña Ribes, Pedro Abizanda Soler, Francisco José García García and Leocadio Rodríguez Mañas participated. This also coincided with the presentation of the Strategic Plan for Geriatrics for Castilla-La Mancha.
- Participation in the IX edition of the International Conference on Frailty and Sarcopenia Research (ICFSR 2019), the most important forum worldwide in this field. It was held from February 20 to 22, 2019 in Miami. CIBERFES was present through its scientific director, Leocadio Rodríguez, member of the ICFSR Scientific Advisory Committee, and José Viña, who moderated one of the programmed symposia: 'Bioenergetics of frailty: from animal models to human evidence'.
- Closing meeting of the European project "FRAILTOOLS" led by the scientific director of CIBERFES, Leocadio Rodríguez, through the Geriatrics Service and the Biomedical Research Foundation of the University Hospi-



tal of Getafe. This European project, which has involved 5 EU hospitals, evaluated the usefulness of existing tools to detect frailty syndrome in healthcare and social centres.

- Kick-off meeting of the Diabfrail-LatAm Programme, coordinated by CIBERFES under the leadership of Leocadio Rodríguez, which aims to implement a model of care for frail and pre-frail elderly people with diabetes in Argentina, Colombia, Mexico, Peru and Chile. The initiative will analyse the effects of a balanced diet, an education programme and an exercise programme on functional capacity and quality of life.
- The Second Meeting on 'Update on the management of elderly people who suffer falls. Are falls the first sign of cognitive failure?', organised by the Spanish Society of Geriatric Medicine (SEMEG), brought together experts in geriatrics on March 22 and 23 at the Infanta Leonor University Hospital in Madrid, with a strong presence of CIBERFES researchers such as Drs. Leocadio Rodríguez Mañas, Pedro Abizanda Soler or Francisco José García García.
- Participation in the organisation of the "1st Euro-Geroscience Conference", held in Madrid on September 19-20, 2019, in which Prof. José Viña Ribes and Prof. Leocadio Rodríguez Mañas made presentations and brought together the best researchers in ageing from around the world.

In 2019, the design of a master's degree in Frailty and Healthy Ageing was started for implementation in the 2019-2020 academic year, although for logistical reasons the decision was taken to postpone this to 2020-2021. We are currently in the process of reviewing time frames due to COVID-19.



# Scientific Production

## Publications

### No. of publications in 2019

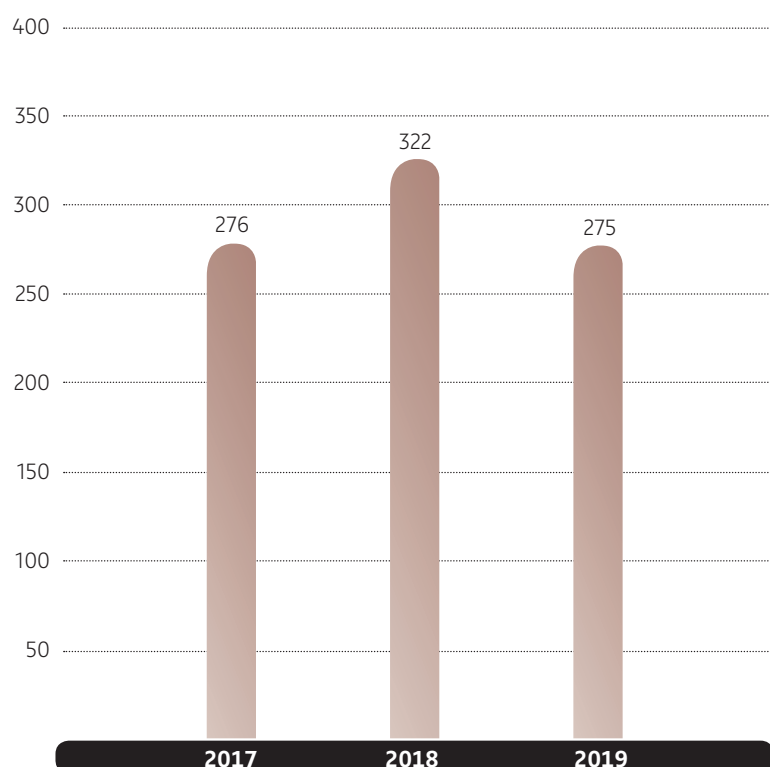
TOTALS	275
Q1	158
D1	63

### Collaborative Publications

CIBERFES	27
CIBER*	57

\*Among various thematic areas

### Evolution of publications 2017-2019












## 10 most relevant publications by impact factor

IF	Publication
59,102	<i>More talk than action: gender and ethnic diversity in leading public health universities</i> (Scopus ID: 85061080145; Pubmed ID: 30739695)
59,102	<i>Knee and hip replacements and the risk of revision</i> (Scopus ID: 85071378623; Pubmed ID: 31478504)
30,641	<i>Healthspan and lifespan extension by fecal microbiota transplantation into progeroid mice</i> (Scopus ID: 85070235329; Pubmed ID: 31332389)
22,415	<i>Regulation of Mother-to-Offspring Transmission of mtDNA Heteroplasmy</i> (Scopus ID: 85075469286; Pubmed ID: 31588014)
15,221	<i>Melatonin alleviates circadian system disruption induced by chronic shifts of the light-dark cycle in Octodon degus</i> (Scopus ID: 85075119375; Pubmed ID: 31677295)
14,548	<i>ER and Nutrient Stress Promote Assembly of Respiratory Chain Supercomplexes through the PERK-eIF2<math>\alpha</math> Axis</i> (Scopus ID: 85065290503; Pubmed ID: 31023583)
14,299	<i>Development and validation of prediction models to estimate risk of primary total hip and knee replacements using data from the UK: Two prospective open cohorts using the UK Clinical Practice Research Datalink</i> (Scopus ID: 85055144444; Pubmed ID: 30337425)
13,965	<i>Most elderly patients hospitalized for heart failure lack the abilities needed to perform the tasks required for self-care: impact on outcomes</i> (Scopus ID: 85070094824; Pubmed ID: 31373161)
12,511	<i>Reference values for handgrip strength and their association with intrinsic capacity domains among older adults</i> (Scopus ID: 85062785956; Pubmed ID: 30843369)
12,511	<i>Gait speed as a mediator of the effect of sarcopenia on dependency in activities of daily living</i> (Scopus ID: 85065526177; Pubmed ID: 31066999)

## CIBERFES Groups. Publications in 2019

Group Leader	Publ.	Q1	D1	Institution/Centre	Province
 Abizanda Soler, Pedro	4	2	0	Servicio de Salud de Castilla La Mancha - Complejo Hospital General de Albacete	Albacete
 Acuña Castroviejo, Darío	11	7	2	Fundación para la Investigación Biosanitaria en Andalucía Oriental (FIBAO) - Hospital Clínico San Cecilio	Granada
 Andrés Lacueva, María Cristina	16	13	9	Universidad de Barcelona - Facultad de Farmacia	Barcelona
 Ara Royo, Ignacio	13	9	2	Universidad de Castilla la Mancha - Facultad de Ciencias del Deporte	Toledo
 Arévalo Arévalo, María Ángeles	15	6	5	Agencia Estatal Consejo Superior de Investigaciones Científicas - Instituto Cajal	Madrid
 Bolaños Hernández, Juan Pedro	7	6	3	Fundación Instituto de Estudios de Ciencias de la salud de Castilla y León - Instituto de Biología Funcional y Genómica	Salamanca
 Enríquez Domínguez, José Antonio	2	2	2	Fundación Centro Nacional de Investigaciones Cardiovasculares	Madrid

Group Leader	Publ.	Q1	D1	Institution/Centre	Province
 García García, Francisco José	9	7	2	Fundación del Hospital Nacional de Paraplégicos	Toledo
 Izquierdo Redín, Miguel	47	25	9	Universidad Pública de Navarra	Navarra
 Madrid Pérez, Juan Antonio	16	9	4	Universidad de Murcia	Murcia
 Matheu Fernández, Ander	10	9	3	Asociación Instituto Biodonostia - Hospital Donostia	Guipúzcoa
 Molinuevo Guix, Jose Luis	8	6	3	Fundación Barcelonabeta Brain Research Center	Barcelona
 Moreno Casbas, Teresa	14	5	1	Instituto de Salud Carlos III - Unidad de Investigación en Cuidados de Salud	Madrid
 Muñoz Torres, Manuel	10	3	0	Fundación para la Investigación Biosanitaria en Andalucía Oriental (FIBAO) - Hospital Clínico San Cecilio	Granada
 Nogues Solán, Francesc Xavier	16	4	1	Consorci Mar Parc Salut de Barcelona - Hospital del Mar	Barcelona
 Priego Capote, Feliciano	9	5	1	Fundación para la Investigación Biomédica de Córdoba (FIBICO) - Hospital Universitario Reina Sofía	Córdoba
 Prieto Alhambra, Daniel	24	13	6	IDIAP Jordi Gol	Barcelona
 Rodríguez Mañas, Leocadio	17	12	4	Servicio Madrileño de Salud - Hospital Universitario de Getafe	Madrid
 Serra Rexach, José Antonio	33	18	7	Servicio Madrileño de Salud - Hospital Gregorio Marañón	Madrid
 Viña Ribes, José	20	14	2	Fundación para la Investigación del Hospital Clínico de la Comunidad Valenciana (INCLIVA)	Valencia

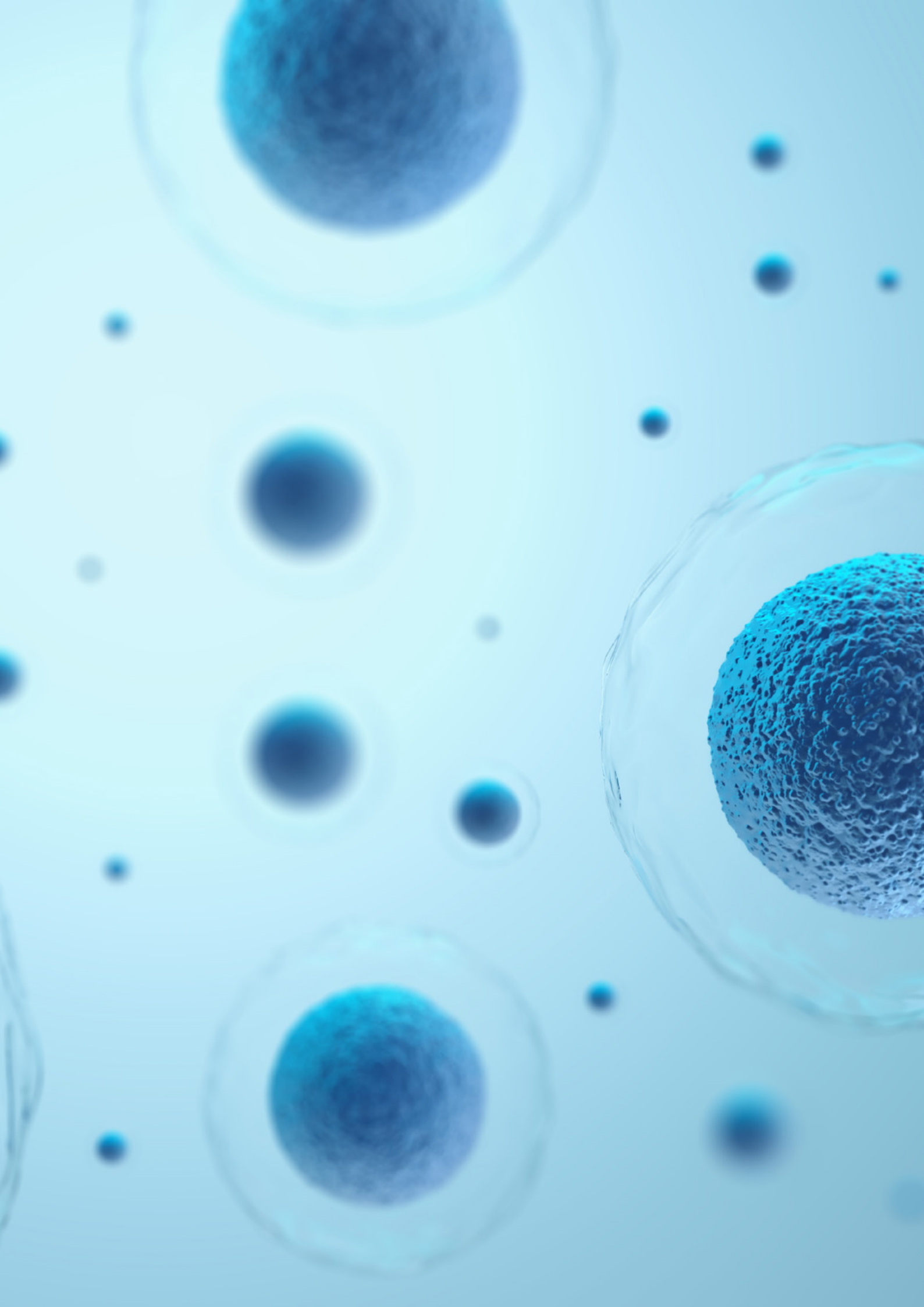
## Clinical Guides

- *Copenhagen Consensus statement 2019: physical activity and ageing.*
- *The next step after anti-osteoporotic drug discontinuation: an up-to-date review of sequential treatment.*
- *Recommendations of the Geriatric Cardiology Section of the Spanish Society of Cardiology for the Assessment of Frailty in Elderly Patients with Heart Disease.*

# **Physiopathology of Obesity and Nutrition**

*cïberobn*





# Presentation by the Scientific Director

**Carlos Diéguez González**



It is a pleasure for me to be presenting the annual report of the activity carried out by the CIBEROBN, representing the scientific area of Obesity and Nutrition area of the public consortium known as CIBER.

The year 2019 was a year in which we continued to consolidate a cooperative research structure, developing medium-long term ambitious projects and proposing and initiating new strategic actions to be increasingly more efficient and effective each year, especially with regard to reaching higher levels of quality, both in terms of knowledge generation and translation. Regarding the latter, we must highlight the CIBEROBN's commitment in both primary and secondary prevention.

2019 has been a highly productive year as the level of publications, internationalisation, development of clinical guidelines and applications for emblematic projects have been maintained, in relation to both the Nutrition and the Obesity Programmes.

In the Nutrition Programme it is noteworthy that PREDIMEDPLUS, in which most of the groups in the programme participate, has reached its fourth year with nearly 7,000 patients under follow-up. This is a randomised, controlled clinical trial of intensive intervention with an energy-restricted Mediterranean diet, increased physical activity and behavioral support compared to a control group. The trial evaluates the effects of this intervention on weight loss and its influence on the reduction of cardiovascular events as the primary outcome. This makes it one of the most ambitious studies in the world in the field of nutrition and will surely have a great impact on future nutrition guides worldwide, even greater than that already achieved by the previous PREDIMED study.

In addition to this study, some "classic" cohorts of this programme have been ongoing such as the SUN cohort (with more than 23,000 subjects) or CORDIOPREV, to name a few. What I would especially like to highlight is that we have reached the goal of one of the strategic lines of our scientific programme which was that our studies encompass ALL AGES OF LIFE. In this context, several cohorts have been promoted, ranging from the prenatal stage "IMPACT (" Improving mothers for a better Prenatal Care ")", to different paediatric populations (CORALS, MELIPOP and STOP), or related to ageing (WAHA). All these developments are leading us to an undoubtedly exciting moment in which the generation of translational knowledge in the field of primary and secondary prevention at all levels is foreseeable.

In the OBESITY Programme, progress has been made in the development of cooperative research, basic and clinical, as well as in promoting the convergence of both aspects. Throughout the year, new pathophysiological mechanisms, new biomarkers, and new therapeutic targets related to obesity and its comorbidities have been proposed. In addition, the development and studies of new cohorts related to neurocognitive aspects and eating disorders have been promoted. This has resulted not only in high-impact publications but also in various clinical guidelines and participation in international consensus documents.

We must highlight 2019 as a year in which our platforms have been consolidated. In the case of FatBank, the sample collection work carried out in recent years has made it possible to plan new large-scale projects, the first of which has been launched this year.

2019 has brought about various changes in governance in line with the challenges set out in our Strategic Plan. Considerable progress has been made in the area of renewal of research talent. Almost half of the CIBEROBN nodes have a CO-PI. It is noteworthy that most of the latter are women and their average age is significantly lower than that of the group leaders. In addition, the renewal of the Steering Committee has begun, with the incorporation of three researchers, which places us in a position of almost equal gender distribution in its composition, with a decrease again in the average age. In this same regard, it should be noted that the External Scientific Advisory Committee has been renewed and new scientific profiles have been incorporated. I would also like to highlight the meeting of this Committee this year with very valuable contributions made in relation to our strategy which we will try to implement throughout 2020.

In summary, the year 2019 has been highly satisfactory as regards the achievement of the objectives set out in the Strategic Plan. The year 2020 presents itself as a year in which we will have to face new challenges for which we are better prepared than ever. To face them, we also count on the fact that we have more and more opportunities for joint actions with other CIBER thematic areas. Only causes outside CIBEROBN itself can prevent us from meeting the high expectations we currently have.





# Programmes

## Nutrition Programme

**Coordinators:** Jordi Salas-Salvadó, Dolores Corella and Estefanía Toledo

The Nutrition Programme is one of the two CIBEROBN programmes (Nutrition and Obesity) that generally includes epidemiological research on obesity and nutrition through different types of epidemiological studies: cross-sectional studies, cases and controls, cohorts and intervention trials- primarily randomised and controlled- where important milestones have been achieved related to recruitment, monitoring and/or publication of results; as well as national and international collaborations in different aspects such as securing new projects, stays, doctoral theses, awards and training, among others.

We highlight as milestones the advances in the follow-up and interventions and publications in the PREDIMED Plus study. This is a randomised controlled trial of intensive intervention with an energy-restricted Mediterranean diet, increased physical activity and behavioral support compared to a control group to assess the effects of this intervention on weight loss and its influence on the reduction of cardiovascular events as the primary outcome, in which most of the programme groups participate. At the end of 2019, an average 4-year follow-up of the more than 6,800 randomized participants was achieved and statistically significant differences in weight loss were found between the intensive intervention groups and the control group.

Other milestones are several publications derived from the PREDIMED study, as well as the follow-up and several publications from the "Seguimiento Universidad de Navarra" (SUN) cohort, with a large sample size ( $n = 23,000$ ). Important milestones have also been achieved in the publications of the CORDIOPREV study, a randomised controlled trial with intervention with a Mediterranean diet in secondary cardiovascular prevention, and in the WAHA (WAlnuts and Healthy Ageing) study, an international intervention trial with walnuts. The advances in the start-up, recruitment and obtaining of the first data from the recently started studies are equally important milestones: MELIPOP (Multicentre randomised, controlled trial with Mediterranean diet and physical activity in children focused on the prevention of childhood obesity.), PREDI-DEP (Prevention of recurrent depression with a Mediterranean diet. PREDI-DEP), PREDIMAR (Prevention with a Mediterranean Diet of Recurrent Arrhythmias in patients with atrial fibrillation), MEDICAR (in collaboration with SEAT, a study in 14,000 workers to evaluate the relationship between lifestyle and health)., IMPACT ("*Improving mothers for a better Prenatal Care*" of the Hospital Clinic of Barcelona in collaboration with other centres), CORALS (agreement between the Instituto Danone España and CIBEROBN for the start of a cohort of children and analysis of obesity risk factors), STOP ("*Science and Technology in Childhood Obesity Prevention*", European H2020 study on policies to prevent and manage childhood obesity, SWEET "*Sweeteners and sweetness enhancers: Impact on health, obesity, safety and sustainability*", European study H2020, PRIME "*Prevention and Remediation of Insulin Multimorbidity in Europe*" European study H2020, among others. In addition, progress has been made on other previously funded projects, including the EU-Project (H2020), entitled: *Effects of Nutrition and Lifestyle on Impulsive, Compulsive, and Externalizing behaviors*.

*Eat2beNICE*, and the NIH project within the PREDIMED Plus study: “Effect of an Intensive Lifestyle Intervention on the Atrial Fibrillation Substrate; 2018–2022”.

Several dozen publications in high impact international journals have been produced in 2019, highlighting among them:

- *Effect of a Nutritional and Behavioral Intervention on Energy-Reduced Mediterranean Diet Adherence Among Patients with Metabolic Syndrome: Interim Analysis of the PREDIMED-Plus Randomized Clinical Trial.* JAMA. 2019.
- *Benefits of the Mediterranean diet: Epidemiological and molecular aspects.* Mol Aspects Med. 2019.
- *Association between consumption of ultra-processed foods and all causes mortality: SUN prospective cohort study.* BMJ. 2019.
- *Plasma metabolites predict both insulin resistance and incident type 2 diabetes: a metabolomics approach within the Prevención con Dieta Mediterránea (PREDIMED) study.* Am J Clin Nutr. 2019.
- *Association Between Fatty Acids of Blood Cell Membranes and Incidence of Coronary Heart Disease.* Arterioscler Thromb Vasc Biol. 2019.
- *Cohort Profile: Design and methods of the PREDIMED-Plus randomized trial.* Int J Epidemiol. 2019.
- *Sex Differences in the Gut Microbiota as Potential Determinants of Gender Predisposition to Disease.* Mol Nutr Food Res. 2019

## Obesity Programme

### Coordinators:

Francisco Tinahones, Fernando Fernández-Aranda, M<sup>a</sup> Pui Portillo and Empar Lurbe

In 2019, the restructuring of the subprogrammes of the CIBEROBN Obesity Programme continued in response to the directives established in the 2017-2019 Strategic Plan. This radical change has meant a challenge aimed, on the one hand, at avoiding fragmentation in the search for common scientific objectives and, on the other hand, at not losing the excellent research already achieved and consolidated in certain areas which had already attained optimal critical mass; along with highly relevant and groundbreaking research. The changes made in this sense have resulted in leading publications both in the field of basic research with preclinical models and in clinical and translational studies.

The following publications deserve particular mention as an example of both intra- and inter-CIBER and international collaborations: Folgueira C et al. *Nat Metab* 2019 Aug; 1 (8): 811-829 / Softic S et al. *Cell Metab* 2019 Oct 1; 30 (4): 735-753.e4 / Seoane-Collazo P et al. *Nat Commun* 2019 Sep 6; 10 (1): 4037 / Al-Massadi O et al. *Diabetes* 2019 Dec; 68 (12): 2210-2222 / Ceperuelo-Mallafre V et al. *Diabetes Care* 2019 Oct; 42 (10): 1956-1965 / Segrestin B et al. *J Clin Endocrinol Metab* 2019 Mar 1; 104 (3): 688-696 / Cairó M et al. *EMBO Rep* 2019 May; 20 (5). pii: e46832.

The Neurocognition subprogramme deserves special mention for the outstanding participation of the groups both in collaborations between the different groups, and in external collaborations with other areas of CIBER (CIBERSAM, CIBERDEM and CIBERESP) and international groups: Oren Contreras-Rodriguez, et al. (2019) *Int J Obes* Mar; 43 (3): 503-511. Yilmaz Z et al. (2019). *Mol Psychiatry*, Aug 7. doi: 10.1038 / s41380-018-0115-4 .; Pettersson E et al. (2019). *Psychol Med*. May; 49 (7): 1166-1173. doi: 10.1017 / S0033291718002039 .; Paslakis G, et al. (2019). *Mol Cell Endocrinol*. Nov 1, 497: 110441.; Steward T et al., (2019). *Sci Rep*. May 27; 9 (1): 7910. Mallorquí-Bagué N, et al (2019). *Eur Psychiatry*. Sep 61: 9-16. Group of the Psychiatric Genomics Consortium (2019). *Cell*. 2019 Dec 12; 179 (7): 1469-1482. e11 .; Steward T, et al. (2019). *Rev Endocr Metab Disord*. 2019 Sep; 20 (3): 263-272 .; Romero X et al. (2019). *Eur Eat Disord Rev*. 2019 Nov; 27 (6): 700-711; Steward T et al (2019). *J Clin Med*. Sep 27; 8 (10). pii: E1551. Monteleone AM, et al. (2019). *World Psychiatry*. Oct; 18 (3): 369-370. doi: 10.1002 / wps.20687; Steward T, et al. (2019). *Transl Psychiatry*. 2019 Aug 20; 9 (1): 194 .; Watson HJ et al. (2019). *Nat Genet*. 2 Aug; 51 (8): 1207-1214 .; Yao S et al. (2019). *Biol Psychiatry*. 2019 Oct 15; 86 (8): 577-586; Hübel C et al., *Nat Commun*. 2019 Dec 18; 10 (1): 5765.



Adipoplast - Thematic network on fatty plasticity and its pathologies (<http://adipoplast.org/>), corresponds to a network of excellence in adipose tissue research funded by the Spanish Ministry of Science, Innovation and Universities, which includes relevant CIBEROBN groups. The cooperative research that it develops addresses the identification of new controlling factors of the browning of adipose tissue, the implication of alterations in fat plasticity in ageing and the interaction with the immune system from a holistic approach aimed at advancing the understanding of adipose tissue and its implications for health.

In the field of internationalisation, CIBEROBN has maintained its regular activity in the organisation of specific Workshops related to obesity and nutrition within the *53rd Annual Scientific Meeting of the European Society for Clinical Investigation (ESCI)*, which took place in Coimbra on 22 -May 24, 2019, as well as at the European Congress on Obesity (ECO), which was held in Glasgow from April 28 to May 1, 2019. In relation to this international event, deserving special mention is the fact that Spain has been selected as the host country for the celebration of ECO 2021. In this context, the members of the CIBEROBN will directly participate in its programming and development. They have already directly participated in the organisation of the *XXV Annual Eating Disorders Research Society Meeting EDRS 2019*, held in Chicago (USA), as members of the board. The appointment of one of the members of CIBEROBN as president of EDRS means that, together with CIBEROBN, they will be responsible for the organisation of the Annual Congress (*XXVI Annual Eating Disorders Research Society Meeting*) that will be held in Sitges in October-2020, where CIBEROBN members will have leadership roles (<https://edresearchsociety.org/2020/index.php>).

As regards translation and social scientific dissemination, various initiatives have been carried out in 2019. Specifically, it has actively participated in the “Guía de Actuación para Familiares con Trastorno de Alimentación” (Action Guide for Families affected by Eating Disorders) ([http://canalsalut.gencat.cat/web/.content/\\_A-Z/T/transtorns-conducta-alimentaria/guia-families-tca.pdf](http://canalsalut.gencat.cat/web/.content/_A-Z/T/transtorns-conducta-alimentaria/guia-families-tca.pdf)), as well as leading the coordination of a special issue on Endocrinology and Environment in Eating Disorders: from Basic to Applied Research, in a leading scientific journal, in which CIBEROBN has had a special role: Fernando Fernandez-Aranda (Guest Editor in Chief). *Cellular and Molecular Endocrinology Journal* (Ed. Elsevier), - Published Nov. 2019 (Ed. (<https://www.sciencedirect.com/journal/molecular-and-cellular-endocrinology/vol/497>)).

The high quality of the healthcare and research activity of our CIBER is also evidenced by the active participation of CIBEROBN groups in clinical trials with international multicentre studies. To the intense scientific activity must be added the participation in the elaboration of Clinical Guidelines and Consensus and Positioning Documents related to clinical obesity and nutrition of National and European Obesity and Diabetes Societies. Among the European collaborations, the joint initiatives with the European Society for Clinical Nutrition and Metabolism (ESPEN) in relation to sarcopenic obesity deserve special mention [Donini LM et al. *Critical appraisal of definitions and diagnostic criteria for sarcopenic obesity based on a systematic review*. Clin Nutr 2019]. Also, the European Association for the Study of Obesity (EASO) regarding the definition of obesity [Frühbeck G et al. The ABCD of Obesity: An EASO Position Statement on a Diagnostic Term with Clinical and Scientific Implications. *Obes Facts* 2019], and the World Psychiatric Association, through a statement about the multidimensional nature of Eating Disorders and Obesity and its multidisciplinary approach, whose committee is made up of members of CIBEROBN [Monteleone AM, Fernandez- Aranda F, Voderholzer U. (2019). *Evidence and perspectives in eating disorders: a paradigm for a multidisciplinary approach*. World Psychiatry. Oct; 18 (3): 369-370. doi: 10.1002 / wps.20687].

# Training Programme

**Coordinator:** Manuel Tena-Sempere

As in previous years, the main focus of the CIBEROBN Training Programme has been towards the youngest members of the teams. Its objective is to promote the training of researchers (especially emerging researchers and those consolidating their careers) in obesity and nutrition, favoring their mobility and helping to consolidate their professional careers as independent researchers in this subject area. Along the same lines, in some cases in collaboration with other CIBER thematic areas, training activities have been carried out aimed at reinforcing the continuous training of the members of our Area.

In line with the development of the programme, the main training measures have involved financing training stays for CIBEROBN members at other national and international research groups. More specifically, in 2019, a total of 5 requests for training stays for CIBEROBN researchers were financed, representing a slight decrease compared to the total number of actions requested the previous year. In any case, all the grant requests submitted have been considered and approved, and many of these actions have had a duration equal to or close to 3 months, which is the maximum financing allowed by the programme per group and year.

The total amount of funds allocated to financing mobility in 2019 was 14,500 EUR, which, as previously indicated, represents a certain decrease with respect to 2018. All this leads us to reassess the maximum limits of the grants awarded per group and year, even though they have already been handled with flexibility. Nevertheless, a noteworthy and positive aspect of the mobility programme is the fact that a high percentage of the actions financed (80%) have been developed in prestigious foreign centres. This reinforces not only the capacity for the acquisition of new knowledge and ground-breaking techniques in the field, but also the establishment of scientific relations and development of collaborations of the highest international level, in addition to promoting knowledge of the CIBEROBN in other institutions and countries.

In addition to the mobility actions indicated above, the programme has continued with the dynamics already established in previous years, aimed at organizing and supporting complementary training activities. Especially noteworthy in this regard is the support, for the fourth consecutive year, of the *Encuentro de Doctorado de Excelencia*, in Mahón, promoted by CIBERESP, and the coordination of the organisation of the scientific programme of the Annual Meeting of our CIBER area, which was this time called "OBESITY AND NUTRITION IN THE 21ST CENTURY" held in Madrid on November 20 and 21, 2019. Most notably, in addition to facilitating the participation of a large number of speakers, both from our CIBER area and external, the training programme financed the endowment of a total of 8 prizes, 4 for the best oral communications and another 4 for the best posters presented at this Annual Meeting of the CIBEROBN 2019, with an endowment of € 750 each, which must be dedicated to training activities of the beneficiaries to be carried out in 2020. This initiative was launched in 2018 and the positive response has led us to continue its implementation this year.

In addition to the above, the CIBEROBN has promoted active participation and has been key in the organisation of scientific events, some of which will be held during the year 2020. An example of this is the Workshop "Fat sensing and the brain control of puberty", which will be held by the International University of Andalusia in November 2020,

after a highly competitive selection process supported by our CIBER area, which took place in 2019. The CIBEROBN supports similar initiatives, in the form of thematic workshops, promoted by some of its groups, such as the group of Prof. Fernando Fernández-Aranda or Prof. Jordi Salas, which will be hosting international scientific meetings, organised with the support of CIBEROBN, in the months of June-July 2020. This set of activities will complement the training components of the programme, extending its scope to practically all CIBEROBN groups, linked to both the obesity and nutrition programmes.

Lastly, and as a training element of utmost importance, we highlight in this section that in 2019 a total of 74 Doctoral Theses (32 of them international) were completed, which represents the consolidation of a growing trend in this major training activity.

# Platforms

**Coordinator:** José Manuel Fernández-Real

## **“FATBANK-Biobank”**

Fat Bank has continued its activity of sample collection throughout 2019. The main milestone of this period has been the request for samples to carry out the project “The effect of outdoor temperature and photoperiod on expression of browning markers in human adipose tissue (OUTBRAT)” led by José Manuel Fernández-Real Lemos, Director of Fat Bank, and supported by all the collaborating nodes of FatBank.

This request represents the first massive exploitation of adipose tissue samples from the FatBank to carry out a research project. The objectives here are two-fold. The first, and most obvious, is the achievement of the scientific objectives set forth in the project; and the second, but no less important, is to take advantage of the publication of the results obtained to present and make the FatBank collection known to the international scientific community. The aim is for this presentation to translate into more requests and the opportunity for scientific collaborations among the members of the FatBank and national and international groups.

The request has involved a thorough purification of the database linked to the FatBank and the update of the stocks of samples available in each node.

# Scientific Production

## Publications

### No. of publications in 2019

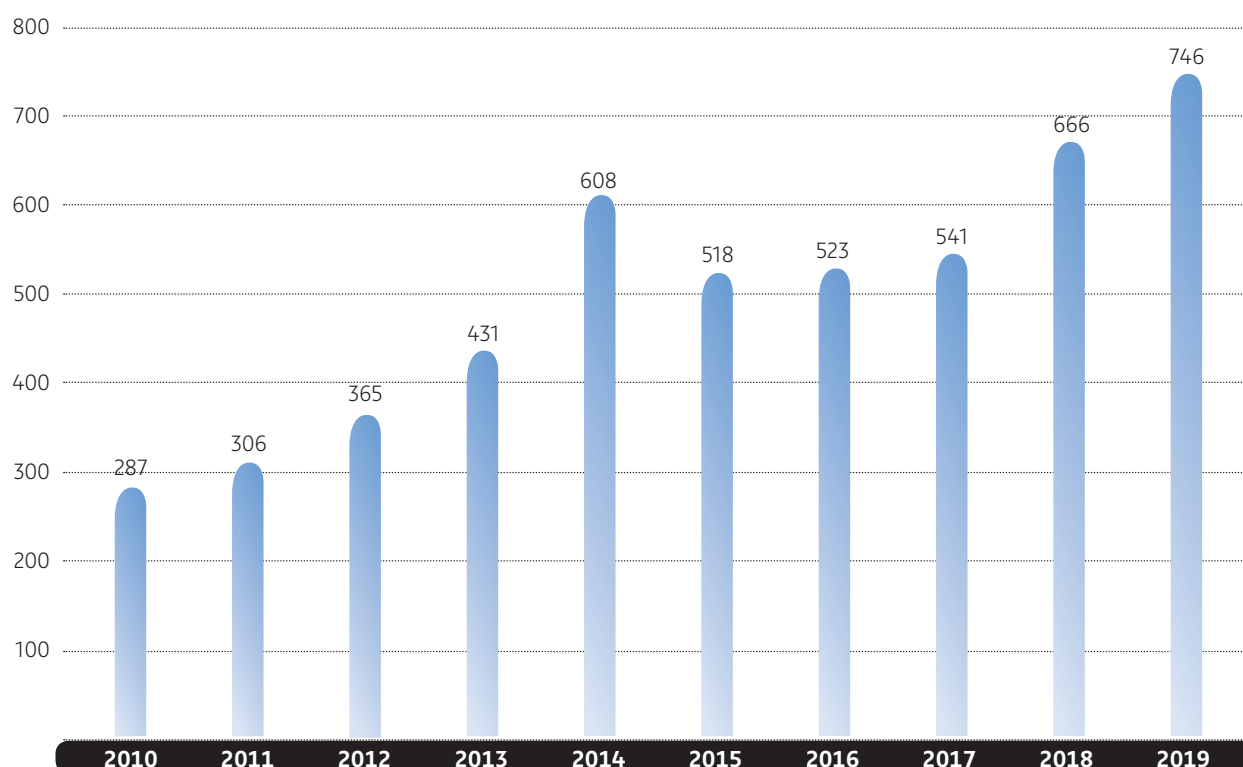
TOTALS	746
Q1	402
D1	296

### Collaborative Publications

CIBEROBN	156
CIBER*	188

\*Among various thematic areas

### Evolution of publications 2010-2019

























## 10 most relevant publications by impact factor

IF	Publication
21,126	<i>Role of astrocytes, microglia, and tanocytes in brain control of systemic metabolism (Pubmed ID 30531847)</i>
27,604	<i>Association between consumption of ultra-processed foods and all cause mortality: SUN prospective cohort study (Pubmed ID 31142450)</i>
15,862	<i>The Mediterranean Diet and Cardiovascular Health: A Critical Review (Pubmed ID 30817261)</i>
38,887	<i>Fine tuning the extracellular environment accelerates the derivation of kidney organoids from human pluripotent stem cells (Pubmed ID 30778227)</i>
15,27	<i>Effect of a lifestyle intervention program with energy-restricted Mediterranean diet and exercise on weight loss and cardiovascular risk factors: One-year results of the PREDIMED-Plus trial (Pubmed ID 30389673)</i>
24,54	<i>Effect of a high-fat Mediterranean diet on bodyweight and waist circumference: a prespecified secondary outcomes analysis of the PREDIMED randomised controlled trial (Pubmed ID 31003626)</i>
43,07	<i>Rising rural body-mass index is the main driver of the global obesity epidemic in adults (Pubmed ID 31068725)</i>
24,646	<i>From conception to infancy — early risk factors for childhood obesity (Pubmed ID 31270440)</i>
22,415	<i>Dietary Sugars Alter Hepatic Fatty Acid Oxidation via Transcriptional and Post-translational Modifications of Mitochondrial Proteins (Pubmed ID 31577934)</i>
51,273	<i>Effect of a Nutritional and Behavioral Intervention on Energy-Reduced Mediterranean Diet Adherence among Patients with Metabolic Syndrome: Interim Analysis of the PREDIMED-Plus Randomized Clinical Trial (Pubmed ID 31613346)</i>

## CIBEROBN Groups. Publications in 2019

Group Leader	Publ.	Q1	D1	Institution/Centre	Province
 Argente Oliver, Jesús	22	7	6	Servicio Madrileño de Salud - Hospital Infantil Universitario Niño Jesús	Madrid
 Baños Rivera, Rosa María	42	6	1	Universidad de Valencia - Facultad de Psicología	Valencia
 Casanueva Freijo, Felipe	24	12	4	Servicio Gallego de Salud - Complejo Hospitalario Universitario Santiago	A Coruña
 Corella Piquer, Dolores	53	39	18	Universidad de Valencia - Facultad de Medicina	Valencia
 Osada García, Jesús de la	11	6	2	Universidad de Zaragoza	Zaragoza
 Diéguez González, Carlos	22	17	4	Universidad de Santiago de Compostela - CIMUS	A Coruña
 Estruch Riba, Ramón	56	40	18	Hospital Clínic de Barcelona	Barcelona
 Fernández Aranda, Fernando	23	14	3	Fundación IDIBELL - Hospital Universitario de Bellvitge	Barcelona



Group Leader	Publ.	Q1	D1	Institution/Centre	Province
 Fernández-Real Lemos, Jose Manuel	22	11	3	Fundación Instituto de Investigación Biomédica de Girona - Hospital Josep Trueta	Girona
 Fiol Sala, Miguel	54	39	19	Fundación Instituto de Investigación Sanitaria Illes Balears (IdISBa) - Hospital Universitario Son Espases	Illes Balears
 Fitó Colomer, Montserrat	64	46	15	Consorci Mar Parc Salut de Barcelona	Barcelona
 Frühbeck Martínez, Gema	32	17	6	Universidad de Navarra - Clínica Universitaria de Navarra	Navarra
 Gil Campos, María Mercedes	33	16	3	Fundación para la Investigación Biomédica de Córdoba (FIBICO) - Hospital Universitario Reina Sofía	Córdoba
 Lamuela-Raventos, Rosa María	34	22	10	Universidad de Barcelona - Facultad de Farmacia	Barcelona
 Lasunción Ripa, Miguel Angel	21	18	6	Servicio Madrileño de Salud - Hospital Ramón y Cajal	Madrid
 López Miranda, José	42	26	9	Fundación para la Investigación Biomédica de Córdoba (FIBICO) - Hospital Universitario Reina Sofía	Córdoba
 Lurbe Ferrer, Empar	14	6	2	Consorcio Hospital General Universitario Valencia - Fundación de Investigación del Hospital General Universitario de Valencia	Valencia
 Martínez González, Miguel Ángel	88	59	29	Universidad de Navarra	Navarra
 Martínez Hernández, Jose Alfredo	73	73	73	Universidad de Navarra	Navarra
 Moreno Aznar, Luis Alberto	43	22	4	Fundación Instituto de Investigación Sanitaria Aragón	Zaragoza
 Ortega Martínez de Victoria, Emilio	48	30	13	Hospital Clínic de Barcelona	Barcelona
 Palou Oliver, Andreu	15	9	4	Universidad de las Islas Baleares - Facultad de Ciencias de Mallorca	Illes Balears
 Pintó Sala, Xavier	32	17	8	Fundación IDIBELL - Hospital Universitario de Bellvitge	Barcelona
 Portillo Baquedá, María del Puy	16	10	4	Universidad del País Vasco - Facultad de Farmacia	Álava
 Remesar Betllloch, Xavier	12	10	2	Universidad de Barcelona - Facultad de Biología	Barcelona
 Santos Lozano, José M. (1)	33	23	11	Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla - Distrito Sanitario Atención Primaria de Sevilla	Sevilla
 Salas Salvadó, Jordi	91	58	23	Fundación Instituto de Investigación Sanitaria Pere Virgili - Universidad Rovira i Virgili	Tarragona
 Serra Majem, Lluís	63	43	17	Universidad de las Palmas de Gran Canaria	Illes Balears
 Tena Sempere, Manuel	30	19	8	Universidad de Córdoba - Facultad de Medicina	Córdoba
 Tinahones Madueño, Francisco	62	37	13	Fundación Pública Andaluza para la Investigación de Málaga en Biomedicina y Salud (FIMABIS) - Hospital Regional Universitario Carlos Haya	Málaga

Group Leader	Publ.	Q1	D1	Institution/Centre	Province
 Tur Mari, Josep Antoni	89	55	16	Universidad de las Islas Baleares - Facultad de Ciencias de Mallorca	Illes Balears
 Villarroya Gombau, Francesc	10	7	4	Universidad de Barcelona - Facultad de Biología	Barcelona

(1) (Replaced José Lopetra-Peralta)

## Patents

### Patent Applications

- MicroRNA based nanosystem for the treatment of obesity
- METHOD FOR PREDICTING OR FORECASTING THE DEVELOPMENT OF RHEUMATOID ARTHRITIS (FIMABIS-18011)

### Software Registration

- PsicologiayTecnologia.COM. Psychology and Technology web platform (www.psicologiaytecnologia.com)''
- PsicologiayTecnologia.COM. Online transversal treatment protocol

## Clinical Guides

### National:

- Guidelines for the management of omics in Primary Care
- Standards for global cardiovascular risk management arteriosclerosis
- Guide to healthy and sustainable fruit consumption
- Integration of omics with a gender perspective in healthy aging: A guide for its implementation
- Guide for healthy and sustainable mobility / physical activity guide in the university environment
- Indications of PCSK9 inhibitors in clinical practice. Recommendations of the Spanish Society of Arteriosclerosis (SEA), 2019
- SEA/SEMERGEN consensus document 2019: *Dietary recommendations in the prevention of cardiovascular di- sease.*
- Document for a comprehensive approach to type 2 diabetes
- Practical guide to interactions between food and drugs
- Practical guide in pregnancy
- ¡Comer sano no es difícil... ni aburrido! Guía de alimentación saludable ( Eating healthy is not difficult ... nor boring! Guide to healthy eating)

### International:

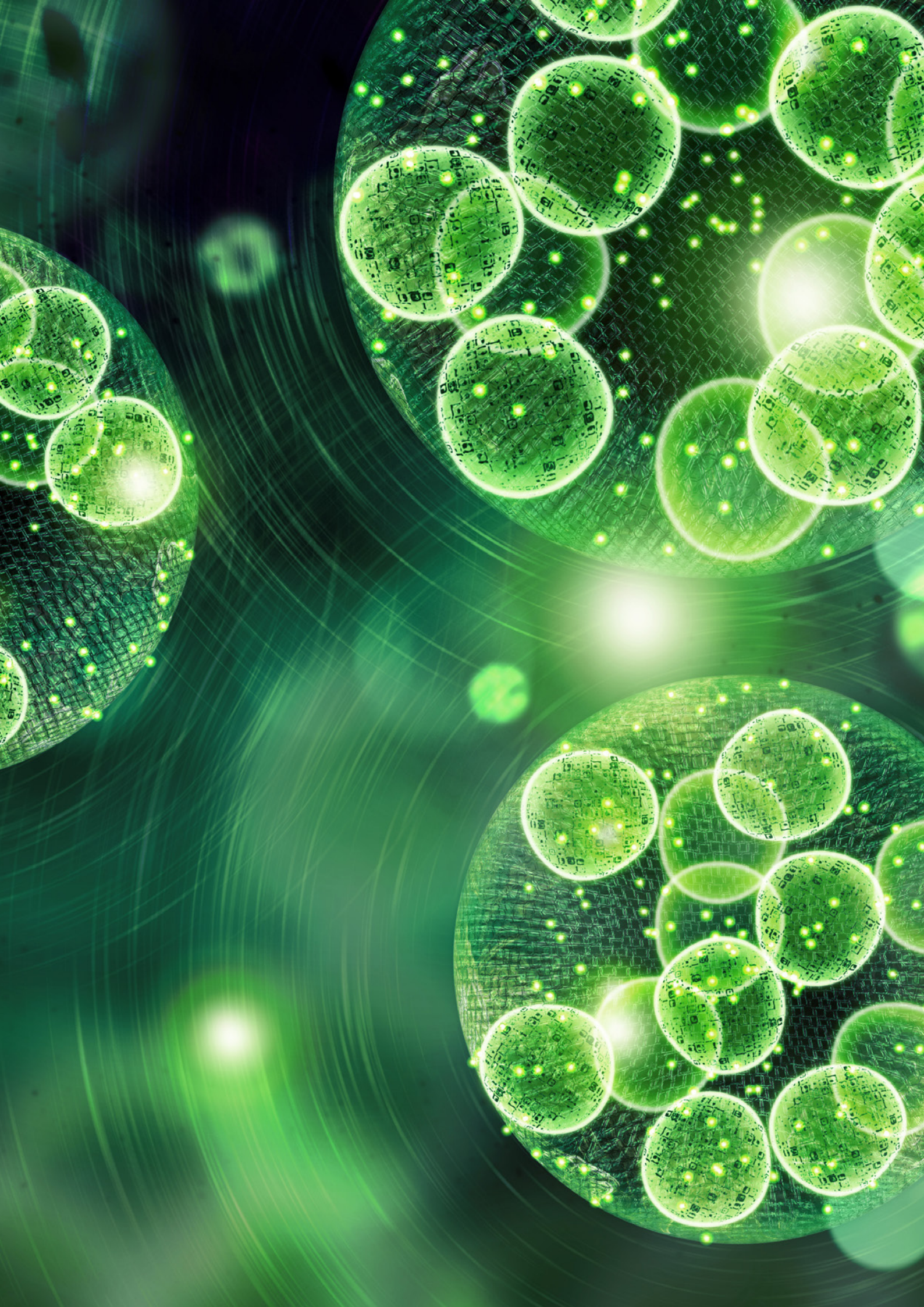
- *A Guide to Applying the Sex-Gender Perspective to Nutritional Genomics*
- *Treatment of Diabetes in Older Adults: An Endocrine Society Clinical Practice Guideline*
- *European Society of Endocrinology Clinical Practice Guideline: Endocrine work-up in obesity*
- *The ABCD of Obesity: An EASO Position Statement on a Diagnostic Term with Clinical and Scientific Implications*



**Cancer**

*cïberonc*







# Presentation by the Scientific Director

**Joaquín Arribas López**



Despite the adverse economic situation that has characterised 2019, CIBERONC has maintained a very satisfactory level of activity and a strong sense of belonging has been consolidated among its members.

Throughout 2019, the CIBERONC Scientific Management focused on 3 main activities: the promotion of young researchers, the fostering of collaborative projects, both within the Programmes and transversally, and defining the main scientific challenges in oncology.

The year started with the awarding of the Best Young Leading Researcher and the *Best Researcher* awards, granted to Ignacio Martín-Subero and Mariona Graupera, respectively. These prizes were awarded during the III General Meeting, together with the grants for the strategic actions of the Work Modules. These grants have yielded excellent results, including two successful CIBERONC workshops - in immuno-oncology and in preclinical models - and the generation of a website on liquid biopsy. In addition to the highlighted strategic actions, two collaborative projects led by the Work Modules were also financed: the generation of a TMA repository of PDXs (Experimental Models Module) and the discovery of biomarkers for liquid biopsy in response to immunotherapy ( Liquid Biopsy Module). It is estimated that the TMAs repository will be complete by mid-2020, with some 500 samples from more than twenty CIBERONC groups. Once completed, a call will be opened to facilitate its use in internal collaborative projects.

Another action aimed at the promotion and visibility of young researchers was the organisation of the II CIBERONC Meeting of Young Researchers, held in Madrid on November 27th. For the second consecutive year, this event was a success with more than a hundred participants.

At the organisational level, the protocol was created to establish the figure of Co-PI in an attempt to give visibility to young leading researchers and facilitate future actions of generational renewal among the leaders of the CIBERONC groups.

The third major action developed by the Management in 2019 was the generation of a recommendations document on current needs in cancer research. This document, prepared from an initial survey of the CIBERONC Principal Investigators and with the suggestions of other CIBER areas, was sent to the advisory committee of the Cancer Mission of the new Horizon Europe Programme. The document highlighted the actual implementation of personalised medicine in healthcare systems as a priority.

In summary, 2019 has been a tremendously productive year. In addition to the activities described, the CIBERONC researchers have once again published their findings in the most relevant scientific journals. We believe that the structure is now consolidated and ready to take a qualitative leap as soon as resources allow.

# Programmes

## Digestive Tract Tumours

**Coordinator:** Gabriel Capellá Munar · **Co-coordinator:** Josep Tabernero Caturla

In 2019, the most relevant results of the Gastrointestinal Tumors Programme include:

The CIBERONC Registry for variants in gastric cancer predisposition genes has been consolidated, coordinated by the ICO-IDIBELL Group and Hospital Clínico San Carlos. The registry for variants of uncertain significance of repair genes already includes 283 variants of 350 affected provided by 12 centres. A pilot study of ATM gene variants has also been completed, where 842 variants from 730 patients have been registered and is helping to develop specific criteria based on the ACMG classification. The Spanish Registry of Familial Pancreatic Cancer already includes 200 individuals from 100 families in which the analysis of subexomes has been completed and the study of exomes of negative cases has begun.

Regarding personalised models, the PDX (Patient Derived Xenografts) collection of colon and pancreatic cancer has been expanded with a focus on tumours with BRAFV600E mutation that are being sequenced using an expanded panel. These PDXs are part of the tissue array that the Experimental Models Work Module is developing. The organoid biobank of murine colorectal tumors has also been expanded to include CRISPR-modified organoids containing, for example, cassettes.

Regarding liquid biopsies, validation studies of KRAS mutation detection technologies with high sensitivity have been completed (*Ann Oncol.* 2019; 30 (3): 439-446) and their clinical utility has been confirmed in a Phase II study in metastatic colorectal cancer. (*Ann Oncol.* 2019 30: 796-803). The impact of detecting the circulating tumour DNA mutant allele fraction has also been explored (*Mol Oncol.* 2019; 13 (9): 1827-1835). Finally, our programme leads the platform of the Liquid Biopsy Work Module to help improve comparability of results between centres.

In 2019, we completed the writing of PREMEDI: Research Program on PRrecision Medicine in GI Oncology, our new collaborative research initiative that focuses on key topics of Precision Medicine in Oncology and which will be our roadmap in 2020 and 2021. This initiative includes three subprojects: Subproject 1. The National Registry of Genetic Variants in gastrointestinal cancer predisposition genes and whose main objective is to define the risks associated with germline variants by combining the different registries that are already working. Subproject 2. Neoadjuvant chemotherapy in pancreatic adenocarcinoma: search for response biomarkers. This is an exploratory study looking for biomarkers that can eventually be validated in the consortium. Subproject 3. Molecular classification of colorectal cancer metastasis based on variables of the tumour microenvironment. The project will explore the prognostic and predictive value of the Consensus Molecular Classification, of the TGF- $\beta$ - associated stromal signature and of immunophenotypes.

# Breast Cancer

**Coordinator:** Joan Albanell Mestres · **Co-coordinator:** Federico Rojo

2019 has been a particularly fruitful year for CIBERONC's Breast Cancer Programme. To promote patient oriented translational research, in 2019 we signed a formal collaboration agreement with GEICAM, an international cooperative group for clinical research in breast cancer. This agreement will allow CIBERONC researchers to access the large biobank of biological samples donated by patients included in clinical trials, as well as the design of new clinical trials based on preclinical studies by CIBERONC. As a result of this collaboration, two proposals were recently awarded, led by G. Moreno-Bueno and A. Lluch, two prominent members of our programme.

In order to encourage the participation of young researchers at CIBERONC, they were granted free registration to the "1st International Symposium on Translational Cancer Research: From Basic Science to Clinical Benefit", held at the Hospital Clínico San Carlos in Madrid.

Scientifically, the Breast Cancer Programme focuses on: 1) HER2-positive tumours, 2) CDK4/6 as a therapeutic target, and 3) Immunotherapy. In 2019, our researchers published their findings in the most prestigious journals, such as *NEJM*, *Cell*, *Science Translational Medicine*, *Nature Cell Biol*, *Annals of Oncology*, *Nature Communications*, *Clinical Cancer Research*, *PNAS*, *Cancer Res*, *Lancet Oncol*, etc. These are some of the most relevant discoveries made by our researchers:

## HER2-positive Tumours

We have continued to develop new therapies to treat these tumours, including bispecific antibodies that target T cells against HER2 positive cells and allogeneic NK transplantation to promote the antitumour activity of trastuzumab. In addition, a translational trial was started to search for biomarkers of response/resistance to T-DM1 (GEICAM KATIA test).

In addition, the collaboration between different groups in our programme has crystallized in the description of gasdermine B (GSDMB) and AXL as promising targets for improving anti-HER2 therapies and overcoming resistance.

## CDK4 / 6 Inhibitors

We have performed relevant clinical trials on hormone receptor-positive disease and the characterisation of gene signatures associated with response. We have also published a differential clinical behavior of double hormone receptor positive breast cancers versus positive ones for a single marker. In luminal disease, we have published, in collaboration with R. Gomis (Mechanisms of tumour progression), the role of MSK1 in adhesion in micrometastatic disease. The role of MSK1 is also being explored in relation to CDK4 / 6 inhibitors. Additionally, in the area of CDK4 / 6 inhibition the clinical trial entitled PARSIFAL (study to evaluate the efficacy and safety of palbociclib in combination with fulvestrant or letrozole in patients with ER +, HER2- locally advanced or metastatic breast cancer) where the programme participates in translational studies in biological samples from patients included in the study. Finally, a follow-up trial, BIOPER, is underway.

## Immunotherapy: preclinical models and TIL analysis

Part of the immunotherapy research has been explained in the section on HER2-positive tumours. In triple negative breast cancer, we have collaborated in a new anti-stromal strategy which seems to fight chemo-resistance and modulate the plasticity of stem cells. The first project of the CIBERONC-GEICAM seed projects also contains analysis of cell plasticity and tumour stem cell markers in TN samples from the CIBOMA clinical trial. Trials with PARP inhibitors, response biomarker studies, trials with selective inhibitors of active transcription of genes encoding proteins in mutated and non-mutated BRCA breast cancer have also been published. Studies on HLA-A and HLA-B expression have demonstrated its association with T cell activation and identify basal-like breast cancers with a favorable prognosis.

Furthermore, using available transcriptomic data, we describe a set of immunological genes that predict the outcome of neoadjuvant chemotherapy in triple negative tumors. In another study, we found a correlation between the mutational load and the expression of most MHC class I molecules. In addition, HLA-A and -B expression identified immunoactivated basal-like breast cancers with a favorable prognosis. Finally, we published a meta-analysis that describes the prognostic role of lymphocyte activation gene 3 (LAG3) in cancer.



# Respiratory Tract Tumours

**Coordinator:** Luis Montuenga Badía · **Co-coordinator:** Luis Paz Ares Rodríguez

## New therapeutic targets and strategies

We have identified a cytoplasmic tyrosine kinase (YES1) as a driver in lung cancer. YES1 expression is able to predict the response to pan-src kinase inhibitors. The publication in the Blue Journal was highlighted by an editorial comment.

The therapeutic benefit of combined EGFR/FGFR inhibition has been demonstrated for patients with FGFR1 or FGFR4 overexpression and EGFR activation. Notch inhibition has been shown to overcome resistances generated by EGFR + lung ADC treatments, offering a proof of concept for an alternative to osimertinib chemotherapy in these patients.

In liquid biopsy, we are studying the possible role of TAS1R3 as a biomarker of metastatic potential. The EURONANOMED initiative (METASTARG project) in turn finances the evaluation of the therapeutic potential of TAS1R3 in NSCLC. Collaborative work has revealed differences in the prognostic value of SRC family members based on the location of the HNSCC.

A massive search for genetic vulnerabilities has also been designed using genomic editing tools (CRISPR / Cas9) HNSCC (Sanger Cancer Institute).

## Immuno-oncology (io) of tumours of the respiratory tract

At present, the prospective cohort of patients with lung cancer treated with simple and combined immunotherapy (in advanced stages) CIBERONC-RESP is being generated.

We have carried out a comprehensive molecular and immune characterisation of part of the retrospective cohort (N = 200). A validation of the clinical utility of 2 NGS platforms (Illumina TSO500, Thermofisher TML) for the evaluation of TMB compared to FoundationOne (N = 100) has also been performed. The programme is working, through multiplexed assays, on the identification of immune markers in BL (soluble receptors, cytokines) and their correlation with the response to immunotherapy and survival. Cooperative efforts are also underway within the Programme to unravel the role of complement activation in NSCLC immunotherapy. Regarding IO in HNSCC, we have performed an immune profile in a large cohort of 372 patients.

## Identification and development of clinically relevant biomarkers

We have identified and validated two clinically viable prognostic models based on protein profiling, one for lung ADC and the other for SCC. The publication in Thorax on the prognostic panel in SCC was accompanied by an editorial. We have also carried out several ddPCR-based LB projects aimed at improving the diagnosis, prediction, and monitoring of response to TKIs. We have extensively characterised exosomes and their loading in cell cultures and plasma samples from patients with NSCLC. Significant differences have been observed between the exosomal load of ADC vs SCC (cell lines and cultures derived from the patient). The clinical relevance of NANOG and SOX2 in the early stages of HNSCC tumorigenesis, and the new role as biomarkers of risk of malignant transformation in patients with precancerous oral and laryngeal lesions have been discovered. Sinonasal tumors with HDI mutations have also been shown to represent a distinct tumor entity with less aggressive clinical behavior. In a collaborative work with CIBER-BBN and CIBERES, the amplification and differential expression of the 11q13 region in relation to HPV status has been found, with an impact on the survival of HNSCC patients.

# Haematological Tumours

**Coordinator:** Dolors Colomer Pujol · **Co-coordinator:** Marcos González Díaz

In the field of hematological tumors, to be highlighted is the collaborative work published in *Nature* (PMID: 31597163), in which U1 mutations in different tumors and especially in chronic lymphatic leukemia (CLL), is described for the first time. This study is the first to demonstrate the presence of mutations in non-coding genes of the spliceosome machinery as another form of alteration in the splicing process in cancer. Also noteworthy are the two collaborative publications published in *Blood* on the characterisation of diffuse lymphomas (DLCL) that present IRF4 rearrangement (PMID: 31738823) and cyclin D1-negative mantle cell lymphoma (PMID: 30538135), and molecular studies in systemic mastocytosis by analysing the frequency and prognostic impact of KIT (*Blood*, PMID: 31151985).

In the development of pre-clinical models, studies in animal models stand out, demonstrating that the loss of p53 and alterations in PDI / PDL1 facilitate tumor progression in LDCG (*Blood*, PMID: 30975638) and that the use of IRAK4 inhibitors, which inhibit TLRs, delay tumor development in CLL (*Leukemia*; PMID: 31197259).

In the field of epigenetics, it has been described that transdifferentiation events in the context of plasticity of the hematopoietic lineage, involve changes in DNA methylation (*Leukemia*, PMID: 31719676) and that long non-coding RNAs regulate the immune response (*Nat. Commun.*, PMID: 30778059). It has also been described that there is a relationship between hereditary predisposition and activity and chromatin accessibility and DNA methylation patterns in CLL (*Nat Commun.* PMID: 31399598).

Also noteworthy are the studies focused on the development of new technologies with the publication of new generation flow cytometry protocols for the study of amyloidosis (*Leukemia* PMID: 30542145) and the analysis of immunofixation in urine for the analysis of response in multiple myeloma (MM) (*Blood*, PMID: 31010846) and the role of Vitamin D in hematopoietic transplantation (*Clin Cancer Res.* PMID: 31043390).

Important milestones include the large number of international clinical trials in MM led by CIBERONC members published in the *Lancet journal* (PMID: 31836199), the ALCYONE study using daratumumab, bortezomib, melfalan, and prednisone published in *Blood* (PMID: 31484647) on induction therapy before autologous transplantation with Bortezomib, lenalidomide, and dexamethasone, and subcutaneous administration of daratumumab (PMID: 31270103); and in *Lancet Haematology* (PMID: 31327687) the KEYNOTE-183 trial using pembrolizumab, pomalidomide and dexamethasone. Most of these have been done in collaboration with the Spanish collaborative group Pethema.

Finally, the clinical trial funded by the Instituto de Salud Carlos III (PIC18 / 00012) based on an academic anti-CD19 CART developed by CIBERONC members (code EudraCT 2016-002972-29) has completed the first recruitment of 47 patients with a follow-up of more than 100 days. This initiative involves the participation of most of the centres that are part of the CIBERONC haematological tumors programme.

## Low Prevalence Tumours

**Coordinator:** Enrique de Álava Casado · **Co-coordinator:** Ignacio Melero Bermejo

The challenge faced by our programme for 2019 was to carry out two cooperative research projects on two low-prevalence tumors, selected based on a very broad and heterogeneous group of organisations such as those covered by the Programme.

The first half of 2019 was dedicated to generating data within the Programme's cooperation project on uveal melanoma, a neoplasm in which no nationwide translational project 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 Tumors) in 2017. The Programme specifically covered these two milestones:

- Evaluation and quantification of the levels of expression of Endoglin (EDG) / MMP14 and the HIPPO TAZ / YAP pathway effectors in 4 independent cohorts of paired uveal melanoma samples.



- Generation models of elimination of EDG, MMP14, TAZ and YAP by means of genome editing using CRISPR-Cas9 technology, used to evaluate the functionality of these molecules in *in vitro* and *in vivo* models of uveal melanoma.

These Programme results were included in an application for the CHALLENGES-collaboration call that was sent in October 2019, and is currently pending evaluation. The generation of additional preliminary results of this first cooperative project of the Programme continues at this time.

Throughout 2019, we carried out a second cooperative project focussing on the immune landscape of uterine tumors. Each group provided tools, samples and clinical data on this tumour, a neoplasm in which no cooperative translational research had been carried out in Spain until now. The project was launched in September 2018, after the approval of the CIBERONC Scientific Advisory Board. Achievements through the end of December 2019 include:

A multiparametric and multicentre pilot study characterising a small series of endometrial carcinomas through the study of stroma and tensegrity (Gomoriopath), immunophenotypic characterisation of stromal cells (Vectra-Polaris), and genomic characterisation of tumour and stromal cells.

The activity of this second cooperative project will be ongoing until the end of 2021.

In 2019, two cooperative projects were awarded to the Programme to finance activity in the field of uterine tumors: Marató-TV3 Endometrial Carcinoma Project (2019: €396k); Excellence Project of the Junta de Andalucía on endometrial stromal sarcoma (2019: €400k).

## Tumour Progression Mechanisms

**Coordinator:** Xosé García Bustelo · **Co-coordinator:** Anna Bigas Salvans

Scientific advances: we have established new *in silico* tools to optimally query data from the PanCancer project. On the one hand, we have expanded the CancerTool programme already described (*Cancer Res* 2018 PMID: 30232219; groups led by Bustelo, Carracedo and López-Otín) to include information on stroma, methylation and metastatic tropism. We have also generated new algorithms and programmes to identify gene copy number alterations (*Fat-Copy*, groups led by Carracedo and Lopez-Otín) as well as correlations between gene copy variations and expression levels (CIBER-Amp, groups led by Bustelo and Lopez-Otín). We have also implemented bioinformatics protocols to query the GEO and PanCancer data to identify changes in expression, methylation, copy number, mutational hot-spots and phenomena of positive/negative selection mutations both in specific tumours and in general. Finally, we have generated algorithms to obtain functional data derived from shRNA and CRISPR-Cas9 genome-wide screens performed in tumor cells (Dr. Bustelo's group).

More outstanding scientific findings include the identification of new drivers and biological processes involved in chemoresistance and responses to immunotherapies in colorectal cancer, bladder cancer and glioma (*Mol Cell* 75: 669, PMID: 31302002; *Nat Med* 25: 1073, PMID: 31270502; *Nat Commun* 10: 2416, PMID: 31186412; Groups led by Drs. Espinosa / Bigas, Paramio and Seoane). Novel surface markers have also been identified for use in CAR-T treatments, one of which has already resulted in a new therapy that is currently undergoing clinical validation (*Blood* 133: 2291, PMID: 30796021; *Leukemia* 33: 1557, PMID: 30635633; Dr. Menéndez's group).

Patents: three patents to protect new diagnostic markers (P201930419 and P201830811, groups led by Drs. Crespo and Paramio, respectively) and CAR-T therapies (EP19382104.8, Dr. Menéndez's group).

Inter-Programme Activities: organisation of a course on bioinformatics techniques for the analysis of genomes in cancer (Dr. Paramio group). Development of three bioinformatics tools for *in silico* analysis of data derived from the Pan-Cancer project (*CancerTool*, *Fat-Copy*, *CIBER-Amp* (groups led by Drs. Carracedo, Bustelo and López-Otín).

Internationally relevant projects: these include projects granted by the PerMed (H2020) programmes, German J Carreras Foundation, *Proof-of-Concept* ERC (all from researchers of Dr. Bigas's group), *Cancer Research UK-AECC-AICR Accelerator* (groups led by Drs. Bustelo, Orfao and Santos) and *Ferring Innovation* (Dr. Paramio's group).

Scientific leadership: three workshops organised through the *European Association for Cancer Research* (Drs. Carracedo and Seoane) and the *European Society of Medical Oncology* (Dr. Seoane). Presidency of the *Spanish*

*Association for Cancer Research* (Dr. Bustelo). Memberships in advisory committees of the *International Society of Experimental Hematology* (Dr. Bigas) and of the National Cancer Strategy of the National Health System of the Spanish Ministry of Health (Dr. Bustelo). Member of the Real Academia Galega de Ciencias (Royal Galician Academy of Sciences) (Dr. Bustelo). Ramiro Carregal Oncology Award for Young Researchers (Dr. Menéndez) and José Cornide Defensa de la I+D+i Award (Dr. Bustelo).

# Training Programme

**Coordinator:** Amparo Cano García · **Co-coordinator:** Anna Bigas Salvans

## Relevant results in 2019

A total of 61 training grants issued, in its different subprogrammes:

- 16 grants for stays in other research centres: 5 intraCIBERONC and 11 international groups.
- 23 grants for training courses: 6 for organisation of courses, 17 for attendance at national internal CIBERONC (9), external (3) and international (5) courses.
- 20 grants for the presentation of results at international conferences.
- Grant for the II Meeting of Young CIBERONC Researchers (II EJI). This is one of the activities with the greatest impact on the training of doctoral students and young doctors. 120 participants, 52 posters and 12 oral presentations.
- Grant to carry out the I Symposium of the transversal working group Experimental Models of Cancer.

# Scientific Production

## Publications

### No. of publications in 2019

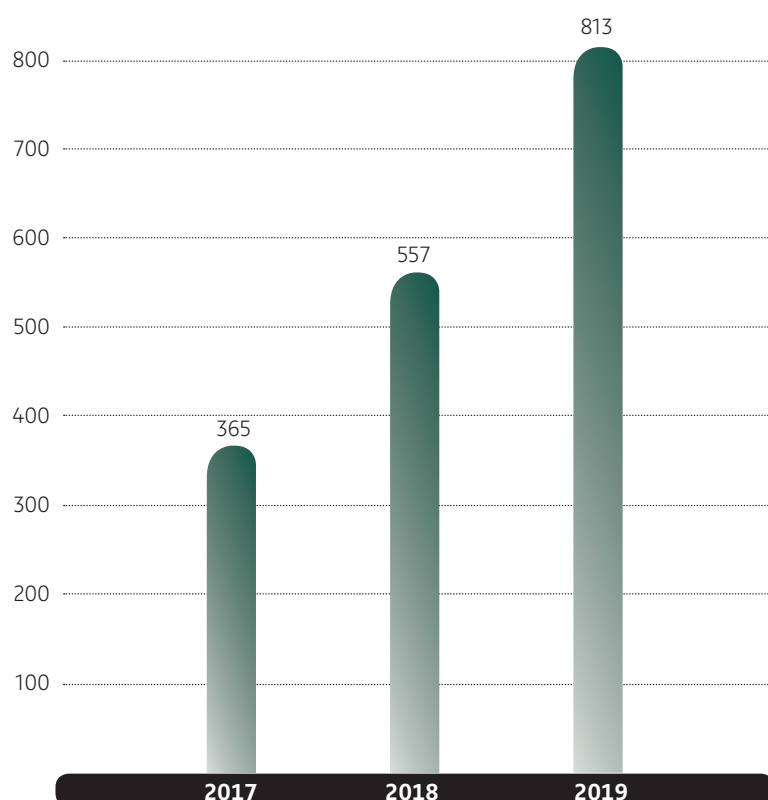
TOTALS	813
Q1	495
D1	233

### Collaborative Publications

CIBERONC	157
CIBER*	151

\*Among various thematic areas

### Evolution of publications 2017-2019






















## 10 most relevant publications by impact factor


















IF	Publication
70,67	Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. <i>N Engl J Med</i> 2019; 381:1535-1546. DOI: 10.1056/NEJMoa1910836.
70,67	Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. <i>N Engl J Med</i> 2019; 381:2020-2031. DOI: 10.1056/NEJMoa1910231 (Pubmed ID 31142450).
59,102	Durvalumab plus platinum–etoposide versus platinum–etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. <i>Lancet</i> . 2019 Nov 23;394(10212):1929-1939. doi: 10.1016/S0140-6736(19)32222-6. Epub 2019 Oct 4.
59,102	Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase 3 study. <i>Lancet</i> . 2019 Dec 7;394(10214):2096-2107. doi: 10.1016/S0140-6736(19)32556-5.
59,102	Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial. <i>Lancet</i> . 2020 Jan 11;395(10218):132-141. doi: 10.1016/S0140-6736(19)32956-3. Epub 2019 Dec 10.
44,019	Dendritic cells in cancer immunology and immunotherapy. <i>Nature Reviews Immunology</i> volume 20, pages7–24(2020).
43,704	Clinical epigenetics: seizing opportunities for translation. <i>Nature Reviews Genetics</i> volume 20, pages109–127(2019).
43,07	Prophylactic TNF blockade uncouples efficacy and toxicity in dual CTLA-4 and PD-1 immunotherapy. <i>Nature</i> . 2019 May;569(7756):428-432. doi: 10.1038/s41586-019-1162-y. Epub 2019 May 1.
43,07	Recurrent noncoding U1 snRNA mutations drive cryptic splicing in SHH medulloblastoma. <i>Nature</i> volume 574, pages707–711(2019).
43,07	The U1 spliceosomal RNA is recurrently mutated in multiple cancers. <i>Nature</i> volume 574, pages712–716(2019).

## CIBERONC Groups. Publications in 2019

Group Leader	Publ.	Q1	D1	Institution/Centre	Province
 Álava Casado, Enrique de	10	7	3	Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla	Sevilla
 Albanell Mestres, Joan	29	20	13	Consorci Mar Parc Salut de Barcelona	Barcelona
 Aranda Aguilar, Enrique	8	6	3	Fundación para la Investigación Biomédica de Córdoba (FIBICO)	Córdoba
 Arribas López, Joaquín	7	7	3	Fundación Privada Instituto de Investigación Oncológica Valle de Hébron-VHIO	Barcelona
 Batlle Gómez, Eduard	4	2	1	Fundación privada Instituto de Recerca Biomédica (IRB-Barcelona)	Barcelona
 Bigas Salvans, Anna	12	6	4	Consorci Mar Parc Salut de Barcelona	Barcelona

Group Leader	Publ.	Q1	D1	Institution/Centre	Province
Bosch José, Francesc Xavier (*)	3	2	1	Fundación Idibell Hospital. Universitario de Bellvite	Barcelona
 Campo Guerri, Elías	17	12	9	Instituto de Investigaciones Biomédicas August Pi i Sunyer	Barcelona
 Camps Herrero, Carlos	18	13	7	Consorcio Hospital General Universitario Valencia	Valencia
Cano García, Amparo	10	7	2	Universidad Autónoma de Madrid	Madrid
 Capellà Munar, Gabriel	31	25	9	Fundación IDIBELL	Barcelona
 Carnero Moya, Amancio	8	7	2	Agencia Estatal Consejo Superior de Investigaciones Científicas	Madrid
 Carracedo Pérez, Arkaitz	7	5	3	CIC BIOGUNE	Vizcaya
 Carrato Mena, Alfredo	20	9	3	Servicio Madrileño de Salud	Madrid
 Cervantes Ruipérez, Andrés	20	12	9	Fundación para la Investigación del Hospital Clínico de la Comunidad Valenciana (Fundación INCLIVA)	Valencia
 Colomer Pujol, Dolors	12	9	4	Instituto de Investigaciones Biomédicas August Pi i Sunyer	Barcelona
 Crespo Baraja, Pedro	2	2	0	Agencia Estatal Consejo Superior de Investigaciones Científicas	Cantabria
Díaz-Rubio García, Eduardo	24	18	8	Servicio Madrileño de Salud	Madrid
 Esteller Badosa, Manel	18	16	9	Fundación Instituto de Investigación contra la Leucemia Josep Carreras	Barcelona
 Feliú Batlle, Jaime	16	8	3	Servicio Madrileño de Salud	Madrid
 García Bustelo, Xosé Ramón	4	2	1	Fundación de Investigación del Cáncer de la Universidad de Salamanca	Salamanca
González Díaz, Marcos	33	19	10	Fundación Instituto de Estudios de Ciencias de la Salud de Castilla y León	Salamanca
Lluch Hernández, Ana	17	10	1	Fundación para la Investigación del Hospital Clínico de la Comunidad Valenciana (Fundación INCLIVA)	Valencia
 López Lopez Rafael	37	27	8	Servicio Gallego de Salud	A Coruña
 López Otín, Carlos	13	11	11	Universidad de Oviedo	Asturias
 Malats Riera, Nuria	7	4	2	Fundación Centro Nacional de Investigaciones Oncológicas	Madrid
 Martín Jiménez, Miguel	23	9	4	Servicio Madrileño de Salud	Madrid
 Matías Guiu-Guía, Francisco Javier	28	14	4	Instituto de Investigación Biomédica de Lleida. Fundación Dr. Pifarre	Lleida
 Melero Bermejo, Ignacio	26	21	15	Universidad de Navarra	Navarra
 Montuenga Badía, Luis	27	23	12	Fundación para la Investigación Médica Aplicada	Navarra
 Muñoz Terol, Alberto	8	4	1	Agencia Estatal Consejo Superior de Investigaciones Científicas	Madrid
 Noguera Salva, Rosa	12	3	0	Fundación para la Investigación del Hospital Clínico de la Comunidad Valenciana (Fundación INCLIVA)	Valencia



Group Leader	Publ.	Q1	D1	Institution/Centre	Province
 Oliver Pozo, Francisco Javier	3	2	1	Agencia Estatal Consejo Superior de Investigaciones Científicas	Granada
 Orfao de Matos Correia e Vale, José Alberto	6	3	3	Fundación de Investigación del Cáncer de la Universidad de Salamanca	Salamanca
 Palacios Calvo, José	5	4	2	Servicio Madrileño de Salud	Madrid
 Pandiella Alonso Atanasio	12	7	1	Fundación de Investigación del Cáncer de la Universidad de Salamanca	Salamanca
 Paramio González, Jesús María	20	15	10	Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas (CIEMAT)	Madrid
 Paz-Arés Rodríguez, Luis	47	25	13	Servicio Madrileño de Salud	Madrid
 Pérez Simón, José Antonio	10	5	2	Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla	Sevilla
 Piris Pinilla, Miguel Ángel	12	8	6	Instituto de Investigación Sanitaria Fundación Jiménez Díaz	Madrid
 Prósper Cardoso, Felipe	15	14	9	Fundación para la Investigación Médica Aplicada	Navarra
 Ramón y Cajal Agueras, Santiago	17	11	6	Fundación Hospital Universitario Vall d'Hebron - Institut de Recerca (VHIR)	Barcelona
 Real Arribas, Francisco Xavier	6	5	3	Fundación Centro Nacional de Investigaciones Oncológicas	Madrid
 Rodrigo Tapia, Juan Pablo	25	19	6	Fundación para la Investigación e Innovación Biosanitaria en el Principado de Asturias (FINBA)	Asturias
 San Miguel Izquierdo, Jesús Fernando	35	24	14	Universidad de Navarra	Navarra
 Santisteban Sanz, María del Pilar	6	4	2	Agencia Estatal Consejo Superior de Investigaciones Científicas	Madrid
 Santos de Dios, Eugenio	5	3	0	Fundación de Investigación del Cáncer de la Universidad de Salamanca	Salamanca
 Sanz Santillana, Guillermo	57	22	7	Fundación para la Investigación del Hospital la Fe	Valencia
 Seoane Suárez, Joan	3	3	2	Fundación Privada Instituto de Investigación Oncológica Valle de Hébron-VHIO	Barcelona
 Tabernero Caturla, José María	6	5	2	Fundación Privada Instituto de Investigación Oncológica Valle de Hébron-VHIO	Barcelona

(\*) Group unsubscribed in 2019

## Patents

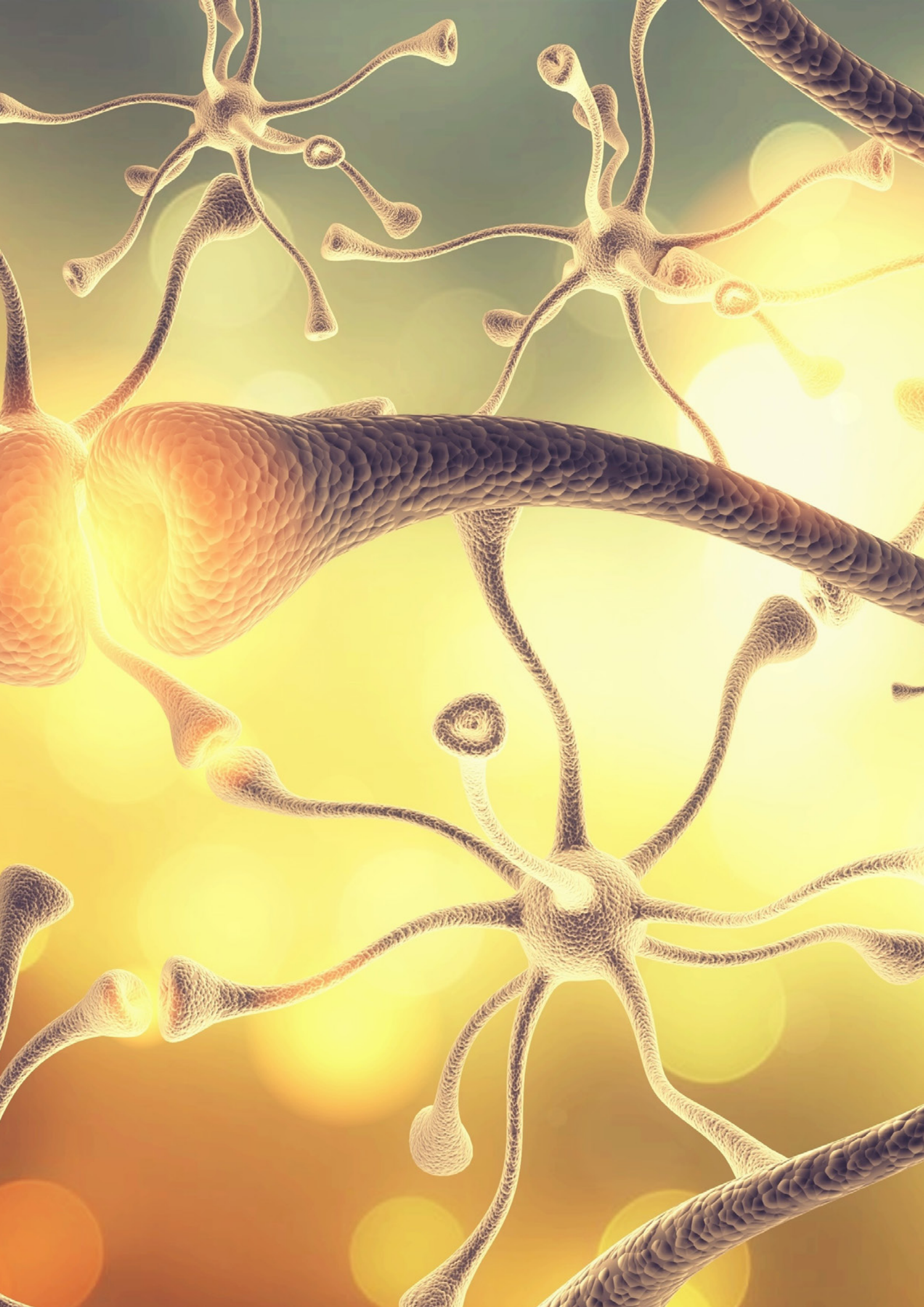
### Patents filed

- Uso de la 4,6-difenil-1h-pyrazolo [3,4-b]piridin-3-amina, o de una sal farmacéuticamente aceptable de la misma, como un inhibidor de serina/treonina quinasa 1 de interacción con map quinasa (mnk1) y serina/treonina quinasa 2 de interacción con map quinasa (mnk2) selectivo y no citotóxico..



**Mental  
Health**

*cïbersam*





# Presentation by the Scientific Director

**Eduard Vieta Pascual**



At the time of writing this introduction to the 2019 CIBERSAM scientific Annual Report we are in the midst of the Covid-19 health emergency which highlights, once again, the fact that research is the key investment in preventing and treating diseases. Only research and innovation will allow us to respond to the health challenges of our times, including mental health. CIBERSAM reached a new record number of scientific publications in 2019 (770), 25% of these in the first decile. In a context of budget extensions and an increasing complexity of administrative processes, CIBERSAM researchers have managed to excel both in the quantity and quality of their scientific production. I would like to highlight some of these advances, beyond their bibliometric merits: for example, the large genetic study, with hundreds of thousands of DNA samples from patients with various mental disorders, which demonstrates the relevance of pleiotropic mechanisms and suggests possible therapeutic targets, a study in which researchers from various CIBERSAM groups have collaborated, in addition to CIBERESP, CIBEROBN and CIBERER. Also, the Mental Health Guide for the elderly, the pioneering technique for diagnosing psychosis based on machine learning, or the new findings in disease burden, or the demonstration of the efficacy of a new treatment for resistant depression, based on a novel mechanism of action involving the glutamatergic pathway. These are extraordinary milestones resulting from the collaboration between research groups, between networks, and between international multidisciplinary teams. Four CIBERSAM researchers are on the prestigious list of the most influential scientists in the world (Julio Bobes, Josep Maria Haro, Joaquim Radua and Eduard Vieta) based on the number of citations to their articles. Our platforms and our introductory master's degree in translational research in mental health have continued to contribute to increasing our potential to generate data and train researchers. The Ideas Laboratory, the Neuroscience course, and the face-to-face and non-face-to-face activities, which are increasingly important, have fostered cooperation between groups and programmes. In difficult times, CIBERSAM has shown a very high capacity to overcome administrative, budgetary and scientific challenges to once again produce advances in knowledge with the ability to transfer these to clinical practice in the short and medium term. I can only say that I am proud of our researchers, the group leaders and all those who make it all possible. Cheers to you all.



# Programmes

## Depression and Suicide Prevention

**Coordinator:** Víctor Pérez Sola

Suicide is the leading preventable cause of death in the world and one of the leading causes of death among young people. The study of suicide was one of the most productive lines of research of the Programme during 2019 in the epidemiological, neurobiological and prevention areas. Several groups have focused their research on evaluating risk factors for suicidal behavior especially in young people and university students. Articles have been published in collaboration with other CIBERs and leading groups in Europe on epidemiological aspects as well as systematic reviews focusing on risk factors and their potential use as preventive strategies. In addition, financing has been obtained to initiate a cohort study led by 9 CIBERSAM groups, financed by the FIS, which aims to create a cohort of 2000 patients with a history of suicide attempt to whom different therapeutic strategies will be offered in the context of three CCTs and that will allow obtaining a platform to monitor the evolution of suicidal behavior in our country.

Researchers from the programme have collaborated in epidemiological studies in national and international initiatives focused on the relationship of depression with: 1) social determinants such as socioeconomic status, unemployment or loneliness; 2) comorbidities with other somatic diseases (cardiovascular, inflammatory, etc.); and 3) comorbidities with other mental illnesses (psychosis, bipolar disorder, or anxiety). The projects started more than 10 years ago on postpartum depression have now revealed the longitudinal evolution of this disease. Also, several groups are leading studies at the national level to evaluate the effect of cognitive symptoms on functionality and quality of life.

Regarding the neurochemical bases of depression, studies led by groups integrated in large international consortia such as ENIGMA confirm the involvement of different brain structures in the pathophysiology of the disease. Several groups are investigating the development and evaluation of possible diagnostic and prognostic biomarkers such as neuroimaging tests and neurocognitive, neurophysiological, inflammatory and genetic evaluations.

In the line of new therapeutic targets, several clinical and basic groups are leading the investigation in the evaluation and study of the mechanism of action of Deep Brain Stimulation and ECT in the treatment of severe resistant mental disorders.

One of the most active lines focuses on the study of the molecular bases and the therapeutic evaluation of drugs with new mechanisms of action such as the glutamatergic pathway or psychodysleptic drugs in the treatment of resistant depression. This is a new therapeutic strategy that will change the current paradigms in the treatment of depression. Also, collaborative projects have been started for the creation and validation of

functional rehabilitation programmes as a therapeutic strategy in cognitive symptomatology. Finally, factors related to therapeutic response have been described, analysing the barriers that limit the response to treatment or the involvement of key symptoms, such as circadian rhythms, pharmacogenetic studies, or the Mediterranean diet in the evolution of the disorder and therapeutic response.

## Schizophrenia

**Coordinator:** Benedicto Crespo-Facorro

In 2019, among the most notable results of the programme are the 115 first quartile publications (63 indexed in the first decile according to the JCR ranking in the areas of psychiatry, neuroimaging, genetics, multidisciplinary sciences, neurology and neuroscience).

In connection with the programme in 2019: 1 project financed by the European Union coordinated by the CIBERSAM group, as well as participation in COST-H2020. At the national level, a total of 7 projects obtained competitive financing in public calls of the AES 2017 and 3 in competitive private calls.

With regard to human resources contracts, we highlight the incorporation of researchers thanks to having obtained a Sara Borrell contract, an ISCIII intensification and two PFIS.

Two patents have been published: 1.- Granting of the patent in Europe (number EP2948563) entitled “Method for the prediction of extrapyramidal symptoms (EPS) induced by treatment based on antipsychotics”, filed by the University of Barcelona, Hospital Barcelona Clinic, IDIBAPS and CIBERSAM. Licensee: AB-BIOTICS. Researchers: P. Gassó, S. Mas, A. Lafuente, M. Bernardo ; 2.- EP19382013. In vitro method for the diagnosis or prognosis of neurodegenerative disorders. Authors: Carlos Spuch; Tania Rivera Baltanás; Jose Manuel Olivares; Miguel Correa Duarte; Moisés Pérez Lorenzo; Verónica Salgueiriño Maceira; Ana Sousa Castillo; María Blanco Formoso. Rights Holder: Fundación Biomédica Galicia Sur and Universidad de Vigo.

11 doctoral theses have been read within the CIBERSAM groups.

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

Among the scientific achievements of 2019, to be highlighted are publications in high impact journals such as *World Psychiatry Nature Genetics*.

## Bipolar Disorder

**Coordinator:** Ana González-Pinto

Among the most relevant results of the programme are the 115 articles published in indexed journals. Of these, 69 are published in the first quartile and 36 in the first decile in prestigious journals such as *Nature Genetics, JAMA Psychiatry, American Journal of Psychiatry, British Journal of Psychiatry, The Lancet Psychiatry o Cell*.

3 new competitive national projects have been obtained (ISCIII, Basque Government), in addition to a private contract:

- Title: “Smart Remote Treatment: medicina personalizada para el tratamiento de pacientes con trastorno bipolar: estudio multicéntrico” Dra. Ana González-Pinto EVERIS-NTT Data.

Competitive HR contracts:

- Severo-Ochoa Postdoctoral Programme of the Government of the Principality of Asturias to Lorena de la Fuente Tomas. Group led by Julio Bobes.
- Sara Borrell postdoctoral contract for Xavier Gallart. Elisabet Vilella’s Group.
- Rio Hortega postdoctoral contract for Estela Salagre. Eduard Vieta’s Group.

#### Awards and distinctions:

- Eduard Vieta and Joaquim Radua among the most influential scientists in the world (Clarivate Analytics). 2019 Highly Cited Researchers.
- Eduard Vieta, "Honorary Member" of the Spanish Society for Biological Psychiatry (SEPB).
- Iria Grande, SEPB "Young Accredited Researchers" Award.
- Diego Hidalgo, SEPB "Reference Investigator" Award.
- Best Doctoral Thesis Award, Clinical modality of the Institute of Health Research of the Principality of Asturias (ISPA): "Construction and validation of a clinical staging model for bipolar disorder." PhD student: Lorena de la Fuente Tomás. Directors: Drs. M<sup>re</sup> Paz García-Portilla and Leticia García.
- Prize for the best research project. Jornadas de Investigación Bioaraba: "Bipolar disorder, lifestyle and oxidative stress". PI: Dra. Ana González-Pinto.
- Prize for the best innovation project. Jornadas de Investigación Bioaraba: "Smart Remote Treatment: personalised medicine for the treatment of patients with bipolar disorder." PI: Dra. Ana González-Pinto.

#### Some of the most significant scientific achievements are:

##### -6 doctoral theses:

- Title: "*Evaluation of antioxidant capacity after the debut of a serious mental disorder.*" PhD candidate: Sainza García. Directors: Drs. Ana González-Pinto and Mónica Martínez.
- Title: "*Philip V. His illness and his reign.*". PhD candidate: Maria Rosa Pigrau Santpere. Directors: Drs. Agustí Alcobarro i Pericay and Eduard Vieta i Pascual
- Title: "*Fetal programming, severe mental illness and metabolic related disturbances.*". PhD candidate: Marina Garriga. Directors: Drs. Miquel Bernardo and Clemente García.
- Title: "*Mood, immunity and brain connectivity in patients with chronic hepatitis C.*". PhD candidate: Giovanni Oriolo. Directors: Drs. Lucile Capuron and Rocío Martín-Santos.
- Title: "*Construction and validation of a clinical staging model for bipolar disorder.*". PhD candidate: Lorena de la Fuente Tomás. Directors: Drs. M<sup>re</sup> Paz García-Portilla González and Leticia García Álvarez.
- Title: "*Biomarkers and bipolar disorder.*". PhD candidate: Mónica Sánchez Autet. Directors: Drs. Belén Arranz Martí and M<sup>re</sup> Paz García-Portilla González.

In addition, Dr. Eduard Vieta has participated in the international collaborative study "*Genome-wide association study identifies 30 loci associated with bipolar disorder*" carried out by the *Bipolar Disorder Working Group of the Psychiatric Genomics Consortium published in Nature Genetics*. This study has revealed 30 genetic loci associated with bipolar disorder, 20 of them not previously described.

## Therapeutic Innovation

### Coordinator: Francesc Artigas Pérez

Among the results of 2019, the publication of 5 clinical guides and 61 articles in the first decile stand out. We highlight those published in *Cell* (IF: 36,216), *World Psychiatry* (IF: 34,024), *Nature Genetics* (IF: 25,455), *Circulation* (IF: 23,054), *Lancet Psychiatry* (IF: 18,329), *JAMA Psychiatry* (IF: 15,916), *American Journal Psychiatry* (IF: 13,655), *Science Advances* (IF: 12,804), *Nature Communications* (IF: 11,878), *Molecular Psychiatry* (IF: 11,973) and *Biological Psychiatry* (IF: 11,501).

In innovation, we highlight one patent granted (ES / 2684418 / B1), one published (WO / 2019/121853) and two applied for.

As regards obtaining funds, 23 projects from state public bodies have been obtained (MICINN: EQC2019- 006674-P, RTI2018-094414-A-I00, RTI2018-098269-B-I00; MSCBS: 2019I021, 2019I041; MINECO: RTI2018-099778 - B-I00; ISCIII: PI18 / 00462, PI18 / 00789, PI18 / 01001, PI18 / 00805, PI19 / 00672, PI19 / 00954, ETC), regional authorities

(CM: Y2018 / NMT-4949; Basque Government: IT211-19,K-2019-00049;INIBICA: LI19 / 10IN-CO22), international (ERAB:EA1819) and foundations (BBVA: DIANE, UMBRELLA; La Caixa: LCF / PR / HR19 / 52160001, I2-IR ligands).

Awards and distinctions received by the member groups:

- Inés Ibarra-Lecue, Joint EPBAR-EACPT *Young Investigator Award*.
- First prize, Video Modality, NeuroART, SENC (Irene López Gutiérrez, Cristina Ulecia Morón, Marta González Prieto).
- Award-winning poster, 5th GEIVEX *Symposium* (MI González, G Sobrino, M Desco, B Salinas) and Best oral communication, 7th Research and Innovation Conference, IISGM, (MI González, G Sobrino, M Desco, B Salinas).
- Group led by Dr. Micó- Prize for the best research in Pain 2019 and Esther Berrocso- Female Researcher Award, UCA.
- Analía Bortolozzi, Outstanding Researcher at CIBER, Women's and Girls' Day in Science.
- Eduard Vieta appointed Professor of Psychiatry (UB). Eduard Vieta and Joaquim Radua, listed among the world's most influential scientists, *Clarivate Analytics*. Ricard Navinés, Best Poster Award of the XXII *National Congress of Psychiatry*. SEPB Awards: Eduard Vieta, "Honorary Member", Norma Verdolini, "Best Doctoral Thesis", Iria Grande, "Reference Researcher" and Diego Hidalgo, "Young Accredited Researchers".

Most important scientific achievements include:

- Development of a murine model of depression with predictive validity, based on the alteration of neuron-glial communication in the infralimbic cortex.
- Development of the synthesis of PET and SPECT radiotracers specific for *Staphylococcus* infections.
- Development of natural exosomes for nanomedicine.
- Elaboration of a type of lipid nanoparticles that are captured by the brain perivascular macrophages, a possible tool to understand the mechanism of entry of systemic inflammatory signals to the brain.
- Demonstration of increased functional selectivity of the 5-HT<sub>2A</sub> serotonin receptor through G<sub>i</sub> / o protein signaling in the brain of subjects with schizophrenia.
- Study demonstrating the role of specific neural pathways (locus coeruleus-amygdala) in chronic pain and its comorbidity with anxiety, which brings us closer to the development of new therapeutic targets (treatment of anxiety induced by chronic pain with beta-blockers).
- Study of the antidepressant effect of cannabidiol in a neuroinflammatory model of depression and its mechanism of action.
- Study in postmortem material finds alterations in the extracellular matrix of the prefrontal cortex of psychotic patients with bipolar disorder.
- Participation in an international study that supports the efficacy and safety of esketamine nasal spray as a fast-acting antidepressant for resistant depression patients.
- Cellular model of the action of antipsychotics in ADAMTS2.

## Mental disorders of the child and adolescent

**Coordinator:** Carmen Moreno Ruiz

This programme, made up of 6 clinical and basic CIBERSAM groups, develops research in mental disorders that have their onset in childhood and adolescence. Linked to the programme are several European projects and collaborative projects with other CIBERSAM groups. Among the projects developed in 2019, worth highlighting are innovative projects on epigenetic modifications and innate immunity in child maltreatment, the implication of genetic and environmental factors in neurodevelopmental disorders and their impact on school performance,

the characterisation of clinical psychiatry and the development of an animal model of anti-NMDA encephalitis, cancer comorbidity and disorders of the central nervous system, a multicentre independent clinical trial for the treatment of nuclear symptoms of autism spectrum disorders (ASDs) and the development of a European network of excellence in childhood clinical trials.

In 2019, publications have been mainly in journals indexed in the first quartile according to the JCR ranking such as *Lancet*, *Lancet Oncology*, *World Psychiatry*, *Lancet Neurology*, *British Medical Journal*, *American Journal of Psychiatry*, *Molecular Psychiatry*, *Nature Communications*, *Biological Psychiatry* or *Journal of the American Academy of Child and Adolescent Psychiatry*, among others.

Among the published results we find the following: neuroimaging studies which have found patterns of reorganization of brain connectivity in strategic regions of cortical integration in individuals with high-functioning ASD that predict clinical severity; A collaborative study including individuals with ASD and controls from 54 cohorts has documented the presence in ASD of alterations in the asymmetry of cortical thickness in various brain regions, more marked in the superior frontalis.

Several works have studied genetic alterations in neurodevelopmental disorders. Environmental adversity during the third trimester of gestation has been found to be associated with developmental immaturity, in terms of epigenetic age, and altered methylation in the EP300 gene. A multi-centre study looking at the genome of more than 50,000 individuals has identified twelve loci related to ADHD susceptibility, as well as finding evidence that common genetic variants explain 21% of the disorder's genetic basis. Another work has compared the gene expression profiles of ASD and different types of cancer, suggesting direct comorbidity between brain, kidney, thyroid, and pancreatic cancers and inversely with lung and prostate, pointing to different molecular mechanisms as mediators of this association. Also in ASD, a meta-analysis on the efficacy of dietary interventions has found no evidence for non-specific interventions, although it suggests a potential role for some specific interventions in the management of certain clinical domains. Furthermore, evidence of immune dysregulation has been found in children and adolescents with Obsessive Compulsive Disorder, with an imbalance in the circulating levels of T helper and T regulatory cells.

In 2019, members of the programme have been awarded, among others, with the EPA Research Prize for the best article published in *European Psychiatry*, the ECIP Travel Award of the World Congress of Genetics, or the Best Communication Award at the AEPNYA Congress.

## Psychosomatic, Anxiety and Impulse Control Disorders

**Coordinator:** José M. Menchón Magriña

The programme focusses on clinical and basic epidemiological research into a wide range of mental disorders and conditions which have a major impact on people's mental health and psychological well-being. It is made up of eight clinical and basic groups. Different projects have been launched and results have been obtained in the areas and disorders that make up this programme.

In the line of neurocognitive impairment, a national project on healthy ageing has been obtained as well as participation in the COSMIC group (*Cohort Studies of Memory in an International Consortium*, international consortium focused on mild cognitive impairment) which has described modifiable factors (smoking, education, physical activity, diabetes, AVC) associated with cognitive impairment. In addition, results have been obtained showing dysfunctions of the functional connectivity of the locus coeruleus in healthy adults with a family history of Alzheimer's disease. We have also participated in an international book on psychosomatic medicine and consultation-liaison psychiatry, "Global Psychosomatic Medicine and Consultation-Liaison Psychiatry" (Leig H, Springer Nature, 2019), in which the situation in Spain is also analysed.

In the area of personality disorders, worth mentioning is a clinical trial in patients with chronic borderline personality disorder (BPD) and dysthymic symptoms comparing psychological therapies with the routine approach and another European project (PROBIA) for treating impulsivity in patients with BPD or ADHD with



probiotics. Also, in the context of psychological therapies, studies of the efficacy of EMDR in different mental disorders are being carried out. In addition, BPD evaluation instruments have been validated.

In the area of the line of compulsivity, several groups are collaborating on a project to determine common and differential factors in neuroimaging, neuroinflammation and clinical aspects. This line also participates in studies of international consortia such as the ENIGMA-OCD consortium.

In the field of neuroinflammation, particularly alterations of the immune system and inflammatory response in mental disorders, studies on autophagy and mitophagy are carried out in animal models, on inflammation in electroconvulsive therapy, or microbiota and microbiome studies. One strategy used is reverse translational research in which alterations in humans are checked in animal models.

In the field of epidemiological studies, two projects stand out: the European project ATHLOS (*Ageing Trajectories of Health: Longitudinal Opportunities and Synergies*) aimed at identifying healthy ageing trajectories and their determinants; and SYNCHROS (SYnergies for Cohorts in Health: integrating the ROLE of all Stakeholders) aimed at promoting the development of a stratified and personalised medicine, identifying the best methods to integrate cohort data and developing recommendations to improve future methods of sample collection, data collection and exchange. Within these projects, twenty ageing databases have currently been harmonized, involving more than 300,000 subjects.

The programme is very varied and this brief summary shows only a small part of the activity of the groups it comprises.



# Training Programme

**Coordinator:** Juan Antonio Micó

In 2019, the Training Programme financed a total of 69 actions, including enrollment in research courses and seminars for a total amount of € 26,783.94. The main activities supported were related to attendance or participation in various events with the presence of CIBERSAM. Among them: 20th Symposium on bipolar and depressive disorders, 26th International Symposium on Updates and Controversies in Psychiatry, 8th International Forum on Schizophrenia, 8th Intensive Meeting on Resistant Pathology, 5th Meeting between Researchers in Mental Health, Patients and Families. In addition, there was broad participation in the sessions assigned to the different CIBERSAM programmes at the 22nd National Congress of Psychiatry.

Regarding the Ideas Laboratory 2019, held in Oviedo under the title "Artificial Intelligence in Life Sciences", 16 oral communications were presented spread over 5 tables during the two days of sessions with a total of 15 scientific posters. The 5th Santiago Reig Prize for the best research work published for young CIBERSAM researchers was awarded to Inés Ibarra-Lecue for the article "*Chronic cannabis promotes pro-hallucinogenic signaling of 5-HT2A receptors through Akt / mTOR pathway*" published in *Neuropsychopharmacology* (PI-CIBERSAM: Javier Meana). In short, nearly a hundred young researchers from our CIBER and other CIBER/Networks participated in the 7th edition of the Ideas Laboratory.

This year the Interuniversity Master's Degree in Mental Health Research completed 52 registrations. The number of students enrolled in type A stays was 39 and 37 in type B. In addition, a total of 30 TFMs (End of Master Projects) were presented.

In May, CIBERSAM held the 17th Intensive Course for Introduction to Research in Neurosciences. The course, taught at the Biology Faculty of the University of Barcelona, was attended by 130 persons including mental healthcare professionals, researchers in neurosciences and students from different scientific disciplines. In this 17th edition, the course was held under the title "Neuroendocrinology of child-adolescent mental disorders."

In September, the 10th 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. This year the course focussed on the introduction to data harmonisation of the ATHLOS project (*Ageing Trajectories of Health: Longitudinal Opportunities and Synergies*).

# Platforms

**Coordinator:** Javier Meana Martínez

Throughout 2019, CIBERSAM platforms have continued a process of expansion, increasing the number of their respective contributions and, above all, making resources available to intraCIBER and external research groups.

Among the significant activities of this period, we highlight the process of adapting the safety procedures and manuals to the new regulations currently in force.

The activity of the official platforms expressed in indicators is reflected in the following table:

	Library of instruments	DNA and sample collections	Neuroimaging
Existing Instruments	336	-	-
Added Instruments	25	-	-
Enquiries or applications for use made	12	-	-
Funded publications	90	-	-
Training activities	1	-	-
Stored images	-	-	23742
Requests for use	-	4	24
Groups contributing	-	8 groups	4
Groups of users	-	(2 consortium)	4
Patients included	-	+1733	-
Requests for coordinated studies	-	2	-

The scientific productivity generated as a result of the use and exploitation of the CIBERSAM platforms in 2019 and the comparison with the 2018 data is reflected in the following table:

Use of CIBERSAM Platforms by intraCIBER or external groups	2018	2019
Total number of Publications	24	37
GRIDSAM platform	12	11
DNA and sample collections platform	3	10
Neuroimaging platform	4	7
Library of Instruments platform	2	8
Brain collections platform	3	8
Total number of Clinical Trials	0	1
Library of Instruments platform	0	1
Total number of Patents	0	1
Brain collections platform	0	1
Total number of Clinical guides	0	1
Library of Instruments platform	0	1

# Scientific Production

## Publications

### No. of publications in 2019

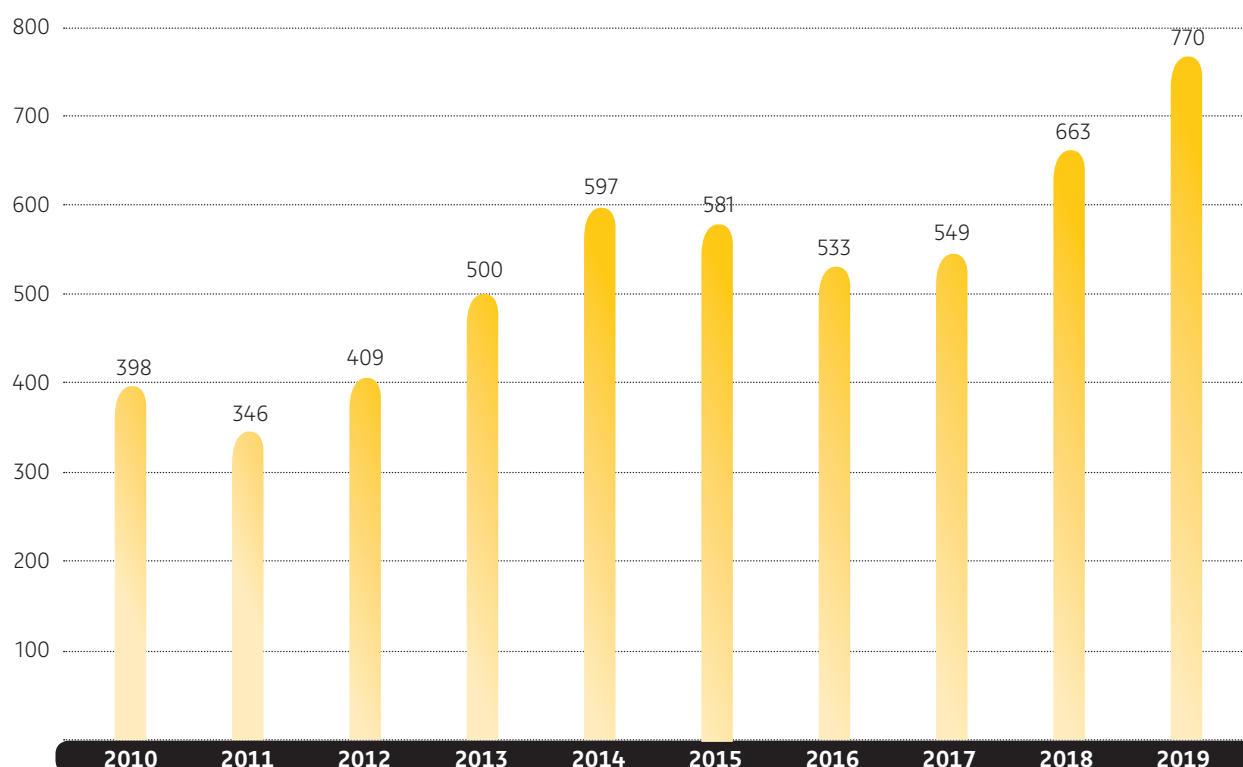
TOTALS	770
Q1	478
D1	190

### Collaborative Publications

CIBERSAM	198
CIBER*	115

\*Entre varios áreas temáticas

### Evolution of publications 2010-2019























## 10 most relevant publications by impact factor

IF	Publication
59,1020	AFSHIN A., SUR P.J., FAY K.A., CORNABY L., FERRARA G., SALAMA J.S. ET AL. <i>Health effects of dietary risks in 195 countries, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet.</i> 2019;393(10184):1958-1972.
59,1020	CHANG A.Y., COWLING K., MICAH A.E., CHAPIN A., CHEN C.S., IKILEZI G. ET AL. <i>Past, present, and future of global health financing: a review of development assistance, government, out-of-pocket, and other private spending on health for 195 countries, 1995–2050. The Lancet.</i> 2019;393(10187):2233-2260.
43,0700	BURSTEIN R., HENRY N.J., COLLISON M.L., MARCZAK L.B., SLIGAR A., WATSON S. ET AL. <i>Mapping 123 million neonatal, infant and child deaths between 2000 and 2017. Nature.</i> 2019;574(7778):353-358.
36,2160	LEE P.H., ANTILA V., WON H., FENG Y.-C.A., ROSENTHAL J., ZHU Z. ET AL. <i>Genomic Relationships, Novel Loci, and Pleiotropic Mechanisms across Eight Psychiatric Disorders. Cell.</i> 2019;179(7):1469-1482.e11.
35,3860	FORCE L.M., ABDOLLAHPOUR I., ADVANI S.M., AGIUS D., AHMADIAN E., ALAHDAB F. ET AL. <i>The global burden of childhood and adolescent cancer in 2017: an analysis of the Global Burden of Disease Study 2017. The Lancet Oncology.</i> 2019;20(9):1211-1225.
34,0240	VANCAMPEFORT D., FIRTH J., CORRELL C.U., SOLMI M., SISKIND D., DE HERT M. ET AL. <i>The impact of pharmacological and non-pharmacological interventions to improve physical health outcomes in people with schizophrenia: a meta-review of meta-analyses of randomized controlled trials. World Psychiatry.</i> 2019;18(1):53-66.
34,0240	REED G.M., FIRST M.B., KOGAN C.S., HYMAN S.E., GUREJE O., GAEBEL W. ET AL. <i>Innovations and changes in the ICD-11 classification of mental, behavioural and neurodevelopmental disorders. World Psychiatry.</i> 2019;18(1):3-19.
34,0240	McKENNA P., LEUCHT S., JAUHAR S., LAWS K., BIGHELLI I., P.J. McKENNA. <i>The controversy about cognitive behavioural therapy for schizophrenia. World Psychiatry.</i> 2019;18(2):235-236.
34,0240	GULOKSUZ S., PRIES L.-K., DELESPAUL P., KENIS G., LUYKX J.J., LIN B.D. ET AL. <i>Examining the independent and joint effects of molecular genetic liability and environmental exposures in schizophrenia: results from the EUGEI study. World Psychiatry.</i> 2019;18(2):173-182.
28,7550	PATEL A.P., FISHER J.L., NICHOLS E., ABD-ALLAH F., ABDELA J., ABDELALIM A. ET AL. <i>Global, regional, and national burden of brain and other CNS cancer, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet Neurology.</i> 2019;18(4):376-393.

## CIBERSAM Groups. Publications in 2019

Group Leader	Publ.	Q1	D1	Institution/Centre	Province
 Arango López, Celso	49	33	19	Servicio Madrileño de Salud	Madrid
 Ayuso Mateos, José Luis	29	26	6	Universidad Autónoma de Madrid	Madrid
 Bernardo Arroyo, Miquel	54	30	20	Hospital Clínic i Provincial de Barcelona	Barcelona
 Bobes García, Julio	46	24	11	Universidad de Oviedo	Asturias
 Casas Brugué, Miguel (1)	26	15	6	Fundación Hospital Universitario Vall d'Hebrón. Institut de Recerca (VHIR)	Barcelona


Group Leader	Publ.	Q1	D1	Institution/Centre	Province
 Bortolozzi Biasoni, Analía	9	8	2	Agencia Estatal Consejo Superior de Investigaciones Científicas	Barcelona
 Crespo Facorro, Benedicto	36	23	13	Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla	Sevilla
 Desco Menéndez, Manuel	20	14	5	Servicio Madrileño de Salud	Madrid
 Fañanas Saura, Lourdes	24	18	5	Universidad de Barcelona	Barcelona
 González Pinto Arrillaga, Ana	40	17	4	Asociación Instituto de Investigación BIOARABA	Álava
 Haro Abad, Josep Maria	162	110	47	Fundación para la Investigación y Docencia Sant Joan de Deu	Barcelona
 Ibáñez Cuadrado, Ángela	35	18	7	Servicio Madrileño de Salud	Madrid
 Leza Cerro, Juan Carlos	16	8	3	Universidad Complutense de Madrid	Madrid
 Meana Martínez, José Javier	25	15	4	Universidad del País Vasco	Vizcaya
 Menchón Magriña, José Manuel	52	34	11	Fundación IDIBELL	Barcelona
 Micó Segura, Juan Antonio	10	5	2	Universidad de Cádiz	Cádiz
 Palomo Álvarez, Tomás (2)	32	28	9	Universidad Complutense de Madrid	Madrid
 Pazos Carro, Ángel Armando	5	5	0	Universidad de Cantabria	Cantabria
 Pérez Sola, Víctor	69	38	16	Consorti Mar Parc Salut de Barcelona	Barcelona
 Pomarol Clotet, Edith	36	28	13	Fundación para la Investigación y Docencia Maria Angustias Gimenez (FIDMAG)	Barcelona
 Sanjuan Arias, Julio (3)	27	17	11	Universidad de Valencia	Valencia
 Tabarés Seisdedos, Rafael	38	24	13	Universidad Valencia	Valencia
 Vieta Pascual, Eduard	125	90	34	Hospital Clínic i Provincial de Barcelona	Barcelona

(1) PI replaced by José Antonio Ramos Quiroga

(2) Merged with the group of Juan Carlos Leza Cerro

(3) PI replaced by Juan Salvador Nacher Roselló

## Linked Clinical Groups


Group leader	Institution/Centre	Province
 Olivares Diez, José Manuel	Servicio Gallego de Salud	Pontevedra
 Rodríguez Jiménez, Roberto	Servicio Madrileño de Salud	Madrid
 Palao Vidal, Diego José	Corporación Sanitaria Parc Taulí	Barcelona

## Patents

### Patents applied for

- Composición farmacéutica para su uso en el tratamiento de la depresión por vía intranasal.
- *In vitro method for the diagnosis or prognosis of neurodegenerative disorders.*

## Clinical guides

- Consenso sobre la depresión en el anciano. 2ª Edición
  - Early intervention for obsessive compulsive disorder: An expert consensus statement.
  - Guía de ejercicio terapéutico para personas diagnosticadas de psicosis.
  - Guía de práctica clínica (basada en el método ADAPTE). Tratamiento farmacológico del trastorno obsesivo compulsivo en adultos.
  - Protocolo de Intervención Temprana en Psicosis de Cantabria (ITPCan).
  - *Treatment-resistant and multi-therapy-resistant criteria for bipolar depression: consensus definition.*
  - *Updated European Consensus Statement on diagnosis and treatment of adult ADHD.*
  - *What is the optimal serum level for lithium in the maintenance treatment of bipolar disorder? A systematic review and recommendations from the ISBD/IGSLI Task Force on treatment with lithium.*
- 



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