CIBER

CENTRO DE INVESTIGACIÓN BIOMÉDICA EN RED

ANNUAL REPORT

2021

INDEX

EL CONSORCIO CENTRO DE INVESTIGACIÓN BIOMÉDICA EN RED

THEMATIC RESEARCH AREAS

Presentation by the President of CIBER's Governing Board

Cristóbal Belda

Director of the ISCIII and President of the Governing Board of the CIBER Consortium

The CIBER Consortium is one of the strategic commitments of the Instituto de Salud Carlos III to support biomedical research in our country. During the COVID-19 pandemic, it has proven to be a tool of the highest level to answer the questions that arose as the spread of the virus progressed. In this sense, the value of CIBER has been fully revealed insofar as it has been the perfect instrument to respond to questions that required the coordination of multiple scientists with complementary but distant perspectives of knowledge, at least on the surface, since the protection of health is the scientific objective that unites us all. This work, designed and carried out for more than a decade, has proven to be extremely useful both for what is currently happening and to provide answers to the big collective questions of the coming years.

The CIBER network research model, unique in our country, has close to over 6,000 researchers between contracted and attached staff, who are integrated into 511 research groups distributed throughout the Spanish geography and working in 11 thematic research areas in 2021. The research groups that make up the CIBER enter the consortium through external evaluation and are also periodically evaluated; only those that meet a rigorous evaluation and demonstrate unquestionable research excellence remain within the consortium, while the gaps left by those who cannot keep up with the pace of growth in health-oriented science are filled by those groups that reach the quality standards, in a dynamic move that does nothing but improve the overall performance of the whole. This method of continuous

evaluation, together with the collaborative work of the network, favors synergies, avoids duplication and promotes the optimization of resources.

The CIBER pursues the objective of protecting health through excellent science with a clear translational vocation as it is a meeting point for researchers from different disciplines and fields of knowledge. This makes it a magnificent translational research center. Thus, adding the efforts of the best research groups in our country improves the applicability of the results, as well as their transfer to the industry and the National Health System.

In terms of results, we can say that 2021 has been an exceptional year. The consortium has obtained more than 10 million euros in financing through national projects and close to 1 million in international projects, highlighting the almost 1.8 M€ for the Nanbiosis ICTS or the projects awarded for Precision Medicine or Clinical research , financed by the ISCIII.

As regards publications, the groups have exceeded the figure of 9,500 articles (58% in the first quartile and 23% in the first decile); 22 new priority patent applications have been filed and 9 developments between software, orphan drug designations and trademarks. In addition, 10 license and license option contracts have been signed, improving the results of the previous year.

The CIBER Scientific Culture Unit (UCC+I) resumed face-to-face activities during Science Week, inviting various educational centers to get to know some of the lines of research that are currently being carried out. Always looking for ways to bring science closer to society, the UCC+I has continued to promote collaborations with institutions for the dissemination of results and the participation of the center through social networks, where there are already nearly 60,000 users who follow CIBER's social accounts on Twitter, more than 1,600 followers on Instagram and nearly 700 on YouTube.

Without dwelling on the innumerable milestones in the CIBER research areas that are already included in the following pages, I would like to highlight the initiative of the CIBERNED training plan with the launch in 2021 of the scientific sessions "CIBERNED Webinar Series", aimed at sharing the latest scientific advances and stimulating interactions and collaborations between groups. Also worth highlighting is the launch of the 'CIBERER Academy for patients', an initiative that aims to empower patients and their families by offering them the necessary tools to understand all aspects related to research. Finally, I would like to point out that the national project CIBERESUCICOVID, for the study of risk factors, personalized prognosis and one-year follow-up of patients admitted for COVID-19 in Spanish ICUs, was successfully completed and that it produced 18 scientific publications and was presented at 9 national and international congresses and conferences.

From the structural point of view, we must highlight the integration of CIBERNED within the CIBER consortium, thus concluding the merger period of all the previous structures. In parallel, the new infectious diseases area was created within CIBER, with a decision marked by the pandemic still affecting us.

But the most important recognition is always linked to people, the thousands of women and men who, having dedicated their talent and effort to health-oriented science, have made it possible for these results to continue to amaze us as a society. With all of them we have a commitment that, throughout the next year 2022, we hope to complete with a reform of the Science Law which will update the commitment we have made as a country of Science.

I cannot end these lines, however, without highlighting the extraordinary work of the person who has been in charge of this great CIBER center in recent years: Manuel Sánchez Delgado. Thanks to the efforts of Manuel, and of all the people on the CIBER team, the Consortium has achieved better results every year and a greater impact on society. His dedication will serve as an example for many people. Our remembrance of him and his family is a sincere gratitude to a life dedicated to science of a person who, without being a scientist, deeply believed in the need to protect it through outstanding management. Margarita Blázquez, former deputy director general of Cooperative Research Networks and Centers of the ISCIII, and a deep connoisseur of the CIBER consortium both from the perspective of the ISCIII and from the years that she worked side by side with Manuel, has been the person who has stepped forward to continue driving this project, at a particularly difficult time for us all. Similarly, allow me to refer to Dr. Raquel Yotti, president of this Consortium until August 2021, when she was appointed Secretary General for Research of the Ministry of Science and Innovation. Only the passage of time will give us an idea of the role that Dr. Yotti has played in the architecture of Science in Spain, but those of us who have had the privilege of learning at her side can already have a pretty good idea of the enormous level of her contributions. IMPACT, ENE-Covid, center for advanced therapies, BSL-4 are some of the structures that were conceived, projected and started under her direction. Consequently, this report is part of her entire legacy.

In light of the above, I trust you will allow me to feel very honored to present this CIBER Annual Report, the largest biomedical research center in our country, and to be able to share the good results achieved for yet another year.

INTERNAL ORGANIZATION

The Consorcio Centro de Investigación Biomédica en Red (Biomedical Research Networking Center Consortium), CIBER, a public research consortium created at the initiative of the **Instituto de Salud Carlos III** (ISCIII), promotes research of excellence in Biomedicine and Health Sciences that is carried out in the National Health System and in the Science and Technology System.

The scientific program of the CIBER is organized around the following **thematic areas** of Research:

THEMATIC AREAS

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

*Due to the impossibility of carrying out a second annual report, and although CIBERNED did not belong to the CIBER Consortium throughout 2021, the decision was finally taken to include CIBERNED data in this annual report.

The CIBER currently has a staff of **881 people** and **5,654 attached researchers**, integrated into **511 research groups**, working in different locations, linked to **104 consortium institutions**, belonging to different Administrations, Institutions and Autonomous Communities, of the public and private sector.

The 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** constitutes a delegated commission, formed by the ISCIII and 8 members of the Governing Council, which can be renewed annually. Both the operation and the purposes of the governing, support and advisory bodies are established in the CIBER statutes.

MANAGEMENT COMMITTEE AND ADVISORY COMMITTEES

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

The Management Committee is made up of the Scientific Management 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 Scientific Advisory Committee is a body providing scientific assessment and support, made up of relevant personalities in the field of health sciences distinguished by their professional or scientific career in line with the objectives of the center. This is the body in charge of carrying out the annual evaluation of the activity of the areas and their research groups.

SCIENTIFIC DIRECTORS 2021

Scientific Director CIBER-BBN: **Dr. Ramón Martínez Máñez**

Scientific Director CIBERCV: **Dr. Francisco Fernández-Avilés**

Scientific Director CIBERDEM: **Dr. Eduard Montanya Mías**

Scientific Director CIBEREHD: **Dr. Rafael Bañares Cañizares**

Scientific Director CIBERER: **Dr. Pablo Lapunzina Badía**

Scientific Director CIBERES: **Dr. Ferran Barbé Illa**

Scientific Director CIBERESP: **Dra. Marina Pollán Santamaría**

Scientific Director CIBERFES: **Dr. Leocadio Rodríguez Mañas**

Scientific Director CIBERNED: **Dr. Adolfo López de Munain**

Scientific Director CIBEROBN: **Dr. Carlos Diéguez González**

Scientific Director CIBERONC: **Dra. Anna Bigas Salvans**

Scientific Director CIBERSAM: **Dr. Eduard Vieta Pascual**

The Scientific Directors of the CIBER represent each of the thematic areas and preside over the Management Committees.

CIBER IN FIGURES 2021

5654 ATTACHED RESEARCHERS

511 RESEARCH GROUPS

104 CONSORTIUM INSTITUCIONS

01 TOTAL INCOME 2021

37.754.950,00€

02 PERSONNEL BY GENDER

649 **232**

TOTAL **881**

03 PERSONNEL BY CATEGORY

DIPLOMA HOLDER	100
DOCTOR	404
GRADUATE	268
TECHNICAL STAFF	109

04 PUBLICATIONS 2021

9552*

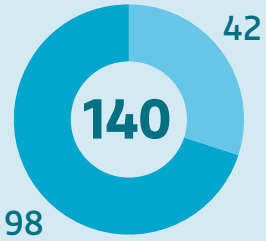
* Data extracted from Web of Science as of May 4, 2022

Q1 **58%**

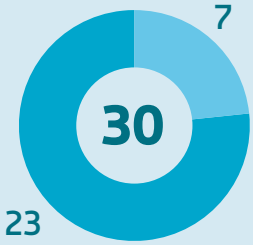
D1 **23%**

05 PROJECTS

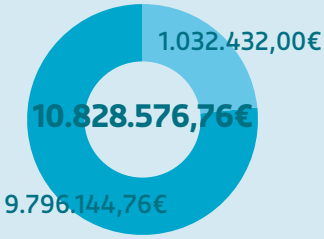
APPLICATIONS FOR COMPETITIVE GRANTS SUBMITTED IN 2021



COMPETITIVE PROJECTS OBTAINED IN 2021



FUNDS OBTAINED IN 2021



NATIONAL INTERNATIONAL

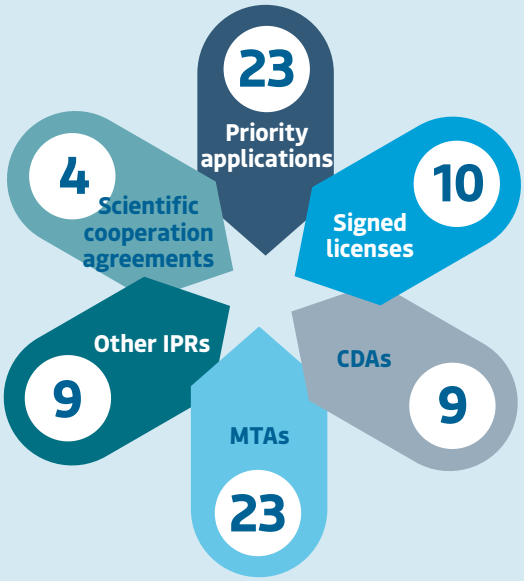
06 COMMUNICATION

193 PRESS RELEASES
13000 MEDIA IMPACTS
12319 DIGITAL MEDIA
875 PRESS
25 RADIO AND TV

1300 NEWS
700 AGENDA EVENTS
5 CIBER NEWSLETTERS
872725 WEBSITE VISITS
440000 WEBSITE USERS

13 TWITTER ACCOUNTS | **60000** FOLLOWERS
1600 INSTAGRAM FOLLOWERS
680 YOUTUBE SUBSCRIBERS

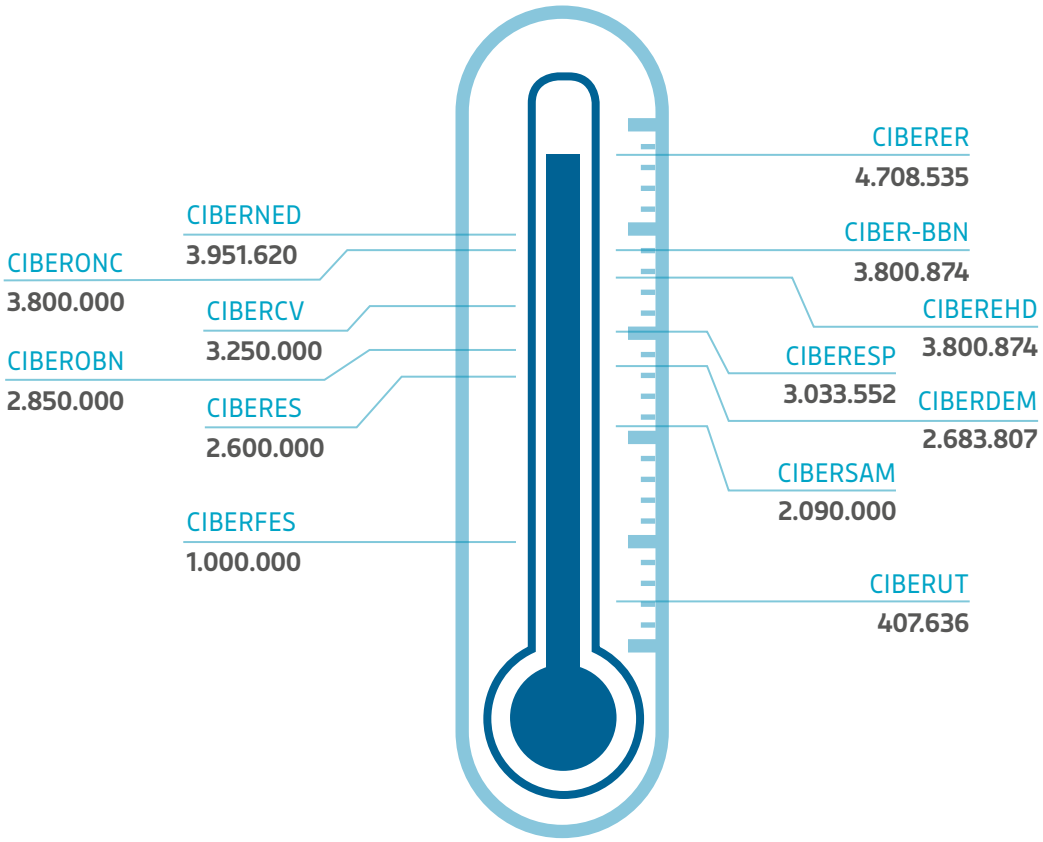
07 TRANSFER



* IPRs: Intellectual Property Rights
MTAs: Material Transfer Agreement
CDAs: Confidential Disclosure Agreement

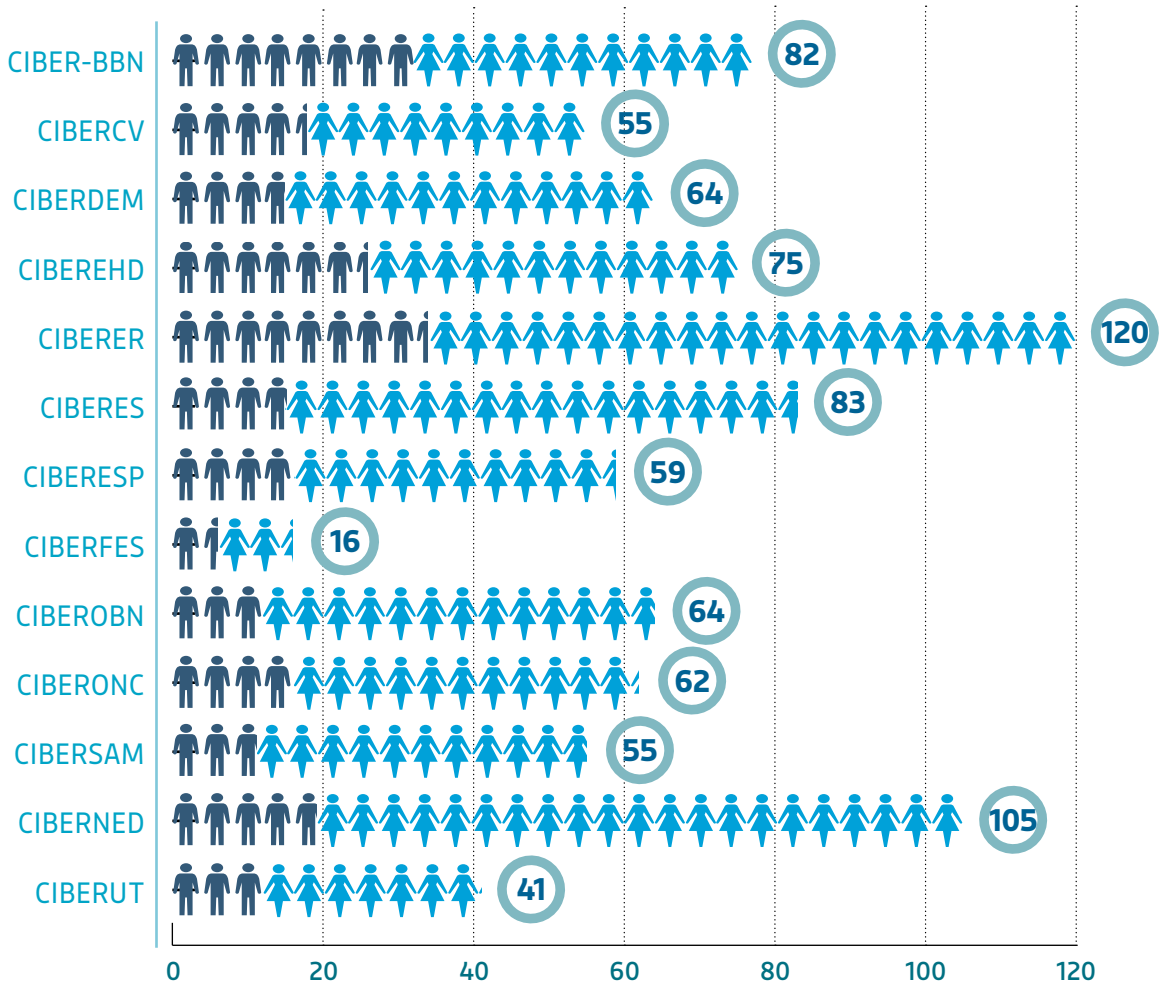
ECONOMIC DATA

08 ECONOMIC RESOURCES OBTAINED IN 2021



PERSONNEL

09 CONTRACTED PERSONNEL BY GENDER AND AREA



10 CONTRACTED PERSONNEL BY CATEGORY AND AREA

THEMATIC AREA	Diploma Holder	Doctor	Graduate	Technical Staff
CIBER-BBN	8	55	16	3
CIBERCV	2	33	15	5
CIBERDEM	1	36	17	10
CIBEREHD	5	36	23	11
CIBERER	1	65	39	15
CIBERES	14	21	35	13
CIBERESP	9	28	20	2
CIBERFES	0	9	7	0
CIBEROBN	7	22	19	16
CIBERONC	11	34	16	1
CIBERSAM	6	19	27	3
CIBERNED	2	32	45	26
CIBERUT	0	4	32	4

TRANSFER

One of the CIBER's main aims is the transfer 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 organizations, public research centers and other innovation agents to establish an effective cooperation between them and ensure that the results of research can finally be applied.

Throughout 2021, and despite the pandemic, CIBER submitted 23 new priority patent applications and another 9 developments were developed between software, orphan drug designations and trademarks. In addition, 10 license and license option contracts have been signed, 4 more than in 2021:

Indicator	Current value
Number of priority patent applications	23
Number of licences/ licence options signed	10
Otros IPRs	9

*Data as of December 31, 2021

**One corresponds to a priority application of December 2020 which was not accounted for at the time.

In addition, throughout 2021, the following activities and initiatives were carried out, among others:

- Four scientific cooperation agreements were signed with different companies.
- Dozens of minor agreements were negotiated: CDAs (9) and MTAs (23) and coownership agreements (28).
- Support was given to Dr. Óscar Yanes (CIBERDEM) in achieving a proof of concept project for the ministry that will be the potential basis of creation of a new CIBER spin-off. In addition, support for Epidisease has been ongoing.
- Various ongoing activities of commercialization and diffusion of technologies have been maintained.
- Participation in online and face-to-face partnering fairs such as: Transfer Forum, where a stand was shared with the ISCIII and the ITEMAS, Biospain and Bioeurope Platforms.
- Support was given to different departments of the CIBER Central Technical Unit in the review of contracts, proposals and other issues.
- From the CIBERER area, 3 online seminars were organized by the CIBERER academy, which is a specific CIBERER instrument for the training of those affected by rare diseases. Three specific seminars were organized together with FIAPAS, which is the Spanish Confederation of Families of Deaf People.
- Calls for internal projects:

  The CIBERER area published their intramural call for cooperative and complementary actions, of which 9 projects were finally approved- projects with the ultimate objective of developing new orphan drugs and new diagnostic tools. The call for translational research projects led by clinical groups was also launched, 2 of which were financed.

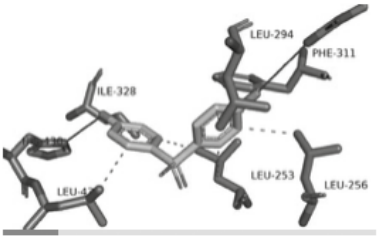
  CIBER-BBN has continued to work on ongoing projects of its valorisation and transfer programs, the former to increase the TRL level of developments, the latter in collaboration with companies. Three new ones have also been started. In addition, new calls were published to continue working in this line.
- Collaboration has been made with various companies and agents on issues of open innovation and project scouting, with dozens of projects sent to different programs. In addition, the CIBER-BBN organized, together with the company Ximbio, (https://ximbio.com/), the Webinar “Unlock the value of your research tools” on the valuation of research tools.
- Finally, the CIBER-BBN and CIBERER areas continue to participate, together with the AEMPS (Spanish Agency for Medicines and Health Products), in the STARS-CSA project: Strengthening Training of Academia in Regulatory Science.

COMMUNICATION

12 relevant CIBER news in 2021:

01/28/2021
Interventions against bullying in Primary and Secondary education centers have proven to be effective.

02/26/2021
A more effective nanomedicine has been developed for the treatment of Fabry disease.



03/30/2021
Current bisphenol-A substitutes also alter pancreatic beta cell function.

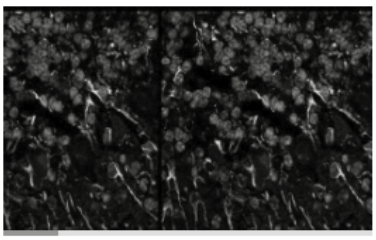
04/09/2021
Good news for the "healthy overweight"; muscle power protects older people also with obesity.

05/10/2021
A new gene has been discovered involved in hereditary cardiac arrhythmias.

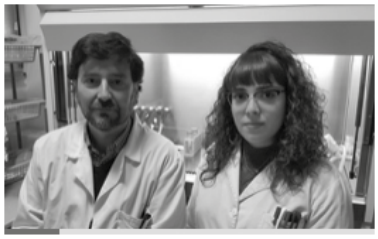
06/08/2021
Changes in eating habits during the first wave of the pandemic did not bring nutritional improvements to our diet.

07/20/2021
A new "actor" identified in metastasis and treatment resistance to breast cancer therapies.

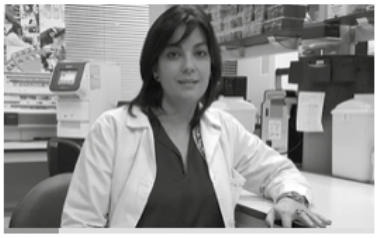
08/31/2021
The ISCIII opens a new thematic area on infectious diseases at the CIBER.



10/14/2021
The first epidemiological study of mitochondrial diseases in Spain has been presented.



11/25/2021
A new therapeutic target has been identified that could reduce resistance to chemotherapy in liver cancer.



10/04/2021
The epigenetic effect of a very low-calorie ketogenic diet in the treatment of obesity has been proven.

12/15/2021
Mortality of patients admitted for COVID-19 in Spanish ICUs was 31%.

Dissemination activities of Ciber's scientific culture unit (UCC+I)

Women scientists who inspire on F11

On the occasion of the International Day of Women and Girls in Science, on February 11, the UCC+I of the CIBER promoted two actions to highlight the work of female researchers in the consortium, about 74% of the CIBER's hired staff.

"Women Scientists who inspire" is a new section on the CIBER website with a search engine to locate women scientists according to area, location or lines of work.

11 vídeos para el 11F consists of a selection of some of the works presented by CIBER scientists in the #Quesigalaciencia (#ScienceMustGoOn!) campaign, developed during the end of 2020 and the beginning of 2021 with a female participation of 70%.

CIBER Activity at the Madrid Science Week

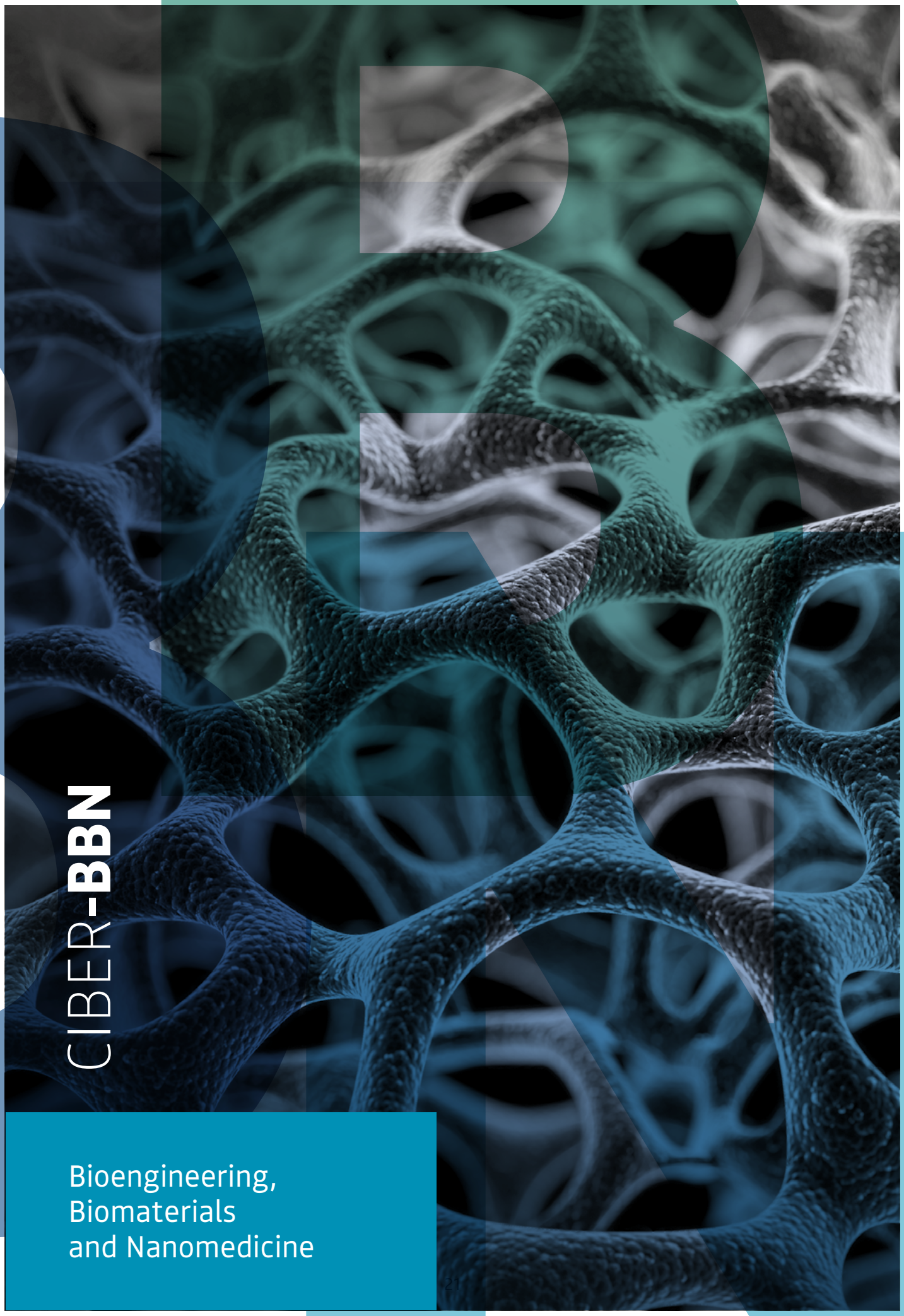
On November 11, the CIBER presented the third edition of #ImproCiencia in which it made known in a fun way what the CIBER is and some of the research carried out in its different thematic areas.

Among them, the CIBER for Frailty and Healthy Ageing (CIBERFES) showed that it is possible to "network from Murcia and Salamanca" led by its researchers María Ángeles Bonmatí and Marina García Macia. Similarly, led by Inés Ibarra on behalf of the Mental Health CIBER (CIBERSAM), we traveled to the USA and explained how to develop a career in research and what is the relationship between cannabis and mental health, the basis of her research. And finally, led by Lucía Pinilla from the CIBER for Respiratory Diseases (CIBERES), we entered a P3 biosafety laboratory to take a look at how the CIBERESUCICOVID project works.

The research projects were interspersed with improvisations and games thanks to the collaboration of the company ImproImpar, which developed the entire dynamic session. .

The activity was attended in person by groups of Secondary, High school and Vocational Training students (**+ 240 attendees**), but it was also open to the general public and could be followed on video streaming by all interested audiences.

YouTube link (**+190 views**)



CIBER-BBN

Bioengineering,
Biomaterials
and Nanomedicine

Presentation by the scientific director

Ramón Martínez Máñez

In 2021, the Covid-19 pandemic has continued to condition our lives and our research activity, although it has been the year in which it has finally been possible to face the devastating effects of the virus thanks to vaccines. We will remember 2021 as the year of mass vaccination in developed countries. It is noteworthy that the Pfizer and Moderna vaccines employ strategies based on nanomedicine, as they use lipid nanoparticles to transport messenger RNA that activates the immune system. Hopefully this result is the first of future and successful vaccines for other diseases.

Despite the circumstances, CIBER-BBN has maintained an outstanding activity in 2021 and it can be said that it is gradually returning to normality. We have become accustomed to exploiting the advantages that online meetings allow and we have been able to hold the Annual Conference and other events such as webinars and meetings in virtual format.

Even the high number of 2020 publications has been exceeded, although the quality indicators have decreased slightly, with 72% of 2021 publications in Q1 and 23% in D1.

Our scientific activity has been maintained in the three research programs (bioengineering, biomaterials, nanomedicine) as regards intramural collaborations and Early Stage projects. Collaborations involving groups from different programs, as well as groups from BBN and other areas, are becoming more and more frequent. CIBER represents the perfect ecosystem for the collective advancement of biomedical science and the synergy of the capacities of all the groups that are a part of it.

In 2021, we also maintained the calls for valorization projects, which aim to increase the level of maturity of our technologies and transfer projects (with industrial co-financing).

In collaboration with other areas, two editions of seed projects have been convened with CIBEREHD and one with CIBERESP, in order to bring our technology closer to specific applications in different areas of CIBER. Together with CIBERONC, a successful Conference for Young Researchers was organized, an initiative that we are encouraged to repeat in the future.

I would also like to highlight the participation of CIBER-BBN groups in European projects of different calls, such as the SAFE-N-MEDTECH project in which the ICTS NANBIOSIS participates, as well as the effort made in the application for all of CIBER of a project of the COFUND modality within the Marie Skłodowska-Curie actions of Horizon Europe. Another result to highlight is the designation by the EMA of a nanoformulation as an orphan drug to treat Fabry disease, a result derived from the European project SMART-4FABRY, coordinated by CIBER.

Regarding communication indicators, efforts have continued to be made in dissemination and the number of press releases sent out originating from CIBER-BBN results has improved.

For yet another year I want to express my gratitude to the CIBER-BBN researchers for their effort, dedication and commitment to science and collaborative research. The development of vaccines that have saved so many lives shows that it is the right path.

On the following pages you will find the most outstanding results of CIBER-BBN throughout 2021. Warm regards to all.

PROGRAMS

PROGRAM 1

Bioengineering and Medical Imaging

COORDINATOR:
Raimon Jané

During 2021, four new proposals for intramural collaborations have been presented in this research program. To these collaborations we must add another 43 that were presented between 2018 and 2020 and that have also remained active in 2021, giving a total of 47 active collaborations coordinated by researchers from the Bioengineering and Medical Imaging program. Of the new proposals presented in 2021, one is in collaboration with CIBERNED:

- *QCRBact, Development of improved methodologies based on quartz crystal resonators for measuring biological fluid viscosity: application to bacterial adhesion studies*, José Javier Serrano.
- *eGLANCE, Development of technical tools for helping the movility of blind people*, José Javier Serrano.

- *Computationally-guided maturation of iPSC-derived cardiomyocytes,* Esther Pueyo.
- *Validation of a novel PET quantification technique using Monte-Carlo simulations,* Aida Niñerola.

The clinical areas addressed by these new proposals have been diverse, one in infectious diseases, one in neurological diseases, one in cardiovascular diseases, and one in ophthalmology.

In addition, a project from the Early Stage 2020 call has been kept active: :

- *ANíMATE, Personalized motivation through mHealth strategies, for improving the patient empowerment and to enhance their adherence,* coordinated by Carmen Pérez Gandía.

During the Annual Conference held virtually in November 2021, a session was dedicated to the presentation of a selection of intramural collaborations that have achieved relevant results, including:

- *Multiparametric MR data processing and software strategies for cancer response biomarker discovery (*Ana Paula Candiota*).*
- *Characterization of the influence of physical activity on age-related cardiac function (*Esther Pueyo*).*

One of the awards for the best article published the previous year (2020) by a young researcher went to Eduardo Santamaría-Vázquez (University of Valladolid), from the group led by Roberto Hornero, for the article "EEG-Inception: A Novel Deep Convolutional Neural Network for Assistive ERP-Based Brain-Computer Interfaces" published in IEEE Transactions On Neural Systems And Rehabilitation Engineering.

During 2021 CIBER-BBN has collaborated in the strategic actions promoted by CIBERONC. Within the framework of these actions, the "Cancer Stroma Assessment through Digital Pathology (CASA-DP)" project is being developed, coordinated by Nuria Malats (CIBERONC) and in which the group led by Andrés Santos participates through the researcher María Jesús Ledesma, performing digital pathology analysis tasks.

Worth mentioning is the participation of CIBER-BBN as a stakeholder of the European Medicines Agency (EMA) in the Second HMA/EMA EU Big Data Stakeholder Forum, held virtually on December 7, 2021. The researcher Gonzalo Gutiérrez, from the group of PI Roberto Hornero (University of Valladolid) attended as an expert on behalf of CIBER-BBN.

PROGRAM 2

Biomaterials and Advanced Therapies

COORDINATOR:
José Luis Gómez Ribelles

The scientific activity of the program was mainly structured around 43 active intramural collaborations, 36 presented during the 2018-2020 period, together with the following seven new proposals:

- *Bioengineered constructs based on Elastin-like recombinamers (ELRs) for cardiac regeneration, Elisabeth Engel.*
- *Effect of secretome from MSC on wound healing, Elisabeth Engel.*
- *Evaluation and validation of cryopreservation as a storage method for encapsulated cells used in cardiac regenerative therapy, Ignacio Ochoa.*
- *BioEngCardTox Human bioengineering for detection and analysis of cardiotoxicity in anti-neoplasic therapy, Estefanía Peña.*
- *CRISPR screen of early driver events contributing to glioblastoma development in CMMRD syndrome, Ángel Raya.*

- *Pre-clinical assessment of human iPSC-derived cell therapy in a large animal model of myocardial infarction, Ángel Raya.*
- *CAMS, Development of a targeted proteomics method useful to improve the diagnostic accuracy of cardiac amyloidosis and facilitate precision medicine approaches, Cristina Ruiz.*

The clinical areas most addressed by these new proposals have been cardiovascular diseases, cancer, rare diseases and regenerative medicine. Regarding inter-CIBER collaboration, two of these new proposals are in collaboration with CIBERCV and another two with CIBERONC.

Throughout 2021 the following projects of the Early Stage 2020 call have remained active: :

- *HydroCartReg, Chemically crosslinked hyaluronic acid-chitosan scaffolds for potential application on cartilage regeneration after microfracture procedure, coordinated by Luis García-Fernández.*
- *OCUSySTEM-II, Mesenchymal stem cells as a next generation drug delivery system for ocular surface diseases: project extension, coordinated by Teresa Nieto Miguel.*
- *SCIELR, A new biomaterial platform for spinal cord recovery, coordinated by Alessandra Girotti.*
- *MYORESTORE, Biomaterial systems to synergistically induce muscle repair, coordinated by Patricia Rico.*
- *HYDROREG II, Engineering hydrogels to promote muscle regeneration II, coordinated by Jesús Ciriza.*

In the results session of intramural collaborations during the Annual Conference, the following presentation was included:

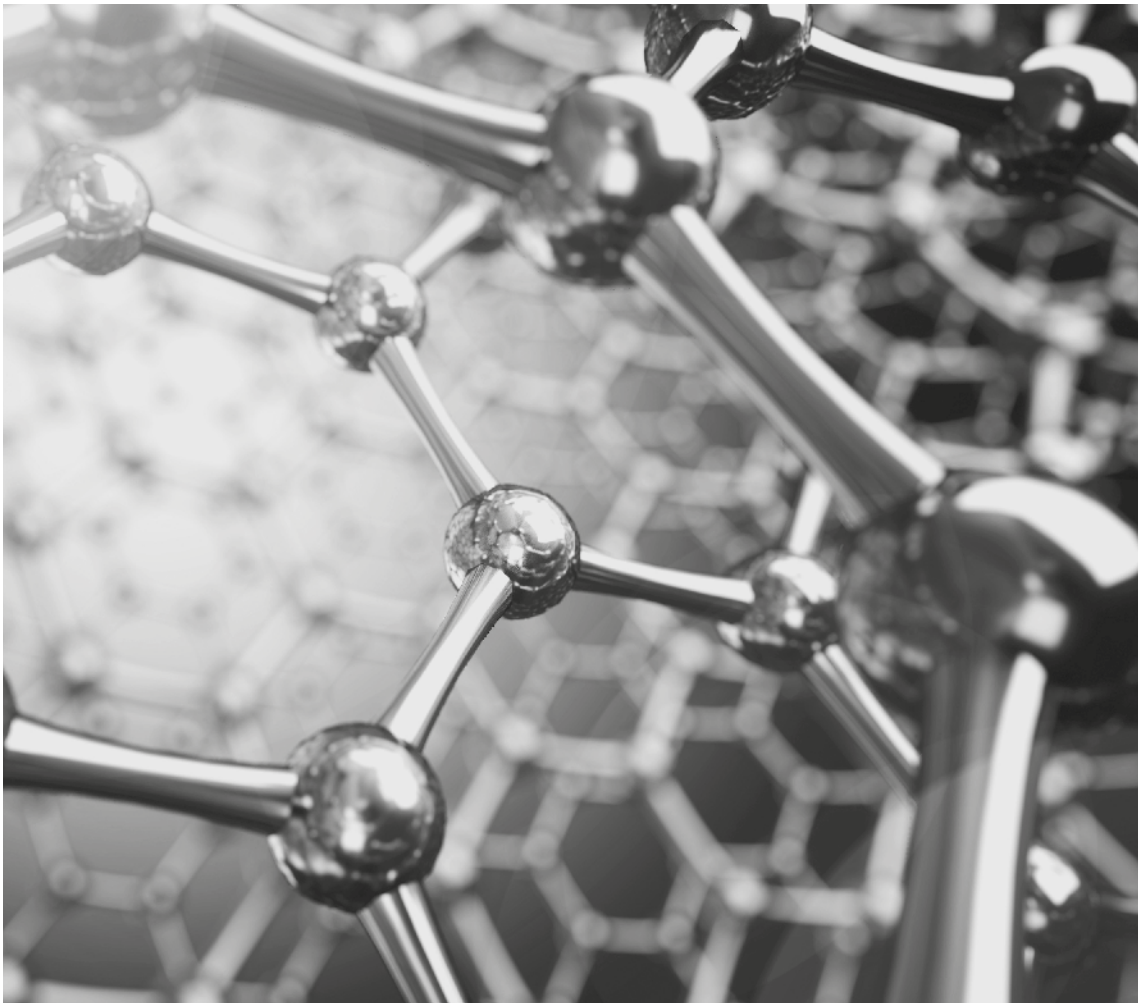
- *Characterization and resistance to microbial colonization of biodegradable magnesium-based material (María Luisa González).*

The award for the best publication by young researchers in the Biomaterials and Advanced Therapies program was awarded to Silvia Sánchez-Casanova (La Paz University Hospital Research Institute), from the group led by Nuria Vilaboa. The award-winning article is entitled "Local delivery of bone morphogenetic protein-2 from near infrared responsive hydrogels for bone tissue regeneration", published in Biomaterials.

Regarding the collaboration of CIBER-BBN in the strategic actions promoted by CIBERONC, it has participated in the project "Patient Derived Organoids 2.0: Recapitulating stromal and immune microenviroment in annotated organoid platforms for advancing towards

personalized cancer treatment", coordinated by Patricia Pérez Galán (CIBERONC) with the participation of the CIBER-BBN groups led by Elisabeth Engel and Nora Ventosa, and in which it is worth highlighting the contribution of Bárbara Blanco in the development of gelatin methacrylate hydrogels (GeIMA).

In relation to the development of innovative medicines, such as advanced therapies, CIBER-BBN has continued its participation as a stakeholder of the AEMPS in the European project STARS-CSA. Most notably, the virtual event Second European STARS Stakeholder Workshop "Towards Improved Strategy Regulatory Support for Academia" was attended, co-organized by the European Medicines Agency (EMA). CIBER-BBN has also continued to form part of the ASEBIO Advanced Therapies Group.



PROGRAM 3

Nanomedicine

COORDINATOR:
M. Pilar Marco Colás

In 2021, 14 new intramural collaborations were started, in addition to another 60 that began between 2018 and 2020 and that were continued in 2021. Thus, there has been a total of 74 active collaborations in this program. Of the 14 new collaborations, one is in collaboration with CIBERNED, 3 with CIBERES and two with CIBERONC:

- *TELOprot, Protein delivery system based on non-covalent PEGylation with telodendrimers, Miriam Royo.*
- *3D bioprinting of an in vitro air-blood barrier for validating lung targeted drug nanocarriers, Dorleta Jimenez de Aberasturi.*
- *NANOLINK, Site-directed conjugation of multivalent protein nanomaterials for precision medicine of cancer, Ugutz Unzueta.*
- *PoC4CoV, Integrated strategies for the COVID19 diagnosis and disease progression, Pilar Marco.*
- *Bioorthogonal chemistry strategies for the selective immobilization of magnetic nanoparticles on living cell membranes, Raluca Fratila.*

- *Photo-activation of prodrugs using plasmonic nanoparticles, Ramón Martínez Máñez.*
- *Gated nanomaterials for fighting chronic diseases, Ramón Martínez Máñez.*
- *Validating multifunctional polymeric nanoparticles as novel therapeutic vehicles for Alzheimer's Disease, Carlos Rodríguez Abreu.*
- *Mechanotherapy approaches on 3D in vitro biomimetic neuroblastoma models, Josep Samitier.*
- *Efficient delivery of inhaled nanoparticles. Development of a pressure pulse nanoaerosol generator for pulmonary drug delivery of antibiotics, Jesús Santamaría.*
- *Real time detection of COVID-19 presence in enclosed environments using SERS, Jesús Santamaría.*
- *3D printed artificial immune tissues on a chip for adoptive cell therapy, Judith Guasch.*
- *MANTRA, Enzyme mutants as tools in the quest for improved therapies for Fabry disease, Neus Ferrer.*
- *TRACC, Targeted reinforcement of the innate immune response against colorrectal cancer, Eloi Parladé Molist.*

The clinical areas addressed by these new proposals have been cancer, rare, infectious, respiratory and neurological diseases and regenerative medicine.

During 2021, the following projects from the Early Stage 2020 call remained active:

- *BL-MOVE, Bivalent ligands as potential therapeutic agents for the treatment of movement disorders, coordinated by Daniel Pulido.*
- *SMARTDELI, Targeted delivery of cytotoxic drugs, coordinated by Ana María Aviñó.*
- *FlexCAB, Highly flexible nanocarrier with integrated antibacterial activity for topical delivery, coordinated by Marina I. Giannotti.*
- *ImmunoMD, Novel approaches based on antibodies for muscular dystrophy therapy, coordinated by J.Pablo Salvador.*
- *MANHATTAN, A step forward in the study of the magnetic hyperthermia as antitumoral treatment, coordinated by Laura Asín.*
- *NANOCOMMUNITY, Smart communication using nanoparticles, coordinated by Elena Aznar.*
- *OLIGOMED, Oligonucleotide-gated nanomaterials for biomedical diagnosis, coordinated by Alba García Fernández.*
- *DUALNANOBRAIN, Dual-targeting shuttle nanocarriers for Alzheimer's therapy, coordinated by Santiago Grijalvo.*

- *NanoBuds, Nanoscale regulation of implantable osteochondral buds, coordinated by Anna Lagunas.*
- *PANTHER II, Production of carbon nanodots and application as theranostic agents, coordinated by Gema Martínez.*
- *HYDROSACGEL, Oligosaccharide-based hydrogels to synergistically induce muscle repair, coordinated by Isabel García Martín.*

In 2021, significant efforts were made to initiate collaborative projects with other scientific areas, and the first call for seed projects was launched with the CIBEREHD thematic area. Seven proposals were submitted, of which two projects were financed with €35,000 each:

- *PyLOC, Advanced Point-of-Care nanobiosensor for the specific identification of H. pylori infections, Carmen Estévez.*
- *OTHELLO, Liver Organoids: a tool to optimize the transfer of therapeutic nanoparticles in hepatocellular carcinoma therapy, Jesús Santamaría.*

Regarding the involvement of CIBER-BBN in the strategic actions of CIBERONC, the groups led by Elisabeth Engel and Nora Ventosa are collaborating on "Patient Derived Organoids 2.0: Recapitulating stromal and immune microenvironment in annotated organoid platforms for advancing towards personalized cancer treatment". Specifically, Judith Guasch, from the group led by N. Ventosa, participates investigating the use of polyethylene glycol (PEG)).

There has been a replacement in the group previously led by Simó Schwartz (VHIR), with Ibane Abasolo, from the same institution, becoming the principal investigator in 2021.

PROGRAM 4

Training

COORDINATOR:
Rosa Villa Sanz

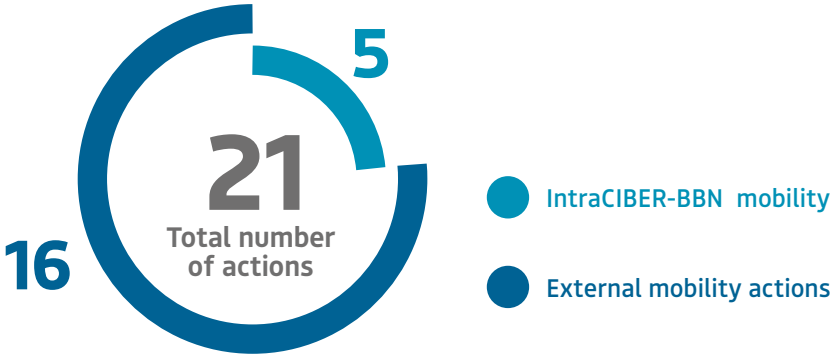
Research grants

During 2021, we were able to recover the mobility actions that finance research stays in other research groups, CIBER-BBN or external.

Mobility between research groups is considered at CIBER-BBN as an essential element to promote the training of group personnel in priority lines of research based on the needs for development and implementation of new techniques at CIBER.

The objective of this initiative is to encourage short-term stays in other research groups to facilitate the transfer of experience and technology, and promote collaboration between the different CIBER groups. Short stays in external groups (national or international) are also contemplated, provided they fall within the priority and strategic lines of work of the CIBER-BBN thematic areas.

Mobility actions in 2021



As regards research initiation grants in the form of internship contracts for young researchers, five six-month internship contracts have been financed for young graduates in the groups of PIs María Vallet, Pau Gorostiza, Ibane Abasolo, Rafael Gómez and M. Rosa Aguilar. The selection was made based on the best project presented.

Also within the framework of the Training program, the IV Meeting of Young Researchers was organized in collaboration with CIBERONC, which took place on December 13 and 14 in face-to-face and virtual format, at the Barcelona Biomedical Research Park. The sessions were organized around the scientific programs of the areas and there were also three round tables on cross-cutting topics such as machine learning in precision medicine, scientific publications in high-impact journals and dissemination on social networks. The meeting was designed and organized by a scientific committee of young researchers from both areas. The attached researchers María Camacho (Cristina Ruiz's group) and Juan Francisco Blández (Ramón Martínez Máñez's group) participated on behalf of CIBER-BBN.

PLATFORMS

Nanbiosis ICTS

NANBIOSIS is an ICTS (Singular Scientific and Technological Infrastructures) made up of three nodes (CIBER, CCMIJU and BIONAND) and 26 units. In 2021, the request to incorporate the new Proteomics unit 30 of the CIBER-BBN and the Biomedical Research Institute of A Coruña was approved.

In 2021, the Ministry of Science and Innovation requested the data and reports for the four-year evaluation of the ICTS, registering more than 1,200 applications in an open and competitive regime, over 3,000 accesses and more than 400 publications citing NANBIOSIS.

The new Strategic Plan for the 2021-2024 period and the new NANBIOSIS Investment Plan were also presented. Regarding this plan, the actions that are prioritized by the Ministry will be financed within the framework of the 2022 call for the Recovery, Transformation and Resilience Plan.

In the Next Generation EU call for the actions foreseen in the ICTS Investment Plans for 2017-2020, NANBIOSIS obtained financing of more than €1.8M.

In terms of scientific activities, in 2021 normality, interrupted or reduced due to the pandemic, was restored and the "COVID-19 Rapic Access Call" was kept open.

To be highlighted is the progress made in the development of POC technologies to monitor possible new outbreaks and contribute to the rapid implementation of containment measures, as in the "POC-4CoV" project led by Pilar Marco, in which the units U2, U3, U29 and U1 collaborate and where it has been possible, through the design of specific probes, to directly detect the genetic material of the virus in 30 minutes. Similarly, the system for rapid, economical and efficient diagnosis based on nanoporous films, developed at the U26 unit led by Ramón Martínez, has demonstrated its effectiveness and trials on clinical samples have already begun.

Regarding therapies to treat cancer, unit 6, led by Nora Ventosa, has participated in the design of nanovesicles that allow a molecule (microRNA) to be encapsulated to be administered in the treatment of tumors. The functionality of quatsomes in delivering microRNAs in a solid extracranial tumor common in pediatric cancer cases has been demonstrated. The optimization of this type of system has also been explored by incorporating peptide targeting units, with the participation of units U3 and U6 in the TAG-SMARTLY valorization project.

Unit U20, led by Ibane Abasolo, has developed a therapeutic system in which a compound that is effective against tumor stem cells is transported in biodegradable nanoparticles, opening a promising path to combat the most aggressive breast cancers, by substituting standard chemotherapy with nanoformulations.

The European project coordinated by the CIBER Smart4Fabry, in which units U6, U1, U3 and U20 collaborated, completed in 2020, released a video the following year explaining the new GLA nanoformulation obtained through nanocapsules that will improve tolerance and efficacy, reducing the costs and improving the quality of life of patients. This nanoformulation has obtained the designation of orphan drug by the European Commission. The U6 has been participating since 2021 in another European project, PHOENIX, within the framework of which this novel nanomedicine will be scaled up and produced under GMP conditions.

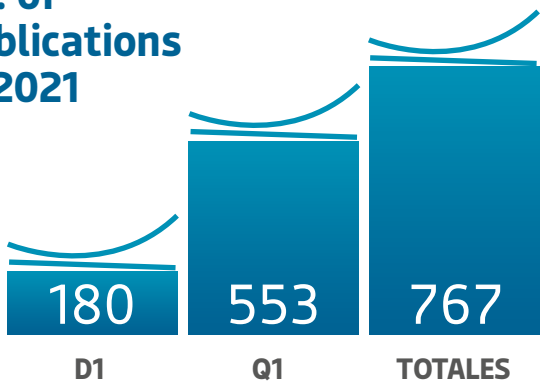
NANBIOSIS has continued to participate in the European project SAFE-N-MEDTECH in order to create an innovation platform for the development, testing, evaluation, scale-up and commercialization of medical and diagnostic devices based on nanotechnology. In 2021 CIBER-BBN coordinated the WP3 on preclinical research in medical technologies, as well as one of the pilot studies.

Since 2021, NANBIOSIS has participated in the cross-cutting action of the CIBER Biobanks and Biomodels Platform (ISCIII), together with teams from CIBERES, CIBERER and CIBERONC.

SCIENTIFIC PRODUCTION

PUBLICATIONS

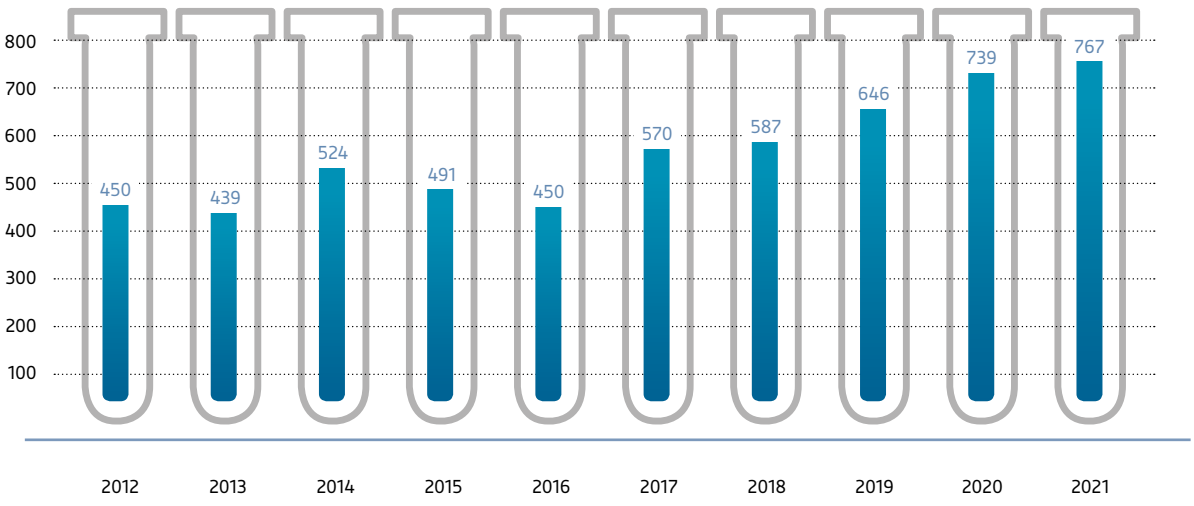
No. of publications in 2021



Collaborations

*Among various thematic areas

Evolution of publications



10 most relevant publications by impact factor

IF	Publication
60,622	Whitaker R., Hernaez-Estrada B., Hernandez R.M., Santos-Vizcaino E., Spiller K.L. Immunomodulatory Biomaterials for Tissue Repair. Chemical Reviews. 2021;121(18):11305-11335.
54,564	Zheng G., He J., Kumar V., Wang S., Pastoriza-Santos I., Perez-Juste J. et al. Discrete metal nanoparticles with plasmonic chirality. Chemical Society Reviews. 2021;50(6):3738-3754.
54,564	De Luis B., Llopis-Lorente A., Sancenon F., Martinez-Manez R. Engineering chemical communication between micro/nanosystems. Chemical Society Reviews. 2021;50(16):8829-8856.
44,544	Glasbey J.C., Nepogodiev D., Simoes J.F.F., Omar O., Li E., Venn M.L. et al. Elective cancer surgery in COVID-19–Free surgical pathways during the SARS-cov-2 pandemic: An international, multicenter, comparative cohort study. Journal of Clinical Oncology. 2021;39(1):66-78.
43,841	Garreta E., Kamm R.D., Chuva de Sousa Lopes S.M., Lancaster M.A., Weiss R., Trepat X. et al. Rethinking organoid technology through bioengineering. Nature Materials. 2021;20(2):145-155.
41,316	COVIDSurg Collaborative., Bellón Caneiro Juan Manuel. Effect of COVID-19 pandemic lockdowns on planned cancer surgery for 15 tumour types in 61 countries: an international, prospective, cohort study.The Lancet. Oncology. 2021;22(11).
39,213	Bonaccini Calia A., Masvidal-Codina E., Smith T.M., Schafer N., Rathore D., Rodriguez-Lucas E. et al. Full-bandwidth electrophysiology of seizures and epileptiform activity enabled by flexible graphene microtransistor depth neural probes. Nature Nanotechnology. 2021.
28,824	Perez-Gonzalez C., Ceada G., Greco F., Matejcic M., Gomez-Gonzalez M., Castro N. et al. Mechanical compartmentalization of the intestinal organoid enables crypt folding and collective cell migration. Nature Cell Biology. 2021;23(7):745-757.
24,094	Cortes-Canteli M., Gispert J.D., Salvado G., Toribio-Fernandez R., Tristao-Pereira C., Falcon C. et al. Subclinical Atherosclerosis and Brain Metabolism in Middle-Aged Individuals: The PESA Study. Journal of the American College of Cardiology. 2021;77(7):888-898.
23,059	Martens S., Coolens K., Van Bulck M., Arsenijevic T., Casamitjana J., Fernandez Ruiz A. et al. Discovery and 3D imaging of a novel Δnp63-expressing basal cell type in human pancreatic ducts with implications in disease. Gut. 2021.

CIBER-BBN Groups, Publications in 2021

Group Leader	Publications	Q1	D1	Institution - Center	Province
Abasolo Olaortua, Ibane	15	14	3	Fund. Hospital Universitario Vall d'Hebron - Institut de Recerca (VHIR)	Barcelona
Aguilar de Armas, María Rosa	15	14	4	Agencia Estatal Consejo Superior de Investigaciones Científicas	Madrid
Albericio Palomera, Fernando	33	15	5	Universidad de Barcelona	Barcelona
Arús Caralto, Carles	9	8	3	Universidad Autónoma de Barcelona	Barcelona
Becerra Ratia, José	13	9	1	Universidad de Málaga	Málaga
Bellón Caneiro, Juan Manuel	15	13	5	Universidad de Alcalá	Madrid
Calonge Cano, Margarita	20	9	3	Universidad de Valladolid	Valladolid
Corcoy Pla, Rosa	14	10	4	Instituto de Investigación del Hospital de la Santa Cruz y San Pablo	Barcelona
Engel López, Elisabeth	14	13	5	Fundación Instituto de Bioingeniería de Cataluña	Barcelona
Eritja Casadellà, Ramón	20	15	1	Agencia Estatal Consejo Superior de Investigaciones Científicas	Barcelona
Fernández Jover, Eduardo	6	2	0	Universidad Miguel Hernández	Alicante
Gómez Ramírez, Rafael	18	13	4	Universidad de Alcalá	Madrid
Gómez Ribelles, José Luis	21	19	2	Universidad Politécnica de Valencia	Valencia
González Martín, María Luisa	11	7	1	Universidad de Extremadura	Badajoz
Gorostiza Langa, Pau	7	5	5	Fundación Instituto de Bioingeniería de Cataluña	Barcelona
Hernando Pérez, María Elena	34	23	2	Universidad Politécnica de Madrid	Madrid
Hornero Sánchez, Roberto	37	24	9	Universidad de Valladolid	Valladolid
Jané Campos, Raimon	26	19	1	Fundación Instituto de Bioingeniería de Cataluña	Barcelona
Laguna Lasaosa, Pablo	32	20	5	Universidad de Zaragoza	Zaragoza
Lechuga Gómez, Laura María	9	6	1	Agencia Estatal Consejo Superior de Investigaciones Científicas	Barcelona
Liz Marzán, Luis Manuel	27	20	13	CIC biomaGUNE	Guipúzcoa
López Higuera, José Miguel	20	17	3	Universidad de Cantabria	Cantabria

Group Leader	Publications	Q1	D1	Institution - Center	Province
Mangues Bafalluy, Ramon	22	14	7	Inst. de Investigación del Hospital de la Santa Cruz y San Pablo	Barcelona
Marco Colás, María Pilar	9	7	2	Agencia Estatal Consejo Superior de Investigaciones Científicas	Barcelona
Martínez Barca, Miguel Ángel	32	24	8	Universidad de Zaragoza	Zaragoza
Martínez De La Fuente, Jesús	23	18	5	Agencia Estatal Consejo Superior de Investigaciones Científicas	Zaragoza
Martínez Mañez, Ramón	33	26	9	Universidad Politécnica de Valencia	Valencia
Muñoz Fernández, María Ángeles	4	3	2	Servicio Madrileño de Salud	Madrid
Pedraz Muñoz, José Luis	42	37	14	Universidad del País Vasco	Álava
Raya Chamorro, Ángel	17	12	6	Fundación IDIBELL	Barcelona
Rodríguez Abreu, Carlos	27	18	5	Agencia Estatal Consejo Superior de Investigaciones Científicas	Barcelona
Rodríguez Cabello, José Carlos	4	4	1	Universidad de Valladolid	Valladolid
Ruiz Romero, Cristina	7	5	2	Servicio Gallego de Salud	Coruña, A
Samitier Martí, Josep	23	19	7	Fundación Instituto de Bioingeniería de Cataluña	Barcelona
Santamaría Ramiro, Jesús	31	22	6	Universidad de Zaragoza	Zaragoza
Santos Lleó, Andrés	17	8	3	Universidad Politécnica de Madrid	Madrid
Setoain Peregó, Javier	49	33	17	Universidad de Barcelona	Barcelona
Trepat Guixer, Xavier	6	6	6	Fundación Instituto de Bioingeniería de Cataluña	Barcelona
Vallet Regí, María	29	27	2	Universidad Complutense de Madrid	Madrid
Ventosa Rull, Leonor	13	8	4	Agencia Estatal Consejo Superior de Investigaciones Científicas	Barcelona
Vilaboa Díaz, Núria	6	5	3	Servicio Madrileño de Salud	Madrid
Villa Sanz, Rosa	14	11	5	Agencia Estatal Consejo Superior de Investigaciones Científicas	Barcelona
Villaverde Corrales, Antonio	20	19	6	Universidad Autónoma de Barcelona	Barcelona

Patents owned by CIBER 2021

Applications

- Liposomes and Its Use for Enzyme Delivery.
- New combinations of boron compounds and adjuvants for the treatment of pathophysiological conditions and muscle regeneration.
- A Flexible Probe.
- Polypurine Reverse Hoogsteen Hairpins and Parallel Clamps and Their Use as Biosensors.

PCT Extensions

- Scaffold Proteins and Therapeutic Nanoconjugates based on Nidogen.
- Método para el diagnóstico, pronóstico y monitorización de la enfermedad de Alzheimer mediante técnicas.
- Method for rapid detection of Candida auris and diagnosis of infection caused by this pathogen. .
- A Synthetic Hydrogel and Its Use for Immunotherapy and 3D-Printing.
- Electrochemical sensor systems for sensing analytical reactions and biological operations and methods.
- Acquisition Device to Limit Leakage Current in Electrophysiological Signal Recording Devices.
- Cell-Penetrating Peptides.
- Material platforms for simultaneous solid-phase presentation of boron and cell adhesion domains as antitumor strategy for carcinomas.
- New combinations of boron compounds and adjuvants for the treatment of pathophysiological conditions and muscle regeneration.
- A stretchable opto-mechanical material composed by a metallic and or dielectric nanostructure array embedded into a wrinkled elastomer.
- Cell-Penetrating Peptides.
- Real Time Trace Detection.

Fases nacionales solicitadas

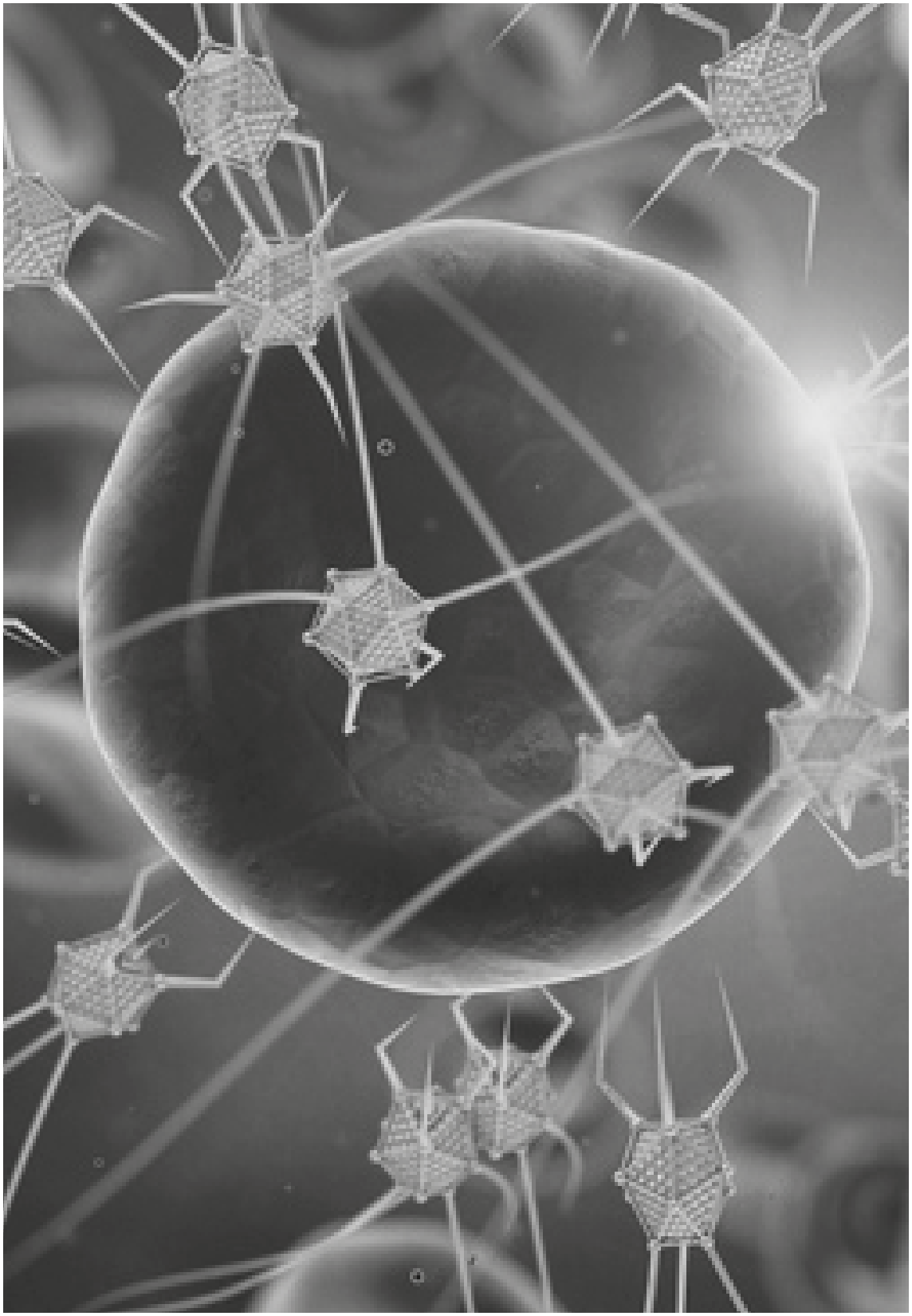
- Nanovesicles and its use for nucleic acid delivery (Europa, EE.UU., Canadá, Australia, Japón).
- Therapeutic nanoconjugates and uses thereof (Europe, USA, China).
- Graphene transistor system for measuring electrophysiological signals (Europa, EE.UU., China, Japón).

Granted

- Self-associated functional acrylic copolymers and terpolymers and their use as vehicles for bioactive compounds.
- Method for rapid detection of Candida auris and diagnosis of infection caused by this pathogen. .
- Release of substances in senescent cells. (Europe).

Clinical Guidelines 2021

- SoHAH clinical guidelines (Hispanic American Hernia Society). Surgical anatomy for abdominal wall specialists. Photo Atlas Dissection. Juan M. Bellón.
- Clinical guide for the use of prosthetic material in incisional hernia repair. Clinical guide for the use of prosthetic material in the repair of incisional hernias. Juan M. Bellón.
- Comprehensive clinical practice guideline for graft-versus-host disease. Margarita Calonge.
- Soft tissue and visceral sarcomas: ESMOeEURACA-NeGENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up. Antonio López Pousa.
- Closed loop systems. User guide Group of technologies applied to diabetes. Spanish Society of Diabetes. Ana Chico Ballesteros.
- SELNET Clinical practice guidelines for soft tissue sarcoma and GIST. Antonio López Pousa.



CIBERCV

Cardiovascular Diseases

Presentation by the scientific director

Francisco Fernández-Avilés

Dear Colleagues from the Biomedical Research Networking Center in Cardiovascular Diseases (CIBERCV): On behalf of the Management Committee and my own, we thank you for the enormous effort you have made in 2021 and your continued commitment. The fifth year of our thematic area has undoubtedly been very satisfactory, both because of the achievements attained and also the strong involvement of all the groups, who have overcome many difficulties.

In 2021, our area has published more than 600 articles in top-level scientific journals. In the field of communication, the CIBERCV has carried out more than 900 press appearances both in online media and in the written press. Our CIBER is currently immersed in several European projects, as well as in two multicenter projects from the ISCIII Independent Clinical Research Projects Call. In addition, we have obtained funding in the Call for Personalized and Precision Medicine for the development of the Spanish Project, a multicenter study to evaluate the non-inferiority of a personalized precision strategy for the prevention of sudden death in patients with non-ischemic dilated cardiomyopathy, in which 21 research groups from our area will participate.

We have passed the third evaluation of the External Scientific Advisory Committee with a favorable report on our performance and very useful recommendations for improvement that include the need to: (1) reinforce internationalization and excellence, (2) identify, attract and retain young talent, (3) act on improving key areas, promoting the main technological capabilities, (4) encourage and reward multidisciplinarity and (5) take advantage of and

enhance the great capacities of the national health system, specifically in the management of data and registries.

We have been grappling with a widespread shortage of resources against the enormous bureaucratic difficulties of the National State Administration. But, on the other hand, and more optimistically, we are aware that science managers are also committed to this battle and we think that the Consortium that welcomes us is an unparalleled venue of excellence that ensures a stable budget, even if it is chronically poor and severely affected by the current political instability. All this is allowing us to place Spanish cooperative cardiovascular research at the highest national and international level of competitiveness. Thanks to all of you.

In closing, during 2021, the CIBERCV has continued to face its challenges with motivation and a high commitment to the CIBER consortium, which has resulted in cooperative scientific activity of the highest level. This is due to the efforts of the people involved and the framework of stability offered by the CIBER. We consider this to be essential to promote cooperative research of excellence in Spain, with the aim of contributing to reducing the impact of cardiovascular diseases in our environment and generating prosperity, leading research, innovation and training in this discipline within the national and international framework.

PROGRAMS

PROGRAM 1

Myocardial Damage and its consequences

COORDINATORS:
Francisco Fernández-Avilés y Juan Delgado Jiménez

Program 1 has generated important advances aimed at understanding and treating myocardial damage and its associated consequences, both of genetic origin and acquired disorders of the heart muscle.

A noteworthy milestone is the Redinscor 3 Registry, focused on patients admitted for de novo acute heart failure and which has included more than 500 patients, despite the difficulties generated by the pandemic. In addition to carrying out the registry, the first analysis has made it possible to evaluate in this multicenter cohort a patent developed by the A Coruña Hospital group. The patent offers a novel and efficient method, based on the algorithm that combines the determination of two proteins, orosomucoid and omentin, (OROME) at discharge, capable of predicting events (rehospitalization for heart failure (HF) and/or death) in patients hospitalized with "de novo" heart failure (HF).

PROGRAM 2

Arterial Disease, Myocardial Ischemia and Structural Damage

COORDINATORS:
Borja Ibáñez Cabeza
& Alberto San Román Calvar

Within Program 2, important work has been carried out on the study and treatment of cardiovascular disorders that can cause premature death and disability, linked to myocardial ischemia and structural pathologies of the heart and arteries.

In the Myocardial Ischemia and Reperfusion research line, the REBOOT (TREatment with Beta-blockers after myOcardial infarction withOut reduced ejection fraction) clinical trial has been launched, which studies the effect of beta-blockers in patients with acute myocardial infarction without reduced ejection fraction and which has already achieved 100% recruitment (4,200 patients). This trial, coordinated by Borja Ibáñez's group, is the world's largest trial in this field, with the participation of numerous CIBERCV groups with the aim of improving clinical practice after infarction. This project has been supported by the Spanish Society of Cardiology and will have the altruistic participation of at least 55 Spanish and 25 Italian hospitals.

To be highlighted within the research line of Diseases of the aorta is the RESA III study on the Spanish Registry of Acute Aortic Syndrome (RESA), whose objective is to assess the re-

sults in the management of this disease through a comparative study that covers the period from 2005-2020. In this work, led by José Antonio Barrabés' group, 30 Spanish hospitals collaborate to analyze advances in the management and reduction in mortality of acute aortic syndrome in Spain, obtaining highly relevant results.

In the research line dedicated to valvular disease and congenital heart disease, the work "Ramipril in High-Risk Patients with COVID-19" has been carried out, coordinated by the group led by José Alberto San Román and in which 14 Spanish hospitals collaborate (nine of them members of the CIBER). This study, which has achieved great clinical significance, investigates the relationship of COVID-19 with cardiovascular disease and the interaction of the virus with inhibitors of the Renin-Angiotensin-Aldosterone system, to the point of debating the need to withdraw this medication in high-risk patients. In this study, the cohort of patients from the RASTAVI clinical trial, randomized to control or Ramipril post-TAVI (percutaneous aortic valve implantation), was used to shed light on this issue and offer solid evidence of the need to maintain said treatment, especially in high-risk patients.

PROGRAM 3

Cardiovascular Epidemiology and risk factors

COORDINATOR:
Jaume Marrugat de la Iglesia

Program 3 has continued to promote research on the mechanism that links cardiovascular risk factors with the serious diseases they entail, with the ultimate goal of preventing and reducing the high impact of cardiovascular diseases on society.

As regards the line of Epidemiology, cohorts, risk factors and cardiovascular risk functions, the beginning of the CARGENCORS study (CARdiovascular GENetic risk score for Risk Stratification of patients positive for SARS-CoV-2 virus) has been of great importance. This study investigates the role of genetic factors of coronary heart disease in the severity of COVID-19 and hopes to improve the risk stratification of serious complications, based on genetic risk scores (GRS) of coronary heart disease to predict the risk of coronary complications, including severe, critical and fatal forms of the disease. This project is led by Jaume Marrugat's group and has had the participation of other groups from CIBERCV (Hospital del Mar and the Girona Biomedical Research Institute) and a group from the REDIAP network.

In the research line of Population studies and evaluation of the genetic/epigenetic basis of complex cardiovascular traits, to be highlighted is the publication of the article "Characteristics of HDL cholesterol particles and risk of coronary heart disease: a Mendelian randomization study" in the scientific journal Metabolism. This study uses Mendelian randomization to analyze whether genetic instruments related to HDL-cholesterol levels, ApoA-I, HDL particle size, and cholesterol levels in HDL particle subtypes are associated with coronary heart disease. The results obtained support a causal relationship between some characteristics of HDL particles (diameter, cholesterol and triglyceride content in large particles, cholesterol content in small particles) and the risk of coronary heart disease. Four groups from CIBERCV (two from Hospital del Mar, one from Hospital de la Santa Creu i Sant Pau and one from the Aragón Health Research Institute) and other groups from CIBERESP and CIBEROBN, coordinated by Roberto Elosua's group, collaborated in this work.

PROGRAM 4

Molecular and Imaging Biomarkers, and Precision Cardiovascular Medicine

COORDINATOR:
Javier Díez Martínez

Program 4 has generated important advances in the field of biomarkers in relation to cardiovascular diseases.

As the most relevant milestone of the program, we highlight the publication "Clonal Hematopoiesis and Risk of Progression of Heart Failure With Reduced Left Ventricular Ejection Fraction. (J Am Coll Cardiol) that involves three research groups of the area and that opens a new way of understanding the association of age with heart failure through clonal hematopoiesis. In particular, it highlights the role of somatic mutations in DNMT3A or TET2 in the progression of heart failure with reduced ejection fraction (HFrEF) of ischemic and non-ischemic etiology, in terms of HF-related mortality and hospitalization due to acute decompensated heart failure.

Thus, this work incorporates specific somatic mutations as new potentially useful biomarkers to increase prognostic accuracy in HFrEF and to design personalized preventive and therapeutic strategies.

PROGRAM 5

Training

COORDINATOR:
José Antonio Barrabés Riu

The main objective of the CIBERCV Training and Mobility Program is to train young people to become cardiovascular researchers of the future in order to improve the cardiovascular health of society. In addition, this program promotes the organization of specific workshops and courses in order to share the valuable advances and knowledge acquired by CIBERCV researchers.

In 2021, the calls for training and mobility grants have been affected by the pandemic and the vast majority of training activities have been carried out online.

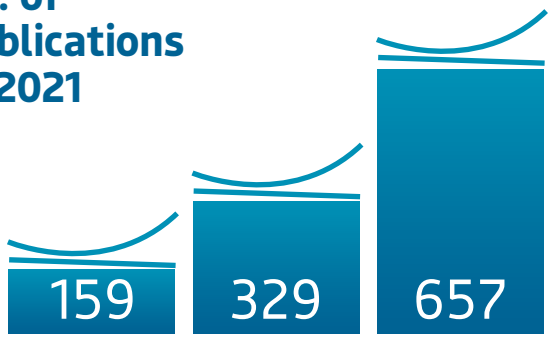
Worth highlighting is the organization of online courses on different topics in the field of cardiovascular research such as atrial fibrillation, cardiac amyloidosis, heart failure, atherosclerosis, arrhythmias, heart transplantation, cardiological applications of 3D printing, and other advances in basic science and clinical excellence.

Within CIBERCV, this program continues to be the main training initiative and in 2021 it has contributed to the strengthening of quality translational research, promoting collaboration between the groups of the CV area and other thematic areas of the CIBER.

SCIENTIFIC PRODUCTION

PUBLICATIONS

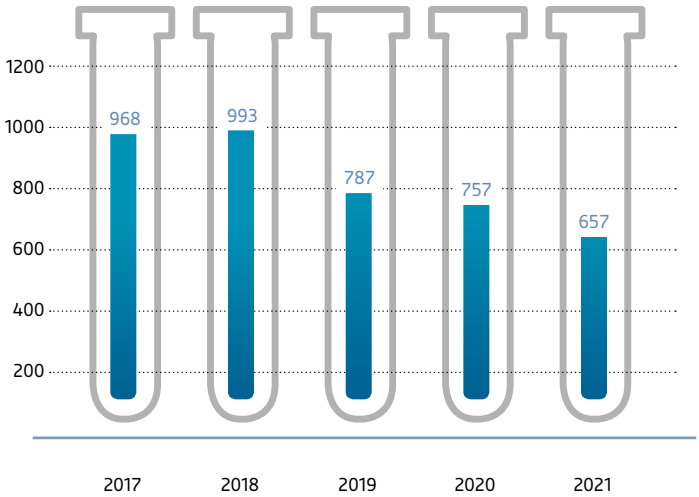
No. of publications in 2021



Collaborations

*Among various thematic areas

Evolution of publications



10 most relevant publications by impact factor

IF	Publication
25,083	da Silva Lima N, Fondevila MF, Nóvoa E, et al. Inhibition of ATG3 ameliorates liver steatosis by increasing mitochondrial function. *J Hepatol*. 2022;76(1):11-24. doi:10.1016/j.jhep.2021.09.008
17,425	Ginès P, Castera L, Lammert F, et al. Population screening for liver fibrosis: Toward early diagnosis and intervention for chronic liver diseases. *Hepatology*. 2022;75(1):219-228. doi:10.1002/hep.32163
9,213	Martinez JA, Sassi F, Moreno LA, Tur JA. Position guidelines and evidence base concerning determinants of childhood obesity with a European perspective. *Obes Rev*. 2022;23 Suppl 1:e13391. doi:10.1111/obr.13391
6,577	Rossing P, Agarwal R, Anker SD, et al. Efficacy and safety of finerenone in patients with chronic kidney disease and type 2 diabetes by GLP-1RA treatment: A subgroup analysis from the FIDELIO-DKD trial. *Diabetes Obes Metab*. 2022;24(1):125-134. doi:10.1111/dom.14558
6,498	Domingo-Relloso A, Bozack A, Kiihl S, et al. Arsenic exposure and human blood DNA methylation and hydroxymethylation profiles in two diverse populations from Bangladesh and Spain. *Environ Res*. 2022;204(Pt B):112021. doi:10.1016/j.envres.2021.112021
5,994	Santoro F, Nuñez-Gil IJ, Vitale E, et al. Antiplatelet therapy and outcome in COVID-19: the Health Outcome Predictive Evaluation Registry. *Heart*. 2022;108(2):130-136. doi:10.1136/heartjnl-2021-319552
4,839	Montejo L, Jiménez E, Solé B, et al. Identifying neurocognitive heterogeneity in Older Adults with Bipolar Disorder: a cluster analysis. *J Affect Disord*. 2022;298(Pt A):522-531. doi:10.1016/j.jad.2021.11.028
4,686	Pérez Cabeza AI, Rivera-Caravaca JM, Roldán-Rabadán I, et al. Antithrombotic therapy and clinical outcomes at 1 year in the Spanish cohort of the EORP-AF Long-term General Registry. *Eur J Clin Invest*. 2022;52(4):e13709. doi:10.1111/eci.13709
3,694	Gobom J, Parnetti L, Rosa-Neto P, et al. Validation of the LUMIPULSE automated immunoassay for the measurement of core AD biomarkers in cerebrospinal fluid. *Clin Chem Lab Med*. 2021;60(2):207-219. Published 2021 Nov 15. doi:10.1515/cclm-2021-0651
2,692	Pacchioni A, Mugnolo A, Sanz Sanchez J, et al. Radial artery occlusion after conventional and distal radial access: Impact of preserved flow and time-to-hemostasis in a propensity-score matching analysis of 1163 patients. *Catheter Cardiovasc Interv*. 2022;99(3):827-835. doi:10.1002/ccd.30005

CIBERCV Groups, Publications in 2021

Group Leader	Publications	Q1	D1	Institution - Center	Province
Andrés Garcia, Vicente	8	6	3	Fundación Centro Nacional de Investigaciones Cardiovasculares	Madrid
Badimón Maestro, Lina	26	17	11	Instituto de Investigación del Hospital de la Santa Cruz y San Pablo	Barcelona
Barrabes, Jose Antonio	48	28	12	Fundación Hospital Universitario Vall d´Hebron - Institut de Recerca (VHIR)	Barcelona
Bayes Genis, Antonio	56	30	19	Fundación Instituto de Investigación Germans Trias i Pujol	Barcelona
Blanco Colio, Luis Miguel	7	4	2	Instituto de Investigación Sanitaria Fundación Jiménez Díaz	Madrid
Bosca Gomar, Lisardo	8	7	4	Agencia Estatal Consejo Superior de Investigaciones Científicas	Madrid
Brugada Terradellas, Ramon	9	5	2	Fundación Instituto de Investigación Biomédica de Girona	Girona
Chorro Gasco, Francisco Javier	22	12	2	Fundación para la Investigación del Hospital Clínico de la Comunidad Valenciana (Fundación INCLIVA)	Valencia
Civeira Murillo, Fernando	14	8	2	Fundación Instituto de Investigación Sanitaria Aragón	Zaragoza
Crespo Leiro, María Generosa	34	15	11	Servicio Gallego de Salud	Coruña, A
De La Pompa Mínguez, Jose Luis	5	5	3	Fundación Centro Nacional de Investigaciones Cardiovasculares	Madrid
Delgado Jiménez, Juan Francisco	60	22	14	Servicio Madrileño de Salud	Madrid
Delpón Mosquera, Eva	18	12	9	Universidad Complutense de Madrid	Madrid
Diez Martínez, Javier	24	14	9	Fundación para la Investigación Médica Aplicada	Navarra
Elosua Llanos, Roberto	13	7	5	Consorci Mar Parc Salut de Barcelona	Barcelona
Fernandez-Avilés Diaz, Francisco	50	18	10	Servicio Madrileño de Salud	Madrid
Garcia Pavía, Pablo	31	16	12	Servicio Madrileño de Salud	Madrid
Gonzalez Juanatey, Jose Ramón	47	12	12	Servicio Gallego de Salud	Coruña, A
Guerra, Jose María	20	8	2	Inst. de Investigación del Hospital de la Santa Cruz y San Pablo	Barcelona

Group Leader	Publications	Q1	D1	Institution - Center	Province
Ibáñez Cabeza, Borja	39	20	14	Instituto de Investigación Sanitaria Fundación Jiménez Díaz	Madrid
Jiménez Navarro, Manuel	33	19	9	Fundación Pública Andaluza para la Investigación de Málaga en Biomedicina y Salud (FIMABIS)	Málaga
Marín Ortuño, Francisco	42	20	6	Fundación para la Formación e Investigación Sanitarias de la Región de Murcia (FFIS)	Murcia
Marrugat De La Iglesia, Jaume	6	1	0	Consorci Mar Parc Salut de Barcelona	Barcelona
Martínez Dolz, Luis	28	8	3	Fundación para la Investigación del Hospital Universitario y Politécnico la Fe de la Comunidad Valenciana	Valencia
Martínez González, Jose	11	6	0	Agencia Estatal Consejo Superior de Investigaciones Científicas	Barcelona
Mayor Menéndez, Federico	5	3	3	Universidad Autónoma de Madrid	Madrid
Mont Girbau, Josep Lluis	41	16	6	Instituto de Investigaciones Biomédicas August Pi i Sunyer	Barcelona
Perez-Villacastín Domínguez, Julián	11	6	3	Servicio Madrileño de Salud	Madrid
Redondo Moya, Juan Miguel	12	10	7	Fundación Centro Nacional de Investigaciones Cardiovasculares	Madrid
Salaices Sánchez, Mercedes	6	5	2	Universidad Autónoma de Madrid	Madrid
San Román Calvar, Jose Alberto	43	16	6	Hospital Clínico Universitario de Valladolid	Valladolid
Sánchez Fernandez, Pedro Luis	21	8	4	Fundación Instituto de Estudios de Ciencias de la salud de Castilla y León	Salamanca
Sánchez Madrid, Francisco	25	17	8	Universidad Autónoma de Madrid	Madrid
Sánchez Margallo, Francisco Miguel	2	1	0	Fundación Centro de Cirugía de Mínima Invasión Jesús Usón	Cáceres
Sanchis Fores, Juan	51	26	10	Fundación para la Investigación del Hospital Clínico de la Comunidad Valenciana (Fundación INCLIVA)	Valencia
Vázquez Cobos, Jesús María	9	5	2	Fundación Centro Nacional de Investigaciones Cardiovasculares	Madrid
Zamorano Gómez, Jose Luis	15	6	2	Servicio Madrileño de Salud	Madrid

CIBERDEM

Diabetes
and Metabolic
Disease

Presentation by the scientific director

Eduard Montanya Mias

In 2021, a remarkable normalization of research activity has been achieved after the impact of the pandemic in 2020, although the successive waves have still led to a significant overload for clinical groups, substantial limitations on mobility and a reduction in face-to-face activities. In terms of scientific production, CIBERDEM has increased production exceeding 400 publications for the first time, maintaining quality, with 23% in the first decile and 68% in the first quartile. The publications also show the maintenance of a high level of collaborative activity both at the CIBER and international level, with 50% and 39% of collaborative publications, respectively. Worth highlighting is the contribution, both in publications and in clinical guidelines, of CIBERDEM researchers to the relationship between COVID-19 and diabetes. Our website shows in detail the most relevant publications of each group and the Annual Report details the main achievements of 2021 of each research program.

Among the actions undertaken in 2021 in the field of collaborative activity, worth highlighting is the participation in joint projects with other areas of CIBER, a good example of which is the call for Independent Clinical Research (AES 2021). At the internal level, CIBERDEM's new call for intramural projects 2021 stands out, especially aimed at enhancing the competitiveness of young CIBERDEM researchers, as well as the mobility actions that have allowed various stays to be carried out in CIBER or international groups despite the limitations derived from the health situation. This year, the CIBEREDEM researchers were able to meet again in person at the fruitful Annual Meeting, which plays an important role not only in research, but also in the cohesion of the research area. This was also the case

with the Meeting of Young Researchers held in virtual format and the Program Research Seminars. In terms of technological platforms, we have completed an important restructuring of the Biorepository for Diabetes and Metabolic Diseases of great value to facilitate and promote its exploitation in scientific projects. To be highlighted at the level of institutional relations is the renewal of the collaboration with the Spanish Diabetes Society (SED) through a new General Action Protocol.

To learn more about the activity and achievements of CIBERDEM in 2021, I invite you to consult the Scientific Report and also to expand the information by visiting our website (www.ciberdem.org), as well as to follow us on Twitter (@ciberdem).

Warm regards to all.

PROGRAMS

PROGRAM 1

Epidemiology, genetics and epigenetics of diabetes mellitus. Chronic complications and comorbilities

COORDINATOR:
Ángela Martínez Valverde

1

EPIDEMIOLOGY OF DIABETES MELLITUS, ITS CHRÓNIC COMPLICATIONS AND COMORBILITIES

Based on the results of the di@bet.es study, the value of the "Fatty Liver Index" has been established as a predictor of type 2 diabetes (Sci Rep 11:16453, 2021), as well as metabolic determinants of mortality in this cohort (Eur J Endocrinol 186:95, 2021).

A questionnaire to assess depression in patients with type 1 diabetes has been developed and validated (Int J Environ Res Public Health 18:12529, 2021).

The incidence of diabetes and risk factors in the adult population of the Basque Country have been determined (Sci Rep 11:3016, 2021).

2 GENETICS, EPIGENÉTICS AND ENVIROMENTAL FACTORS IN THE DEVELOPMENT OF DIABETES AND ITS COMPLICATIONS

In collaboration with CIBEROBN, the usefulness of some epigenetic biomarkers in the metabolic deterioration of the metabolically healthy obese has been determined (Int J Mol Sci, 22:10417, 2021). The influence of air pollution on the prevalence and incidence of metabolic diseases has been investigated (Sci Rep 11:197022021, 2021).

3 MOLECULAR MECHANISMS ASSOCIATED WITH THE APPEARANCE AND PROGRESSION OF CHRONIC COMPLICATIONS OF DIABETES: THERAPEUTIC STRATEGIES

The risk of cardiovascular events among more than 12,000 patients with type 2 diabetes treated with SGLT2 inhibitors has been evaluated in comparison with that of other glucose-lowering drugs. Treatment with these drugs was associated with a lower risk of all-cause mortality, progression to chronic kidney disease, heart failure, and the combined MACE endpoint (Cardiovasc Diabetol 20:139, 2021).

Glycoproteins (GlycA, GlycB) analyzed by 1H-NMR have been studied in relation to inflammation, ectopic fat deposition, and arteriosclerosis (Atherosclerosis 330:1, 2021). Increased platelet activation and CXCR6 expression have been found in conjunction with aggregation of cells involved in endothelial dysfunction in subjects with metabolic syndrome (Front Pharmacol 12:656244, 2021).

Semaglutide administered in eye drops has been shown to exert a neuroprotective effect on the retina and prevent vascular hyperpermeability in an experimental model of diabetic retinopathy (Biomedicines 9:926, 2021).

In an experimental model of diabetic nephropathy, treatment with the synthetic flavonoid hidrosmin has been shown to improve kidney function and reduce markers associated with kidney damage, inflammation, oxidative stress, and cellular senescence (Antioxidants 10:1920, 2021).

The anti-inflammatory role of metformin in brown adipose tissue in obese animals has been revealed, as well as the molecular mechanisms involved (Redox Biology 48:102171, 2021).

4 NUTRITIONAL AND LIFESTYLE ASPECTS IN THE DEVELOPMENT AND PREVENTION OF DIABETES.

In collaboration with the CIBER-BBN, it has been shown that a derivative of vitamin B3, nicotinamide, prevents obesity induced by a diet rich in saturated fats in mice by increasing energy expenditure without modifying intake (Mol Nutr Food Res 5: e2100111, 2021).

The association between a low intake of iodine from food in the pre-pregnancy period and the rates of suboptimal levels of plasmatic levothyroxine that are associated with adverse metabolic events during pregnancy and the importance of implementing nutritional preventive strategies has been demonstrated (Nutrients 13:4458, 2021).

PROGRAM 2

Molecular and cellular determinants of the function, damage and protection of pancreatic islets. Regenerative medicine and advanced therapies

COORDINATOR:
Franz Martín Bermudo

1 FUNCTION AND REGULATION OF PANCREATIC ISLETS: MOLECULAR AND CELLULAR BASES AND THERAPEUTIC TARGETS

It has been described that BACE2 protects against metabolic alterations secondary to the ingestion of a high-fat diet, since its loss of function aggravates weight gain, hyperphagia, and insulin resistance, and alters the hypothalamic response to leptin (Diaz-Catalan et al., *Mol Metab* 2021).

The GRK2 kinase has been found to have a regulatory role in insulin secretion in response to incretins, by modulating the early phase of insulin secretion induced by GLP-1 receptor activation (Arcones et al., *BMC Biology* 2021).

As regards aging, it has been seen that despite the existence of different alterations in the events involved in insulin secretion, the ß cell is capable of generating an adequate secretory response. This is something that does not happen if there is insulin resistance (Tuduri et al., J *Gerontol A Biol Sci Med Sci* 2021).

Oral treatment with the chemical chaperone 4-PBA has been shown to reduce hyperglycemia and amyloid deposition in an obese and diabetic mouse model (De Pablo et al., *Sci Rep* 2021).

It has been seen that the intake of extra virgin olive oil improves weight gain and insulin sensitivity in a murine model of type 2 diabetes lacking the LDL receptor. (Álvarez-Amor et al., *Sci Rep* 2021).

2 PREVENTIVE AND THERAPEUTIC STRATEGIES IN REGENERATIVE MEDICINE, CELLULAR THERAPY AND GENE THERAPY

It has been seen that the overexpression of BMP7 in adipose tissue and liver, in ob/ob mouse models, increases the proportion of small adipocytes, decreases hepatic steatosis and insulin resistance. (Casana et al., Int J Obes 2021).

It has been verified, in a humanized mouse model, that GLIS3 has a function of activating the insulin gene during embryonic development. In addition, regulatory mutations of the insulin gene, which cause monogenic diabetes, impede this function (Akerman et al., Cell Rep 2021).

Using mouse and human models, the transcription factor REST has been found to be a modulator of endocrine differentiation, and its inhibition is a potential tool for the production of insulin-producing cells. (Rovira et al., Genes Dev 2021).

3 APPLICATION OF NEW TECHNOLOGIES TO THE TREATMENT OF DIABETES

A new methodology has been developed for glucose prediction that requires only information from continuous glucose monitoring and the time of intake (Mon- taser et al., Sensors 2021).

A new unihormonal artificial pancreas system with automatic recommendation of rescue carbohydrates has been evaluated for announced and unannounced exercise (Viñals et al., JECM 2021). (Viñals et al., JECM 2021).

It has been studied that alcohol intake and the nutritional composition of the intake in the postprandial response is not a relevant factor in the detection of unannounced meals in the artificial pancreas (García et al., BMJ Open Diabetes Res Care 2021).

PROGRAM 3

Cellular and molecular mechanisms involvedin the development and progression of type 2 diabetes and identification of new therapeutic targets

COORDINATOR:
Antonio Zorzano Olarte

1

INFLAMMATION AS A PATHOGENIC PROCESS IN DIABETES MELLITUS.

A new proinflammatory signaling pathway has been identified in macrophages that involves the participation of the TRPC3 ion channel, which is activated by diacylglycerol produced by lipin-1 and its blockade reduces inflammation induced by bacterial lipopolysaccharide and the development of sepsis in animal models (Casas et al., *Cell. Mol. Life Sci.* 2021).

2

IDENTIFICATION OF MOLECULAR MECHANISMS AND NEW THERAPEUTIC TARGETS FOR THE DEVELOPMENT OF PERSONALIZED EARLY INTERVENTIONS.

The stress cytokine GDF15 has been described to activate AMPK and that it is necessary for the antidiabetic effects of PPARbeta/delta nuclear receptor activators. (Aguilar-Recarte et al., Cell Rep 2021).

3

IDENTIFICATION OF BIOMARKERS OF RISK OF DIABETES PROGRESSION.

A methodology has been developed that significantly improves the ability to identify and describe biomedical markers and to know their chemical structure. The results of the research have been published in the scientific journal Nature Methods (Giné, Roger, et al., Nature Methods 2021). With this methodology, the research team has managed to take advantage of the chemical information found in the human metabolome databases massively projecting it on the data and spectral signals and, in this way, decipher which signals contain relevant biological information.

The decrease in tissue iron stores by elective phlebotomies does not improve the alterations in carbohydrate metabolism, and could even be accompanied by a deterioration of the glycemic profile associated with iron deficiency in women with functional hyperandrogenism (Ortiz-Flores et al., J Clin Endocrinol Metab 2021, doi.org/10.1210/clinem/dgaa978).

The activity of brown adipose tissue (BAT) and the concentrations of its marker CXCL14 are sex-specific in the first year of life. BAT activity is inversely associated with body adiposity indexes only in girls (García-Beltran et al., J Clin Endocrinol Metab 2021, doi: 10.1210/clinem/dgab761).

A coordinated project has been launched to study, from a comprehensive perspective, the metabolic connection mediated by succinate between the intestine-adipose tissue-brain, financed by the Caixa Health Research call. Along these lines, succinate in peripheral blood has been described as a key element in the regulation of energy metabolism, modulable through intake, which also has a predictive value as an early biomarker of cardiovascular risk in a young, apparently healthy population (Osuna-Prieto et al., Cardiovasc Diabetol. 2021).

PROGRAM 4

Training

COORDINATOR:
Ángel Nadal Navajas

The main objectives of the CIBERDEM Training Program have been to promote cohesion and collaboration between research groups of the area and boost the competitiveness of its young researchers. The most notable actions are detailed below.

A new call for intramural projects for young people has been opened, which has financed 3 intramural projects, with the participation of a total of 7 CIBERDEM groups, and the three intramural projects granted in the previous call have been completed.

The Mobility Actions have made it possible to carry out 3 stays in CIBER groups and 3 international stays.

The XII CIBERDEM Annual Meeting has recovered its face-to-face format and was held on November 3 and 4 with the participation of more than 130 researchers. In addition to constituting an important unifying element, the most innovative aspects of diabetes research carried out at CIBERDEM were addressed.

The second Meeting of Young Researchers, organized by and for young people, took place on October 20-21 in virtual format and was attended by more than 70 young researchers.

In 2021, Program Research Seminars have been organized in online format, to enhance the scientific capacities of the working groups and boost their lines of research.

For the fourth consecutive year, CIBERDEM has organized the joint SED-CIBERDEM Symposium at the XXXII National Congress of the Spanish Diabetes Society (June 17). The Symposium focused on the new data from the di@bet.es study, on research on neuronal vulnerability due to hyperglycemia and the connection between diabetes and Parkinson's disease, and on the role of the vitamin D receptor in the development of diabetes.

In the context of the various training activities that CIBERDEM organizes in collaboration with Merck Sharp & Dohme Spain, this year the CIBERDEM/MSD 2021 Annual Symposium regained face-to-face attendance, held on November 3 in the context of the Annual Meeting with monogenic diabetes as its theme.

CIBERDEM has developed the third edition of the Expert Postgraduate Course of the University of Barcelona 2020-2021 "Chronic complications of Diabetes Mellitus," which awards 15 European ECTS credits and has started its fourth edition 2021-2022.

Based on the institutional ties established with the German Center for Diabetes Research (DZD), CIBERDEM has facilitated the participation of Young researchers in the DZD Diabetes Research School (October 5-14, online).

Finally, it is important to mention the impossibility of detailing in the Annual Report the numerous training activities organized at the individual level by the CIBERDEM groups.

Communication and dissemination to society

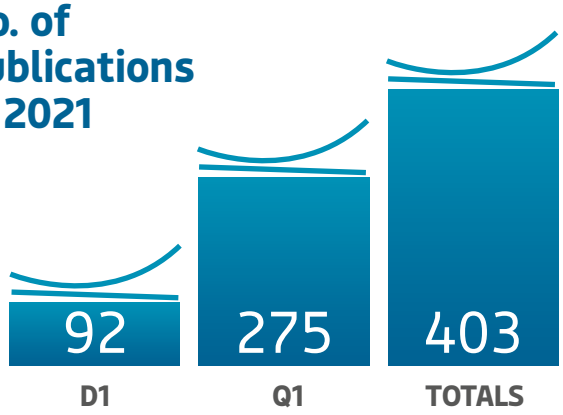
CIBERDEM maintains its commitment to bring the results of research closer to society, participating in dissemination actions and has collaborated throughout the year with various initiatives of patient associations, the Spanish Diabetes Federation (FEDE) and DiabetesCero, as well as with Canal Diabetes.

Regarding its presence at an institutional level in scientific societies, CIBERDEM has been present at the Congresses of the Spanish Society of Diabetes, the European Association for the Study of Diabetes and has participated in the EURADIA meetings.

SCIENTIFIC PRODUCTION

PUBLICATIONS

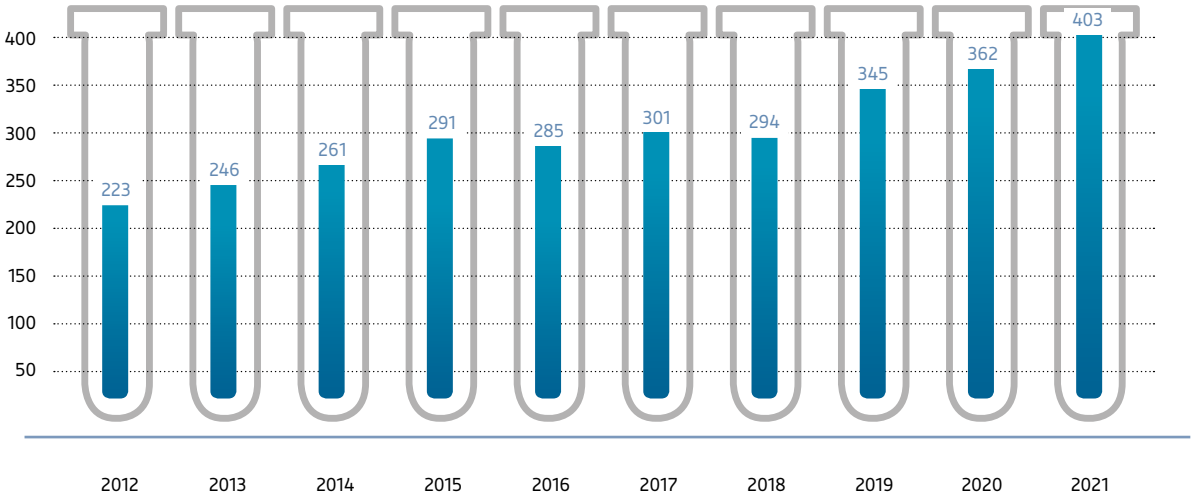
No. of publications in 2021



Collaborations

*Among various thematic areas

Evolution of publications



10 most relevant publications by impact factor

IF	Publication
79,321	Borobia A.M., Carcas A.J., Perez-Olmeda M., Castano L., Bertran M.J., Garcia-Perez J. et al. Immunogenicity and reactogenicity of BNT162b2 booster in ChAdOx1-S-primed participants (CombiVacS): a multicentre, open-label, randomised, controlled, phase 2 trial. *The Lancet*. 2021;398(10295):121-130.
43,33	Escobar-Morreale H.F., Bayona A., Nattero-Chavez L., Luque-Ramirez M. Type 1 diabetes mellitus and polycystic ovary syndrome. *Nature Reviews Endocrinology*. 2021;17(12):701-702.
32,069	Magliano D.J., Chen L., Islam R.M., Carstensen B., Gregg E.W., Pavkov M.E. et al. Trends in the incidence of diagnosed diabetes: a multicountry analysis of aggregate data from 22 million diagnoses in high-income and middle-income settings. *The Lancet Diabetes and Endocrinology*. 2021;9(4):203-211.
29,983	Ray KK, Reeskamp LF, Laufs U, Banach M, Mach F, Tokgözoğlu LS et al. Combination lipid-lowering therapy as first-line strategy in very high-risk patients. *European Heart Journal*. 2021; Oct 12;ehab718. doi: 10.1093/eurheartj/ehab718. Online ahead of print.
28,547	Gine R., Capellades J., Badia J.M., Vughs D., Schwaiger-Haber M., Alexandrov T. et al. HERMES: a molecular-formula-oriented method to target the metabolome. *Nature Methods*. 2021;18(11):1370-1376.
27,287	Gomez-Valades A.G., Pozo M., Varela L., Boudjadja M.B., Ramirez S., Chivite I. et al. Mitochondrial cristae-remodeling protein OPA1 in POMC neurons couples Ca2+ homeostasis with adipose tissue lipolysis. *Cell Metabolism*. 2021;33(9):1820-1835.e9.
25,083	Simon J., Goikoetxea-Usandizaga N., Serrano-Macia M., Fernandez-Ramos D., Saenz de Urturi D., Gruskos J.J. et al. Magnesium accumulation upon cyclin M4 silencing activates microsomal triglyceride transfer protein improving NASH. *Journal of Hepatology* 2021; 75(1):34-45.
25,083	Claria J., Curto A., Moreau R., Colsch B., Lopez-Vicario C., Lozano J.J. et al. Untargeted lipidomics uncovers lipid signatures that distinguish severe from moderate forms of acutely decompensated cirrhosis. *Journal of Hepatology*. 2021; 75(5):1116-1127.
21,566	Boada M., Rodrigo A., Jessen F., Wimblad B., Kramberger M., Visser P.J. et al. Complementary pre-screening strategies to uncover hidden prodromal and mild Alzheimer's disease: Results from the MOPEAD project. *Alzheimer's and Dementia*. 2021; Jul 26. doi: 10.1002/alz.12441. Online ahead of print.
19,112	Ludvigsson J., Sumnik Z., Pelikanova T., Chavez L.N., Lundberg E., Rica I. et al. Intralymphatic glutamic acid decarboxylase with vitamin d supplementation in recent-onset type 1 diabetes: A double-blind, randomized, placebo-controlled phase iib trial. *Diabetes Care*. 2021;44(7):1604-1612.

CIBERDEM Groups, Publications in 2021

Group Leader	Publications	Q1	D1	Institution - Center	Province
Álvarez Escolá, Carmen	5	3	2	Universidad Complutense de Madrid	Madrid
Balsinde Rodríguez, Jesús	8	5	0	Agencia Estatal Consejo Superior de Investigaciones Científicas	Valladolid
Benito de las Heras, Manuel R.	8	4	3	Universidad Complutense de Madrid	Madrid
Blanco Vaca, Francisco	39	31	6	Instituto de Investigación del Hospital de la Santa Cruz y San Pablo	Barcelona
Bondia, Jorge	16	11	3	Universidad Politécnica de Valencia	Valencia
Bosch Tubert, Fàtima	5	3	2	Universidad Autónoma de Barcelona	Barcelona
Burks, Deborah	3	3	0	Fundación Centro de Investigación Príncipe Felipe	Valencia
Calle Pascual, Alfonso L.	13	12	3	Servicio Madrileño de Salud	Madrid
Castaño González, Luis	22	17	4	Asociación Instituto de Investigación Sanitaria de Biocruces	Vizcaya
Correig Blanchart, Francesc X.	27	23	8	Fundación Instituto de Investigación Sanitaria Pere Virgili	Tarragona
Egido de los Ríos, Jesús	14	11	6	Instituto de Investigación Sanitaria Fundación Jiménez Díaz	Madrid
Escobar Morreale, Héctor F.	7	5	1	Servicio Madrileño de Salud	Madrid
Ferrer Marrades, Jorge	6	5	3	Fundación Centro de Regulación Genómica	Barcelona
Ibáñez Toda, Lourdes	11	7	1	Fundación para la Investigación y Docencia Sant Joan de Deu	Barcelona
Martín Bermudo, Francisco	16	11	4	Universidad Pablo de Olavide	Sevilla
Martínez Valverde, Ángela María	10	9	4	Agencia Estatal Consejo Superior de Investigaciones Científicas	Madrid
Masana Marín, Luis	31	17	5	Fundación Instituto de Investigación Sanitaria Pere Virgili	Tarragona
Mauricio Puente, Diego	51	33	9	Instituto de Investigación del Hospital de la Santa Cruz y San Pablo	Barcelona
Montanya Mias, Eduard	10	7	1	Fundación IDIBELL	Barcelona
Nadal Navajas, Ángel	10	8	2	Universidad Miguel Hernández	Alicante

Group Leader	Publications	Q1	D1	Institution - Center	Province
Novials Sardà, Anna María	5	4	1	Instituto de Investigaciones Biomédicas August Pi i Sunyer	Barcelona
Tomás Real, José	22	11	1	Fundación para la Investigación del Hospital Clínico de la Comunidad Valenciana (Fundación INCLIVA)	Valencia
Rojo Martínez, Gemma	22	17	8	Fundación Pública Andaluza para la Investigación de Málaga en Biomedicina y Salud (FIMABIS)	Málaga
Simó Canonge, Rafael	42	26	5	Fundación Hospital Universitario Vall d´Hebron - Institut de Recerca (VHIR)	Barcelona
Vallejo-Fernández de la Regera, Mario	4	4	2	Agencia Estatal Consejo Superior de Investigaciones Científicas	Madrid
Vázquez Carrera, Manuel	8	6	2	Universidad de Barcelona	Barcelona
Vendrell Ortega, Joan J.	26	22	11	Fundación Instituto de Investigación Sanitaria Pere Virgili	Tarragona
Vidal Cortada, Josep	48	30	14	Instituto de Investigaciones Biomédicas August Pi i Sunyer	Barcelona
Zorzano Olarte, Antonio	15	15	6	Fundación privada Instituto de Recerca Biomédica (IRB-Barcelona)	Barcelona

Patents owned by CIBER 2021

Applications

- Biomarkers and diagnostic method for monogenic diabetes in young adults carrying deleterious HNF1A alleles
- Epigenetic biomarkers for the diagnosis and prevention of the evolution of metabolically healthy obese subjects to metabolically unhealthy obese subjects (with CIBEROBN)

PCT Extensions applied for

- Method and system for the identification of compounds in complex biological or environmental samples.

Clinical Guidelines 2021

- Practical guidance for combination lipid-modifying therapy in high- and very-high-risk patients: A statement from a European Atherosclerosis Society Task Force. M Averna , M Banach , E Bruckert , H Drexel, M Farnie et al. *Atherosclerosis* 2021, 325:99-109.
- A disease state approach to the pharmacological management of Type 2 diabetes in primary care: A position statement by Primary Care Diabetes Europe. S Seidu, X Cos, S Brunton, SB Harris, SPO Jansson, M Mata-Cases, AMJ Neijens, P Topsever, K Khunti. Primary Care Diabetes 2021, 15:31-51. doi: 10.1016/j.pcd.2020.05.004.
- Diabetes mellitus and cardiovascular risk: an update of the recommendations of the Diabetes and Cardiovascular Disease Working Group of the Spanish Society of Diabetes (SED, 2021). F Arrieta , J Pedro-Botet , P Iglesias , JC Obaya , L Montanez , et al. *Clin Investig Arterioscler* 2021, doi: 10.1016/j.arteri.2021.05.002. Epub 2021 Jul 28.
- Consensus document on actions to prevent and to improve the management of diabetic foot in Spain. Sociedad Española de Diabetes (SED) y Sociedad Española de Angiología y Cirugía Vascular (SEACV). JL Lázaro Martínez, MC Almaraz, Á Álvarez, I Blanes, JR Escudero et al. *Endocrinología, Diabetes y Nutrición* 2021, 68: 509-513.
- SEEN Comprehensive Clinical Survey of Adult Obesity: Executive Summary. Obesity Group of the Spanish Society of Endocrinology and Nutrition (GOSEEN), Nutrition Area (NutriSEEN) and Endocrinology, Nutrition and Physical Exercise Working Group (GENEFSEEN). M D Ballesteros, N Vilarrasa, MÁ Rubio, MJ Barahona, Marta Bueno et al. *Endocrinología, Diabetes y Nutrición* 2021, 68:130-136.

- Executive summary: update on the dietary treatment of prediabetes and type 2 diabetes mellitus. Spanish Society of Arteriosclerosis, Spanish Society of Diabetes and Spanish Society of Internal Medicine. V Pascual Fuster, A Pérez Pérez, J Carretero Gómez, A Caixàs Pedragós, R Gómez-Huelgas y P Pérez-Martínez. *Endocrinología, Diabetes y Nutrición* 2021, 68: 277-287.
- Obesity and COVID-19. A necessary position statement. Obesity Group of the Spanish Society of Endocrinology and Nutrition (GOSEEN) and the Spanish Society for the Study of Obesity (SEEDO). IBretóna, A de Hollanda, N Vilarrasa, MA. Rubio, A Lecube et al. *Endocrinología, Diabetes y Nutrición* 2021, 68:573-576.
- User Guide: Closed-loop Systems. Group of Technologies Applied to Diabetes, Spanish Society of Diabetes (2021). Nuria Alonso, María Pilar Bahíllo, Raquel Barrio, Pilar Isabel Beato, Jorge Bondia, et al. (https://www.sediabetes.org/consensos_guias_reco/guia-de-sistemas-de-asa-cerrada/)


Plan 1x

CIBEREHD

Liver and
Digestive Diseases

Presentation by the scientific director

Rafael Bañares Cañizares

During the year 2021, the area of liver and digestive diseases (CIBEREHD), has maintained its research development in diseases of the liver and the gastrointestinal tract, characterized as a whole by their high prevalence, their marked negative influence on the quality of life of patients and for their not insignificant mortality.

The research activity of the CIBEREHD is structured around three major programs i) Mechanisms of liver damage, progression to advanced cirrhosis and transplantation ii) Gastrointestinal pathophysiology: inflammatory disease and motility disorders and iii) Hepatic and digestive oncology. Each program has clinical and translational research groups, which allows for a multidisciplinary approach that is clearly promoted by the area's scientific policy.

The CIBEREHD has always been characterized by the high quantity and quality of its scientific production. In 2021, more than 700 publications showing great international leadership were produced. Furthermore, this activity is clearly reflected in the generation of clinical practice documents of great value to society.

In 2021, the CIBEREHD has maintained its global strategy aimed at training researchers to address generational renewal. For this reason, this year the pre-doctoral training program (Jaume Bosch contract) has been launched, aimed at promoting the collaborative activity of translational groups. On the other hand, and within the same strategy of generating training activities with added value, interesting transversal programs have been developed, such as the bioinformatics course, and very importantly, the first edition of the CIBEREHD Research School. This action aimed at researchers in the early stages of

their research careers has allowed training in advanced translational research techniques.

In 2021, in the overall context of the CIBERISCIII providing its groups with research support services, the CIBEREHD has remodeled and strengthened its bioinformatics platform with a notable increase in its visibility.

We must not forget that in 2021 the CIBEREHD face-to-face research sessions were resumed, at least partially, which has undoubtedly allowed for the renewal of relations between the groups and the structuring of the collective research project. In these sessions, the first steps were taken to incorporate the voice of patients both in the design of the research strategy of the area and their participation in the governing bodies, which we hope will lead to substantial advances in the year 2022.

The area will undoubtedly face important challenges in the coming years: adapting its strategy to the changing context of diseases in this research area (especially metabolic fatty liver disease, inflammatory bowel disease, hepatocarcinoma or colon cancer), the need to increase its financing, the definitive incorporation of the voice of patients, as well as clearly communicating the results obtained to society. Our commitment is to be up to the challenges posed to provide society with the necessary return of our research activity.

PROGRAMS

PROGRAM 1

Mechanism of liver damage, evolution and progression of cirrhosis and liver transplantation.



COORDINATORS:
Jordi Gracia Sancho, Javier Ampuero Herrojo y Manuel Luis Rodríguez Perálvarez

In 2021, high-impact studies have been published on the mechanisms of liver damage, evolution to advanced cirrhosis and transplantation. Specifically in the area of liver transplantation, the CIBEREHD groups have collaborated closely with the Spanish Society of Liver Transplantation (SETH) and with the International Liver Transplant Society (ILTS) to produce two consensus documents, one on antiplatelet therapy and anticoagulation in liver transplantation, and another on cancer screening and management in the transplant population (PMID: 34999660 y PMID: 34905760, respectively).

Similarly, in line with the national multicenter study on COVID-19 in liver transplantation published in the Journal of Hepatology (PMID: 32750442), the humoral response to vaccines against SARS-CoV-2 in immunosuppressed patients has been analyzed, obtaining results of great interest (PMID: 33835707 y PMID: 34919762).

In metabolic liver disease, CIBEREHD researchers have shown how this entity can lose histological elements as it progresses, which could mean that there are patients who cannot be included in clinical trials and receive a therapy that could benefit them (PMID: 33896100). Moreover, in viral hepatopathies interesting results have been obtained published in journals of maximum international impact. On the one hand, it has been shown how the number of admissions due to complications of cirrhosis associated with hepatitis C fell by more than 50% from 2015, coinciding with the introduction of direct-acting antivirals and that in 2025 they will be a marginal cause of hospital admissions (PMID: 32697948). On the other hand, certain baseline characteristics have been identified in patients treated with antivirals for hepatitis B that would make it possible to anticipate functional cure of the infection after discontinuation of treatment (PMID: 34762906). Finally, in liver cirrhosis, CIBEREHD has contributed, among others, to the preparation of the Baveno VII consensus document (PMID: 35120736) and pioneering reviews on immune system dysfunction in liver cirrhosis (PMID: 34703031).

From the point of view of translational research, new therapeutic targets have been proposed for the treatment of chronic liver disease, fibrosis and portal hypertension, including sphingosine 1-phosphate antagonists (PMID: 34890841), receptor agonists activated by peroxisome proliferation (PMID: 33278455 and new inhibitors of platelet-derived growth factor (PMID: 33720693). In addition, a new therapeutic target to promote liver regeneration in older animals was described (PMID:34510498) and the protocol for obtaining hepatic stellate cells from progenitor cells was published (PMID: 33864055).

PROGRAM 2

Gastrointestinal pathophysiology: inflammatory disease and motility disorders

COORDINATOR:
Pere Clavé Civit

Program 2 of the CIBEREHD covers a group of highly prevalent digestive pathologies with a great impact on the health and quality of life of patients. This program houses three main lines of research: Esophageal-gastroduodenal diseases; Inflammatory Bowel Disease (IBD); and Functional digestive disorders and neuro-gastroenterology; and this year the participation of the groups in COVID-19 studies. The program's studies focus on the epidemiology, pathophysiology, diagnosis, prevention and treatment of these diseases through cooperative research, very often international and multidisciplinary, clinical and basic; and with a high level of clinical translation thanks to the high participation in consensus documents and national and international clinical practice guidelines. The most significant results in 2021 are:

1 ESÓPHAGEAL-GASTRODUODENAL PATHOLOGY

The publication of different studies from the European Registry on Helicobacter pylori management (Hp-Eu-Reg) on the eradication efficacy of various combinations of drugs in first and second line, their potential adverse effects and resistance to antibiotics in patients infected with Helicobacter pylori (HP). Also worth highlighting is the publication of the V Spanish Consensus Conference on the treatment of HP infection, including first-line treatment guidelines, rescue therapies after eradication failure, and treatment of HP in peptic ulcer. In addition, there have been a group of cooperative studies and consensus documents developed with different Spanish societies (AEG, SED, SEAP) on the screening of premalignant lesions associated with gastric cancer.

2 INFLAMMATORY BOWEL DISEASE (IBD)

Yet another year, this is probably the area with the greatest interaction among the CIBEREHD research groups due to the great activity of the GETECCU Group and the Eneida Registry as well as the participation in multiple international consortiums that has allowed testing new emerging agents still in early stages of clinical-preclinical development, highlighting various biological treatments and mesenchymal progenitor cells. Also noteworthy are advances in the diagnosis of celiac disease through the cytometric pattern of intraepithelial lymphocytes and an interesting group of studies that place the patient with the quality of care evaluated by the patient and its impact on the clinical results of inflammatory bowel disease.

3

NEURO-GASTROENTEROLOGY AND FUNCTIONAL DIGESTIVE DISORDERS

To be highlighted is the publication of different clinical practice consensuses with European societies on the management of dysphagia associated with phenotypes (Stroke, Parkinson's, Cerebral Palsy and Head and Neck Cancer). Also, the publication of randomized studies on neurorehabilitation techniques using peripheral electrical or pharmacological sensory stimuli (TRPV1 agonists). The gastrointestinal sensory and motor response to intake, the trial of different treatment alternatives for patients with IBS- diarrhea, and the participation of researchers in large epidemiological studies with the new Rome criteria (IV) for functional digestive disorders have been another great milestone in this area.

4

COOPERATIVE STUDIES COVID-19

Many of the groups of the area have participated in international cooperative studies on COVID-19. Gustatory and oropharyngeal sensory dysfunctions and their relationship with the appearance of swallowing disorders; the impact of COVID-19 on patients with IBD and its digestive involvement, the nutritional status of patients, and the genetic factors associated with the prognosis of COVID-19 patients have been the subject of relevant studies and publications.

PROGRAM 3

Hepatic and Digestive Oncology

COORDINATOR:
María Reig Monzón

Scientific activity in Hepatic and Digestive Oncology has maintained its high level of quality and the advancement of knowledge has been transferred to society through various clinical practice guidelines.

The molecular profile of cholangiocarcinoma with its impact on resistance to treatment and the usefulness of liquid biopsy or sequencing of bile cell-free DNA for its diagnosis has been explored. The clinical pattern of this cancer in Europe has been characterized, as well as the need to refine the definition of its evolutionary stages. CIBEREHD researchers lead an extensive international collaborative research network.

The risk of tumor recurrence after curative treatment and of liver cancer after hepatitis C cure has been defined and the BCLC decision model followed internationally for liver cancer treatment has been updated. Moreover, progress has been made in the evaluation and prediction of benefit from surgical or locoregional treatments, the rational basis for combined treatment using immunological agents has been provided and

the Spanish guidelines for liver cancer have been updated and incorporated into the National Health System Guidelines and the European guidelines for systemic treatment.

In gastrointestinal cancer, research has continued in the field of colorectal cancer screening with a particular focus on hereditary forms, their molecular profile and their detection in the initial phase. The need to harmonize the anatomical-pathological criteria for the classification of serrated vs. sessile polyps has been identified, and the usefulness of various endoscopic techniques for both diagnosis and non-invasive treatment has been defined.

Simultaneously, as reflected in the Annual Report, innumerable high-impact reviews have been published that have updated knowledge regarding epidemiology, diagnosis, molecular pattern and application of treatment

Liver

- *Reig M et al. Diagnosis and treatment of hepatocellular carcinoma. Update of the consensus document of the AEEH, AEC, SEOM, SERAM, SERVEI, and SETH. 2021 May*
- *Yau T et al. Nivolumab versus sorafenib in advanced hepatocellular carcinoma (CheckMate 459): a randomised, multicentre, open-label, phase 3 trial. Lancet Oncol. 2022 Jan*
- *Kelley RK et al. Safety, Efficacy, and Pharmacodynamics of Tremelimumab Plus Durvalumab for Patients With Unresectable Hepatocellular Carcinoma: Randomized Expansion of a Phase I/II Study. J Clin Oncol. 2021 Sep*
- *Arechederra M et al. Next-generation sequencing of bile cell-free DNA for the early detection of patients with malignant biliary strictures. Gut. 2021 Jul*

Colorectal

- Wada Y et al. A Liquid Biopsy Assay for Noninvasive Identification of Lymph Node Metastases in T1 Colorectal Cancer. *Gastroenterology*. 2021 Jul
- Burke CA et al. Eflornithine plus Sulindac for Prevention of Progression in Familial Adenomatous Polyposis. *N Engl J Med*. 2020 Sep
- Carballal S et al. Prevalence of adenomatous polyposis in a fecal immunochemical test-based colorectal cancer screening program and risk of advanced neoplasia during follow-up. *Endoscopy*. 2021 Oct
- Soares de Lima Y et al. Germline and Somatic Whole-Exome Sequencing Identifies New Candidate Genes Involved in Familial Predisposition to Serrated Polyposis Syndrome. *Cancers* (Basel). 2021 Feb
- Guo X et al. Identifying Novel Susceptibility Genes for Colorectal Cancer Risk From a Transcriptome-Wide Association Study of 125,478 Subjects. *Gastroenterology*. 2021 Mar

PROGRAM 4

Training

COORDINATOR:
Sofía Pérez del Pulgar Gallart

The CIBEREHD training program this year has carried out numerous actions of great interest to researchers, especially younger ones:

- **"Jaume Bosch" CIBEREHD Predoctoral Training Action**: A procedure has been established to select a CIBEREHD research group with the best scientific and training proposal so that it can hire a researcher to carry out a doctoral thesis in basic/translational research in a collaborative project between groups in the area of Liver and Digestive Diseases.

  > **1st Predoctoral Training Action "Jaume Bosch" CIBEREHD 2021**, the selected project is entitled Role of mitochondrial cholesterol and gender influence in NASH development: from bench to bedside. Tutored by the Principal Investigators José Carlos Fernández Checa as coordinator and Manuel Romero as the group that will host the stay of at least one year. The contracted predoctoral researcher is Laura Fabrega.

> **2nd Predoctoral Training Action "Jaume Bosch" CIBEREHD 2022** the call for this action was held during the last quarter of 2021, once evaluated it will be resolved in the first quarter of 2022.

- **CIBEREHD Bioinformatics Course**, this first edition was coordinated by Juanjo Lozano and Sofía Pérez del Pulgar with a duration of 5 days in online format. The methodology of the course was 3 theoretical classes (fundamental concepts of statistics, massive data analysis with R and differential expression analysis) and 2 practical sessions (examples of research with bioinformatics). Number of people registered: **60**.
- **CIBEREHD Research School** this training action was conceived with the aim of creating an annual edition to deal with different topics, areas (basic, translational, technological, clinical...) to be held in different locations.
- **1st CIBEREHD Research School: Update on translational research methods in Liver and Digestive Diseases**, this first edition was organized by the CIBEREHD researchers Jordi Gracia and Sofía Pérez del Pulgar, over a 2-day period (November 26-27, 2021) at the IDIBAPS in Barcelona. The methodology was organized as follows: the first day in the afternoon, the theoretical sessions and the keynote lecture were given; and on the second day in the morning, each attendee carried out two practical activities (to choose from among five proposals) in the IDIBAPS laboratories. The total number of people registered was 23.
- **Young Researchers Workshop - XV CIBEREHD Scientific Conference** This action was a novelty in 2020 and has two fundamental purposes: to make known the possibilities offered by the CIBEREHD Training Program to young researchers and to offer the possibility for young researchers to present the results of their work and/or research projects. In 2021 the following actions were carried out:

  > **Success stories of Mobility Actions:** Marina Fuertes (Paloma Martín Sanz Group, Alberto Sols Biomedical Research Institute, Madrid) and Mario Sanduzzi (María Reig Group, Hospital Clínic, Barcelona) explained their experience and results obtained during their stays in the groups led by Pau Sancho (IDI-BAPS, Barcelona) and Johannes Hov (Oslo University, Norway), respectively.

  > **Best poster awards:** The winners were Ester González Sánchez (IDIBELL, UB), Miriam Tarrado Castellarnau (IBUB, UB) and Marina Fuertes Agudo (IIBM Alberto Sols; IBV-CSIC).

Other training actions:

- **Participation in courses/workshops/seminars:** 23 national and 3 international actions.
- **Organization of seminars/symposiums:** 17 actions endorsed by CIBEREHD, 4 of them developed internationally: "OGiP Seminars" organized by Sergi Castellví, "The future in liver cancer – The BCLC 35th Anniversary Celebration" organized by María Reig and Jordi

Bruix, "Baveno VII" chaired by Jaume Bosch and "Liver Seminars" (https://liverseminars.eu/), an initiative led by Jordi Gracia and Rafael Bañares.

- **Mobility Actions 2021**: Rocío Montero (Group: Manuel Romero) carried out a 3-month international stay at the University of Lisbon (Portugal). Petar Dianov Petrov (Group: José Vicente Castell) carried out a 4-month national stay under the supervision of Malu Martínez-Chantar at the Liver Diseases Laboratory of the CIC BioGUNE (Derio).

The tables below show the different training actions carried out:

CIRRHOSIS		
PI	Courses	Endorsed
A. Albillos	•	
R. Andrade		•
R. Bañares	•	
M. Berenguer	•	
M. Buti	•••	
J.V. Castell		
J.I. Esteban		
J.C. Fernández-Checa	••	
C. Fondevila		
X. Forns	•••••	
J.C. Gracía Pagán	••••••	•••
J. García-Samaniego		
J. Genescà		
P. Ginés	•	•
J. Gómez		
J. González Gallego		
C. Guarner	•	
P. Martín Sanz		
M. de la Mata		
J.M. Mato	•	
A. Parés		
M. Romero	••••	•
P. Zapater	•	

GASTROENTEROLOGY		
PI	Courses	Endorsed
F. Azpiroz		•
X. Calvet		
P. Clavé		•
E. Domenech		
J.V. Esplugues		•
M. Esteve		
A. Lanas	•	
A. Salas	•	
J. Pérez Gisbert	•••	•••
Medina		

LINKED GROUPS		
PI	Courses	Endorsed
L. Caballería		
J.L. Calleja		
J. Crespo		
J. Cubiella		••
C. García		
J. Molina		
F.J. Padillo	•	

ONCOLOGY		
PI	Courses	Endorsed
C. Armengol	•	
J. Bruix	•	•
L. Bujanda	•	
M. Cascante		
A. Castells		•
I. Fabregat		
Marín		
M. Pastor		
B. Sangro	•	

BIOINFORMATICS PLATFORM		
PI	Courses	Endorsed
J.J. Lozano	••	

● International

● National

PLATAFORMS

Bioinformatics

The year 2021 has been a fruitful one as reflected by the number of publications as a result of the support offered by the CIBEREHD Bioinformatics platform.

Together with Dr. Sofía Pérez del Pulgar, the Training and Teaching Coordinator, the first CIBEREHD bioinformatics course has been organized. The follow-up questionnaire shows that it was favorably evaluated by the students with a remarkable degree of acceptance.

The collaboration established with the Gastrointestinal and Pancreatic Oncology area has generated a very relevant publication related to the biological function of microRNA mir-181a-5p in the regulation of changes in the structure and metabolism of pancreatic cells during pre-cancer stages. The platform participated in all of the bioinformatic analysis, including data processing, as well as in the development of new software for the analysis of miRNA-mRNA networks.

- Fernández-Castañer E, Vila-Casadesus M, Vila-Navarro E, Parra C, Lozano JJ, Castells A, Gironella M. MicroRNAs Deregulated in Intraductal Papillary Mucinous Neoplasm Converge on Actin Cytoskeleton-Related Pathways That Are Maintained in Pancreatic Ductal Adenocarcino-

ma. *Cancers* (Basel). 2021 May 14;13(10):2369. doi: 10.3390/cancers13102369. PMID: 34069007; PMCID: PMC8155860.

Together with the CIBEREHD inflammatory bowel disease research group led by Dr. Azucena Salas, a new methodology has been developed to identify interactions between different omics studies and their most relevant clinical variables, published during 2021.

- Revilla L, Mayorgas A, Corraliza AM, Masamunt MC, Metwaly A, Haller D, Tristán E, Carrasco A, Esteve M, Panés J, Ricart E, Lozano JJ, Salas A. Multi-omic modelling of inflammatory bowel disease with regularized canonical correlation analysis. *PLoS One*. 2021 Feb 8;16(2):e0246367. doi: 10.1371/journal.pone.0246367. PMID: 33556098; PMCID: PMC7870068.

The staff of the platform has been part of a team of researchers in the international field -among them the CIBEREHD- and organizations from nine European countries, coordinated and led from Barcelona by the European Foundation for the Study of Chronic Liver Failure (EF Clif), generating high-impact publications such as:

- Clària J, Curto A, Moreau R, Colsch B, López-Vicario C, Lozano JJ, Aguilar F, Castelli FA, Fenaille F, Junot C, Zhang I, Vinaixa M, Yanes O, Caraceni P, Trebicka J, Fernández J, Angeli P, Jalan R, Arroyo V. Untargeted lipidomics uncovers lipid signatures that distinguish severe from moderate forms of acutely decompensated cirrhosis. *J Hepatol*. 2021 Nov;75(5):1116-1127. doi: 10.1016/j.jhep.2021.06.043. Epub 2021 Jul 7. PMID: 34245803.

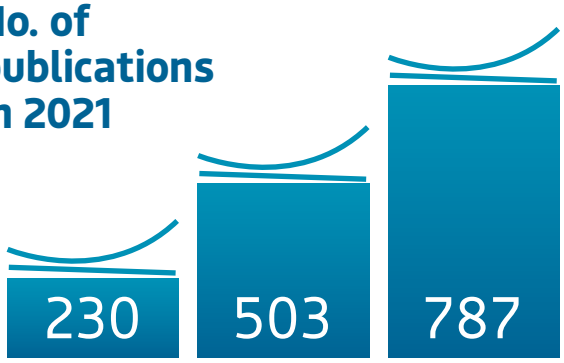
In the area of inflammation in liver disease, a study has been published investigating the genes involved in endothelial dysfunction in alcoholic hepatitis and which are related to increased mortality.

- Blaya D, Rubio-Tomás T, Rodrigo-Torres D, Lozano J, Coll M, Argemi J, Altamirano J, Affò S, Morales-Ibanez O, Gratacós-Ginès J, Pose E, Tanguy M, Issoufaly T, Rautou PE, Bataller R, Caballería J, Sancho-Bru P. Endothelial dysfunction markers predict short-term mortality in patients with severe alcoholic hepatitis. *Hepatol Int*. 2021 Aug;15(4):1006-1017. doi: 10.1007/s12072-021-10165-y. Epub 2021 May 5. PMID: 33954832.

SCIENTIFIC PRODUCTION

PUBLICATIONS

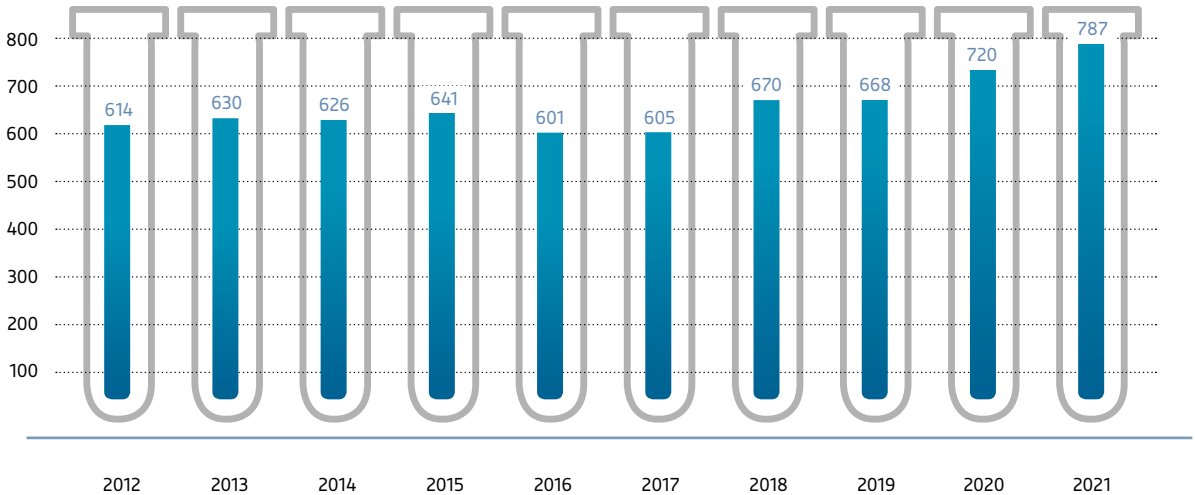
No. of publications in 2021



Collaborations

*Among various thematic areas

Evolution of publications



10 most relevant publications by impact factor

IF	Publication
46,802	Gracia-Sancho J., Caparros E., Fernandez-Iglesias A., Frances R. Role of liver sinusoidal endothelial cells in liver diseases. *Nature Reviews Gastroenterology and Hepatology*. 2021.
46,802	Sangro B., Sarobe P., Hervas-Stubbs S., Melero I. Advances in immunotherapy for hepatocellular carcinoma. *Nature Reviews Gastroenterology and Hepatology*. 2021.
46,802	Lazarus J.V., Anstee Q.M., Hagstrom H., Cusi K., Cortez-Pinto H., Mark H.E. et al. Defining comprehensive models of care for NAFLD. *Nature Reviews Gastroenterology and Hepatology*. 2021;18(10):717-729.
46,802	Masoodi M., Gastaldelli A., Hyotylainen T., Arretxe E., Alonso C., Gaggini M. et al. Metabolomics and lipidomics in NAFLD: biomarkers and non-invasive diagnostic tests. *Nature Reviews Gastroenterology and Hepatology*. 2021;18(12):835-856.
46,802	Gomollon F. Inflammatory bowel disease and corticosteroids: the first RCT. N*ature Reviews Gastroenterology and Hepatology*. 2021;18(12):833.
39,397	Fresquet V, Garcia-Barchino MJ, Larrayoz MJ, Celay J, Vicente C, Fernandez-Galilea M et al. Endogenous retroelement activation by epigenetic therapy reverses the Warburg effect and elicits mitochondrial-mediated cancer cell death. *Cancer discovery*. 2021.
31,777	Yau T., Kang Y.-K., Kim T.-Y., El-Khoueiry A.B., Santoro A., Sangro B. et al. Efficacy and Safety of Nivolumab plus Ipilimumab in Patients with Advanced Hepatocellular Carcinoma Previously Treated with Sorafenib: The CheckMate 040 Randomized Clinical Trial. *JAMA Oncology*. 2021.
25,841	Seras-Franzoso J., Diaz-Riascos Z.V., Corchero J.L., Gonzalez P., Garcia-Aranda N., Mandana M. et al. Extracellular vesicles from recombinant cell factories improve the activity and efficacy of enzymes defective in lysosomal storage disorders. *Journal of Extracellular Vesicles*. 2021;10(5).
25,083	Ferrusquia-Acosta J., Bassegoda O., Turco L., Reverter E., Pellone M., Bianchini M. et al. Agreement between wedged hepatic venous pressure and portal pressure in non-alcoholic steatohepatitis-related cirrhosis. *Journal of Hepatology*. 2021.
25,083	Boyer-Diaz Z., Aristu-Zabalza P., Andres-Rozas M., Robert C., Ortega-Ribera M., Fernandez-Iglesias A. et al. Pan-PPAR agonist lanifibranor improves portal hypertension and hepatic fibrosis in experimental advanced chronic liver disease. *Journal of Hepatology*. 2021.

CIBEREHD Groups, Publications in 2021

Group Leader	Publications	Q1	D1	Institution - Center	Province
Albillos Martínez, Agustín	26	16	10	Universidad de Alcalá	Madrid
Andrade, Raúl	23	20	9	Fundación Pública Andaluza para la Investigación de Málaga en Biomedicina y Salud (FIMABIS)	Málaga
Armengol Niell, Carolina	13	8	5	Fundación Instituto de Investigación Germans Trias i Pujol	Barcelona
Azpiroz Vidaur, Fernando	33	17	3	Fund. Hospital Universitario Vall d´Hebron - Institut de Recerca (VHIR)	Barcelona
Bañares Cañizares, Rafael	42	24	12	Servicio Madrileño de Salud	Madrid
Berenguer Haym, Marina	24	15	11	Fundación para la Investigación del Hospital Universitario y Politécnico la Fe de la Comunidad Valenciana	Valencia
Bruix Tudó, Jordi	33	22	13	Hospital Clínico y Provincial de Barcelona	Barcelona
Bujanda Fernández de Pierola, Luis	56	40	23	Asociación Instituto Biodonostia	Guipúzcoa
Buti Ferrer, María Asunción	40	21	13	Fundación Hospital Universitario Vall d´Hebron - Institut de Recerca (VHIR)	Barcelona
Calvet Calvo, Xavier	21	6	2	Corporación Sanitaria Parc Taulí	Barcelona
Cascante Serratosa, Marta	15	10	1	Universidad de Barcelona	Barcelona
Castell Ripoll, José Vicente	8	7	3	Fundación para la Investigación del Hospital Universitario y Politécnico la Fe de la Comunidad Valenciana	Valencia
Castells Garangou, Antoni	64	41	18	Hospital Clínico y Provincial de Barcelona	Barcelona
Clave Civit, Pere	17	11	3	Fundación Privada Salud del Consorcio Sanitario del Maresme	Barcelona
Domenech Morral, Eugeni	25	6	2	Fundación Instituto de Investigación Germans Trias i Pujol	Barcelona
Esplugues Mota, Juan Vicente	16	12	5	Universidad de Valencia	Valencia
Esteban Mur, Juan Ignacio	22	11	7	Fundación Hospital Universitario Vall d´Hebron - Institut de Recerca (VHIR)	Barcelona
Esteve Comas, María	37	17	7	Fundación Mutua Terrassa	Barcelona
Fabregat Romero, Mª Isabel	15	11	4	Fundación IDIBELL	Barcelona
Fernández-Checa Torres, José Carlos	20	17	12	Agencia Estatal Consejo Superior de Investigaciones Científicas	Barcelona

Group Leader	Publications	Q1	D1	Institution - Center	Province
Fondevila Campo, Constantino	47	29	18	Servicio Madrileño de Salud	Madrid
Forns Bernhardt, Xavier	16	8	4	Hospital Clínico y Provincial de Barcelona	Barcelona
García Marín, José Juan	14	13	4	Universidad de Salamanca	Salamanca
García Pagán, Juan Carlos	50	39	22	Hospital Clínico y Provincial de Barcelona	Barcelona
García-Samaniego Rey, Javier	6	3	2	Servicio Madrileño de Salud	Madrid
Genesca Ferrer, Joan	34	22	13	Fund. Hospital Universitario Vall d'Hebron - Institut de Recerca (VHIR)	Barcelona
Gines Gibert, Pere	45	37	29	Hospital Clínico y Provincial de Barcelona	Barcelona
Gómez Castilla, Jordi	9	4	1	Agencia Estatal Consejo Superior de Investigaciones Científicas	Granada
González Gallego, Javier	14	12	6	Universidad de León	León
Guarner Aguilar, Carlos	13	8	5	Inst. de Investigación del Hospital de la Santa Cruz y San Pablo	Barcelona
Lanas Arbeloa, Ángel	30	18	5	Fundación Instituto de Investigación Sanitaria Aragón	Zaragoza
Martín Sanz, Paloma	6	4	2	Agencia Estatal Consejo Superior de Investigaciones Científicas	Madrid
Mata García, Manuel de la	8	6	3	Fundación para la Investigación Biomédica de Córdoba (FIBICO)	Córdoba
Mato De La Paz, José María	40	31	17	CIC BIOGUNE	Vizcaya
Pares Darnaculleta, Albert	12	6	4	Hospital Clínico y Provincial de Barcelona	Barcelona
Pastor Anglada, Marçal	3	3	0	Universidad de Barcelona	Barcelona
Pérez Gisbert, Javier	64	33	13	Servicio Madrileño de Salud	Madrid
Romero Gómez, Manuel	29	19	11	Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla	Sevilla
Salas Martínez, Azucena	23	13	3	Hospital Clínico y Provincial de Barcelona	Barcelona
Sánchez De Medina López Huertas, Fermín	20	19	5	Universidad de Granada	Granada
Sangro Gómez-Acebo, Bruno Carlos	54	41	23	Universidad de Navarra	Navarra
Zapater Hernández, Pedro	22	13	6	Instituto de Investigación Sanitaria y Biomédica de Alicante	Alicante

Linked clinical groups

Group Leader	Institution - Center	Province
Caballería Rovira, Llorenç	Universidad Autónoma de Barcelona	Barcelona
Calleja Panero, Jose Luis	Servicio Madrileño de Salud	Madrid
Crespo García, Javier	Instituto de Investigación Marqués de Valdecilla	Cantabria
Cubiella Fernández, Joaquín	Servicio Gallego de Salud	Coruña, A
García Monzón, Carmelo	Servicio Madrileño de Salud Madrid	Madrid
Minguela Puras, Alfredo	Fundación para la Formación e Investigación Sanitarias de la Región de Murcia (FFIS)	Murcia
Molina Infante, Javier	Fundación para la Formación y la Investigación de los Profesionales de la Salud (FUNDESALUD)	Cáceres
Padillo Ruiz, Francisco Javier	Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla	Sevilla

Patents owned by CIBER 2021

Applications

- Method for the diagnosis and/or prognosis of eosinophilic esophagitis in saliva. (Patent now in PCT phase).
- Informative Biomarkers of Portal Hypertension.

Granted

- In vitro method for identifying pancreatic cancer.

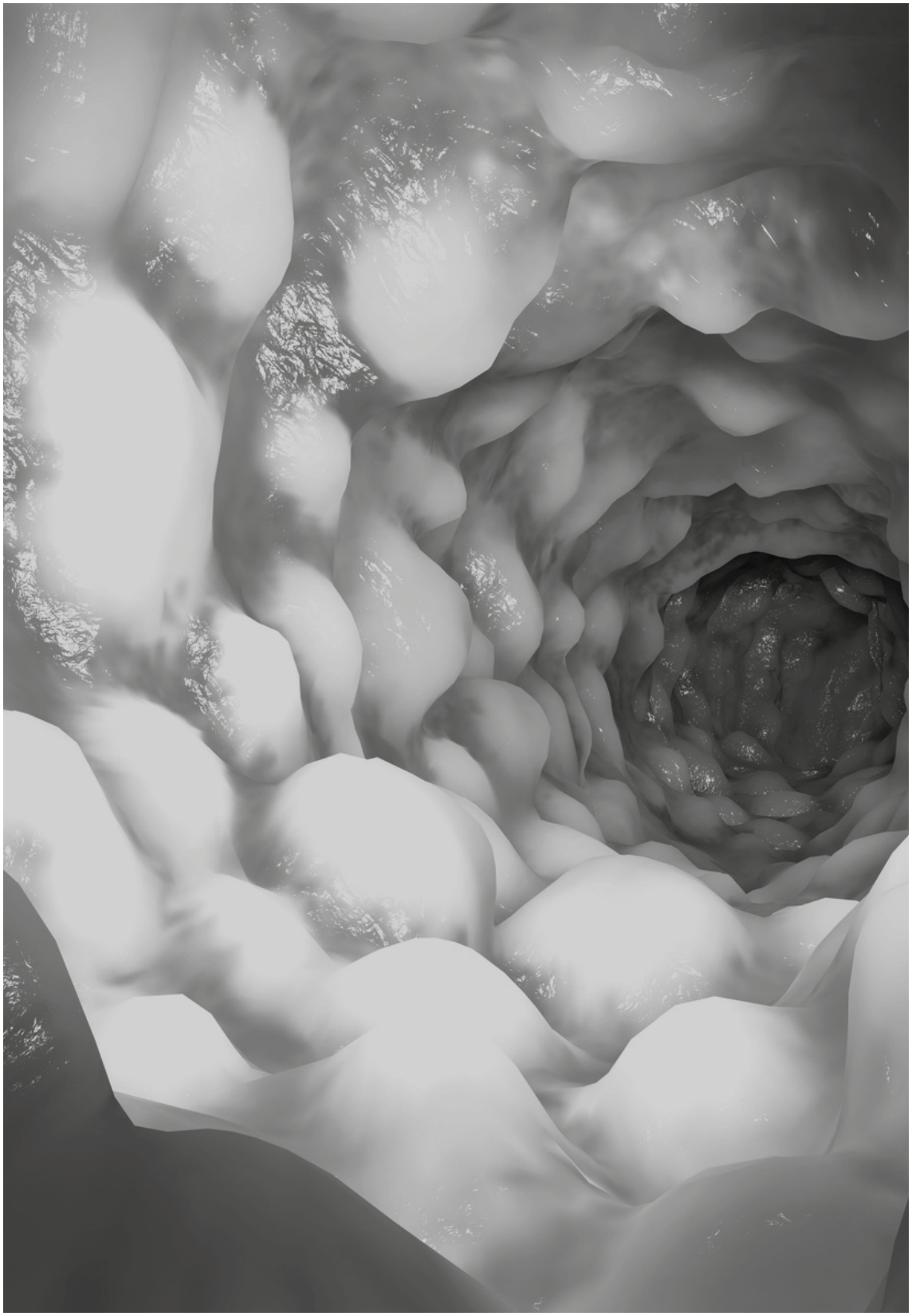
Clinical Guidelines 2021

- 2020 position statement and recommendations of the European Liver and Intestine Transplantation Association (ELITA): management of hepatitis B virus-related infection before and after liver transplantation
- BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update
- Chronic pancreatitis for the clinician. Part 2: Treatment and follow-up. Interdisciplinary Position Paper of the Societat Catalana de Digestologia and the Societat Catalana de Pàncrees
- Clinical Considerations Regarding the Use of Thiopurines in Older Patients with Inflammatory Bowel Disease
- Diagnosis and treatment of hepatocellular carcinoma. Update of the consensus document of the AEEH, AEC, SEOM, SERAM, SERVEI, and SETH
- Diagnosis, Evaluation, and Management of Ascites, Spontaneous Bacterial Peritonitis and Hepatorenal Syndrome: 2021 Practice Guidance by the American Association for the Study of Liver Diseases
- AEG, SEED and SEAP position statement on gastric cancer screening in low incidence populations.
- ECCO Guidelines on the Prevention, Diagnosis, and Management of Infections in Inflammatory Bowel Disease
- Endoscopic evaluation of surgically altered bowel in inflammatory bowel disease: a consensus guideline from the Global Interventional Inflammatory Bowel Disease Group
- Esophageal stenting for benign and malignant disease: European Society of Gastrointestinal Endoscopy (ESGE) Guideline - Update 2021
- Expanding Indications of Liver Transplantation in Spain: Consensus Statement and Recommendations by the Spanish Society of Liver Transplantation

- Guidelines for the use and interpretation of assays for monitoring autophagy (4th edition)
- Hematopoietic stem cell transplantation for autoimmune diseases in the time of COVID-19: EBMT guidelines and recommendations
- Indicacions i valoració del risc de les exploracions endoscòpiques en persones d'edat avançada o fràgils
- International consensus on methodological issues in standardization of fecal calprotectin measurement in inflammatory bowel diseases
- International recommendations for personalised selective internal radiation therapy of primary and metastatic liver diseases with yttrium-90 resin microspheres
- Chronic pancreatitis for the clinician. Part 1: etiology and diagnosis. Interdisciplinary position statement of the Catalan Society of Digestology and the Catalan Pancreatic Society
- Chronic pancreatitis for the clinician. Part 2: Treatment and follow-up. Interdisciplinary position statement of the Catalan Society of Digestology and the Catalan Pancreatic Society
- Patient-Evaluated Quality of Care is Related to Better Inflammatory Bowel Disease Outcomes: The IQCARO II Project
- Position Statement. Recommendations of the Spanish Group on Crohn's Disease and Ulcerative Colitis (GETECCU) on the treatment of strictures in Crohn's disease
- Quality in diagnostic upper gastrointestinal endoscopy for the detection and surveillance of gastric cancer precursor lesions: Position paper of AEG, SEED and SEAP
- Recommendations on the use of generic immunosuppressants in transplantation: Second consensus document. Promoted by the Spanish Transplant Society (SET). May 2021
- Recommendations and Guidance on Nutritional

Supplementation in the Liver Transplant Setting

- Recommendations of the Spanish Working Group on Crohn's Disease and Ulcerative Colitis (GETECCU) on screening and treatment of tuberculosis infection in patients with inflammatory bowel disease
- Recommendations of the Spanish Working Group on Crohn's Disease and Ulcerative Colitis (GETECCU) on the use of abdominal ultrasound in inflammatory bowel disease
- Recommendations of the Spanish Working Group on Crohn's disease and Ulcerative Colitis (Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa - GETECCU) on dysplasia screening in inflammatory bowel disease patients
- Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of hepatocellular carcinoma
- Systemic treatment of hepatocellular carcinoma: An EASL position paper
- United European Gastroenterology (UEG) and European Society for Neurogastroenterology and Motility (ESNM) consensus on functional dyspepsia
- United European Gastroenterology (UEG) and European Society for Neurogastroenterology and Motility (ESNM) consensus on gastroparesis
- V Spanish Consensus Conference on Helicobacter pylori infection treatment
- When and How to Use Endoscopic Tattooing in the Colon: An International Delphi Agreement




CIBERER
Rare Diseases

Presentation by the scientific director

Pablo Lapunzina Badía

The main challenges of CIBERER, in line with the International Rare Diseases Research Consortium (IRDiRC), are to develop new therapies and support diagnostic developments, so that anyone affected by a known rare disease is diagnosed in less than a year.

In this sense, I am proud to present in this report a sample of some of our milestones that show that we are meeting these objectives. It is important to point out the arduous collaborative work and the incredible involvement of all the members of CIBERER, including patient groups, who are an active part of the operation of our center.

The 78 groups that currently make up the CIBERER (including research groups and linked clinical groups) have made great progress in the search for therapies for different diseases and groups of pathologies, such as leukodystrophies, Fanconi anemia, ataxia-telangiectasia, Diamond-Blackfan anemia, hereditary hemorrhagic telangiectasia, epidermolysis bullosa, or hereditary metabolic diseases. These projects are at different stages of the research process, from the search for therapeutic targets in cellular, animal or bioinformatics models, through the designation of orphan drugs, to clinical trials with cell or gene therapies in their final phases.

Proof of this is that CIBERER continues to be a leader in the development of orphan drugs, as it has been a sponsor of 14 European orphan drug designations. Specifically, in 2021, 4 new drugs have been designated for adrenoleukodystrophy, Diamond-Blackfan anemia, cystinuria, and megalencephalic leukoencephalopathy with subcortical cysts.

In addition, the CIBERER is contributing to improving the diagnosis of rare diseases, among other aspects thanks to the identification of more than 100 new genes that cause rare diseases. One of the center's star programs is contributing to this result, the Program for Undiagnosed Diseases (ENoD), with a diagnostic rate of 30%.

In this field, a large national project led by the CIBERER is to be added, IMPaCT-GENóMICA, which, thanks to the experience of ENoD, is laying the foundations for an infrastructure that will make it possible to improve the diagnosis of rare diseases in an equitable manner throughout the Spanish territory.

I would also like to highlight the consolidation of the Low Prevalence and Genetic Diseases Registry (GenRaRe), which currently houses 5 sub-registries that will make it possible to advance knowledge of mitochondrial diseases, Pompe disease, transthyretinal amyloidosis, epileptic encephalopathy due to mutation in the KCNA2 gene and congenital defects of glycosylation (CDG).

Finally, CIBERER is also present internationally, proof of this is its participation in the most important projects in the field of RD, such as the European Joint Program on Rare Diseases (EJP-RD), whose objective is to establish a comprehensive strategy to improve research, as well as Orphanet Spain, which is the international portal of reference in RD.

Thanks to everyone for making CIBERER possible.

PROGRAMS

PROGRAM 1

Translational Genomic Medicine

COORDINATOR:
Ángel Carracedo

The main objective of the Translational Genomic Medicine program is the implementation of the new genomic medicine and omics applications to hospital diagnostic practices.

Among the main milestones of the program in 2021, we highlight the start-up of the IMPACT-Genome Program, one of the 3 financed in the Precision Medicine Infrastructure associated with Science and Technology (IMPaCT) of the ISCIII. The program is endowed with 7.25 million euros. The objective of the IMPaCT Program on Genomic Medicine is to create a collaborative structure for the implementation of genomic medicine in coordination with the National Health System (NHS).

Among the most outstanding results of 2021 we find a new

work published in the journal Blood by the unit led by Santiago Rodríguez de Córdoba at the Margarita Salas Biological Research Center (CIB-CSIC) that provides the functional characterization of Factor H (FH) variants associated with Atypical Hemolytic Uremic Syndrome (aHUS). This study rationalizes the classification of FH variants found in genetic studies of patients with a clinical diagnosis of aHUS and therefore aims to improve the medical use of genetic information.

PROGRAM 2

Mitochondrial and inherited metabolic medicine

COORDINATOR:
Rafael Artuch

As an important milestone we highlight the consolidation of the Low Prevalence and Genetic Diseases Registry (GenRaRe). The Spanish sub-registry of mitochondrial diseases has allowed the first epidemiological study of mitochondrial diseases in Spain: 2761 cases from 49 provinces. Clinical groups from the CIBERER (PMID: 34680984) participate, coordinated by the groups led by Julio Montoya, MA. Martin and Rafael Artuch.

Diagnostics:

- New genes have been identified involved in brain development diseases (Raúl Estévez - PMID: 34186028), and in a new neurological disease (gene 'PI4KA', Aurora Pujol y Alfons Macaya, PMID: 34415322).
- Roser Urreizti, Andrés Nascimento y Aurora Pujol provide evidence that mutations in the GEMIN5 protein can be the cause of rare neurological disorders characterized by developmental delay. (PMID: 33963192).
- The group led by Antònia Ribes has clinically and functionally characterized two families with mitochondrial disorders associated with the 'NDUFAF4' and 'NDUFA8' genes (PMIDs: 32949790 / 33153867).

- A new biomarker for the study of mitochondrial diseases has been identified: free circulating mitochondrial DNA, with the participation of the groups led by Rafael Artuch, Julio Montoya and Glòria Garrabou. (PMID: 34352085).
- The group led by Ramon Martí, in collaboration with JM Grau's group, describes an expanded phenotype in patients with YARS2 mutations and participates in an international initiative to set diagnostic and treatment recommendations for MNGIE (PMIDs: PMID: 34441767 y 32898308).
- The group led by Plácido Navas (Carlos Santos) has developed an online query platform for the phenotypic characteristics of primary Coenzyme Q10 deficiency for use in establishing its diagnosis and to facilitate the study of the genotype-phenotype correlation. (PMID: 33677064).

Therapies:

- The groups of V. Rubio and B. Pérez support the use of pharmacological chaperones as treatment in PMM2-CDG thanks to structural biology studies. (PMID: 34859900).
- Aurora Pujol's group advances in the development of treatments for adrenoleukodystrophy: clinical trial with dimethyl fumarate and the designation of fingolimod as an orphan drug.
- The groups led by José M. Cuezva and Francesc Palau propose preventing mitochondrial oxidative damage as a therapeutic target for Charcot-Marie-Tooth disease. (PMID: 34274972).
- Gene therapy to treat megalencephalic leukoencephalopathy with subcortical cysts (MLC) has been designated an orphan drug thanks to the work of the group led by Raúl Estévez.
- C. Jiménez's group recovers normal production of the protein deficient in muscular dystrophy due to collagen VI deficiency thanks to gene editing with CRISPR-Cas9.

Other milestones:

- Groups of the Program have described new developments in:

  > heteromeric transport of amino acids. Manuel Palacín (PMID: 34848541).

  > genetics of atypical femoral fractures. Susanna Balcells (PMID: 34299011).

  > pathophysiological aspects of hyperoxaluria. Eduardo Salido (PMID: 34433051).

  > development of cellular models for CoQ deficiencies. Carlos Santos-Ocaña (PMID: 34638552).

  > development of a murine model of OXPHOS deficiency due to GFM1 mutations (PMID: 34919756).
- Also noteworthy is the collaborative work of several groups in the program (Ramon Martí, MA Martín Casanueva) for the diagnosis and treatment of thymidine kinase 2 deficiency. (PMID: 34600563).

PROGRAM 3

Neurological disorders

COORDINATOR:
Pía Gallano

This Research Program (RP) is made up of 7 groups from different fields, from clinical, genetics and pathophysiology in neurological pathologies, both of genetic and acquired origin.

At the scientific level, the publications by Jordi Díaz-Manera (Eduard Gallardo unit) in *The Lancet Neurology* stand out, on the results of two clinical trials carried out on patients with Pompe disease.

A study on hereditary distal motor neuropathies was published, coordinated by Teresa Sevilla and with the participation of Eduard Gallardo, selected by the *European Journal of Neurology* for its special issue on Neurogenetics.

In *Expert Reviews in Molecular Medicine* a review on neuroinflammation and progressive myoclonic epilepsies was published by Pascual Sanz and José María Serratosa. In addition, two articles by Pascual Sanz were published in GLIA and *Molecular Neurobiology*, on the potential therapeutic efficacy of different substances in Lafora disease.

Similarly, the research published in *Redox Biology*, led by Pilar González-Cabo (Federico Pallardó's unit) together with INCLIVA researchers, shows that facilitating the transport of calci-

um to the mitochondria allows the reversal of defects due to the loss of frataxin, opening up new proposals of potential therapies for Friedrich's ataxia.

In the Call for Working Groups, 7 proposals were financed, in 3 of which groups from the Program participated: Federico Pallardó, Pascual Sanz and José Serratosa.

Worth highlighting is the success of the RP groups in the Call for Intramural Cooperative Complementary Actions, where of the 9 awarded projects, two are coordinated by researchers of the program, and in which 6 groups of the program participate.

Lidia González-Quereda (Pía Gallano's unit) coordinates a project on CANVAS syndrome, with the participation of the units led by Federico Pallardó, Teresa Sevilla and Eduard Gallardo. The units led by Federico Pallardó and Pascual Sanz participate in Marina Sánchez's project (José Serratosa's unit) on the search for biomarkers and new therapies for Lafora disease.

EpiDisease, a company specialized in epigenetics and a CIBER spin-off, whose executive director is José Luis García (Federico Pallardó's unit), has obtained a new investment from Arquimea and Fundación Botín for a total value of €535,000. This boost will allow the company to advance in the development of diagnostic tests based on epigenetic biomarkers.

José Luis García has been the editor of the book Epigenetics in Precision Medicine, published by *Elsevier-Academic Press*, which includes the latest advances in epigenetic markers in precision medicine.

This research program stands out for its great harmony with patient associations. Within the framework of the CIBERER Academy for patients, two seminars on gene therapy have been held, organized in collaboration with the ASEM Federation: "Applicability of gene therapy in rare diseases" (March 17), given by Lluis Montoliu and "Gene therapy in neuromuscular diseases" (April 13), given by Andrés Nascimiento and Jordi Díaz-Manera.

Pía Gallano received the "*Fem Pinya*" award by ASEM-Catalunya in recognition of her professional career and for her active collaboration with this patient association over the years.

PROGRAM 4

Pediatric and developmental medicine

COORDINATOR:
Cristina Fillat

The main activities and results linked to the objectives defined in the 2021 Action Plan are summarized below.

Within the objectives of promoting the development of genomic diagnostic tools and focusing on therapies for diseases of interest to this Program, we highlight the following:

- Identification of the genetic causes of a new syndrome with multisystem involvement, led by the group coordinated by Pablo Lapunzina;
- Proposal to prevent mitochondrial oxidative damage as a future therapeutic target, observing defects in mitochondrial and calcium transport in neuronal axons caused by GDAP1 deficiency in Charcot-Marie-Tooth disease, led by the group coordinated by Francesc Palau;
- Demonstration, in a cell model, of the therapeutic potential of CRISPR/Cas9 tools in Ewing's sarcoma, led by Javier Alonso's group;
- Participation in the description of facial dysmorphism associated with Axenfeld-Rieger syndrome and in the development of a preventive therapy for congenital de-

fects in Williams-Beuren syndrome in a murine model, led by the group coordinated by Luis Pérez Jurado.

Beyond these contributions, there are numerous individual or collaborative publications of the different groups on aspects related to the objectives of the Program.

Also noteworthy is the participation of 4 groups of the program in 6 intramural projects awarded during 2021 in the ACCI and Development of New Experimental Models in Rare Diseases calls.

In addition, the program has contributed to the training of young researchers, health professionals and the general population through the organization of courses and hospital conferences sponsored by this Research Program. It has also collaborated in training patients on the diagnostic process, in the context of the second EURORDIS summer school.

PROGRAM 5

Sensorineural pathology

COORDINATOR:
Lluís Montoliu

During 2021, the 7 groups that make up the Research Program (RP) have obtained important scientific, dissemination and collaboration results with patient associations, both independently and in collaboration with other CIBERER groups.

It has been a fruitful year for the groups that make up this program, since all of them have obtained funding in one of the 4 intramural calls that CIBERER published.

In the Call for Working Groups, 7 proposals were financed, 4 of which are coordinated by groups of this Program: Matías Moreno, Almudena Fernández, José María Millán and Silvia Murillo, and which also have the participation of 6 groups from this Research Program.

In the Call for Intramural Cooperative Complementary Actions, of the 9 projects granted, one is coordinated by Gemma Marfany, on the regulation of proteostasis in cilium formation.

In the Call for new experimental models for rare diseases, the of the program participate in 2 of the 5 awarded projects, one on DYRK1A haploinsufficiency syndrome, in which

Paola Bovolenta participates, and another on abnormalities of sexual development, with the participation of Almudena Fernandez.

In the Call for Translational Research Projects, of the two awarded projects, one of them is led by the Linked Clinical Group recently incorporated into the program, whose Coordinator is José Antonio López Escámez, in which the units of Carmen Ayuso, Joaquín Dopazo, Miguel Ángel Moreno Pelayo and José María Millán participate. The objective is to design and validate a computer tool based on sequencing data to classify patients with rare diseases.

In 2021, a CIBER unit was created, incorporated into the new Biobanks and Biomodels Platform (2021-2023) of the Instituto de Salud Carlos III (ISCIII). It is one of the 41 units that make up this platform in which the groups led by Isabel Varela and Lluis Montoliu participate.

Events organized:

- **Research Conference: The key to advancing in the diagnosis and treatment of hearing loss,** March 10 (online) coordinated by Isabel Varela.
- **Seminar on gene therapy in rare diseases for patients and families,** March 17 (online) CIBERER Academy for patients, given by Lluis Montoliu.
- **V Course "Bioinformatic analysis of massive sequencing data applied to genetic diagnosis and translational research",** May 31 to June 9 (online) coordinated by Miguel Ángel Moreno and Matías Morín.
- **IV Practical Course on "Genomic Editing and Gene Therapy", J**uly 12 (online) coordinated by Lluis Montoliu and Almudena Fernández, with Gemma Marfany and Matías Morín.
- **Course on Ophthalmogenetics: Understanding genetics through clinical cases,** November 12 (online) coordinated by Carmen Ayuso and Elena Vallespín.
- **International Symposium: Novel approaches to study rare genetic diseases,** November 12, coordinated by Gemma Marfany, Susana Balcells, Daniel Grinberg and Roser Corominas.
- **Three CIBERER Academy seminars for patients on deafness** (online) co-organized with FIAPAS, Miguel Ángel Moreno and Isabel Varela.

PROGRAM 6

Endocrine medicine

COORDINATOR:
Susan Webb

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

As this is a program made up of clinical groups, its capacities have been greatly affected by the pandemic situation during this period due to the increased burden of care suffered. Among the publications of the groups associated with this Research Program during 2021, we highlight several works on Cushing's Syndrome.

The most relevant works on Cushing's syndrome are the research results in the groups led by Susan Webb, one of them focused on updating the diagnosis and management guide for Cushing's syndrome (Consensus on diagnosis and management of Cushing's disease: a guideline update. *Lancet Diabetes Endocrinol*. 2021 Dec;9(12):847-875) and the other on the description of its psychological complications (Psychological complications of Cushing's syndrome. *Curr Opin Endocrinol Diabetes Obes*. 2021 Jun 1;28(3):325-329). Similarly, several videos aimed at patients have been

published in which strategies are offered to improve the lives of patients with this disease.

Also noteworthy is the collaborative work between several groups in the program focused on sporadic pituitary adenomas in young patients (Clinical and genetic characteristics in patients under 30 years with sporadic pituitary adenomas. *Eur J Endocrinol*. 2021 Aug 27;185 (4):485-496) and in somatotropic adenomas (Molecular determinants of enhanced response to somatostatin receptor ligands after debulking in large GH-producing adenomas. *Clin Endocrinol* (Oxf). 2021 May;94(5):811-819).

PROGRAM 7

Inherited cancer, hematologic and dermatological diseases

COORDINATOR:
Juan Antonio Bueren

During the year 2021 the groups of this research program have continued working towards the IRDiRC objectives. This year, due to the limitations resulting from pandemic, face-to-face events have been limited, including the annual meeting of the program. Among the main milestones, we highlight the following:

Regarding the development of tools for the study of diseases, a study led by Guillermo Güenechea, a researcher in Juan Bueren's group at the CIEMAT/IIS-FJD, and Rosario Perona, at the Alberto Sols Biomedical Research Institute (CSIC/UAM), has succeeded in developing a new cellular model of X-linked dyskeratosis congenita in progenitor and hematopoietic stem cells.

In diagnostics, we highlight the studies by Javier Corral's group at the Morales Meseguer University Hospital in Murcia, which has identified a new genetic variant responsible for the congenital pathology of the cyclooxygenase-1 enzyme (COX-1), a **haematological disorder** characterized by increased bleeding. In addition, the group has published a study on the application of high-throughput sequencing in

routine clinical practice, which has made it possible to obtain a genetic diagnosis in 70% of patients with congenital platelet disorders. On the other hand, Víctor Mulero's group at the University of Murcia and the Biomedical Research Institute of Murcia (IMIB) has discovered that those affected by dyskeratosis congenita with a certain genetic mutation are more likely to suffer from acute myeloid leukemia. The study has been published in the journal PNAS.

Various CIBERER groups coordinated by Julián Sevilla, from the Linked Clinical Group of the Hospital Niño Jesús in Madrid, have developed a project based on genetic study using massive sequencing panels for the diagnosis of congenital bone marrow failure syndromes. This panel has shown to be a useful tool for the molecular diagnosis of these diseases.

As regards therapeutic developments, this year has once again been very productive. We highlight the work of Javier Corral's group at the IMIB, which has led a study that suggests that patients with FXI deficiency can be treated with anticoagulants without increased risk of serious bleeding, and that of Rosario Perona's group, which has published a study in which they have managed to prevent and reverse pulmonary fibrosis in experimental models with PLGA/PEI nanoparticles loaded with GSE4 peptide. These results are the first steps to study its possible antifibrotic effect in patients with idiopathic pulmonary fibrosis and other progressive fibrosing diffuse interstitial lung diseases that present altered telomere function.

Finally, worth highlighting are the advances made by Marcela del Río's group, which have managed to increase the levels of precision and efficacy of genome editing technology for the treatment of recessive dystrophic epidermolysis bullosa, opening the door to future clinical trials.

PROGRAM 8

Training

COORDINATOR:
Luis Pérez Jurado

In 2021, the CIBERER Training Program has developed its key actions along three general lines:

- Courses: Organization and call for attendance grants.
- Organization of a program aimed at patients with rare diseases.
- Mobility grants.

The normal development of the activities of this program has been altered by the COVID-19 pandemic. Some courses were able to be reorganized in virtual format, but others were canceled due to the impossibility of taking them to that format due to their distinct face-to-face nature..

Organization of courses and seminars

The CIBERER Training Program participated in the organization or co-organization of the following courses and seminars:

- *EURORDIS SUMMER SCHOOL*, 5ª Edición. Desarrollado en formato online.
- *Orphanet nomenclature and RD ontologies for RD research.*

- IV Gene editing course with CRISPR.
- Presentation of the registry of congenital platelet diseases.

Call for attendance grants

Grants were also offered to attend the following courses and conferences coordinated by CIBERER researchers:

- Bioinformatic analysis of massive sequencing data applied to genetic diagnosis and translational research. 10 grants.
- XLII Congress of the Spanish Society of Genetics. 14 grants.
- Summer course: diagnosis of hereditary mitochondrial and metabolic diseases: a step forward. 7 grants.
- Organization of a program aimed at patients with rare diseases.

In 2020 we started the "CIBERER Academy for Patients" program to contribute to the training of people affected by rare diseases and their families in relevant aspects of research in rare diseases. Once the seminars are over, they are made public on the CIBER YouTube channel.

In 2021, the program consisted of two seminars focused on gene therapy:

- Gene therapy in rare diseases.
- Gene therapy in neuromuscular diseases.

Mobility grants

In 2021, mobility grants continued to be open to internal and external, national and international mobility, the former being provided preferentially. In this way, various researchers were able to benefit from this program to expand their training and advance the projects in which they were involved.

The following table shows the mobilities carried out in 2021:

Beneficiary	Issuing Group	Receiving Group
Laura Castilla Vallmanya	PI: Susanna Balcells Comas	Stem Cells, Aging and Neurodegeneration Group (Lund)
Alicia Vilas Lagoa	PI: Belén Pérez González	PI: Alberto Marina Moreno
Rebeca Osca Verdegal	PI: Federico Pallardó Calatayud	Instituto de Bioingeniería de Cataluña (Barcelona)
Serena Mirra	PI: Gemma Marfany Nadal	Istituto di Genetica e Biofisica Adriano Buzzati-Traverso (IGB), CNR (Napoli)
Jordi Minguillón Pedreño	PI: Jordi Surrallés Calonge	PI: Juan Antonio Bueren
Marisa Flook Pereira	PI: José Antonio López Escámez	Charité - Universitätsmedizin Berlin (Berlin)
Elena Torres Campos	PI: Isabel Varela Nieto	Institute for Neuroscience of Montpellier (Montpellier)
Laura Ugalde Díaz	PI: Juan Antonio Bueren	Institute for Molecular Health Sciences, ETH Zurich (Zurich)
Yolanda Benítez Quesada	PI: Pablo D. Lapunzina Badía	PI: Joaquín Dopazo Blázquez

PLATFORMS

PLATFORM 1

CIBERER Biobank

The activities carried out by the CIBERER Biobank have been aligned with the strategic objectives included in the Action Plan and aimed at promoting the proper functioning of the platform. Overall, the following points should be noted:

The number of biological samples in the Biobank system eis 920 from 84 different pathologies that can be consulted in the online catalog search engine (http://www.ciberer-biobank.es/Catalogo/). During this year, the number of **biological samples transferred** to research projects has been a total of 486 samples.

Also, two new **custody** services have been established and another two started in previous years are maintained. The provision of services to CIBERER researchers has continued and our growing offer of processing services has meant that the number of **processing services provided** continues to increase annually, reaching a total of 318 services in 2021.

A part of the custody and processing services has been provided to external groups and biotechnological companies, which has allowed for their billing (3.830 €).

QWe continue to maintain **collaborations with Biobank networks**. We are a member of the Valencian Network of Biobanks, of the ISCIII Platform National Network of Biobanks and Biomodels and of the Eurobiobank. Collaboration agreements in force this year have been signed with Biobank IBSP-CV/FISABIO and the National DNA Bank as well as a sample deposit agreement with INCLIVA for the creation of a collection of fibroblasts from control donors. Collaboration is being made with **patient associations** (ENACH Association and AFASW, Alliance of families affected by Wolfram Syndrome) to make prospective collections that will be deposited in a biobank system. Regarding **agreements with the industry**, collaboration agreements are maintained with EpiDisease SL in two projects TEST ScoliPro® and TESTIVDEIA and with Seqplexing SL a Know-how license for the development of a kit for the detection of SARS-Cov-2 in cell cultures.

We have attended and participated in seven different events to **disseminate our activity**. The participation of the biobank in **Research Projects** has been: i) ISCIII Platform for Biobanks and Biomodels (PT20). Support for R&D&I in Biomedicine and Health Sciences of the Strategic Action in Health PT20/00118. ii) ACCI-CIBERER Call and iii) Update of Biobank Infrastructures and Incorporation of Technological Innovation and Reinforcement of the Valencian Network of Biobanks (2022 - 2028). These projects have made it possible to obtain a funding of €8,000 for the CBK.

Publications: as a result of the assignment to research groups, an article has been published: Parrado, A. et al. (2021).). Dissecting the transcriptional program of phosphomanno- mutase 2 deficient cells: B-LCL as a valuable model for congenital disorders of glycosylation studies.

PLATFORM 2

Bioinformatics for Rare Diseases (BIER)

One of the main activities of BiER is its dedication to the ENoD project which not only searches for SNP-type variants or small indels in patient sequencing data, but also other more complex variants such as structural variants or triplet expansions.

It is important to highlight that the high confidence variant detection rate (STRONG) is 23%, almost double that reported in the literature for the reanalysis of undiagnosed cases. Although we don't receive feedback from all, in general the feedback we receive is confirmatory. Collaborations have also been extended to more groups, including the group led by A. Moreno from VHIR and V. Mulero from the Institute of Biomedical Research of Murcia.

Following the pattern of previous years, the ENoD data have increased and made more precise the genetic variability database of the Spanish population, CSVS, (http://csvs.babelomics.org/), which has continued to show its utility for filtering local polymorphic variants in numerous studies and putting different researchers into contact, thus making the samples it contains discoverable. The CSVS has been published this year in a highly collaborative article (Peña-Chilet et al. Nucleic Acids Res. 2021; 49,D1:D1130-D1137), an example of crowdsourcing. As an offshoot of CSVS the SPACNACS database has been set up- Spanish Copy Number Alterations Collaborative Server (http://csvs.clinbioinfosspa.es/spacnacs/).

Aware of the importance of taking into account other types of mutations that are not clearly detectable with conventional prioritization of exomes, a bioinformatics tool, MIGNON, has been developed for the analysis of gene expression data. It detects mutations in the transcripts and allows their expression levels to be quantified (Garrido-Rodriguez M, Lopez-Lopez D, Ortuno FM, Peña-Chilet M, Muñoz E, Calzado MA, Dopazo J. PLoS Comput Biol. 2021;17:e1008748). This application is part of BiER's contribution to the RNAseq working group, in which it actively participates. It also participates in other working groups, such as Modald-ER and Bioinformatics.

The ACCI "Mathematical models of disease mechanisms for the reformulation of drugs in rare diseases", led by María Peña, to propose second uses of drugs for rare diseases using machine learning, was extended to 2021 due to the pandemic and generated new results. Several of these drugs have been validated (for Fanconi anemia) or are in the process of being validated with promising initial results (retinitis pigmentosa).

Also, with the opening of the possibilities of traveling, we had Yolanda Benítez from the group led by Beatriz Morte in a training stay.

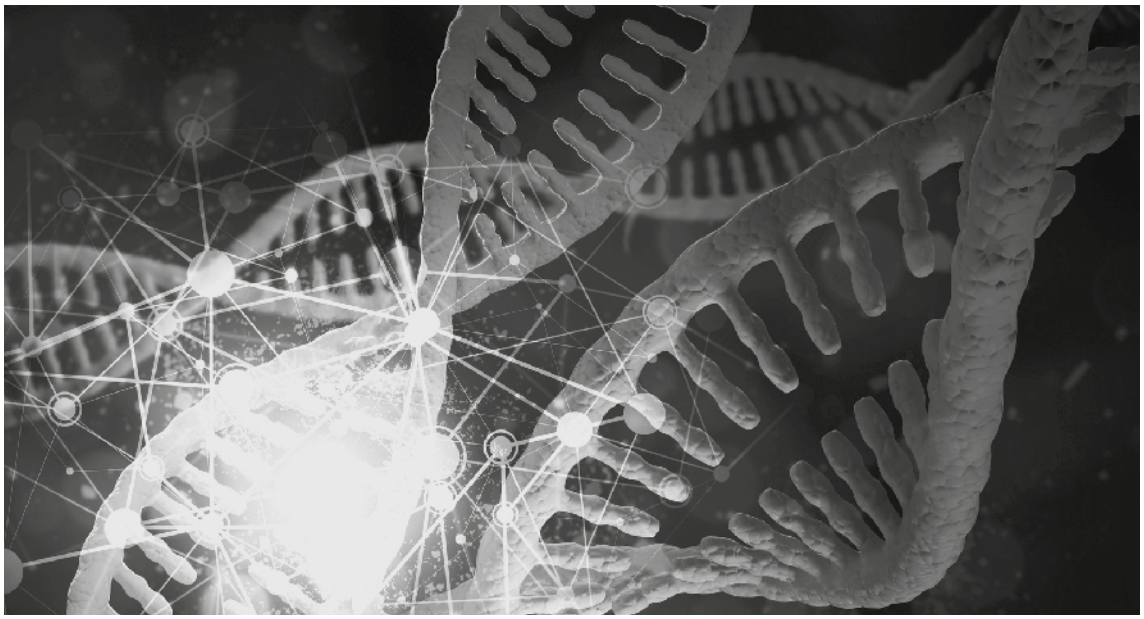
Finally, an agreement has been formalized with Ipsen for the detection of suspected rare diseases within the Health Population Database of the Andalusian public health system, specifically fibrodysplasia ossificans progressiva, but which is a model to be exported for the search for other rare diseases and can be of great help for the regional registry of rare diseases.

PLATFORM 3

Resource Map for Rare Diseases (MAPER)

In 2021, information continued to be collected for the MAPER database. The data on research projects and clinical trials accessible through the MAPER website are as follows:

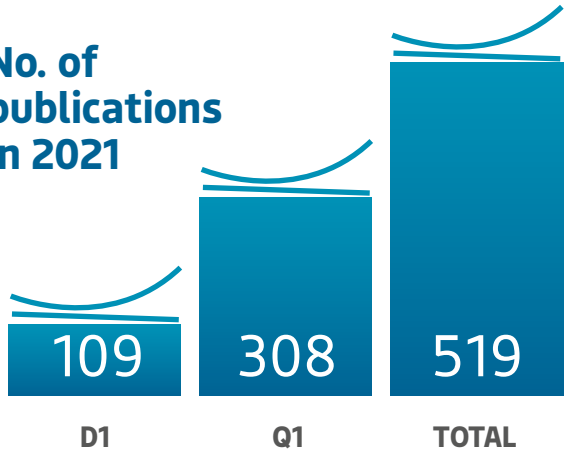
- 1,258 biomedical research projects and 797 clinical trials.
- 896 Principal Investigators with at least 1 project or trial are included in the database.



SCIENTIFIC PRODUCTION

Publications

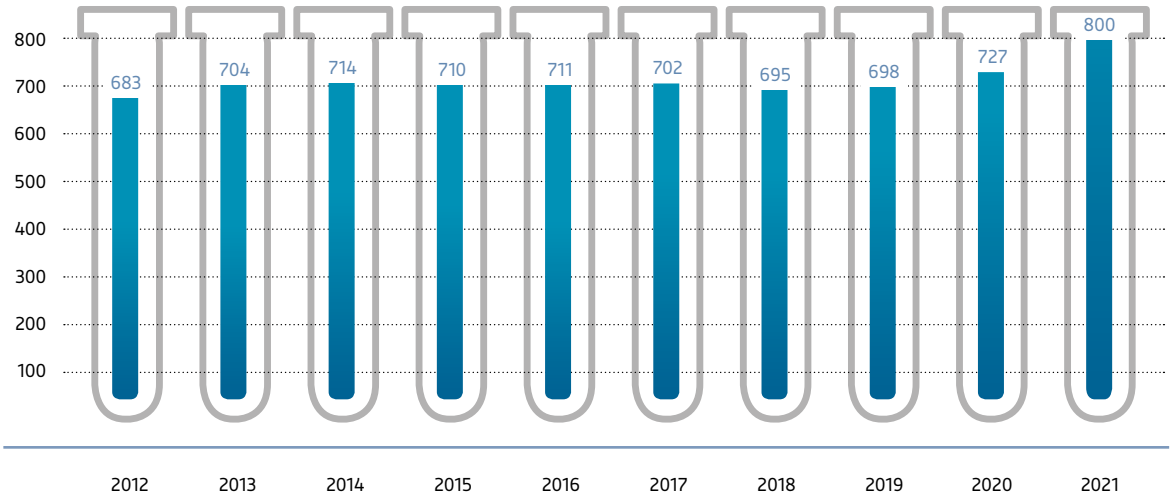
No. of publications in 2021



Collaborations

*Among various thematic areas

Evolution of publications



10 most relevant publications by impact factor

IF	Publication
91,245	Breast Cancer Association Consortium, Dorling L, Carvalho S, et al. Breast Cancer Risk Genes - Association Analysis in More than 113,000 Women. N Engl J Med. 2021;384(5):428-439. doi:10.1056/NEJMoa1913948
79,321	Borobia AM, Carcas AJ, Pérez-Olmeda M, et al. Immunogenicity and reactogenicity of BNT162b2 booster in ChAdOx1-S-primed participants (CombiVacS): a multicentre, open-label, randomised, controlled, phase 2 trial [published correction appears in Lancet. 2021 Aug 14;398(10300):582]. Lancet.2021;398(10295):121-130. doi:10.1016/S0140-6736(21)01420-3
43,330	Amar L, Pacak K, Steichen O, et al. International consensus on initial screening and follow-up of asymptomatic SDHx mutation carriers. Nat Rev Endocrinol. 2021;17(7):435-444. doi:10.1038/s41574-021-00492-3
41,316	Eggermont AMM, Blank CU, Mandalà M, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma (EORTC 1325-MG/KEYNOTE-054): distant metastasis-free survival results from a double-blind, randomised, controlled, phase 3 trial. Lancet Oncol. 2021;22(5):643-654. doi:10.1016/S1470-2045(21)00065-6
41,316	Stratigos AJ, Sekulic A, Peris K, et al. Cemiplimab in locally advanced basal cell carcinoma after hedgehog inhibitor therapy: an open-label, multi-centre, single-arm, phase 2 trial. Lancet Oncol. 2021;22(6):848-857. doi:10.1016/S1470-2045(21)00126-1
38,330	Conti DV, Darst BF, Moss LC, et al. Trans-ancestry genome-wide association meta-analysis of prostate cancer identifies new susceptibility loci and informs genetic risk prediction [published correction appears in Nat Genet. 2021 Jan 20;:]. Nat Genet. 2021;53(1):65-75. doi:10.1038/s41588-020-00748-0
22,113	Martin Merinero H, Subías M, Pereda A, et al. Molecular bases for the association of FHR-1 with atypical hemolytic uremic syndrome and other diseases. Blood. 2021;137(25):3484-3494. doi:10.1182/blood.2020010069
22,113	Martín Merinero H, Zhang Y, Arjona E, et al. Functional characterization of 105 factor H variants associated with aHUS: lessons for variant classification. Blood.2021;138(22):2185-2201. doi:10.1182/blood.2021012037
20,808	Bayona-Bafaluy MP, Montoya J, Ruiz-Pesini E. Oxidative phosphorylation system and cell culture media. Trends Cell Biol. 2021;31(8):618-620. doi:10.1016/j.tcb.2021.05.003
17,956	Hedrich UBS, Lauxmann S, Wolff M, et al. 4-Aminopyridine is a promising treatment option for patients with gain-of-function KCNA2-encephalopathy. Sci Transl Med. 2021;13(609):eaaz4957. doi:10.1126/scitranslmed.aaz4957

CIBERER Groups, Publications in 2021

Group Leader	Publications	Q1	D1	Institution - Center	Province
Alonso García de la Rosa, Francisco Javier	10	3	6	Instituto de Salud Carlos III	Madrid
Artuch Iriberri, Rafael	50	8	30	Fundación para la Investigación y Docencia Sant Joan de Deu	Barcelona
Ayuso, Carmen	30	6	14	Instituto de Investigación Sanitaria Fundación Jiménez Díaz	Madrid
Balcells Comas, Susanna	17	3	14	Universidad de Barcelona	Barcelona
Borrego, Salud	11	1	5	Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla	Sevilla
Botella Cubells, Luisa María	11	0	10	Agencia Estatal Consejo Superior de Investigaciones Científicas	Madrid
Bovolenta, Paola	5	3	5	Agencia Estatal Consejo Superior de Investigaciones Científicas	Madrid
Bueren, Juan Antonio	17	3	15	Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas (CIEMAT)	Madrid
Caballero Molina, María Teresa	25	4	15	Servicio Madrileño de Salud	Madrid
Carracedo, Ángel	19	5	15	Universidad de Santiago de Compostela	A Coruña
Castaño González, Luis	23	0	18	Asociación Instituto de Investigación Sanitaria de Biocruces	Vizcaya
Corral de la Calle, Javier	28	4	20	Fundación para la Formación e Investigación Sanitarias de la Región de Murcia (FFIS)	Murcia
Cuezva, José M.	3	2	3	Universidad Autónoma de Madrid	Madrid
Dalmau Obrador, Josep	9	9	9	Instituto de Investigaciones Biomédicas August Pi i Sunyer	Barcelona
del Río Nechaevsky, Marcela	12	4	8	Universidad Carlos III	Madrid
Dopazo Blázquez, Joaquín	14	3	12	Fundación Pública Andaluza Progreso y Salud	Sevilla
Fernández Fraga, Mario	6	2	5	Agencia Estatal Consejo Superior de Investigaciones Científicas	Asturias
Fillat, Cristina	17	1	9	Instituto de Investigaciones Biomédicas August Pi i Sunyer	Barcelona
Gallano Petit, Pía	22	1	13	Instituto de Investigación del Hospital de la Santa Cruz y San Pablo	Barcelona

Group Leader	Publications	Q1	D1	Institution - Center	Province
Gallardo Vigo, Eduardo	24	8	15	Instituto de Investigación del Hospital de la Santa Cruz y San Pablo	Barcelona
Gratacòs, Eduard	56	19	33	Hospital Clínico y Provincial de Barcelona	Barcelona
Grau Junyent, Josep María	13	2	10	Universidad de Barcelona	Barcelona
Lapunzina Badía, Pablo D	27	6	12	Servicio Madrileño de Salud	Madrid
López Granados, Eduardo	14	3	8	Fundación para la Investigación Biosanitaria en Andalucía Oriental (FIBAO)	Granada
Marfany Nadal, Gemma	5	1	4	Universidad de Barcelona	Barcelona
Marina Moreno, Alberto	13	7	11	Agencia Estatal Consejo Superior de Investigaciones Científicas	Madrid
Martí Seves, Ramón	10	0	7	Fundación Hospital Universitario Vall d´Hebron - Institut de Recerca (VHIR)	Barcelona
Martín Casanueva, Miguel Ángel	20	1	8	Servicio Madrileño de Salud	Madrid
Medina Torres, Miguel Ángel	12	3	8	Universidad de Málaga	Málaga
Millán Salvador, José María	21	3	13	Fundación para la Investigación del Hospital Universitario y Politécnico la Fe de la Comunidad Valenciana	Valencia
Montoliu José, Lluís	7	0	4	Agencia Estatal Consejo Superior de Investigaciones Científicas	Madrid
Moreno Galdó, Antonio José	8	0	1	Fundación Hospital Universitario Vall d´Hebron - Institut de Recerca (VHIR)	Barcelona
Moreno Pelayo, Miguel Ángel	8	3	4	Servicio Madrileño de Salud	Madrid
Mulero Méndez, Víctor	7	4	7	Universidad de Murcia	Murcia
Nieto Toledano, María Ángela	1	0	0	Agencia Estatal Consejo Superior de Investigaciones Científicas	Alicante
Palacín , Manuel	13	0	9	Fundación privada Instituto de Recerca Biomédica (IRB-Barcelona)	Barcelona
Palau Martínez, Francesc	12	1	10	Fundación para la Investigación y Docencia Sant Joan de Deu	Barcelona
Pallardó Calatayud, Federico	13	2	9	Universidad de Valencia	Valencia
Pérez González, Belén	10	2	7	Universidad Autónoma de Madrid	Madrid
Pérez Jurado, Luis	15	5	10	Universidad Pompeu Fabra	Barcelona

Group Leader	Publications	Q1	D1	Institution - Center	Province
Perona Abellón, Rosario	8	4	7	Agencia Estatal Consejo Superior de Investigaciones Científicas	Madrid
Puig Sardà, Susana	43	15	29	Hospital Clínico y Provincial de Barcelona	Barcelona
Pujol Onofre, Aurora	18	12	17	Fundación IDIBELL	Barcelona
Ribes, Antonia	15	2	6	Hospital Clínico y Provincial de Barcelona	Barcelona
Robledo Batanero, Mercedes	30	12	26	Fundación Centro Nacional de Investigaciones Oncológicas	Madrid
Rodríguez de Córdoba, Santiago	8	3	7	Agencia Estatal Consejo Superior de Investigaciones Científicas	Madrid
Ruiz Pérez, Víctor Luis	6	2	3	Agencia Estatal Consejo Superior de Investigaciones Científicas	Madrid
Ruiz Pesini, Eduardo	11	3	6	Universidad de Zaragoza	Zaragoza
Salido, Eduardo	7	2	6	Fundación Canaria Instituto de Investigación Sanitaria de Canarias	Las Palmas de Gran Canaria
Santos Ocaña, Carlos	9	0	5	Universidad Pablo de Olavide	Sevilla
Sanz, Pascual	6	0	6	Agencia Estatal Consejo Superior de Investigaciones Científicas	Madrid
Serratosa, José	4	1	4	Instituto de Investigación Sanitaria Fundación Jiménez Díaz	Madrid
Sevilla Mantecón, María Teresa	16	2	10	Fundación para la Investigación del Hospital Universitario y Politécnico la Fe de la Comunidad Valenciana	Valencia
Surrallés, Jordi	8	1	3	Instituto de Investigación del Hospital de la Santa Cruz y San Pablo	Barcelona
Varela Nieto, Isabel	13	4	8	Agencia Estatal Consejo Superior de Investigaciones Científicas	Madrid
Webb, Susan	19	1	10	Instituto de Investigación del Hospital de la Santa Cruz y San Pablo	Barcelona

Patents owned by CIBER 2021

Applications

- P202130576. Treatment of Charcot-Marie-Tooth disease.
- PCT/ES2021/070343- Lentiviral vectors and their uses.
- EP21382363.6 In vivo lentiviral gene therapy for the treatment of primary hyperoxaluria type 1.
- EP21382173. Methods for the measurement of protein c and activated protein c.

Clinical Guidelines 2021

- Consensus on treatment goals in hereditary angioedema: A global Delphi initiative.
- Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE): Position paper on diagnosis, prognosis, and treatment by the MNGIE International Network.
- International consensus guidelines for phosphoglucomutase 1 deficiency (PGM1-CDG): Diagnosis, follow-up, and management.
- Genetics and epidemiology of aniridia: Updated guidelines for genetic study.
- The first European consensus on principles of management for achondroplasia.
- A standard of care for individuals with PIK3CA-related disorders: An international expert consensus statement.
- Screen Time and Bone Status in Children and Adolescents: A Systematic Review.
- Assessment and management of disease burden and quality of life in patients with hereditary angioedema: a consensus report.

- Corticotroph tumor progression after bilateral adrenalectomy (Nelson's syndrome): systematic review and expert consensus recommendations.
- Perspective of the GEMSTONE Consortium on Current and Future Approaches to Functional Validation for Skeletal Genetic Disease Using Cellular, Molecular and Animal-Modeling Techniques.
- The association of telomere length with substance use disorders: a systematic review and meta-analysis of observational studies.
- Cycloid psychosis as a psychiatric expression of anti-NMDAR encephalitis. A systematic review of case reports accomplished with the authors' cooperation.
- International BEAT-PCD consensus statement for infection prevention and control for primary ciliary dyskinesia in collaboration with ERN-LUNG PCD Core Network and patient representatives.
- Consensus recommendations on flow cytometry for the assessment of inherited and acquired disorders of platelet number and function: Communication from the ISTH SSC Subcommittee on Platelet Physiology.
- Current Practices on Diagnosis, Prevention and Treatment of Post-Transplant Lymphoproliferative Disorder in Pediatric Patients after Solid Organ Transplantation: Results of ERN TransplantChild Healthcare Working Group Survey.
- Social Camouflaging in Females with Autism Spectrum Disorder: A Systematic Review.
- Guidelines of the Spanish ITP Group for the diagnosis, treatment and follow-up of patients with immune thrombopenia.

CIBERES

Respiratory Diseases

Presentation by the scientific director

Ferran Barbé Illa

Dear Friends:

Once again this year we present in the following report the most relevant data of the CIBERES scientific activity of 2021.

First of all, allow me to welcome Esther Barreiro, Jaime Corral and Julio Cortijo who in 2021 were appointed by the CIBER Governing Board as heads of their respective groups. I am sure that they will continue the excellent research work of their predecessors, Joaquín Gea, Fernando Masa and Esteban Morcillo, whom I would like to thank for their work at CIBERES over the last few years.

2021 was a year still very marked by the impact of the COVID pandemic-both in terms of the healthcare activity of clinical groups and a large part of the research activity. I want to point out that CIBERES successfully completed the CIBERESUCICOVID project led by Antoni Torres. The results were presented at a Conference that took place at the ISCIII last December. I would like to congratulate Dr. Torres for his excellent management of the project and all the researchers, managers and institutions involved. The volume and quality of the results obtained speak for themselves of the success of the project and its management model.

Nevertheless, aside from COVID-19, CIBERES carried out a high level of scientific activity in the rest of its lines of research, with very notable results in some of them. I encourage

you to review the news published on our website where you will find a significant number of examples of the excellent results achieved by our researchers.

Allow me to end with two painful goodbyes. First of all, I would like to remember Vicente Ausina, promoter of Tuberculosis research in our country, coordinator of the Tuberculosis research line and member of the CIBERES steering committee. Secondly, Manuel Sánchez Delgado, Manager of CIBER, an example of professionalism and effort- without him CIBER would not be understood as it is now. His work leaves a huge mark on us- both professionally and personally. May they rest in peace.

Warm greetings and my best wishes to all.

PROGRAMS

PROGRAM 1

Chronic respiratory diseases

COORDINATOR:
José Luis López Campos

1

ASTHMA

This research line has continued working on the development of its strategic project:

Databases with which they are working:

- MEGA study: 530 asthma patients with a follow-up of around 4 years.
- Asthma patients treated with biologics with a 4-year follow-up (545 patients).

Publications (most relevant):

- Rial MJ, Valverde M, Del Pozo V, González-Barcala FJ, et al. Clinical characteristics in 545 patients with severe asthma on biological treatment during the COVID-19 outbreak. J Allergy Clin Immunol Pract. 2021 Jan;9(1):487-489.e1.

- Rial MJ, Álvarez-Puebla MJ, Arismendi E, et al. Clinical and inflammatory characteristics of patients with asthma in the Spanish MEGA project cohort. Clin Transl Allergy. 2021 Mar;11(1):e12001.
- Baptista-Serna L, Rodrigo-Muñoz JM, Mínguez P, et al. Anxiety and body mass index affect asthma control: data from a prospective Spanish cohort. J Allergy Clin Immunol Pract. 2022 Mar;10(3):863-866.e1.
- Rodrigo-Muñoz JM, Cañas JA, Sastre B, et al. Role of miR-185-5p as modulator of periostin synthesis and smooth muscle contraction in asthma. J Cell Physiol. 2022 Feb;237(2):1498-1508.

2 COPD

During 2021, the CIBERES COPD strategic line has continued with the development of each of the project's work packages. The DELICATO cohort finished according to schedule, which allowed progress in the final processing of the line of biomarkers. Specifically, an article has been published on cellular aging in COPD patients, both young and old, and three more articles on proteomics on the stable phase of the frequent exacerbator phenotype and the findings during exacerbation and on the analysis of the transcriptomic fingerprint of the eosinophilic phenotype are in the final drafting stage. A proprietary cancer screening cohort has been created of patients with COPD-emphysema, with 1,600 cases collected, and progress has been made in the in vitro and in vivo experimental identification of markers of damage caused by tobacco smoke.

In COPD activity and its relationship with the microbiome, azithromycin has been studied to improve the control of exacerbations. In addition, the lung microbiome by bronchoalveolar lavage and the microbiome of the oropharynx have been evaluated.

As regards the analysis of the different trajectories of pulmonary function, analyses have been completed on cohorts of patients with various publications. The observations of previous projects of other national and European cohorts have been validated and the clinical and biological characteristics of young COPD patients have been described. Finally, the

identification of biomarkers associated with clinical profile and therapeutic response has completed its recruitment and proteomics studies are being carried out.

3 LUNG CANCER

Work has continued in the lung cancer and COPD research lines. Various original works have been published in Q1 journals throughout 2021. To be highlighted is the work identifying the role of systemic oxidative and antioxidant markers, which are differentially expressed in these patients with chronic respiratory diseases, and which are, therefore, implicated in the development of lung cancer.

Work has continued on the SAIL and SAILS studies of nocturnal hypoxia and lung cancer. The TRAIL 1 project on radiomics and response to immunotherapy in lung cancer and projects related to metabolomics and lung cancer are ongoing. Regarding biomarkers, the REFINE project integrated within the SEPAR oncology integrated research program consisting of a register of the use of the EarlyCDT autoantibody test in the characterization of pulmonary nodules is ongoing.

Several manuscripts related to these works have been published in Q1 journals.

4 SLEEP

As in the previous year, work has continued on the key objectives of the proposal, combining experimental and clinical research:

- Characterization of the phenotypes of sleep-disordered breathing through the use of Big Data and biomarkers.
- Implementation of telemedicine and simplified diagnostic systems, an innovative model for personalized care for patients with sleep apnea.
- Study of the impact of sleep-disordered breathing at a systemic level and on diseases related to aging such as cancer, alterations and the molecular mechanisms involved.
- Relationship between sleep disturbances and chronicity.

PROGRAM 2

Infectious respiratory diseases

COORDINATOR:
Antoni Torres Martí

1 TUBERCULOSIS

40 new publications related to the different investigations of this research line have been presented.

9 new projects: i) tuberculosis and COVID-19: genome sequencing-based surveillance; immune response. ii) tuberculosis: control through genomic epidemiology; biomarkers to personalize treatments; susceptibility according to gender; response to host-directed therapies.

7 clinical trials: MTBVAC in adults with and without latent tuberculosis infection, safety and immunogenicity in neonates; efficacy of Nyaditum Resae against tuberculosis and COVID-19, impact on microbiota; short regimens against mycobacteria; NSAIDs against tuberculosis.

PNEUMONIA

During the year 2021, part of the research of this Line has been directed towards the COVID pandemic to which it has contributed with numerous publications improving the knowledge of the disease, the identification of markers, the design of new therapies (monoclonal antibodies), management and treatment and immunity after vaccination.

In addition, the research of the line has generated different collaborative publications.

Thus, biomarkers have been identified associated with viral infection by transcriptomics and also markers associated with the development of cardiovascular events in patients hospitalized for PDA.

Pneumococcal vaccination against 13 serotypes (PCV13) in children has reduced invasive and non-invasive disease caused by these serotypes in children and adults. The long-term impact with decreased antibiotic resistance has also been analyzed.

Novel results have been generated around the microbiome and the importance of biofilms in patients with bronchiectasis, as well as new therapies with Genetically Modified Organisms (GMOs) and antimicrobial synergies against biofilms.

We have participated in the preparation of national and international guidelines for the management of pneumonia in the general population, in specific pathologies (influenza, aspergillosis) or in special situations (nebulized antibiotics). In addition, scores have been validated to predict special situations.

2 doctoral theses have been defended.

3

NEW THERAPEUTIC TARGETS

Dissemination: 42 publications and 25 communications.

Defense of 3 doctoral theses.

Application for 2 patents.

Milestones:

- Characterization of emerging serotypes, resistance patterns, vaccine and antimicrobial candidates against pneumococcus.
- Patterns of glycosylation and molecular recognition of carbohydrates present in pathogens, serum exosomes or other cell surfaces, by receptors and lectins. Residue-specific identification method for galectin-ligand interactions.
- Potentiation of the immune response of the DTP vaccine mediated by TB vaccines. New routes of administration of attenuated vaccines against TB, and their application for protection against TB and asthma.
- Association of the positive effect of treatment with azithromycin in the control of COPD exacerbations with replacement of circulating opportunistic pathogens and increased resistance to macrolides.
- Haemophilus parainfluenzae emerges as a reservoir and possible source of transmission of antibiotic resistance.
- Development of an animal model of COPD frequent exacerbator.
- Molecular bases that control epithelial transition invasion-biofilm formation during persistent infection by Haemophilus influenzae.

PROGRAM 3

Diffuse respiratory diseases

COORDINATOR:
Francisco Pérez Vizcaino

PULMONARY HYPERTENSION, ACUTE LUNG INJURY AND PULMONARY FIBROSIS.

- The CIBERESUCICOVID study, a multicenter, observational, prospective/retrospective strategic study that has followed a cohort of more than 8,000 patients with COVID-19 and has collected thousands of biological samples.
- Metabolomic changes in COVID-19.
- Clinical and biological prognostic markers and radiological characteristics in COVID-19.
- Role of IL-6 in intrapulmonary shunt in COVID-19
- MicroRNAs in COVID-19.
- The liver-lung axis in ARDS.
- New models of ARDS and pneumonia.
- Cell therapy in acute lung injury in animal models.
- Machine learning in ARDS classification.
- Early corticosteroids and COVID-19 mortality.
- Role of guanylate cyclase stimulators in the damage induced by tobacco smoke.

- Exercise is feasible, safe, and effective in pulmonary arterial hypertension.
- Severe vitamin D deficiency predicts poor endothelial function and poor therapeutic response to phosphodiesterase inhibitors in PAH.
- Risk associated with COVID-19 in patients with pulmonary hypertension.
- Circulating markers of pulmonary hypertension.
- Transcriptome of cationic channels in lungs of patients with pulmonary hypertension.
- Predictors of response to phosphodiesterase inhibitors in pulmonary arterial hypertension.
- Characterization of endothelial cells in patients with chronic thromboembolic pulmonary hypertension.
- 5th Research Meeting on Pulmonary Hypertension (Ciberes), online, March 2021.
- Start-up of the Biobank of tissues from animal models of pulmonary hypertension.
- Role of IL11 in pulmonary hypertension.
- MicroRNAs in plasma in patients with chronic thromboembolic pulmonary hypertension.
- Cellular senescence in pulmonary hypertension and pulmonary fibrosis.
- Role of JAK/STAT in diffuse interstitial diseases.
- MUC1 in pulmonary fibrosis.
- IL-8 as a marker of silicosis and predictor of mortality.
- Awarded: FIS PI21/01287 Looking for predictive factors and preventive Measures of post-covid19 interstitial lung sequelae (POST-COVID)
- Inclusion in CIBERES of new ILD researchers of recognized prestige and high H index through the CB21/06/00007 group recently incorporated into the consortium; Claudia Valenzuela, Diego Castillo, M.A. Pujana.
- 6 outstanding original articles in which different CIBERES groups of the Pulmonary Fibrosis Program participate, 2 of them in collaboration CIBERES-CIBERER. All of them in Q1.
- Funding obtained to carry out the FIBRO-COVID CLINICAL TRIAL, a randomized, double-blind, national multicenter clinical trial to evaluate the effect of Pirfenidone as prevention of persistent pulmonary fibrosis in those patients who 1-2 months after discharge (after suffering from severe pneumonia due to covid) present more than 5% pulmonary fibrosis in chest HRCT + restrictive alteration in PFTs.

PROGRAM 4

Training

COORDINATOR:
Laura Amado

Despite the ongoing pandemic, the actions carried out by the CIBERES Training Program in 2021 have increased compared to the previous year. In the development and mobility subprogram, one intraCIBER stay grant has been awarded, six registration grants for online training courses, and two congress registration grants (one online, one face-to-face) in which results of CIBER investigations were presented.

Within the subprogram for promoting interest in respiratory research, the CIBERES Training Sessions were held in virtual format on October 26 and 27 in morning and afternoon sessions. In this edition, the number of attendees increased compared to the previous year, and the number of communications received also increased, taking into account the impact of the pandemic on the scientific activity of the clinical-care groups.

Number of people registered: 166 researchers.

Number of communications received and evaluated:53.

Number of oral communications selected: 28.

Number of posters: 25.

The Conference program, as well as the link to the online sessions and posters, is accessible through the Conference website: https://jornadasdocencia.ciberes.org/

As in previous years, all the abstracts evaluated have been published in the Congress Supplement of the journal Archivos de Bronconeumología. The publication is available at: https://www.archbronconeumol.org/es-vol-57-num-sc2-sumario-X0300289621X00C20

On the other hand, the remodeling of numerous events from face-to-face to online format has meant a drastic reduction in the number of endorsements requested, which has resulted in a total of 6 endorsements, compared to 10 granted in the previous year.

Finally, within the framework of the Training Sessions, a call was launched for the organization and delivery of training workshops to create a CIBERES training program of its own. 2 were offered during the Conference (Pre-clinical in vivo models of COPD and IPF; and a high-impact scientific publication as the culmination of the scientific cycle: necessity and relevance). The remaining 6 will be offered during the first semester of 2022. The calendar can be consulted on the CIBERES Web Agenda. They are open to the public, and registration must be made by e-mail to formacion@ciberes.org.

PLATFORMS

PLATAFORM 1

Pulmonary Biobank

In addition to the CIBERES Pulmonary Biobank Platform's own activity, 4,426 donations have been collected with an accumulation of 133,241 samples between tissue and blood products. The Pneumology, Anatomical Pathology, Thoracic Surgery and IC units of our hospital and 10 other hospitals throughout the Spanish territory participate in the collection of samples: (https://biobancopulmonar.ciberes.org/). This has allowed the development of more than 22 projects in the field of respiratory diseases.

Participation in the following scientific events:

Cristina Villena Portella. 4th Virtual Congress of Clinical Biochemistry, VIRTUALAB 2021. Impact of biobanks on the reproducibility of analytical data in research. Guest Speaker. Virtual Conference. 1-13 November,2021. Organizing entity: Fundación Bioquímica Argentina.

"Biobanks and Biomodels Platform of the Instituto de Salud Carlos III" **Cristina Villena Portella**. XIV CIBERES Training Conference 2021. 27-28 October, 2021. Online.

Research Projects:

Biobanks and Biomodels Platform (PT20). ISCIII Platforms to support R&D&I in Biomedicine and Health Sciences of the Strategic Action in Health 2017-2020. PT20/00118. FIS (ISCIII). 2021- 2023. PI: **Cristina Villena Portella**. Granted: 132.825€.

Coordination of the Biobanks Platform (PT17). ISCIII Platforms to support R&D&I in Biomedicine and Health Sciences of the Strategic Action in Health 2017-2020. PT17/0015/0001. FIS (ISCIII). 2018- 2021. PI: **Cristina Villena Portella**. Granted: 597.300€.

Coordination of Work Package 4- Definition of procedures for handling biological samples and biobank of the IMPaCT Predictive Medicine Program Cohort. 2021- 2023. PI: **Marina Pollán Santamaría** (CIBERESP). Granted: 14.000.000€.

Extraordinary Activities:

Development and implementation of the Transition Plan for the coordination of the Biobanks Platform (PT17). ISCIII Platforms to support R&D&I in Biomedicine and Health Sciences of the Strategic Action in Health 2017-2020. PT17/0015/0001, to the new Biobanks and Biomodels Platform (PT20).

Design, launch and management of a cross-cutting action of the CIBER, coordinated by Cristina Villena, made up of teams from 4 thematic areas of the CIBER (CIBERES, CIBERER, CIBER-BBN and CIBERONC) financed by the new Platform of Biobanks and Biomodels of the Instituto de Salud Carlos III (ISCIII), for the (i) creation of a **CIBER catalogue of biological samples and biomodel services** available to R&D+i that can be consulted, and with a common integrated management to be able to develop a CIBER Virtual Biobank; (ii) identification of new biomodels existing in the CIBER, as well as technical capacities and services that could be of interest, which can also be offered to researchers external to the institution itself; and (iii) creation of alliances with other similar structures to harmonize procedures and processes in the provision of research services.

Participation in the piloting working group for the start of recruitment of participants in the IMPaCT Predictive Medicine Program Cohort.

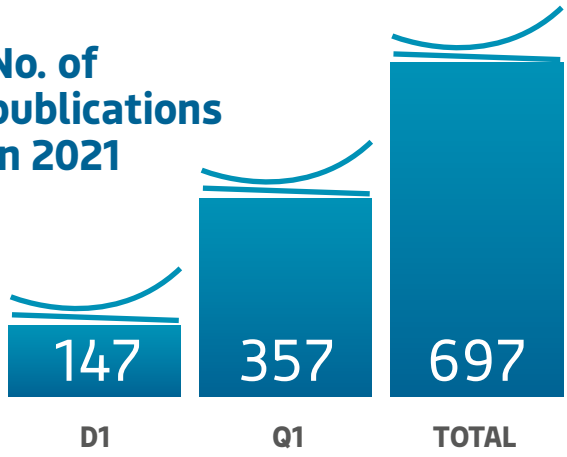
Doctoral Theses directed:

Optimization of tissue samples for the development and validation of disease biomarkers: OPTIMARK project. University of the Balearic Islands. Doctoral candidate: **Esteva Socías, Margalida**. Director: **Cristina Villena Portella**; Antònia Obrador Hevia.

SCIENTIFIC PRODUCTION

Publications

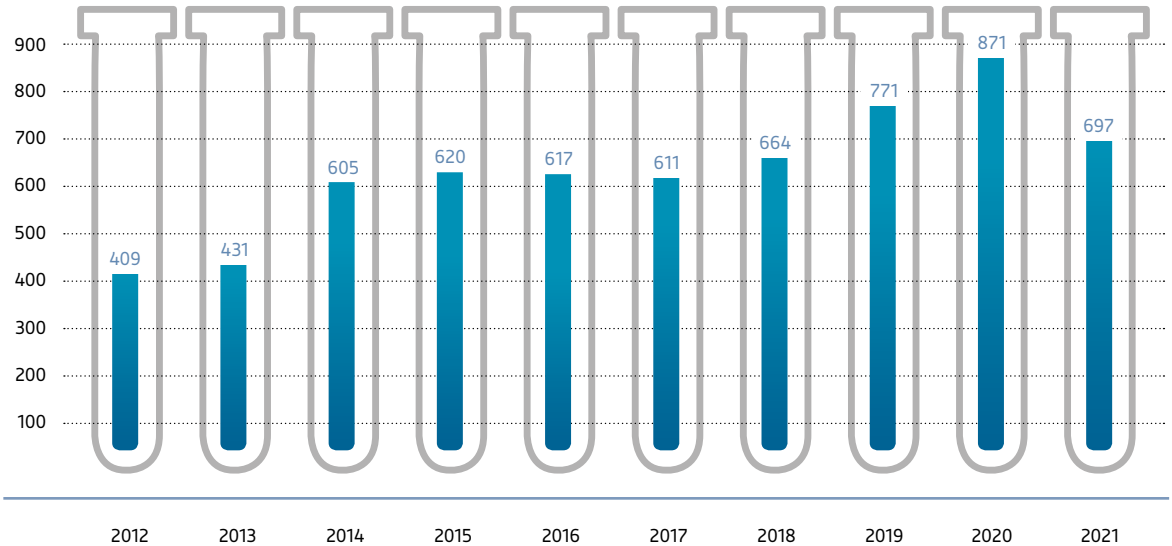
No. of publications in 2021



Collaborations

*Among various thematic areas

Evolución de las Publications



10 most relevant publications by impact factor

FI	Publication
56,270	Jimenez D., Agusti A., Tabernero E., Jara-Palomares L., Hernando A., Ruiz-Artacho P. et al. Effect of a Pulmonary Embolism Diagnostic Strategy on Clinical Outcomes in Patients Hospitalized for COPD Exacerbation: A Randomized Clinical Trial. JAMA - Journal of the American Medical Association. 2021;326(13):1277-1285.
52,320	Torres A., Cilloniz C., Niederman M.S., Menendez R., Chalmers J.D., Wunderink R.G. et al. Pneumonia. Nature Reviews Disease Primers. 2021;7(1).
44,180	Iranzo A., Fairfoul G., Ayudhaya A.C.N., Serradell M., Gelpi E., Vilaseca I. et al. Detection of α-synuclein in CSF by RT-QuIC in patients with isolated rapid-eye-movement sleep behaviour disorder: a longitudinal observational study. The Lancet Neurology. 2021;20(3):203-212.
39,890	Perez-Lopez A., Irwin A., Rodrigo C., Prat-Aymerich C. Role of C reactive protein and procalcitonin in the diagnosis of lower respiratory tract infection in children in the outpatient setting. The BMJ. 2021;373(11).
38,330	Lopez M.G., Chiner-Oms A., Garcia de Viedma D., Ruiz-Rodriguez P., Bracho M.A., Cancino-Munoz I. et al. The first wave of the COVID-19 epidemic in Spain was associated with early introductions and fast spread of a dominating genetic variant. Nature Genetics. 2021;53(10):1405-1414.
30,700	Agusti A., Torres F., Faner R. Early treatment with inhaled budesonide to prevent clinical deterioration in patients with COVID-19. The Lancet Respiratory Medicine. 2021.
24,090	Clemente-Moragon A., Martinez-Milla J., Oliver E., Santos A., Flandes J., Fernandez I. et al. Metoprolol in Critically Ill Patients With COVID-19. Journal of the American College of Cardiology. 2021;78(10):1001-101.
22,110	Martin Merinero H., Subias M., Pereda A., Gomez-Rubio E., Juana Lopez L., Fernandez C. et al. Molecular bases for the association of FHR-1 with atypical hemolytic uremic syndrome and other diseases. Blood. 2021;137(25):3484-3494.
21,400	Casas-Recasens S., Noell G., Mendoza N., Lopez-Giraldo A., Garcia T., Guirao A. et al. Lung DNA Methylation in Chronic Obstructive Pulmonary Disease: Relationship with Smoking Status and Airflow Limitation Severity. American Journal of Respiratory and Critical Care Medicine. 2021;203(1):129-134.
21,400	López-Campos JL, Fernández-Villar A, Ruano-Ravina A. Triple Therapy Trials for COPD: Methodological Considerations in the Mortality Effect. American journal of respiratory and critical care medicine. 2021.

CIBERES Groups, Publications 2021

Group Leader	Publications	Q1	D1	Institution - Center	Province
Agusti García Navarro, Alvar	63	32	19	Hospital Clínico y Provincial de Barcelona	Barcelona
Almendros López, Isaac	8	7	2	Universidad de Barcelona	Barcelona
Álvarez Martínez, Carlos José	7	3	2	Servicio Madrileño de Salud	Madrid
Ardanuy Tisaire, María Carmen	14	7	1	Fundación IDIBELL	Barcelona
Barbé Illa, Ferrán	52	25	9	Instituto de investigación Biomédica de Lleida. Fundación Dr. Pifarre	Lleida
Barberá Mir, Joan Albert	26	15	8	Hospital Clínico y Provincial de Barcelona	Barcelona
Barreiro Portela, Esther	25	10	3	Consorci Mar Parc Salut de Barcelona	Barcelona
Blanch Torra, Lluis	38	29	8	Corporación Sanitaria Parc Taulí	Barcelona
Cardona Iglesias, Pere Joan	11	8	3	Fundación Instituto de Investigación Germans Trias i Pujol	Barcelona
Corral Peñafiel, Jaime	14	2	0	Fundación para la Formación y la Investigación de los Profesionales de la Salud (FUNDESALUD)	Cáceres
Cortijo Gimeno, Julio	12	7	4	Universidad de Valencia	Valencia
Fernandez Muñoz, Ángel Esteve	18	10	4	Fundación IDIBELL	Barcelona
García Río, Francisco José	33	5	2	Servicio Madrileño de Salud	Madrid
Garmendia García, Juncal	10	7	2	Agencia Estatal Consejo Superior de Investigaciones Científicas	Madrid
Jiménez Castro, David	33	21	9	Servicio Madrileño de Salud	Madrid
López-Campos Bodineau, José Luis	41	11	6	Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla	Sevilla
Lorente Balanza, José Ángel	21	12	7	Servicio Madrileño de Salud	Madrid
Martín Montañés, Carlos	14	9	2	Universidad de Zaragoza	Zaragoza
Monsó Molas, Eduard	15	6	2	Corporación Sanitaria Parc Taulí	Barcelona
Mullol Miret, Joaquim	34	18	13	Hospital Clínico y Provincial de Barcelona	Barcelona
Muñiz Albaiceta, Guillermo	14	9	3	Fundación para la Investigación e innovación Biosanitaria en el Principado de Asturias (FINBA)	Asturias

Group Leader	Publications	Q1	D1	Institution - Center	Province
Muñoz Gall, Xavier	67	25	13	Fundación Hospital Universitario Vall d´Hebron - Institut de Recerca (VHIR)	Barcelona
Muñoz García, Patricia	57	28	12	Servicio Madrileño de Salud	Madrid
Peces Barba Romero, Germán	16	7	3	Instituto de Investigación Sanitaria Fundación Jiménez Díaz	Madrid
Pérez Vizcaíno, Francisco	9	7	6	Universidad Complutense de Madrid	Madrid
Pozo Abejón, Mª Victoria del	19	13	4	Instituto de Investigación Sanitaria Fundación Jiménez Díaz	Madrid
Relló Condomines, Jordi	43	17	11	Fundación Hospital Universitario Vall d´Hebron - Institut de Recerca (VHIR)	Barcelona
Ruiz Cabello Osuna, Jesús	14	12	3	CIC biomaGUNE	Guipúzcoa
Torres Martí, Antoni	76	42	21	Hospital Clínico y Provincial de Barcelona	Barcelona
Villar Hernández, Jesús	42	23	8	Fundación Canaria Instituto de Investigación Sanitaria de Canarias	Palmas, Las
Yuste Lobo, José Enrique	7	4	2	Instituto de Salud Carlos III	Madrid

Patents owned by CIBER 2021

Applications

- P202130180 Date 03/03/2021 Biomarkers for the prognosis of patients who have suffered an aneurysmal subarachnoid hemorrhage (SAH) Holders: FIBHULP y CIBER.
- EP21382403.0 05/05/2021 Carvacrol as disinfectant against legionell.
- 26/07/2021 In vitro method for prognosis of patientes suffering from sepsis.
- PCT/EP2021/070131 19/07/2021 In vitro method for predicting mortality in COVID-19 patients. Titulares: IECSCYL-IBSAL, David J. Kelvin, CIBER, UVA, GRS, IDIBAPS, FBG, HCB.

Licensed

- EP18382403.6, PCT/EP2019/064885 In vitro method for the diagnosis or detection of non-tuberculous mycobacteria.

Clinical Guidelines 2021

- Spanish COPD Guidelines (GesEPOC) 2021 Update Diagnosis and Treatment af COPD Exacerbation Syndrome.
- Spanish COPD Guidelines (GesEPOC) 2021: Updated Pharmacological treatment of stable COPD.
- COVID-19 pandemic: Practical considerations on the organization of an allergy clinic-An EAACI/ARIA Position Paper.
- Treatment of Community-Acquired Pneumonia in Immunocompromised Adults: A Consensus Statement Regarding Initial Strategies.
- Clinical Practice Guideline recommendations on examination of the upper airway for adults with suspected obstructive sleep apnoea-hypopnoea syndrome.
- Validation of the DECA criteria for allergic conjunctivitis severity and control.
- Position statement and recommendations on climate change and respiratory health 2021.
- Recommendations for the treatment of anti-melanoma differentiation associated gene 5-positive dermatomyositis-associated rapidly progressive interstitial lung disease.


CIBERESP
Epidemiology
and Public Health

Presentation by the scientific director

Marina Pollán Santamaría

In 2021, a year marked by the pandemic, the CIBERESP groups have continued to provide information and new evidence on COVID-19. We highlight the collaboration with the Area of Respiratory Diseases in the CIBERPOSTCOVID project, in which CIBERESP leads two work packages aimed at proposing an operational definition of what has come to be called long-COVID or persistent COVID, and the MIND-COVID project, which provides information on the impact of the pandemic on the mental health of health professionals and patients. In addition, in the summer of 2021, after the approval of the Strategic Plan, we began the implementation of the Precision Medicine infrastructure associated with Science and Technology (IMPaCT), in which CIBERESP plays a relevant role coordinating the creation of the IMPaCT cohort, in which more than 100 researchers from all over the country collaborate actively through the working groups created to develop this important infrastructure. Regarding the work carried out in the CIBERESP Programs, in the Chronic Diseases Program a new CIBER-Spanish Association Against Cancer agreement will allow the development of an interactive website that provides up-to-date information on the main indicators of this disease in our country in collaboration with the Cancer Registry Network (REDECAN). In the Program for the Prevention, Surveillance and Control of Communicable Diseases (PREVICET), we highlight the determination of the effectiveness of influenza vaccines, as well as of the new vaccines against SARS-CoV-2 and the research carried out in emerging diseases. In the Biological and Behavioral Determinants of Communicable Diseases Program (DAPET), research has also been focused on the pandemic, on aspects of molecular epidemiology, modeling of viral dispersion and impact on vulnerable population. The Social Determinants of Health Program has been providing, information on gender violence generating a Report

on the Impact of the pandemic on this relevant public health problem. In the Epidemiology and Prevention in Environmental and Occupational Health Program, the Children and Environment subprogram (INMA) has continued to contribute with a significant scientific production, initiating new lines of research. The Evaluation of Healthcare Services Program has played an important role in the aforementioned CIBERPOSTCOVID project, and has launched a new subprogram on Evaluation of the effectiveness, costs and quality of health services. In the Clinical Epidemiology Program, the MAPAC subprogram has created a collaborative network of NHS hospitals to develop procedural protocols aimed at improving healthcare and clinical practice. These last two Programs have been preparing their merger which will be effective as of 2022, developing a joint plan. From the BIBLIOPRO Platform we highlight the organization of an international Webinar on Self-reported Health in clinical practice. Finally, the Training Program has maintained mobility actions in 2021 to promote collaboration with national and international groups.

PROGRAMS

PROGRAM 1

Epidemiology and control of chronic diseases

COORDINATOR:
Mª José Sánchez Pérez

1

MCC-SPAIN

The MCC-Spain Project, led by Manolis Kogevinas and Marina Pollán, is being used to study prognostic factors in patients with colorectal, breast or prostate cancer. The control groups have been contacted again to carry out 2 surveys: 1) control cohort follow-up survey, and 2) a survey framed within the CONTENT project (financed by La Caixa, PI: Manolis Kogevinas) on COVID, mental health and social inequalities, also collecting data on other variables, such as vaccination, environmental exposures and lifestyles.

In 2021, 17 scientific articles have been published in indexed journals, some in the SToP and PRACTICAL consortia, and another 2 from the CONTENT/COVICAT project.

2 GEN-RISK

The Genrisk project, led by Victor Moreno, relies heavily on the MCC-Spain study. In 2021, GSA array genotyping (660945 SNPs) of a total of 5,188 samples from the MCC-Spain consortium was completed. In addition, the GWAS database of the entire consortium has been generated, with a total of 7,103 samples and is now in the process of imputing the SNPs with the TOPMED reference panel, which will allow obtaining more than 30 million SNPs useful for genetic analysis. A training workshop on SNP imputation was held in May, with more than 100 participants.

Epidemiological and genetic data were obtained from the UK Biobank to validate the results obtained in the studies carried out in Spain and to develop instruments for Mendelian Randomization analysis (MR).

The remote computing and analytical platform is underway to facilitate the genetic and statistical analysis of all the groups. At: https://remote.genrisk.org/jhub

3 EPIDEMIOLOGICAL SURVEILLANCE OF CANCER

The Epidemiological Surveillance of Cancer subprogram, coordinated by Mª José Sánchez and Pablo Fernández, has signed, through CIBER, an AECC-CIBER collaboration agreement for the development of the Cancer Epidemiological Information System in Spain (SIEC), in collaboration with the Spanish Network of Cancer Registries (REDECAN).

In 2021, the methodology used to estimate the incidence of cancer in Spain, based on mortality data and the mortality/incidence ratio of data available in population-based cancer registries, was validated and published, and the data on socioeconomic inequalities in the incidence of colorectal, lung and breast cancer in Spain have also been analyzed and published. Men of lower socioeconomic status, compared with those of higher socioeconomic status, had a higher risk of lung cancer (weak evidence) and a lower risk of colorectal cancer. Women of lower socioeconomic status, compared

with those of higher socioeconomic status, had a lower risk of breast cancer.

Two training workshops were held on advanced survival analysis and on analysis of ad hoc processes for Public Health, and the website of the subprogram has been published (https://vica-ciberesp.isciii.es/).

6 collaborative scientific articles have been published in indexed journals and four communications have been presented at scientific congresses (2 at national congresses and 2 at international ones).

PROGRAM 2

Prevention, surveillance and control of communicable diseases (PREVICET)

COORDINATOR:
Pere Godoy García

1 FLU AND RESPIRATORY VIRUSES

The groups led by Ángela Domínguez and Cristina Rius have worked on the characteristics of hospitalized patients with severe and non-severe flu in the 2017-18 season in Catalonia (Sci Rep.11; 13587 and Viruses.13;1465). Work has continued on the collaborative project on the effectiveness of influenza and pneumococcal vaccination (PI19/00354) and funding has been obtained for the project on household transmission of SARS-CoV-2 and non-pharmacological measures and vaccines to reduce transmission (PI21/01883).

The groups led by Juan E. Echevarría and Amparo Larrauri have participated in collaborative publications with other CIBER groups. Several of these derive from national and international studies on respiratory diseases such as ENE COVID, I-MOVE-COVID-19, ECDC SARI NETWORK, ECDC COVID-VE or SeroSOS on COVID-19.

2 VACCINE-PREVENTABLE DISEASES

An article on the effectiveness of whooping cough vaccination in mothers in the third trimester of pregnancy to prevent the disease in children under 3 months of age has been published as a result of project PI15/01348. (J Infect. 83:554-58).

The groups led by Juan E. Echevarría, María Carmen Muñoz and Amparo Larrauri have participated in the PSERENADE study on pneumococcal infection and have published an article on lower respiratory tract infections due to enteroviruses, hand-foot-and-mouth disease, and measles in vaccinated individuals (Viruses 13;1982).

The groups led by Juan E. Echevarría and Amparo Larrauri, together with the group led by Mª Dolores Chirlaque, worked on the response to the case of imported polio and published a communication in Euro Surveill.26 (50).

3 VIRAL HEPATITIS

An article has been published on the characteristics of hepatitis A outbreaks to compare the different vaccination strategies in different Spanish autonomous regions between 2010 and 2018 with the participation of the groups led by Ángela Domínguez, Jesús Castilla, Cristina Rius, Juan E. Echevarría and Amparo Larrauri (Vaccines. 9:1214). An article on seroprevalence of hepatitis C at the national level has also been published.

Work is underway on a study of hepatitis A outbreaks in men who have sex with other men, reported in Spain in 2016 and 2017.

4 TUBERCULOSIS

Collaborative work has been carried out on the project on tuberculosis risk factors in contacts of pulmonary TB cases (PI18/01751). Preliminary results were presented at the International Tuberculosis Day 2021 in Barcelona.

5 OUTBREAKS

Results of the collaborative project on Norovirus outbreaks (PI16/02005) were presented in three articles (Viruses. 13:1100; Viruses. 13:1792 and Sci Rep. 11:23218).

6 EMERGING AND RE-EMERGING DISEASES

The groups led by Juan E. Echevarría and Jordi Figuerola have described a new HIV recombinant that is widely used in South America and non-invasive sampling methods in AIDS patients. A fatal case of Crimean-Congo hemorrhagic fever in Spain has been described and an article on congenital Zika and neurodevelopmental problems has been published. These works have been carried out in collaboration with groups from CIBEREHD, CIBERSAM, CIBERESP or CIBERDEM.

The groups led by Amparo Larrauri and Jordi Figuerola have published an article on the situation of WNV in Spain in 2020. A WNV project was prepared and granted together with several PREVICET groups.

The following CIBERESP intramural collaborative project has been financed: “Metagenomic sequencing to identify viral aetiologies in undiagnosed paediatric cases of meningitis and encephalitis”.

PROGRAM 3

Biological and behavioral determinants in the contraction and spread of communicable diseases in vulnerable populations (DAPET program)

COORDINATOR:
Juan Carlos Galán Montemayor

For yet another year, the COVID-19 pandemic has marked the strategic lines of the program. One of our program objectives is "to improve our knowledge of the diagnosis and dissemination in the population of communicable diseases that contribute to the highest disease burden". It is evident that our COVID activity has driven every other activity.

4 groups participated in the European project for the epidemiological surveillance of SARS-CoV-2, coordinated from the ISCIII.

3 groups of this program received funding for COVID-projects, in aspects such as molecular epidemiology, mathematical modeling of viral dispersion or impact of SARS-CoV-2 on vulnerable populations. Another group obtained a GRANT to characterize the virus in biopsy samples from deceased patients with SARS-CoV-2 bilateral pneumonia.

These projects resulted in publications in journals such as Nature (vol 595), Nature Genetics (doi: 10.1038/s41588-021-00936-6), for the molecular epidemiology studies; microLife (doi:10.1093/femsml/uqab011),for the mathematical modeling studies; Thorax (doi: 10.1136/thorax-jnl-2020-216714), Frontiers in Cardiovascular Medicine (doi: 10.3389/fcvm.2021.748396), for the studies on the impact of COVID on different organs in individuals who die from COVID; Lancet (doi: 10.1016/S0140-6736(21)00146-X); Clin Microbiol. Infect (doi: 10.1016/j.cmi.2021.03.018) on the impact of COVID on vulnerable populations such as pregnant women and healthcare personnel. Other outstanding works are the genetic analysis of vulnerability to severe COVID infection (Nature doi: 10.1038/s41586-021-03767-x.).

1 COMMUNICABLE INFECTIONS THROUGH ORGANIC FLUIDS

Several groups have worked on the impact of COVID on STI screening and surveillance programs. Among these works are the impact of HIV on the severity of severe COVID (Lancet HIV, doi: 10.1016/S2352-3018(21)00240-X); the loss of diagnostic opportunities for STIs/HIV and hepatitis during the pandemic period (Euro Surveill doi: 10.2807/1560-7917.ES.2020.25.47.2001943), or the increase in STIs in vulnerable groups during confinement (Euro Surveill doi: 10.2807/ 1560-7917.ES.2021.26.18.2100422). A spontaneous roundtable on the impact of COVID on surveillance programs has been presented at the congress of the Spanish Society of Epidemiology with the participation of 4 groups from this subprogram.

Other groups have made important advances in the molecular characterization of syphilis (Mol Biol Evol. doi: 10.1093/molbev/msab318) or post-vaccination humoral response against HPV-16 (Nat. Commun doi: 10.1038/s41467- 021-26151-9).

2 ANTIMICROBIAL RESISTANCE

As stated above, much of the work carried out in this subprogram has also been conditioned by the impact of COVID. For example, a clinical trial on hydroxychloroquine in COVID patients (NEJ Med doi: 10.1056/NEJMoa2021801), alteration of the flora of the respiratory tract in ICU patients during the pandemic period (Fron Microbiol, doi: 10.3389/fmicb.2021.709421), or the spread of multidrug-resistant bacteria during the pandemic period (J Hosp Infect 10.1016/j.jhin.2020.10.029)

Other groups have maintained a research activity independent of the impact of COVID. One of the most outstanding works was published in Clin Microbiol. Rev (doi: 10.1128/ CMR.00050-19).

PROGRAM 4

Social determinants of health

COORDINATOR:
Mª José López Medina

We highlight below some of the actions and products derived from two of the active subprograms in 2021:

Within the framework of the subprogram that deals with the line of research related to **gender violence**, 4 projects have been obtained in competitive national calls, among them the call for intramural projects of CIBER-RESP, in which the project *Sexual Violence associated factors and perceptions among youth. A mixed method approach was obtained. Also worth noting is the European project Masculinities and violence against women among young people: Identifying discourses and developing strategies for change using a mixed methods approach*. Within the framework of this subprogram, 12 collaborative articles have been published in international journals, mostly in the first quartile. Among the various publications is, for example, *Positive Masculinities and Gender-Based Violence Educational Interventions Among Young People: A Systematic Review in the journal Trauma, violence and abuse* (first decile journal)

It is also important to highlight other transfer products such as the Health and Gender Report. Impact of the COVID-19 pan-

demic on gender-based violence and the responses of the health sector of the Women's Health Observatory of the Ministry of Health, and the "Temporal analysis of the murders of women due to gender-based violence in Spain over a 15-year period (2003-2017)", of the Government Delegation against gender violence. In addition, and with the aim that the results of the research always revert to the development and implementation of policies and interventions, it is worth highlighting the publication of the policy brief "Learning about the impact of the COVID-19 pandemic on the resources for attention to gender-based violence ". Finally, it is also noteworthy that researchers from this subprogram have advised the ISCIII in the discussion of the amendments presented by the parliamentary groups to the Organic Law Project for the comprehensive protection of children and adolescents against violence.

The Real World Data subprogram published various collaborative articles in 2021, including the article *Impact of COVID-19 on the health of the general and more vulnerable population and its determinants: health care and social survey-ESSOC, study protocol, published in the International Journal of Environmental Research and Public Health*. As regards research projects, worth highlighting is the completion of the IMPSEROCOVID19 project. Impact and Seroprevalence of the COVID-19 disease and the implementation of the Pfizer Global Medical Grants project. COVID-19 Competitive Grant Program 'Seroprevalence and the socioeconomic and health impact of COVID-19 on general and vulnerable populations', developed between January and December 2021.

Finally, it should be noted that during this year work has been carried out on the proposal of two new subprograms which will be put into action next year, and in which all the groups of the Program will be involved: one of them on "Social Inequalities in Health and behaviors of young people" and another on 'Health Inequalities and COVID-19".

PROGRAM 5

Epidemiology and prevention in environmental and occupational health

COORDINATOR:
Marieta Fernández Cabrera

The program has continued to participate in international projects (ORCHESTRA, HBM4EU), **leading** many of them (Air-NB, ATHLETE, LIFECYCLE, HELIX-NAFLD, Traffic-related air pollution and birth weight, MOBILISE-D). Thus, the group led by Tardon and Vioque has maintained collaborations in **international cancer consortiums** (ILCCO: lung and survival according to gender, race, BMI, and tobacco; SYNERGY: lung cancer in painters, PanGenEU: gallbladder disease and pancreatic cancer; Stop Project; PREDIMED Plus), and Sunyer's group in **leading advocacy activities in physical activity** as an endpoint (European Medicines Agency, Food & Drug Administration), publishing works of interest on exercise and development of asthma (Russell, ERJ Open Res. 2021). In this sense, Olea's group has participated in **clinical trials in therapeutic exercise** and cardiotoxicity (ATOPE) or neurotoxicity due to chemotherapy (ATENTO). Also noteworthy is the international **leadership** funding for young postdoctoral (HDSA, Human Biology Project Grant) obtained by Martí-Puig's group. The groups have achieved financing in state projects and human resources calls, defended several doctoral theses and estab-

lished **collaborations with the industry** (Grífols Foundation).

Among the transfer products, to be highlighted is the participation of several groups (Lopez-Espinosa and Sunyer) in the new Air Quality Guide (WHO), and in national Air Quality Guides (Tardón-Asturias). Several articles have been published in this line: i) climate change and mortality (Lancet Planet Health. 2021; Royé. 2021; Urban, 2021); ii) air pollution and brain morphology, dementia and Alzheimer. Mortamais, Environ Int. 2021; Alemany, Environ Int. 2021; Pujol, Neuroimaging. 2021; Lubczyńska, Environ Res. 2021.

The collaborations of Martí-Puig's group in the identification of molecular biomarkers in rare and complex diseases together with CIBERESP groups (environmental exposure, placental epigenetics and age acceleration), CIBERNED (diagnostic strategies in prion diseases and triplet expansion) and CIBERER (genomic analysis) are of the greatest interest.

Also noteworthy are the transversal activities of the group led by Olea in **validation and implementation of biomarkers of effect and early damage**, non-persistent pesticides and puberty and hormonal alterations in adolescents, women's health (endometriosis), and **intervention in pregnant women** to reduce their exposure (intramural) as well as that of their offspring.

The group led by Vioque has continued to investigate **dietary, environmental and social factors** associated with maternal and child health, cardiometabolic and respiratory health, mental health, neurodevelopment and obesity. To be highlighted: 1) Dietary exposure to toxic (arsenic) and essential elements in childhood, 2) Dietary factors and lifestyles and cardio-metabolic risk, 3) Coffee and survival.

Some of the collaborative work has also focused on the COVID-19 pandemic (López-Espinosa) and its relationship with environmental factors and health effects.

Within the framework of the INMA Subprogram, we highlight its participation in 32 collaborative projects (19 national, 16 international, 1 CIBERESP-intramural) intra-CIBERESP (another 16 groups), inter-CIBERs (CIBEROBN, CIBERDEM, CIBERES, CIBERSAM). 47 articles have been published and the 17th Scientific Conference was organized. In addition, **follow-up** was made of **1,500 adolescents** (14-16 years old) and **new lines of research** have been initiated: i) **Health in adolescence** (puberty, obesity, cardiometabolic and respiratory disorders, sleep, mental health; ii) new environmental and social exposures: exposome (and cognitive-motor function, blood pressure and obesity), microbiome, inequality/social exclusion/poverty, 5G.

PROGRAM 6

Health services evaluation

COORDINATOR:
Antonio Serrano Blanco

During 2021, Program 6 has developed the 2 strategic subprograms "Health and social burden of diseases" and "Efficiency and equity of the health system", in addition to collaborative projects with CIBERESP, CIBERSAM, CIBERES, REDETS, REDISSEC, FECEC and RedIAPP. In addition, its researchers lead the CIBER BiblioPRO platform.

1 HEALTH AND SOCIAL BURDEN OF DISEASES

Work is ongoing with the **Continuous Work History Sample** (MCVL)and the WORKs platform (www.upf.edu/cisal/workss), focusing on the analysis of the return to work after cancer, showing that salaried workers with a temporary incapacity (TI) due to cancer are less likely to accumulate days in employment than those without TI. During 2021, the analysis of the impact of TI trajectories on work trajectories has been completed, applying sequence analysis and latent class analysis. Premature mortality due to specific causes has been analyzed according to the type of work trajectory, and the following project has been continued "**Work after cancer. Return to work of a Catalonian working sample after a cancer diagnosis**". Collaborations with several hospitals have been carried out in the study of the impact of COVID on healthcare professionals.

Another study focused on COVID is **MINDCOVID Mental health Impact and NeeDs associated with COVID-19** (https://mindcovid.org), led by Jordi Alonso and with the participation of 6 CIBERESP and 7 CIBERSAM groups. The analysis of the first survey has been carried out and 5 articles have been published.

2 EFICIENCIA Y EQUIDAD DEL SISTEMA SANITARIO (EYESS)

The website https://costesunitariosprisma.org/ has been developed where data on unit costs and rates related to complimentary health services for all CIBER researchers can be found.

As a collaborative project, we highlight the leadership of work package 1 (WP1) of the **CIBERPOSTCOVID** project in collaboration with groups from Program 1 and 7. This project, commissioned by the Ministry of Health and financed with CIBER funds, is directed by Prof. Ferran Barbé (CIBERES). Groups 07, 09, 15 and 58 participate in WP1. Its objective is to identify, through qualitative research and evidence synthesis, the definition of persistent COVID to develop future epidemiological, burden and cost analyses, as well as identifying biological factors.

Other collaborative projects are: 1 **The Measurement of Mental Well-being as an Indicator for Population Health Monitoring (WEMWEBS)** in which CIBERESP and CIBERSAM groups participate; 2) **Mental-GPS. Promoting Interna- tional Comparability of Mental Health Indicators in General Population Surveys**. CIBERESP 2021-23 (with collaboration between CIBERESP and CIBERSAM groups); and 3) **Evaluation of Adherence to Antipsychotics Based on Data from Real Clinical Practice** led by Antonio Serrano with the participation of Victoria Serra's group.

The program's groups have published more than 90 articles (mostly Q1) to improve health care and facilitate clinical, organizational, research or service planning management. Jordi Alonso has positioned himself among the "highest cited researchers (Psychiatry/Psychology) 2021" (WOS ranking).

During 2021 P6 and P7 have been merged..

PROGRAM 7

Clinical epidemiology

COORDINATOR:
José Ignacio Pijoan Zubizarreta

The program has a strategic subprogram, MAPAC, a synthesis research line, and a methodological development line.

1 MAPAC (IMPROVEMENT OF THE ADEQUACY OF HEALTH CARE AND CLINICAL PRACTICE)

The subprogram is based on hospital MAPAC commissions led by program researchers. In 2021, a collaborative network of MAPAC Commissions was created that includes groups of more than 15 NHS hospitals. A program of regular meetings has been initiated to assess the starting situation of each center and develop protocols for collaborative work that guarantee homogeneity of procedures and comparability of results. Work has begun with three protocols with field work to be developed in 2022: evaluation of the adequacy of medication in hospitalized patients over 74 years of age, adequacy of the indication for bladder catheterization in hospitalized patients and evaluation of the request for preoperative tests in scheduled surgery. The coordination of this network is carried out by the CIBERESP group led by Xavier Bonfill and his group, with the participation of three other groups from this program.

Five collaborative original articles have been published in this area. More than twenty MAPAC recommendations have been generated by the MAPAC groups belonging to the program. These recommendations are progressively incorporated into DianaSalud (www.dianasalud.com). In 2021, Dianasalud included 5,838 recommendations, of which 30 are of its own production.

Scientific dissemination work has been carried out through the publication and dissemination of the book "**Testing Treatments**" to key people of the NHS and agencies related to the generation, dissemination and application of scientific knowledge (health and research managers, clinical researchers) as well as representatives of patient associations.

2 RESEARCH SYNTHESIS

In 2021, the research synthesis line has published articles in relation to the methodological development in conducting systematic reviews of prognostic studies and is working using mixed methods in the area of joint decision-making with patients in the screening of prostate cancer and the prevention of thromboembolism in pregnancy, within two projects with competitive financing and the leadership and participation of the groups led by Blanca Lumbreras, Javier Zamora and Xavier Bonfill. Work has also been carried out to adapt the PRESS tool (P*eer Review of Electronic Search Strategies*) and RIGHT-Adapt Checklist (*Reporting Guidelines under development for other study designs*) into Spanish.

16 additional intra and/or inter-program and/or interCIBER cooperative articles have been published and participation in cooperative projects has begun: intramural and commissioned initiatives such as the project on CIBERPOSTCOVID.

One of the cooperative projects led by researchers of the Program has generated an online educational platform that has trained and accredited more than 6,000 NHS professionals in best practices for the use of central vascular catheters and identified, in the midst of a complicated situation due to the pandemic, a 13% reduction in neonatal sepsis associated with the use of these catheters in the participating neonatal units.

TRANSVERSAL PROGRAM

Training

COORDINATOR:
Beatriz Pérez Gómez

In 2021, the Training Program has continued to maintain the two basic lines of action of its program: mobility actions, aimed at facilitating contact and work with other national or international groups; and improvement actions, aimed at enhancing the quality of scientific work and its dissemination in Public Health forums.

In 2021, the modalities of **mobility actions** created to promote the collaboration of CIBERESP researchers among themselves and with other groups have been maintained. These grants are intramural in nature, and are aimed at all CIBERESP research staff. At the **national level**, 2 short stays between CIBERESP groups have been financed. **International mobility** has also been promoted with the financing of 5 stays in total this year, through short stays of a maximum of three months in international research centers that CIBERESP convenes annually and that allow obtaining the international mention, in the case of doctoral students, and promote the professional development of its own research staff.

Within **the further professional training actions**, in 2021 and due to the uncertainty regarding the epidemiological situation derived from the pandemic, it has not been possible to hold the *Extramural Meeting for Excellence in Public Health Research*, a tool to enhance the collaboration with other CIBER areas and promote quality research in Public Health, and which CIBERESP had been organizing annually at the Public Health Summer School Lazareto de Maó in Menorca.

Once again this year, CIBERESP's collaboration with the Spanish Society of Epidemiology (SEE) has continued with the funding of the **Awards for the 10 best papers** presented by young research staff at the SEE Annual Scientific Meeting, which is held together with the Congress of the Portuguese Association of Epidemiology, the Ibero-American Congress of Epidemiology and Public Health SESPAS/SEE. The award includes a diploma and covers the cost of registration at the following year's meeting. Also, within the meeting of the SEE held in September 2021, the CIBERESP spontaneous roundtable took place, which through the *Awards for the best communications presented to the CIBERESP table*, finances the registration of the 7 best communications selected for their presentation.

The Training Program also promotes that the training or scientific activities carried out by other entities establish special conditions for the members of CIBERESP, encouraging their participation.

PLATFORMS

Bibliopro

BiblioPRO is a virtual repository of Patient Reported Outcomes (PROs). Its mission is to promote the measurement of PROs including: **exhaustive inclusion and standardized information of instruments in Spanish** through systematic reviews; **scientific evaluations**; and **training**.

The BiblioPRO Scientific Committee includes **17 researchers** from **15 institutions (CIBERESP, CIBERSAM, CIBERNED y REDISSEC)**.

Repositorio (2021):

- **Registered Users:** 3.222 new users (accumulated users=25.538), 20,1% increase compared to 2020.
- **Instruments:** 40 new PROs (accumulated=2269 in- struments); plus 70 new PROs in BiblioPRO interna- tional.
- **Annual Website Visits:** 51.000, 24,5% increase compared to 2020.
- **Sublicences:** 409 (619 in 2020; accumulated=3.737 licences). The number of licences requested is lower than the previous year because many studies were stopped in 2020.
- **Systematic Review:** A **search algorithm** has been developed using NLP (natural language processing) with researchers from the University of the Basque Country.

BiblioPRO International:

- 70 instruments have been included on the **BiblioPRO International website** (www.biblioprointernational.org) launched in September, 2020.
- New distribution agreements:

  > Computer Vision Syndrome- Questionnaire (4 languages);

  > Hereditary Angioedema-QoL for adults (19 languages).

EMPRO Platform:

- 5 evaluations are being carried out with the EMPRO **online platform** (https://empro.imim.es):

  > **ischemic heart disease** (promoter: group 09 CIBERESP)

  > **oral health in older adults** (promoter: Universidad de Chile)

  > **vocal health** (promoter: University of Argentina)

  > **quality of life in mental health** (promoter: Group 11 CIBERSAM)

  > **DUKE instrument for social support** (promoter: Group 09 REDISSEC).

Research:

- **Competitive research** projects:

  > "CEAD-Contextualizing Evidence for Action in Diabetes in low-resource Settings" (H2020 European Research Council 2018 Starting Grant (804761–CEAD). PI: LA Parker. Scientific Advisory Committee.

  > "SISAQOL-Setting International Standard in Analyzing Patient-Reported Outcomes and Quality of Life endpoints. (IMI-Project: 945052) PI: Andrew Bottomley. CScientific Advisory Committee.

Training and research support activities:

- **International Webinar** "PROMs & PREMs in Practice: Clinical Care, Healthcare Management and Health Systems Evaluation". 12/07/2021. Presenters: Judy Baumhauer, José María Valderas and Tanja Stam; Moderators: CC BiblioPRO. 230 registrations plus 121 views on YouTube.
- **Advisory:**

  > **IMPACT** (Call for precision medicine infrastructure associated with science and technology). Coordinator: ISCIII.

  > **Naveta:** Telepharmacy platform with PROMs and PREMs. Coordinator: FARUPEIB (Outpatient Pharmaceutical Units- Balearic Islands), Spanish Society of Hospital Pharmacy Award (SEFH) 2021.

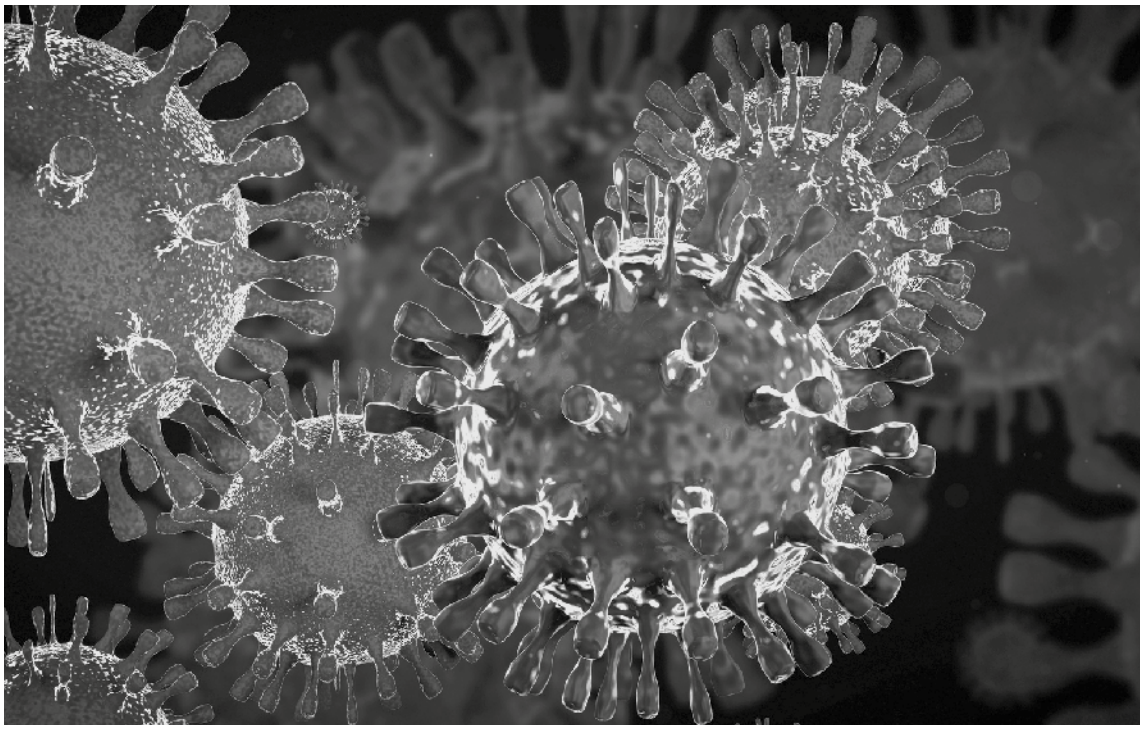
> **Implementation of the Electronic Medical Records in Catalonia.** Coordinator: Depart ment of Health, Government of Catalonia.

> H2O Project (Health Outcomes Observatory). Coordinator: University of Vienna.

- Collaboration with the **CIBERSAM Instruments Bank**: facilitating the connection be-tween websites and coordinated informative sessions.

Publications in 2021:

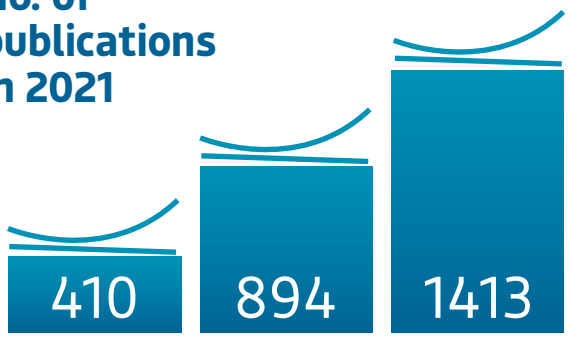
- Mayoral K, et al. Smartphone App for monitoring Asthma in children and adolescents. *Qual Life Res* 2021; 30(11):3127-3144.
- Benazizi I, et al. Adaptation and psychometric validation of Diabetes Health Profile (DHP-18) in patients with type 2 diabetes in Quito, Ecuador: a cross-sectional study. *Health Qual Life Outcomes* 2021; 19(1):189.
- Zamora V, et al. Mapping the Patient-Oriented Prostate Utility Scale From the Expanded Prostate Cancer Index Composite and the Short-Form Health Surveys. *Value Health*. 2021 Nov;24(11):1676-1685.



SCIENTIFIC PRODUCTION

Publications

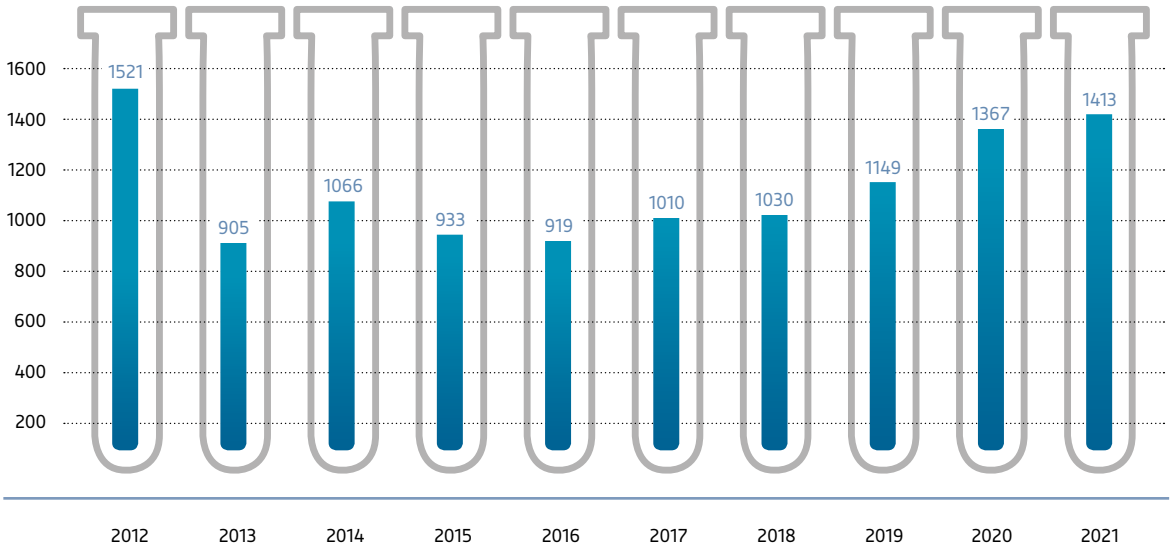
No. of publications in 2021



Collaborations

*Among various thematic areas

Evolution of publications



10 most relevant publications by impact factor

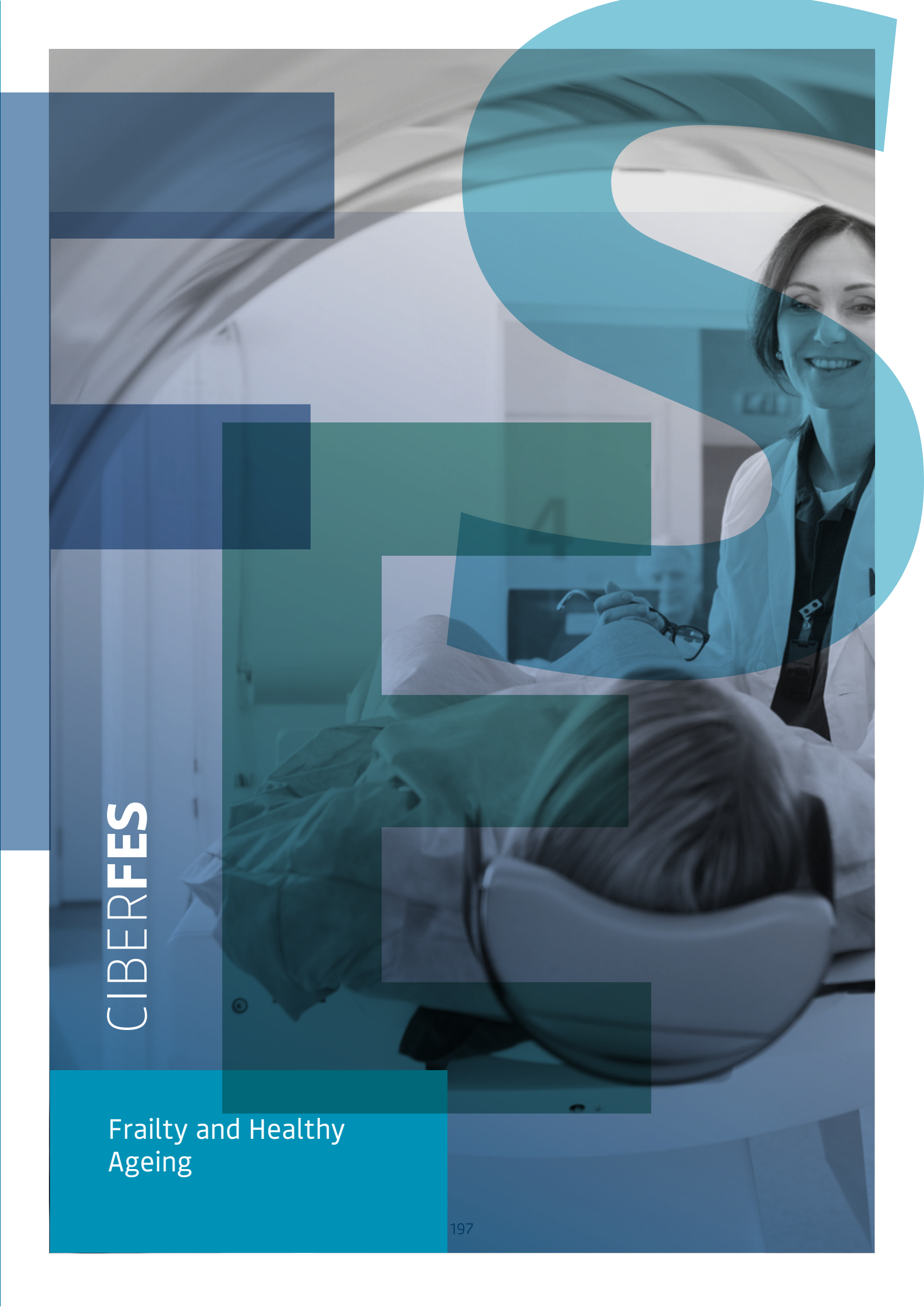
IF	Publication
38,330	Lopez M.G., Chiner-Oms A., Garcia de Viedma D., Ruiz-Rodriguez P., Bracho M.A., Cancino-Munoz I. et al. The first wave of the COVID-19 epidemic in Spain was associated with early introductions and fast spread of a dominating genetic variant. Nature Genetics. 2021;53(10):1405-1414.
21,648	Arias-de la Torre J., Vilagut G., Ronaldson A., Serrano-Blanco A., Martin V., Peters M. et al. Prevalence and variability of current depressive disorder in 27 European countries: a population-based study. The Lancet Public Health. 2021;6(10):e729-e738.
17,425	Politi J., Guerras J.-M., Donat M., Belza M.J., Ronda E., Barrio G. et al. Favorable impact in hepatitis C–related mortality following free access to direct-acting antivirals in Spain. Hepatology. 2021;.
14,919	Everson T.M., Vives-Usano M., Seyve E., Cardenas A., Lacasana M., Craig J.M. et al. Placental DNA methylation signatures of maternal smoking during pregnancy and potential impacts on fetal growth. Nature Communications. 2021;12(1).
11,799	Garcia-Esquinas E., Carrasco-Rios M., Ortola R., Sotos Prieto M., Perez-Gomez B., Gutierrez-Gonzalez E. et al. Selenium and impaired physical function in US and Spanish older adults. Redox Biology. 2021;38.
11,117	Lopez de Maturana E., Rodriguez J.A., Alonso L., Lao O., Molina-Montes E., Martin-Antoniano I.A. et al. A multilayered post-GWAS assessment on genetic susceptibility to pancreatic cancer. Genome Medicine. 2021;13(1).
10,588	Carrizosa C., Murcia M., Ballesteros V., Costa O., Manzano-Salgado C.B., Ibarluzea J. et al. Prenatal perfluoroalkyl substance exposure and neuropsychological development throughout childhood: The INMA Project. Journal of Hazardous Materials. 2021;416.
10,570	Perez-Martinez V., Marcos-Marcos J., Cerdan-Torregrosa A., Briones-Vozmediano E., Sanz-Barbero B., Davo-Blanes M. et al. Positive Masculinities and Gender-Based Violence Educational Interventions Among Young People: A Systematic Review. Trauma, Violence, and Abuse. 2021;.
9,621	Villanueva C.M., Espinosa A., Gracia-Lavedan E., Vlaanderen J., Vermeulen R., Molina A.J. et al. Exposure to widespread drinking water chemicals, blood inflammation markers, and colorectal cancer. Environment International. 2021;157.
9,621	Barrios-Rodriguez R., Perez-Carrascosa F.M., Gomez-Pena C., Mustieles V., Salcedo-Bellido I., Requena P. et al. Associations of accumulated selected persistent organic pollutants in adipose tissue with insulin sensitivity and risk of incident type-2 diabetes. Environment International. 2021;155.

CIBERESP Groups, Publications 2021

Group Leader	Publications	Q1	D1	Institution - Center	Province
Alemany Vilches, Mª Eulalia	26	16	5	Instituto Catalan de Oncología	Barcelona
Alonso Caballero, Jordi	42	30	11	Consorci Mar Parc Salut de Barcelona	Barcelona
Belza Egozcue, Maria José	44	23	5	Instituto de Salud Carlos III	Madrid
Bonfill Cosp, Xavier	82	47	25	Instituto de Investigación del Hospital de la Santa Cruz y San Pablo	Barcelona
Borrell Thio, Carme	44	15	3	Agencia de Salud Pública de Barcelona	Barcelona
Bueno Cavanillas, Aurora	74	54	21	Universidad de Granada	Granada
Calderón Sandubete, Enrique	10	7	4	Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla	Sevilla
Casabona Barbara, Jordi	29	15	6	Fundación Instituto de Investigación Germans Trias i Pujol	Barcelona
Castilla Catalán, Jesús	76	56	26	Instituto de Salud Pública de Navarra	Navarra
Chirlaque López, Mª Dolores	81	66	28	Fundación para la Formación e Investigación Sanitarias de la Región de Murcia (FFIS)	Murcia
Daponte Codina, Antonio	20	12	5	Escuela Andaluza de Salud Pública	Granada
Delgado Rodríguez, Miguel	67	49	12	Universidad de Jaén	Jaen
Domínguez García, Ángela	35	13	4	Universidad de Barcelona	Barcelona
Echevarría Mayo, Juan Emilio	26	15	7	Instituto de Salud Carlos III	Madrid
Emparanza Knörr, José Ignacio	5	1	1	Asociación Instituto Biodonostia	Guipuzcoa
Ferreira González, Ignacio	28	11	6	Fundación Hospital Universitario Vall d´Hebron - Institut de Recerca (VHIR)	Barcelona
Figueiras Guzmán, Adolfo	74	42	13	Universidad de Santiago de Compostela	Coruña, A
Figuerola Borrás, Jordi	28	20	15	Agencia Estatal Consejo Superior de Investigaciones Científicas	Sevilla
Galán Montemayor, Juan Carlos	43	25	15	Servicio Madrileño de Salud	Madrid

Group Leader	Publications	Q1	D1	Institution - Center	Province
García Benavides, Fernando	28	9	3	Universidad Pompeu Fabra	Barcelona
Gómez de la Cámara, Agustín	16	10	4	Servicio Madrileño de Salud	Madrid
Ibarluzea Maurolagoitia, Jesús	73	65	33	Asociación Instituto Biodonostia	Guipuzcoa
Larrauri Cámara, Amparo	29	16	13	Instituto de Salud Carlos III	Madrid
López Espinosa, María José	48	38	27	Fundación para la Investigación Sanitaria y Biomédica de la Comunidad Valenciana (FISABIO)	Valencia
López Medina, María José	33	11	5	Agencia de Salud Pública de Barcelona	Barcelona
Lumbreras Lacarra, Blanca	26	12	2	Universidad Miguel Hernández	Alicante
Martí Puig, Eulalia	8	7	5	Universidad de Barcelona	Barcelona
Menéndez Santos, Clara	39	27	18	Hospital Clínico y Provincial de Barcelona	Barcelona
Morales Suárez-Varela, María Manuela	24	15	3	Universidad de Valencia	Valencia
Moreno Aguado, Víctor	38	28	12	Instituto Catalan de Oncología	Barcelona
Moya Simarro, Andrés	69	47	24	Universidad de Valencia	Valencia
Muñoz Almagro, María Carmen	102	53	32	Fundación para la Investigación y Docencia Sant Joan de Deu	Barcelona
Olea Serrano, Nicolás	48	43	27	Fundación para la Investigación Biosanitaria en Andalucía Oriental (FIBAO)	Granada
Pollán Santamaría, Marina	48	34	13	Instituto de Salud Carlos III	Madrid
Porta Serra, Miquel	24	18	9	Consorci Mar Parc Salut de Barcelona	Barcelona
Rius Gibert, Cristina	29	17	7	Agencia de Salud Pública de Barcelona	Barcelona
Rodríguez Artalejo, Fernando	55	47	20	Universidad Autónoma de Madrid	Madrid
Ruiz Pérez, Isabel	30	19	6	Escuela Andaluza de Salud Pública	Granada
Sáez Zafra, Marc	30	17	7	Universidad de Gerona	Girona
Sánchez Pérez, Maria José	72	55	22	Escuela Andaluza de Salud Pública	Granada
Schröder, Helmut	38	26	11	Consorci Mar Parc Salut de Barcelona	Barcelona
Serra Sutton, Victoria	20	10	4	Agència de Qualitat i Avaluació Sanitàries de Catalunya (AQuAS)	Barcelona

Group Leader	Publications	Q1	D1	Institution - Center	Province
Serrano Blanco, Antonio	15	12	6	Fundación para la Investigación y Docencia Sant Joan de Deu	Barcelona
Sunyer Deu, Jordi	108	86	61	Fundación Privada Instituto de Salud Global Barcelona (ISGlobal)	Barcelona
Tardón García, Adonina	68	51	18	Universidad de Oviedo	Asturias
Villanueva Belmonte, Cristina	125	103	72	Fundación Privada Instituto de Salud Global Barcelona (ISGlobal)	Barcelona
Vioque López, Jesús	49	34	14	Universidad Miguel Hernández	Alicante
Zamora Romero, Javier	71	38	17	Servicio Madrileño de Salud	Madrid



CIBERFES

Frailty and Healthy Ageing

Presentation by the scientific director

Leocadio Rodríguez-Mañas

In 2021, the activity of CIBERFES has been marked, like so many other things, by the COVID pandemic We highlight the number of publications and participation in national and international research projects related to the pandemic, its specific factors and biomarkers in the elderly population (function as a prognostic factor) or the role of vitamin D in its treatment, having provided experimental evidence (the only one available to date) on its usefulness in patients hospitalized with COVID. In this respect, our area is involved in the CIBER project to contribute to the definition of post-COVID syndrome.

Within the CIBERFES research lines of interest, mechanisms that explain and condition frailty have continued to be published, with a special mention of the role of the mitochondria and its collapse, of free radicals and autophagy, exemplified in the award received by José Antonio Enríquez from the CNIC for his article on mechanisms that contribute to the maintenance of cardiac mitochondrial homeostasis. From the clinical point of view, worth highlighting are findings in sarcopenia, osteoporosis, and nutrition, providing evidence that suggests the existence of different clinical frailty phenotypes (with/without sarcopenia; with/without disability), studies on chronodisruption associated with aging and its role in functional deterioration, as well as the review led by Mikel Izquierdo (University of Navarra) on physical activity in the elderly.

From the organic point of view, worth highlighting is the completed renewal of the External Scientific Council with the incorporation of Alan Sinclair (King's College) and the renewal of several of the group PIs has continued. We hope to be able to replace one of the groups, which left CIBERFES in 2019, during the next year.

During 2021, thanks to a small increase in the budget allocation, we have been able to make the first call for collaborative intramural projects. In this sense, collaborations with other CIBER areas have continued to be strengthened, while collaborations with leading groups, already mentioned in last year's report, have been consolidated. Collaboration continues with the WHO aging program through the Clinical Consortium of Healthy Aging-CCHA, in the generation of documents on the management of COVID in the elderly population and in the approach towards these patients when they are institutionalized. Three CIBERFES groups (PIs: L Rodriguez Mañas, FJ García Garcia and JA Serra) will lead and participate together with a group from CIBERESP (PI: F. Rodriguez Artalejo) in the validation of different aspects of the WHO ICOPE program.

In 2021, we have participated and led European calls. To be highlighted is the continuation of the H2020 DIABFRAIL-LATAM project, coordinated by CIBERFES and in which 4 groups from our CIBER participate; the pilot study for the validation of the POSITIVE technological platform, in which two CIBERFES groups participate, and the CAREPATH project.

Finally, regarding institutional relations with international research and health policy organizations, worth mentioning are the contacts established with our collaboration in the United Nations initiative "Decade of Healthy Aging" led by the WHO.

PROGRAMS

PROGRAM 1

Basic, clinical and environmental mechanisms associated with the development of frailty. Impact on healthcare systems

COORDINATOR:
José Viña Ribes

Program 1 brings together a group of laboratories and clinical research centers based on the analysis of major gerontological problems that affect healthy aging and frailty. We come together to study major divisions: the metabolism division and the intervention division. Within the metabolism division there are groups that work on mitochondria (Enríquez A., Viña J), groups that work on neuroscience and also on mitochondria (Bolaños, J) and groups specialized in bone metabolism (Muñoz M). Similarly, there are intervention groups, among which Dr. Arévalo and Dr. Andrés-Lacueva stand out with their work in nutrition. Regarding exercise as an intervention, the work of groups such as those led by Ignacio Ara, Mikel Izquierdo and José Viña stand

out. There is a specific group for sleep analysis and its interventions, headed by María Ángeles Rol. Finally, there are several groups working on supplements such as Germaine Escámez's, on melatonin.

Ander Matheu's group has identified and validated, in collaboration with 3 other CIBERfes groups, a molecular pattern associated with frailty. In addition, together with the group from Valencia they have resumed the activity of the Spanish Research Group on Centenarians.

Juan P. Bolaños' group has identified new regulatory mechanisms for: Mitochondrial ROS. A special issue of the journal Neurochemical Research was published in honor of Dr. Bolaños' scientific career (https://link.springer.com/article/10.1007/ s11064-020-03184-y).

To be highlighted is the collaborative work between researchers Rol A. and Moreno M., both in publications and in intramural projects: "Preventing chronodisruption by inadequate light exposure though ambulatory circadian monitoring in frail people. CHRONOFRAIL". The researcher Mª Ángeles Arévalo et al. has described that a high-fat diet induces anxiety, alterations in the intestinal microbiota and neuroinflammation, in wild-type and TgAPP mice, and has elaborated "Guidelines for the use and interpretation of assays for monitoring autophagy". The researcher Enríquez A., has received the "Constantes y Vitales" award for the best biomedical publication of the year for: "A Network of Macrophages Supports Mitochondrial Homeostasis in the Heart", and intraCIBERFES has collaborated with the Valencia group in detecting frailty and sarcopenia in animal models. Ignacio Ara's group has worked on the project: "Identification and validation of Biomarkers of frailty". Mikel Izquierdo has collaborated in the development of "International Exercise Recommendations in Older Adults (ICFSR): Expert Consensus Guidelines." published in the Journal of Nutrition and Healthy Aging. Dr. Escames' group has started two new research projects in addition to continuing with the existing ones. In addition, they have completed the MELCOVID clinical trial (2020-001808-42; https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001808-42/results).

José Viña's group has identified molecular modifications (Glucose 6P dehydrogenase) and supplements (glucosamine) that serve to delay frailty and its transition to dependence. Finally, Manuel Muñoz's group has published studies aimed at developing non-invasive imaging diagnostic tools to identify bone fragility in patients with various endocrinopathies.

PROGRAM 2

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

COORDINATOR:
Xavier Nogués Solan

The translational clinical research in frailty of the CIBERFES program, to a high degree made up of clinicians, has once again been affected by the need to provide care, as frail patients are the most vulnerable to COVID. However, we highlight the following important activity of the program in various fields:

The group in Granada led by Manuel Muñoz has published relevant studies on non-invasive imaging diagnostic tools (Trabecular Bone Score and 3D Shaper) that allow the identification of bone fragility in patients with type 2 diabetes (*Diabetes & Metabolism*, 2021) and other endocrine disorders (J Clin Med 2021).

The group in Albacete led by Pedro Abizanda has participated in the elaboration of the "Consensus Document on the prevention of frailty in the elderly" of the Ministry of Health, which will be the basis for the prevention and care of frailty throughout the Spanish territory. It has participated in the elaboration of the "Recommendations for addressing Frailty in a health crisis situation generated by COVID-19", and continues with the European

project H2020 CAREPATH to monitor and treat frailty and multimorbidity in elderly people with mild cognitive impairment at home.

During 2021, the group in Madrid led by José Antonio Serra has published more than 20 articles in high impact indexed journals on frailty, several of them the result of inter- or intra-ciber collaboration.

The group in San Sebastián led by Ander Matheu has continued to validate an already patented molecular pattern associated with frailty. In collaboration with 3 additional groups from CIBERfes, they have obtained a project from the Alberto Salgado and Jaime Miquel intramural Call and a project from the Basque Government.

The group in Navarra led by Mikel Izquierdo has published new relevant results related to frailty and exercise, especially in reference to COPD patients, hospitalized patients and cancer patients. It has also published an International Exercise Recommendations in Older Adults (ICFSR): Expert Consensus Guidelines and a review in The Lancet Healthy Longevity.

The group in Barcelona led by Francesc X. Nogués has demonstrated the importance of vitamin D to avoid hospitalization in the ICU and reduce mortality in frail patients affected by COVID 19. It has restarted the courses on microindentation to extend bone quality measurement techniques.

Teresa Moreno's group has published various results on the reduction of falls in the elderly through the OTAGO multicenter clinical trial (financed by the FIS) and the Program of Centers Committed to Excellence in Care.

Feliciano Priego's group has focused on the evaluation of vitamin D metabolism in different scenarios. Thus, in premenopausal women, the influence of external factors on the levels of the main metabolites has been evaluated [Mena-Bravo et al., *The Journal of Steroid Biochemistry and Molecular Biology*, 2021, 211, 105884, Toribio et al., Nutrients, 2021, 13, 3747].

PROGRAM 3

Training

COORDINATOR:
Pedro Abizanda Soler

During 2021, the CIBERFES training activity, interrupted in 2020 due to the pandemic, was restarted. The main achievements were the holding of two plenary training meetings, which have been called "Francisco Guillén Llera Seminars". At CIBERFES we have planned to hold 2 to 3 seminars per year, in face-to-face or online methodology, a methodology that allows not only the dissemination of the research carried out by the different groups but also the identification of synergies for future collaborations.

In the first meeting, held on May 25 in webinar mode, the scientific activities carried out during the pandemic in relation to COVID-19 and frailty were presented. The event was moderated by Professors Pedro Abizanda Soler, CIBERFES Training Coordinator, and Leocadio Rodríguez Mañas, Director of CIBERFES, and was attended by more than 30 nodes. Six original works were presented by the groups of Drs. Darío Acuña, José Viña, Ignacio Ara, Pedro Abizanda, José Antonio Serra and Leocadio Rodríguez-Mañas. Specifically, aspects related to melatonin in patients with COVID-19, ACE-2 and COVID-19 transcriptome, the use of renin-angiotensin-aldosterone inhibitors and COVID-19, as well as the repercussions

of confinement in community, hospital and residential settings in older people regarding frailty and function.

The reception of this new format was excellent, which is why the possibility of opening it to scientific societies that carry out research on frailty and healthy ageing, as well as other CIBERs interested in this field, is being assessed. The abstracts of the presentations were communicated through the usual CIBER channels.

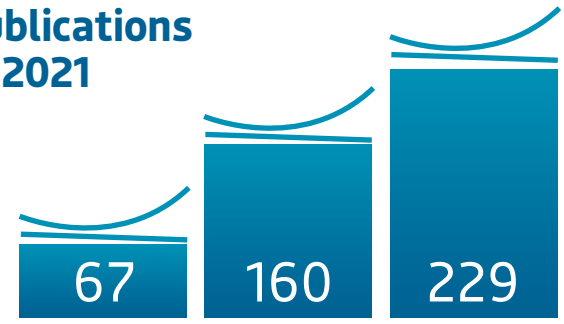
The second "Francisco Guillén Llera Seminar" was a face-to-face event, and took place in Madrid on November 15, 2021. It was moderated by Leocadio Rodríguez Mañas and José Viña Ribes, and the main clinical and basic research papers developed by all CIBERFES groups during 2021 were presented. Over 40 people attended. The Seminar began with a keynote presentation by Plácido Navas, who discussed aspects of CYB5R3/Coenzyme Q as a protector of healthy ageing. Next, clinical aspects related to the prevalence of frailty in residential settings, screening for frailty in Primary Care, frailty phenotypes, models, interventions and health care in frailty and aspects of the functional and biological response of frailty in exercise programs in community and hospital settings were addressed. Also addressed were basic aspects of mitochondrial function and desynchronization of clock genes, intestinal microbiota and metabolome in frailty, eating habits for healthy brain aging, mitochondrial models of aging and frailty, influence of aging and decreased hormones on the phagocytic capacity of glial cells, aspects of the circadian rhythm on frailty, molecular studies in centenarians, pathophysiological aspects of Alzheimer's, and the relationship between bone mineral metabolism and aging.

The next face-to-face meeting is being prepared for March-April 2022.

SCIENTIFIC PRODUCTION

Publications

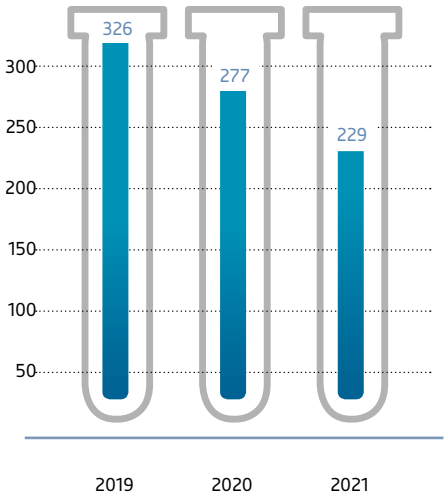
No. of publications in 2021



Collaborations

*Among various thematic areas

Evolution of publications

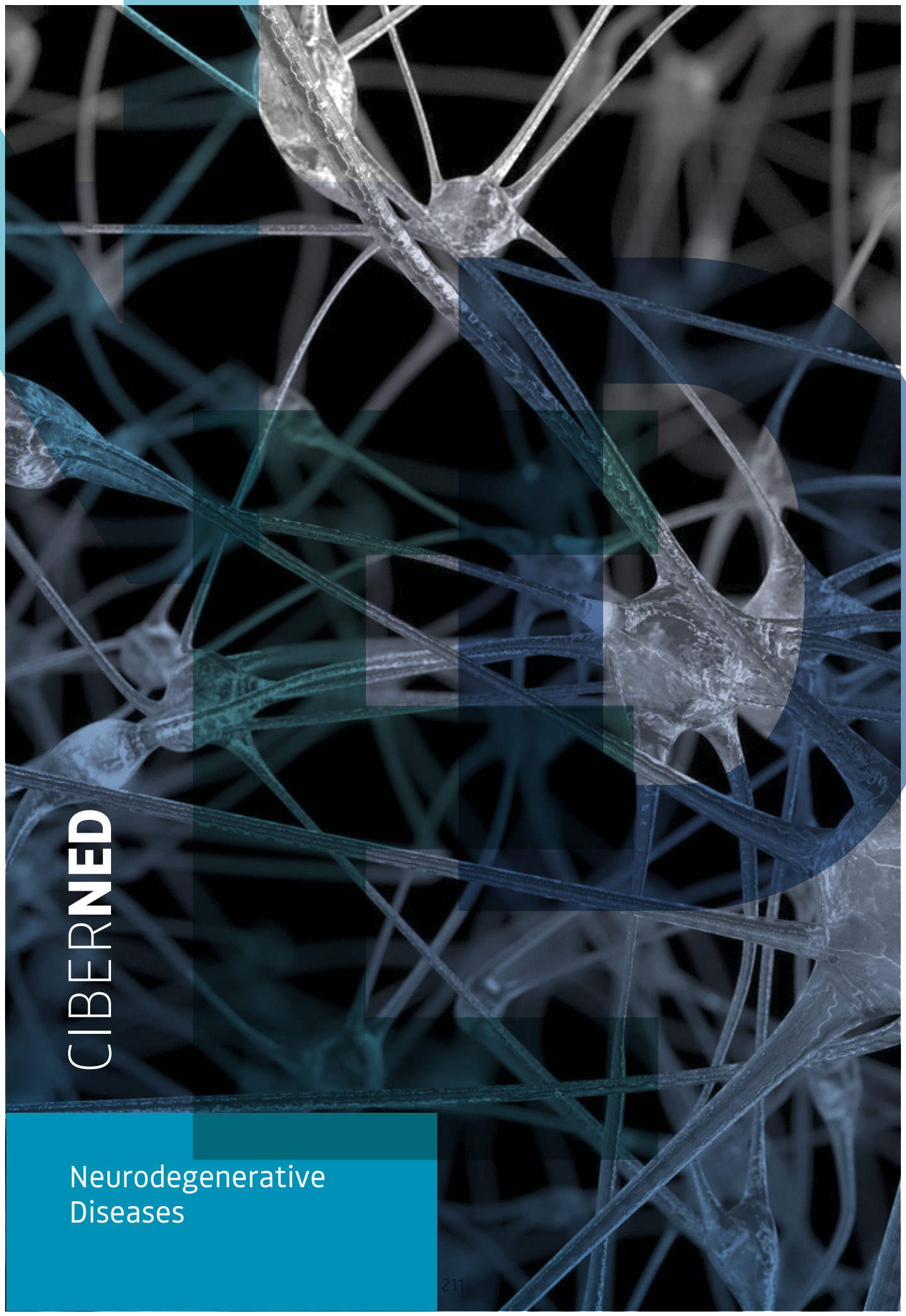


10 most relevant publications by impact factor

FI	Publication
56,272	Association of Tramadol vs Codeine Prescription Dispensation with Mortality and Other Adverse Clinical Outcomes
47,728	Muscle repair after physiological damage relies on nuclear migration for cellular reconstruction
27,287	Astrocyte-neuron metabolic cooperation shapes brain activity
24,094	Subclinical Atherosclerosis and Brain Metabolism in Middle-Aged Individuals: The PESA Study
21,566	Cerebral amyloid-β load is associated with neurodegeneration and gliosis: Mediation by p-tau and interactions with risk factors early in the Alzheimer's continuum
21,566	The serum metabolome mediates the concert of diet, exercise, and neurogenesis, determining the risk for cognitive decline and dementia
18,302	Longitudinal Associations of Blood Phosphorylated Tau181 and Neurofilament Light Chain with Neurodegeneration in Alzheimer Disease
17,659	Effects of a Mindfulness-Based Intervention versus Health Self-Management on Subclinical Anxiety in Older Adults with Subjective Cognitive Decline: The SCD-Well Randomized Superiority Trial
17,425	A Mammalian Target of Rapamycin-Perilipin 3 (mTORC1-Plin3) Pathway is essential to Activate Lipophagy and Protects Against Hepatosteatosis
16,016	Guidelines for the use and interpretation of assays for monitoring autophagy (4th edition)1

CIBERFES Groups, Publications in 2021

Group Leader	Publications	Q1	D1	Institution - Center	Province
Abizanda Soler, Pedro	8	6	5	Servicio de Salud de Castilla La Mancha	Albacete
Andrés Lacueva, María Cristina	8	10	5	Universidad de Barcelona	Barcelona
Ara Royo, Ignacio	29	24	11	Universidad de Castilla la Mancha	Toledo
Arévalo Arévalo, María Angeles	6	5	1	Agencia Estatal Consejo Superior de Investigaciones Científicas	Madrid
Bolaños Hernández, Juan Pedro	7	7	6	Fundación Instituto de Estudios de Ciencias de la salud de Castilla y León	Salamanca
Enríquez Domínguez, José Antonio	5	3	2	Fundación Centro Nacional de Investigaciones Cardiovasculares	Madrid
Escames Rosa, Germaine	1	0	0	Fundación para la Investigación Biosanitaria en Andalucía Oriental (FIBAO)	Granada
Garcia García, Francisco José	15	8	4	Fundación del Hospital Nacional de Parapléjicos	Toledo
Grau Rivera, Oriol	22	15	8	Fundación Barcelonabeta Brain Research Center	Barcelona
Izquierdo Redin, Mikel	33	15	5	Universidad Pública de Navarra	Navarra
Matheu Fernández, Ander	9	8	4	Asociación Instituto Biodonostia	Guipuzcoa
Moreno Casbas, Teresa	15	9	6	Instituto de Salud Carlos III	Madrid
Muñoz Torres, Manuel	6	6	0	Fundación para la Investigación Biosanitaria en Andalucía Oriental (FIBAO)	Granada
Nogués Solan, Francesc Xavier	10	8	2	Cons. Mar Parc Salut de Barcelona	Barcelona
Priego Capote, Feliciano	8	6	1	Fundación para la Investigación Biomédica de Córdoba (FIBICO)	Cordoba
Rodríguez Mañas, Leocadio	16	11	5	Servicio Madrileño de Salud	Madrid
Rol de Lama, María Ángeles	6	5	2	Universidad de Murcia	Murcia
Serra Rexach, José Antonio	22	12	4	Servicio Madrileño de Salud	Madrid
Viña Ribes, José	25	18	5	Fundación para la Investigación del Hospital Clínico de la Comunidad Valenciana (Fundación INCLIVA)	Valencia



CIBERNED

Neurodegenerative Diseases

Presentation by the scientific director

Adolfo López de Munain Arregui

Dear Colleagues,

At the end of my introductory letter to last year's Report, I told you that surely 2021 would be better than the terrible year 2020. When it comes to taking stock, as is almost always the case, the year 2021 has had its highs and lows. Despite the vaccine against COVID, which has been available since the beginning of the year, we have ended the year in the midst of the sixth epidemic wave, although with a lower cost in lives and less social impact. As I write these lines, the country is trying to get back on its feet while we are witnessing a nearby war conflict, as anachronistic, unfair and absurd as it is dangerous, with serious consequences, first of all, for the Ukrainians who suffer from it firsthand, and indirectly all throughout Europe, with images that we thought were banished. It therefore seems that in 2022 we will continue to be subscribing to new uncertainties that, due to their social and, above all, economic impact, will undoubtedly affect the country's scientific activity in the coming months. Let us hope that sanity prevails and a just and lasting peace is reached as soon as possible.

As an institution, CIBERNED closes 2021 after completing a prolific trajectory of more than 15 years as an independent entity and remaining at the forefront of Spanish Biomedicine centers both for scientific production and for other activities, as you will see in the following pages of this report.

Despite the improvement in the epidemic situation, we were also unable to celebrate the Salamanca 2020 event in 2021, the celebration of which has been definitively set for June 2022. Thanks to the efforts of the CIEN Foundation, in the person of Mari Ángeles

Pérez and Miguel Medina, the original program has remained practically untouched and we hope it will be a scientific success and also a milestone in making CIBERNED's activity visible in society. We look forward to seeing each other's faces there, -still masked, I'm afraid-, for the first time in almost three years. In the meantime, we have continued with the online sessions of CIBERNED with a remarkable attendance.

As you know, since January 1 we have been sharing our fate, projects and dreams at CIBER with 13 other thematic areas. Our arrival coincided with the unexpected death of the CIBER Manager, Mr. Manuel Sánchez Delgado, which was an emotional shock for everyone. Since that date, Margarita Blazquez has joined CIBER as Manager and with her we are beginning to adapt our structures and ways of doing things to those in place at CIBER. Like many of you, we await with a mixture of concern and hope the approval of the new Science Law that will help us resolve the complex situations created as a result of the application of the labor reform, in an area that, in my humble opinion, should be regulated in another way, more appropriate to what is the activity of a research center.

In relation to one of the objectives outlined when accepting the Scientific Management of CIBERNED, which was to promote the transfer of knowledge to the business world, I have found myself with the pleasant surprise that there is a team in CIBER very hard at work in these tasks led by Luzma García whom I encourage you to contact with any questions you may have on these issues. Soon this team will contact each of the groups to find out their needs in this regard and promote this important aspect.

This year is also a year of farewells and welcomes. We bid farewell to Jesús Ávila, Eduardo Tolosa and Lupe Mengód as PIs responsible for the group, though not as researchers, all 3 with exemplary careers and whose work has been essential to CIBERNED's growth. We also welcome the arrival of María Llorens and Fina Martí as researchers now responsible for these groups. In the coming months, other replacements will take place and I encourage you to carefully prepare these always complex processes to ensure the competitiveness of CIBERNED. In the meantime, and despite everything that is going on, try to keep up your good work with the same spirit of resilience required to deal with the uncertainties associated with the profession of being a researcher in Spain. I wish you all the best and look forward to seeing you in Salamanca!

PROGRAMS

PROGRAM 1

Alzheimer's disease and other degenerative dementias

COORDINATOR:
Alberto Lleó y Eva Carro

During 2021, important scientific work has been carried out in this program focused on improving the diagnosis and treatment of patients with Alzheimer's disease and other dementias. To this end, several multi-center projects have been carried out focused on the need to obtain biomarkers that allow diagnosing the disease in early stages, which would allow a greater probability of success of the therapeutic strategies under investigation. In 2021, several works have been published on biomarkers in Alzheimer's disease with a particular focus on the use of less invasive biological fluids such as blood or saliva. Among these, worth highlighting are studies that show the value of neurofilaments or phosphorylated tau in people with Alzheimer's and in people with Down syndrome.

The importance of early diagnosis as one of the great challenges for Alzheimer's research was also highlighted at the VIII CIIIEN/International Congress on Innovation and Research in Neurodegenerative Diseases chaired by Queen Sofía.

In 2021, a special effort has also been made to investigating the physiological bases and molecular mechanisms that contribute to the development of Alzheimer's disease in order to identify new therapeutic targets. Among them, studies have been published focused on neuroinflammation processes, including glial activation or expression of TREM2 or new pathological forms of tau in Alzheimer's disease. In addition, worth highlighting is the work published on the capacity for neurogenesis and the presence of stem cells in the adult brain, as well as their impact on the development of neurodegenerative diseases.

It should also be noted that Adolfo López de Munain, scientific director of Ciberned, and Miguel Calero participated last February in the digital forum "Strengthening research on Alzheimer's in times of COVID-19", organized by Sigma Dos in collaboration with El Mundo and in which Raquel Yotti, current General Secretary of Research, also participated. The repercussion that the current situation of the pandemic is having on a population as particularly vulnerable as Alzheimer's patients was also discussed.

In June, the Roundtable "Scientific controversies around Aducanumab" took place with the participation of Alberto Lleó, Mercé Boada, Jordi Alom and Miguel Medina, in which the trials carried out by their respective research groups on the effects of Aducanumab in Alzheimer's disease, as well as future expectations, were discussed. In addition to this roundtable, regular seminars have been held by young researchers with a high number of attendees.

In short, the program has obtained outstanding results in both the translational and clinical aspects, with discoveries of great potential for clinical application.

PROGRAM 2

Parkinson's disease and other neurodegenerative movement disorders

COORDINATORS:
José Javier Lucas y José Ángel Obeso

The most relevant results and milestones of the program during 2021 have resulted in high-impact publications and patents, and in the participation in and promotion of clinical trials.

Regarding molecular and cellular mechanisms involved in neurodegeneration and regeneration, a study carried out in mice has shown that systemic inflammation is capable of temporarily preparing brain stem cells for their activation. Once the inflammation subsides, and in the absence of local damage, these cells return to their quiescent state (Belenguer et al. *Cell Stem Cell* 2021, 28:285-299.e9). Another study has shown an important role of the D2 receptor in the neurons of the brain structure called the hippocampus. It is a dopamine receptor, one of the main neurotransmitters in the brain and whose deficit plays an important role in Parkinson's disease. The study shows that this receptor modulates the synaptic changes responsible for memory acquisition and consolidation (Espadas et al. *Cereb Cortex* 2021, 31:2187-2204). Another study has identified a key protein in the development of hydrocephalus.

Specifically, ventriculomegaly, a pathology in which the ventricles of the cerebral hemispheres present an abnormal enlargement, which is characteristic of psychiatric, neurological and neurodegenerative diseases. The study indicates that the Kidins220 protein is necessary to maintain aquaporin-4 (AQP4) protein levels, the main brain water channel and key to preventing excessive accumulation of cerebrospinal fluid (Del Puerto et al. *Mol Psychiatry* 2021, 26: 6411-26).

As regards Huntington's disease, two new pathogenic mechanisms have been described that may give rise to therapeutic strategies. On the one hand, a harmful increase in lamin-B1 (LMNB1), one of the proteins that make up the nuclear lamina, has been seen. The nuclear lamina is a filamentary mesh on the inner face of the cell nuclei that gives them mechanical stability and participates in different physiological processes. The research showed that pharmacological normalization of LMNB1 levels improves cognitive symptoms in an animal model of Huntington's disease (Alcalá-Vida et al. *EMBO Mol Med.* 2021 13:e12105). On the other hand, a deficit in the production of the ThTr2 protein encoded by the SL-C19A3 gene has been observed. The ThTr2 protein transports vitamin B1 (also known as thiamine) into cells and especially across the blood-brain barrier. As a result, Huntington's patients have thiamine deficiency in the brain and cerebrospinal fluid. Brain thiamine deficiency is known to cause various syndromes, some of them similar to Huntington's disease, which respond well to high doses of thiamine to compensate for its decreased transport, and of vitamin B7 (biotin), because it increases the production of ThTr2. The study also demonstrated a beneficial effect of high-dose thiamine and biotin combination therapy in animal models of Huntington's disease (Picó et al. *Sci Transl Med.* 2021 13:eabe7104) and has led to a clinical trial named HUNTIAM.

PROGRAM 3

ALS and other neuromuscular disorders

COORDINATORS:
Rafael Fernández Chacón y Carmen Paradas

During 2021, the group led by Abraham Acevedo, in collaboration with the University of London (UCL), has developed the first fully humanized mouse models of genes associated with ALS, with which various groups in academia and industry are already working. (Devoy et al, *iScience* 2021).

We highlight the work carried out by Xavier Navarro's group focused on the study of new sigma1 receptor ligand drugs to prevent motor neuron death and gene therapy trials to over-express neuregulins and GDNF in the animal model of ALS. They have obtained orphan drug designation for the treatment of megalencephalic leukoencephalopathy with subcortical cysts (EMA/ OD/0000059436).

Jon Infante Ceberio's group has participated in the IGOS program (International Guillain-Barré Outcome Study) developing the modified ERASMUS scale and identifying diagnostic and prognostic biomarkers (Lleixà et al, *J Neuroinflammation* 2021). The group has contributed to describing CMT2P associated with heterozygous mutations (Palaima et al, *Orphanet J Rare Dis* 2021).

The project led by Ana Martínez, in collaboration with the CIBERNED groups of Eva de Lago and Javier Ruiz, "Targeting TDP-43 with protein kinase inhibitors: an effective and measurable therapy for ALS" has been selected by the La Caixa Foundation and Luzon Foundation. This group has received the 1st Prize for scientific research in ALS, from the HNA Foundation. They have developed and patented (P202130653, 7/9/2021) different protein kinase inhibitors capable of modulating TDP-43 in cell models and in animal models with therapeutic potential in ALS and FTD.

Rafael Fernández Chacón's group, focused on the molecular mechanisms of nerve terminal maintenance, has implemented two-photon microscopy to monitor neural activity in the motor cortex of awake mice with synaptic degeneration.

The group led by Dr. Carmen Paradas has participated in the natural history follow-up of the largest cohort of patients with muscular dystrophy due to dysferlin deficiency (COS study), defining this unique historical cohort, useful for the imminent gene therapy trial (Moore et al, Neuromuscul Disord. 2021; Jacobs et al, Ann Neurol. 2021). Its coordinating role in the description of mitochondrial myopathy due to thymidine kinase-2 deficiency in adults, has made clear the importance of the work of collaborative network reference centers, within a public and universal health system, for the diagnosis and treatment of neuromuscular diseases (Domínguez-González et al, *Orphanet J Rare Dis*. 2021).

To complete this summary of CIBERNED's activity in 2021, Dr. Pura Muñoz, principal investigator of CIBERNED Program 3 and the National Center for Cardiovascular Research (CNIC), and professor of Cell Biology at the University Pompeu Fabra was awarded the Santiago Ramón y Cajal National Research Award in the area of Biology. The award recognizes the contribution of her research on stem cells in the fields of muscle regeneration and aging, as well as the application of her discoveries to the treatment of different pathologies such as muscular dystrophy.

PROGRAM 4

Training

COORDINATOR:
Teresa Iglesias Vacas

During 2021, the activities that are part of the Training and Mobility Plan within the CIBERNED Training Program have been slowly resumed. These types of activities were interrupted by the COVID-19 pandemic in 2020. In May 2021, the 6th call for these types of grants was launched once again to be carried out in the second half of the year. Although participation has been clearly lower than in previous years due to the difficulties associated with the pandemic, three Mobility grants were awarded and one for training. In November 2021, the call for grants to be carried out during the first half of 2022 was launched.

At the beginning of 2021, the Training Program also launched a new initiative of virtual Scientific Sessions "CIBERNED Webinar Series". The objective of this new tool has been to share the latest scientific advances, to make different members of the groups known through their active participation, as well as to stimulate interactions and collaborations within CIBERNED. A total of 18 webinars have been organized, in which numerous predoctoral students (8), postdoctoral (4) and senior researchers (6) from the different programs have participated. These seminars have been very well received and attendance has been

very successful, with an average attendance of approximately 70-80 participants, having exceeded one hundred attendees in some cases. Certificates have been issued to CIBERNED predoctoral students as speakers or attendees, thus contributing to increase their scientific activities within their respective Doctoral Programs at the different Universities.

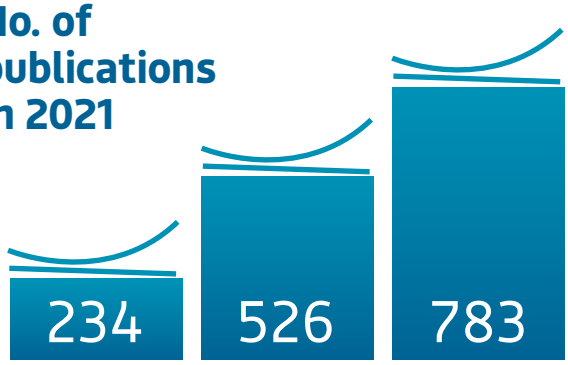
In addition to the program of fortnightly internal seminars, a special session was held on the occasion of the approval by the FDA of Aducanumab, a drug for the treatment of Alzheimer's disease. Following an online round table format, this session on "Scientific controversies around Aducanumab" had the participation of Dr. Alberto Lleó, Dr. Mercé Boada, Dr. Jordi Alom and Dr. Miguel Medina as moderator. The trials carried out by their respective research groups on the effects of Aducanumab in Alzheimer's disease were discussed, as well as future expectations and its impact in the field of research and clinical practice.

On the occasion of World Alzheimer's Day, H.M. Queen Sofía presided over the inauguration of the VIII International Congress on Research and Innovation in Neurodegenerative Diseases – CIIIEN, which addresses the latest advances in research on Alzheimer's and other neurodegenerative diseases such as Parkinson's, Huntington's and ALS. As in every edition, during the event the Young Investigator and Young Clinical Investigator Awards were presented, which this year have gone to Drs. Germán Belenguer Sánchez and Ignacio Illán Gala, respectively.

SCIENTIFIC PRODUCTION

Publications

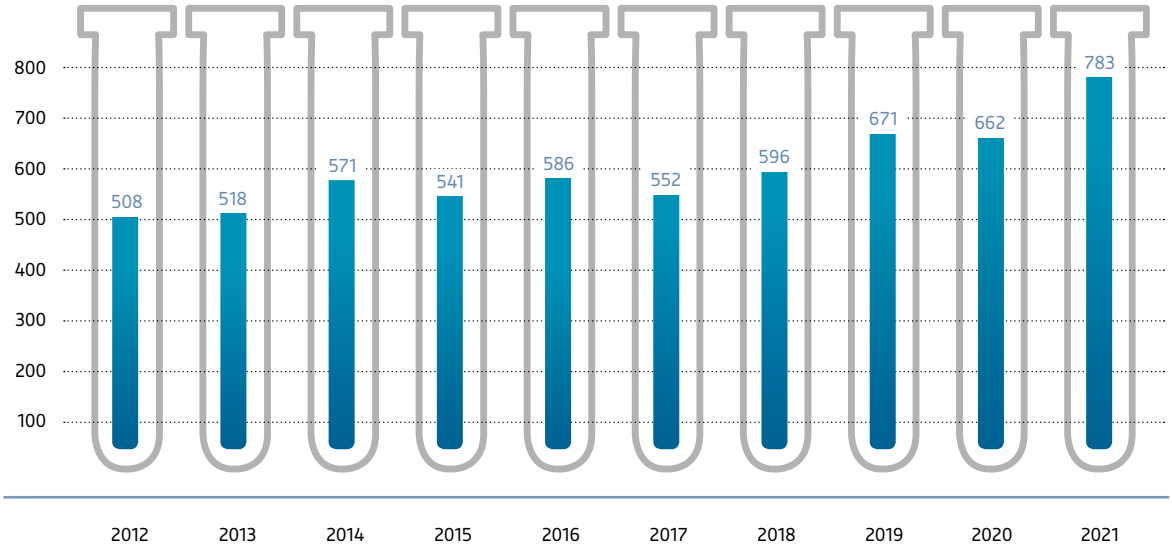
No. of publications in 2021



Collaborations

*Among various thematic areas

Evolution of publications



10 most relevant publications by impact factor

FI	Publication
94,444	Sousa-Victor P, García-Prat L, Muñoz-Cánoves P. Control of satellite cell function in muscle regeneration and its disruption in ageing. Nat Rev Mol Cell Biol. 2022;23(3):204-226. doi:10.1038/s41580-021-00421-2
53,44	Salloway S, Farlow M, McDade E, et al. A trial of gantenerumab or solanezumab in dominantly inherited Alzheimer's disease. Nat Med. 2021;27(7):1187-1196. doi:10.1038/s41591-021-01369-8
49,962	González-Rodríguez P, Zampese E, Stout KA, et al. Disruption of mitochondrial complex I induces progressive parkinsonism [published correction appears in Nature. 2022 Mar;603(7899):E1]. Nature. 2021;599(7886):650-656. doi:10.1038/s41586-021-04059-0
49,962	Hodcroft EB, Zuber M, Nadeau S, et al. Spread of a SARS-CoV-2 variant through Europe in the summer of 2020. Nature. 2021;595(7869):707-712. doi:10.1038/s41586-021-03677-y
49,962	COVID-19 Host Genetics Initiative. Mapping the human genetic architecture of COVID-19. Nature. 2021;600(7889):472-477. doi:10.1038/s41586-021-03767-x
47,728	Terreros-Roncal J, Moreno-Jiménez EP, Flor-García M, et al. Impact of neurodegenerative diseases on human adult hippocampal neurogenesis. Science. 2021;374(6571):1106-1113. doi:10.1126/science.abl5163
47,728	Roman W, Pinheiro H, Pimentel MR, et al. Muscle repair after physiological damage relies on nuclear migration for cellular reconstruction. Science. 2021;374(6565):355-359. doi:10.1126/science.abe5620
44,182	Miglis MG, Adler CH, Antelmi E, et al. Biomarkers of conversion to β-synucleinopathy in isolated rapid-eye-movement sleep behaviour disorder. Lancet Neurol. 2021;20(8):671-684. doi:10.1016/S1474-4422(21)00176-9
44,182	Iranzo A, Fairfoul G, Ayudhaya ACN, et al. Detection of β-synuclein in CSF by RT-QuIC in patients with isolated rapid-eye-movement sleep behaviour disorder: a longitudinal observational study. Lancet Neurol. 2021;20(3):203-212. doi:10.1016/S1474-4422(20)30449-X
44,182	Fortea J, Zaman SH, Hartley S, Rafii MS, Head E, Carmona-Iragui M. Alzheimer's disease associated with Down syndrome: a genetic form of dementia. Lancet Neurol. 2021;20(11):930-942. doi:10.1016/S1474-4422(21)00245-3
44,182	Carmona-Iragui M, Alcolea D, Barroeta I, et al. Diagnostic and prognostic performance and longitudinal changes in plasma neurofilament light chain concentrations in adults with Down syndrome: a cohort study. Lancet Neurol. 2021;20(8):605-614. doi:10.1016/S1474-4422(21)00129-0

CIBERNED Groups, Publications in 2021

Group Leader	Publications	Q1	D1	Institution - Center	Province
Acevedo Arozena, Abraham	2	2	1	Fundación Canaria Instituto de Investigación Sanitaria de Canarias	Santa Cruz De Tenerife
Alberch Vie, Jordi	10	6	3	Universidad de Barcelona	Barcelona
Boada Rovira, Merce	33	23	12	Fundació ACE, Institut Català de Neurociències Aplicades	Barcelona
Bullido Gómez Heras, María Jesús	6	4	1	Universidad Autónoma de Madrid	Madrid
Calero Lara, Miguel	30	19	8	Instituto de Salud Carlos III	Madrid
Camins Espuny, Antonio	20	14	4	Universidad de Barcelona	Barcelona
Cantero Lorente, José Luis	7	6	2	Universidad Pablo de Olavide	Sevilla
Carro, Eva	14	8	3	Instituto de Salud Carlos III	Madrid
Ceña Callejo, Valentín	1	1	1	Universidad de Castilla la Mancha	Albacete
Comella Carnice, Joan Xavier	4	3	0	Fundación Hospital Universitario Vall d´Hebron - Institut de Recerca (VHIR)	Barcelona
Cuadrado Pastor, Antonio	7	7	2	Universidad Autónoma de Madrid	Madrid
de Felipe Oroquieta, Javier	9	7	4	Agencia Estatal Consejo Superior de Investigaciones Científicas	Madrid
Del Río Fernández, José Antonio	7	6	3	Fundación Instituto de Bioingeniería de Cataluña	Barcelona
Fariñas Gómez, Isabel	9	4	1	Universidad de Valencia	Valencia
Fernández Chacón, Rafael	-	-	-	Universidad de Sevilla	Sevilla
Fernández Ruiz, Javier	18	12	4	Universidad Complutense de Madrid	Madrid
Ferrer Abizanda, Isidro	39	28	13	Fundación IDIBELL	Barcelona
Franco Fernandez, Rafael	24	18	6	Universidad de Barcelona	Barcelona
Fuentes Rodríguez, José Manuel	12	7	6	Fundación para la Formación y la Investigación de los Profesionales de la Salud (FUNDESALUD)	Cáceres
García Verdugo, José Manuel	14	11	5	Universidad de Valencia	Valencia
Gutiérrez Pérez, Antonia	19	13	6	Universidad de Málaga	Málaga

Group Leader	Publications	Q1	D1	Institution - Center	Province
Guzmán Pastor, Manuel	6	5	3	Universidad Complutense de Madrid	Madrid
Iglesias Vacas, Teresa	2	2	2	Agencia Estatal Consejo Superior de Investigaciones Científicas	Madrid
Infante, Jon	39	28	13	Instituto de Investigación Marques de Valdecilla	Cantabria
Kulisevsky Bojarski, Jaime	43	26	12	Instituto de Investigación del Hospital de la Santa Cruz y San Pablo	Barcelona
Labandeira García, José Luis	14	13	7	Universidad de Santiago de Compostela	Coruña, A
Lanciego Pérez, José Luis	5	5	1	Fundación para la Investigación Médica Aplicada	Navarra
Lleó Bisa, Alberto	71	55	32	Instituto de Investigación del Hospital de la Santa Cruz y San Pablo	Barcelona
Llorens, María	13	11	5	Agencia Estatal Consejo Superior de Investigaciones Científicas	Madrid
López Barneo, José	8	7	4	Universidad de Sevilla	Sevilla
López de Munain Arregui, Adolfo	40	29	16	Asociación Instituto Biodonostia	Guipúzcoa
Lucas Lozano, José Javier	4	4	3	Agencia Estatal Consejo Superior de Investigaciones Científicas	Madrid
Martí, María José	64	40	23	Hospital Clínico y Provincial de Barcelona	Barcelona
Martínez Gil, Ana	21	20	9	Agencia Estatal Consejo Superior de Investigaciones Científicas	Madrid
Matute Almau, Carlos	13	8	3	Universidad del País Vasco	Vizcaya
Mengod Los Arcos, Guadalupe	1	1	0	Instituto de Investigaciones Biomédicas IDIBAPS-CSIC	Barcelona
Mir Rivera, Pablo	47	30	21	Universidad de Sevilla	Sevilla
Moratalla Villalba, Rosario	3	2	1	Agencia Estatal Consejo Superior de Investigaciones Científicas	Madrid
Muñoz Cánoves, Pura	16	13	7	Universidad Pompeu Fabra	Barcelona
Naranjo Orovio, José Ramón	9	7	3	Agencia Estatal Consejo Superior de Investigaciones Científicas	Madrid

Group Leader	Publications	Q1	D1	Institution - Center	Province
Navarro Acebes, Xavier	29	24	5	Universidad Autónoma de Barcelona	Barcelona
Obeso Inchausti, José Ángel	4	3	1	Fundación HM Hospitales Madrid	Madrid
Osta Pinzolas, Rosario	12	12	2	Fundación Instituto de Investigación Sanitaria Aragón	Zaragoza
Paradas López, Carmen	14	9	5	Universidad de Sevilla	Sevilla
Pérez Castillo, Ana María	3	3	2	Agencia Estatal Consejo Superior de Investigaciones Científicas	Madrid
Pérez Tur, Jordi	7	7	3	Agencia Estatal Consejo Superior de Investigaciones Científicas	Valencia
Rodríguez Álvarez, José	5	3	2	Universidad Autónoma de Barcelona	Barcelona
Rodríguez Díaz, Manuel	7	5	2	Universidad de La Laguna	Santa Cruz De Tenerife
Sáez Valero, Javier	5	4	1	Universidad Miguel Hernández	Alicante
Soriano García, Eduardo	9	9	3	Universidad de Barcelona	Barcelona
Torres Alemán, Ignacio	2	2	0	Achucarro Basque Center for Neuroscience	Vizcaya
Trullas Oliva, Ramón	23	20	15	Agencia Estatal Consejo Superior de Investigaciones Científicas	Barcelona
Vicario Abejón, Carlos	3	2	0	Agencia Estatal Consejo Superior de Investigaciones Científicas	Madrid
Vila Bover, Miquel	19	13	7	Fundación Hospital Universitario Vall d´Hebron - Institut de Recerca (VHIR)	Barcelona
Vitorica Ferrández, Francisco Javier	5	3	2	Universidad de Sevilla	Sevilla
Wandosell Jurado, Francisco	7	6	3	Agencia Estatal Consejo Superior de Investigaciones Científicas	Madrid

CIBEROBN

Physiopathology
of Obesity
and Nutrition

Presentation by the scientific director

Carlos Diéguez González

A year has passed since the previous report for 2020. As in the previous year, the COVID-19 pandemic has had a considerable impact on our work. Nevertheless, we can definitely confirm that despite the adversities we have managed to continue on the path of consolidation and growth of the CIBEROBN. This is reflected in the number of publications in high-quality journals (e.g. 159 in D1), researcher training (56 doctoral theses, 23 of them international) or the securing of international projects including funding from the NIH. In addition, we have continued to attract new researchers, contributing to the generational turnover and thereby ensuring for the future the continuance of the quality inherent to what is expected in a CIBER structure. On the downside, we have had to carry out all our training activities virtually and many of them, most of international nature, have had to be postponed to the current year.

In light of the fact that our mission is to improve the health of the population, both at the level of primary prevention and based on basic and translational research, an inherent characteristic of CIBEROBN is our continuous interaction with the final recipients of our activity, represented by all those people involved in cohort studies. Despite the challenge posed by the pandemic, an average follow-up of 5.3 years of the more than 6,800 randomized participants was achieved by the end of 2021. The fact that this milestone has been reached in such a large project illustrates the high level of dedication and professionalism of the researchers involved. This is extensible to the rest of the cohort studies carried out in this period. It should be noted that in most of the studies carried

out there has been a very high degree of integration of different CIBEROBN Groups, as well as other CIBER thematic areas, both basic and clinical, which illustrates the need for structures of this type to carry out ambitious studies that have a high impact on the health of our population.

PROGRAMS

PROGRAM 1

Nutrition

COORDINATOR:
Jordi Salas-Salvadó

The Nutrition program is one of the two CIBEROBN (Nutrition and Obesity) programs that includes epidemiological research on obesity and nutrition for which important milestones have been achieved related to recruitment, follow-up and/or publication of results, as well as national and international collaborations. We highlight the advances in follow-up and interventions and publications in the PREDIMED Plus study – a randomized and controlled clinical trial with an intensive intervention with an energy-restricted Mediterranean diet, increased physical activity and behavioral support compared to a control group to assess its effects in weight loss and reduction of cardiovascular events. By the end of 2021, a mean follow-up of 5.3 years was achieved for the more than 6,800 randomized participants, even in times of COVID-19. Other milestones are

publications derived from the PREDIMED study (n=42), as well as the follow-up and publications of the "Seguimiento Universidad de Navarra" (SUN) cohort study (n=23,000). There have also been milestones in the publications of the CORDIOPREV study, a randomized controlled trial with a Mediterranean diet intervention in secondary cardiovascular prevention that has been successfully completed. Further milestones are the advances in recruitment, follow-up and publication of results of studies initiated, many of them in collaboration with different CIBER groups or outside CIBER: 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, n=720), MEDICAR (in collaboration with SEAT, a study of 14,000 workers evaluating lifestyle and health), IMPACT "Improving mothers for a better Prenatal Care " of the Hospital Clinic of Barcelona in collaboration with other centers, CORALS (cohort of children to evaluate risk factors for obesity, n=1270), and the European studies H2020 STOP "Science and Technology in Childhood Obesity Prevention", on prevention policies and approach to childhood obesity; SWEET "Sweeteners and sweetness enhancers: Impact on health, obesity, safety and sustainability", and PRIME "Prevention and Remediation of Insulin Multimorbidity in Europe", among others. In addition, other projects have been ongoing, such as the EU-Project (H2020), entitled: Effects of Nutrition and Lifestyle on Impulsive, Compulsive, and Externalizing behaviors. Eat2beNICE, and the NIH projects within the PREDIMED Plus study: "Effect of an Intensive Lifestyle Intervention on the Atrial Fibrillation Substrate; 2018–2022" and PREDIMED: "Mediterranean diet, metabolomics and cardiovascular disease". In addition, different projects have been obtained: 2 on personalized medicine from the ISCIII, a PROMETEO-HG Project, several European projects (Vegan screener), a new NIH Project on multi-fluid-metabolomics and a project from the Soria Melguizo Foundation on COVID in PREDIMED and PREDIMED-plus respectively.

In 2021, dozens of publications have been published in journals with high international impact, highlighting among them:

- Effects of Mediterranean Diet or Mindfulness-Based Stress Reduction on Prevention of Small-for-Gestational Age Birth Weights in Newborns Born to At-Risk Pregnant Individuals: The IMPACT BCN Randomized Clinical Trial. JAMA 2021.
- Choline Metabolism and Risk of Atrial Fibrillation and Heart Failure in the PREDIMED Study. Clinical Chemistry 2021.
- Effect on gut microbiota of a 1-y lifestyle intervention with Mediterranean diet compared with energy-reduced Mediterranean diet and physical activity promotion: PREDIMED-Plus Study. Am J Clin Nutr 2021.
- Mediterranean Diet Reduces Atherosclerosis Progression in Coronary Heart Disease: An Analysis of the CORDIOPREV Randomized Controlled Trial. Stroke 2021.

PROGRAM 2

Obesity

COORDINATOR:
Fernando Fernández-Aranda

During 2021, the subprograms of the Obesity Program have continued to strengthen the ties of collaboration between the different groups, collaborations between the Obesity and Nutrition program, and with international groups. Actions in this regard have crystallized in **leading publications** both in the field of **basic research**, with preclinical models, and in **clinical and translational** work, as well as obtaining European **research resources** and international leadership. The main achievements grouping together all the subprograms are described below.

Relevant International Publications

As regards **production**, the following publications deserve particular mention as an example of both intra- and inter-CIBER, as well as international collaborations: Publications in First Decile journals, leaders in the field, such as: *Journal of Experimental Med* (PMID: 33635944), *Nat Metab.* (PMID: 34675439), *Nat Comm.* (PMID: 34489410; PMID: 34417460; PMID: 33199701), *Gut* (PMID: 33514598), *Clinical Nutrition*

(PMID: 34474192), *Hypertension* (PMID: 33390043); *Lancet* (PMID: 33894837); *Cells* (PMID: 33800837; PMID: 34944082); *Nat Rev. Endocrinolog.* (PMID: 34608277); *Autophagy* (PMID: 33634751); *Journal of Hepatology* (PMID: 33096086); *Hepatology* (PMID: 32329085); *Journal of Behavioral Addictions* (PMID: 33784249; PMID: 35029544).

International Projects

Regarding the securing of international resources, where members of the CIBEROBN obesity program participate as PIs and/or coordinators, the following projects deserve special mention: 1) Network for blood pressure research in children and adolescents. HyperChildNET (CA 19115). COST Action (2020-25). Coordinator: E.Lurbe/ PI: F. Fernández-Aranda; 2) Stratification of Obese Phenotypes to Optimize Future Obesity Therapy (SOPHIA). PIs: G Frühbeck/ JM Fernández-Real-(2020-25)-Horizon 2020 Ref 875534-2; 3) International Training Network (Marie Curie-H2020): Gut-brain-axis: Targets for improvement of cognition in the elderly (SMARTAGE) (2020-24)- Ref. 859890, PI JM Fernández-Real; 4) Personalized prediction of cognition through the human microbiota. (ThinkGut) Interreg-POCTEFA (Horizon 2020) (2019-2022), (Ref EFA345/195) 5) Effects of Nutrition and Lifestyle on Impulsive, Compulsive, and Externalizing behaviors (Eat2beNICE) Horizon 2020 (2017-22) (Ref 728018); PI: F. Fernández-Aranda and J. Salas-Salvado; 6) Prevention and Remediation of Insulin Multimorbidity in Europe. Horizon 2020 (2020-24) (Ref. PRIME 847879). The last two in collaboration with the nutrition program. 7) Identification and validation of integrative biomarkers of physical activity level and health in children and adolescents (Ref: INTEGRActiv), ERA-Net HDHL-INTIMIC, PI: E. Lurbe.

National Projects

In addition to the above, other nationally funded projects in which members of the Obesity program participate as PIs are: 1) Neurocognition, Neuronal Activity and Biomarkers in Patients with Extreme Weight Conditions: Prospective Study on Response to Treatment (PI20/00132), financed by the ISCIII (2021-2023), PI: F. Fernandez-Aranda; 2) Impact of birth weight and growth pattern on cardiometabolic risk factors in postpubertal adolescents: clinical and molecular approach (PI20/00269) funded by ISCIII, PI: E. Lurbe; 3) Therapy in your Pocket: Effectiveness of Serious Games in Behavioral Addictions (GAME4HEALTH) (Ref. 347/21), financed by the Institut d'Investigació Biomèdica de Bellvitge (IDIBELL) / PECT-II-IDIBELL Internal call for innovation projects (01 /01/2022 – 09/30/2022), PI: S. Jiménez-Murcia; 4) Psychoneuroendocrine substrates in gaming disorder and their association with treatment outcome: usefulness of gamification in the rehabilitation process (Ref: 2021I031), funded by the Ministry of Health / Call for grants for the development of research projects on addictions 2021 (2022-2024), PI: S. Jiménez-Murcia; 5) DTG/3TC vs. BIC/FTC/TAF Maintenance Therapy in People Living With HIV: (PASO-DOBLE), substudy: "Change in subcutaneous and visceral fat" (2020-003686-18), financed by the SEIMC-GESIDA Foundation (2021-2024), PI: F. Villarroya; 6) Paternal RNA-mediated epigenetic inheritance of metabolic disorders: impact of

weight loss on the human sperm (HEROS) (AC18/00012), financed by JPI HDL / Instituto de Salud Carlos III (2019-2023). PI: J.M. Fernández-Real (workpackage leader).

Participation in International Guidelines

Similarly, worth adding to the intense scientific activity is the participation in the elaboration of the following **Clinical Guidelines**:

- Stergiou GS, Palatini P, Parati G, O'Brien E, Januszewicz A, Lurbe E, Persu A, Mancia G, Kreutz R; European Society of Hypertension Council and the European Society of Hypertension Working Group on Blood Pressure Monitoring and Cardiovascular Variability. 2021 European Society of Hypertension practice guidelines for office and out-of-office blood pressure measurement. *Journal of Hypertension*. 2021;39:1293-1302.
- Klionsky DJ, et al. Guidelines for the use and interpretation of assays for monitoring autophagy (4th edition)1. *Autophagy*. 2021 Jan;17(1):1-382. doi: 10.1080/15548627.2020.1797280. Epub 2021 Feb 8. PMID: 33634751; PMCID: PMC7996087.
- Fleseriu M, et al. Consensus on diagnosis and management of Cushing's disease: a guideline update. Lancet *Diabetes Endocrinol*. 2021 Dec;9(12):847-875. doi: 10.1016/S2213-8587(21)00235-7. Epub 2021 Oct 20. PMID: 34687601; PMCID: PMC8743006.

Dissemination

In the field of **internationalization**, the Obesity program of the CIBEROBN, and the members that compose it, have maintained their usual activity in the organization of specific **Workshops and symposiums** related to obesity and nutrition, within the **European Society for Clinical Investigation (ESCI)**, **European Congress on Obesity (ECO)** and **European Society of Endocrinology (ESE)**.

Furthermore, we highlight the organization of the **HYPERCHILDNET NETWORK FOR BLOOD PRESSURE RESEARCH IN CHILDREN AND ADOLESCENTS**, meeting held in hybrid mode in Valencia, October 13-14, 2021; as well as the European HyperChildNET Week, organized by HyperChildNET (November 20, 2021) whose central topic was hypertension in children and adolescents.

Regarding leadership and social/scientific dissemination, 2 members of the Obesity program (F-Fernandez-Aranda and E. Lurbe) have led the special issue "Eating Disorders and Obesity: Through the Life Course", in the journal *Nutrients* (Q1) (https://www.mdpi.com/journal/nutrients/special_issues/Eating_Disorders_Obesity_Through_Life_Course), with the following collaborative contributions: PMID: 35057485; PMID: 35010974; PMID: 34959979; PMID: 34201433; PMID: 34199265; PMID: 34959873; PMID: 34836431). Regarding social dissemination and promotion of the scientific spirit among young people, during 2021 the annual Mad

for Nutrition course (sponsored by the La Pedrera Foundation) has continued to be organized at the Bellvitge Hospital (Coordinator: F. Fernández-Aranda).

Participation/creation of specific Networks

Various members of the subprograms participate in international associations, which allows for synergies with other groups with high research potential, the design of leading projects in the area and dissemination in the scientific community. Among these, we highlight the following: Academy of Eating Disorders (AED); Eating Disorders Research Society (EDRS); International Neuropsychological Society; International Society of Addiction Medicine; International Society for the Study of Behavioral Addictions

- **Members of the "European College of Neuropsychopharmacology Nutrition Network (BrainFood)"** which includes other members from the Netherlands, Sweden, Italy, Ireland, United Kingdom, France, Estonia, Germany, Switzerland.
- Members of the **"Value of Treatment"** Workgroup of the European Brain Council/ European Psychiatric Association.
- **Adipoplast – Thematic network on adipose plasticity and its pathologies** (http://adipoplast.org/), corresponds to a network of excellence in adipose tissue research financed by the Ministry of Science, Innovation and Universities, led by CI- BEROBN and includes relevant CIBEROBN groups.
- **Members of the "European College of Neuropsychopharmacology Nutrition Network (BrainFood)"** which includes other members from the Netherlands, Sweden, Italy, Ireland, United Kingdom, France, Estonia, Germany, Switzerland.
- Members of the **"Value of Treatment"** Workgroup of the European Brain Council/ European Psychiatric Association.

PROGRAM 3

Training

COORDINATOR:
Manuel Tena-Sempere

As in previous years, the main focus of the CIBEROBN Training Program has been on the youngest members of the groups. Unfortunately, the still persistent impact of the COVID-19 pandemic, and the various restrictions still in operation during most of 2021, have had a very notable impact on the development of the activities of the training program of our CIBER area. These have been severely affected by the restrictions on mobility and free movement, both nationally and internationally, reducing our ability to support training activities for members of our CIBER area through training stays in both national and foreign centers.

On the other hand, during the year 2021, and specifically in its second half, a process of unification of the Training activities and procedures of the different CIBER Areas was begun. This homogenization process, coordinated from the Instituto de Salud Carlos III, aims to multiply the training offer of the CIBER as a whole, unifying the protocols for requesting and receiving grants. Due to the operational needs of the program, this process has put a slight hold on some of the activities until the new procedures have been defined, and which are expected to be operational in the first quarter of 2022.

Furthermore, the CIBEROBN training program had promoted active participation and/or organization of scientific events for 2021, the development of which has also been impacted by the pandemic. For example, the Workshop "Fat sensing and the brain control of puberty", organized by the International University of Andalusia, which was postponed to 2021, was unable to be held. Nevertheless, we continue to be committed to supporting the holding of this event, which will take place in October 2022.

Similarly, the pandemic prevented the development of the Doctoral Meeting of Excellence, in Mahón, promoted by CIBERESP, where CIBEROBN was still scheduled to participate until its cancellation due to the start of the pandemic.

In the same vein, the annual meeting of our CIBER area, called "OBESITY AND NUTRITION IN THE 21STCENTURY", organized under the coordination of the Training area, has been forced to maintain its virtual format in 2021, similar to the one already adopted in 2020. Since this annual meeting is considered a priority element in the CIBEROBN training program, many of the efforts of the training program have been aimed at ensuring its holding, albeit in a virtual format. In the end, the meeting took place between October 26 and 28, 2021. Despite the remote format, the program managed to gather a large panel of top-level national and international speakers, including three plenary speakers and 10 regular speakers, linked to the CIBEROBN and other institutions. As in 2020, the number of registrants and attendees at the sessions of this scientific meeting exceeded that of previous years in face-to-face format.

The recognition of the need to adapt to the new situation marked by the pandemic has promoted other complementary activities which, without causing excessive exhaustion given the multiple online meetings available, has expanded the CIBEROBN training offer. As examples of initiatives initiated or executed during 2021, virtual scientific meetings were promoted in conjunction with other societies, such as SEEDO, and initiatives closely related to CIBEROBN areas of interest have been actively disseminated. Similarly, during the first half of 2021, a joint cycle of CIBEROBN virtual conferences was launched, in collaboration with the CiMUS and IMIBIC Institutes, which allowed the holding of various conferences with top-level international speakers. We trust that the development of these and other initiatives of virtual training activities has made it possible not only to alleviate the limitations of the program's mobility activities, still affected by the pandemic, but also to consolidate a lasting addition to the training actions promoted by our CIBEROBN.

Finally, and as a training element of primary importance, we highlight that in 2021 a total of 56 Doctoral Theses have been completed (23 of them international), representing the consolidation of a growing trend in this important training activity.

PLATFORMS

PLATAFORM 1

Biobancos-Fatbank

During 2021, the activity of the FatBank Biobank began a normalization process after the alterations suffered in previous years due to the health crisis and the resulting reorganization of the surgeries from which biopsies of adipose tissue were obtained.

The main milestone achieved during 2021 has been in relation to the request for samples for the following projects:

- OutBrat project: transfer of 1,007 aliquots of plasma.
- Adipobrain project: transfer of 43 aliquots of plasma and 82 aliquots of adipose tissue.

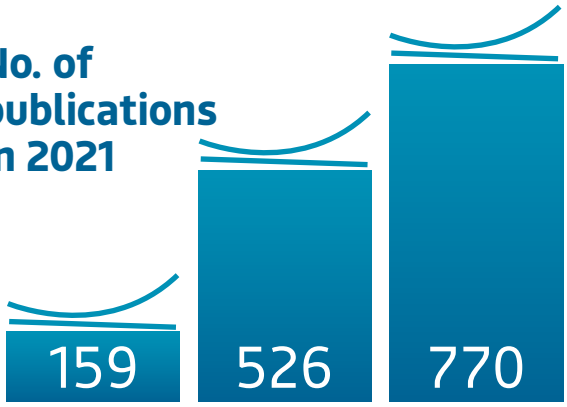
Work has also been carried out on purging the database and filling in incomplete fields.

Simultaneously, work has been carried out on authorship regulations for collective projects that use FatBank samples.

SCIENTIFIC PRODUCTION

Publications

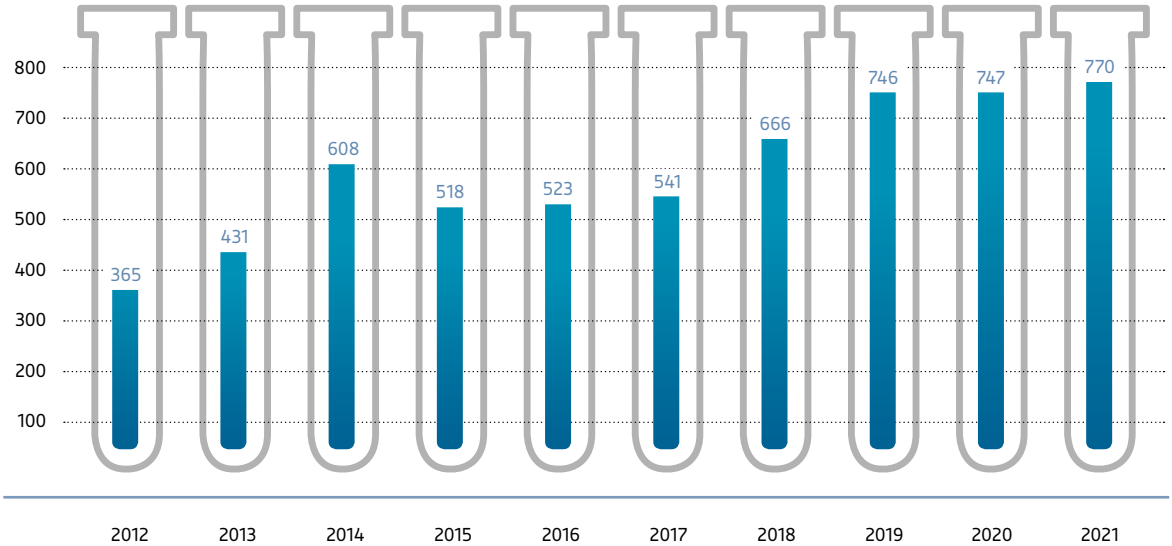
No. of publications in 2021



Collaborations

*Among various thematic areas

Evolution of publications



10 most relevant publications by impact factor

FI	Publication
39,397	Endogenous retroelement activation by epigenetic therapy reverses the Warburg effect and elicits mitochondrial-mediated cancer cell death.
29,983	Lipoprotein(a), LDL-cholesterol, and hypertension: Predictors of the need for aortic valve replacement in familial hypercholesterolaemia
27,287	Mitochondrial cristae-remodeling protein OPA1 in POMC neurons couples Ca2+ homeostasis with adipose tissue lipolysis
23,059	Obesity-Associated Deficits in Inhibitory Control Are Phenocopied to Mice through Gut Microbiota Changes in One-Carbon and Aromatic Amino Acids Metabolic Pathways
17,956	Increasing breast milk betaine modulates Akkermansia abundance in mammalian neonates and improves long-term metabolic health
17,425	Metabolic Landscape of the Mouse Liver by Quantitative 31P Nuclear Magnetic Resonance Analysis of the Phosphorome
17,425	The L-α-Lysophosphatidylinositol/G Protein–Coupled Receptor 55 System Induces the Development of Nonalcoholic Steatosis and Steatohepatitis
16,195	The return of malonyl-CoA to the brain: Cognition and other stories
14,919	O-GlcNAcylated p53 in the liver modulates hepatic glucose production
14,919	BMP8 and activated brown adipose tissue in human newborns
14,919	MMAB promotes negative feedback control of cholesterol homeostasis

CIBEROBN Groups, Publications in 2021

Group Leader	Publications	Q1	D1	Institution - Center	Province
Argente Oliver, Jesús	35	23	3	Servicio Madrileño de Salud	Madrid
Baños, Rosa María	55	32	32	Universidad de Valencia	Valencia
Corella Pique, Dolores	56	39	18	Universidad de Valencia	Valencia
Diéguez, Carlos	30	29	15	Universidad de Santiago de Compostela	Coruña, A
Estruch Riba, Ramón	54	36	13	Hospital Clínico y Provincial de Barcelona	Barcelona

Group Leader	Publications	Q1	D1	Institution - Center	Province
Fernandez Aranda, Fernando	44	30	3	Fundación IDIBELL	Barcelona
Fernandez Real, José Manuel	19	15	7	Fundación Instituto de Investigación Biomédica de Girona	Girona
Fito Colomer, Monserrat	79	51	18	Consorci Mar Parc Salut de Barcelona	Barcelona
Frühbeck Martínez, Gema	33	20	3	Universidad de Navarra	Navarra
Gil Campos, Mercedes	25	19	3	Fundación para la Investigación Biomédica de Córdoba (FIBICO)	Córdoba
Lamuela, Rosa María	25	19	13	Universidad de Barcelona	Barcelona
Lasunción Ripa, Miguel Ángel	27	20	7	Servicio Madrileño de Salud	Madrid
López Miranda, José	52	37	15	Fundación para la Investigación Biomédica de Córdoba (FIBICO)	Córdoba
Lurbe Ferrer, Empar	17	8	3	Consorcio Hospital General Universitario Valencia	Valencia
Martínez González, Miguel Ángel	96	59	26	Universidad de Navarra	Navarra
Moreno Aliaga, María Jesús	78	55	14	Universidad de Navarra	Navarra
Moreno Aznar, Luis Alberto	54	37	11	Fundación Instituto de Investigación Sanitaria Aragón	Zaragoza
Ortega, Emilio	64	38	12	Hospital Clínico y Provincial de Barcelona	Barcelona
Osada, Jesús	18	13	2	Universidad de Zaragoza	Zaragoza
Palou Oliver, Andreu	16	15	4	Universidad de las Islas Baleares	Illes Balears
Pintó Salas, Xavier	41	31	10	Fundación IDIBELL	Barcelona
Portillo Baquedano, María Del Pui	19	13	3	Universidad de Barcelona	Barcelona
Herrero, Laura	20	16	4	Universidad del País Vasco	Álava
Romaguera Bosch, M. Adoración	50	36	15	Fundación Instituto de Investigación Sanitaria Illes Baleares (IdISBa)	Illes Balears
Salas Salvadó, Jordi	83	62	23	Fundación Instituto de Investigación Sanitaria Pere Virgili	Tarragona
Santos Lozano, José M.	30	21	7	Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla	Sevilla

Group Leader	Publications	Q1	D1	Institution - Center	Province
Seoane Camino, Luisa María	18	12	5	Servicio Gallego de Salud	Coruña, A
Serra Majem, Lluís	49	36	15	Universidad de las Palmas de Gran Canaria	Palmas, Las
Tena Sempere, Manuel	33	25	10	Universidad de Córdoba	Córdoba
Tinahones Madueño, Francisco José	69	52	15	Fundación Pública Andaluza para la Investigación de Málaga en Biomedicina y Salud (FIMABIS)	Málaga
Tur Mari, Josep A	107	74	24	Universidad de las Islas Baleares	Illes Balears
Villarroya Gombau, Francesc	20	14	7	Universidad de Barcelona	Barcelona

Patents owned by CIBER 2021

Applications

- Method for monitoring or predicting whether a patient suffering from obesity is responding or will respond to a very-low-calorie ketogenic diet (VLCKD) - EP21382469.1
- Bacteriophage for therapeutic use- P202130786
- Epigenetic biomarkers for the diagnosis and prevention of the evolution of metabolically healthy obese subjects to metabolically unhealthy obese subjects- P202130903
- Gut microbiota composition and uses thereof - PCT/EP2021/068078
- Compositions and methods for treating metabolic disorders - PCT/US21/65757
- Nanosystem based on MicroRNA for the treatment of obesity (FIMABIS-18002) - EP20755751.3
- Nanosystem based on MicroRNA for the treatment of obesity (FIMABIS-18002) - US17/599,463

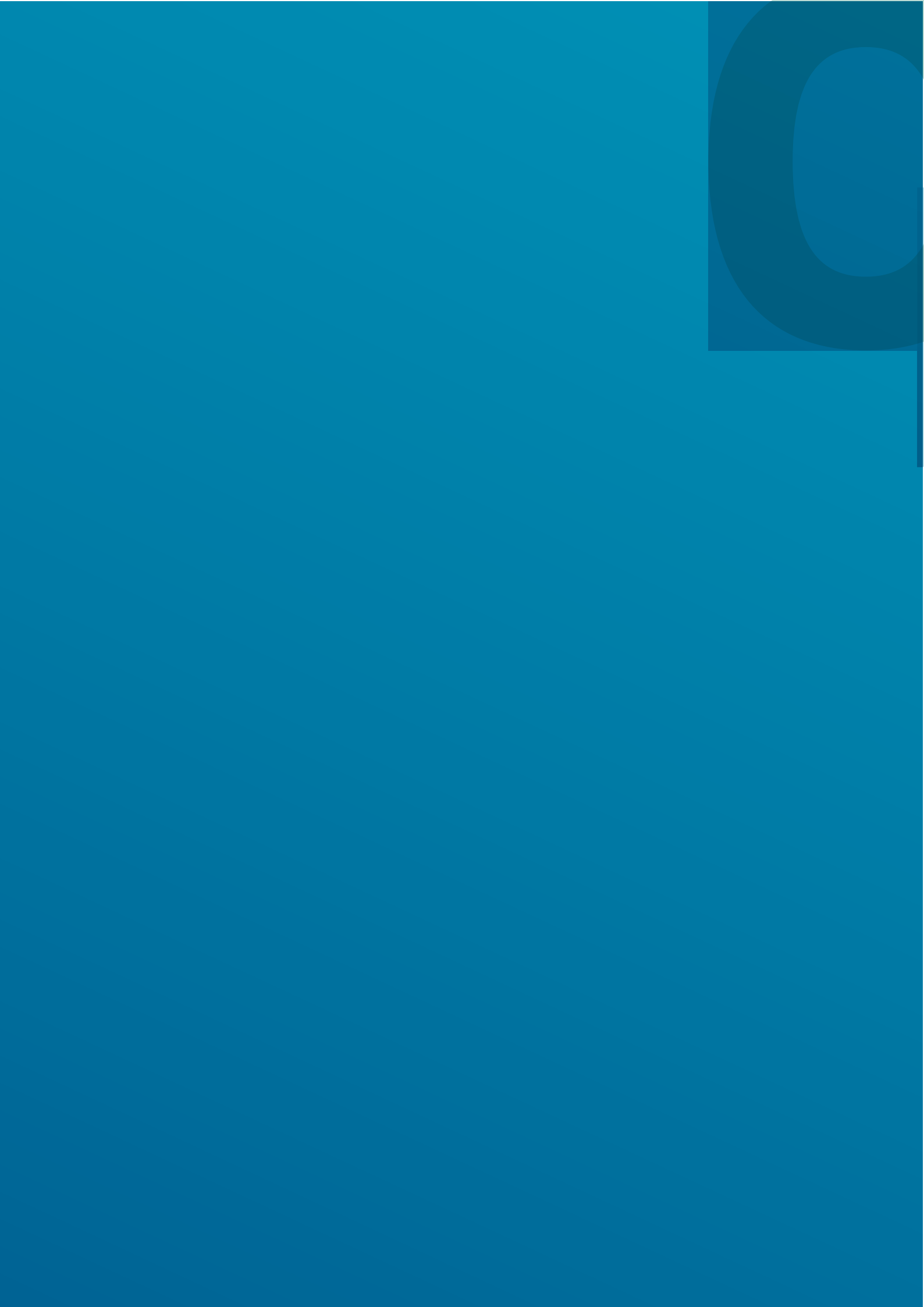
Clinical Guidelines 2021

- Personalized nutrition: Guide of basic recommendations in research and its application
- How to achieve a healthier and more sustainable diet: Guide in the university setting
- Design of studies and analysis of omics data with a gender perspective and sustainability in cardiometabolic and neurocognitive diseases: Guide for its implementation
- Mendelian randomization studies: A guide for clinicians
- Metagenomics in the integration of omics with a gender perspective: Guide for its implementation
- Consensus on the nomenclature of hospital diets
- Food guide and healthy and sustainable lifestyle.
- Position statement on the definition of added sugars and their declaration on the labeling of foodstuffs in Spain
- Impact of statin therapy on LDL and non-HDL cholesterol levels in subjects with heterozygous familial hypercholesterolaemia
- Monograph: Diagnosis of triglyceride metabolism disorders: from pathophysiology to clinical practice
- Obesity is a chronic disease. Positioning statement of the Diabetes, Obesity and Nutrition Workgroup of the Spanish Society of Internal Medicine (SEMI) for an approach centred on individuals with obesity
- Executive Summary of Expert Consensus on the effectiveness and safety of iDPP-4 in the treatment of patients with diabetes and COVID-19
- 2021 European Society of Hypertension practice guidelines for office and out-of-office blood pressure measurement

- SEEN Comprehensive Clinical Approach to Obesity in Adulthood: Executive Summary
- Executive summary: Updates to the dietary treatment of prediabetes and type 2 diabetes mellitus
- Recommendations for the diagnosis and treatment of hypoglycemia after bariatric surgery
- Consensus on diagnosis and management of Cushing's disease: a guideline update
- Practical guidance for combination lipid-modifying therapy in high- and very-high-risk patients: A statement from a European Atherosclerosis Society Task Force
- Practical guide for the management of anemia of nutritional origin
- Practical guide to nutrition in childhood
- Guidelines for the use and interpretation of assays for monitoring autophagy
- Could the covid-19 pandemic be an opportunity for improvement of our care, training and research activities?
- Obesity and COVID-19. A necessary position statement
- Non-alcoholic fatty liver disease: A patient guideline
- Vaccinating People with Obesity for COVID-19: EASO Call for Action

CIBERONC

Cancer



Presentation by the scientific director

Anna Bigas Salvans

Dear Colleagues,

For the second year in a row, it is a pleasure for me to present to you the work that has been developed in the CIBERONC network throughout 2021. This year has been a successful year for CIBERONC and a gradual return to the old normality in the laboratories. Scientific activity has been able to be recovered and the results of the scientific activity reflect this, as will be shown in the following pages of this document. In addition, collaborative work and the strengthening of relationships have also borne fruit, resulting in the presentation of collaborative research projects that have been granted and that now face an ambitious program to be developed.

Thus, at an international level, CIBERONC participates in a strategic European project framed within the Cancer Mission and led by the researcher Josep Tabernero, which will be key to defining the scientific priorities of the mission and of cancer research until 2027.

At the national level, CIBERONC is actively involved in the recent commitment to Personalized Medicine that has been carried out by the ISCIII, with the INGENIO project-led by the researcher Luis Paz-Ares, being the most important project developed in our network since our creation.

Internally, the call for intramural projects resolved in 2021 has financed two highly collaborative projects, led by the researchers Núria Malats Riera and Patricia Pérez Galán, addressing tumor analysis in selected pathologies from the perspectives of digital pathology and the development of experimental models, respectively. These two initiatives

aspire to converge, giving rise to a perfectly characterized cohort of patient samples that will serve as an added value for CIBERONC for our participation in large international research initiatives.

Finally, two big events have taken place this year. On the one hand, the annual general meeting, at the beginning of the year and in online format, was the meeting point for all our main researchers and groups to share the advances in the research developed by the programs. This meeting served as a framework to hold the annual awards for the Best Young Lead Researcher and the Best Researcher, awarded in this edition to Pedro Berraondo López and Sílvia Beà Bobet, respectively.

On the other hand, the meeting of Young Researchers, towards the end of the year and held in person, had an excellent reception and was an unbeatable opportunity for the development of connections and contacts by the youngest members of our network.

I would like to end by thanking all of you for the work you do and the commitment you show to CIBERONC, without which none of what is presented here would be possible.

Warm regards to all.

PROGRAMS

PROGRAM 1

Digestive tract tumors

COORDINATOR:
Gabriel Capellà Munar

PREMEDGI (*Research Program on PRecision MEdicine in GI Oncology*) has structured the activity of the CIBERONC Gastrointestinal Tumors Program since last year with a focus on colorectal and pancreatic tumors. In 2021, the most relevant results of the Program have been the following.

As regards objective 1 led by Dr. Capellá's group, the project has evolved towards the creation of the National Registry of Genetic Variants in Cancer Predisposition Genes, which will be of great help in refining the classification of germline genetic variants identified in cancer predisposition genes, as well as determining their population prevalence, associated risks, etc. This registry can be linked with an identifier to the national database of clinical information on patients with hereditary cancer (SEOM Foundation, VHIO and ICO). Objective

2, on the independent research project on predictive factors of response in the neoadjuvant treatment of PDAC (clinically led by the groups of Drs Feliú and Carrato and with the participation of 4 more groups), has begun to be weighed down by the impact of COVID-19 which has led to a significant decrease in patients diagnosed with locoregional disease. Objective 3 of our program deals with the molecular classification of metastatic colorectal cancer led by Dr. Cervantes's group with the collaboration of 5 groups of the program. The expression profiles of 102 of the paired samples of primary tumor and liver metastases are being analyzed.

Regarding cross-cutting projects, we highlight the leadership of Dr. Malats, principal investigator of the *Cancer Stroma Assessment through Digital Pathology* (CASA-DP) strategic action, in which Dr. Real also participates. Dr. Toledo from Dr. Tabernero's group leads the liquid biopsy work module that promotes comparability of results between centers. Finally, we highlight that Drs. Capella and Tabernero lead the Cancer WP of the IMPaCT-Genomics Project, which aims to create an infrastructure for the implementation of Genomic Medicine in the National Health System.

PROGRAM 2

Breast cancer

COORDINATOR:
Joaquín Arribas López

Despite the difficulties caused by the latest waves of the pandemic, the Breast Cancer Program has managed to advance in its objectives during 2021. In terms of precision therapies, Joan Albanell's group has made a significant discovery in the field of **immunotherapy** based on immune checkpoint inhibitors. In collaboration with other groups of the Program (Joaquín Arribas) and other Programs (Roger Gomis), Dr. Albanell's group has characterized how the LCOR protein mediates the tumor immune response independently of interferon, and favors the efficacy of treatment with ***checkpoint inhibitors*** (Celià et al. *Nature Cancer*). These results open up new therapeutic avenues that the group is currently investigating. On the other hand, using samples from patients included in a phase III clinical trial, Miguel Martín's group has shown that palbociblib in combination with endocrine therapy does not provide a significant advantage over treatment with capecitabine in HER2-positive and ER+ metastatic breast cancer resistant to aromatase inhibitors (Martin et al. *Annals of Oncology*).

Regarding new treatments directed against HER2-positive tumors, Dr. Atanasio Pandiella's group has shown that BETi-PROTAC can restore sensitivity to tumors that have developed resistance to standard treatment based on trastuzumab (Noblejas-López et al. *J Exp Clin Cancer Res*).

Regarding the identification of new **resistance mechanisms**, the group of Dr. Joaquín Arribas has made great advances, describing a mechanism that makes cancer cells resistant to cytotoxic lymphocytes redirected against them -whether the redirection is mediated by bispecific T-cell antibodies or CAR T- by repressing JAK2 expression (Arenas et al. 2021; Martínez-Sabadell et al. 2021). On the other hand, the group led by Dr. Gema Moreno has characterized how the E2A factor modulates resistance and tumor progression in breast cancer (López-Menéndez et al. *Cancer Research*)

Finally, in relation to the generation of **experimental models**, the number of PDXs (Patient-Derived Xenograts) established from all breast cancer subtypes has increased. With samples of these PDXs, a Tissue Micro Array (TMA) has been generated that is being used to analyze various markers by the groups of the program. This activity has been carried out in collaboration with the Experimental Models Work Module. It is expected that this tool will be used in numerous collaborative projects in the coming years.

Lastly, it is worth noting that we have been able to resume our coordination activities. After a year without face-to-face meetings, the Program was able to hold a semi-face-to-face meeting in Madrid, where the groups presented their progress and new lines of collaboration were established in line with the Program's objectives. In 2022, we hope to continue these meetings which are critical for the coordination of the program.

PROGRAM 3

Respiratory tract tumors

COORDINATOR:
Luis Montuenga Badía

Throughout 2021, the respiratory tract program has continued its collaborative research between CIBER groups in the three fundamental areas of the program: new drivers, immuno-oncology and biomarkers.

In the group led by Dr. Silve Vicent, and in collaboration with Dr. Fernando Lecanda, cell lines have been developed with alterations in tumor suppressor genes in which they have made an exhaustive characterization using cyto-flex, single-cell RNAseq and multispectral immunofluorescence, opening the door to seeing the sensitivity to different compounds depending on the genotype.

Dr. Juan Pablo Rodrigo Tapia's group has been working to identify new therapeutic targets in head and neck cancer, such as VAP2, YAP/TAZ, YES1 and IDH in sinonasal cancers. They have also described for the first time the immune checkpoint LLT1, which is related to a worse prognosis in patients. Finally, thanks to biomarkers that they have identified for an early diagnosis of head and neck cancer, they have managed to segregate lesions with cancer risk into three subtypes.

Dr. Luis Paz-Ares leads the INGENIO project, in which numerous groups from CIBERONC and other CIBERs participate. This project aims to search for predictive biomarkers from the creation of a cohort of patients with lung cancer, in whom digital pathology of histopathological and radiological images will also be performed. During the year 2021, a genomic and transcriptomic landscape study of lung cancer has been carried out, where groups of tumors with similar transcriptomic and genomic signatures have been determined to identify subgroups of tumors that give rise to specific immune phenotypes making it possible to identify which therapeutic targets could be useful.

The group led by Dr. Carlos Camps has generated Trametinib-resistant cell lines, where they have identified different resistance mechanisms and are testing drugs in combination with Trametinib and Sotorasib, carrying out transcriptomic analyzes in parental and resistant lines. Additionally, they participate in CIBERONC collaborative projects, such as PDO 2.0. of the Strategic Actions of CIBERONC and Euronanomed, which has the objective of generating drug-decorated nanoparticles.

Finally, Dr. Amancio Carnero's group has identified a new target in laryngeal cancer, with the ability to inhibit and eradicate tumors. In combination with cisplatin or capecitabine, it is capable of eradicating tumors in head and neck tumor lines.

In lung cancer, they have identified a 6-gene predictive and prognostic signature based on transcriptional expression that is capable of predicting the response to radiotherapy. Studies have been carried out on 15 cell lines and it has also been validated in patients treated with radiotherapy, regardless of the chemotherapy treatment they received.

It should be noted that the researchers of this program are involved in CIBERONC's transversal collaborative projects. On the one hand, the INGENIO project, led by Dr. Luis Paz-Ares and which includes the collaboration of other program researchers, as well as in strategic actions, with the outstanding participation of program researchers in both Projects.

PROGRAM 4

Hematological tumors

COORDINATOR:
Dolors Colomer Pujol

In 2021, the program has continued with numerous collaborative works between CIBER groups and with the Spanish and international collaborative hematology working groups.

The most relevant collaborative results of the Hematological Tumors Program in line with the objectives of the program are detailed below.

The results have been published on the importance of the analysis of minimal residual disease by flow cytometry in acute myeloblastic leukemia (AML) (*Leukemia*;35:2358-70, 2021), in acute lymphoblastic leukemia (ALL) (*Blood* 137:1879-94, 2021; *Hematol Oncol.* 39:529-38, 2021) and in multiple myeloma (MM) (*Blood.* 137:49-60, 2021), as well as the description of the importance of networking in the Pethema-AML project (*Haematologica*, 106:3079-89, 2021).

In monoclonal gammopathies, the differentiation of a normal plasma cell and its transcriptional rearrangement in amyloidosis have been analyzed using single-cell RNAsequencing technology (*Blood*, 138:1583-9, 2021) and immunogenetic characterization in amyloidosis has been de-

scribed (*Leukemia*, 35:245-9, 2021). lncRNAs have been characterized in MM (*Leukemia*, 35:1438-50, 2021) and it has been described that gene expression derived from alternative promoters improves the prognostic stratification of these patients (*Leukemia* 35:3012-6, 2021). A new prognostic score for mastocytosis has also been proposed (*Lancet Haematol*.8:e194-e204, 2021).

In mantle cell lymphoma (MCL) it has been described that SOX11, CD70, and Treg cells configure the tumor microenvironment (*Blood*;138:2202-15, 2021). The importance of using cfDNA for mutational analysis in diffuse large cell lymphoma (DLCL) has been described (*Clin Cancer Res.*;27:513-21, 2021) and work has been furthered in the molecular classification of the peripheral T lymphomas (*Blood Adv*, 5:5588-98, 2021).

Epigenetic studies have described the dynamics of genome architecture and chromatin function during B differentiation and its neoplastic transformation (*Nat Commun*, 12:651, 2021) and that the loss of m1A RNA demethylase ALKBH3 in Hodgkin's lymphoma confers a worse prognosis (*Blood*, 137:994-9, 2021).

As for new therapies, it has been described that epigenetic therapies remodel mitochondrial metabolism and sensitize BCL2 inhibitors, thus supporting the use of hypomethylating agents and venetoclax in AML (*Cancer Discov*, 11:1268-85, 2021) and that CSF-1R may be a new target in follicular lymphoma (*Leukemia*, 35:2635-49, 2021).

In terms of clinical trials, worth noting is the publication of the results obtained in the clinical trial of the first academic CART (chimeric antigen receptor T cells) (CAR-T-ARI-001) led by CIBERONC researchers and authorized by the AEMPS (Spanish Agency for Medicines and Medical Devices) for patients with ALL. (*Mol Ther*.29:636-44, 2021)).

As regards collaborative projects, to be highlighted is the awarding of the project "PRE-GEN-LINF: Genomic precision medicine in Lymphoid Neoplasms", (PMP21/00015) led by Elías Campo and with the participation of 6 CIBERONC groups to be developed over the next 4 years.

PROGRAM 5

Low prevalence tumors

COORDINATOR:
Enrique de Álava Casado

A. The challenge of our program for 2021 was to carry out two cooperative research projects on two low-prevalence tumors, selected from a group of entities as broad and heterogeneous as are those targeted by this Program.

A.1. Between 2020 and 2021, the focus was on generating data within the cooperation project of the program on uveal melanoma, a neoplasm in which until now it had not been possible to carry out a translational project at the national level. For this project, the program had obtained additional funding through an award given by GETHI (Spanish task force group for orphan and infrequent tumors) in 2017. Specifically, the program achieved the following two milestones.

- Evaluation and quantification of Endoglin (EDG) / MMP14 expression levels and HIPPO pathway YAP/TAZ effectors in 4 independent cohorts of paired uveal melanoma samples.
- Generation of EDG, MMP14, TAZ and YAP deletion models by genome editing using CRISPR-Cas9 technology,

which were used to assess the functionality of these molecules in in vitro and in vivo models of uveal melanoma. The generation of additional results from this first cooperative project of the Program continues at this time.

A.2. Throughout 2021 we have continued a second cooperative project, which has as its object the **immunological panorama of uterine tumors**. Each group provided tools, samples and clinical data on this tumor, 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 Scientific Advisory Board of CIBERONC*. Milestones through the end of December 2021 included:

- Performance of the multiparametric and multicenter pilot study on the characterization of a small series of endometrial carcinomas by studying the stroma and tensegrity (Gomoripath), the immunophenotypic characterization of the stromal cells (Vectra-Polaris), and the genomic characterization of tumor and stromal cells. This has allowed the molecular and architectural characterization of the invasive tumor front of uterine malignancies: specifically, we have assessed whether these findings provide information of additional prognostic value on established prognostic factors.

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

B. During 2021, the execution of two cooperative projects has continued in which the Program is involved for the financing of activity in uterine tumors: Marató-TV3 Project endometrial carcinoma (2019: €396k); Project of excellence of the Junta de Andalucía (Government of Andalusia) on endometrial stromal sarcoma (2019: €400k). A new project has been obtained: ECLAI: Personalized Clinical Management of Endometrial Cancer using Liquid Biopsy, Genomics and Artificial Intelligence" (EraPerMed2021 call) (PIs Laura Muinelo/Gema Moreno).

PROGRAM 6

Tumor progression mechanisms

COORDINATOR:
Xosé R. García Bustelo

In the research area of discovery and characterization of protumorigenic molecules, Xosé Bustelo's group has cataloged 51 VAV1 proto-oncogene mutations detected in cancer patients. This work made it possible to demonstrate that most of these mutations differentially altered the downstream signaling pathways of the protein encoded by this gene, which allowed their classification into 5 different functional categories. This work also demonstrated that the most frequent functional subclass acts as a "driver", giving rise to the rapid formation of peripheral T-cell lymphomas that are very similar at the immunophenotypic and molecular level to those of patients (EMBO J 7: e108125). In addition to identifying the functional impact of these mutations, this work has allowed the development of a new animal model of interest for the study of the etiology of this disease as well as the pre-clinical testing of new drugs against it. Dr. Eugenio Santos, for his part, has established the leading role of SOS proteins (RAS oncoprotein activators) in skin cancer (Cancers 13:2152). These data suggest that these proteins could be good therapeutic targets, which has led to the search for inhibitors against them (see below).

In the area focused on developing new diagnostic and therapeutic tools, Pablo Menéndez's group (Dr. Anna Bigas' group) has identified therapeutic vulnerabilities in a subtype of childhood B-cell lymphoblastic leukemia through integrative analysis of the methylome and transcriptome from a large number of patient samples (J Clin Inv 131: e138833). This work has had repercussions in the field, given how little was known about this type of childhood leukemia. Dr. Joan Seoane's group has developed a new method for analyzing immune system cells present in cerebrospinal fluid that allows the characterization of the microenvironment created by brain metastases (Nat Commun 12: 1503). This method will have a direct impact on clinical decisions, such as the appropriateness of using specific immunotherapy protocols in patients with this type of metastasis. The laboratory of Roger R. Gomis (Arkaitz Carracedo's group) has established the role of MAF gene amplification in various therapeutic responses in breast cancer patients (JNCI Cancer Spectr 5: pkab054) which, in turn, offers a very relevant diagnostic tool from the clinical point of view. The laboratories of Drs. Lluis Espinosa (Anna Bigas' laboratory) and Jesús M. Paramio have patented new biomarkers that will allow a better diagnosis of colorectal cancer patients (EP21382269.5) and the response of bladder cancer patients to bacillus Calmette-Guérin (PCT/ES2021/070204), respectively. Finally, Eugenio Santos' group has developed new inhibitors against the catalytic activity of SOS proteins (Biomolecules 11:1128). These inhibitors have potential interest for RAS-dependent tumors.

During this year, the researchers of the Program have obtained international funding through 11 research projects. I addition, 3 meetings of the Program have been organized specifically aimed at principal, pre-doctoral and post-doctoral researchers.

PROGRAM 7

Training

COORDINATOR:
Gema Moreno Bueno

The most outstanding activities of the Training and Mobility Program have been focused on the following sub-programs:

Promotion of young researchers

SThe IV edition of the Young Researchers Conference (IV YRM, December 13-14, 2021) was held in a hybrid format, with the face-to-face part being held at the PRBB-Barcelona (Barcelona Biomedical Research Park). 142 attendees participated in this event and it was followed online by 95 participants. For the first time, these conferences were held in collaboration with another CIBER, specifically CIBER-BBN. The organization of the meeting was carried out by a scientific committee made up of young researchers (pre-doctoral and junior postdoctoral) from both CIBERONC and CIBER-BBN. In this edition, 107 abstracts were received, with two papers selected from each CIBERONC program and also from CIBER-BBN to be presented in a talk. In addition, the congress included two keynote presentations, one given by Dr. López-Bigas (CIBERONC) and another by Dr. Trepat (CIBER-BBN). Finally, three discussion tables focused on machine learning and precision medicine,

publications in high-impact journals, and dissemination of scientific findings on social networks were included. Two prizes were awarded, one for the best oral communication and one for the best poster, voted for among the attendees. After the event, a survey was carried out to analyze their evaluation, which obtained an excellent or very good rating.

Initiation to research

To be highlighted is the research initiation contract program, which are fully financed by the Training and Mobility Program. During 2021, nine 6-month contracts were offered and 16 proposals were received. The number of contracts offered was significantly higher than in other years because the Program received an additional budget from the CIBERONC Management.

Mobility

4 short stays in international groups and 4 in national groups were financed, 3 of them between CIBERONC laboratories and one interdisciplinary stay in a laboratory belonging to another CIBER area..

Training

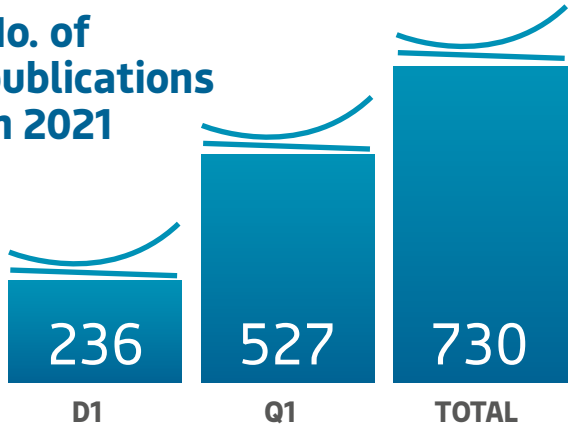
The attendance of researchers from our network to 10 courses outside CIBERONC was financed, which were mostly online registrations for an international congress and attendance at a course on fluorescent imaging techniques.

The activities carried out by the Mobility and Training Program were evaluated as excellent at the meeting held with the external advisory committee in October 2021.

SCIENTIFIC PRODUCTION

Publications

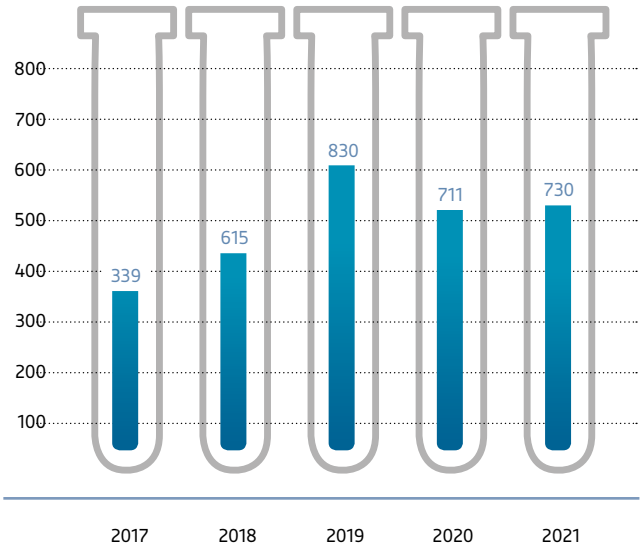
No. of publications in 2021



Collaborations

*Among various thematic areas

Evolution of publications



10 most relevant publications by impact factor

IF	Publication
91,245	Nathan P, Hassel JC, Rutkowski P, et al. Overall Survival Benefit with Tebentafusp in Metastatic Uveal Melanoma. N Engl J Med. 2021;385(13):1196-1206. doi:10.1056/NEJMoa2103485
91,245	Munshi NC, Anderson LD Jr, Shah N, et al. Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma. N Engl J Med. 2021;384(8):705-716. doi:10.1056/NEJMoa2024850
66,675	Melero I, Castanon E, Alvarez M, Champiat S, Marabelle A. Intratumoural administration and tumour tissue targeting of cancer immunotherapies. Nat Rev Clin Oncol. 2021;18(9):558-576. doi:10.1038/s41571-021-00507-y
60,716	Tauriello DVF, Sancho E, Batlle E. Overcoming TGFβ-mediated immune evasion in cancer. Nat Rev Cancer. 2022;22(1):25-44. doi:10.1038/s41568-021-00413-6
49,962	Powles T, Assaf ZJ, Davarpanah N, et al. ctDNA guiding adjuvant immunotherapy in urothelial carcinoma. Nature. 2021;595(7867):432-437. doi:10.1038/s41586-021-03642-9
46,802	Sangro B, Sarobe P, Hervás-Stubbs S, Melero I. Advances in immunotherapy for hepatocellular carcinoma. Nat Rev Gastroenterol Hepatol. 2021;18(8):525-543. doi:10.1038/s41575-021-00438-0
44,544	Piulats JM, Espinosa E, de la Cruz Merino L, et al. Nivolumab Plus Ipilimumab for Treatment-Naïve Metastatic Uveal Melanoma: An Open-Label, Multicenter, Phase II Trial by the Spanish Multidisciplinary Melanoma Group (GEM-1402). J Clin Oncol. 2021;39(6):586-598. doi:10.1200/JCO.20.00550
44,544	Bersanelli M, Travaglino E, Meggendorfer M, et al. Classification and Personalized Prognostic Assessment on the Basis of Clinical and Genomic Features in Myelodysplastic Syndromes. J Clin Oncol. 2021;39(11):1223-1233. doi:10.1200/JCO.20.01659
44,544	Bellini A, Pötschger U, Bernard V, et al. Frequency and Prognostic Impact of ALKAmplifications and Mutations in the European Neuroblastoma Study Group (SIOPEN) High-Risk Neuroblastoma Trial (HR-NBL1). J Clin Oncol. 2021;39(30):3377-3390. doi:10.1200/JCO.21.00086
44,544	Avet-Loiseau H, San-Miguel J, Casneuf T, et al. Evaluation of Sustained Minimal Residual Disease Negativity With Daratumumab-Combination Regimens in Relapsed and/or Refractory Multiple Myeloma: Analysis of POLLUX and CASTOR. J Clin Oncol. 2021;39(10):1139-1149. doi:10.1200/JCO.20.01814
44,544	Buske C, Tedeschi A, Trotman J, et al. Ibrutinib Plus Rituximab Versus Placebo Plus Rituximab for Waldenström's Macroglobulinemia: Final Analysis From the Randomized Phase III iNNOVATE Study. J Clin Oncol. 2022;40(1):52-62. doi:10.1200/JCO.21.00838

CIBERONC Groups, Publications in 2021

Group Leader	Publications	Q1	D1	Institution - Center	Province
Álava Casado, Enrique de	16	9	5	Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla	Sevilla
Alba, Emilio	15	15	3	Universidad de Málaga	Málaga
Albanell, Joan	20	13	6	Consorci Mar Parc Salut de Barcelona	Barcelona
Aranda, Enrique	24	16	4	Fundación para la Investigación Biomédica de Córdoba (FIBICO)	Córdoba
Arribas, Joaquín	8	8	5	Consorci Mar Parc Salut de Barcelona	Barcelona
Batlle, Eduard	7	6	6	Fundación privada Instituto de Recerca Biomédica (IRB-Barcelona)	Barcelona
Bigas, Anna	19	16	9	Consorci Mar Parc Salut de Barcelona	Barcelona
Campo, Elías	31	24	20	Instituto de Investigaciones Biomédicas August Pi i Sunyer	Barcelona
Camps, Carlos	25	17	3	Consorcio Hospital General Universitario Valencia	Valencia
Capella, Gabriel	35	26	9	Fundación IDIBELL	Barcelona
Carnero, Amancio	8	7	2	Agencia Estatal Consejo Superior de Investigaciones Científicas	Sevilla
Carracedo, Arkaitz	14	11	7	CIC BIOGUNE	Vizcaya
Carrato, Alfredo	22	15	3	Servicio Madrileño de Salud	Madrid
Cervantes, Andrés	13	13	5	Fundación para la Investigación del Hospital Clínico de la Comunidad Valenciana (Fundación INCLIVA)	Valencia
Colomer, Dolors	31	22	12	Instituto de Investigaciones Biomédicas August Pi i Sunyer	Barcelona
Crespo, Pedro	5	2	2	Agencia Estatal Consejo Superior de Investigaciones Científicas	Cantabria
Esteller, Manel	30	25	13	Fundación Instituto de Investigación contra la Leucemia Josep Carreras	Barcelona
Feliú, Jaime	38	20	4	Servicio Madrileño de Salud	Madrid

Group Leader	Publications	Q1	D1	Institution - Center	Province
García Bustelo, Xosé Ramon	8	6	1	Fundación de Investigación del Cáncer de la Universidad de Salamanca	Salamanca
García Sanz, Ramon	62	41	18	Fundación Instituto de Estudios de Ciencias de la salud de Castilla y León	Salamanca
López López, Rafael	49	36	10	Servicio Gallego de Salud	Coruña, A
López Otín, Carlos	7	5	5	Universidad de Oviedo	Asturias
Malats, Núria	10	7	3	Fundación Centro Nacional de Investigaciones Oncológicas	Madrid
Martin, Miguel	22	15	7	Servicio Madrileño de Salud	Madrid
Matias-Guiu, Francisco J.	38	31	14	Instituto de Investigación Biomédica de Lleida. Fundación Dr. Pifarre	Lleida
Melero, Ignacio	25	22	17	Universidad de Navarra	Navarra
Montuenga, Luis	18	15	11	Fundación para la Investigación Médica Aplicada	Navarra
Moreno, Gema	7	6	2	Universidad Autónoma de Madrid	Madrid
Muñoz, Alberto	6	6	1	Agencia Estatal Consejo Superior de Investigaciones Científicas	Madrid
Noguera, Rosa	11	5	2	Fundación para la Investigación del Hospital Clínico de la Comunidad Valenciana (Fundación INCLIVA)	Valencia
Orfao, Jose Alberto	32	24	10	Fundación de Investigación del Cáncer de la Universidad de Salamanca	Salamanca
Palacios, Jose	7	4	1	Servicio Madrileño de Salud	Madrid
Pandiella, Atanasio	21	19	4	Agencia Estatal Consejo Superior de Investigaciones Científicas	Madrid
Paramio, Jesús María	23	16	10	Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas (CIEMAT)	Madrid
Paz-Ares, Luis	46	31	19	Servicio Madrileño de Salud	Madrid
Piris, Miguel Ángel	14	11	6	Instituto de Investigación Sanitaria Fundación Jiménez Díaz	Madrid
Prósper, Felipe	26	24	15	Fundación para la Investigación Médica Aplicada	Navarra

Group Leader	Publications	Q1	D1	Institution - Center	Province
Ramón y Cajal, Santiago	18	6	1	Fundación Hospital Universitario Vall d´Hebron - Institut de Recerca (VHIR)	Barcelona
Real, Francisco	8	7	6	Fundación Centro Nacional de Investigaciones Oncológicas	Madrid
Rodríguez Tapia, Juan Pablo	32	17	2	Fundación para la Investigación e innovación Biosanitaria en el Principado de Asturias (FINBA)	Asturias
San Miguel, Jesús Fernando	47	39	29	Universidad de Navarra	Navarra
Santisteban Sanz, M. Pilar	8	8	2	Agencia Estatal Consejo Superior de Investigaciones Científicas	Madrid
Santos de Dios, Eugenio	7	4	1	Fundación de Investigación del Cáncer de la Universidad de Salamanca	Salamanca
Sanz Santillana, Guillermo	40	19	9	Fundación para la Investigación del Hospital Universitario y Politécnico la Fe de la Comunidad Valenciana	Valencia
Seoane, Joan	9	9	7	Fundación Privada Instituto de Investigación Oncológica Valle de Hébron-VHIO	Barcelona
Tabernero, Josep María	13	11	8	Fundación Privada Instituto de Investigación Oncológica Valle de Hébron-VHIO	Barcelona

Patents owned by CIBER 2021

Applications

- PCT/ES2021/070951 Biomarkers and method to predict treatment response with BRAF and MEK inhibitors (BRAFi + MEKi) and for patient follow-up
- EP21382269.5 Genomic predictor of outcome in cancer

CIBERSAM

Mental Health

Presentation by the scientific director

Eduard Vieta Pascual

To speak of CIBERSAM in 2021 is to once again speak of the Covid-19 pandemic and also of its terrible impact on the mental health of the world population. In 2021 the pandemic entered a phase of a certain measure of control, thanks to mass vaccination and what we have learned from research, but we are witnessing an outbreak of cases of various psychiatric pathologies derived from pandemic-induced stress, difficulties in accessing care and the post-covid aftermath. CIBERSAM has responded with collaborative and translational work, publishing a record number of articles (957), including 149 on Covid-19 and mental health. In addition, the training activities have been adapted to virtual formats and a great effort has been made to combine research, care and teaching. 32 clinical practice guidelines have been published, 3 patents have been registered, and the Programs, Platforms and research groups have coordinated like never before to exploit data and cooperate remotely. Seven articles on the burden of mental illness, published in The Lancet, Nature and Nature Medicine, have identified the disability of children, adolescents and adults, focusing not only on Covid but also on aspects such as tobacco consumption, hearing loss, and other pathologies. A pioneering study, published in JAMA, has shown that stress reduction training in pregnant women is capable of reducing the risk of having a low-birth-weight infant and a whole series of obstetric and neonatal complications. In a record year for suicides in Spain, the findings of CIBERSAM have begun to be applied to programs for the prevention of suicidal behavior in various autonomous communities, and patients at risk continue to be recruited for the SURVIVE cohort, in which 8 CIBERSAM groups participate.

All programs participate in international consortiums, such as the *Psychiatric Genomics Consortium* (PGC) and ENIGMA, which have published works of the highest scientific value such as the identification of risk genes for the development of bipolar disorder (with more than 400,000 subjects) or on structural and functional neuroimaging of psychoses. In addition, our researchers have received numerous awards and recognitions and 3 of them appear on the Clarivate list of the "world's most influential minds". It is also worth highlighting the success this year in calls for international projects and human resources and the reading of dozens of doctoral theses. CIBERSAM has been especially active in disseminating and sharing the scientific advances that it has been involved in, with a clear improvement in its media visibility. Finally, CIBERSAM continues to stress its meritocratic policies, transparency in management, gender perspective and generational change policies, and care for those aspects that can contribute to mitigating climate change. We trust that 2022, which began with a war in the making, will end up being the year of the end of the pandemic and the beginning of the end of the wave of cases of mental disorders that we are suffering.

PROGRAMS

PROGRAM 1

Depression and suicide prevention

COORDINATOR:
Diego Palao Vidal

In the first year of the COVID-19 pandemic, the year 2020, there was an increase in suicide in Spain of 7.4% and, for the first time since records began, more than 1,000 cases were women. The pandemic has also been associated with an increase of more than 25% in the incidence of depression, the most prevalent mental illness, closely related to death by suicide, and also the leading cause of disability worldwide. Suicide is also associated with other mental illnesses and, the fact that it can be prevented, makes it a cross-sectional research objective for CIBERSAM and, especially, for the groups of the program and a linked group.

During 2021, more than 300 articles on depression and more than 100 on suicide have been published in collaboration with other CIBER and international research groups in epidemiol-

ogy, neurobiology and prevention. The 5 groups of the Program have published more than 130 articles in high-quality journals (e.g., JAMA Psych, Nature Communications, Br J Pharmacol,). Competitive funding has been obtained for 26 national and 10 international projects. The investigation of the SURVIVE cohort also continues, which involves 8 CIBERSAM groups and studies preventive interventions for suicide and facilitates the monitoring of suicidal behavior in Spain.

In epidemiology, we highlight the studies that analyze the impact of COVID-19 on the mental health of the general population, in people with mental illness and in different groups such as pregnant or lactating mothers and, of great interest, the emotional impact on healthcare professionals.

At a more general level, the results of studies on the costs of depression and treatment-resistant depression in Spain have been published. New results have also been published on various associated factors (socio-demographics, lifestyles, aging, loneliness, pain). We highlight the dissemination of new achievements in the study of cognitive deficits in depression or the risk of suicide in behavioral addictions and the response to psychological treatments.

Particularly relevant are the participatory publications in international consortia, such as GEMRIC and ENIGMA, which have made progress in the identification of brain areas involved in the mechanism of action of electroconvulsive therapy and associated genetic, environmental, demographic, cognitive and psychosocial factors. Several groups continue to investigate the development and evaluation of potential diagnostic and prognostic biomarkers in neuroimaging and neurocognitive, neurophysiological, inflammatory, and genetic assessments.

In the research lines of molecular bases and evaluation of new drugs and therapeutic targets in depression, glutamatergic pathways, antidepressant effects of oligonucleotides in animal models and psilocybin continue to be investigated in clinical trials in patients. During the year 2021, 8 competitive contracts have been obtained and 29 doctoral theses have been presented. Also worth noting is the progressive involvement of groups in scientific outreach activities, through webinars and online events, and the coordination of suicide prevention programs that also contribute to promoting research (for example, PLAPRESC in Catalonia).

PROGRAM 2

Schizophrenia

COORDINATOR:
Edith Pomarol-Clotet

In 2021, more than 200 articles have been published in high impact scientific journals, including World Psychiatry, JAMA Psychiatry, The Lancet Psychiatry and Molecular psychiatry, Biological Psychiatry, among others.

35 new competitive projects have been started, among which 2 European ones stand out: Horizon RIA and Marie Skłodowska-Curie COFUND, in addition to 19 ISCIIII projects, 1 Alicia Koplowitz, 1 Intramural CIBERSAM, 1 from the Ministry of Science and Innovation and 1 from the Ministry of Health.

Furthermore, we highlight the recruitment of human resources with 27 contracts, 10 Instituto de Salud Carlos III (1 Juan Rodés, 3 Sara Borrell, 2 Río Hortega, 2 PFIS, 2 Miguel Servet), 3 Ministry of Universities (FPU), 3 Generalitat de Catalunya (FI and PIF Salut), 2 Basque Government and 1 Marie Sklodowska-Curie Individual Fellowships.

In addition, 15 doctoral theses have been read this year in the program and three extraordinary prizes have been obtained: Helena García-Mieres (Josep Mª Haro's Group); Laura

Ortega (Elisabet Vilella's Group) and Lorena de la Fuente (Pilar Sáiz's Group).

Also worth mentioning are the 22 awards that have been received, 4 of which are international:

- 1st prize ''WPA 3 minutes Presentations Competition'' (WPA World Congress of Psychiatry - World Psychiatric Association): Joan Soler-Vidal. Edith Pomarol's Group.
- European Psychiatric Association Research Prize, category "Child and Adolescent Psychiatry". (European Psychatric Association): Covadonga Martínez Díaz Caneja. Celso Arango's Group.
- Rising Star Award (European College of Neuropsychopharmacology (ECNP): Covadonga Martínez Díaz Caneja. Celso Arango's Group.
- ECNP Excellence award (European College of Neuropsychopharmacology (ECNP): Luis F. Callado Hernando and Leyre Urigüen Echeverría. Javier Meana's Group.
- Best oral presentation award (III European Meeting on Women's Mental Health): Marta Ferrer-Quintero. Josep Mª Haro's Group.

Finally, regarding other merits, we mention two patents: "Biocompatible extracellular vesicles obtained from by-products of the food fermentation industry, their compositions and applications" and "Method for predicting the onset of extrapyramidal symptoms (EPS) induced by an antipsychotic-based treatment".

PROGRAM 3

Bipolar Disorder

COORDINATOR:
Vicent Balanzá-Martínez

Among the most relevant results of the program, 226 first quartile and 76 first decile articles published in prestigious journals such as *JAMA, Nature Genetics, Molecular Psychiatry, Neuroscience and Biobehavioral Reviews* or *Lancet* stand out.

During 2021, 37 new national and international projects were obtained with competitive funding (FIS, ISCIII, European Union, European Commission, Milken Foundation, Canadian Institutes of Health Research) and two private contracts:

- "Study of the neurotrophic effect of adult bone marrow mesenchymal stem cells in adrenoleukodystrophies". Rafael Tabarés group - The Walk on Project Foundation.
- "Consultoría para actividad en el Comité de Monitorización de Seguridad del ensayo clínico FAB117-CT-01. Rafael Tabarés Group - Ferrer Internacional, S.A.

Contratos competitivos en RRHH

- Río Hortega: Anna Giménez and Gerard Anmella. Eduard Vieta's Group.
- Sara Borrell: Paola Fuentes-Claramonte. Edith Pomaro's Group.
- Basque Government Predoctoral Program, UPV: Jessica Fernán dez. Ana González-Pinto's Group.
- FPI-UAM predoctoral contract: Blanca Dolz. J. Luis Ayuso's Group.

Awards and distinctions:

- Eduard Vieta and Joaquim Radua among the most influential scientists in the world (Clarivate Analytics), 2021, Highly Cited Researchers.
- 2021 Hestia Chair Award for the best publication on COVID-19: "Changes in depression and suicidal ideation under severe lockdown restrictions during the first wave of the CO- VID-19 pandemic in Spain: A longitudinal study in the general population". PI: José Luis Ayuso.
- ECNP Poster Excellence Award: "Relevance of immunometabolic status for the evaluation of cognitive performance in patients with major depressive disorder". Yolanda Sánchez-Carro. Ayuso Grupo.
- Extraordinary PhD Award to Lorena de la Fuente: "Construction and validation of a clinical staging model for bipolar disorder", directed by Drs. Paz García-Portilla and Leticia García.
- 1st prize TOP10 Psiquiatría: "Factors of resilience, cognition and retinal thickness. The years of study as a factor of resilience". Edurne Garcia. Gonzalez-Pinto Group.
- Ana González-Pinto: Obieta Award for Professional Career 2021. Royal National Academy of Medicine.
- Dr. González-Pinto obtains the Chair of Psychiatry at the University of the Basque Country.
- Communication with the greatest clinical impact of the XXV International Meeting on Research in Care. Investén – ISCIII. Raymond Salvador-Civil. Pomarol Group.
- Eduard Vieta: "Josep Trueta" Research Excellence Award. Academy of Medical and Health Sciences of Catalonia and the Balearic Islands.

Finally, we mention the patent: "Biocompatible extracellular vesicles obtained from by-products of the food fermentation industry, their compositions and applications". Elisabeth Vilella Group.

Scientific achievements include:

- A total of 22 doctoral theses.
- Clinical Guidelines

  > "COVID-19 Clinical management Living guidance (WHO)" (Ayuso).

  > "Consensus document on the microbiota and the use of probiotics/prebiotics in neurological and psychiatric pathologies" (González-Pinto, Leza, Tabarés, Ramos-Quiroga)

  > "Clinical practice guideline on pharmacological and psychological management of adult patients with bipolar disorder and comorbid substance use" (González-Pinto, Baeza, Sáiz, Haro, Vieta).
- Participation of Dr. Eduard Vieta in the most extensive study in history on the genetic risk of bipolar disorder, published in Nature Genetics and which has identified 15 therapeutic targets.

PROGRAM 4

Therapeutic Innovation

COORDINATOR:
Juan Carlos Leza

Scientific Publications, a high percentage of articles in the first decile. Among them: *Lancet Psychiatry, Biological Psychiatry, Brain, Nature Communications, Neuropsychopharmacology, Neuron, Nature Genetics, JAMA, Traslational Psychiatry, Journal of Neuroscience, Cell Reports, Brain Imaging and Behavior, Pain, Pharmacology and Therapeutics, International J Mol Science, Journal of Neurology, European J Neurology, JAMA Psychiatry*...

Most of the articles are collaborative between groups of the Program and in CIBERSAM, or with other CIBER consortiums, Networks or IIS of the ISCIII, and a good number with international collaborations.

17 Clinical Guidelines, several of them international.

Fundraising, numerous competitive projects from state public bodies: MCINN, ISCIII-FIS; regional bodies: Generalitat Valenciana (Prometeo), Junta de Andalucía, Comunidad de Madrid, Generalitat de Catalunya. Also supranational: several EU projects, as well as Foundations: La Marató TV3, Koplowitz and Milken (USA).

Contracts with companies for the development or evaluation of models, procedures or evaluation of new molecules of therapeutic interest: Monteloeder, miCure Therapeutics, Siemens Gamesa, Janssen Cilag, Pfizer, GW Pharmaceuticals, Hoffmann-La Roche, Janssen Pharmaceutica, Lundbeck and Brainhealth Solutions SL..

Human Resources: Supranational: UNA4CAREER-UE. National: CIBER LC postdocs, Margarita Salas, Miguel Servet, FPU, FPI, JAE-intro, Río Hortega, Sara Borrell, PFIS, Juan de la Cierva. Regional: Talent Recruitment (Univ. Valencia), Post-doc and talent recruitment EMERGIA (Junta de Andalucía) and Predoctoral Program of Non-Doctoral Researcher Training (Basque Country).

Science dissemination events: International Day of Women and Girls in Science, Science Week 2021, visits to High Schools, informative publications, events with patient associations, articles in the press and interviews on radio and TV. Likewise, many groups maintain twitter accounts and web pages that are very active in disseminating scientific news.

Members of the Program have coordinated, participated in or been invited to **National or international scientific forums**.

Among the most important **scientific achievements** of the groups of the program are:

- Identification of different patterns of intestinal microbiota in patients with depression and their relationship with systemic immune activation pathways.
- Exposure to stress during adolescence modifies the inhibitory circuits of the prefrontal cortex, particularly in females.
- The comorbidity of depression and chronic pain produces different adaptations over time at the level of the locus coeruleus.
- Intranasal administration of a synthetic miR-135 induces antidepressant responses in a murine model.
- A biased signaling mechanism (biased agonism) altered in the cell signaling of 5-HT2A receptors in the brain of subjects with schizophrenia has been described.
- 33 new genetic variants associated with bipolar disorder have been identified.
- Effects of minocycline during adolescence on the partial reversal of volumetric abnormalities and anti-inflammatory/antioxidant pathways in a maternal immune activation model.
- Mechanisms behind the differences in the symptoms of schizophrenia according to sex at the clinical, genetic and brain image analysis levels.
- Coordination of the Pla de Prevenció del Suïcidi de Catalunya (Suicide Prevention Plan of Catalonia) for real-time access to the forensic reports of suicides.

PROGRAM 5

Mental disorders of the child and adolescent

COORDINATOR:
Carmen Moreno Ruíz

This Program is made up of 6 clinical and basic groups that develop research in mental disorders that start in childhood and adolescence with several European projects and collaborative projects. In 2021, projects have been developed on the influence of vaccines, infectious and immunological biomarkers and analysis of transcriptome-interactome networks in tic disorders; neural, hormonal and neuropsychological correlates during pregnancy and postpartum, gene-environment interaction in children of patients with schizophrenia or bipolar disorder, the epigenetic mechanisms involved in autism spectrum disorders in extremely premature infants and the characterization of individuals at risk for psychosis, among others.

The publications have been mostly in journals indexed in the first quartile according to the JCR such as Lancet, World Psychiatry, Nature Genetics, Lancet Psychiatry, JAMA Psychiatry, JAMA Pediatrics, Molecular Psychiatry, Small, Neurology or Schizophrenia Bulletin.

The results include a systematic review and meta-analysis on the usefulness of universal and selective interventions to prevent poor mental health outcomes in young people,

an umbrella review on interventions for the primary prevention of depression, and the development of an atlas of the non-genetic risk and protection factors of mental disorders, which finds that they are mainly involved in the early period of development and underlines the relevance of early intervention for the prevention of mental disorders. Studies in adolescents at high risk of psychosis show that alterations in theory of mind and decreased prefrontal connectivity precede the onset of psychosis and that this population presents more stressful events and greater sensitivity to stress than controls groups as well as a high presence of major depression and attenuated negative symptoms. Neuroimaging studies have found an association between gray matter volume loss and worsening of working memory in adolescents with a first psychotic episode and, in children and adolescents with familial risk and a relationship between the onset of psychotic symptoms and greater cortical thinning. As a result of participation in international consortiums, structural asymmetries have been described in ADHD compared to controls and, after analysis using machine learning, similar structural alterations in children and adults with ADHD. Brain changes induced by pregnancy have been detected up to 6 years postpartum, findings that are in line with a review also carried out by members of the program. In children and adolescents exposed to child abuse, dose-response alterations in the functioning of the HPA axis and a correlation between emotional dysregulation and recent stress with suicidal behavior have been described. A study on adolescent mortality worldwide has documented that in 2019, 8.2% of deaths between 10-24 years of age were due to self-harm.

Members of the program have been awarded the Rising Star Award of the European College of Neuropsychopharmacology (ECNP), the European Psychiatric Association Research Prize, category “Child and Adolescent Psychiatry”, Research Excellence Award of the Spanish Society of Biological Psychiatry (SEPB) and Best doctor of the year award from the ABC Salud awards.

PROGRAM 6

Psychosomatic, anxiety and impulse control disorders

COORDINATOR:
Virginia Soria

Worth highlighting is the dissemination of results from the main lines of research (aging and cognition, anxiety disorders, obsessive-compulsive and impulsive spectrum disorders, neuroinflammation and pain) in prestigious journals (D1) such as Nature Communications, JAMA Psychiatry, Lancet Psychiatry, Molecular Psychiatry, Biological Psychiatry, Translational Psychiatry, Brain Behaviour and Immunity and Neuroscience and Biobehavioral Reviews, among others. Also worth noting is the dissemination in the media and in events aimed at citizens, the contribution to the development of new researchers with doctoral theses with quality mentions, as well as the awarding of prizes and distinctions.

The securing of funds through competitive calls has been remarkable. From the participation in international consortiums, such as ATHLOS, ENIGMA, COSMIC and the PGC, notable achievements include the identification of shared neurobiological processes between different psychiatric disorders associated with differences in cortical thickness; the typification of education in early ages and occupation in adulthood as independent predictors of dementia; and detection

of increased burden of genetic risk variants in ADHD with disruptive behavior.

During 2021, the results of studies driven by COVID-19 have come to light, evaluating the impact of the pandemic on the mental health of the general population and healthcare workers and on mental disorders such as anxiety disorders, eating disorders, pathological gambling, OCD, autism, substance use and suicidal behavior. The problematic use of the internet during the pandemic has also been addressed, with recommendations developed for professionals and the general population.

Regarding e-Health, we highlight the development of a mobile application for the longitudinal evaluation of anxiety, instruments for the evaluation of suicide risk and digital tools to maintain social connectedness and physical activity in mental disorders.

International projects in OCD have identified clinical risk factors for suicide, the safety and efficacy of deep brain stimulation in severe treatment-resistant OCD have been reviewed, and patterns of abnormal brain activation during fear conditioning processes have been observed to predict response to cognitive-behavioral therapy in OCD.

Epigenetic alterations have been detected in the X chromosome and estrogen regulatory genes, modulated by childhood trauma, which could contribute to the development of borderline personality disorder.

In eating disorders, the superiority of virtual reality exposure has been demonstrated over in-vivo exposure therapies in the treatment of self-image distortion and fear of weight gain; and a systemic inflammatory dysregulation has been confirmed.

A consensus document has been published on the microbiota and the use of probiotics/prebiotics in neurological and psychiatric pathologies, and different patterns of gut microbiota have been identified in patients with depression and their relationship with systemic immune activation pathways.

Also, to be highlighted is a review of the activity of the locus coeruleus and its projections in the comorbidity between depression, anxiety and chronic pain, underlining the importance of the translational tools available to elucidate the underlying mechanisms. In addition, the role of specific neuronal pathways in this comorbidity has been demonstrated, involving alpha-adrenergic receptors in the cingulate cortex.

PROGRAM 7

Training

COORDINATOR:
Esther Berrocoso

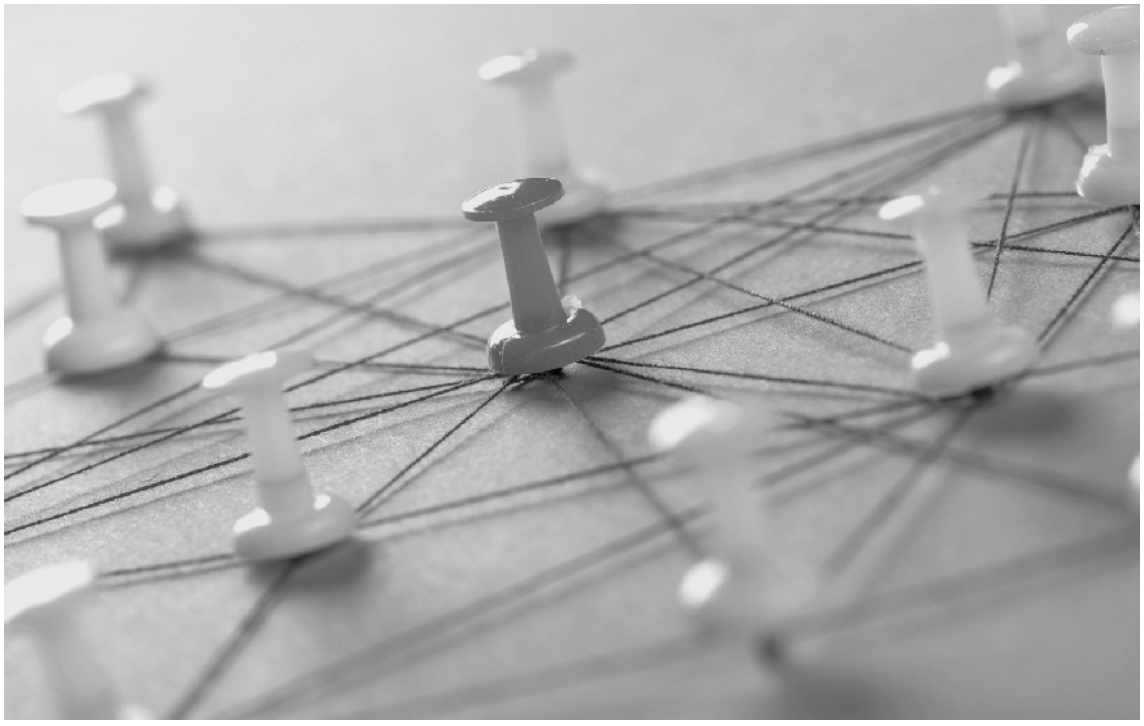
During 2021, the Training Program has financed a total of 64 actions. Among these, 3 training stays and registrations for research courses and seminars were carried out, 32 activities were with online participation and 25 face-to-face, in various events with the presence of CIBERSAM.

Among them:

- XXII Symposium on bipolar and depressive disorders
- 8th Edition of the CIBERSAM Ideas Lab
- XVIII CIBERSAM Intensive Course on Introduction to Neuroscience research
- 28 International Symposium on Controversies in Psy- chiatry
- XI Workshop of the Cibersam Bank of Instruments
- Theoretical-practical course in Electroconvulsive therapy
- XIV National Congress of Psychiatry
- VII Meeting between researchers in Mental Health, patients and relatives

- CIBERSAM International Forum Congress of Research in Psychiatry
- Use of human brain samples in the study of psychiatric diseases
- X Conference on Treatment-Resistant Pathologies
- Due to the Covid-19 pandemic, this year's edition of the Ideas Lad was not able to be held in person, and was held online.

In 2021, the Interuniversity Master's Degree in Initiation to Research in Mental Health had 68 registrations. The number of students enrolled in type A stays was 44 and 45 in type B. In addition, a total of 40 Master's Thesis were presented. Furthermore, two new elective subjects have been offered: Neurodevelopment (4 ECTS CREDITS) and Animal well-being in Animal Experimentation (3 ECTS CREDITS). It is also interesting to note that ANECA has granted the renewal of the accreditation of the official university degree of Master's Degree in Initiation to Research in Mental Health by the Autonomous University of Barcelona; the Complutense University of Madrid; the University of Barcelona; the University of Cádiz and the University of Cantabria (https://www.mastersaludmental.unican.es/sites/default/files/RCU-M1-MENTAL_RESOLUCION%20CONSEJO%20DE%20UNIVERSIDADES.pdf).



PLATAFORMS

- **Instruments Library**
- **DNA and biological samples collections**
- **Neuroimaging**

CIBERSAM's own three platforms and the linked external platform have continued acting as support instruments for projects and activities. The respective indicators, both of their own activity and of productivity (publications, etc.) guarantee a sustained trajectory over time.

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

	INSTRUMENTS LIBRARY	DNA and SAMPLES COLLECTIONS	NEUROIMAGING
Existing Instruments	333		
Added Instruments	7		
Requests for use	28		8
Funded Publications	100		
Training Activities	1		
Stored Images			24727
Contributing Groups		10	4
User Groups		1	1
Patients included		25666	

The scientific productivity generated as a result of the use and exploitation of the CIBERSAM platforms in 2021 and the comparison with the data from 2018 is reflected in the following table:

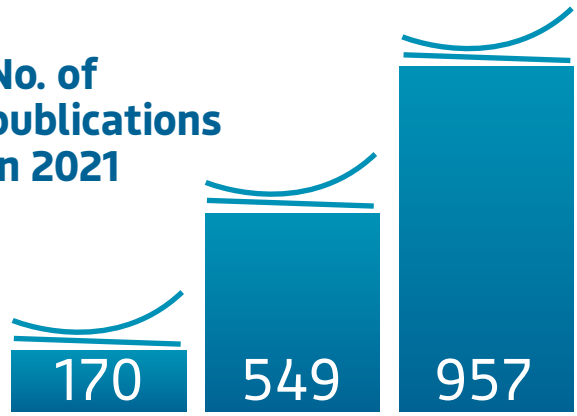
Use of CIBERSAM Platforms by intraCIBER or external groups

	2018	2019	2020	2021
Total Publications	**24**	**37**	**37**	**75**
GRIDSAM Publications	12	11	15	25
DNA Publications	3	10	10	11
Neuroimaging Publications	4	7	10	8
Instruments Publications	2	8	6	39
Total number of Clinical Trials	**0**	**1**	**1**	**0**
Instruments Trials	-	1	1	-
Total Clinical Guides	**0**	**1**	**0**	**0**
Clinical Guides Instruments	-	1	-	-

SCIENTIFIC PRODUCTION

Publications

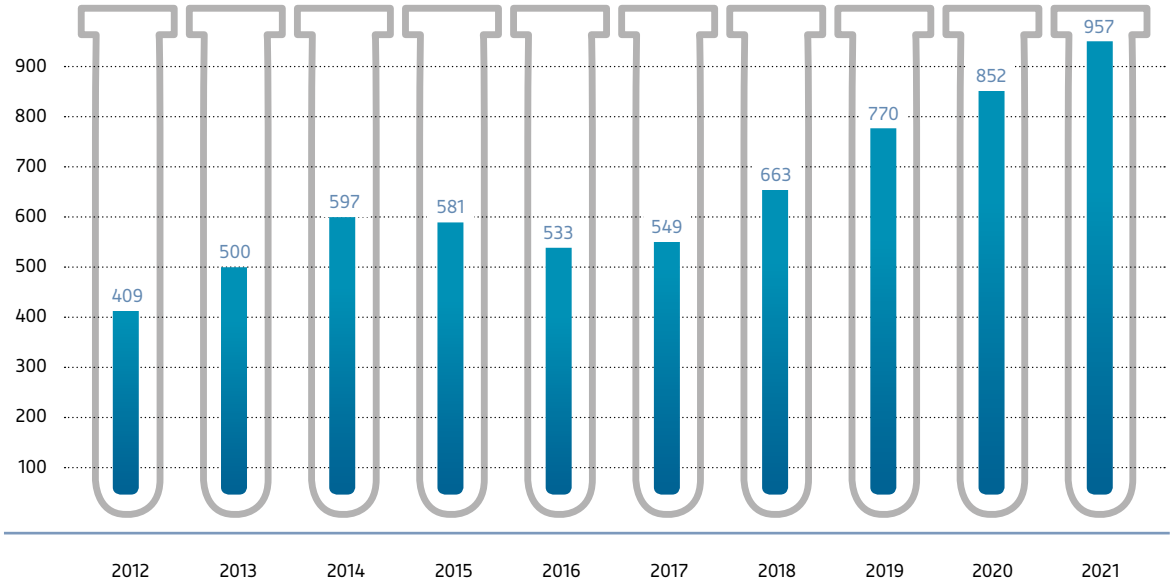
No. of publications in 2021



Collaborations

*Among various thematic areas

Evolution of publications



10 most relevant publications by impact factor

IF	Publication
79,321	GBD 2019 Adolescent Mortality Collaborators. Global, regional, and national mortality among young people aged 10-24 years, 1950-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2021 Oct 30;398(10311):1593-1618. doi: 10.1016/S0140-6736(21)01546-4. Epub 2021 Oct 28. PMID: 34755628.
79,321	GBD 2019 Under-5 Mortality Collaborators. Global, regional, and national progress towards Sustainable Development Goal 3.2 for neonatal and child health: all-cause and cause-specific mortality findings from the Global Burden of Disease Study 2019. Lancet. 2021 Sep 4;398(10303):870-905. doi: 10.1016/S0140-6736(21)01207-1. PMID: 34416195.
79,321	GBD 2019 Hearing Loss Collaborators. Hearing loss prevalence and years lived with disability, 1990-2019: findings from the Global Burden of Disease Study 2019. Lancet. 2021 Mar 13;397(10278):996-1009. doi: 10.1016/S0140-6736(21)00516-X. PMID: 33714390.
79,321	GBD 2019 Tobacco Collaborators. Spatial, temporal, and demographic patterns in prevalence of smoking tobacco use and attributable disease burden in 204 countries and territories, 1990-2019: a systematic analysis from the Global Burden of Disease Study 2019. Lancet. 2021 Jun 19;397(10292):2337-2360. doi: 10.1016/S0140-6736(21)01169-7. Epub 2021 May 27. PMID: 34051883.
79,321	Global Burden of Disease 2020 Health Financing Collaborator Network. Tracking development assistance for health and for COVID-19: a review of development assistance, government, out-of-pocket, and other private spending on health for 204 countries and territories, 1990-2050. Lancet. 2021 Oct 9;398(10308):1317-1343. doi: 10.1016/S0140-6736(21)01258-7. PMID: 34562388
56,272	Crovetto F, Crispi F, Casas R, Martín-Asuero A, Borràs R, Vieta E, Estruch R, Gratacós E; IMPACT BCN Trial Investigators. Effects of Mediterranean Diet or Mindfulness-Based Stress Reduction on Prevention of Small-for-Gestational Age Birth Weights in Newborns Born to At-Risk Pregnant Individuals: The IMPACT BCN Randomized Clinical Trial. JAMA. 2021 Dec 7;326(21):2150-2160. doi: 10.1001/jama.2021.20178. PMID: 34874420.
53,440	Kinyoki D, Osgood-Zimmerman AE, Bhattacharjee NV; Local Burden of Disease Anaemia Collaborators, Kassebaum NJ, Hay SI. Anemia prevalence in women of reproductive age in low- and middle-income countries between 2000 and 2018. Nat Med. 2021 Oct;27(10):1761-1782. doi: 10.1038/s41591-021-01498-0. PMID: 34642490.
49,962	Local Burden of Disease Vaccine Coverage Collaborators. Mapping routine measles vaccination in low- and middle-income countries. Nature. 2021 Jan;589(7842):415-419. doi: 10.1038/s41586-020-03043-4. PMID: 33328634.
49,548	Fusar-Poli P, Radua J, Jauhar S. Lack of robust meta-analytic evidence to favour cognitive behavioural therapy for prevention of psychosis. World Psychiatry. 2021 Oct;20(3):443-444. doi: 10.1002/wps.20896. PMID: 34505393.
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CIBERSAM Groups, Publications in 2021

Group Leader	Publications	Q1	D1	Institution - Center	Province
Arango López, Celso	90	63	24	Servicio Madrileño de Salud	Madrid
Ayuso Mateos, José Luis	45	20	7	Universidad Autónoma de Madrid	Madrid
Baeza Pertegaz, María Inmaculada	86	56	21	Hospital Clínico y Provincial de Barcelona	Barcelona
Berrocoso Domínguez, Esther	19	14	3	Universidad de Cádiz	Cádiz
Bortolozzi Biasoni, Analia	5	4	1	Agencia Estatal Consejo Superior de Investigaciones Científicas	Barcelona
Crespo Facorro, Benedicto	44	31	5	Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla	Sevilla
Desco Menéndez, Manuel	22	12	2	Servicio Madrileño de Salud	Madrid
Fañanás Saura, Lourdes	31	15	7	Universidad de Barcelona	Barcelona
González-Pinto Arrillaga, Ana	62	24	4	Asociación Instituto de Investigación Sanitaria BIOARABA	Álava
Haro Abad, Josep Maria	204	120	47	Fundación para la Investigación y Docencia Sant Joan de Deu	Barcelona
Ibáñez Cuadrado, Ángela	73	41	6	Servicio Madrileño de Salud	Madrid
Leza Cerro, Juan Carlos	54	36	4	Universidad Complutense de Madrid	Madrid
Meana Martínez, José Javier	44	27	8	Universidad del País Vasco	Vizcaya
Menchón Magriña, José Manuel	67	41	9	Fundación IDIBELL	Barcelona
Nácher Roselló, Juan Salvador	39	28	6	Universidad de Valencia	Valencia
Olivares Diez, José Manuel	14	5	1	Servicio Gallego de Salud	Pontevedra
Palao Vidal, Diego José	54	32	14	Corporación Sanitaria Parc Taulí	Barcelona
Pérez Sola, Víctor	88	55	9	Consorci Mar Parc Salut de Barcelona	Barcelona
Pomarol Clotet, Edith	39	23	6	Fundación para la Investigación y Docencia María Angustias Giménez (FIDMAG)	Barcelona
Ramos Quiroga, José Antonio	65	38	14	Fundación Hospital Universitario Vall d´Hebron - Institut de Recerca (VHIR)	Barcelona

Group Leader	Publications	Q1	D1	Institution - Center	Province
Rodríguez-Jiménez, Roberto	48	34	9	Servicio Madrileño de Salud	Madrid
Sáiz Martínez, Pilar Alejandra	46	24	5	Universidad de Oviedo	Asturias
Tabarés Seisdedos, Rafael	39	31	9	Universidad de Valencia	Valencia
Vieta Pascual, Eduard	173	101	36	Hospital Clínico y Provincial de Barcelona	Barcelona
Vilella Cuadrada, Elisabet	16	8	3	Fundación Instituto de Investigación Sanitaria Pere Virgili	Tarragona

Patents owned by CIBER 2021

Applications

- Bilateral pupillometry platform for small animals.
- Biocompatible extracellular vesicles obtained from fermented food industry by-products, compositions and applications thereof.

Granted

- "Modified mir-135, conjugated form thereof, and uses of same"

Clinical Guidelines 2021

- Approach to the mental health of chemsex users.
- Body dysmorphic disorder: a treatment synthesis and consensus on behalf of the International College of Obsessive-Compulsive Spectrum Disorders and the Obsessive Compulsive and Related Disorders Network of the European College of Neuropsychopharmacology.
- Good clinical practice for the support of people with mental disorders in a state of agitation.

- Clinical practice guideline on pharmacological and psychological. management of adult patients with an Anxiety Disorder and comorbid substance use.
- Clinical practice guideline on pharmacological and psychological management of adult patients with attention deficit and hyperactivity disorder and comorbid substance use.
- Clinical practice guideline on pharmacological and psychological management of adult patients with bipolar disorder and comorbid substance use.
- Clinical practice guideline on pharmacological and psychological management of adult patients with depression and a comorbid substance use disorder.
- Clinical practice guideline on pharmacological and psychological management of adult patients with schizophrenia spectrum disorders and a comorbid substance use.
- Consensus on nomenclature for clinical staging models in bipolar disorder: A narrative review from the International Society for Bipolar Disorders (ISBD) Staging Task Force.
- COVID-19 Clinical management Living guidance.
- Depression. Action and monitoring guidelines.
- Consensus document on the microbiota and the use of probiotics/prebiotics in neurological and psychiatric disorders.
- Drug development for Autism Spectrum Disorder (ASD): Progress, challenges, and future directions.
- Electroconvulsive Therapy (ECT) Guide.
- Humanization in mental health plans in Spain.
- Identification and management of cardiometabolic risk in subjects with schizophrenia spectrum disorders: A Delphi expert consensus study.
- Quality indicators in Psychiatry.

- International Consensus Statement for the Screening, Diagnosis, and Treatment of Adolescents with Concurrent Attention-Deficit/Hyperactivity Disorder and Substance Use Disorder.
- Learning to deal with problematic usage of the internet.
- Manifesto for an ECNP Neuromodulation Thematic Working Group (TWG): Non-invasive brain stimulation as a new Super-subspecialty.
- Mental health services during the first wave of the COVID-19 pandemic in Europe: Results from the EPA Ambassadors Survey and implications for clinical practice.
- Patient care, right to information and consent for minors in situations of parental conflict. Clinical guidelines in the context of Spanish legislation
- Suicide Prevention Plan of Catalonia 2021-2025 (PLAPRESC).
- Practical recommendations for the management of treatment-resistant depression with esketamine nasal spray therapy: Basic science, evidence-based knowledge and expert guidance.
- Prevalence and correlates of current suicide risk in an international sample of OCD adults: A report from the International College of Obsessive-Compulsive Spectrum Disorders (ICOCS) network and Obsessive Compulsive and Related Disorders Network (OCRN) of the European College of Neuropsychopharmacology.
- Clinical Protocol for Early Intervention in Obsessive Compulsive Disorder.
- Protocol for Early Intervention in First Psychotic Episodes.
- Protocol for the prevention of suicide in adults.
- Recommendations for the diagnosis and treatment of Functional Movement Disorders.

- Reconceptualising treatment-resistant depression as difficult-to-treat depression.
- Specialty knowledge and competency standards for pharmacotherapy for pediatric obsessive-compulsive disorder.
- The World Federation of ADHD International Consensus Statement: 208 Evidence-based conclusions about the disorder.

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