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LETTER FROM
THE SCIENTIFIC DIRECTOR

As in previous years, I would like to begin by highlighting the excellent work of the research groups that make up CIBERNED and that has allowed us, once again, to be at the forefront of the Centers in biomedical research regarding the quality of publications in high-impact index scientific journals. In order to carry out this work, we have counted on the help and collaboration of the Management Office and the Steering Committee of the Center, as well as its support staff, and the help of the Carlos III Institute of Health and the Associated Institutions.

A very important novelty has been the incorporation of six new research groups to CIBERNED, led by Drs. Boada, Mir, Acevedo, Paradas, Ostas and Martinez, to whom I want to welcome to our Center, hoping and wishing, as the groups that preceded them, to carry out a rigorous, efficient and quality work.

During this year, 24 scientific papers have been published with an impact index greater than 20 in journals such as the New England Journal of Medicine, Nature, Science, Nature Medicine or Lancet Neurology, and 59 papers with an index greater than 10. In addition, 10 patents remain active, two clinical guidelines have been published and 85 clinical trials are in progress. In addition, courses and seminars have been organized, and the Training Plan has continued as planned. Due to the quality of the scientific activity carried out, some of our researchers have received awards and mentions at international and national level, so on behalf of the Center, I would like to congratulate them.

Finally, I would like to highlight the success of our last Congress in Santiago de Compostela, carried out with the invaluable help of Dr. Labandeira and the collaboration of the CIEN and Queen Sofia Foundations.

We continue to progress properly. Thank you all.
INTRODUCTION

Biomedical Research Network Centers are created to promote research excellence in Biomedicine and Health Sciences, which is carried out in the National Health System and the Science and Technology System. Behind this initiative is the purpose of generating large Translational Research Centers, of multidisciplinary and multi-institutional nature where basic, clinical and epidemiological research can be integrated, in order to develop a single common research program, focused on certain pathologies that are relevant for the National Health System due to its prevalence or that are considered strategic because of its social impact.

The genesis of CIBERNED was conducted through a coordination research strategy of exploiting synergies between the different groups involved in biomedical research in these areas. It seeks to promote quality research in neurodegenerative diseases being carried out within the National Health System and the Science and Technology System through the development and promotion of a Network Research structures. The goal is to promote and finance, through the Carlos III Institute of Health, Centers for Biomedical Research in the Network (CIBER) through the association of research groups, linked to the National Health System, that contribute to scientifically substantiate the programs and policies of the National Health System in the priority areas of the National R+D+I Plan.

In particular, the Network Center for Biomedical Research in Neurodegenerative Diseases (CIBERNED) was born in 2006 as the heir of the Center for Research in Neurological Diseases (CIEN), which together with the CNIO, CNIC or CNMVIS constituted the four Centers created with the mission of fighting the most prevalent health problems of Spanish society: cancer, cardiovascular diseases, infectious diseases and neurodegenerative disorders. As for the other Centers, a supporting foundation named CIEN Foundation was created in 2003 as the CIEN’s management body, although unlike the other Centers, it was created as the first Network Center in Spain, eventually being renamed as CIBERNED. Since 2007 the CIEN Foundation has its headquarters in the Alzheimer Center of the Reina Sofia Foundation, created with the collaboration of CIBERNED and the CIEN Foundation, and located in Vallecas (Madrid).

CIBERNED was founded under the auspices of the Carlos III Institute of Health, under a cooperation agreement signed by the Government and other participating institutions with
the idea of creating a Research Center in which basic, clinical and population-based studies are integrated in order to develop a single joint research program, focusing on certain pathologies of great importance for the National Health System either for its prevalence or because of its social impact. It has a multidisciplinary and multi-institutional character and it is aimed at boosting the impact of cutting research in neurodegenerative disorders through a Network Research Structure, thus contributing to scientifically substantiate the programs and policies of the National Health System in the priority areas of the National R+D+i Plan.

CIBERNED is a research organism, endowed with legal status under the Article 6.5 of Law 30/1992 of November 26 on the Legal Regime of Public Administrations and Common Administrative Procedure. It is formed by the association of research groups, with no physical contiguity, belonging to different administrations, institutions and regional governments, from public and private sectors with research lines and goals focused on the specific common area of neurodegenerative diseases and being coordinated to achieve scientific objectives that could hardly be considered in a more restricted execution context. CIBERNED is governed in the internal operating rules, by way of a Regulation.

Currently, the CIBERNED-CIEN Foundation partnership is the only research center in Spain (and one of the few in the world) integrated into the international network of Centres of Excellence in Neurodegeneration (COEN), an initiative arising from the European Union Joint Programme for Research in Neurodegenerative Diseases (JPND). This joint program constitutes an innovative collaborative research initiative created to address the growing challenges posed by this group of diseases. Its goal is to boost the impact of research by aligning existing national research programs and identifying the common objectives whose scope would benefit through joint action.

Its own statutes govern CIBERNED and since the end of 2018 its activity is structured around two Scientific Programs:

- **Program 1:** Alzheimer’s disease and other degenerative dementias.
- **Program 2:** Parkinson’s and Huntington’s disease and other degenerative movement disorders
- **Program 3:** Amyotrophic Lateral Sclerosis and other neuromuscular disorders.

During 2017 CIBERNED has consisted of 50 research groups supported by different universities, hospitals and the Research Council (CSIC), each led by a principal investigator or responsible. CIBERNED is a network research center, composed of research groups belonging to different Administrations and affiliated Institutions: researcher members physically work in their parent institutions they belong to while simultaneously and actively participating on CIBERNED’s own cooperative research agenda. It should be noted that during 2018 the Carlos III Institute of Health convened, within its annual call for aid of the Strategic Action of Health (AES), the incorporation of new groups to the CIBERNED consortium. This call has allowed the incorporation of 6 new groups (a new group for Program 1, another for Program 2 and four new groups for Program 3).
Thus, it is the result of a collaborative partnership between different institutions and the sum of 50 research groups. Depending on the results of the scientific evaluation of the various research groups, there is the possibility to agree on the discontinuation of some groups. Depending on budget availability, it may also consider adding some new research group currently outside CIBERNED that satisfy the requirements of scientific quality and translational activity and aligns with CIBERNED priorities.

The Scientific Director Office has been set since October 2011 at the Center for Molecular Biology “Severo Ochoa” (CSIC) in Madrid. The headquarters, including the General Manager Office is located in the Alzheimer Center of the Queen Sofia Foundation, 5 Valderrebollo Street in Madrid.
AIMS

CIBERNED has as its ultimate goal the promotion of scientific and technical research of excellence in the field of human health, with the generic purpose of producing results quickly transferable to clinical practice in order to improve the health and wellbeing of patients suffering of neurodegenerative diseases, as well as their families and caregivers, providing in turn economic and social benefits. Among its specific aims, the following should be highlighted:

• Promote and develop cooperative translational research excellence in neurodegenerative diseases.
• Fostering the impact of science on the health system and on the welfare of patients.
• Enhance participation in coordinated actions and calls promoted by funding agencies and the international and national level.
• Encourage the development of new therapeutic or and preventive interventions.
• Implement an infrastructure of strategic value for the development of research on prevention, diagnosis and treatment.
• Develop plans for specialized training.
• Promote support cross-cutting platforms (biobanks, brain imaging, DEGESCO...)
• To involve society in the enormous medical and socioeconomic impact of neurodegenerative diseases and facilitate their involvement in the fight against neurodegeneration.
### DIRECTORY OF RESEARCH GROUPS AND ASSOCIATED INSTITUTIONS

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<td>Wandosell Jurado, Francisco</td>
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GEOGRAPHIC DISTRIBUTION OF CIBERNED RESEARCH GROUPS

17
Extremadura
1
Comunidad Canaria
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Murcia
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Islas Baleares
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Cataluña
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Comunidad Valenciana
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Navarra
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La Rioja
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Cantabria
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Asturias
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Cataluña
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Andalucía
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Aragón
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Madrid
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Castilla y León
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Castilla-La Mancha
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ORGANIZATIONAL STRUCTURE

CIBERNED governing bodies are the Governing Council, the Permanent Commission and the Scientific Director.

The Governing Council, CIBERNED highest body, consists of three representatives of the Carlos III Health Institute, that include the legal representative of the collaborating organization, the Foundation Research Centre of Neurological Diseases (CIEN) and one representative from each of the institutions participating in the consortium.

The President of the Executive Council is the Director of the Carlos III Health Institute. The Secretary of the Governing Council will be the Manager of the consortium.

The Scientific Director and Manager of CIBERNED are also part of the Governing Council, without a right to vote.

The Standing Committee is composed of the Vice President of the Executive Council or his delegate, and four members representing the consortium institutions in the Governing Council.

The Scientific Director of the consortium and the Manager, who acts as secretary, are also part of the Permanent Commission, without a right to vote.

The Scientific Director is appointed by the President of the Governing Council for a period of four years, renewable by agreement of the parties. The current Scientific Director of CIBERNED is Dr. Jesús Avila de Grado.

CIBERNED Management is entrusted to the Managing Director of the Foundation CIEN, Ms. María Ángeles Pérez Muñoz.

Support and advisory bodies to governing bodies:

a. The Steering Committee  
b. The External Scientific Advisory Committee

The Steering Committee consists of:

- Dr. Jesús Ávila de Grado · Scientific Director
- Dña. Mª Ángeles Pérez Muñoz · Manager
- Dr. Miguel Medina Padilla · Deputy Scientific Director

and the Program coordinators:

- Dr. Eduardo Tolosa Sarró
- Dr. Alberto Lleó Bisa
- Dr. José Javier Lucas Lozano
- Dr. Adolfo López de Munain
- Dra. Teresa Iglesias Vacas
- Dr. Rafael Fernández Chacón
- Dra. Isabel Fariñas Gómez
ORGANIZATION CHART

INSTITUTE OF HEALTH CARLOS III

ASSOCIATED INSTITUTIONS

GOVERNING COUNCIL

STANDING COMMITTEE

Steering Committee

SCIENTIFIC DIRECTOR

MANAGER

DEPUTY SCIENTIFIC DIRECTOR

RESEARCH PROGRAM COORDINATORS

RESEARCH GROUPS
EXTERNAL SCIENTIFIC ADVISORY COMMITTEE

- Dr. George Perry  
  University of Texas, San Antonio, USA (Chair)

- Dr. Werner Poewe  
  Innsbruck Medical University, Austria

- Dr. Ángel Cedazo-Minguez  
  Karolinska Institute, Stockholm, Sweden

- Dra. Mary Reilly  
  Institute of Neurology, London, United Kingdom
CONSORTIUM MEMBERS

The Central Administration, represented by:

- The **Ministry of Economy, Industry and Competitiveness** (until June 2018) and the **Ministry of Science, Innovation and Universities** (since June 2018) through the **Carlos III Institute of Health**.

- The **Spanish National Research Council (CSIC)**.

The following Autonomous Regions:

- **Autonomous Region of Andalusia**, through the Andalusian Public Foundation for Health Research Management at Seville, University of Seville, Pablo de Olavide University, and University of Málaga.

- **Autonomous Region of Canary Islands**, through the University of La Laguna.

- **Autonomous Region of Cantabria**, through the Marqués de Valdecilla Foundation (IDIVAL).

- **Autonomous Region of Castilla La Mancha**, through the University of Castilla-La Mancha.

- **Autonomous Region of Catalonia**, through the Pompeu Fabra University, Vall d’Hebron Research Institute (VHIR), Bellvitge Biomedical Research Institute (IDIBELL), Catalan Institute of Bioengineering (IBEC), University of Barcelona and Autonomous University of Barcelona.

- **Autonomous Region of Valencia**, through the University of Valencia and the Miguel Hernández University at Elche.

- **Autonomous Region of Extremadura**, through the Foundation for Research and Training of Health Professionals (FUNDESALUD).

- **Autonomous Region of Madrid**, through the General Directorate of Planning, Research and Training (Council of Health), Autonomous University of Madrid, and Complutense University of Madrid.

- **Autonomous Region of the Basque Country**, through the University of the Basque Country and Biodonostia Research Institute.

- **Autonomous Region of Galicia**, through the University of Santiago de Compostela.

Other centers and institutions not affiliated to the previously cited public administrations:

- **Santa Creu i Sant Pau Hospital Biomedical Research Institute Foundation** (Catalonia).

- **Hospital Clinic of Barcelona** (Catalonia).

- **Center for Applied Medical Research** (Navarra).

- **HM Hospitales Research Foundation** (Madrid).
RESEARCH PROGRAMMES
PROGRAM 1

ALZHEIMER’S DISEASE AND OTHER DEGENERATIVE DEMENTIAS
The aging population and longer life expectancy in our society have led in recent decades to a significant increase in cases of people with Alzheimer’s disease (AD) in the last decades being the most common cause of dementia in the elderly and against which there is no effective treatment to date. Currently, it is estimated that between 500,000 and 1,000,000 people suffer from this disease in Spain. This figure could quadruple in the next 50 years, with devastating consequences not only for affected individuals and their families but also for the very stability of our health system. The hallmarks of AD are the presence in the patient’s brain of two aberrant structures, senile plaques and neurofibrillary tangles, as well as synapse loss (it is considered a synaptopathy), mainly between hippocampal and cortical neurons, and significant neurodegeneration. Some aspects of these pathologies can be reproduced in cellular or animal models.

Currently, laboratories around the world work with great interest in identifying new causal and risk genes involved in this pathology that could help clarify its pathophysiological basis and lead to the identification of new therapeutic targets. One of the main problems in the EA is that at the time of clinical diagnosis, the brain has already suffered too extensive and irreparable damage. This requires urgent finding of biomarkers as a way to detect the disease much earlier, even asymptomatic, phases when any therapeutic strategy would have a greater chance of success.

The 20 groups of clinical and basic researchers from this program, committed both to the diagnosis and care of patients suffering from AD and to research in the laboratory, continue to combine experiences and effort to work in a coordinated manner in the search for new genetic factors, disease biomarkers and new therapeutic strategies in AD and other degenerative dementias.

The main research lines are the following:

- Genetic Epidemiology
- Research on disease-related biomarkers
- Cellular and animal models of Alzheimer’s disease and other degenerative dementias
- Molecular pathology of Alzheimer’s disease
- Mechanisms of neurodegeneration, neuroprotection and design of new therapies.

The number of people with Alzheimer’s disease could quadruple in the next 50 years.
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Program 1 is coordinated by Drs. Alberto Lleó (Santa Creu i San Pau Hospital) and Jesús Avila de Grado (Center of Molecular Biology “Severo Ochoa” CSIC-UAM, Madrid).
ABSTRACT

After looking at the toxic effects of extracellular tau on neurons and microglia, in a process that could explain the propagation of tau pathology taking place in tauopathies, like Alzheimer disease, we have found that the effect of the presence of extracellular tau on adult hippocampal neurogenesis is similar to that found due to the absence of fractalkine receptors in microglia. On the other hand, the interaction of extracellular tau with fractalkine receptor activates the p38 kinase signaling pathway, resulting in a toxic effect for microglia cells. In a complementary study, we have found a decrease in the level, at their cerebrospinal fluid, of the levels of fractalkine in Alzheimer disease patients, compared to those of non demented subjects.

Finally, in collaboration with the group of Prof Soriano (CIBERNED), we have described a novel method to look at single nucleotide polymorphism in brain cells, mainly in those present in Alzheimer disease’s patients.
KEYWORDS

PUBLICATIONS 2018


Dávila E, Targa G, Avila J, Soriano E, Pascual M. Differential accumulation of Tau phosphorylated at residues Thr231, Ser262 and Thr205 in hippocampal interneurons and its modulation by Tau mutations (VLW) and amyloid-β peptide. Neurobiology of disease. 2018. PMID: 30553886.


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RESEARCH PROJECTS 2018

**Code:** 2016-COHORTE BBN-NED.
**Title:** COHORTE-BBN-NED. Busqueda de biomarcadores para la detección temprana de la enfermedad de Alzheimer en la cohorte del proyecto Vallecas.
**Principal investigator:** Miguel Medina.
**CIBERNED’s collaboration:** Yes.
**CIBERNED groups:** G209 ; G401. **Other CIBER’s collaboration:** CIBER-BBN.
**Type:** Nacional.
**Funding agency:** Instituto de Salud Carlos III.
**Funding:** 150000. **Duration:** 2016-2018.

**Code:** PI2016/02.
**Title:** Monitoring the Onset and Evolution of Neuronal Dysfunctions in Propagative Neural Disorders using Microfluidic Devices and Translational approaches.
**Principal investigator:** Jose Antonio Del Rio.
**CIBERNED’s collaboration:** Yes.
**CIBERNED groups:** G114 ; G401; G201. **Other CIBER’s collaboration:** No.
**Type:** Intramurales.
**Funding agency:** CIBERNED.
**Funding:** 210000. **Duration:** 2016-2018.
To identify genes and mechanisms involved in the neurodegeneration process characteristic of Alzheimer’s disease (AD), we carry out functional and genomic analysis of cellular models, validating the most relevant candidates in biological samples of patients by means of genetic association and study of biomarkers. We have models of infection by the virus herpes simplex 1 (HSV 1) and oxidative stress (EO) which present characteristic markers of AD, including alterations in the metabolism of the amyloid precursor protein (APP) and in tau phosphorylation.

Analysis of global gene expression of these models indicated the lysosomal pathway as the main process altered by HSV 1 and EO, and functional studies corroborated the existence of a marked effect in several stages of the route, including an increase of lysosomal burden, an inhibition of lysosomal hydrolases (cathepsins, glucosidases) activity, and alteration in the EGFR receptor trafficking. Our data suggest that lysosome dysfunction include alterations in the levels of cholesterol, very interesting fact since that failures in cholesterol homeostasis continue being consistently identified as important in the pathogenesis of AD. Altogether, the data support the hypothesis that lysosomal dysfunction is part of the mechanism of neurodegeneration in our models, so we are studying the role of several candidates of this functional route. During last year, we have found that the decrease of LAMP2 by gene si-
lencing or disruption partially reversed the markers of neurodegeneration induced by HSV 1 on different cell models that include mouse primary cells, and that the lysosomal related proteases CTSB and MMP14 are involved in non-canonical APP proteolysis and could be part of the mechanism of amyloidogenesis induced by EO. To replicate the neuroblastoma findings in more physiological cell models, we have generated pluripotent stem cells from AD patients and initiated its differentiation into neural phenotypes; to date, results indicate that OS modulates APP metabolism and lysosomal markers similarly to its effect in the neuroblastoma model.

To assess the involvement of these candidates in the disease, we have initiated the study of biomarkers related to lysosomal function and HSV infection in AD cases at different clinical and prodromal phases. For this, we count with retrospective collections of hundreds of samples, as well as a new collection that is being recruited by the clinical team at the moment. This collection includes a longitudinal follow-up of participants, as well as the collection of CSF samples from all of them. The biomarkers that we are studying include the determination of anti-HSV antibodies in serum and CSF, and the quantification of cholesterol and several lysosomal markers on leukocytes, in addition to genetic association studies. The data obtained to date suggest a genetic association of LAMP2 with AD in a gender and APOE genotype-dependent manner, as well as an increase of anti-HSV antibody titer in serum and of lysosomal contents in leukocytes of the patients. Altogether, the results of functional studies, gene expression and biomarkers performed to date support the hypothesis that the failure of the lysosomal function could be a relevant mechanism in neurodegeneration, not only in our cell models but also in the patients.

On the other hand, we have begun to study the role of microRNAs associated with frontotemporal dementia in the modulation of global gene expression in our cellular models, in the context of an intraCIBER collaborative project, and we continue participating in the research of the genetic architecture of AD, as components of the Dementia Genetics Spanish Consortium (DEGESCO), and of international projects and consortia such as the European Alzheimer’s Disease Bank (EADB) or the International Genomics of Alzheimer’s Project (IGAP).

**KEYWORDS**

Alzheimer’s disease, biomarkers, Herpesvirus, neurodegeneration, Lysosomal pathway, genetics, oxidative stress.

**PUBLICATIONS 2018**


RESEARCH PROJECTS 2018

Code: PI2017/01.
Title: Estudio del microRNA en el compartimento exosomal del líquido cefalorraquídeo como biomarcador de la demencia frontotemporal y herramienta para el conocimiento de las bases biológicas de la enfermedad.
Principal investigator: Jordi Clarimon.
CIBERNED’s collaboration: Yes.
CIBERNED groups: G504; G406; G510. Other CIBER’s collaboration: No.
Type: Intramurales.
Funding agency: CIBERNED.

Code: SAF2017-85747-R.
Title: funcion lisosomal y homeostasis de colesterol en la neurodegeneracion inducida por HSV-1 y en la enfermedad de alzheimer: mecanismos patogenicos y biomarcadores.
Principal investigator: María Jesus Bullido Gomez-Heras.
CIBERNED’s collaboration: No.
CIBERNED groups: G510. Other CIBER’s collaboration: No.
Type: Nacional.
Funding agency: MICINN.

Code: No figura codigo.
Title: Role of the lysosomal protein LAMP2 in the AD-like phenotype induced by HSV-1: Study of the LAMP2 interactome in virus infected neurons.
Principal investigator: Maria J Bullido Gomez-Heras.
CIBERNED’s collaboration: No.
CIBERNED groups: G510. Other CIBER’s collaboration: No.
Type: Privado.
Funding agency: Fundacion Ramon Areces.

PHD DISSERTATIONS 2018

Author: Patricia Llorente Ginés.
Title: Role of proteases implicated in the lysosomal pathway on APP processing in a cellular model of neurodegeneration.
Date: 20/12/2018. Supervisor: María Jesús Bullido Gómez-Heras.
PRINCIPAL INVESTIGATOR
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Damián Moreno, Francisco Javier. PhD.
De Pedro Cuesta, Jesús. PhD.
Frades Payo, Mª Belén. Bachelor degree.
García López, Fernando José. PhD.
Kun González, Alejandra Elizabeth. PhD.
Martínez Martín, Pablo. PhD.
Moreno García, Alexandra. Bachelor degree.
Rodríguez Blázquez, María del Carmen. Bachelor degree.
Ruiz Tovar, María. PhD.

ABSTRACT
Public Health/aging Subgroup

Regarding development initiatives, the group has contributed to the creation of the Spanish Multiple Sclerosis Registry, which promotes Pharmacovigilance tasks in collaboration with the Spanish Medicines Agency (AEMPS) and the Spanish Neurology Society. The group has contributed with a member to the Scientific Advisory group for the drafting of the new version.

The subgroup participates in the European Project CHRODIS+ (2017-20) in relation to the coordination and execution of an activity for active aging / healthy aging that entails at the neuromotor level the trans-institutional implementation in Spain of the “Icelandic 65+ multimodal intervention Program”, focused on physical activity.

**Assessment and Outcomes Subgroup**

After the critical review of the Non-Motor Symptoms Scale for Parkinson’s Disease (2014) a new version was promoted, the Movement Disorder Society sponsored Non-Motor Symptoms Rating Scale, whose pilot study was published in 2018 and the validation study (sponsored by the International Parkinson and Movement Disorder Society, IPMDS) has also been completed this year.

Within international collaborations, studies and publications on outcomes of second-line therapies for patients with advanced Parkinson’s Disease (APD) have been carried out; development and validation of a scale (Parkinson’s Disease Composite Scale) promoted by the European Parkinson’s Disease Association and an instrument for the detection of APD; assessment scales of sleep disorders in movement disorders; gradation of severity, health-related quality of life and evaluation of urinary and pain symptoms in Parkinson’s disease, and motor and functional evaluations for Huntington’s disease.

**Molecular Biology Subgroup**

The current objectives of this subgroup are (I) molecular diagnosis, (II) basic research on genetic susceptibility factors in Alzheimer’s disease and prion diseases, and (iii) molecular basis of conformational diseases, including AD, PD and CJD. The subgroup maintains a close collaboration with different CIBERNED groups in two collaborative projects: the DEGESCO consortium, and the Spanish Prion Network (AGL2017-90665-REDT Network of Excellence).

In collaboration with Dr. M. Medina (PI1 of the project and CIBERNED deputy director), we are carrying out the project entitled “miRNA and lipid metabolism markers as potential links between vascular dysfunction and Alzheimer’s pathophysiology” (MINECO). The group also collaborates with the biotech company Biocross, SL for the development of a new commercial test (e4Risk®) intended for the detection of the isoform apoE4 in clinical routine by an immunoturbidimetric assay. On the other hand, the group collaborates with other institutions that provide a fundamental support, highlighting the collaboration with the CIEN Foundation for the early diagnosis of Alzheimer’s disease (Vallecas project, and the University of the República de Uruguay in the study of peripheral expression of CNS neurodegenerative diseases.
KEYWORDS
Alzheimer’s disease, Parkinson’s disease, Creutzfeldt-Jakob disease, epidemiology, neurodegeneration, disability, assessment scales, conformational diseases

PUBLICATIONS 2018


Skorvanek M, Martinez-Martin P, Stebbins G.T, Goetz C.G. Reply: Hoehn and Yahr stage 3 and Postural stability item in the Movement Disorder Society-Unified Parkinson’s Disease Rating


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**RESEARCH PROJECTS 2018**

**Code:** PI15CIII/00037.

**Title:** Mortalidad en poblacion que vive en residencias de ancianos de Madrid.

**Principal investigator:** Javier Damian.

**CIBERNED’s collaboration:** No.

**CIBERNED groups:** G509. Other CIBER’s collaboration: No.

**Type:** Nacional.

**Funding agency:** Instituto de Salud Carlos III.

**Funding:** ND. **Duration:** 2015-2019.
ABSTRACT

Pre-clinical model of Alzheimer’s disease.

The results obtained during the last years with APPSwe / PS1dE9 (APP / PS1) mice produce higher levels of β-amyloid than wild type (WT) mice, treated with a high-fat diet, develop memory loss compared with mice fed with a normal diet. Although the reason is unknown, there are many studies that point out that the inactivation of the insulin receptor, at the level of the hippocampus, area of the brain related to the process of memory and learning, is the main responsible of this cognitive loss.

In this line, different works suggest that cognitive loss associated with metabolic disorders (type II diabetes), is a key factor in the onset of Alzheimer’s disease. Moreover, some hypotheses suggest that Alzheimer’s disease not only affects the brain, it should be considered as a whole organism disease. A key molecule involved in the regulation of the activity of the insulin receptor is JNK1, which in turn responds to different types of stress signals and, in particular, glial activation and the release of pro-inflammatory mediators.
For this reason, we are working with Licochalcone A, this drug is an inhibitor of JNK1 kinase. Through this inhibition, the inactivation of the brain insulin receptor can be prevented being a potential treatment for cognitive loss in Alzheimer’s disease.

General objective: To act specifically on the inhibition of JNK1, as a key target, preventing phosphorylation and inhibition of the insulin receptor in the hippocampus and preventing the cognitive loss and also the neuropathological process development of AD.

Concrete objectives:

1.- Assessment of cognitive loss in the process of obesity in relation to the activity of JNK, in C57Bl6 mice of the wild strain exposed to a chronic intake during 8 months of a high-fat diet (HFD).

2.- To evaluate and characterize the impact of the chronic administration of a selective inhibitor of JNK1, licochalcone A, in APPsw / PS1E9 mice, subjected to a chronic intake of a high-fat diet (HFD), for 8 months.

Neurodegeneration, brain aging and innate immunity

In recent studies we have determined that during aging, degenerative granular structures containing neo-epitopes that are recognized by natural antibodies that exist from birth in the same mice appear in the brain of mice. This same situation has been determined later in the corpora amylacea of the human brain. These facts indicate a certain relationship and possible interaction between the degenerative and aging processes on the one hand and the natural immune system on the other.

Objective: Study the relationship between degenerative and aging processes on the one hand and the natural immune system on the other

Concrete objectives:

1.- Characterize, in different neurodegenerative diseases and in aging, brain structures that present neo-epitopes

2.- Determine the nature of these neo-epitopes

3.- Determine the natural immune response that occurs in relation to the formation of these epitopes during aging or neurodegeneration.

Development of drugs for the treatment of Alzheimer’s disease and neurodegenerative diseases in general.

Studying and clarifying the process of neuronal death after the stimulation of the ionotropic glutamate receptors is key to understanding neuronal death. We already have drugs synthesized to the Pharmaceutical Chemistry Unit of the Faculty of Pharmacy that can potentially be effective in treating Alzheimer’s disease. On the one hand it is a series of more than 400 compounds from 2008 until now (Campos et al., Bioorg Med Chem, 2008, 16, 9925-9936, Duque et al., Bioorg Med Chem, 2009, 17, 3198-3206 and 2010, 18, 46-57, Torres et al., Bioorg Med Chem, 2012, 20, 942-948, Valverde et al., Bioorg Med Chem, 2014, 22, 2678-2683, Leiva et al., Tetrahedron. Lett, 2015, 56, 1272-1275). On the other hand, it is derived from huprins (Canudas et al., Exp. Neurol, 2003, 180, 123-130), which may have multidian activity, both on NMDA receptors and on acetylcholinesterase.

General purpose

To determine the activity of drugs developed as NMDA receptor antagonists and neuro-
toxins of marine origin, as well as their action on other targets that provide them with neuroprotective capacity.

Concrete objectives

1.- To evaluate the activity of the new compounds against the increase of calcium induced by NMDA in cultures of cerebellar granule neurons

2.- Determine the activity on the monoamine oxidase (MAO) of both type A and B

3.- To evaluate the neuroprotective activity of the compounds against the induced neurodegeneration in cultures of granular calcium neurons and in animal models (APP / PS1 mice)

KEYWORDS

Alzheimer’s disease, cerebral insulin resistance, ipo 3, obesity, cognition, drug development, aging.

PUBLICATIONS 2018


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RESEARCH PROJECTS 2018

**Code:** PI2016/01.

**Title:** Alteraciones del metabolismo gluco-lipídico y desarrollo de la demencia de Alzheimer.

**Principal investigator:** Ignacio Torres Aleman.

**CIBERNED’s collaboration:** Yes.

**CIBERNED groups:** G409; G402; G511; G502; G412.

**Other CIBER’s collaboration:** No.

**Type:** Intramurales.

**Funding agency:** CIBERNED.

**Funding:** 2000000. **Duration:** 2016-2018.
**Code:** ART.
**Title:** Design of an age-dependent corneal membrane model for in vitro interaction studies of biodegradable polymeric nanoparticles. In vitro/ex vivo/in vivo correlation.
**Principal investigator:** Elena Sanchez Lopez.
**CIBERNED’s collaboration:** No.
**CIBERNED groups:** G402. **Other CIBER’s collaboration:** No.
**Type:** CCAA.
**Funding agency:** Universitat de Barcelona.
**Funding:** 8000. **Duration:** 2018-2019.

**Code:** SAF2016-77703-C2-1-R.
**Title:** Estudio de la Epoxido hidrolasa soluble como una nueva diana farmacologica para la enfermedad de Alzheimer: modulacion del estres oxidativo y la funcion mitocondrial.
**Principal investigator:** Merce Pallas.
**CIBERNED’s collaboration:** No.
**CIBERNED groups:** G402. **Other CIBER’s collaboration:** No.
**Type:** Nacional.
**Funding agency:** MICINN.
**Funding:** 100000. **Duration:** 2015-2019.

**Code:** BFU2016-78398-P.
**Title:** Estudio de la presencia de neo-epitopos en estructuras degenerativas cerebrales y de la existencia en el plasma de anticuerpos naturales dirigidos contra dichos neo-epitopos.
**Principal investigator:** Carme Pelegri Gabalda.
**CIBERNED’s collaboration:** No.
**CIBERNED groups:** G402. **Other CIBER’s collaboration:** No.
**Type:** CCAA.
**Funding agency:** Generalitat de Catalunya.
**Funding:** 120000. **Duration:** 2016-2020.

**Code:** SAF2017-84283-R.
**Title:** Modulacion de la via del receptor de insulina hipocampal como estrategia terapeutica para el tratamiento de la perdida cognitiva.
**Principal investigator:** Antonio Camins Espuny.
**CIBERNED’s collaboration:** No.
**CIBERNED groups:** G402. **Other CIBER’s collaboration:** No.
**Type:** Nacional.
**Funding agency:** MICINN.
**Funding:** 133000. **Duration:** 2018-2020.

**Code:** La Marato de TV3.
**Title:** Noves polimixines per al tractament d’infeccions causades per bacteris multiresistents.
**Principal investigator:** Francesc Rabanal Anglada.
**CIBERNED’s collaboration:** No.
**CIBERNED groups:** G402.
**Other CIBER’s collaboration:** No.
**Type:** Privado.
**Funding agency:** Fundacio La Marato de TV3.
**Funding:** 60000. **Duration:** 2018-2019.
PHD DISSERTATIONS 2018

Author: Miren Ettcheto Arriola.
Title: Efecto del síndrome metabólico provocado por una dieta rica en grasa en ratones APPswe/PS1dE9, modelo experimental de la enfermedad de Alzheimer, y posibles terapias farmacológicas.

Author: Amanda Cano Fernandez.
Title: Diseño y caracterización de nanopartículas poliméricas de Epigallocatequina-3-galacto para el tratamiento de enfermedades del sistema nervioso central.
Using the cohort of the SIGNAL project, we have established the pattern of cerebral changes in asymptomatic older adults at risk for Alzheimer’s disease (AD). The Abeta+ group exhibited thickening of middle temporal regions, while p-tau+ individuals showed thinning in the superior parietal and orbitofrontal cortices. Subjects with abnormal CSF biomarkers further showed white matter atrophy and more segregated cortical networks. These results revealed a very precise pattern of cerebral changes preceding the onset of AD symptoms (Cantero et al., 2018). Further experiments performed in patients with mild cognitive impairment (MCI) showed that ApoE4 carriers are unsuccessful in recruiting accessory cortical regions to improve memory performance; this aspect depended largely on the loss of integrity and functionality of the temporal lobe. These findings may be helpful to increase our knowledge about cerebral dysfunctions hampering neural compensation in MCI patients carrying the ApoE4 genotype (Prieto del Val et al., 2018). Given that circadian rhythmicity is progressively disrupted in senescence, we have assessed the effects of PER3 genotype, one of the most studied clock genes in humans, on aging-related changes in cognitive function and cortical integrity. Our results revealed that PER35/5 carriers had poorer cognitive performance and lower cortical integrity (structural and functional) than PER34/4. These findings may reflect cerebral vulnerabil-
ity associated with PER3 genotypes in late life (Dewandre et al., 2018). We have further reviewed evidence supporting the potential mediating role of chronic low-grade systemic inflammation in the complex relationship between impaired sleep, dysfunctional adiposity, and cognitive decline through the common pathway of neuroinflammation. This work led to a multi-factor model of aging-related cognitive decline that identifies sleep and adiposity as modifiable lifestyle factors that can be targeted to maximize cognitive function and quality of life in the elderly (Atienza et al., 2018).

**KEYWORDS**
Alzheimer’s disease, aging, biomarkers, brain imaging markers.

**PUBLICATIONS 2018**


RESEARCH PROJECTS 2018

Code: PI2016/01.
Title: Alteraciones del metabolismo gluco-lipidico y desarrollo de la demencia de Alzheimer.
Principal investigator: Ignacio Torres Aleman.
CIBERNED’s collaboration: Yes.
CIBERNED groups: G409; G402; G511; G502; G412.
Other CIBER’s collaboration: No.
Type: Intramurales.
Funding agency: CIBERNED.

Code: PSI2016-81881-REDT.
Title: Aplicaciones clinicas de la neuroimagen funcional.
Principal investigator: Fernando Maestu Unturbe.
CIBERNED’s collaboration: No.
CIBERNED groups: G511.
Other CIBER’s collaboration: No.
Type: Nacional.
Funding agency: MICINN.

Code: SAF2017-85310-R.
Title: Efectos de la concentracion de beta amiloide cerebral sobre el sueno fisiologico en personas mayores sin deterioro cognitivo.
Principal investigator: Jose Luis Cantero Lorente.
CIBERNED’s collaboration: No.
CIBERNED groups: G511. Other CIBER’s collaboration: No.
Type: Nacional.
Funding agency: MICINN.

Title: Efectos de la concentracion de beta amiloide cerebral sobre el sueno fisiologico en personas mayores.
Principal investigator: Jose Luis Cantero Lorente.
CIBERNED’s collaboration: No.
CIBERNED groups: G511. Other CIBER’s collaboration: No.
Type: Privado.
Funding agency: Sociedad Espanola de Sueno.

Code: PSI2017-85311-P.
Title: La corteza prefrontal como posible mediador de la actividad fisica aguda y de la aptitud cardiorrespiratoria sobre la memoria asociativa.
Principal investigator: Mercedes Atienza Ruiz.
CIBERNED’s collaboration: No.
CIBERNED groups: G511. Other CIBER’s collaboration: No.
Type: Nacional.
Funding agency: MICINN.
502 | Eva María Carro Díaz

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Benito León, Julián.
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Llamas Velasco, Sara.
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Pérez martínez, David Andrés.
Bachelor degree.

Villarejo Galende, Alberto.
PhD.

ABSTRACT
Our scientific activity has been focused at studying pathophysiological mechanisms of neurodegenerative diseases, mainly Alzheimer’s disease and associated dementias, identifying new therapeutic targets, risk factors and biomarkers. Specific activities are:


   a) Research on risk factors that highlight the relationship between alteration in blood cells (platelets) and Alzheimer’s disease (AD), through mechanisms and inflammatory responses at central and peripheral level. These findings complement and expand previous reports concerning the morphological and functional alterations in AD platelets, and provide more insights into possible mechanisms.
that participate in the multifactorial and systemic damage in AD.

b) Preclinical research searching for new therapeutic targets and design of potential drugs using cellular and animal experimental models of AD and Parkinson’s disease (PD).

c) Studies on molecular pathology in neurodegenerative disorders analysing new pathophysiological mechanisms, in particular, mitochondrial physiology, and regulation on neurogenic and memory processes

2. Epidemiological research on neurodegenerative diseases, particularly risk factors. Epidemiological analysis NEDICES cohort.


KEYWORDS
Alzheimer’s disease, Parkinson’s disease, Frontotemporal Dementia, biomarkers, systemic alterations, bioenergetics, therapeutic drugs.

PUBLICATIONS 2018


Benito-Leon J, Laurence M. Malassezia in the central nervous system and multiple sclerosis.


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**RESEARCH PROJECTS 2018**

**Code:** CAM-B2017/BMD-3700.

**Title:** Bases metabólicas de la neurodegeneración (NEUROMETAB-CM) Programas de Actividades de I+D entre Grupos de Investigacion de la Comunidad de Madrid en Tecnologias y en Biomedicina.

**Principal investigator:** Jose Gonzalez Castano.

**CIBERNED’s collaboration:** Yes.

**CIBERNED groups:** G401; G502; G111; G409; G412; G205; G110.

**Other CIBER’s collaboration:** No.

**Type:** CCAA.

**Funding agency:** Comunidad de Madrid.

**Funding:** 87499,89. **Duration:** 2014-2020.

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**Code:** PI2016/01.

**Title:** Alteraciones del metabolismo gluco-lipidico y desarrollo de la demencia de Alzheimer.

**Principal investigator:** Ignacio Torres Aleman.

**CIBERNED’s collaboration:** Yes.

**CIBERNED groups:** G409; G402; G511; G502; G412.

**Other CIBER’s collaboration:** No.

**Type:** Intramurales.

**Funding agency:** CIBERNED.

**Funding:** 200000. **Duration:** 2016-2018.
Code: DTS15/00141.
Title: Evaluacion del impacto de la imagen PET de amiloide en el diagnostico de los pacientes con deterioro cognitivo evaluados por sospecha de Alzheimer.
Principal investigator: Dr. Javier Arbizu.
CIBERED's collaboration: Yes.
CIBERED groups: G504 ; G502; G609. Other CIBER’s collaboration: No.
Type: Nacional.
Funding agency: Instituto de Salud Carlos III.

Title: Inflamacion periferica como factor de riesgo en la patologia de la enfermedad de Alzheimer: nuevas herramientas diagnosticas y dianas terapeuticas.
Principal investigator: Eva Carro.
CIBERED's collaboration: No.
CIBERED groups: G502. Other CIBER’s collaboration: No.
Type: Nacional.
Funding agency: Instituto de Salud Carlos III.
ABSTRACT

Our main interest is to characterize the mechanisms controlling neuronal death induced by a group of receptors collectively known as death receptors, and also the relevance of some of their intracellular antagonists. Among those, we are most interested in the antagonists expressed in nervous system, such as FAIM-L, as well as their molecular partners. Our main objective is to characterize these proteins at the molecular level, their involvement in neuronal differentiation and physiology, and their possible role in different pathologies, mainly neurodegenerative diseases. The knowledge of the molecular basis of these receptor antagonists and the activation of survival signaling pathways could be of high relevance to understand the etiology or to open new therapeutic strategies for the treatment of neurodegenerative diseases, such as Alzheimer’s disease.

We have recently characterized, in collaboration with different CIBERNED groups, the role of FAIM-L in the development of Alzheimer’s disease, both in animal models (APP/PS1) and patients (Carriba et al., 2015). At present we are further characterizing this role of FAIM-L, and with this aim we have started the characterization of the Faim knockout model, through immunohistochemistry, electrophysiological and behavior studies (Calleja-Yagüe et al, submitted). Surprisingly, this model shows an epileptic phenotype, as well as some behavior alterations, which enlarge the rele-
vance of FAIM-L functions in nervous system. We have also developed adenoassociated viral vectors, which will allow us to overexpress or downregulate FAIM-L levels in brain, at present in use in the murine models of Alzheimer’s disease (in the frame of a CIBERNED collaborative project), in order to study the role of FAIM-L in the development or progression of the disease, or its potential protector effect in these models.

Our lab has recently characterized new unexpected physiological roles for FAIM-L, since we have observed that it is implicated in the control of some non-apoptotic effects of caspases, such as axonal degeneration and long term depression (LTD), through modulation of XIAP levels (Martínez-Mármol et al., 2016). These events of synaptic plasticity are also modulated in neurodegenerative diseases, thus positioning FAIM-L as a good candidate for the treatment of the disease. At present we are also characterizing the interaction among FAIM-L and XIAP with other proapoptotic partners such as Siva-1. We have verified that Siva-1, XIAP and FAIM-L interact among them. Also, Siva-1 regulates GluA2 receptors internalization, and plays an opposite role to FAIM-L and XIAP on the apoptotic and non-apoptotic functions of caspase-3 (Coccia et al., submitted), which may help better explain the role of FAIM-L in neuron physiology.

We have also characterized two new isoforms of FAIM, one of them specific from neurons (Coccia et al., 2017), although their physiological role is still not fully characterized.

Our main research lines at present are:

1) To study FAIM-L function in in vitro and in vivo models of AD, and its relation with TNF (its duality as a pro-apoptotic molecule and at the same time as a survival promoter) and its signaling pathways, particularly NFkB, as well in the cross-talk neuron/glia.

2) To characterize FAIM-L functional partners, particularly XIAP and Siva-, and their implications in neuron physiology (neuronal plasticity) and different neurodegenerative diseases (neuronal apoptosis, synaptic degeneration).

3) To study microRNAs that could modulate FAIM expression levels, both in physiological and pathologic states.

4) To study the role of FAIM-L in the retina, and its likely association with neurodegeneration associated to type II diabetes, as a proxy of AD neurodegeneration.

**KEYWORDS**

Alzheimer, neuroinflammation, death receptors, FAIM, TNF, Fas.

**PUBLICATIONS 2018**


RESEARCH PROJECTS 2018

**Code:** PI2017/04.
**Title:** Disfunción glial en la enfermedad de Alzheimer: implicaciones patogénicas y potencial clínico.
**Principal investigator:** Javier Vitorica.
**CIBERNED’s collaboration:** Yes.
**CIBERNED groups:** G411; G415; G101; G407; G413.
**Other CIBER’s collaboration:** No.
**Type:** Intramurales.
**Funding agency:** CIBERNED.
**Funding:** 240000. **Duration:** 2017-2019.

**Code:** PI2015-2/02.
**Title:** Potencial patológico de los astrocitos: una nueva perspectiva en la enfermedad de Alzheimer.
**Principal investigator:** Joan X. Comella.
**CIBERNED’s collaboration:** Yes.
**CIBERNED groups:** G413; G415; G204; G108; G411.
**Other CIBER’s collaboration:** No.
**Type:** Intramurales.
**Funding agency:** CIBERNED.
**Funding:** 350000. **Duration:** 2016-2018.

**Code:** SAF2016-80236-R.
**Title:** Relevancia del antagonista de receptores de muerte, FAIM-L, en la enfermedad de alzheimer.
**Principal investigator:** Joan X. Comella.
**CIBERNED’s collaboration:** No.
**CIBERNED groups:** G413. **Other CIBER’s collaboration:** No.
**Type:** Nacional.
**Funding agency:** MICINN.
**Funding:** 273459. **Duration:** 2016-2019.
PRINCIPAL INVESTIGATOR
De Felipe Oroquieta, Javier.

LIST OF PERSONNEL
Alonso Nanclares, Lidia. PhD.
Alvarez Pérez, Maria del Carmen. Technician.
Antón Fernández, Alejandro. Bachelor degree.
Aparicio Torres, Guillermo. Bachelor degree.
Barbado Amigo, Marta. Bachelor degree.
Benavides Piccione, Ruth. PhD.
Blázquez Llorca, Lidia. PhD.
Cano Laiseca, Débora. Technician.
Dominguez Alvaro, Marta. Bachelor degree.
Fernández Bouzo, Montserrat. Bachelor degree.
Fernández García, Laura. Bachelor degree.
Fernaud Espinosa, Isabel. PhD.
Flores Romero, Pilar. PhD.
García Rámirez, Ana Isabel. Technician.
González Soriano, Juncal M. Bachelor degree.
Kastanauskaite, Asta. PhD.
León Espinosa, Gonzalo. PhD.
Marin Horcajadas, Mirian. Technician.
Merchán Pérez, Ángel. PhD.
Miguëns Vázquez, Miguel. Bachelor degree.
Montero Crespo, Marta. Bachelor degree.
Muñoz Céspedes, Alberto. PhD.
Ostos Campillo, Sandra. Bachelor degree.
Regalado Reyes, Mari Carmen. Bachelor degree.
Rodríguez Cela, Yago. Technician.
Rodríguez Sanchez, José Rodrigo. Bachelor degree.
rojo Salvador, Concepción. PhD.
Sánchez Ponce, Diana. PhD.
Santuy Muñoz, Andrea. Bachelor degree.
Tapia Gonzalez, Silvia. Bachelor degree.
Turégano López, Marta. Bachelor degree.
Valdés Lora, Lorena. Technician.
ABSTRACT

The two main lines of research that we have developed are:

1. Neurochemical and microanatomical analysis of the cerebral cortex in different mouse models for Alzheimer’s disease, with the idea of obtaining data about the substrate and temporal course of the microanatomical alterations that occur in Alzheimer’s disease.

2. Neurochemical and microanatomical analysis of the cerebral cortex of patients with Alzheimer’s disease. In particular, we are performing a quantitative and qualitative analysis of the synaptic circuits and neurochemical characteristics of the cerebral cortex of these patients. The aim of this objective is to try to know in detail the alterations of the neuronal circuits in relation with the senile plaques and the presence of neurofibrillary tangles.

KEYWORDS

Cerebral cortex, microorganization, neuronal circuits, electron microscopy, Alzheimer.

PUBLICATIONS 2018


Code: Cajal Blue Brain Project.  
**Title:** Cajal Blue Brain Project. International Blue Brain Project.  
**Principal investigator:** Javier De Felipe.  
**CIBERNED’s collaboration:** Yes.  
**CIBERNED groups:** G204; G403.  
**Other CIBER’s collaboration:** No.  
**Type:** Internacional.  
**Funding agency:** Ecole Polytechnique Federale de Lausanne (Suiza).  
**Funding:** ND.  
**Duration:** 2009-2019.

Code: SAF2015-66603-P.  
**Title:** Estudio de la microorganizacion de la corteza cerebral en pacientes de Alzheimer y del amster como modelo para estudiar la Fosforilacion de Tau.  
**Principal investigator:** Javier Defelipe.  
**CIBERNED’s collaboration:** No.  
**CIBERNED groups:** G403.  
**Other CIBER’s collaboration:** No.  
**Type:** Nacional.  
**Funding agency:** MICINN.  
**Funding:** 196000.  
**Duration:** 2016-2018.

**Title:** The Pyramidal Neuron in Cognition and Alzheimer’s Disease.  
**Principal investigator:** Javier Defelipe.  
**CIBERNED’s collaboration:** No.  
**CIBERNED groups:** G403.  
**Other CIBER’s collaboration:** No.  
**Type:** Internacional.  
**Funding agency:** Alzheimer’s Association.  
**Funding:** ND.  
**Duration:** 2015-2018.

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**PHD DISSERTATIONS 2018**

**Author:** Andrea Santuy Muñoz.  
**Title:** Estudio tridimensional de la ultraestructura de la Estudio tridimensional de la ultraestructura de la corteza cerebral de la rata.  
**Date:** 11/1/2018.  
**Supervisor:** Javier De Felipe Oroquieta.

**Author:** Alejandro Antón Fernández.  
**Title:** Estudio del aparato de Golgi y del segmento inicial del axón de neuronas corticales en el cerebro normal y en la enfermedad de Alzheimer.  
**Date:** 11/5/2018.  
**Supervisor:** Javier De Felipe Oroquieta.
ABSTRACT

As a result of the retirement of the PI in the Bellvitge University Hospital (HUB), the laboratories of the former Institute of Neuropathology (INP) at the HUB have been dismantled including the Biosecurity P3 facility used for the study of prion diseases. The Brain Bank of the INP is now a branch of the HUB-ICO-IDIBELL biobank; the management of the brain bank, including the procedures and availability of brain samples for research, is under the direction of IDIBELL. The INP laboratories of cell cultures at the Hospital Duran i Reynals now under the control of IDIBELL have been partially occupied by another group.

The laboratory at the Barcelona University (UB) is maintained due to the position of the PI as a professor at the UB. An agreement has been signed between CIBERNED and IRTA/CRESA to continue the studies of prion diseases.

As a consequence of pruning, the number of members of the group is reduced. However, internal research and collaboration with national and international scientists have suffered from little modifications. We have continued with old topics and have developed new lines including: 1) the research of biomarkers in blood and CSF for the diagnosis and prognosis of several neurodegenerative diseases manifested with
cognitive impairment and dementia, and ALS, with the work of Marta Barrachina, PhD and Franc Llorens, PhD; 2) combined clinical and pathological studies in motor neuron diseases with the doctoral student Pol Andrés-Benito in collaboration with the reference Unit of ALS and neuromuscular diseases of the Service of Neurology at the HUB led by Dr. Mónica Povedano; 3) study of molecular neuropathology of cerebral cortex, based on the combined use of “omics” and bioinformatics in aging, Alzheimer’s disease, dementia with Lewy bodies and Parkinson’s disease without and with dementia, in addition to frontotemporal lobar degeneration-TDP, ALS, and Creutzfeldt-Jakob disease, with the help of Paula García-Esparcia, PhD and the technician Margarita Carmona, and the valuable external collaborations with various national and international centres and groups; 4) study of protein-protein interactions and of the progression of neurodegenerative diseases with abnormal protein aggregates using natural and recombinant proteins in animal and cellular models in collaboration with the CIBERNED’s group led José Antonio del Río, PhD; 5) studies dealing with the role of astroglialopathy and oligodendrogliopathy in the pathogenesis of human neurodegenerative diseases with abnormal protein aggregates; and 6) experimental procedures testing new putative treatments of Alzheimer’s disease in mouse models, mainly performed by Ester Aso, PhD. The list of the names of the valuable collaborators inside and outside CIBERNED, fundamental in the work of the neuropathology group, is too long to be named here.


Finally, a major event in the history of the group has been the creation by Dr. Marta Barrachina of the Company ADMIT THERAPEUTICS, S.L. focused on the delineation and development of predictor biomarkers of Alzheimer’s disease based on her recent and robust discoveries in the laboratory.

Other aspects have not been less important: the training of different students who have come to the laboratory, for variable periods to learn neuropathology techniques or to do collaborative work, from different Spanish groups but also from Austria, Germany, Italy, Greece, UK, Colombia and Venezuela. The experience of working with young people is also enriching for the persons who act as tutors during the stay of the students. In addition, different seminars and invited communications for associations of patients and relatives, and the general public, thus favoring the interaction of research with civil society have been conducted. Another interesting point has been the demand of topic-free compulsory written own studies in the third course of medicine of the UB focused on the impact of diseases in the personal life of individuals or in the history of the humankind with the aim of inviting students to have and develop a more humanistic perspective of medicine.

I am also very grateful to have received the International Prize Mano Amiga for “his professional involvement and international recognition in the research and teaching on Alzheimer’s disease”. No need to say that the prize must be shared with all the people who had worked with me over time.
KEYWORDS
Neurodegenerative diseases with aggregates of abnormal proteins, molecular neuropathology, Alzheimer’s, synucleinopathies, taupathies, prion diseases, biomarkers.

PUBLICATIONS 2018


Hou X, Fiesel F.C, Truban D, Castanedes Casey M, Lin W.-L, Soto A.I. et al. Age- and disease-de-


2018. PMID: 30052585.


**RESEARCH PROJECTS 2018**

**Code:** PI2016/04.
**Title:** The ALS CIBERNED Challenge: Accelerating New Drug Discovery.
**Principal investigator:** Adolfo Lopez De Munain.
**CIBERNED’s collaboration:** Yes.
**CIBERNED groups:** G609 ; G303; G503; G408. **Other CIBER’s collaboration:** No.
**Type:** Intramurales.
**Funding agency:** CIBERNED.
**Funding:** 200000. **Duration:** 2016-2018.

**Code:** 000.
**Title:** The part of the cloud challenge on neuroinflammation. SATIVEX. Alzheimer’s Association.
**Principal investigator:** Ferrer Abizanda, Isidro.
**CIBERNED’s collaboration:** No.
**CIBERNED groups:** G503. **Other CIBER’s collaboration:** No.
**Type:** Internacional.
**Funding agency:** Alzheimer’s Association.
**Funding:** ND. **Duration:** 2017-2018.
ABSTRACT

In 2018 we have continued studying glial pathology in Alzheimer’s patients and animal models. We analyzed the microglial response in the frontal cortex of patients and, unlike the hippocampus which shows microglial degeneration, a strong activation of these immune cells was detected. This regional difference maybe due to a greater accumulation and/or Abeta aggregation in the cortex while in the hippocampus phospho-tau is preferentially accumulated, therefore, we have characterized the microglial response in two models of taupathy (P301S and ThyTau22). The P301S model showed higher microglial activation and phospho-tau accumulation. Soluble phospho-tau from P301S was not toxic to the microglia whereas that from ThyTau22 produced a strong toxicity. Consequently, it is necessary to generate new models that integrate the complexity of human microglial pathology to guarantee success at the clinical level. Another of our objectives, part of a CIBERNED collaborative project, has been to analyze the astroglial pathology. We have described, both in patients and in amyloidogenic models, a subtype of reacti-
ve astrocytes that phagocytose aberrant synapses although with a limited intracellular degradation capacity. In addition, reactive astrocytes seem to have decreased their metabolic capacities. Taking into account the primordial functions of these cells in neuronal maintenance, a decrease in their functionality could lead to neuronal vulnerability. These results were presented this year as a Doctoral Thesis by a member of our team who has received the 2018 Malaga Research Award. Overall, our work supports microglial and astroglial dysfunction, with loss of their beneficial and neuroprotective capacities, as a pathogenic mechanism in Alzheimer’s disease. This novel approach opens the door to the development of therapies aimed at restoring glial functionality and modifying the course of this disease. Finally, our scientific activity includes collaboration with various national and international groups on common objectives on Alzheimer’s.

**KEYWORDS**

Alzheimer, microglia, astroglia, pathology, neuroinflammation, transgenic models, patients, therapeutic target.

**PUBLICATIONS 2018**


RESEARCH PROJECTS 2018

**Code:** PI2017/04.
**Title:** Disfunción glial en la enfermedad de Alzheimer: implicaciones patogénicas y potencial clínico.
**Principal investigator:** Javier Vitorica.
**CIBERNED’s collaboration:** Yes.
**CIBERNED groups:** G411; G415; G101; G407; G413.
**Other CIBER’s collaboration:** No.
**Type:** Intramurales.
**Funding agency:** CIBERNED.
**Funding:** 240000. **Duration:** 2017-2019.

**Code:** PI2015-2/02.
**Title:** Potencial patológico de los astrocitos: una nueva perspectiva en la enfermedad de Alzheimer.
**Principal investigator:** Joan X. Comella.
**CIBERNED’s collaboration:** Yes.
**CIBERNED groups:** G413; G415; G204; G108; G411.
**Other CIBER’s collaboration:** No.
**Type:** Intramurales.
**Funding agency:** CIBERNED.
**Funding:** 350000. **Duration:** 2016-2018.

**Code:** FIS PI15/00796.
**Title:** Evaluando la disfunción microglial y astrogial como base del proceso neurodegenerativo y la demencia en la enfermedad de Alzheimer: nuevas aproximaciones terapéuticas.
**Principal investigator:** Antonia Gutierrez Perez.
**CIBERNED’s collaboration:** Yes.
**CIBERNED groups:** G415; G411. **Other CIBER’s collaboration:** No.
**Type:** Nacional.
Funding agency: Instituto de Salud Carlos III.  

Title: Generacion y caracterizacion de nuevos modelos murinos de Alzheimer con deficiencias en la respuesta inmune microglial.  
Principal investigator: Raquel Sanchez Varo.  
CIBERNED’s collaboration: No.  
CIBERNED groups: G415. Other CIBER’s collaboration: No.  
Type: CCAA.  
Funding agency: Universidad de Malaga.  

PHD DISSERTATIONS 2018

Author: Angela Gómez Arboledas.  
Title: Patología glial en el hipocampo de modelos transgénicos de la Enfermedad de Alzheimer: un enfoque ultraestructural.  
Date: 15/1/2018. Supervisor: Antonia Gutiérrez Pérez.
ABSTRACT

Our group is composed of a multidisciplinary team of neurologists, neuropsychologists, biologists, engineers and lab technicians. The activities of the group are focu-
sed on translational and clinical aspects of neurodegenerative dementias. In 2018 the
group has been working on novel genetics factors and novel biomarkers of the
most common neurodegenerative dementias. We have investigated new genetic risk
variants in Alzheimer’s disease (AD) and frontotemporal dementia (FTD). In para-
allel, the group has worked on novel biomarkers in cerebrospinal fluid and plasma
along the continuum of AD, dementia with Lewy bodies, FTD and Down syndrome.
The group is also involved in different imaging studies, using magnetic resonance
imaging and amyloid positron emission tomography (PET) to determine the structu-
ral correlates of different biomarkers along the AD continuum, Down syndrome and
other neurodegenerative dementias. Finally, the group also has uncovered important
aspects of the molecular basis of neurodegenerative in human brain. We have used
novel microscopy techniques (Array Tomography) and Super-resolution Microscopy
techniques to show the structure of human amyloid plaques in Alzheimer’s disease.
The group offers a unique environment for clinicians and investigators to tackle basic
and translational aspects of neurodegeneration.

KEYWORDS
Alzheimer, dementia, cerebrospinal fluid, amyloid, imaging, biomarkers

PUBLICATIONS 2018
low sAPPβ:YKL-40 ratio in antemortem cerebrospinal fluid of patients with pathologically
epub2018. PMID: 30297518.

volume on the analysis of Alzheimer’s disease biomarkers on an automated platform. Clinica

elevated high-density lipoprotein cholesterol through the cholesteryl ester transfer protein
gene does not associate with risk of Alzheimer’s disease. Alzheimer’s and Dementia: Diagno-
sis, Assessment and Disease Monitoring. 2018;10:595-598.

Blauwendraat C, Reed X, Kia D.A, Gan-Or Z, Lesage S, Pihlstrom L. et al. Frequency of Loss of
PMID: 30039155.

locus is associated with age of onset in C9orf72 carriers. Brain : a journal of neurology.
2018;141(10):2895-2907. PMID: 30252044.

of the functional speech production network in non-fluent/agrammatic variant of PPA. Cor-


Kishore A, Ashok Kumar Sreelatha A, Sturm M, von-Zweydorf F, Pihlstrom L, Raimondi F. et


### RESEARCH PROJECTS 2018

**Code:** AMEND.  
**Title:** Early Diagnosis of Alzheimer in a Multiplexed approach based on New blood biomarkers.  
**Principal investigator:** Monica Mir (CiberBBN).  
**CIBERNED’s collaboration:** Yes.  
**CIBERNED groups:** G504; G114. **Other CIBER’s collaboration:** CIBER-BBN.  
**Type:** Intramurales.  
**Funding agency:** CIBERBBN.  
**Funding:** ND. **Duration:** 2018-2018.

**Code:** PI2017/01.  
**Title:** Estudio del microRNA en el compartimento exosomal del líquido cefalorraquídeo como biomarcador de la demencia frontotemporal y herramienta para el conocimiento de las bases biológicas de la enfermedad.  
**Principal investigator:** Jordi Clarimon.  
**CIBERNED’s collaboration:** Yes.  
**CIBERNED groups:** G504; G406; G510. **Other CIBER’s collaboration:** No.  
**Type:** Intramurales.  
**Funding agency:** CIBERNE.  
**Funding:** 200000. **Duration:** 2017-2019.

**Code:** DTS15/00141.  
**Title:** Evaluacion del impacto de la imagen PET de amiloide en el diagnostico de los pacientes con deterioro cognitivo evaluados por sospecha de Alzheimer.  
**Principal investigator:** Dr. Javier Arbizu.  
**CIBERNED’s collaboration:** Yes.  
**CIBERNED groups:** G504 ; G502; G609. **Other CIBER’s collaboration:** No.  
**Type:** Nacional.  
**Funding agency:** Instituto de Salud Carlos III.  
**Funding:** 59139. **Duration:** 2016-2018.

**Code:** PI17/01896.  
**Title:** Aplicacion de Tomografia de Array (AT) para el estudio sistematico a gran escala del dano sinaptico en las demencias neurodegenerativas.  
**Principal investigator:** Alberto Lleo.  
**CIBERNED’s collaboration:** No.  
**CIBERNED groups:** G504. **Other CIBER’s collaboration:** No.  
**Type:** Nacional.
Funding agency: Instituto de Salud Carlos III.

Code: 1 R21 AG056974-01.
Title: Biological Correlates of Alzheimer in Down Syndrome.
CIBERNED's collaboration: No.
CIBERNED groups: G504. Other CIBER's collaboration: No.
Type: Internacional.
Funding agency: National Institute of Aging.

Code: 201437 10.
Title: Biomarkers profile in different phenotypes of Motor Neuron Disease.
Principal investigator: Ricard Rojas.
CIBERNED's collaboration: No.
CIBERNED groups: G504. Other CIBER's collaboration: No.
Type: Privado.
Funding agency: Fundacio La Marato de TV3.

Code: SLT006/17/00125.
Title: Contractes per a la intensificacio de l'activitat investigadora de professionals facultatius especialistes 2017.
Principal investigator: Daniel Alcolea.
CIBERNED's collaboration: No.
CIBERNED groups: G504. Other CIBER's collaboration: No.
Type: CCAA.
Funding agency: Generalitat de Catalunya.

Code: SLT006/17/00119.
Title: Contractes per a la intensificacio de l'activitat investigadora de professionals facultatius especialistes 2017. Estudios longitudinales de RM magnetica estructural, de diffusion y funcional en la EA preclinica esporadica y asociada al SD.
Principal investigator: Juan Fortea.
CIBERNED's collaboration: No.
CIBERNED groups: G504. Other CIBER's collaboration: No.
Type: CCAA.
Funding agency: Generalitat de Catalunya.

Title: Development of prototype immunoassays on the SimoA Technology for quantification in biological samples of oligomeric forms of α-Synuclein using new antibody combinations (Acronym: SynOligo).
Principal investigator: Hugo Vanderstichele.
CIBERNED's collaboration: No.
CIBERNED groups: G504. Other CIBER's collaboration: No.
Type: Internacional.
Funding agency: Michael J Fox Foundation.
**Code:** GBHI_ALZ-18-543740.
**Title:** Domiciliary Alzheimer Visiting in Down syndrome.
**Principal investigator:** Maria Carmona Iragui.
**CIBERNED's collaboration:** No.
**CIBERNED groups:** G504. **Other CIBER's collaboration:** No.
**Type:** Internacional.
**Funding agency:** Alzheimer’s Association.
**Funding:** 20974,19. **Duration:** 2017-2019.

**Code:** 4560/6393 La caixa-Down Alzheimer.
**Title:** Down Alzheimer Barcelona Neuroimaging Initiative (DABNI).
**Principal investigator:** Rafael Blesa.
**CIBERNED’s collaboration:** No.
**CIBERNED groups:** G504. **Other CIBER's collaboration:** No.
**Type:** Privado.
**Funding agency:** Fundacio La Caixa.
**Funding:** 870000. **Duration:** 2017-2020.

**Code:** EMIF-AD.
**Title:** EMIF-AD. A biomarker platform for AD biomarkers.
**Principal investigator:** Simon Lovestone, Pieter J. Visser.
**CIBERNED’s collaboration:** No.
**CIBERNED groups:** G504. **Other CIBER's collaboration:** No.
**Type:** Nacional.
**Funding agency:** Instituto de Salud Carlos III.
**Funding:** 15000. **Duration:** 2013-2018.

**Code:** PI13/01532.
**Title:** Enfermedad de Alzheimer y sindrome de Down. Estudios multimodales de liquido cefalorraquideo, resonancia magnetica y PET de amiloide.
**Principal investigator:** Rafael Blesa.
**CIBERNED’s collaboration:** No.
**CIBERNED groups:** G504. **Other CIBER's collaboration:** No.
**Type:** Nacional.
**Funding agency:** Instituto de Salud Carlos III.
**Funding:** 130075. **Duration:** 2014-2018.

**Code:** SLT002/16/00408.
**Title:** Estudio de biomarcadores y desarrollo de nuevas estrategias terapeuticas en una cohorte multicentrica de Demencia Frontotemporal.
**Principal investigator:** Alberto Lleo.
**CIBERNED’s collaboration:** No.
**CIBERNED groups:** G504. **Other CIBER's collaboration:** No.
**Type:** CCAA.
**Funding agency:** Generalitat de Catalunya.
**Funding:** 399363. **Duration:** 2017-2019.

**Code:** PI15/00026.
**Title:** Estudio del perfil de expresion de microRNA exosomal en biofluidos para la identificacion de biomarcadores de uso diagnostico en la demencia frontotemporal.
**Principal investigator:** Jordi Clarimon.
CIBERNED’s collaboration: No.
CIBERNED groups: G504. Other CIBER’s collaboration: No.
Type: Nacional.
Funding agency: Instituto de Salud Carlos III.

Title: Estudio del splicing alternativo en ARN de muestras con diagnostico neuropatologico de ELA asociada a TDP-43.
Principal investigator: Jordi Clarimon.
CIBERNED’s collaboration: No.
CIBERNED groups: G504. Other CIBER’s collaboration: No.
Type: Privado.
Funding agency: FUNDELA.

Code: PI16/01825.
Title: Estudio del trazador de tomografia por emision de positrones (PET) para Tau [18F] THK-5351 en pacientes con diferentes Taupatias.
Principal investigator: Rafael Blesa.
CIBERNED’s collaboration: No.
CIBERNED groups: G504. Other CIBER’s collaboration: No.
Type: Nacional.
Funding agency: Instituto de Salud Carlos III.

Code: SLT002/16/00099.
Title: Evaluation and characterization of synaptic proteins as biomarkers for the synaptic damage related to AD.
Principal investigator: Olivia Belbin.
CIBERNED’s collaboration: No.
CIBERNED groups: G504. Other CIBER’s collaboration: No.
Type: CCAA.
Funding agency: Generalitat de Catalunya.

Title: Grup de recerca en demències: Sant Pau (Consolided Group of Research 2017 SGR 547 “Generalitat de Catalunya”).
Principal investigator: Jordi Clarimon.
CIBERNED’s collaboration: No.
CIBERNED groups: G504. Other CIBER’s collaboration: No.
Type: CCAA.
Funding agency: Generalitat de Catalunya.

Code: EU-JG1.
Title: Horizon 21 Genetics Consortium (H21GC): Large-scale pooling/genotyping of individuals with Down syndrome for insight into predictive pathways for Alzheimer’s disease.
Principal investigator: Cornelia Van Duijn And Tonnie Coppus.
CIBERNED’s collaboration: No.
CIBERNED groups: G504. Other CIBER’s collaboration: No.
Type: Privado.
Funding agency: Fundacion Jerome Lejeune.

Title: Horizon 21-Clinical and trial outcome measures for dementia in individuals with Down Syndrome – the DS-1000 cognitive test study group.
Principal investigator: Juan Fortea.
CIBERNED’s collaboration: No.
CIBERNED groups: G504. Other CIBER’s collaboration: No.
Type: Privado.
Funding agency: Fundacion Jerome Lejeune.

Code: PI17/00279.
Title: Inflamación hipotalámica en obesidad. Papel de la dieta y efectos de la cirugía bariátrica.
Principal investigator: Amanda Gimenez.
CIBERNED’s collaboration: No.
CIBERNED groups: G504. Other CIBER’s collaboration: No.
Type: Nacional.
Funding agency: Instituto de Salud Carlos III.

Code: 201412 10.
Title: La malaltia d’Alzheimer a la sindrome de Down. Estudis multimodals amb LCR, RM, EEG i PET.
Principal investigator: Juan Fortea.
CIBERNED’s collaboration: No.
CIBERNED groups: G504. Other CIBER’s collaboration: No.
Type: Privado.
Funding agency: Fundació La Marato de TV3.

Code: PI14/01561.
Title: Marcadores sinapticos en la enfermedad de Alzheimer.
Principal investigator: Alberto Lleo.
CIBERNED’s collaboration: No.
CIBERNED groups: G504. Other CIBER’s collaboration: No.
Type: Nacional.
**Funding agency:** Instituto de Salud Carlos III.  
**Funding:** 134915.  
**Duration:** 2015-2019.

**Code:** 201614 31.  
**Title:** Pre-clinical Alzheimer’s disease and Type 2 diabetes and obesity. Effects of bariatric surgery: a multimodal study.  
**Principal investigator:** Rafael Blesa, Amanda Jimenez.  
**CIBERNED’s collaboration:** No.  
**CIBERNED groups:** G504.  
**Other CIBER’s collaboration:** CIBEROBN.  
**Type:** Privado.  
**Funding agency:** Fundacio La Marato de TV3.  
**Funding:** ND.  
**Duration:** 2017-2020.

**Code:** TAUDEM.  
**Title:** Study with the tau Positron Emission Tomography radiotracer [18F]THK-5351 in patients with different Tauopathies.  
**Principal investigator:** Alberto Lleo.  
**CIBERNED’s collaboration:** No.  
**CIBERNED groups:** G504.  
**Other CIBER’s collaboration:** No.  
**Type:** Privado.  
**Funding agency:** Fundación BBVA.  
**Funding:** ND.  
**Duration:** 2016-2019.

**Code:** 20142610.  
**Title:** Synaptic markers in preclinical Alzheimer’s disease.  
**Principal investigator:** Alberto Lleo.  
**CIBERNED’s collaboration:** No.  
**CIBERNED groups:** G504.  
**Other CIBER’s collaboration:** No.  
**Type:** Privado.  
**Funding agency:** Fundacio La Marato de TV3.  
**Funding:** 199878,75.  
**Duration:** 2015-2018.

**Code:** 2018-3570, NIH-PA-16-161.  
**Title:** The role of Inflammation and NGF Dysfunction in the Evolution of Alzheimer Disease Pathology in Down syndrome.  
**Principal investigator:** Juan Fortea.  
**CIBERNED’s collaboration:** No.  
**CIBERNED groups:** G504.  
**Other CIBER’s collaboration:** No.  
**Type:** Internacional.  
**Funding agency:** NIH.  
**Funding:** 462800,34.  
**Duration:** 2018-2022.

**Code:** PI15/00058.  
**Title:** Valoración y caracterización de biomarcadores en la fase preclínica de la enfermedad de Alzheimer.  
**Principal investigator:** Olivia Belbin.  
**CIBERNED’s collaboration:** No.  
**CIBERNED groups:** G504.  
**Other CIBER’s collaboration:** No.  
**Type:** Nacional.  
**Funding agency:** Instituto de Salud Carlos III.  
**Funding:** 68365.  
**Duration:** 2016-2018.
ABSTRACT
Our laboratory is focused on the study of the molecular and cellular mechanisms of neurons and glia contributing to the pathophysiology of Alzheimer disease (AD) and
Parkinson (PD). In 2018 we have found that morin and mangiferin strongly protect against Aβ-induced mitochondrial dysfunction and neuronal cell death. Specifically, these two natural antioxidants preserve cell respiration, promote detoxification of reactive oxygen species, protect from some forms of apoptosis, and regulate mitochondrial matrix calcium in neurons exposed to Aβ. In another study we observed that Aβ1-42 oligomers induce early, rapid, changes in the dendritic tree and spine density which is mediated by integrin β1 and downstream activation of PKC. In addition, we have analyzed the effects of mitochondrial division inhibitor-1 (mdivi-1) on mitochondrial dynamics, calcium signaling, mitochondrial bioenergetics and cell viability during neuronal excitotoxicity in vitro. We found that mdivi-1 induces a dynamin related protein 1 (Drp1)-independent protective phenotype that prevents predominantly NMDA receptor-mediated excitotoxicity through the modulation of mitochondrial function and intracellular calcium signaling. Moreover, we deepened on the search for signaling pathways initiating excitotoxic oligodendrocyte death and found that inhibition of casein kinase 2 protects these cells from dying via JNK/P53 activation. Finally, in an international coordinated effort we contributed to the characterization of the therapeutic potential of a molecular tweezer (CLR01) that is capable of decreasing α−synuclein aggregation in induced pluripotent stem cell-derived dopaminergic cultures. Thus, CLR01 reduces neurotoxicity induced by post-mortem brain extracts of PD patients; and in microfluidic assays decreases α-synuclein aggregation in cell somas when axonal terminals are exposed to α-synuclein oligomers.

KEYWORDS
β-amiloid, α−synuclein, neurons, oligodendrocytes, oxidative stress

PUBLICATIONS 2018


Ruiz A, Alberdi E, Matute C. Mitochondrial division inhibitor 1 (Mdivi-1) protects neurons against excitotoxicity through the modulation of mitochondrial function and intracellular Ca2+ signaling. Frontiers in Molecular Neuroscience. 2018;11. PMID: 29386996.


RESEARCH PROJECTS 2018

Title: Bases moleculares y celulares de la neurodegeneracion.
Principal investigator: Carlos Matute.
CIBERNED’s collaboration: No.
CIBERNED groups: G404. Other CIBER’s collaboration: No.
Type: CCAA.
Funding agency: Gobierno Vasco.

Code: BIO17/ND/008.
Title: Caracterizacion molecular de la mutacion E46K en la enfermedad de Parkinson: una mutacion vasca.
Principal investigator: Fabio Cavaliere.
CIBERNED’s collaboration: No.
CIBERNED groups: G404. Other CIBER’s collaboration: No.
Type: Privado.
Funding agency: Eitb Maratoia.

Code: PL_2016_1_0009.
Title: Modulacion de la interaccion glia-sinapsis como diana terapeutica en la enfermedad de Alzheimer.
Principal investigator: Estibaliz Capetillo.
CIBERNED’s collaboration: No.
CIBERNED groups: G404. Other CIBER’s collaboration: No.
Type: CCAA.
Funding agency: Gobierno Vasco.

Code: PL_2016_1_0016.
Title: Plasticidad de la mielina como estrategia reparadora.
Principal investigator: Maria Domercq.
CIBERNED’s collaboration: No.
CIBERNED groups: G404. Other CIBER’s collaboration: No.
Type: Nacional.
Funding agency: Instituto de Salud Carlos III.

Title: Polifenoles bioactivos con probado efecto neuroprotector: desarrollo de ingredientes innovadores para la industria alimentaria vasca.
Principal investigator: Estibaliz Capetillo.
CIBERNED’s collaboration: No.
CIBERNED groups: G404. Other CIBER’s collaboration: No.
Type: CCAA.
Funding agency: Gobierno Vasco.
**CIBERNED 2018 ANNUAL REPORT**

**Code:** SAF2016-75292-R.  
**Title:** Regulation of myelination and remyelination by neurotransmitters.  
**Principal investigator:** Carlos Matute.  
**CIBERNED's collaboration:** No.  
**CIBERNED groups:** G404.  
**Other CIBER’s collaboration:** No.  
**Type:** Nacional.  
**Funding agency:** MiCINN.  
**Funding:** 340000.  
**Duration:** 2017-2019.

**Code:** PI1800513.  
**Title:** Relevancia terapeutica de los receptores CB1 astrogliales en la esclerosis multiple.  
**Principal investigator:** Susana Mato Santos.  
**CIBERNED’s collaboration:** No.  
**CIBERNED groups:** G404.  
**Other CIBER’s collaboration:** No.  
**Type:** Nacional.  
**Funding agency:** Instituto de Salud Carlos III.  
**Funding:** 99220.  
**Duration:** 2018-2021.

**Code:** SAF2015-74332-JIN.  
**Title:** Role of lactate and monocarboxylate transporters in oligodendrocyte progenitor cell energy metabolism and remyelination.  
**Principal investigator:** Vanja Tepavcevic.  
**CIBERNED’s collaboration:** No.  
**CIBERNED groups:** G404.  
**Other CIBER’s collaboration:** No.  
**Type:** Nacional.  
**Funding agency:** MiCINN.  
**Funding:** 160000.  
**Duration:** 2017-2019.

**PHD DISSERTATIONS 2018**

**Author:** Tania Quintela López.  
**Title:** Role of beta-amyloid in the oligodendrocyte lineage.  
**Date:** 18/1/2018.  
**Supervisor:** Elena Alberdi Alfonso.
Our research focuses on the study of the cellular and molecular aspects of neurodegenerative diseases with an inflammatory component. The main line of research is “cAMP and neuroinflammation”. During 2018, we continued to investigate the relationship between cAMP and the cellular and molecular aspects of neurodegenerative diseases with an inflammatory component. We study the effect of specific inhibitors of phosphodiesterases PDE4, PDE7 and other drugs in clinical use or under development, acting on different targets, on the course of experimental autoimmune encephalitis (EAE), a mouse model of multiple sclerosis. We analyze the expression of inflammatory cytokines and PDEs and neuropathological changes in cellular populations of the brain and spinal cord. In primary cell cultures of bone marrow macrophages of mice and in the macrophage cell line Raw264.7 we study the effect of molecular regulation of intracellular signaling by cAMP, on the macrophage polarization towards pro-inflammatory or anti-inflammatory phenotypes. We have ended the collaboration with the group of Dr Tata of the Sapienza University of Rome with...
the publication of a comparative study of the expression of components of the cholinergic system in the central nervous system and the spinal cord of EAE mice in two different phases of the disease: acute phase and remitting phase.

KEYWORDS
Neurodegeneration, neuroinflammation, molecular neuropharmacology.

PUBLICATIONS 2018

RESEARCH PROJECTS 2018
Code: PI15/00148.
Title: ¿Están implicados los cambios fenotípicos de las microglia/macrofagos en los efectos beneficiosos de los inhibidores de PDEs del AMPc en la EAE crónica?.
Principal investigator: Guadalupe Mengod.
CIBERNED’s collaboration: No.
CIBERNED groups: G508. Other CIBER’s collaboration: No.
Type: Nacional.
Funding agency: Instituto de Salud Carlos III.
PRINCIPAL INVESTIGATOR
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ABSTRACT
Synaptic dysfunction and loss of synapses are major correlates of cognitive impairment in AD but the cellular mechanisms underlying these changes are still unclear. In the past years our research efforts were focused on deciphering the molecular events underlying synaptic dysfunction at early stages of AD. Synapse-to-nucleus signaling causes synapse dysfunction, neurodegeneration and memory loss in dementia disorders, particularly in Alzheimer’s disease (AD). Using genome-wide transcriptome analysis, we found that a gene expression program regulated by the synapse-to-nucleus factor CREB-regulated transcription coactivator-1 (CRTC1) is essential for hippocampal-dependent memory and is associated with early pathological and memory changes in AD. During this year we have found that CRTC1 binds to promoter regions of neuronal excitability and plasticity genes, including glutamate receptors. Remarkably, CRTC1 plays essential roles on long-term memory and dendritic spine morphology favorable to enhance synaptic plasticity, including long-term potentiation and depression. CRTC1-dependent synaptic potentiation involves enhancement of NMDA receptor transmission through PKC-mediated phosphorylation and recruitment of GluN1 receptors at synapses. Moreover, Nr4a2, one of the CRTC1 target genes reg-
ulates activity-dependent CREB/CRTC1-dependent expression of the neurotrophin BDNF in the hippocampus and BDNF-mediated expression of AMPA receptors (AMPA) subunits. Altogether suggests that the CRTC1-Nr4a2 axis controls the expression of several NMDA and AMPAR subunits in the hippocampus. On the other hand, several studies have shown that some miRNAs control the formation, maturation and function of synapses and alteration in their levels could underlie synaptic dysfunction in pathological states. During this year we have identified the alteration of several miRNAs related to synaptic targets in plasma and brain samples from MCI and AD dementia patients. Moreover, we have obtained preliminary data to support the identification of a miRNAs signature in plasma that could be used as an early AD biomarker, predicting the progression from MCI to AD.

**KEYWORDS**
Alzheimer disease, memory, gene regulation, glutamate receptors, CRTC1, early synaptic dysfunction, miRNAs, biomarker.

**PUBLICATIONS 2018**


RESEARCH PROJECTS 2018

Code: PI2017/01.
Title: Estudio del microRNA en el compartimento exosomal del líquido cefalorraquídeo como biomarcador de la demencia frontotemporal y herramienta para el conocimiento de las bases biológicas de la enfermedad.
Principal investigator: Jordi Clarimon.
CIBERNED’s collaboration: Yes.
CIBERNED groups: G504; G406; G510. Other CIBER’s collaboration: No.
Type: Intramurales.
Funding agency: CIBERNED.

Code: SAF2017-89271-R.
Title: Implicacion de Nr4a2/Nurr1 en la disfuncion sinaptica y deficits cognitivos en fases tempranas de la Enfermedad de Alzheimer.
Principal investigator: Jose Rodriguez Alvarez.
CIBERNED’s collaboration: No.
CIBERNED groups: G406. Other CIBER’s collaboration: No.
Type: Nacional.
Funding agency: MICINN.

Title: Searching new biomarkers and therapeutic targets related to cognitive deficits in early stages of Alzheimer’s Disease: Role of AKAP79/150, CPT1C and SSAO/VAP-1 in Ab-mediated AMPAR dysfunction.
Principal investigator: Jose Rodriguez Alvarez.
CIBERNED’s collaboration: No.
CIBERNED groups: G406. Other CIBER’s collaboration: No.
Type: Privado.
Funding agency: Fundacio La Marato de TV3.

Code: SAF2016-80027-R.
Title: Transcriptional mechanisms of synaptic plasticity in memory circuits in a mouse mouse of neurodegeneration.
Principal investigator: Carlos A. Saura.
CIBERNED’s collaboration: No.
CIBERNED groups: G406. Other CIBER’s collaboration: No.
Type: Nacional.
Funding agency: MICINN.

PHD DISSERTATIONS 2018

Author: Dolores Siedlecki-Wüllich.
Title: Analysis if miRNA expression in Alzheimer’s disease. Potential use as early biomarkers.
Date: 16/11/2018. Supervisor: José Rodriguez Álvarez.
ABSTRACT

Our research team has been working for years on the characterization of alterations in key proteins related with the progression Alzheimer’s disease (AD), attempting to prove malfunctions, as well interconnect β-amyloid (Aβ) and tau hyperphosphorylation (P-tau) pathologies. We have developed tools to study alteration in formation of active protein complexes, proteolytic processing by secretases, glycosylation pattern and others, all of them that could be relevant for understand the impairment of several pathways related with AD. In the past we have described an altered expression of reelin in AD. Reelin is a signaling protein that modulates synaptic function and plasticity in the brain. Our effort was focus to demonstrate a mechanism by which β-amyloid regulates reelin expression, thereby influencing its signaling cascade that ultimately controls tau phosphorylation. Intriguingly, we found that reelin expression levels are increased in the AD brain, but the β-amyloid (Aβ) protein impairs reelin activity. Reelin binding to their receptor, ApoER2, activates downstream signaling and induces the proteolytic cleavage of ApoER2, resulting in the generation of intracellular and extracellular soluble fragments. Previously, we also demonstrated that the intracellular fragment ApoER2-CTF exerts a modulatory role on reelin expression. Our recent data indicated that Aβ is able to trigger increased reelin expression through a mechanism that involved the decrease generation of ApoER2-CTF (Mata-Balaguer et al., FASEB J 2018). Moreover, to evaluate the impaired efficiency of reelin signaling in AD in vivo, we have quantified the levels the soluble
ectodomain fragment of ApoER2 (ectoApoER2) in the human cerebrospinal fluid (CSF). Our data suggest that the determination of decreased levels of ecto-ApoER2 in CSF could be a suitable read-out of an impaired reelin signaling in AD, but also indicate differences between sporadic AD and familiar AD (Lopez-Font et al., Clin Chem Acta 2019).

We not only aim to clarify the pathological mechanisms behind these diseases, but also to define potential diagnostic tools and/or processes with therapeutic relevance. We also demonstrated that AD therapy with γ-secretase inhibitors (GSIs) affects the levels of the catalytic subunit, presenilin-1 (PS1). This rebound increase in PS1 levels after sustained γ-secretase inhibition can result in an undesirable gain of γ-secretase activity which maybe contributes to the worsening condition reported in volunteers enrolled in discontinued clinical trials (Sogorb-Esteve et al., Mol Neurobiol 2018).

Furthermore, we evaluate the diagnostic potential of the disintegrin metalloproteinase 10 (ADAM10). ADAM10 is the main α-secretase acting in the non-amyloidogenic processing of the amyloid precursor protein (APP). We have demonstrated the presence of several forms of ADAM10 in CSF, including mature and immature full-length forms, as well truncated species. Our data indicated that the determination of decreased levels of mature forms of CSF-ADAM10 may be useful as a biomarker for AD (Sogorb-Esteve et al., J Neuroinflammation 2018). Finally, in a collaborative CIBERNED project we extended our experience characterizing CSF protein in the CSF to the study of ErbB4 in amyotrophic lateral sclerosis (ALS). ErbB4 is a transmembrane receptor tyrosine kinase that binds to neuregulins to activate signaling, and disruption of the neuregulin-ErbB4 pathway has been suggested to be involved in the pathogenesis of ALS. In this study we have demonstrated that soluble proteolytic fragments of the ErbB4 ectodomain (ecto-ErbB4) can be detected in CSF and plasma, and if that the levels are decreased in ALS subjects. Likewise, the ecto-ErbB4 fragments were decreased in the plasma of the two transgenic mouse models of ALS (SOD1G93A and TDP-43A315T). We conclude that the determination of circulating ecto-ErbB4 fragments could be a tool to evaluate the impairment of the ErbB4 pathway and may be a useful biomarker in ALS (Lopez-Font et al., Neurobiol Dis 2019).

**KEYWORDS**

Alzheimer, Amyotrophic Lateral Sclerosis, ADAM10, biomarker, ApoER2, reelin, PS1, GSI.

**PUBLICATIONS 2018**


**RESEARCH PROJECTS 2018**

**Code:** PI2017/04.  
**Title:** Disfunción glial en la enfermedad de Alzheimer: implicaciones patogénicas y potencial clínico.  
**Principal investigator:** Javier Vitorica.  
**CIBERNED’s collaboration:** Yes.  
**CIBERNED groups:** G411; G415; G101; G407; G413.  
**Other CIBER’s collaboration:** No.  
**Type:** Intramurales.  
**Funding agency:** CIBERNED.  
**Funding:** 240000.  
**Duration:** 2017-2019.

**Code:** PI17/00261.  
**Title:** Descifrando las alteraciones en la expresion de acetilcolinesterasa en al enfermedad de Azlheimer.  
**Principal investigator:** Maria Salud Garcia Ayllon.  
**CIBERNED’s collaboration:** No.  
**CIBERNED groups:** G407.  
**Other CIBER’s collaboration:** No.  
**Type:** Nacional.  
**Funding agency:** Instituto de Salud Carlos III.  
**Funding:** 99220.  
**Duration:** 2018-2020.

**Code:** PI15/00665.  
**Title:** Interacciones de las vías Reelina/ApoE y ligandos alternativos con el β-amiloide, su disfuncion en la enfermedad de Alzheimer.  
**Principal investigator:** Javier Saez Valero.  
**CIBERNED’s collaboration:** No.  
**CIBERNED groups:** G407.  
**Other CIBER’s collaboration:** No.  
**Type:** Nacional.  
**Funding agency:** Instituto de Salud Carlos III.  
**Funding:** 80465.  
**Duration:** 2016-2018.

**Code:** AICO/2018/090.  
**Title:** Redefiniendo nuevos marcadores para el diagnostico y terapia de la enfermedad de Alzheimer.  
**Principal investigator:** Javier Saez Valero.  
**CIBERNED’s collaboration:** No.
CIBERNEd groups: G407. Other CIBER's collaboration: No.
Type: CCAA.
Funding agency: Generalitat de Valencia.

Code: TAUPATH.
Title: Tau pathology – common and differing pathways in neurodegenerative tauopathies.
Principal investigator: Javier Saez Valero y Maria Salud Garcia Ayllon.
CIBERNEd's collaboration: No.
CIBERNEd groups: G407. Other CIBER's collaboration: No.
Type: Europeo.
Funding agency: Comision Europea.

Title: Tau protein – a key but highly complex protein in the pathogenesis of Alzheimer’s disease and other tauopathies.
Principal investigator: Javier Saez Valero.
CIBERNEd’s collaboration: No.
CIBERNEd groups: G407. Other CIBER’s collaboration: No.
Type: CCAA.
Funding agency: Generalitat de Valencia.

PHD DISSERTATIONS 2018

Author: Aitana Sogorb-Esteve.
Title: Secretases as potential biomarkers and therapeutic target for Alzheimer’s Disease.
408 | Eduardo Soriano García

ABSTRACT

Somatic brain wiring in AD: We have deeply characterized somatic genetic wiring in Alzheimer Disease brains by determining novel somatic variations and copy number variations (CNVs) (Gómez-Ramos et al., 2017; Lobón et al., in preparation). We have also analyzed somatic genetic events in Parkinson Diseased brains, leading to the identification of brain somatic variants (Lobón et al., in preparation). Finally, a review discusses current methods to validate somatic mutations present in low percentage of neural cells (Picher et al., 2018). Reelin and Neurodegeneration: We have submitted a manuscript showing that overexpression of Reelin protects against tau pathology in AD by: a) reducing abnormal dendritic Tau translocation, b) reducing Tau phosphorylation, and c) rescuing Tau-associated behavioral deficits. We have completed studies determining the role of Reelin in proteinopathies transmissibility.
in AD and in Parkinson’s Disease: Overexpression of Reelin in living mice reduced the spreading of amyloid plaques generated by the injection of J20 protein extracts. Similarly, Reelin also reduced the transmissibility of alfa-synuclein in a model of Parkinson’s Disease. These findings are important because, to our knowledge, this is the first therapeutic tool that reduces misfolded protein aggregation and prion-like propagation in living mice. Similarly, we have characterized the role in vivo of APP and Tau mutations on tau-associated pathology, in particular the accumulation of phosphorylated Tau in interneurons (Dávila et al., 2018). SNAREs, axonal growth and regeneration: We have determined a fundamental role of the centrosomal protein Augmin in the polarization of neuronal microtubules and in the outgrowth of developing axons and dendrites (Freixo et al., 2018). Similarly, we have demonstrated a fundamental role of SNARE proteins in neurotrophin/Trk mediated axonal growth (Fuschini et al., 2018) and that disruption of lipid rafts enhances axonal growth and regeneration in vitro and in vivo (Roselló et al., 2018). The Armcx gene cluster: We have discovered a role of Armcx protein in the control of cell cycle and in neuronal migration (Mirra et al., 2016) and have identified TDP43 (an ALS gene) and Parkin (Parkinson) as Armcx interaction proteins. The generation of CNS specific KOs (nestin-cre) for the armcx3 gene has allowed us the discovery of a phenotype associated to ALS, i.e., with spinal cord motorneuron death and severe motor deficits. In collaboration with Dr. F Villarroya we have discovered that Armcx3 inactivation (conditional KO) dramatically reduces liver tumor formation by controlling cell proliferation, cell death and lipid accumulation.

**KEYWORDS**

Reelin, Synapses, Alzheimer Disease, Somatic Mutations.

**PUBLICATIONS 2018**

Dávila E, Targa G, Ávila J, Soriano E, Pascual M. Differential accumulation of Tau phosphorylated at residues Thr231, Ser262 and Thr205 in hippocampal interneurons and its modulation by Tau mutations (VLW) and amyloid-β peptide. Neurobiology of disease. 2018. PMID: 30553886.


**RESEARCH PROJECTS 2018**

**Code:** PI2016/04.
**Title:** The ALS CIBERNED Challenge: Accelerating New Drug Discovery.
**Principal investigator:** Adolfo Lopez De Munain.
**CIBERNED’s collaboration:** Yes.
**CIBERNED groups:** G609; G303; G503; G408. **Other CIBER’s collaboration:** No.
**Type:** Intramurales.
**Funding agency:** CIBERNED.
**Funding:** 200000. **Duration:** 2016-2018.

**Code:** 2017SGR1280 (Solicitado).
**Title:** Ayudas para apoyar las actividades de los grupos de investigación de Catalunya SGR 2017-2019.
**Principal investigator:** Eduardo Soriano Garcia.
**CIBERNED’s collaboration:** No.
**CIBERNED groups:** G408. **Other CIBER’s collaboration:** No.
**Type:** CCAA.
**Funding agency:** Generalitat de Catalunya.
**Funding:** 70500. **Duration:** 2017-2019.

**Code:** SAF2016-76340-R.
**Title:** Novel approaches to understand Alzheimers Disease pathogenesis and therapeutics.
**Principal investigator:** Eduardo Soriano Garcia.
**CIBERNED’s collaboration:** No.
**CIBERNED groups:** G408. **Other CIBER’s collaboration:** No.
**Type:** Nacional.
**Funding agency:** MICINN.
**Funding:** 380010. **Duration:** 2017-2019.

**Code:** (PI17/02285) (Solicitado).
**Title:** Potencial de los Inhibidores de proteinas SNARE como agentes terapeuticos antitumorales.
**Principal investigator:** Fausto Ulloa.
**CIBERNED’s collaboration:** No.
**CIBERNED groups:** G408. **Other CIBER’s collaboration:** No.
**Type:** Nacional.
**Funding agency:** MICINN.
**Funding:** 151250. **Duration:** 2018-2020.
Code: La Marató TV3 2016 (Denegado).
Title: Synergistic effect of cholesterol depletion and semaphorin blockade in peripheral and central nervous system regeneration.
Principal investigator: Ignacio Alfonso Rodriguez / Eduardo Soriano.
CIBERNED's collaboration: No.
CIBERNED groups: G408. Other CIBER's collaboration: No.
Type: Privado.
Funding agency: Fundació La Marató de TV3.

Code: 15/C/2014.
Title: The role of reelin at the crossroads of alzheimer’s disease mechanisms: tauopathy, amyloid toxicity and transmissibility.
Principal investigator: Lluis Pujadas Puigdomènech.
CIBERNED's collaboration: No.
CIBERNED groups: G408. Other CIBER's collaboration: No.
Type: Privado.
Funding agency: Fundació La Marató de TV3.
ABSTRACT

Ever since its inception, the laboratory works in the neurobiology of mammalian insulin factors (ILPs). During 2018 we have analyzed the role of insulin in brain metabolism, linking it to neurovascular coupling and exploring underlying mechanisms. The latter may be of great significance in vascular brain aging. We also bred transgenic mice with impaired insulin or IGF-I signaling and brain Alzheimer’s disease pathology to explore the impact of these signaling pathways in disease progression. The line of research that we started last year related to IGF-I crosstalk with the hypothalamic orexinergic system, is yielding observations that will help us better understand the neurobiology of ILPs. We focused on this multifunctional circuit because shares many of the multiple actions exerted by IGF-I on the brain. We are finding that this relatively small hypothalamic nucleus is involved in the effects of IGF-I on sleep, amyloidosis, mood and response to exercise, and even unveiled a striking impact on peripheral glucose metabolism. Further, we are analyzing mechanisms underlying
the neuron-astrocyte dialog in glucose metabolism and its potential impact on Abeta handling. Also, we are completing the characterization of an interaction between IGF-I and ApoE in Abeta metabolism.

KEYWORDS
Insulin factors, neuronal plasticity, and degenerative diseases/ Therapeutic targets in neurodegeneration/ the aging brain and cognition/ Blood brain barrier/ Mood homeostasis/Orexin circuitry.

PUBLICATIONS 2018

RESEARCH PROJECTS 2018

Code: SAF2016-76462-C2-1-P.
Title: El sistema IGF-I/orexina/acetylcolina como nexo de union entre co-morbilidad.
Principal investigator: Ignacio Torres Aleman.
CIBERNED's collaboration: No.
CIBERNED groups: G409. Other CIBER's collaboration: No.
Type: Nacional.
Funding agency: MICINN.

**PHD DISSERTATIONS 2018**

Author: Andrea Santi Miño.
Title: Vulnerabilidad a estrés del cerebro lesionado: el IGF-I como modulador de la sensibilidad del eje HPA.
Date: 21/2/2018. Supervisor: Ignacio Torres Alemán.
During the year 2018, we have characterized a new digital PCR method to measure directly the concentration of circulating extracellular mitochondrial DNA in cerebrospinal fluid. This new method allows the detection and absolute quantification of the amount of mitochondrial DNA with high analytical sensitivity, specificity and precision. Using this new technique, we have initiated studies to determine whether the content of mitochondrial DNA in the cerebrospinal fluid of patients with Alzheimer’s disease is related with disease progress. Other studies from our group have shown that high cholesterol levels prevent the degradation by autophagy of beta amyloid and tau while promoting their secretion. Specifically, we have shown that high cholesterol levels increase the formation of autophagosomes, but at the same time inhibit the fusion of autophagosomes with lysosomal vesicles. In addition, treatment with 2-hydroxypropyl-β-cyclodextrin reduces cholesterol levels and completely reverses the alterations evoked by cholesterol, which may represent a new therapeutic strategy in the treatment of Alzheimer’s disease. Another line of research of our group has studied the role of the ATP-sensitive potassium channel (KATP) in the pathology of amyotrophic lateral sclerosis (ALS). The results indicate that the expression of the KATP channel is increased in post-mortem human tissue samples from the motor cor-
tex and the cervical and thoracic spinal cord of people with sporadic ALS. Likewise, the results indicate that polymorphisms of genes that encode subunits of KATP are related to the progression of the disease, which suggests that this channel plays a key role in the pathophysiology of ALS.

**KEYWORDS**


**PUBLICATIONS 2018**


**RESEARCH PROJECTS 2018**

**Code:** PI2016/06.
**Title:** Identificacion de vias fisiopatologicas y biomarcadores candidatos en la fase pre-diagnostica de la enfermedad de Parkinson.
**Principal investigator:** Miquel Vila Bover.
**CIBERNED’s collaboration:** Yes.
**CIBERNED groups:** G109 ; G601; G207; G410.
**Other CIBER’s collaboration:** No.
**Type:** Intramurales.
**Funding agency:** CIBERNED.
**Funding:** 196000. **Duration:** 2016-2018.
**Code:** SAF2017-89791-R.
**Title:** Replication and transcription of mitochondrial DNA as a central mechanism of the pathological sequence leading to neurodegeneration.
**Principal Investigator:** Ramon Trullas.
**CIBERED's collaboration:** No.
**CIBERED groups:** G410. **Other CIBER's collaboration:** No.
**Type:** Nacional.
**Funding agency:** MICINN.
**Funding:** 242000. **Duration:** 2018-2020.
ABSTRACT

In 2018, we continued with the characterization of the microglial and astroglial response in murine models of Alzheimer’s disease, Abeta and Tau, and in AD patient samples. Within this characterization, we are developing new models to mimic the microglial dysfunction observed in Alzheimer’s patients. Specifically, we are developing Abeta and Tau models, conditional knockouts of the Csf1R gene specifically in microglial cells with the idea of diminishing their ability to survive and function. These models will allow us to establish the function of microglial cells in the development of Abeta and/or tau pathology. On the other hand, we have also transcriptionally characterized the microglia and isolated astrocytes of Abeta (APPsI) and Tau (P301S) models. In this sense, the microglial cells have been isolated by cell sorting using both classical markers, CD11b and CD45, and the activation marker DAM Clec7a (see attached figure). Astrocytes from the same animals were isolated using ACSA2 (see figure). This approach was carried out at two ages, prepatology (3 months) or established pathology (12 or 9 months for APP and Tau, respectively). Among the most relevant results, and contrary to what might be expected based on their morphology, the astrocytes of both models present a clear pattern of metabolic deficiencies. We are currently completing this analysis for publication. On the other hand, the microglia in both models also presents a clear profile of activation to the
phenotype called DAM (disease associated microglia). Interestingly, although APP and Tau proteinopathies are completely different, we did not observe large differences in their transcriptional profile. We are currently characterizing its function in pathology. This objective is encompassed within an intramural CIBERNED project (IP Javier Vitorica) and has been carried out in collaboration with Dr. E. Galea (Marató de TV3). Finally, we have established collaborations to determine, on the one hand, the role of hypoxia in the microglial response in the pathology of Alzheimer’s and, on the other hand, we are studying the role of possible ligands of Trem2 in the microglial activation in this pathology.

**KEYWORDS**

Alzheimer, degeneration, inflammation, Abeta, tau, oligomers, soluble, transgenic models, neuropathology.

**PUBLICATIONS 2018**


**RESEARCH PROJECTS 2018**

Title: Disfunción glial en la enfermedad de Alzheimer: implicaciones patogénicas y potencial clínico.
Principal investigator: Javier Vitorica.
CIBERNED’s collaboration: Yes.
CIBERNED groups: G411; G415; G101; G407; G413.
Other CIBER’s collaboration: No.
Type: Intramurales.
Funding agency: CIBERNED.
**Code:** PI2015-2/02.
**Title:** Potencial patológico de los astrocitos: una nueva perspectiva en la enfermedad de Alzheimer.
**Principal investigator:** Joan X. Comella.
**CIBERNED’s collaboration:** Yes.
**CIBERNED groups:** G413; G415; G204; G108; G411.
**Other CIBER’s collaboration:** No.
**Type:** Intramurales.
**Funding agency:** CIBERNED.
**Funding:** 350000. **Duration:** 2016-2018.

**Code:** FIS PI15/00796.
**Title:** Evaluando la disfunción microglial y astrogial como base del proceso neurodegenerativo y la demencia en la enfermedad de Alzheimer: nuevas aproximaciones terapéuticas.
**Principal investigator:** Antonia Gutierrez Perez.
**CIBERNED’s collaboration:** Yes.
**CIBERNED groups:** G415; G411. **Other CIBER’s collaboration:** No.
**Type:** Nacional.
**Funding agency:** Instituto de Salud Carlos III.
**Funding:** 99220. **Duration:** 2016-2018.
ABSTRACT

Our group, “Molecular mechanisms of Neurodegeneration”, is generated from an established line in the CBM over several years. At present, this CIBERNED line is formally composed by three sub-groups (IP’s-F Wandosell (CBM), I. Anton (CNB) and J. J. Garrido, Cajal Inst.). Our group is mostly devoted to the analysis of neurodegenerative disorders. Now is focusing in a group of brain disorders associated with aging, such as Alzheimer, disease, Stroke and some type of brain tumours. We are interested in the analysis of which cellular signals are altered throughout the aging process and how the modification of some of them triggers a pathological process. Thus one open question is ... are there common molecular mechanisms underlying the age-dependency of several disorders?. Data from different animal models strongly support that idea that -PI3K-Akt pathway is deregulated in several brain pathologies. First, we are interested in the analysis of the molecular mechanisms of both brain disorders, mainly focusing in the role of PI3K-Akt and some of the Akt substrates. Our previous work has led us to analyze in more detail some Akt downstream element such as, mTORC1. This protein complex controls general aspects of protein synthesis.
and autophagy; whereas its dysfunction has been considering a key factor of beta amyloid generation and/or degradation in Alzheimer disease (AD). We just analyze the role of mTORC1 activity in the generation of amyloid in AD transgenic models, and we are interested in the analysis of early stages of this pathology. (CoIPs: Dr. J.J.Garrido & F Wandosell). Our second goal is the analysis of a new oncogenic pathway that we recently described: Akt/WIP/YAP/TAZ. Our data indicated that Akt and WIP are responsible of the cell division of cancer-stem cells and the maintenance of its stem-like phenotype. Our work is about defining the elements of this path that are between Akt and WIP and YAP/TAZ that regulate the conversion from astrocyte-astrocytoma-glioma (CoIPs: Dr. I. Anton & F.Wandosell). In summary, we are analysing some signalling and elements that control physiological process, from cell division to differentiation, and how some of these proteins are modified in pathology.

diferenciación, y cómo de PI3K-Akt algunas de estas proteínas se modifican en patología.

KEYWORDS

PUBLICATIONS 2018


### RESEARCH PROJECTS 2018

**Code:** CAM-B2017/BMD-3700.  
**Title:** Bases metabólicas de la neurodegeneración (NEUROMETAB-CM) Programas de Actividades de I+D entre Grupos de Investigacion de la Comunidad de Madrid en Tecnologias y en Biomedicina.  
**Principal investigator:** Jose Gonzalez Castano.  
**CIBERNED’s collaboration:** Yes.  
**CIBERNED groups:** G401; G502; G111; G409; G412; G205; G110.  
**Other CIBER’s collaboration:** No.  
**Type:** CCAA.  
**Funding agency:** Comunidad de Madrid.  
**Funding:** 87499,89.  
**Duration:** 2014-2020.

**Code:** PI2016/01.  
**Title:** Alteraciones del metabolismo gluco-lipidico y desarrollo de la demencia de Alzheimer.  
**Principal investigator:** Ignacio Torres Aleman.  
**CIBERNED’s collaboration:** Yes.  
**CIBERNED groups:** G409; G402; G511; G502; G412.  
**Other CIBER’s collaboration:** No.  
**Type:** Intramurales.  
**Funding agency:** CIBERNED.  
**Funding:** 200000.  
**Duration:** 2016-2018.

**Code:** SAF2015-70368-R.  
**Title:** Analisis de la senalizacion mediada por akt en neurodegeneracion y en proliferacion, migracion/invasion celulares.  
**Principal investigator:** Francisco Wandosell, Ines M. Anton Gutierrez.  
**CIBERNED’s collaboration:** No.  
**CIBERNED groups:** G412.  
**Other CIBER’s collaboration:** No.  
**Type:** Nacional.  
**Funding agency:** MICINN.  
**Funding:** 220000.  
**Duration:** 2016-2018.

**Code:** OC-2015-1-19840.  
**Title:** European Network of multidisciplinary research and translation of autophagy knowledge.  
**Principal investigator:** Caty Casas.  
**CIBERNED’s collaboration:** No.  
**CIBERNED groups:** G412.  
**Other CIBER’s collaboration:** No.  
**Type:** Europeo.
**Funding agency:** Comision Europea.
**Funding:** ND. **Duration:** 2016-2020.

**Code:** Fundacion RAMON ARECES.
**Title:** Interactoma diferencial de WIP: Actividad oncogenica versus supresora de tumores”.
**Principal investigator:** Francisco Wandosell, Ines Anton.
**CIBERNED’s collaboration:** No.
**CIBERNED groups:** G412. **Other CIBER’s collaboration:** No.
**Type:** Privado.
**Funding agency:** Fundacion Ramon Areces.
**Funding:** 40000. **Duration:** 2017-2019.

**Code:** PCIN-2016-108.
**Title:** Regulacion del reflejo de miccion despues de lesionmedular: abolicion por silenciamiento de los aferentes de las fibras C de la vejiga hiper-excitados mediante terapia genica para restaurar la continencia y la miccion”.
**Principal investigator:** Francisco Wandosell.
**CIBERNED’s collaboration:** No.
**CIBERNED groups:** G412. **Other CIBER’s collaboration:** No.
**Type:** Europeo.
**Funding agency:** Comision Europea.
**Funding:** 150000. **Duration:** 2017-2019.
PROGRAM 2

PARKINSON’S AND HUNTINGTON’S DISEASE AND OTHER DEGENERATIVE MOVEMENT DISORDERS
This Program brings together 25 basic and clinical research groups with a mainly translational character, joining forces to study neurodegenerative diseases of different etiology that cause important problems in patient’s mobility. Among this group of diseases we can find, by decreasing prevalence: Parkinson’s disease, Huntington’s chorea, and different kinds of ataxias among other movement disorders.

RESEARCH LINE 1: PARKINSON’S DISEASE

Parkinson’s disease (PD) is mainly characterized by neuronal loss, the formation of Lewy bodies and neurites in the substantia nigra and the consequent loss of striatal dopamine (DA). However, it is currently well known that PD is a multisystem neurodegenerative process, in which, as the neurodegenerative process evolves, many areas of the nervous system are affected and there exists a deficit in several neurotransmission and neuromodulation systems. It is estimated to affect around 160,000 people in Spain, a figure that is expected to be increasing due to the progressive aging of the population.

Although preventing and correcting DA deficit are still important goals, they cannot be considered the ultimate challenge in PD nowadays. Within this area, it is considered of vital importance to make progress on defining the following issues:

- **a)** Key aspects related to the ethiopathogenesis in PD.
- **b)** Physiopathological mechanisms related to disease onset and progression.
- **c)** Development of symptomatic treatments, especially neuroprotective and curative. Thus, a truly translational research is sought, having the disease and the patients as the main targets.

Thus, this line of research intends to achieve a true translational research nature, whose main objectives are the disease and the patient.

The main research topics in this line are the following:

- Cognitive impairment and non-motor problems in PD.
Biomarkers in Parkinson’s disease.

Problems related to symptomatic treatment: diskynesias.

New targets and novel therapeutic strategies in Parkinson’s disease.

Circuits and physiopathology of basal ganglia.

Neuronal stress, cell protection and death in Parkinson’s disease.

Neurogenesis and cell therapy in Parkinson’s disease.

Early biomarkers in Parkinson’s disease.

**RESEARCH LINE 2: HUNTINGTON’S DISEASE AND ATAXIAS**

This program also focuses on the research into other movement disorders such as Huntington’s disease (HD) and ataxias. HD is characterized by the initial loss of spiny interneurons of the striatum. It is an autosomal dominant neurodegenerative pathology with complete penetrance produced by polyglutamine expansion in the huntingtin N-terminus. HD has no treatment and leads to death in around 10-20 years depending on the number of polyglutamines, the age of onset, some unknown environmental factors and the modulation of some genes, some of which have been located but remain unidentified. HD has a much lower prevalence than AD or PD, 10 cases/100,000 inhabitants, and it is estimated that there are about 4,000 patients in Spain and about 50,000 in the European Union. Its social health cost is considerable because of the importance of cognitive and motor deficits, as well as the severe behavioral problems that patients present.

There is a large number of studies with neuroprotective drugs which modify the supposed pathogenic mechanisms or that are used in other neurodegenerative diseases. These drugs include inhibitors of neuronal excitation, coenzymes of the respiratory chain, vitamins, antioxidants, co-adjuvants in energy production, etc. Some of these products offer encouraging results in experimental models of the disease but, unfortunately, not confirmed in the clinic.

The study of HD is important because is the best studied and most prevalent model of neurodegenerative diseases caused by triplet expansions, which also includes some ataxias. Discovering the pathogenic mechanisms of HD and finding an effective, either neuroprotective or curative, would have immediate implications on any of the other neurodegenerative pathologies caused by triplet expansions.

The main research topics in this line are the following:

- Identification of molecular and cellular basis of Huntington’s disease.
- Experimental studies in animal models of Huntington’s disease.
- Clinic, genetics and neuropathology of Huntington’s disease.
<table>
<thead>
<tr>
<th>PRINCIPAL INVESTIGATOR</th>
<th>INSTITUTION</th>
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<tr>
<td>Alberch Vie, Jordi</td>
<td>University of Barcelona</td>
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<td>Canela Campos, Enric Isidre</td>
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Program 2 is coordinated by Drs. José J. Lucas (Center for Molecular Biology, CSIC, and Eduardo Tolosa (Clinic Hospital, Barcelona). Teresa Iglesias Vacas (Biomedical Research Institute CSIC-UAM, Madrid), and Isabel Fariñas (University of Valencia).
ABSTRACT

The lines of research during 2018 have focused on identifying new therapeutic targets for Huntington’s disease (HD) and in the study of the intracellular mechanisms activated by mutant huntingtin that produce neuronal dysfunction. We have also continued our studies on the role of mutant huntingtin during development and in the differentiation of iPSCs to striatal neuronal phenotypes.

Following our interest in the contribution of neurotrophic factors and their receptors in the pathology of HD, we have validated the imbalance between TrkB / p75NTR receptors as a mechanism involved in the appearance of alterations in the motor coordination of this disease (Suelves et al, 2018). In addition, we have demonstrated the participation of the ARMS protein in the deregulation of BDNF secretion in the hippocampus of HD models, which could be contributing to cognitive deficits (Lopez-Benito et al, 2018). We have also described a new molecule with therapeutic potential for HD as the pituitary adenylate cyclase activating polypeptide (PACAP). This factor enhances the expression of BDNF and reduces the formation of aggregates. Treatment with PACAP produced an improvement in cognitive alterations in models of HD.

During this year we have extended the studies on the implication of reduced levels of STEP phosphatase in the pathophysiology of HD. For this we obtained a model of the HD and deficient in STEP, and we also inhibited the activity of STEP through pharmacological treatment. The lack of expression of STEP delays the onset of motor symptoms and prevents cognitive dysfunction. In addition, the acute inhibition of its activity improves cognitive function in a
model of HD. Therefore, the inhibition of STEP would be a good therapeutic strategy for HD (Garcia-Forn, Martinez-Torres et al., 2018). We also analyzed the expression of STEP during postnatal development in control mice, and its modulation by BDNF. The results obtained show that STEP levels decrease with age in the striatum and their levels are regulated by BDNF in the striatum and in the cerebral cortex during postnatal development (Cases et al., 2018). We have also observed that the activity of the mTORC2 kinase is increased in the striatum of HD mice due to an increase in Rictor levels. Our results indicate that it is a compensatory mechanism to avoid the toxicity of mutant huntingtin, suggesting the modulation of Rictor levels in the striatum as a new therapeutic target for HD (Creus-Muncunill et al., 2018).

For the study of the contribution of Cdk5 in the depressive aspects in HD, we have created a new murine model that expresses mutant huntingtin and is heterozygous for the phosphorylation site of DARPP32 controlled by Cdk5. In these mice we have shown that the depressive phenotype manifested at two months of age was not observed, suggesting a critical role of the Cdk5 / DARPP32 pathway in the development of psychiatric disorders such as depression in HD.

In our studies on how the development of the striatum affects the progression of HD, we have demonstrated that the regulation of the expression of Kv7 channels are crucial for the functional maturation of striatal neurons in the mouse and in human iPSC striatal neurons (Telezhkin et al., 2018).

KEYWORDS
Neuronal plasticity - Neurotrophic factors - Depression - Neurodevelopment - Huntington’s disease.

PUBLICATIONS 2018


### RESEARCH PROJECTS 2018

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<th>Code</th>
<th>Title</th>
<th>Principal investigator</th>
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<td>RD16/0011</td>
<td>Red de Terapia Celular</td>
<td>Isabel Farinas</td>
<td>Yes</td>
<td>G607 ; G301 ; G102 ; G113 ; G208 ; G105 ; G207</td>
<td>No</td>
<td>Nacional</td>
<td>Instituto de Salud Carlos III</td>
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<td>SAF2016-08573-R</td>
<td>Alteraciones de la lamina nuclear y de la traduccion proteica como nuevos mecanismos patogenicos en la enfermedad de Huntington</td>
<td>Esther Perez Navarro</td>
<td>No</td>
<td>G301</td>
<td>No</td>
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<td>181500</td>
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<td>SAF2015-67474-R</td>
<td>Cdk5 como nueva diana terapeutica y biomarcador del trastorno depresivo en la enfermedad de Huntington</td>
<td>Silvia Gines</td>
<td>No</td>
<td>G301</td>
<td>No</td>
<td>Europeo</td>
<td>Comision Europea</td>
<td>3749403</td>
<td>2018-2022</td>
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Code: 713140.
Title: Custom architecturally defined 3D stem cell derived functional human neural networks for transformative progress in neuroscience and medicine (MESO_BRAIN).
Principal investigator: Jordi Soriano.
CIBERNED’s collaboration: No.
CIBERNED groups: G301. Other CIBER’s collaboration: No.
Type: Europoe.
Funding agency: Comision Europea.

Code: 307272.
Title: Desarrollo experimental del tratamiento con AAT-1 como terapia antiinflamatoria en la isquemia neonatal (el estudio A) y ensayo de la AAT-1 en la lesion aguda de la medula espinal (Estudio B).
Principal investigator: Jordi Alberch Vie.
CIBERNED’s collaboration: No.
CIBERNED groups: G30. Other CIBER’s collaboration: No.
Type: Privado.
Funding agency: Instituto Grifols.

Code: SAF2015-66505-R.
Title: Desarrollo, diferenciacion y maduracion neuronal en la enfermedad de Huntington.
Principal investigator: Josep M. Canals.
CIBERNED’s collaboration: No.
CIBERNED groups: G301. Other CIBER’s collaboration: No.
Type: Nacional.
Funding agency: MICINN.

Title: European Training Network for Cell-based Regenerative Medicine.
Principal investigator: Jordi Alberch.
CIBERNED’s collaboration: No.
CIBERNED groups: G301. Other CIBER’s collaboration: No.
Type: Europeo.
Funding agency: Comision Europea.

Code: 309965.
Title: Identification of chorein function in neurodegeneration of the basal ganglia for developing new therapeutical approaches in Chorea-Acanthocytosis.
Principal investigator: Jordi Alberch Vie.
CIBERNED’s collaboration: No.
CIBERNED groups: G301. Other CIBER’s collaboration: No.
Type: Privado.
Funding agency: Fundacion ChAc.
CIBERNED 2018 ANNUAL REPORT

**Code:** A14079.
**Title:** In vitro Study of Neurodevelopment in Huntington's disease.
**Principal investigator:** Josep M. Canals.
**CIBERNED's collaboration:** No.
**CIBERNED groups:** G301. **Other CIBER’s collaboration:** No.
**Type:** Internacional.
**Funding agency:** CHDI.
**Funding:** 1731009. **Duration:** 2018-2021.

**Code:** RL000776.
**Title:** Mitochondrial outcomes measures in fibroblasts of HD patients.
**Principal investigator:** Silvia Gines.
**CIBERNED's collaboration:** No.
**CIBERNED groups:** G301. **Other CIBER’s collaboration:** No.
**Type:** Internacional.
**Funding agency:** HDSA.
**Funding:** 75000. **Duration:** 2017-2018.

**Code:** 20140130/1.
**Title:** Modulacion del deficit de la plasticidad sinaptica como estrategia terapeutica en la enfermedad de Huntington.
**Principal investigator:** Jordi Alberch.
**CIBERNED's collaboration:** No.
**CIBERNED groups:** G301. **Other CIBER’s collaboration:** No.
**Type:** Privado.
**Funding agency:** Fundacio La Marato de TV3.
**Funding:** 299375. **Duration:** 2015-2018.

**Code:** FBG 308408.
**Title:** Obtaining, processing an/or preserving non-human tissues, cells and related products.
**Principal investigator:** Josep M. Canals.
**CIBERNED’s collaboration:** No.
**CIBERNED groups:** G301. **Other CIBER’s collaboration:** No.
**Type:** Intramurales.
**Funding agency:** Cytes Biotechnologies.
**Funding:** 450000. **Duration:** 2015-2020.

**Code:** FBG 308841.
**Title:** Servicio de Salas Blancas para produccion de vacuna de HIV en condiciones GMP.
**Principal investigator:** Josep M. Canals, Raquel Martin Ibanez.
**CIBERNED's collaboration:** No.
**CIBERNED groups:** G301. **Other CIBER’s collaboration:** No.
**Type:** Intramurales.
**Funding agency:** IDIBAPS.
**Funding:** 360000. **Duration:** 2016-2018.

**Code:** A12076.
**Title:** Studying Human MSN Differentiation from PSC using Single-Cell RNAseq and Rodent Chimeric Models.
Principal investigator: Josep M. Canals.
CIBERNED’s collaboration: No.
CIBERNED groups: G301.
Other CIBER’s collaboration: No.
Type: Internacional.
Funding agency: CHDI.

PHD DISSERTATIONS 2018

Author: Elena Alvarez Periel.
Title: Dual role of Cdk5 in cognitive deficits and striatal vulnerability in Huntington’s disease.

Author: Nuria Suelves Caballol.
Title: Evaluation of therapeutic targets for the treatment of behavioral alterations and neuropathology in Huntington’s disease.
Date: 19/6/2018. Supervisor: Silvia Ginés Padrós.

Author: Alfonso Gerardo García Díaz Barriga.
Title: Therapeutic strategies based on neuroprotective mechanisms of neurotrophic factors in Huntington’s Disease models.
Date: 17/7/2018. Supervisor: Jordi Alberch Vié.

Author: Andrea Comella Bolla.
Title: Neuronal differentiation and maturation of human pluripotent stem cells for modeling Huntington’s disease.

Author: Jordi Creus Muncunill.
Title: Dual role of mTOR in Huntington’s disease: contribution to striatal neuronal survival and dysfunction.
Date: 24/10/2018. Supervisor: Esther Pérez Navarro.
ABSTRACT

The research of the Neurodeath group has been focused on 3 different areas: a) the use of nanoparticles, mainly dendrimers (but also polymers derived from cyclodextrin) to transfect genetic material, mainly siRNA, into different cell types to knock down specific proteins involved in tumoral progression and neurodegenerative diseases; b) to show that certain dendrimers, having themselves anti-inflammatory activity, are able to prevent, in mice, the development of experimental allergic encephalitis, a generally accepted animal model for multiple sclerosis, and c) to study the mechanisms involved in nanoparticle blood-brain-barrier crossing and to investigate the different approaches used to facilitate such a crossing. We have developed two nanoparticles that are able to transport fluorescent siRNA to the brain following injection in the mouse tail vein. The use of siRNA as therapeutic agent will produce, in a short period of time, new generations of drugs, based on siRNA, with the potential to revolutionize therapeutics in different areas. In addition, our group has focused on the development of dendrimers to transfect neuronal cultures with the aim of targeting the nanoparticles and their therapeutic cargo to the brain in a near future.
KEYWORDS
Gene therapy, dendrimers, nanoparticles, neurodegeneration, siRNA, transfection, glioblastoma, multiple sclerosis, hematobcephalic barrier.

PUBLICATIONS 2018


RESEARCH PROJECTS 2018
Code: PI2016/05.
Title: Dream inhibitors and Alzheimer’s Disease.
Principal investigator: Jose Ramon Naranjo Orovio.
CIBERNED’s collaboration: Yes.
CIBERNED groups: G307 ; G106; G403. Other CIBER’s collaboration: No.
Type: Intramurales.
Funding agency: CIBERNED.
ABSTRACT

Our team studies the neuropathological processes associated with Parkinson’s disease (PD) and Alzheimer’s disease (AD) in order to identify new therapeutic targets to prevent or stop the development of these diseases. Studies in animal models and post-mortem brain tissues of patients indicate that many pathological changes in the brain derive from various types of local stresses, such as proteotoxic stress, closely related to oxidative and inflammatory stress. Therefore, in our group we studied the role of the transcription factor NRF2, master regulator of several neuroprotection pathways, as a new therapeutic target. During the last year we have carried out two main lines of research:

1) We are studying the role of the transcription factor NRF2 in the protection against stimuli that induce neurodegeneration. NRF2 is a protein that regulates the expression of about 250 genes that participate in adaptive responses to oxidative, inflammatory and proteotoxic stress and in the regulation of enzymes involved in biotransformation and metabolic reprogramming. Using genetically modified rodents, during 2018 we studied the contribution of this transcription factor to the protection against neuroinflammation and proteinopathy in transgenic mice that possess amyloidopathy (APPV717I) and tauopathy (TauP301L), which are characteristic of AD. In these mice the deficiency in NRF2 correlated with exacerbated astrogliosis and microgliosis, as evidenced by the increase...
in the levels of the GFAP, IBA1 and CD11b markers. We have also described that chape-
rone-mediated autophagy, responsible for the degradation of alpha-synuclein and other
neurotoxic proteins, is regulated by NRF2 at the level of the expression of the LAMP2
gene, which encodes the autophagy receptor LAMP2A.

La pérdida sináptica está relacionada con la presencia de péptido soluble de Abeta en
las sinapsis. Dado que en estudios previos mostramos que la proteína Dickkopf-1 (Dkk1),
activadora de la vía Wnt-PCP (Wnt-planar cell polarity) conduce a tauopatía y muerte
neuronal, hemos comparado el efecto de Abeta y Dkk1 en la morfología sináptica y en
alteraciones cognitivas mediante la modulación de elementos clave de la vía Wnt-PCP.
Hemos descrito que la sinaptotoxicidad inducida por Abeta es dependiente de Dkk1 y de
la vía Wnt-PCP, a nivel de la dinámica del citoesqueleto por vía de Daam1, RhoA and ROCK.
Estos resultados muestran la relevancia de la alteración de la vía Wnt en la neuropatolo-
gía asociada a la EA.

2) Through a novel approach based on systems medicine related to chronic diseases,
we have analyzed possible drugs that could activate NRF2 in the brain and provide a
therapeutic benefit. We have described that the immunomodulatory effect of dimethyl
fumarate (DMF), a drug currently used for the treatment of multiple sclerosis, improves
cognition and reduces motor complications in the mouse model with amyloidopathy and
tauopathy. Dimethyl fumarate also decreases the inflammatory response in this model
and, therefore, provides a novel strategy to reposition this drug in the treatment of AD.

As previously mentioned, the pathway (Wnt-PCP) induces synaptic retraction and is ac-
tivated by soluble Abeta peptides. We have observed that the inhibitor of ROCK, fasudil,
which inhibits the Abeta-Dkk1 pathway, prevents the loss of dendritic spines in vitro, and
reduces the Abeta load in mice with advanced amyloidopathy. These results suggest the
importance of the Wnt pathway in AD and propose the repositioning of fasudil, currently
used for the treatment of cerebral vasospasm, for the treatment of AD.

KEYWORDS
NRF2, Wnt-PCP, dimethyl fumarate, fasudil, amyloidopathy, tauopathy, neuroinflammation,
autophagy.

PUBLICATIONS 2018
Egea J, Fabregat I, Frapart YM, Ghezzi P, Görlach A, Kietzmann T et al. Corrigendum to Eu-
ropean contribution to the study of ROS: A summary of the findings and prospects for the
future from the COST action BM1203 (EU-ROS) [Redox Biol. 13 (2017) 94-162]. Redox biol-
ogy. 2018;14. PMID: 29107648.

Cuadrado A, Kugler S, Lastres-Becker I. Pharmacological targeting of GSK-3 and NRF2 pro-
vides neuroprotection in a preclinical model of tauopathy. Redox Biology. 2018;14:522-
534. PMID: 29121589.

Sellers KJ, Elliott C, Jackson J, Ghosh A, Ribe E, Rojo AI et al. Amyloid β synaptotoxicity is Wnt-
PCP dependent and blocked by fasudil. Alzheimer’s & dementia : the journal of the Alzheim-
er’s Association. 2017. PMID: 29055813.


**RESEARCH PROJECTS 2018**

**Code:** PI2017/04.

**Title:** Disfunción glial en la enfermedad de Alzheimer: implicaciones patogénicas y potencial clínico.

**Principal investigator:** Javier Vitorica.

**CIBERNED’s collaboration:** Yes. **CIBERNED groups:** G411; G415; G101; G407; G413.

**Other CIBER’s collaboration:** No.

**Type:** Intramurales.

**Funding agency:** CIBERNED.

**Funding:** 240000. **Duration:** 2017-2019.

**Code:** PCIN-2016-071.

**Title:** Advanced theranostic approach in cancer combining photodynamic therapy and nanoparticles.

**Principal investigator:** Luis Felipe Ferreira.

**CIBERNED’s collaboration:** No.

**CIBERNED groups:** G101. **Other CIBER’s collaboration:** No.

**Type:** Nacional.

**Funding agency:** MICINN.

**Funding:** 490000. **Duration:** 2016-2019.
**Code:** P_37_732.
**Title:** Knowledge transfer in redox biology for developing advanced molecular tools in neurodegenerative diseases.
**Principal investigator:** Antonio Cuadrado.
**CIBERNED’s collaboration:** No.
**CIBERNED groups:** G101. **Other CIBER’s collaboration:** No.
**Type:** Europeo.
**Funding agency:** Comision Europea.
**Funding:** 1915000. **Duration:** 2016-2020.

**Code:** SAF2016-76520-R.
**Title:** Papel de NRF2 en la función y el destino del cerebro con alzheimer.
**Principal investigator:** Antonio Cuadrado.
**CIBERNED’s collaboration:** No.
**CIBERNED groups:** G101. **Other CIBER’s collaboration:** No.
**Type:** Nacional.
**Funding agency:** MICINN.
**Funding:** 340000. **Duration:** 2017-2019.

**Code:** BMD2017/BMD3813.
**Title:** Diseno y desarrollo de farmacos innovadores para el tratamiento de la esclerosis lateral amiotrofica.
**Principal investigator:** Eva de Lago.
**CIBERNED’s collaboration:** Yes.
**CIBERNED groups:** G101; G303. **Other CIBER’s collaboration:** CIBERER.
**Type:** CCAA.
**Funding agency:** Comunidad de Madrid.
**Funding:** 767395. **Duration:** 2018-2021.

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**PHD DISSERTATIONS 2018**

**Author:** Marta Pajares Cabetas.
**Title:** Transcription Factor NRF2 regulates the expression of autophagy genes.
**Date:** 19/10/2018. **Supervisor:** Antonio Cuadrado Pastor.
Our laboratory develops two lines of research in neurodegeneration and cell therapy: 1) the study of cellular and molecular alterations underlying dopaminergic neurodegeneration associated with Parkinson’s disease (PD) through the analysis of alpha-synuclein effects, and 2) the study of neural stem cell (NSC) regulation. We use experimental mouse models in which to identify and evaluate cellular and molecular mechanisms that may underlie dopaminergic neurodegeneration or that can be used for the manipulation of NSC with therapeutic purposes. In the context of the CIBERNED program, we work on aspects that combine both of these lines, i.e. those related with the regulation of adult...
neurogenesis in parkinsonism and during aging. During 2018, we continued to characterize the role of alpha-synuclein and dopamine as regulators of NSCs. In collaboration with groups of CIBERSAM and with the group of Miquel Vila (Hospital Vall d’Hebron) in CIBERNED, we have analyzed the potential of a strategy based on the use of specific oligonucleotides administered intra-nasally for the reduction of alpha-synuclein levels in the brain. In parallel, and in collaboration with the group from the University of Barcelona led by Oriol Bachs, we have shown that negative regulator of the cell cycle of the Cip/Kip family of inhibitors of cyclin-dependent kinases, p27, is a transcriptional modulator of alpha-synuclein, opening the possibility of manipulating its levels of expression. On the other hand, we have initiated studies to analyze the interaction of microglia with toxic and aggregated forms of alpha-synuclein and how this interaction can influence the pathological transmission of this molecule during aging.

**KEYWORDS**

Neural stem cells, adult neurogenesis, Parkinson’s disease, cell therapy.

**PUBLICATIONS 2018**


**RESEARCH PROJECTS 2018**

**Code:** RD16/0011.

**Title:** Red de Terapia Celular.

**Principal investigator:** Isabel Farinas.

**CIBERNED’s collaboration:** Yes.

**CIBERNED groups:** G607; G301; G102; G113; G208; G105; G207.

**Other CIBER’s collaboration:** No.

**Type:** Nacional.

**Funding agency:** Instituto de Salud Carlos III.

**Funding:** 284999. **Duration:** 2016-2020.
Code: RD16/0011.
Title: Red de Terapia Celular.
Principal investigator: Isabel Farinas.
CIBERNED’s collaboration: Yes.
CIBERNED groups: G607; G301; G102; G113; G208; G105; G207.
Other CIBER’s collaboration: No.
Type: Nacional.
Funding agency: Instituto de Salud Carlos III.

Title: Combined protective/restorative cell-mediated strategies for neurodegenerative diseases.
Principal investigator: Jose Luis Labandeira Garcia.
CIBERNED’s collaboration: Yes.
CIBERNED groups: G208; G102; G113; G105; G207. Other CIBER’s collaboration: No.
Type: Nacional.
Funding agency: Instituto de Salud Carlos III.

Code: PI2015-2/06.
Title: Molecular mechanisms of brain and muscle stem cell function in aging and neurodegeneration.
Principal investigator: Pura Munoz Canoves.
CIBERNED’s collaboration: Yes.
CIBERNED groups: G604; G102; G606; G111; G306. Other CIBER’s collaboration: No.
Type: Intramurales.
Funding agency: CIBERNED.

Title: Efectos directos y remotos de la respuesta inflamatoria sobre las celulas madre.
Principal investigator: Isabel Farinas.
CIBERNED’s collaboration: No.
CIBERNED groups: G102. Other CIBER’s collaboration: No.
Type: CCAA.
Funding agency: Generalitat de Catalunya.

Code: Convenio Botin-UV.
Title: Estudio de celulas madre en el ambito de las investigaciones basicas en terapia celular.
Principal investigator: Isabel Farinas.
CIBERNED’s collaboration: No.
CIBERNED groups: G102. Other CIBER’s collaboration: No.
Type: Privado.
Funding agency: Fundacion Botin-Banco Santander.

Code: SAF2016-78845-R.
Title: Papel de la impronta genomica y su regulacion epigenetica en celulas madre neu-
rales: relacion con la formacion de tumores.
Principal investigator: Sacramento Rodriguez Ferron.
CIBERNED's collaboration: No.
CIBERNED groups: G102. Other CIBER's collaboration: No.
Type: Nacional.
Funding agency: MICINN.

Code: SAF2017-86690-R.
Title: Regulacion del comportamiento de celulas madre neurales por el medio sistemico: el nicho extendido.
Principal investigator: Isabel Farinas.
CIBERNED’s collaboration: No.
CIBERNED groups: G102. Other CIBER’s collaboration: No.
Type: Nacional.
Funding agency: MICINN.
ABSTRACT

The activity of the group has been again concentrated in the development of cannabinoid-based medicines with neuroprotective potential useful for several chronic neurodegenerative disorders, as well as in the identification of cellular and molecular mechanisms that underlie this potential. Again, during this year, the work has been concentrated in Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD) and spinocerebellar ataxia type-3 (SCA-3).

We have enhanced our collaboration with groups of Medicinal Chemistry working in different directions: development of selective agonists of the CB2 receptor, allosteric modulators of this receptor, CB2/PPAR-γ hybrid compounds, GPR55 agonists, which have been investigated in vitro studies of receptor binding and activity, as well as in cell-based models. We have
also increased our collaboration with companies in this activity, adding Roche, Emerald Health Pharmaceuticals and Symrise to the previous collaborations already in progress with GW Pharmaceuticals and VivaCell Biotechnology-Spain. With these companies, we are working in the development and evaluation of cannabinoids with CB2 and/or PPAR-γ activity as novel neuroprotectants. One of the new compounds in whose evaluation we have participated, EHP-101, just entered in a clinical trial due to its anti-inflammatory potential in skin disorders, so we expect it can be soon in clinical evaluation for some of the neurodegenerative disorders that we investigate.

In the case of PD, the work has consisted in investigating the advantages of the combination of cannabidiol and Δ9-THCV (GW Pharmaceuticals) for the symptomatic and neuroprotective treatment of this disease, including their antidyskinetic effects which are studied in collaboration with the CIBERNED group leaded by Rosario Moratalla, results that we are presently preparing for publication. Other line of research has consisted in determining the potential of cannabigerol-quinones (they are PPAR-γ agonists) and cannabidiol-quinones (CB2 and PPAR-γ agonists) in experimental models of this disease, for which we have identified two derivatives particularly active (VivaCell Biotechnology-Spain and Emerald Health Pharmaceuticals). We have extended our research to a novel endocannabinoid-related receptor, so-called GPR55, for which we are developing selective ligands in collaboration with a CSIC group of Medicinal Chemistry.

In the case of ALS, the work has continued the evaluation of CBDA and other phytocannabinoids for their neuroprotective effects (GW Pharmaceuticals), and of different phytocannabinoid derivatives (Vivacell Biotechnology and Emerald Health Pharmaceuticals), using SOD-1 mutant and TDP-43 transgenic mice. The targets we are investigating include mainly CB2 receptors, but also PPAR-γ and GPR55 receptors as potential targets. All this work has been carried out as the final part of our project funded by the MINECO-Biomedicine National Program, concentrated in ALS and FTD, which is a joint project with a group of the CSIC Medical Chemistry Institute, and addressed to the development of new therapies based on targeting GPR55, GPR18, CB2 receptors using allosteric modulators, and CB2/PPAR-γ using hybrid compounds, as well as within a CIBERNED project with the groups of Adolfo López de Munain (coordinator), Isidre Ferrer and Eduardo Soriano concentrated in the development of new therapies for ALS.

Lastly, in the case of SCA-3 (Machado-Joseph disease), we have finished the biochemical and histopathological studies addressed to demonstrate the occurrence of an endocannabinoid dysregulation in different CNS areas during the course of the disease, and now we are using SCA-3 transgenic mice to investigate potential pharmacological treatments addressed to correct such dysregulation and to elicit neuroprotective effects, including CB2 and GPR55 as new therapeutic targets.

**KEYWORDS**

Cannabinoids, CB1 receptors, CB2 receptors, GPR55, PPAR-γ, neuroprotection, Parkinson’s disease, amyotrophic lateral sclerosis/frontotemporal dementia, spinocerebellar ataxias

**PUBLICATIONS 2018**


**RESEARCH PROJECTS 2018**

**Code:** PI2016/04.

**Title:** The ALS CIBERNED Challenge: Accelerating New Drug Discovery.

**Principal investigator:** Adolfo Lopez De Munain.

**CIBERNED’s collaboration:** Yes.

**CIBERNED groups:** G609; G303; G503; G408. **Other CIBER’s collaboration:** No.
Type: Intramurales.
Funding agency: CIBERNED.

Code: NEUROLATAM.
Title: Unraveling the neurobiological sustrate of protective cannabinoid actions in the brain.
Principal investigator: Ismael Galve Roperh, Jose A. Ramos Atance.
CIBERNED's collaboration: Yes.
CIBERNED groups: G303 ; G305. Other CIBER's collaboration: No.
Type: Nacional.
Funding agency: Unión Iberoamericana de Universidades.

Code: SAF2015-68580-C2-1-R.
Title: Dianas del sistema endocannabinoide para el desarrollo de terapias frente a la neurodegeneracion: enfasis en la ELA y otras enfermedades neurodegenerativas.
Principal investigator: Javier Fernandez Ruiz/Eva de Lago Femia.
CIBERNED's collaboration: No.
CIBERNED groups: G303. Other CIBER's collaboration: No.
Type: Nacional.
Funding agency: MICINN.

Code: PR26/16-18B.
Title: Estudio de nuevas dianas en demencias neurodegenerativas basadas en tratamientos neuroprotectoras y neurogenicos.
Principal investigator: Eva De Lago, Maria Gomez Ruiz, Felipe Ortega De La O.
CIBERNED's collaboration: No.
CIBERNED groups: G303 . Other CIBER's collaboration: No.
Type: Privado.
Funding agency: Banco Santander - UCM.

Code: 2017/VIVACELL/JFR.
Title: Investigation in the anti-inflammatory and neuroprotective properties of the phytocannabinoid derivative VCE003.2 in Parkinson’s disease using LPS-lesioned alpha-synuclein transgenic mice.
Principal investigator: Javier Fernandez Ruiz, Maria Concepcion Garcia.
CIBERNED's collaboration: No.
CIBERNED groups: G303 . Other CIBER's collaboration: No.
Type: Privado.
Funding agency: VivaCell Biotechnology Espana.

Code: EMERALD.
Title: Investigation in the anti-inflammatory and neuroprotective properties of the phytocannabinoid derivatives VCE-004.8 and VCE-003.2 (and its analogs CBG-Q-Salt and CBGA-Q) in Parkinson’s disease using 6-hydroxydopamine-lesioned mice.
Principal investigator: Javier Fernandez Ruiz y Mª Concepcion Garcia Garcia.
CIBERNED's collaboration: No.
CIBERNED groups: G303 . Other CIBER's collaboration: No.
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**PHD DISSERTATIONS 2018**

**Author:** Francisco Espejo Porras.

**Title:** Relevancia del receptor cannabinoide CB2 en la esclerosis lateral amiotrófica (ELA).

**Date:** 17/4/2018. **Supervisor:** Javier Fernández Ruiz.
ABSTRACT

The research in the Molecular Neurobiology (NBM) group at the University of Barcelona is eminently translational and focused on receptors coupled to G proteins (GPCRs) involved in the pathophysiology of neurodegenerative diseases. The laboratory has identified new therapeutic targets and new molecules with potential to combat these diseases have been designed and developed in collaboration with medicinal chemistry groups.

During 2018 there have been several research projects developed in parallel. Within the framework of projects funded by the Fundació la Marató de TV3, one related to Huntington’s disease and another related to Parkinson’s disease, therapies have been proposed based on molecular studies focused on receptors that are expressed in both neurons and glia.
At the molecular level, the functional peculiarities of complexes formed by two or more GPCRs have been characterized and structural models have been proposed that would explain all the results obtained in the laboratory as well as those described in the literature. Complexes are often formed by two homodimers of two GPCRs (tetramers) that are coupled to two different G proteins. Two highly relevant results, which have been published in journals with a high impact factor, reflect a pre-coupling of G proteins to inactive GPCRs (i.e. not yet activated by their corresponding neurotransmitters) and discover additional / unexpected functionalities of GPCR heteromers coming from long C-terminal domains (>80 amino acids). The length of terminal C end of GPCRs is very diverse and our data shows, for a specific case, the reason. It is the “tail” of the A2A adenosine receptor that is responsible for adenosine increasing or decreasing the release of glutamate from cortical neurons according to the concentration. The structure of the adenosine “concentration sensor” that is regulating glutamatergic neurotransmission is unique.

The GPCRs upregulated in reactive microglia and their functional role have been the focus of a glia-centered research theme. The expression of cannabinoid CB2 receptors is increased in activated microglia and the endocannabinoids go from being molecules that prevent nonspecific activation to be regulators of activation. Complexes formed by CB2 receptors and other GPCRs, such as A2A adenosine receptors, constitute potential targets to ensure that the microglia skewing towards the M2 or neuroprotective phenotype. In animal models of neurodegenerative diseases, primary cultures, obtained from neonates, show that the microglia displays an activated phenotype. Given that the newborn animals do not present neuronal death or cognitive deficits, the hypothesis that we contemplate is that activated microglia is exerting a neuroprotective effect (M2 phenotype).

A detailed study of the pharmacology of the CB2 receptor has shown that cannabidiol, which is currently approved for the therapy of epilepsy, is a negative allosteric modulator (a NAM according to the current nomenclature). Based on the mutants developed in the laboratory and the recent elucidation of the three-dimensional structure of the receptor, we have identified the allosteric center with high reliability. Looking to the future there are two strategies in relation to this discovery: i) design more potent allosteric compounds and ii) test the neuroprotective potential of cannabidiol and the new compounds, some of which are already synthesized. The efficacy of the allosteric modulators of the CB2 receptor will be tested in animal models of Parkinson’s, Alzheimer’s and stroke. The potential of the compounds to regulate the M1/M2 conversion in microglia will also be determined.

**KEYWORDS**

Targeting G-protein-coupled receptors (GPCRs) for neuroprotection, GPCR heteromers as targets to combat neurodegenerative diseases, GPCR heteromers in the pathophysiology of Parkinson’s, Huntington’s and Alzheimer’s disease, Natural and synthetic cannabinoids for neuroprotection, Strategies to convert reactive M1 microglia into the neuroprotective (M2) phenotype.


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**RESEARCH PROJECTS 2018**

**Code:** PI2016/02.

**Title:** Monitoring the Onset and Evolution of Neuronal Dysfunctions in Propagative Neural Disorders using Microfluidic Devices and Translational approaches.

**Principal investigator:** Jose Antonio Del Rio.

**CIBERNED’s collaboration:** Yes.

**CIBERNED groups:** G114 ; G401; G201. **Other CIBER’s collaboration:** No.

**Type:** Intramurales.

**Funding agency:** CIBERNED.

**Funding:** 210000. **Duration:** 2016-2018.

**Code:** CI18-00045.

**Title:** Fighting pain with cannabis avoiding side-effects.

**Principal investigator:** Maldonado.

**CIBERNED’s collaboration:** No.

**CIBERNED groups:** G201 . **Other CIBER’s collaboration:** No.

**Type:** Privado.

**Funding agency:** Fundacio La Caixa.

**Funding:** 70000. **Duration:** 2018-2019.
**Code:** SAF2017-87629-R.
**Title:** Validacion de los heteromeros entre receptores de dopamina D1 y de adenosina A1 como una nueva diana terapeutica para el tratamiento de disfunciones motoras medulares y cerebrales.
**Principal investigator:** ENRIC I. CANELA CAMPOS.
**CIBERNED’s collaboration:** No.
**CIBERNED groups:** G201.
**Other CIBER's collaboration:** No.
**Type:** Nacional.
**Funding agency:** MICINN.
**Funding:** 229900. **Duration:** 2018-2020.

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**PHD DISSERTATIONS 2018**

**Author:** Iñigo Javier Etayo Labiano.
**Title:** Heterómeros de receptores CB1, CB2 Y GPR55 y su implicación en enfermedades neurodegenerativas y alcoholismo.
**Date:** 15/5/2018. **Supervisor:** Gemma Navarro Brugal.

**Author:** Irene Reyes Resina.
**Title:** Heterómeros de receptores CB1, CB2, GPR55 y GPR18: señalización celular, farmacología y análisis de su potencial como dianas terapéuticas de enfermedades neurodegenerativas.
**Date:** 11/6/2018. **Supervisor:** Rafael Franco Fernández.

**Author:** Verónica Casadó Anguera.
**Title:** Allosteric interactions between catecholamine receptors and other G protein-coupled receptors: pharmacological and functional characterization.
**Date:** 14/6/2018. **Supervisor:** Enric Isidre Canela Campos.

**Author:** Edgar Angelats Canals.
**Title:** Relevant molecular and functional G-protein coupled receptors interactions in neuroinflammation and addiction.
**Date:** 7/9/2018. **Supervisor:** Rafael Franco Fernández.

**Author:** Mar Rodríguez Ruiz.
**Title:** Heterómeros de receptores de dopamina D1 y de histamina H3 como potenciales dianes terapéuticas en transtornos adictivos y enfermedades neurodegenerativas.
**Date:** 10/9/2018. **Supervisor:** Vicente Casadó Burillo.
ABSTRACT

Our lines of work during 2018 have continued focused on the study of basic molecular mechanisms related to the etiopathogenesis of Parkinson’s disease, regulation of autophagy and role of proteins derived from PARK genes in both processes. On the other hand we have also continued our collaboration and provision of services to the Extremadura Health Service in the field of molecular diagnosis of Parkinson’s disease, as well as we have initiated contacts to establish scientific projects with the Isabel Gemio Foundation on the role of autophagy in certain neuromuscular pathologies.

As a continuation of the work we have been doing since 2009 in collaboration with the group of Dr. Adolfo López de Munain (CIBERNED), we have continued with characterization of the basal deregulation of macroautophagy in fibroblasts from Parkinson’s patients carriers of the G2019S pathogenic mutation and R1441G in LRRK2. In 2018 this work has focused on the role of the histone acetyltransferase (HATs) and histone deacetylases (HDACs) activities on mitophagy. For this, fibroblasts from patients with PE (with or without the LRRK2 G2019S mutation) and control subjects were used to evaluate the different phenotypes between idiopathic and genetic EP.
The group G2019S shows an increase in mitophagy due to the activation of HDAC class III, while the idiopathic group shows a down regulation of the elimination of defective mitochondria. This reduction in mitophagy is accompanied by an increase in oxygen species (ROS). In parallel, protein acetylation levels of idiopathic individuals and carriers of the G2019S mutation are different due to a positive regulation in HDAC class I and II. Despite this upregulation, total HDAC activity decreases in idiopathic PE and total HAT activity does not vary significantly. The up-regulation of mitophagy is beneficial in reducing the damage induced by ROS in genetic EP. Defective mitophagy in idiopathic PE is inherent in the decrease of class III HDACs. Therefore, there is an imbalance between the activities of total HAT and HDAC in idiopathic PD, which increases cell death. The inhibition of HAT in PD idiopathic cells shows a cytoprotective effect.

As an intraCiberned collaboration we continue working on the results of a Cooperative Project (PI2015 / 03) together with the Groups of Dr. Pérez Tur and Dr. Pérez Castillo (with the participation of Dr. López de Munain) in which we have addressed the study of Differential metabolic profiles in Parkinson’s disease. During 2018 we completed the process of statistical analysis of results, which we can be published in 2019.

Also in the framework of collaboration between groups of CIBERNED (Dres Kulisewski, Gutierrez and Vicario) and led by Dr. Moratalla we have described in samples of Parkinson’s patients carriers of the N370P mutation in the gene GBA1 (β-glucocerebrosidase 1) produces a reduction of this enzyme both at the level of protein and activity and its accumulation at the level of the endoplasmic reticulum generating reticulum stress (UPR response) and Golgi apparatus fragmentation, accumulation of autophagosomes and alteration of the autophagic flow with lysosomal dysfunction and cholesterol accumulation. This phenotype modifies the capacity for mitochondrial turnover, generation of oxidative stress and cell death. This work has been a continuation of the work carried out in 2017.

In relation to our collaboration with the Extremadura Health Service, we emphasize that we maintain the agreement to provide services in relation to the molecular diagnosis of Parkinson’s and Alzheimer’s disease. We have also been a promoter of the creation of the Institute of Biosanitary Research of Extremadura (INUBE), which has the support of the Ministry of Health and Social Policy of the Junta de Extremadura and the Extremeño Health Service itself. During 2018 the definitive approval of the same has taken place by the university and autonomous government bodies, waiting for its effective starts in 2019.

KEYWORDS
**PUBLICATIONS 2018**


Re RESEARCH PROJECTS 2018

**Code:** PI15/00034.

**Title:** Alteraciones del perfil metabolico inducidas por mutaciones patogenicas de LRRK2 como biomarcadores de la enfermedad de Parkinson.

**Principal investigator:** Jose Manuel Fuentes Rodriguez.

**CIBERNED’s collaboration:** No.

**CIBERNED groups:** G103. **Other CIBER’s collaboration:** No.

**Type:** Nacional.

**Funding agency:** Instituto de Salud Carlos III.

**Funding:** 98615. **Duration:** 2016-2018.

**Code:** GR18063.

**Title:** Ayudas para la realización de actividades de investigación y desarrollo tecnológico, de divulgación y de transferencia de conocimiento por los grupos de investigación de Extremadura.

**Principal investigator:** Jose Manuel Fuentes Rodriguez.

**CIBERNED’s collaboration:** No.

**CIBERNED groups:** G103. **Other CIBER’s collaboration:** No.
Type: CCAA.
Funding agency: Junta de Extremadura.

Code: PI16/01840.
Title: Influencia del tratamiento anticoagulante sobre la funcion cognitiva de los pacientes con fibrilacion auricular no valvular.
Principal investigator: Ignacio Casado Naranjo.
CIBERNED’s collaboration: No.
CIBERNED groups: G103. Other CIBER’s collaboration: No.
Type: Nacional.
Funding agency: Instituto de Salud Carlos III.

Code: Rol patogenico de la disfuncion autofagica/lisosomal en enfermedades neuromusculares.
Title: Rol patogenico de la disfuncion autofagica/lisosomal en enfermedades neuromusculares.
Principal investigator: Jose Manuel Fuentes Rodriguez.
CIBERNED’s collaboration: No.
CIBERNED groups: G103. Other CIBER’s collaboration: No.
Type: Privado.
Funding agency: Fundacion Isabel Gemio.

PHD DISSERTATIONS 2018

Author: Mario Rodriguez Arribas.
Title: Caracterización de autofagia en células procedentes de enfermos de Párkinson.
Date: 6/7/2018. Supervisor: José Manuel Fuentes Rodriguez.
ABSTRACT

Our group has traditionally been focused on the study of regions with possible adult neurogenesis, analyzing them in different groups of vertebrates, including the human species. We also analyze the behavior of neural stem cells in various pathological conditions of the central nervous system.

During the last year we have advanced in the characterization of the neurogenic regions from a comparative point of view, including the study, both at a morphological and molecular level, of these areas in the nervous system of different species. For example, in the ventricular-subventricular zone (V-SVZ) of the canine brain we have described characteristics at the organizational level that are more similar to the human brain than that of the mouse brain. Following this line, we also performed a work on amphibians comparing the spinal cord channel of tadpoles and adult frogs. Using molecular markers of cell proliferation and electron microscopy we were able to describe the regionalization of said channel in a dorsal zone, a ventral zone and two lateral ones, with different proliferative activity throughout the different life stages of the animal.

From the point of view of the behavior of the neural stem cells, we wanted to deepen into the mechanism of self-renewal of the murine V-SVZ neural stem cells. Neural stem cells, known as B1 cells, are mainly responsible for neurogenesis in V-SVZ. With age, it is shown that this neurogenic activity decreases, as it does the number of B1...
cells. The stem cells of different somatic tissues are capable of self-renewal, either by asymmetric division, or by symmetric division and subsequent differentiation. In our work, we describe by clonal labeling and lineage tracing that most of these B1 cells divide symmetrically, remaining 20-30% of them in the neurogenic niche, while 70-80% end up differentiating and, therefore, resulting in the depletion of B1 cells over time. Also using the mouse as an experimental model, we have participated in two works in which we try to improve functional recovery in brain injury models, both in the neonatal and adult stages. For this, we relied on the implantation of soluble hydrogels combined with chemoattractant molecules, which improved the migration of new neurons to the injury region. This strategy allowed us to observe significant improvements at functional level in the treated animals.

Finally, another of the points of interest of our group is the study of neurogenic processes in the human brain. After recently describing three routes of migration of new neurons in infant stages from the V-SVZ to the ventral prefrontal cortex, the olfactory bulb and the dorsal prefrontal cortex, we decided to address this analysis in the dentate gyrus of the hippocampus, the other main neurogenic region described in mammals. Given that previous studies suggested that the dentate gyrus incorporated hundreds of new neurons daily in a process affected to some extent by stress and physical exercise, we wanted to delve into aspects about the nature of the stem cells as its rate of proliferation, or the presence of migrating cells. However, in the samples examined, what we observed was a dramatic decrease in the number of immature neurons of this region during the first year of life, being already very scarce in juvenile stages. These results raised important questions about the neurogenic capacity of this region in the adult human. However, these observations have generated an interesting debate due to the contributions of different groups that describe diverging results. Therefore, it is necessary to further dig into this field through the combination of different techniques and the study of quality samples to clarify this dilemma.

KEYWORDS
Adult neurogenesis, V-SVZ, neural stem cells, dentate gyrus, hippocampus.

PUBLICATIONS 2018


RESEARCH PROJECTS 2018

**Code:** RD16/0011.
**Title:** Red de Terapia Celular.
**Principal investigator:** Isabel Farinas.
**CIBERNED's collaboration:** Yes.
**CIBERNED groups:** G607; G301; G102; G113; G208; G105; G207.
**Other CIBER's collaboration:** No.
**Type:** Nacional.
**Funding agency:** Instituto de Salud Carlos III.
**Funding:** 284999. Duration: 2016-2020.

**Code:** RD16/0011/0016.
**Title:** Combined protective/restorative cell-mediated strategies for neurodegenerative diseases.
**Principal investigator:** Jose Luis Labandeira Garcia.
**CIBERNED's collaboration:** Yes.
**CIBERNED groups:** G208; G102; G113; G105; G207.
**Other CIBER's collaboration:** No.
**Type:** Nacional.
**Funding agency:** Instituto de Salud Carlos III.
**Funding:** 240245. Duration: 2017-2021.

**Code:** BFU2015-64207-P.
**Title:** Estudio del cerebro humano: caracterizacion de nichos neurogenicos y nuevas vías de migracion.
**Principal investigator:** Jose Manuel Garcia Verdugo.
**CIBERNED's collaboration:** No.
**CIBERNED groups:** G113. Other CIBER's collaboration: No.
**Type:** Nacional.
**Funding agency:** MICINN.
**Funding:** 166012. Duration: 2016-2018.
ABSTRACT

Our research focuses globally on the study of the molecular and cellular mechanisms underlying the control of neural cell physiopathology by the endocannabinoid system. Thus, in 2018 we have kept on studying how this system tunes neural progenitor proliferation, differentiation and survival. Specifically, in the context of our CIBERNED program, we have evaluated the role of the endocannabinoid system in Huntington’s disease. As a matter of fact, Huntington’s disease constitutes, in our opinion, the best currently available model disease to assess the pathophysiological relevance and therapeutic potential of the endocannabinoid system in neurodegenerative diseases. This is due to several reasons: (1) CB1 is the most abundant G protein-coupled receptor in the brain; specifically, it is highly expressed in the basal ganglia at synapses established by neurons containing GABA [especially medium spiny neurons (MSNs), the cells that primarily degenerate in Huntington’s disease] or glutamate (especially corticos-
triatal projecting neurons, which critically control MSN function) as transmitters, and play a key role in the control of motor behaviour (one of the processes that is most characteristically affected in Huntington’s disease). (2) A remarkable and dorsolaterally-selective down-regulation of the CB1 receptor has been documented in the basal ganglia of Huntington’s disease patients and animal models, and, of interest, this loss of CB1 receptors seems to reflect, at least in part, the neuron-damage pattern characteristic of the disease. (3) This loss of CB1 receptors occurs at early stages of Huntington’s disease and prior to the appearance of overt clinical symptoms, neurodegeneration and bulk changes in other neurochemical parameters. In 2018, our studies on the endocannabinoid system in Huntington’s disease have aimed at defining (1) whether stimulation of the endocannabinoid system in Huntington’s disease models promotes neuroprotection and therefore delays the onset and/or attenuates the progression of the pathology, (2) whether the alterations of CB1 cannabinoid receptors observed in MSNs and/or corticostriatal terminals at early stages of the disease are involved in the pathogenesis of Huntington’s disease, and (3) whether the induction of CB2 cannabinoid receptors in reactive microglial cells modulates the excitotoxicity processes associated with Huntington’s disease. We aim at unravelling the molecular and cellular bases as well as the potential clinical relevance of those processes.

KEYWORDS
Endocannabinoid system; Huntington’s disease; neuroprotection; neurogenesis; cell signalling; experimental therapeutics

PUBLICATIONS 2018


RESEARCH PROJECTS 2018

Code: NEUROLATAM.
Title: Unraveling the neurobiological sustrate of protective cannabinoid actions in the brain.
Principal investigator: Ismael Galve Roperh, Jose A. Ramos Atance.
CIBERNE’s collaboration: Yes.
CIBERNE groups: G303 ; G305. Other CIBER’s collaboration: No.
Type: Nacional.
Funding agency: Unión Iberoamericana de Universidades.

Code: SAF2017-83516.
Title: Diseccionando el papel de los receptores CB1 en el desarrollo y la regeneracion de celulas oligodendrogliales.
Principal investigator: Javier Palazuelos Diego.
CIBERNE’s collaboration: No.
CIBERNE groups: G305 . Other CIBER’s collaboration: No.
Type: Nacional.
Funding agency: MICINN.

Code: SAF2015-64945-R.
Title: Identificacion y caracterizacion de subpoblaciones del receptor CB1 cannabinoide con actividad neuroprotectora.
Principal investigator: Manuel Guzman Pastor.
CIBERNE’s collaboration: No.
CIBERNE groups: G305 . Other CIBER’s collaboration: No.
Type: Nacional.
Funding agency: MICINN.

Code: P15/00339.
Title: Papel de la autofagia en cancer: mecanismos de muerte mediada por autofagia en celulas tumorales y participacion de genes reguladores de la autofagia en el control de la tumorigenesis.
Principal investigator: Guillermo Velasco Diez.
CIBERNE’s collaboration: No.
CIBERNE groups: G305 . Other CIBER’s collaboration: No.
Type: Nacional.
Funding agency: Instituto de Salud Carlos III.
Code: PI15/00310.
Title: Papel del sistema endocannabinoide en malformaciones del desarrollo cortical asociadas a epilepsia refractaria.
Principal investigator: Ismael Galve Roperh.
CIBERNED's collaboration: No.
CIBERNED groups: G305. Other CIBER's collaboration: No.
Type: Nacional.
Funding agency: Instituto de Salud Carlos III.

Code: 2016-T1-BMD-1060.
Title: The role of the endocannabinoid system in oligodendrocyte development and regeneration during CNS myelination and myelin repair.
Principal investigator: Javier Palazuelos Diego.
CIBERNED's collaboration: No.
CIBERNED groups: G305. Other CIBER's collaboration: No.
Type: CCAA.
Funding agency: Comunidad de Madrid.

Code: EUR.TRAIN16.
Title: Tribbles Research and Innovation Network.
Principal investigator: Guillermo Velasco Diez.
CIBERNED's collaboration: No.
CIBERNED groups: G305. Other CIBER's collaboration: CBERONC.
Type: Europeo.
Funding agency: Comision Europea.

PHD DISSERTATIONS 2018

Author: Sandra Blasco Benito.
Title: El receptor cannabinoide CB2 como diana terapéutica y herramienta pronóstico/predictiva en cáncer de mama HER2+.
ABSTRACT

During the last years our research group has been interested in the study of molecules, processes and mechanisms involved in neuronal death taking place in neuropathologies that produce acute neurodegeneration (such as stroke, traumatic brain injury or epilepsy) and in chronic neurodegenerative diseases (such as amyotrophic lateral sclerosis, Parkinson’s disease, Huntington disease and Alzheimer’s disease). Excitotoxicity is a type of neuronal death that takes place in numerous human neuropathologies as a consequence of an excess of the excitatory amino acid glutamate. It is evident that knowing the molecular mechanisms of excitotoxicity will facilitate to design therapeutic strategies that may result neuroprotective for a wide range of acute or chronic neurodegenerative conditions. Our studies also aim to identify molecules and pathways that participate in neuronal survival, searching how to potentiate their activity and confer neuroprotection. In this sense, we have deepen into the study of two molecules PKD1 (Protein Kinase D1) and its substrate Kidins220 (Kinase D interacting substrate of 220 kDa), and demonstrated that both play a key role enhancing neuronal viability. Last year we published that PKD1 activity participates in the elimination of mitochondrial free radicals in healthy neurons, decreasing this way neuronal death under conditions of high oxidative stress. Excitotoxicity provokes PKD1 inactivation, increases reactive oxygen species, neuronal damage and neurodegeneration. These harming processes can be rescued using lentivirus for the expression of a constitutively active mutant of PKD1 that confers strong neuroprotection in animal models (Pose-Utrilla & García-Guerra et
al, Nat Commun, 2017). More recently, we have designed adenoviral vectors for the neurospecific expression of this mutant in preclinical studies of neuroprotection using different animal models of neurodegenerative diseases.

In the context of cooperative project CIBERNED 2013/07 we have discovered the differential regulation of two Kidins220 isoforms in Huntington’s disease, that show significant changes from early presymptomatic stages. We will continue our research to determine the contribution of the observed modifications in Kidins220 and PKD1 to the etiopathology of different neurodegenerative diseases, and to design novel neuroprotective strategies.

Finally, we have generated conditional PKD1 or Kidins220 deficient mice in different cell lineages and are analysing their phenotype. Our studies this last year show alterations in brain homeostasis, neuroinflammation, and mitochondrial, metabolic, synaptic and neurogenic dysfunctions, accompanied by behavioral and memory deficiencies. At present, we continue elucidating the molecular mechanism involved in the appearance of the observed phenotypes highly related to neurodegeneration.

**KEYWORDS**

Alzheimer, Excitotoxicity, Huntington, Kidins220, Neuroprotection, Oxidative Stress, Protein Kinase D1 (PKD1)

**PUBLICATIONS 2018**


RESEARCH PROJECTS 2018

**Code:** CAM-B2017/BMD-3700.
**Title:** Bases metabólicas de la neurodegeneración (NEUROMETAB-CM) Programas de Actividades de I+D entre Grupos de Investigacion de la Comunidad de Madrid en Tecnologias y en Biomedicina.
**Principal investigator:** Jose Gonzalez Castano.
**CIBERNED’s collaboration:** Yes.
**CIBERNED groups:** G401; G502; G111; G409; G412; G205; G110.
**Other CIBER’s collaboration:** No.
**Type:** CCAA.
**Funding agency:** Comunidad de Madrid.
**Funding:** 87499,89. **Duration:** 2014-2020.

**Code:** PI2015-2/06.
**Title:** Molecular mechanisms of brain and muscle stem cell function in aging and neurodegeneration.
**Principal investigator:** Pura Munoz Canoves.
**CIBERNED’s collaboration:** Yes.
**CIBERNED groups:** G604; G102; G606; G111; G306.
**Other CIBER’s collaboration:** No.
**Type:** Intramurales.
**Funding agency:** CIBERNED.
**Funding:** 350000. **Duration:** 2016-2018.

**Code:** SAF2017-88885-R.
**Title:** Mecanismos moleculares implicados en dano cerebral y neurodegeneracion causados por deficiencias en Kidins220 o por eliminacion selectiva de PKD1 en neuronas y astrocitos.
**Principal investigator:** Teresa Iglesias Vacas.
**CIBERNED’s collaboration:** No.
**CIBERNED groups:** G111. **Other CIBER’s collaboration:** No.
**Type:** Nacional.
**Funding agency:** MICINN.
**Funding:** 242000. **Duration:** 2018-2020.
ABSTRACT

Directed by Jaime Kulisevsky MD, PhD (Movement Disorders Unit, Sant Pau Hospital, Biomedical Research Institute), we focus on research of Parkinson’s Disease (PD) and other Movement Disorders. During 2018 we initiated new projects and achieved different objectives:

1. PARKINSON’S DISEASE (PD)
   A. General
      • COPPADIS: COhort of Patients with PAarkinsson’s Disease in Spain (national collaborative study).
B. Cognition

- FIS PI14 / 02058: Blood and neurophysiological markers of progression of cognitive impairment.
- DuoCog: randomized, double blind and crossed study (immediate levodopa vs. intraduodenal in cognition and mood).
- Ciberned intramural project: randomized, double-blind, placebo-controlled trial of efficacy and safety of candesartan in mild cognitive impairment.
- Diagnostic accuracy and neuronal correlates of the Buschke memory test in mild cognitive impairment.
- Study of perception of colors and visuospatial functions in PD.
- Collaboration in the study of Normative data of the PD-CRS in Brazilian population, with Pedro Brandao, University of Brasilia.

C. Neuropsychiatric disorders

- Marató TV3 (nº 477, 2013): Prediction of impulse control disorders (TCI) and apathy.
- FIS (PI15 / 00962): Anatomical-functional correlates of TCI and apathy
- Minor hallucinations: analysis of functional correlates (rEEG) and neuroimaging (structural MR, fMRI).
- Prospective study on the efficacy of music therapy in apathy and depression of PD.
- Collaborative study of Normative Data of the PD-CRS scale (Pedro Brandao, University of Brasilia).

D. Advanced PD

- Analysis of nutritional status in patients with intraduodenal levodopa.
- Prospective cognitive, behavioral, sleep and quality of life study in patients with deep brain stimulation and intraduodenal levodopa.
- Prospective study of patient satisfaction after functional surgery.

2. ENFERMEDAD DE HUNTINGTON (EH)

A. Coordination of the “Cognitive Phenotype Working Group” (European Huntington’s Disease Network).

B. Spanish coordination of Enroll-HD: A Prospective Registry Study in a Global Huntington’s Disease Cohort (PI in Spain: J. Kulisevsky)

C. Validation of cognition scales (HD-CRS) and functionality (HD-CFRS).

D. Project FIS PI17/01885. Longitudinal study of clinical and neuroradiological correlates associated with levels of huntingtin and other biomarkers in CSF and plasma in HD (BCN-HD project) (PI: Jesús Pérez)

E. Collaboration in: a) FIS PI14 / 00834: Longitudinal changes of functional and structural connectivity in pre-symptomatic patients; b) FIS PI15 / 02227: Phenotype and haplotypes associated with intermediate alleles of the EH gene; c) Overcoming Depression in HD: Cdk5 as a potential biomarker and pharmacological target (HD’s disease Society of America); d) The nuclear lamina in HD: physiopathology and therapeutic applications (Ramón Areces Foundation).

F. Oxytocin study, plasma levels and modifications in its receptor, and association with apathy and impairment of social cognition in HD (Financing: Regional Health Management and Ministry of Health, Junta de Castilla y León).

G. Identification of molecular signatures in exosomes associated with HD.
3. TREMOR
A. Development of a hardware-software system for a portable neurophysiological study. Collaborative project (SEIDOR company and University of Vic).
B. Development of diagnostic system through mobile App and software. Collaborative project with Mediktor company.
C. Perampanel in primary orthostatic tremor (pilot study) Collaboration with Association of Patients TOP (Paris, France).

4. OTHER NEURODEGENERATIVE DISEASES
A. Neuronal correlates of hypofrontality in subtypes of progressive supranuclear palsy (PSP).
B. Neuropsychiatric and behavioral symptoms in subtypes of PSP.
C. Multicenter study to validate the diagnosis of neurodegenerative diseases through OS-CANN oculographic registry (Alzheimer’s, PD and frontotemporal dementia vs. controls).
D. Lewy Bodies Dementia: participation in an international multi-center study integrated in the “Joint Program for Neurodegenerative Diseases” (European Commission).
E. MSA: Collaborative project within the Catalan MSA Registry (CMSAR).
F. FXTAS: Collaborative research with Genetics Hospital Clinic (Barcelona) and Associació Catalana X Fràgil (ACXF).

5. NEUROIMAGING AND DATA ENGINEERING
A. Functional and structural cerebral correlates in HD: cognitive deterioration, apathy, depression and irritability.
B. Neuronal correlates of the classification of cognitive impairment of PD according to the MDS.
C. Dynamic connectivity models in cognitive impairment of PD (collaboration with Center for Brain and Cognition, Pompeu Fabra University).
D. Effects of dopaminergic treatment of PE on neurocognitive networks.
E. Analysis of public databases (“big-data”): ENROLL (HD) and PPMI (PD).

KEYWORDS

PUBLICATIONS 2018


Bellota Diago E, Perez-Perez J, Santos Lasaosa S, Viloria Alebesque A, Martinez-Horta S,


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**RESEARCH PROJECTS 2018**

**Code:** PI2017/02.

**Title:** Glucocerebrosidasa y Proteinopatías Neurodegenerativas.

**Principal investigator:** Jose L. Lanciego.

**CIBERNED’s collaboration:** Yes.

**CIBERNED groups:** G203; G208; G202. **Other CIBER’s collaboration:** No.

**Type:** Intramurales.

**Funding agency:** CIBERNED.

**Funding:** 210000. **Duration:** 2017-2019.
Code: MARATO 20142910.
Title: Blood-based and neurophysiological markers of cognitive deterioration and dementia in Parkinson's disease.
Principal investigator: Javier Pagonabarraga.
CIBERNED's collaboration: No.
CIBERNED groups: G202 . Other CIBER's collaboration: No.
Type: Privado.
Funding agency: Fundacio La Marato de TV3.

Code: PI15/00962.
Title: Correlatos anatomico-funcionales de los trastornos del control de impulso y apatia en la enfermedad de parkinson.
Principal investigator: Jaime Kulisevsky.
CIBERNED's collaboration: No.
CIBERNED groups: G202 . Other CIBER's collaboration: No.
Type: Nacional.
Funding agency: Instituto de Salud Carlos III.

Code: PI17/01885.
Title: Estudio longitudinal de los asociados a los niveles de huntingtina y otros biomarcadores en LCR y plasma en la enfermedad de Huntington.
Principal investigator: Jesus Perez Perez.
CIBERNED's collaboration: No.
CIBERNED groups: G202 . Other CIBER's collaboration: No.
Type: Nacional.
Funding agency: Instituto de Salud Carlos III.

Code: MARATO 20142410.
Title: Prediction of apathy and impulse control disorders in Parkinson's disease based on feedback related negativity.
Principal investigator: Jaime Kulisevsky.
CIBERNED's collaboration: No.
CIBERNED groups: G202 . Other CIBER's collaboration: No.
Type: Privado.
Funding agency: Fundacio La Marato de TV3.
PRINCIPAL INVESTIGATOR
Labandeira García, José Luis.

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Costa Besada, María Alicia.
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PhD.
Muñoz Patiño, Ana María.
PhD.
Pedrosa Sánchez, María Ángeles.
Bachelor degree.
Rodríguez Pallarés, Jannette.
PhD.
Rodríguez Pérez, Ana Isabel.
Bachelor degree.
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PhD.
Valenzuela Limiñana, Rita.
Bachelor degree.
Villar Cheda, María Begoña.
PhD.

ABSTRACT
In 2018, we have investigated mechanisms involved in progression of Parkinson's disease (PD) and higher vulnerability of dopaminergic neurons with aging. We investigated the role of mechanisms involved in the protective effect of physical exercise on aging-related dopaminergic vulnerability, including effects of exercise on levels of nigral angiotensin, IGF-1, SIRT1, SIRT3 or VEGF (J. Gerontol. A Biol. Sci. Med. 10, 1594-1601, 2018). We have also investigated the role of brain renin-angiotensin system (RAS) on neuroinflammation and dopaminergic degeneration, using new animal models in which dopaminergic degeneration was induced by over-expression of alpha-synuclein in dopaminergic neurons using adeno-associated viral vectors (AAV9) (Neurotherapeutics 15, 1063-1081, 2018). Furthermore, we have identified an Ang1-7/MAS receptor axis in dopaminergic neurons of rodents and primates and
clarified its functional role (Mol. Neurobiol. 58-47-5867, 2018). We have studied new mechanisms that counteract oxidative stress induced by activation of angiotensin-type 1 receptors (AT1) in dopaminergic neurons that involve the compensatory over-regulation of the NFR2/KLF9 pathway (Free Radic Biol Med 129, 394-406, 2018; Data in Brief 21: 934-942, 2018). We also observed that prostaglandin EP2 receptors may be a new target for dopaminergic neuroprotection, and that these receptors mediate mesenchymal stromal cell-neuroprotective effects on dopaminergic neurons (Mol Neurobiol 55: 4763-4776, 2018). There is an interesting interaction between Parkinson’s disease and gastrointestinal (GI) dysfunction. In 2018, we have published two studies on this question, in which we observed that a nigral dopamine depletion induces changes in intestinal neurotransmitters that may lead to GI motility dysfunction, as well as an increase in GI inflammatory markers. Conversely, GI inflammation led to early changes in dopaminergic components and inflammatory markers in the nigra that may induce an increase in dopaminergic neuron vulnerability (Mol Neurobiol 7297-7316, 2018; Oncotarget 9: 10834-10846, 2018).

Finally, we have also collaborated with other groups in their research lines on neurodegeneration. This included studies on relevance of CB1/CB2 receptors in Alzheimer disease (AD) or L-DOPA-induced dyskinesias (Brain Behav Immun 139-151, 2018), Glucocerebrosidase expression in primates as possible new target for neuroprotection in PD (Brain Struct Func 343-355, 2018), or Alzheimer’s disease DNA methylome of pyramidal layers in human frontal cortex (Epigenomics 1365-1382, 2018). An important part of the above-mentioned studies and experiments undertaken in 2018 have been performed in collaboration with different Ciberned research groups: Dr. Lanciego, Dr. R. Franco, Dr. Kulisevsky, Dra. Moratalla.

KEYWORDS
Neurodegeneration, neuroprotection, neuroinflammation, Parkinson, aging, angiotensin, cell therapy.

PUBLICATIONS 2018


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**RESEARCH PROJECTS 2018**

**Code:** RD16/0011.

**Title:** Red de Terapia Celular.

**Principal investigator:** Isabel Farinas.

**CIBERNED’s collaboration:** Yes.

**CIBERNED groups:** G607 ; G301; G102; G113; G208; G105; G207.

**Other CIBER’s collaboration:** No.

**Type:** Nacional.

**Funding agency:** Instituto de Salud Carlos III.

**Funding:** 284999. **Duration:** 2016-2020.
Title: Combined protective/restorative cell-mediated strategies for neurodegenerative diseases.
Principal investigator: Jose Luis Labandeira Garcia.
CIBERNED’s collaboration: Yes.
CIBERNED groups: G208; G102; G113; G105; G207. Other CIBER's collaboration: No.
Type: Nacional.
Funding agency: Instituto de Salud Carlos III.
Funding: 240245.
Duration: 2017-2021.

Code: PI2017/02.
Title: Glucocerebrosidasa y Proteinopatías Neurodegenerativas.
Principal investigator: Jose L. Lanciego.
CIBERNED’s collaboration: Yes.
CIBERNED groups: G203; G208; G202. Other CIBER's collaboration: No.
Type: Intramurales.
Funding agency: CIBERNED.

Title: Consolidacion y estructuracion de grupos de referencia competitiva.
Principal investigator: Jose Luis Labandeira Garcia.
CIBERNED’s collaboration: No.
CIBERNED groups: G208. Other CIBER's collaboration: No.
Type: CCAA.
Funding agency: Xunta de Galicia.

Code: PI17/00828.
Title: Estudio experimental y clinico para identificacion de marcadores de mecanismos de progresion de la Enfermedad de Parkinson y posibles dianas terapeuticas para neuroproteccion.
Principal investigator: Ana Isabel Rodriguez Perez.
CIBERNED’s collaboration: No.
CIBERNED groups: G208. Other CIBER's collaboration: No.
Type: Nacional.
Funding agency: Instituto de Salud Carlos III.

Code: BFU2015-70523.
Title: Sistema renina-angiotensina cerebral en neuroinflamacion y degeneracion dopaminergica. Mas alla del eje All/AT1/NADPH-oxidase.
Principal investigator: Jose Luis Labandeira Garcia.
CIBERNED’s collaboration: No.
CIBERNED groups: G208. Other CIBER's collaboration: No.
Type: Nacional.
Funding agency: MICINN.
Code: R2014/050.
Title: Red Gallega de Terapia celular.
Principal investigator: Jose Luis Labandeira García.
CIBERNED's collaboration: No.
CIBERNED groups: G208. Other CIBER's collaboration: CIBEROBN.
Type: Nacional.
Funding agency: Instituto de Salud Carlos III.

PHD DISSERTATIONS 2018

Author: María Alicia Costa Besada.
Title: Sistema renina-angiotensina mitocondrial y nuclear en neuronas. Implicaciones en la enfermedad de Parkinson.
Date: 27/4/2018. Supervisor: José Luis Labandeira García.
PRINCIPAL INVESTIGATOR
Lanciego Pérez, José Luis.

LIST OF PERSONNEL
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ABSTRACT

1. Studies on heteromers made of G protein-coupled receptors (GPCRs).
It might be argued that GPCRs have a natural tendency to form heteromeric complexes that represent novel molecular entities with properties distinct from those of each component receptor, when considered separately. GPCR heteromers represent novel targets for pharmacological developments in the field of Parkinson’s disease. At present, our main activities focus on GPCR heteromers made of dopaminergic receptors (D1 and D2), as well as those formed by endocannabinoid receptors (CB1, CB2 and GPR55).

2. Gene therapy for Parkinson’s disease.
We are currently using adeno-associated viral vectors for modeling a number of synucleinopathies in non-human primates, these including Parkinson’s disease, demetia with Lewy bodies (DLB) and multiple system atrophy (MSA).
- NHP models of PD with AAV9-SynA53T.
- NHP models of DLB with AAV2-retro-SynA53T
- NHP models of MSA with AAV-Olig001-SynA53T
The ultimate goal is to use gene therapy approaches to further increase the activity of glucocerebrosidase (GCase). GCase enhanced activity is expected to induce a safe and efficient clearance of aggregated alpha-synuclein, thus slowing-down (and ideally arrest), the progressive course that typically characterizes these neurodegenerative disorders.

- Gene therapy with AAV9-GBA1 for PD
- Gene therapy with AAV2-retro-GBA1 for DLB
- Gene therapy with AAV-Olig001-GBA1 for MSA

**KEYWORDS**

GPCR, dopamine, cannabis, basal ganglia, gene therapy, adeno-associated viral vectors, alpha-synuclein, glucocerebrosidase, Gaucher disease.

**PUBLICATIONS 2018**


Navarro G, Borroto-Escuela D, Angelats E, Etayo I, Reyes-Resina I, Pulido-Salgado M  et al. Receptor-heteromer mediated regulation of endocannabinoid signaling in activated micro-


PRINCIPAL INVESTIGATOR
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D’anglemont de Tassigny, Xavier.
PhD.
Gao Chen, Lin.
PhD.
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Technician.
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PhD.
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PhD.
Ortega Sáenz, Patricia.
PhD.
Rho, Hee-Sool.
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Toledo Aral, Juan José.
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Villadiego Luque, Francisco Javier.
PhD.

ABSTRACT
In 2018 our group has continued with the work in the two main research lines: a) Molecular nature of oxygen sensors in cells, especially in the glomus cells of the carotid body (CB); and b) Neuroprotection and pathogenesis in Parkinson’s disease (PD), especially the early modifications of the dopaminergic neurons of the nigrostriatal pathway.

a) In this line of work we have developed several models of genetically modified KO animals for NDUFS2 (a component of mitochondrial complex I) and other mitochondrial proteins. The results derived from this study support our proposal of the mitochondrial-cell membrane interaction, which explains the sensitivity to hypoxia of the CB chemoreceptor cells. In addition, based on the fact that the CB is a chemoreceptor...
and knowing that hypoxia produces an increase in blood lactate, we have analyzed the role of the olfactory receptor Olfr78, expressed atypically in CB, in this process. The results obtained in the KO mice for the atypical olfactory receptor Olfr78 indicate that this receptor does not participate in the activation of the glomus cells by hypoxia or by lactate. The CB is not only a peripheral chemoreceptor, but acts as a sensor of the global metabolic state of the organism, capable of integrating multiple stimuli such as hypoxemia, hypoglycemia, hypercapnia, acidosis and lactatemia.

b) Neuroprotection and pathogenesis of Parkinson’s disease

b.1. To carry out this line of research we are using several animal models with ablation of the gene encoding GDNF. We have studied the physiological function of GDNF on the protection of central catecholaminergic neurons. In addition, we have searched for potential pharmacological targets to increase the endogenous production of GDNF. We have confirmed the neuroprotective effect of GDNF on the dopaminergic nigrostriatal neurons. We have also been able to establish a possible model of regulation of GDNF through different intracellular signaling pathways and activation of certain receptors, which would allow the pharmacological stimulation of GDNF production. In collaboration with the group of Dr. José Obeso, we continue with the characterization of the PV+ interneurons producing GDNF in the monkey, using different histological and molecular biology techniques. In parallel, with this work, we continue our collaboration with the group of Dr. James Surmeier from Northwestern University (Chicago, USA) to study in detail the role of mitochondrial dysfunction on PD pathogenesis.

b.2. Cell therapy in PD. We continue our collaboration with Dr. Juan José Toledo-Aral’s group on the trophic effects of carotid body (CB) transplants in models of PD. We have analyzed several factors (i.e., age and sex of the human donors) that may influence the action exerted by the transplanted CB tissue. In this regard, age is a limiting factor that reduces the therapeutic efficacy of carotid tissue. Currently, we are further studying the molecular mechanisms involved in this phenomenon.

**KEYWORDS**

Hypoxia, mitochondria, carotid body (CB), ion channels, glial cell line derived neurotrophic factor (GDNF), Parkinson’s disease (PD), nigrostriatal pathway, neurodegeneration, parvalbumin positive interneurons (PV+).

**PUBLICATIONS 2018**


RESEARCH PROJECTS 2018

Code: RD16/0011.
Title: Red de Terapia Celular.
Principal investigator: Isabel Farinas.
CIBERNED’s collaboration: Yes.
CIBERNED groups: G607; G301; G102; G113; G208; G105; G207.
Other CIBER’s collaboration: No.
Type: Nacional.
Funding agency: Instituto de Salud Carlos III.

Title: Combined protective/restorative cell-mediated strategies for neurodegenerative diseases.
Principal investigator: Jose Luis Labandeira Garcia.
CIBERNED’s collaboration: Yes.
CIBERNED groups: G208; G102; G113; G105; G207. Other CIBER’s collaboration: No.
Type: Nacional.
Funding agency: Instituto de Salud Carlos III.

Code: PI-0125-2016.
Title: Complicaciones cardiovasculares y Metabolicas del Sindrome de Apnea del Sueno. Patoginia y modulacion farmacologica de la actividad del eje cuerpo carotideo/medula adrenal.
Principal investigator: Gracia Patricia Ortge Saenz.
CIBERNED’s collaboration: No.
CIBERNED groups: G105. Other CIBER’s collaboration: No.
Type: CCAA.
Funding agency: Junta de Andalucia.

Code: Retos-Colaboracion 15.
**Title:** Desarrollo de una terapia para el tratamiento de variantes genéticas de alfa-sinucleína en la enfermedad de Parkinson.

**Principal investigator:** Pablo Mir Rivera.

**CIBERNED’s collaboration:** No.

**CIBERNED groups:** G105. **Other CIBER’s collaboration:** No.

**Type:** Nacional.

**Funding agency:** MICINN.

**Funding:** 317528. **Duration:** 2016-2018.

**Code:** FIS 16 (PI16/01575).

**Title:** Estudio integral de los biomarcadores implicados en el desarrollo y evolución de la enfermedad de Parkinson.

**Principal investigator:** Pablo Mir Rivera.

**CIBERNED’s collaboration:** No.

**CIBERNED groups:** G105. **Other CIBER’s collaboration:** No.

**Type:** Nacional.

**Funding agency:** Instituto de Salud Carlos III.

**Funding:** 160325. **Duration:** 2017-2019.

**Code:** ERC 2014.

**Title:** Molecular mechanisms of acute oxygen sensing (OXYGENSENSING).

**Principal investigator:** Jose Lopez Barneo.

**CIBERNED’s collaboration:** No.

**CIBERNED groups:** G105. **Other CIBER’s collaboration:** No.

**Type:** Europeo.

**Funding agency:** Comision Europea.

**Funding:** 2843750.

**Duration:** 2016-2020.

**Code:** SAF2016-74990-R.

**Title:** Sensibilidad al oxígeno y Neurodegeneracion.

**Principal investigator:** Jose Lopez Barneo, Lin Gao Chen.

**CIBERNED’s collaboration:** No.

**CIBERNED groups:** G105. **Other CIBER’s collaboration:** No.

**Type:** Nacional.

**Funding agency:** MICINN.

**Funding:** 484000. **Duration:** 2016-2019.

**Code:** PROPAG-AGEING 2014.

**Title:** The continuum between healthy ageing and idiopathic Parkinson Disease within a propagation perspective of inflammation and damage: the search for new diagnostic, prognostic and therapeutic targets.

**Principal investigator:** Pablo Mir Rivera.

**CIBERNED’s collaboration:** No.

**CIBERNED groups:** G105. **Other CIBER’s collaboration:** No.

**Type:** Europeo.

**Funding agency:** Comision Europea.

**Funding:** 671167.5. **Duration:** 2015-2019.
ABSTRACT

Huntington’s disease (HD) is the most prevalent genetic neurodegenerative disease, caused by an expansion of the trinucleotide CAG in the huntingtin gene. In our lab we study the molecular basis of HD through in vitro and in vivo (generating and characterizing transgenic models that could mimic as well as revert the disease) approaches. This way, we discovered an isoform imbalance in tau, a protein related with Alzheimer’s disease and other dementias, and a new histopathological hallmark (the Tau Nuclear Rods or TNRs) in HD. Furthermore, the splicing factor SRSF6, involved in tau splicing and capable to binding CAG-repeats, is altered in HD and sequestered in the mutant huntingtin inclusion bodies (Nat Med. 20(8):881-5 2014). To characterize if tau alteration is enough for TNR appearance, we have tested a mouse model of FTDP17, a disease caused by altered tau. The TNR appearance in this model let us conclude that TNR detection could be useful as marker of tau imbalance (Brain Pathol. 27(3):314-322 2017).

We have also studied levels and isoforms of MAP2, another microtubule-associated protein which is related to tau. Its levels drop, its isoforms are imbalanced and its subcellular localization is aberrant in HD. In cell models, this splicing can be perfor-

More recently, we were able to demonstrate ATF5 expression in adult human neurons and found decreased levels and sequestration into huntingtin inclusion bodies in HD, rendering neurons more vulnerable to mutant huntingtin-induced apoptosis (Acta Neuropathol 134(6):839-850 2017). Our last important finding has relied in a serendipitous finding which has related HD with idiopathic Autism Spectrum Disorder (ASD). Studying the polyadenylation-related proteins CPEBs in HD, we found that CPEB4 binds transcripts of ASD-risk genes. In ASD cases, CPEB4 splicing is imbalanced and an equivalent alteration of CPEB4 isoforms in mice mimics the polyadenylation and protein alterations found in ASD and gives rise to ASD-like phenotype (electrophysiological, neuroanatomical and behavioral), identifying CPEB4 as regulator of ASD risk genes (Nature 560(7719):441-446 2018).

**KEYWORDS**

Huntington’s disease, autism, ASD, splicing, ATF5, CPEBs.

**PUBLICATIONS 2018**


RESEARCH PROJECTS 2018

Code: PI2015-2/06.
Title: Molecular mechanisms of brain and muscle stem cell function in aging and neurodegeneration.
Principal investigator: Pura Munoz Canoves.
CIBERNED’s collaboration: Yes.
CIBERNED groups: G604; G102; G606; G111; G306.
Other CIBER’s collaboration: No.
Type: Intramurales.
Funding agency: CIBERNED.
PRINCIPAL INVESTIGATOR
Moratalla Villalba, Rosario.

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Granado Martínez, Noelia.
PhD.
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Ruiz de Diego, Irene.
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Suárez González, Luz María.
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ABSTRACT
During 2018, we have studied the functional and structural synaptic remodeling in Parkinson’s disease (PD) and in L-DOPA-induced dyskinesia in a genetic model of the disease, the Pitx3−/− or Aphakia mouse. Pitx3−/− mice exhibit a parkinsonian phenotype because their dopaminergic neurons of the substantia nigra do not develop normally and therefore, the dorsal striatum (related to motor performance) lacks dopamine. In addition, Pitx3−/− mice are the only genetic model of PD that develops dyskinesias after L-DOPA treatment. We have demonstrated that in Pitx3−/− mice this lack of dopamine reduces the density of the dendritic spines in the main striatal neurons, the striatal projection neurons (SPNs) of both pathways, direct and indirect, which control motor function. The spine pruning concurred with an increase in the firing rate of the SPNs, probably due to compensatory mechanisms to maintain overall neuronal activity. After L-DOPA treatment, which induces dyskinesias, the spine density and the firing rate selectively recover in the indirect SPNs. By contrast, the direct-SPNs remain with lower spines and higher firing rate. All these synaptic alterations are similar to those observed in other well-establish models of PD and in human patients, and therefore, our results indicate that Pitx3−/− mice are an excellent mice...
model to study the synaptic remodeling in PD. In addition, our results demonstrates that dopamine-mediated synaptic remodeling and plasticity is independent of dopamine innervation during SPN development (Suarez et al., 2018 J Neurosci). In addition, using 6-OHDA-lesion mice, we have further confirm that L-DOPA increases the activation of direct-SPNs despite the spine pruning whereas indirect-SPNs recover their activation. Therefore, L-DOPA produces an imbalance of striatal function, in favor of direct-SPNs, (Gomez et al., 2019 Mol Neurobiol). In this sense, we have also shown that the reducing the activation of direct-SPNs with an mGluR5 antagonist, dyskinesia were also reduced (Garcia-Montes et al., 2018 Mol Neurobiol). Moreover, we have demonstrated that in dyskinetic mice, L-DOPA produces a maximal activation of the Ras-ERK signaling mediated by D1R stimulation and that upregulation of its intracellular signaling does not further increase dyskinesias while its down-regulation reduce them (Ruiz deDiego et al., 2018 Sci Rep).

We have also studied the detailed morphology and distribution of dopaminergic fibers in mice treated with methamphetamine which induces regeneration after the degeneration (demonstrated with silver staining) of dopaminergic fibers in the striatum. We have demonstrated that striatal regeneration was associated with an increase in GAP-43, a sprouting marker, and the presence of growth cone-like TH-ir structures astroglia, indicative of a new terminal generation. Striatal re-generation was associated with an increase in astroglia and decrease in microglia expression, suggesting a possible role for the neuroimmune system in regenerative processes induced by methamphetamine (Granado et al., 2018 Neurotox Res).

Finally we have studied the association between alteration in cholesterol pathways and PD. We have demonstrated that the presence of the N370S mutation in the GBA genes (related with autophagy and lysosomal function) produces an accumulation of cholesterol, which alters autophagy-lysosome function with the appearance of multilamellar bodies (MLBs), rendering the cell more vulnerable and sensitive to apoptosis (Garcia-Sanz et al., 2018 Autophagy).

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**KEYWORDS**

Parkinson's disease, dyskinesia, neurotoxicity, dopamine cell death, addiction and autophagy.

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**PUBLICATIONS 2018**


**RESEARCH PROJECTS 2018**

**Code:** PI2015-2/02.
**Title:** Potencial patologico de los astrocitos: una nueva perspectiva en la enfermedad de Alzheimer.
**Principal investigator:** Joan X. Comella.
**CIBERNED’s collaboration:** Yes.
**CIBERNED groups:** G413; G415; G204; G108; G411. **Other CIBER’s collaboration:** No.
**Type:** Intramurales.
**Funding agency:** CIBERNED.
**Funding:** 350000. **Duration:** 2016-2018.

**Code:** Cajal Blue Brain Project.
**Title:** Cajal Blue Brain Project. International Blue Brain Project.
**Principal investigator:** Javier De Felipe.
**CIBERNED’s collaboration:** Yes. **CIBERNED groups:** G204; G403.
**Other CIBER’s collaboration:** No.
**Type:** Internacional.
**Funding agency:** Ecole Polytechnique Federale de Lausanne (Suiza.
**Funding:** ND. **Duration:** 2009-2019.

**Code:** Fundacion Ramon Areces 2017.
**Title:** Efecto de las mutaciones del gen glucocerebrosidasa-1 en neuronas derivadas de células IPS de enfermos de Parkinson. Rescate del fenotipo y trasplante celular. Area: Terapia celular en enfermedades neurodegenerativas.
**Principal investigator:** Carlos Vicario Abejon.
**CIBERNED’s collaboration:** Yes.
**CIBERNED groups:** G204; G108. **Other CIBER’s collaboration:** No.
**Type:** Privado.
**Funding agency:** Fundacion Ramon Areces.
**Funding:** 120000. **Duration:** 2017-2020.
**Code:** SAF2016-48532-R.
Title: Bases moleculares de la plasticidad sinaptica estriatal en las disquinesias y el trastorno de control de impulsos inducidos por L-DOPA en la enfermedad de Parkinson.
Principal investigator: Rosario Moratalla.
CIBERNED's collaboration: No.
CIBERNED groups: G204.
Other CIBER's collaboration: No.
Type: Nacional.
Funding agency: MICINN.


Title: Development of a new in vivo radiotracer for alpha-synuclein.
Principal investigator: Mireille Dumoilin.
CIBERNED's collaboration: No.
CIBERNED groups: G204. Other CIBER's collaboration: No.
Type: Europeo.
Funding agency: Comision Europea.

Code: PNSD 2016I033.

Title: Estudio del consumo de metanfetamina en la adolescencia como factor de riesgo para la adiccion y la vulnerabilidad dopaminergica en el adulto: papel de la glia y del glutamato.
Principal investigator: Rosario Moratalla.
CIBERNED's collaboration: No.
CIBERNED groups: G204. Other CIBER's collaboration: No.
Type: Nacional.
Funding agency: MSSSI.

Code: MHE-200017.

Title: Mecanismos involucrados en la generacion de disquinesias por L-DOPA en un modelo experimental de la enfermedad de Parkinson.
Principal investigator: Rosario Moratalla.
CIBERNED's collaboration: No.
CIBERNED groups: G204. Other CIBER's collaboration: No.
Type: Nacional.
Funding agency: CSIC.
ABSTRACT

We investigate changes in neuronal calcium and protein homeostasis that are associated with neurodegenerative pathologies, like Alzheimer’s (AD), Down syndrome (DS) and Huntington’s disease (HD). Dysfunction of calcium and/or protein homeostasis trigger early compensatory changes in transcriptional programs and in synaptic function that precede and, with time, are responsible of disease symptoms characteristic of these pathologies.

In particular, our work is focused on the protein DREAM (Downstream Responsive Element Antagonist Modulator), a Ca2+-dependent transcriptional repressor, also known as calsenilin due to its interaction with presenilins. DREAM may have an important role in neurodegenerative diseases (NDD) through the control of Ca2+ and protein homeostasis. Importantly, an early reduction in DREAM levels is found in mouse models for these pathologies (AD, DS and HD) and, genetic experiments show that this could be part of a neuroprotective mechanism operating in HD. The mechanism involves the protein-protein interaction between DREAM and ATF6, a key protein in the early activation of the unfolded protein response (UPR), as well as in the regulation at the transcriptional level of several cytoskeletal proteins that are im-
important for axonal transport and synaptic function. Our results point out the DREAM-ATF6 interaction as a new target for pharmacological intervention in HD.

During 2018, we have developed an ELISA assay to check the DREAM-ATF6 interaction in the test tube in a reproducible and quantitative manner. This new ELISA assay will allow for high-through-put screening of chemical libraries to identify new active compounds to displace the DREAM-ATF6 interaction and to modify the functional properties of DREAM. We aim to identify new DREAM inhibitors for the treatment of neurodegenerative pathologies. Also during this past year we have reexamined the DREAM-Presenilin interaction to evaluate new therapeutical opportunities. From these studies we have found that i) DREAM increases Presenilin-2 (PS2) endoproteolysis in vivo, in mouse brain and, ii) DREAM inhibition with repaglinide reduces basal Presenilin-2 endoproteolysis in N2a mouse neuroblastoma cells. Ongoing experiments are investigating the effect of new DREAM inhibitors on PS-2 endoproteolysis and γ-secretase activity. Special attention will be devoted to the analysis of potential inhibition of γ-secretase activity on APP cleavage without compromising Notch processing, an unwanted secondary effect that trigger neuronal death and that has blocked the use of previous γ-secretase inhibitors for AD treatment.

KEYWORDS
DREAM, Alzheimer, ATF6, UPR, DREAM inhibitors, γ-secretase, presenilins.

PUBLICATIONS 2018


RESEARCH PROJECTS 2018

Code: PI2016/05.
Title: Dream inhibitors and Alzheimer’s Disease.
Principal investigator: Jose Ramon Naranjo Orovio.
CIBERNED’s collaboration: Yes.
CIBERNED groups: G307; G106; G403. Other CIBER’s collaboration: No.
Type: Intramurales.
Funding agency: CIBERNED.

Code: SAF2017-89554-R.
Title: INHIBIDORES DE DREAM, PROCESAMIENTO DE ATF6 Y PERDIDA COGNITIVA EN AD.
Principal investigator: Jose R Naranjo Orovio.
CIBERNED’s collaboration: No. CIBERNED groups: G307.
Other CIBER’s collaboration: No.
Type: Nacional.
Funding agency: MICINN.
PRINCIPAL INVESTIGATOR
Obeso Inchausti, José Ángel.

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Alonso Frech, Fernando.
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**ABSTRACT**

Dr. Obeso heads HM CINAC, a movement disorders research center, which is mainly focused on the study of Parkinson’s disease (PD) from a multidisciplinary approach. The principal objective is the study of the onset and progression of the disease using basic and clinical experiments aiming to define the etiopathogenesis of the disease, optimizing the diagnosis and advancing in the treatment of neurodegenerative and neuropsychiatric diseases.

**ONSET OF THE DISEASE: COMPENSATORY MECHANISMS AND SELECTIVE VULNERABILITY**

So far, treatments for PD have not been successful and one of the reasons is because diagnosis tends to be delayed respect to the onset of the neurodegenerative process. At CINAC, patients are treated with magnetic stimulation (TMS) and neuroimaging directed to define the onset of the disease. Interestingly, PD is principally characterized by the progressive degeneration of dopaminergic neurons of the substantia nigra pars compacta (SNc), which are crucial during learning and habit acquisition. Additionally, since the dopaminergic loss is previous to the diagnosis it is assumed that there might be a series of compensatory mechanisms which delay the rise of the symptoms. At CINAC, in vivo neuronal activity recordings in PD animals models are used to define these mechanisms.


**EVOLUTION AND TREATMENT OF THE DISEASE**

HIFU (High Intensity Focused Ultrasound) is a novel technique which allows performing controlled and focused brain lesions without surgery. Thus, mobility, mortality and economic costs are greatly reduced compared to current surgical treatments. This technique has demonstrated efficacy and safety in the performance of thalamotomies aimed to cease essential tremor and PD tremor. HM CINAC has been the first center to perform subthalamotomies to treat cardinal manifestations of Parkinson Disease (rigidity, akinesia, tremor). This study has been published in The Lancet Neurology Journal (IF= 26.28).


**PHARMACOLOGICAL TREATMENT OF PARKINSON’S DISEASE AND MOTOR COMPLICATIONS**

Dopamine replacement therapy has been largely used when treating PD. Both dopamine agonists and levodopa (LDOPA) are the main treatments. After long term use, this therapy is also associated not only with involuntary movements and dyskinesias, but also with motor complications, which make reduce patients. At CINAC animal models showing progressive dopamine depletion are utilized in order to determine the molecular base and mechanisms involved in the onset of LDOPA dyskinesias (LID) using recording and optogenetic techniques which allow a more specific and selective neuronal modulation.


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**KEYWORDS**

Parkinson’s disease, Substantia nigra pars compacta, Basal Ganglia, Dopamine, Vulnerability, Dyskinesias, Compensatory mechanisms


Humphries M.D, Obeso J.A, Dreyer J.K. Insights into Parkinson’s disease from computational


Monje M.H.G, Sanchez-Ferro A. Tor1a gene in GABApre interneurons: The new player in the “impaired inhibition” game of dystonia?. Movement Disorders. 2018;33(9):1408-. PMID: 30216539.


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**RESEARCH PROJECTS 2018**

**Code:** CAM-B2017/BMD-3700.

**Title:** Bases metabólicas de la neurodegeneración (NEUROMETAB-CM) Programas de Actividades de I+D entre Grupos de Investigacion de la Comunidad de Madrid en Tecnologias y en Biomedicina.

**Principal investigator:** Jose Gonzalez Castano.
CIBERNED’s collaboration: Yes.
CIBERNED groups: G401; G502; G111; G409; G412; G205; G110.
Other CIBER’s collaboration: No.
Type: CCAA.
Funding agency: Comunidad de Madrid.

Title: Bases metabólicas de la neurodegeneración (NEUROMETAB-CM) Programas de Actividades de I+D entre Grupos de Investigacion de la Comunidad de Madrid en Tecnologias y en Biomedicina.
Principal investigator: Jose Gonzalez Castano.
CIBERNED’s collaboration: Yes.
CIBERNED groups: G401; G502; G111; G409; G412; G205; G110.
Other CIBER’s collaboration: No.
Type: CCAA.
Funding agency: Comunidad de Madrid.

Title: Ayuda para la contratacion de ayudantes de investigacion.
Principal investigator: Ines Trigo Damas.
CIBERNED’s collaboration: No.
CIBERNED groups: G205. Other CIBER’s collaboration: No.
Type: CCAA.
Funding agency: Comunidad de Madrid.

Code: BES2016-077493.
Title: Ayudas para contratos predoctorales para la formacion de doctores.
Principal investigator: Jose A. Obeso.
CIBERNED’s collaboration: No.
CIBERNED groups: G205. Other CIBER’s collaboration: No.
Type: Nacional.
Funding agency: MICINN.

Code: CD15/00092.
Title: Contrato Posdoctoral de Perfeccionamiento Sara Borrell. Grupo habitual.
Principal investigator: Ignacio Obeso Martin.
CIBERNED’s collaboration: No.
CIBERNED groups: G205. Other CIBER’s collaboration: No.
Type: Nacional.
Funding agency: Instituto de Salud Carlos III.

Title: Convocatoria de ayudas de investigadores predoctorales.
Principal investigator: Ignacio Obeso.
CIBERNED’s collaboration: No.
CIBERNED groups: G205. Other CIBER’s collaboration: No.
Type: CCAA.
Funding agency: Comunidad de Madrid.

Code: EULACH16/T01-0047.
Title: DASYN - Early detection and cellular disintegration of \(\alpha\)-synuclein aggregates using nanobodies.
Principal investigator: Prof. Pedro Chana.
CIBERNED's collaboration: No.
CIBERNED groups: G205. Other CIBER's collaboration: No.
Type: Europeo.
Funding agency: Comision Europea.

Code: SAF2017-86246-R.
Title: Estimulacion transcraneal por campo magnetico estatico en la Enfermedad de Parkinson.
Principal investigator: Guglielmo Foffani.
CIBERNED's collaboration: No.
CIBERNED groups: G20. Other CIBER’s collaboration: No.
Type: Nacional.
Funding agency: MICINN.

Code: AC16/00044.
Title: Harmonisation metabolic FDG brain pattern characteristics.
Principal investigator: Jose Angel Obeso Inchausti.
CIBERNED's collaboration: No.
CIBERNED groups: G205. Other CIBER’s collaboration: No.
Type: Nacional.
Funding agency: Instituto de Salud Carlos III.

Code: Sin codigo_Tatiana.
Title: Objetivo \(\alpha\)-synucleina: entender la vulnerabilidad celular y detener la progresion en la Enfermedad de Parkinson.
Principal investigator: Javier Blesa De Los Mozos, Jose Angel Obeso Inchausti.
CIBERNED’s collaboration: No.
CIBERNED groups: G205. Other CIBER’s collaboration: No.
Type: Privado.
Funding agency: Fundacion Tatiana Perez de Guzman el Bueno.

Code: Sin codigo.
Title: Selective Vulnerability, progression and Synuclein Toxicity in Parkinson’s disease.
Principal investigator: Jose Angel Obeso Inchausti.
CIBERNED’s collaboration: No.
CIBERNED groups: G205. Other CIBER’s collaboration: No.
Type: Privado.
Funding agency: Fundacion BBVA.
ABSTRACT

Our research is focused on identification of new therapeutic targets for the treatment of neurodegenerative diseases. To that purpose our work is based on the use of several preclinical models that mimics some of the aspects that characterize Alzheimer’s and Parkinson’s diseases. Using these models we identify and analyze potential cellular targets in order to develop new drugs for the treatment of these diseases. During the year 2017 we have continued working on this topic, studying the processes that characterize these pathologies. In that sense, we have studied the involvement of several genes in different brain disorders such as C/EBP\(\beta\), whose inhibition has been shown to have a potent neuroprotector in a Parkinson’s model. Some other gen of interest we have analyzed is PDE7, which codes for an enzyme involved in the degradation of cAMP. Our results suggest that this gene is expressed early in degenerative processes that affect the dopaminergic neurons of the substantia nigra, as well as promotes the appearance of pro-inflammatory phenomena.

Also, a main focus of the lab concerns research on neurogenesis and aging. In this regard we are expanding our previous observations that describe the neurogenic effect of certain components of the brew known as Ayahuasca. In this sense, we are currently working in the role of different new cellular targets which can expand our knowledge of the processes that lead to improved neurogenesis and that can be of use for a better understanding and new treatments of aging-related disorders.
KEYWORDS
Alzheimer, APP, Ayahuasca, C/EBPβ, LRRK2, neurogenesis, neuroinflammation, neuroprotection, Parkinson.

PUBLICATIONS 2018

RESEARCH PROJECTS 2018
Title: Bases metabólicas de la neurodegeneración (NEUROMETAB-CM) Programas de Actividades de I+D entre Grupos de Investigacion de la Comunidad de Madrid en Tecnologias y en Biomedicina.
Principal investigator: Jose Gonzalez Castano.
CIBERNED’s collaboration: Yes.
CIBERNED groups: G401; G502; G111; G409; G412; G205; G110.
Other CIBER’s collaboration: No.
Type: CCAA.
Funding agency: Comunidad de Madrid.

Code: SAF2017-85199-P.
Title: CCAAT/Enhancer binding protein β (C/EBPβ) como modulador de la neuroinflamación. Una nueva diana terapéutica en la enfermedad de Parkinson.
Principal investigator: Ana Maria Perez Castillo.
CIBERNED’s collaboration: No.
CIBERNED groups: G110. Other CIBER’s collaboration: No.
Type: Nacional.
Funding agency: MICINN.

Code: MARIE SKŁODOWSKA-CURIE ACTIONS. H2020-MSCA-ITN-2016
Title: Blood Biomarker-based Diagnostic Tools for Early-stage Alzheimer’s Disease.
Principal investigator: Ana Perez Castillo.
CIBERNED’s collaboration: No.
CIBERNED groups: G110. Other CIBER’s collaboration: CIBERER.
Type: Europeo.
Funding agency: Comision Europea.
ABSTRACT

Throughout 2018, our group has continued with the characterization of Mendelian forms of neurological diseases. Thus we have determined the presence of several mutations related to Alzheimer’s disease, primary lateral sclerosis, frontotemporal dementia or paroxysmal kinesigenic dystonia. In this area, we have determined the segregation of the mutations found in the families, although the small size of these does not allow to reach definitive conclusions about this, as well as the population frequency of the same. In addition, we have begun the study of two other family forms with rare neurological disorders. On the one hand, an atypical form of what appears to be frontotemporal dementia and, on the other, a form of disease that presents as optic atrophy with or without ataxia, mental retardation and epileptic seizures but that is not related to mutations in RTN4IP.

In a second phase of this same project, we are advancing in the description of the mechanisms through which some of these mutations could be causing the pathological process with which they are related, developing cellular models of the respective diseases on which to study the degradation of the mRNA of the mutated allele and the possible haploinsufficiency that said degradation produces. This seems to be the mechanism involved in the appearance of paroxysmal kinesigenic dystonia. However, in the case of Alzheimer’s disease, our data, even preliminary, suggest that the mutation we have found affects intracellular signalling pathways.

On the other hand, we have begun the study of non-Mendelian forms of Alzheimer’s disease through the genomic analysis of part of the Vallecas cohort, collected by the CIEN Foundation. This is a collaborative study with the group of Dr. Máñez (CiberBBN) in which we will combine information on metabolites present in
these same patients with genetic information to determine characteristics of the disease that help to know its appearance and progression. In parallel, we continue analyzing the results of the study of expression in patients with Parkinson’s disease of genetic origin, combining them with metabolomic data on the same patients.

Finally, we have initiated a collaboration with groups of other entities in which it is sought to determine if it is possible to advance in a very early diagnosis of the appearance of cognitive deficits by combining neuropsychological, genetic and lifestyle data. This project, has the particularity of that the population that is intended to study is collected in community pharmacies. This is a novel approach that takes as reference the trust that is established between a person and their pharmacist when there is a continuous treatment between them.

**KEYWORDS**

Alzheimer’s, Parkinson’s, Frontotemporal dementia, Mendelian diseases, Neurodegeneration, Neurogenetics, ALS

**PUBLICATIONS 2018**


**RESEARCH PROJECTS 2018**

**Code:** 2016-COHORTE BBN-NED.
**Title:** COHORTE-BBN-NED. Busqueda de biomarcadores para la deteccion temprana de la enfermedad de Alzheimer en la cohorte del proyecto Vallecas.
**Principal investigator:** Miguel Medina.
**CIBERNED’s collaboration:** Yes.
**CIBERNED groups:** G209 ; G401. **Other CIBER’s collaboration:** CIBER-BBN.
**Type:** Nacional.
**Funding agency:** Instituto de Salud Carlos III.
**Funding:** 150000. **Duration:** 2016-2018.
MOLECULAR AND CELLULAR NEUROBIO TECHNOLOGY INSTITUTE FOR BIOENGINEERING OF CATALONIA (IBEC).
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ABSTRACT

1) Development of new lab on chip devices for Neurobiology. One of our focus is to mimic the developing and neurodegenerating nervous system in lab on chip devices. We believe that combining several different stimuli in the chip resembles a more realistic environment that nerve cells will encounter in the living animal in normal and disease conditions. Thus, we developed last year a new device able to reproduce the formation of the neuromuscular junction (NMJ) in lab on chip devices (Sala et al., submitted). Members of our lab used biophysics and image analysis to study changes in muscle contraction in particular diseases (Figure 1). In addition, a device designed to analyze axon lesions of cortical neurons was also developed (Mesquida et al., submitted). Current experiments of our group in collaboration with several groups of Ciberned and other labs aimed at developing new lab on chip devices to mimics and modulate particular neurodegenerative processes. For example: I) on chip lab platform to monitor drug delivery and network connectivity between different neuronal populations; II) cortico-spinal chips to develop axon regenerative studies of new drug formulation (in collaboration with Imperial College; UK) or, IV) in silico 3D modeling for neurodegenerative diseases (Alzheimer and Parkinson chip) (Figure 2)

2) New strategies to monitor and overcome α-synuclein and tau transport in neurons and
glial cells during neurodegeneration. \(\alpha\)-Synuclein is a key player in the pathogenesis of synucleinopathies, including Parkinson's disease (PD), Dementia with Lewy Bodies (DLB), and multiple system atrophy (MSA). Tau is present as neurofibrillary tangles (NFT) in different neurodegenerative diseases including Alzheimer's disease (AD) or Frontotemporal dementia-tau (FTD-tau). Transmission of synthetic \(\alpha\)-synuclein or Tau aggregates has been demonstrated in several cellular and animal models. However, the basis of the spreading process remains poorly understood although cell to cell transport via classical exocytosis, exosomes, nanotubes or receptor mediated endocytosis has been proposed. We described in 2018 that the cellular prion protein PrPC is a new receptor for \(\alpha\)-synuclein involved in their seeding and propagation (Urrea et al., 2018a; 2018b) reviewed in Progress in Neurobiology (Del Rio, Ferrer et al., 2018). Our new objectives aimed to block this interaction to reduce the neuropathological transport of \(\alpha\)-synuclein. Similar experiments are also developed in the case of Tau since recent data of our group showed that Tau also binds to PrPC during its inter-neuronal propagation. In addition, we also described a feed-back neuroprotective answer to affected neurons since intracellular soluble Tau fractions also trigger PrPC production at its promoter level enhancing neuronal survival at early neurodegenerative stages of different tauopathies including AD (Lidón et al., submitted).

3) Understanding axon regeneration: from reactive oxygen species to epigenetics. Our group in a fruitful collaboration with Prof. Simone di Giovanni (Imperial College, UK) published in Nat. Cell Biology we demonstrated that the generation of ROS and NOX2 activity is mandatory to enhance axon regeneration in the lesioned spinal injury in vivo (Hervera et al., 2018). In fact, exosomes containing NOX2 are released from macrophages and incorporated into injured axons via endocytosis and transported to the cell body through an importin-\(\beta\)1-dynein-dependent mechanism. Endosomal NOX2 oxidizes PTEN stimulating PI3K-Akt inducing axon regeneration (Hivera et al., 2018). These data have been reviewed recently in Trends in cell biology (Hervera et al., 2019). Recently accepted publication points to epigenetic changes in the lesioned neurons that might enhance axon regeneration (Hervera et al., 2019a; Hervera et al., EMBOJ in press).

KEYWORDS
\(\alpha\)-synuclein, tauopathies, interneuronal spreading, axon regeneration, lab-on-chip.

PUBLICATIONS 2018


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**RESEARCH PROJECTS 2018**

**Code:** AMEND.

**Title:** Early Diagnosis of Alzheimer in a Multiplexed approach based on New blood biomarkers.

**Principal investigator:** Monica Mir (CiberBBN).

**CIBERNED’s collaboration:** Yes.

**CIBERNED groups:** G504; G114. **Other CIBER’s collaboration:** CIBER-BBN.

**Type:** Intramurales.

**Funding agency:** CIBERBBN.

**Funding:** ND. **Duration:** 2018-2018.

**Code:** INTRAMURAL CIBERBBN-CIBERNED.

**Title:** Gamma-peptides as anti–alzheimer drugs with BBB crossing properties (GAM-MA-AD).

**Principal investigator:** Miriam Royo Exposito.

**CIBERNED’s collaboration:** No.

**CIBERNED groups:** G114 . **Other CIBER’s collaboration:** CIBER-BBN.

**Type:** Intramurales.

**Funding agency:** CIBERBBN.

**Funding:** ND. **Duration:** 2018-2018.
Code: PI2016/02.
Title: Monitoring the Onset and Evolution of Neuronal Dysfunctions in Propagative Neural Disorders using Microfluidic Devices and Translational approaches.
Principal investigator: Jose Antonio Del Rio.
CIBERNED’s collaboration: Yes.
CIBERNED groups: G114; G401; G201. Other CIBER’s collaboration: No.
Type: Intramurales.
Funding agency: CIBERNED.

Code: TEC2015-72718-EXP.
Title: Robots biologicos basados en el control de la union neuromuscular.
Principal investigator: Josep Samitier.
CIBERNED’s collaboration: No.
CIBERNED groups: G114. Other CIBER’s collaboration: CIBER-BBN.
Type: Nacional.
Funding agency: MICINN.

Code: BFU2015-6777-R.
Title: Funciones de genes implicados en angiogenesis y remodelacion vascular durante el desarrollo cortical y en neurodegeneracion.
Principal investigator: Jose Antonio Del Rio.
CIBERNED’s collaboration: No.
CIBERNED groups: G114. Other CIBER’s collaboration: No.
Type: Nacional.
Funding agency: MICINN.

Title: Grupo de investigación de calidad de la Generalitat de Catalunya.
Principal investigator: Jose A Del Rio.
CIBERNED’s collaboration: No.
CIBERNED groups: G114. Other CIBER’s collaboration: No.
Type: CCAA.
Funding agency: Generalitat de Catalunya.

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**PHD DISSERTATIONS 2018**

Author: Laura Urrea Zazurca.
Title: Funciones de la proteína prionica celular, a-sinucleína y reclina en enfermedades neurodegenerativas.
Date: 16/3/2018. Supervisor: José Antonio Del Ríó Fernández.
ABSTRACT

We studied the action of astrocytes in Parkinson’s disease. During the process of degeneration of the dopaminergic terminals in the striatum dopaminergic, spheroids of 1-8 microns accumulate the intracellular detritus of these neurons, detritus involving proteins such as the APP, the TH and DAT and organelles such as mitochondria. This accumulation prevents scattered detritus that would facilitate the inflammatory response and would alter the functioning of the tissue surrounding the dopaminergic degeneration. In addition, the clustering of detritus in spheroids facilitates disposal. Dopaminergic spheroids present autophagosomes (LC3) but not lysosomes (Lamp1 or Lamp2), which suggests that autophagy starts but does not end in the spheroids. We found evidence suggesting that the autophagy that begins at dopaminergic terminals ends in surrounding astrocytes, and that astrocytes are keys to the cleaning of the dopaminergic debris generated in the normal brain with the age. We also observed microglial activation, but activated microglia does not present phagocyte characteristics (e.g. it does not increase the expression of CD68). These data suggest that, under basal conditions, the detritus cleaning is
done by astrocytes rather than by the microglia. Last year, we have proceeded to assess the evolution of the dopaminergic organelles which are also accumulated in spheroids during the dopaminergic degeneration. Studies with different transgenic mice suggest that astrocytes are also involved in the recovery/metabolization of these organelles. These studies were conducted in animal models of Parkinson’s disease, and now we are proceeding to validate these findings in striatal samples of of parkinsonian patient which were provided by the Brain Bank of the CIEN Foundation. Finally, these studies are also being verified through additional techniques such as electron microscopy.

During the year 2018, we have expanded our studies on the functional connectivity of the basal ganglia of normal human brain, proceeding to evaluate the changes in connectivity caused by Parkinson’s disease. We had previously studied the basal ganglia by means of neuroimaging techniques based on the correlation of BOLD signals. These studies showed a circular cortico-subcortical interaction which, as a whole, was similar to that described in experimental animals. However the correlation techniques have some important limitations, since they assume normality in the sample and a linear relationship between basal ganglia that does not occur in reality (in previous studies we showed non-linear activity in centers like the substantia nigra). In addition, correlation only provide information about the relationship between two centers at the same time, and basal ganglia present multiple simultaneous interactions which cannot be properly assessed with this technique. For this reason we developed a new analytical procedure based on the Multiple Correspondence Analysis, a procedure that can be used for the study of multiple non-linear interactions. This method identified up to seven functional groupings in the cortico-subcortical motor circuit of the basal ganglia, clusters that showed significant changes in the parkinsonian brain. However, the Multiple Correspondence Analysis also has limitations. It does not offer the possibility of carrying out a statistical evaluation of the results (a circumstance that it shares with other techniques such as independent component analysis), and can only identify a limited number of functional groupings (7 groupings in our study). For this reason we have developed a new technique that allows the identification of multiple functional interactions (without the limit showed by the Multiple Correspondence Analysis) in brain centers with non-linear relationships, and that check these interactions through a proper statistical contrast. With this new technique we have identified more than 16 functional groupings in the activity of the basal ganglia. We are presently proceeding to determine the effect of Parkinson’s disease in these functional groupings.

**KEYWORDS**

Basal ganglia, astrocytes, dopaminergic vulnerability, neuroinflammation, functional neuroimaging.

PRINCIPAL INVESTIGATOR
Tolosa Sarró, Eduard

LIST OF PERSONNEL
Compta Hirnyj, Yaroslav. PhD.
Ezquerra Trabalón, Mario. PhD.

Fernández Sánchez, Manuel. Technician.
Gaig Ventura, Carlos. PhD.
Garrido Pla, Alicia. PhD.
Iranzo de Riquer, Alejandro. PhD.
Junqué Plaja, Carmen. PhD.
Maragall Moreno, Laura. Auxiliar Administrativo.
Marti Doménech, Maria

José. PhD.
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Simonet Hernández, Cristina. Bachelor degree.
Valdeoriola Serra, Francesc. PhD.
Vilas Rolán, Dolores. Bachelor degree.

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ABSTRACT
In 2018 we continued our research on clinical and biological aspects of LRRK2-associated Parkinson’s disease (LRRK2-PD) which include results on microRNA alterations in iPSC-derived dopaminergic neurons from LRRK2-PD and sporadic PD (Neurobiol Aging; Tolosa et al., 2018), characterization of mitochondrial function in a cell model of LRRK2-PD (J Transl Med, Juárez-Flores et al., 2018), a study of candidate genetic modifiers of age at onset in LRRK2-PD (Mov Disord, Fernandez-Santiago et al., 2018).

We have described the lack of central and peripheral nervous system synuclein pathology in R1441G LRRK2-PD, unlike the case of G2019S LRRK2 mutations (JNNP, Vilas et al., 2018) and studies on the traits associated to healthy carriers of LRRK2 mutations (Mov Disord; Mestre et al., 2018).

We are currently working towards deepening our knowledge of existing models of PD epigenetic alterations by using iPSC-DAn models and patient blood samples, work on miRNA/RNA prognostic and diagnostic biomarkers in blood, serum and cultured pri-
mary fibroblast of parkinsonisms (MSA, idiopathic PD, LRRK2-PD, healthy controls) (work in progress). We have described reduced levels of Q10 in multisystem atrophy (MSA) (Compta et al., Park Rel Dis 2018) and initiated recruitment of patients for the collection of CSF and brain MRI images in MSA patients. Experiments with the protein cyclic amplification method RTQuIC for synuclein have been initiated in our lab (IPIs: Dr. Y. Compta y Dra. M.J. Martí) using both CSF and brain tissue. We have also contributed to the International DLB consortium (Lancet Neurol, Guerreiro et al., 2018) and, in the field of experimental therapeutics described the effects of subthalamic and substantia nigra pars reticulata deep brain stimulation upon the gait of patients with PD (Park Rel Dis, Valdeoriola et al., 2018).

The research line MRI of the neuroanatomical and neurofunctional bases of cognitive impairment in PD, led by Dr C. Junque and supported by two grants (MINECO PSI2017-86930 and Marato201423.10), provided evidence about the utility of MRI techniques to identify subtle degenerative changes in PD over time. MRI data-driven analyses techniques proved useful to detect subtypes of cortical atrophy even in de novo patients. (Park Re Dis, Uribe et al 2018) and we described that the gray/white matter contrast is an excellent MRI marker of ageing effects. Moreover, searching for variables sensitive to PD progression, we detected a differential vulnerability to hippocampal subfields atrophy in PD compared to normal ageing. (Frontiers in Aging Neuroscience, Uribe et al. 2018). In addition, we showed functional connectivity deficits in PD and found that connectivity threshold-free network-based statistics (TFNBS) is an appropriate technique for the statistical assessment of brain graphs (Hum Brain Mapping 2018 Baggio et al).

We report the neuroanatomical correlates of several visuospatial/visuoperceptual tests, as markers of cognition (J Intern Neuropsychol; Garcia Diaz et al. 2018; Park Rel Dis; Garcia Diaz et al, 2018) and the psychometric characteristics of the Spanish version of the UPSIT test (Arch Clin Neuropsychol; Campabadal et al. 2018,).

In studies published in 2018 year in journals including Lancet Neurology, Brain and Sleep, we shown that idiopathic REM sleep behavior disorder represents the prodromal phase of Parkinson disease, alpha-synuclein can be found in living subjects in the minor labial salivary glands and in the parotid gland, and we assessed the factors that determine its early conversion. We described in in conjunction with the PET center in Aahrus, extrastriatal monoaminergic involvement as well as microglial activation in the subjects with prodromal PD (Neurobiol Dis. 2018). In addition, we have continued characterizing anti-IgLON5 disease, a newly described tauopathy with prominent RBD and movement disorders.

KEYWORDS
Prodromal Parkinson; RBD, LRRK2; biomarkers, CSF, neuroimaging, multisystem atrophy, progressive supranuclear palsy
PUBLICATIONS 2018


Iranzo A. The REM sleep circuit and how its impairment leads to REM sleep behavior disorder. Cell and Tissue Research. 2018;373(1):245-266. PMID: 29846796.


Compta Y, Munoz E, Marti M.J. Ubiquinone, ubiquinol, 4-hydroxybenzoic acid... What ‘coenzyme Q10’ should we care about in multiple system atrophy?. Parkinsonism and Related Disorders. 2018;50:117-118. PMID: 29433994.


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**RESEARCH PROJECTS 2018**

**Code:** RD16/0011.

**Title:** Red de Terapia Celular.

**Principal investigator:** Isabel Farinas.

**CIBERNED’s collaboration:** Yes.

**CIBERNED groups:** G607; G301; G102; G113; G208; G105; G207.

**Other CIBER’s collaboration:** No.

**Type:** Nacional.

**Funding agency:** Instituto de Salud Carlos III.

**Funding:** 284999. **Duration:** 2016-2020.
Title: Combined protective/restorative cell-mediated strategies for neurodegenerative diseases.
Principal investigator: Jose Luis Labandeira Garcia.
CIBERNED’s collaboration: Yes.
CIBERNED groups: G208; G102; G113; G105; G207.
Other CIBER’s collaboration: No.
Type: Nacional.
Funding agency: Instituto de Salud Carlos III.

Code: PI2016/06.
Title: Identificacion de vias fisiopatologicas y biomarcadores candidatos en la fase pre-diagnostica de la enfermedad de Parkinson.
Principal investigator: Miquel Vila Bover.
CIBERNED’s collaboration: Yes.
CIBERNED groups: G109; G601; G207; G410. Other CIBER’s collaboration: No.
Type: Intramurales.
Funding agency: CIBERNED.

Title: 2017 SGR/1502.
Principal investigator: Maria Jose Marti Domenech.
CIBERNED’s collaboration: No.
CIBERNED groups: G207. Other CIBER’s collaboration: No.
Type: CCAA.
Funding agency: Generalitat de Catalunya.

Code: PI17/00096.
Title: Amplification of alpha-synuclein & 4R-tau auto-aggregation by RTQuIC in brain tissue and CSF as a differential biomarker of degenerative parkinsonisms.
Principal investigator: Maria Jose Marti/ Yaroslau Compta.
CIBERNED’s collaboration: No.
CIBERNED groups: G207. Other CIBER’s collaboration: No.
Type: Nacional.
Funding agency: Instituto de Salud Carlos III.

Title: Catalan Network of Multiple System Atrophy: Biomarkers and Pathophysiology.
Principal investigator: Maria Jose Marti Domenech.
CIBERNED’s collaboration: No.
CIBERNED groups: G207. Other CIBER’s collaboration: No.
Type: Privado.
Funding agency: Fundacio La Marato de TV3.

Title: FAIR-PARK-II A multicentre, parallel group, randomized, placebo-controlled trial of
deferiprone (DFP) 15 mg/kg BID.
**Principal investigator:** Yaroslau Compta Hirnjy.
**CIBERNED’s collaboration:** No.
**CIBERNED groups:** G207. **Other CIBER’s collaboration:** No.
**Type:** Europeo.
**Funding agency:** Comision Europea.
**Funding:** 282452. **Duration:** 2016-2021.

**Code:** MJFF _DYSK_2014.
**Title:** Gene-gene interaction analysis of the mTOR pathway in L-DOPA induced dyskinesia’.
**Principal investigator:** Maria Jose Marti Domènech, Cristina Malagelada.
**CIBERNED’s collaboration:** No.
**CIBERNED groups:** G207. **Other CIBER’s collaboration:** No.
**Type:** Internacional.
**Funding agency:** Michael J. Fox Foundation.
**Funding:** 125000. **Duration:** 2015-2018.

**Code:** ID11849.
**Title:** LRRK2 peripheral blood mononuclear cells and urine biosample collection’.
**Principal investigator:** Maria Jose Marti Domenech, Eduardo Tolosa.
**CIBERNED’s collaboration:** No.
**CIBERNED groups:** G207. **Other CIBER’s collaboration:** No.
**Type:** Internacional.
**Funding agency:** Michael J Fox Foundation.
**Funding:** 138506. **Duration:** 2016-2018.

**Code:** FUNDTATIANA16_PROY03.
**Title:** MicroRNAs as biomarker of conversion of REM behaviour disorder to Parkinson’s disease.
**Principal investigator:** Mario Ezquerra Trabalon.
**CIBERNED’s collaboration:** No.
**CIBERNED groups:** G207. **Other CIBER’s collaboration:** No.
**Type:** Privado.
**Funding agency:** Fundacion Tatiana Perez de Guzman el Bueno.
**Funding:** 77000. **Duration:** 2018-2018.

**Code:** 0002018.
**Title:** MicroRNAs AS BIOMARKERS OF THE PRODROMAL STAGE OF PARKINSON DISEASE(EX-PANSION OF microRNA FINDINGS TO ASHKENAZI JEWS PD COHORTS).
**Principal investigator:** Mario Ezquerra Trabalon; Ruben Fernandez Santiago.
**CIBERNED’s collaboration:** No.
**CIBERNED groups:** G207. **Other CIBER’s collaboration:** No.
**Type:** Internacional.
**Funding agency:** Michael J Fox Foundation.
**Funding:** 185803,06. **Duration:** 2018-2019.

**Code:** TAPP - Telematic Applications in Medicine.
**Title:** Prediction of cognitive properties of new drug candidates for neurodegenerative diseases in early clinical development. Acronym: PHARMACOG.
**Principal investigator:** Carme Junque.
CIBERNED’s collaboration: No.
CIBERNED groups: G207. Other CIBER’s collaboration: No.
Type: Intramurales.
Funding agency: Comision Europea.

Code: SAF2015-73508-JIN.
Title: The beginnings of Parkinson Disease: a study of early disease mechanisms in a humanized in-vitro model.
Principal investigator: Ruben Fernandez-Santiago.
CIBERNED’s collaboration: No.
CIBERNED groups: G207. Other CIBER’s collaboration: No.
Type: Nacional.
Funding agency: MICINN.

Code: 00000.
Title: The Parkinson’s Progression Markers Initiative (PPMI).
Principal investigator: Eduardo Tolosa.
CIBERNED’s collaboration: No.
CIBERNED groups: G207. Other CIBER’s collaboration: No.
Type: Internacional.
Funding agency: Michael J Fox Foundation.
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PRINCIPAL INVESTIGATOR
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PhD.

Defterali, Cagla. Bachelor degree.

Díaz Guerra, Eva.
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Nieto Estévez, Vanesa.
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Fernández Rodríguez, Pablo.
Bachelor degree.

Oueslati Morales, Carlos Omar.
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Román Alonso, María José.
Bachelor degree.

ABSTRACT
1. My research group has deposited in the Spanish National Bank of Stem Cell Lines (BNLC) of the ISCIII, 9 lines of induced pluripotent stem cells (iPS cells or iPSCs) derived from Parkinson’s disease patients (4 lines), from Alzheimer’s disease patients (2 lines) and from healthy subjects (3 lines). The generation (by reprogramming human fibroblasts) and characterization of all the iPSC lines has required an extraordinary effort, as each deposit document consists of 7-8 figures with results. I would like to emphasize that these results have been evaluated by the Technical Committee of the BNLC, which has considered that our iPSC cells comply with all the quality parameters required nationally and internationally. The documents justifying the generation and characterization of the 9 lines of iPSCs have been published on the WEB page http://www.isciii.es/ISCIII/es/contenidos/fd-el-instituto/fd-organizacion/fd-estructura-directiva/fd-subdireccion-general-investigacion-terapia-celular-medicina-regenerativa/fd-centros-unidades/fd-banco-nacional-lineas-celulares/fd-lineas-celulares-disponibles/lineas-de-celulas-iPS.shtml.

We are currently writing the corresponding articles (manuscripts in preparation) (E. Rodríguez-Traver, ..., C. Vicario; E. Díaz-Guerra, ..., C. Vicario).

2. We have made significant progress in the study of the effects of N370S and L444P...
mutations in the GBA1 gene on dopaminergic neurons derived from iPS cells of Parkinson’s patients. The results obtained with the participation of Dr. Rosario Moratalla’s research group (Cajal Institute-CSIC and CIBERNED), have been presented (as both oral communication and poster) in the VI International Congress of Research and Innovation in Neurodegenerative Diseases CIIEN (E. Rodríguez-Traver, ..., C. Vicario, 2018) and we are preparing the corresponding article. In addition and in collaboration with Dr. Moratalla, we have published a commentary-article in the journal Autophagy (P. García-Sanz, ..., C. Vicario, R. Moratalla, 2018).

3. We have also made great progress in studying the effects of familial Alzheimer’s and sporadic Alzheimer’s on astrocytes and neurons obtained by differentiating our iPSCs. Specifically, we are studying the phenotypes caused by the APOE gene alleles and by the G206D mutation in the PRESEN1 gene, in collaboration with Dr. Moratalla. Some of the new results have been presented (as a poster) in the VI International Congress of Research and Innovation in Neurodegenerative Diseases CIIEN (E. Díaz-Guerra, ..., C. Vicario, 2018) and we are preparing the corresponding article. A Master Project (TFM) has been successfully defended. We participate in the European project ADAPTED, funded in the IMI call, in which we collaborate with Dr. Agustín Ruiz (Fundació ACE), among other researchers. The generation of isogenic iPSCs has been presented at the IMI 10th Anniversary Scientific Symposium held in Brussels under the title “An iPSC technology development collaboration - a critical component to enable ADAPTED” (P. Reinhardt and B. Schmid, ..., C. Vicario, ..., A. Ruiz, 2018).

4. We have completed the characterization of local neural stem / progenitor cells of the adult mouse olfactory bulb and demonstrated its neurogenic potential in vivo (Defterali et al., manuscript in preparation).

5. We have completed a study on the effects of the neurotrophins BDNF and NT-3 on the differentiation and maturation of olfactory bulb interneurons (Nieto-Estévez et al., manuscript in preparation).

6. We are studying the role of IGF-I factor (specifically, that synthesized in the brain) in the induction of hippocampal Long-Term Potentiation and in the behavior of a conditional IGF-I knockout mouse, in collaboration with Drs. Gertrudis Perea (Cajal Institute-CSIC) and Ignacio Torres Alemán (Cajal Institute-CSIC and CIBERNED). In order to find possible molecular targets of IGF-1, we are conducting proteomic analyzes in the olfactory bulb and hippocampus, in collaboration with Dr. Enrique Santamaría (Navarrabiomed, Pamplona).

KEYWORDS
iPS cells, neural stem cells, Parkinson’s disease, Alzheimer’s disease, adult neurogenesis, olfactory bulb, hippocampus, IGF-1.

PUBLICATIONS 2018
RESEARCH PROJECTS 2018

Title: Potencial patológico de los astrocitos: una nueva perspectiva en la enfermedad de Alzheimer.
Principal investigator: Joan X. Comella.
CIBERNED’s collaboration: Yes.
CIBERNED groups: G413; G415; G204; G108; G411.
Other CIBER’s collaboration: No.
Type: Intramurales.
Funding agency: CIBERNED.

Title: Efecto de las mutaciones del gen glucocerebrosidasa-1 en neuronas derivadas de células iPS de enfermos de Parkinson. Rescate del fenotipo y trasplante celular. Area: Terapia celular en enfermedades neurodegenerativas.
Principal investigator: Carlos Vicario Abejón.
CIBERNED’s collaboration: Yes.
CIBERNED groups: G204; G108. Other CIBER’s collaboration: No.
Type: Privado.
Funding agency: Fundacion Ramon Areces.

Title: Alzheimer’s Disease Apolipoprotein Pathology for Treatment Elucidation and Development.
Principal investigator: Carlos Vicario Abejón.
CIBERNED’s collaboration: No.
CIBERNED groups: G108. Other CIBER’s collaboration: No.
Type: Europeo.
Funding agency: Comision Europea.

Code: SAF2016-80419-R.
Title: Regulacion de la multipotencialidad de celulas madre neurales humanas y la neurogenesis en modelos de Alzheimer esporadico y Alzheimer familiar.
Principal investigator: Carlos Vicario Abejón.
CIBERNED’s collaboration: No.
CIBERNED groups: G108. Other CIBER’s collaboration: No.
Type: Nacional.
Funding agency: MICINN.

PHD DISSERTATIONS 2018

Author: Manuel Antonio Oria Muriel.
Title: Caracterización de una línea de iPSCs humanas con una mutación en Presenilina1 como modelo celular para el estudio de la enfermedad de Alzheimer familiar.
Date: 24/9/2018. Supervisor: Carlos Vicario Abejón.
ABSTRACT

In 2018 we have developed a new therapeutic strategy to selectively decrease the brain levels of α-synuclein in vivo selectively within monoaminergic neurons, the type of neurons most susceptible to neurodegeneration in Parkinson’s disease (PD). This technique is based on the intranasal administration of chemically-modified oligonucleotides. In addition, we have shown that PD-derived peripheral α-synuclein aggregates are not pathogenic when injected into the brains of experimental animals. We have also described a neuroprotective role of transcription factor EB (TFEB) in a neurotoxic model of PD and demonstrated that the beneficial effect of TFEB goes beyond the activation of autophagy and implies a neurotrophic effect on dopaminergic neurons.
KEYWORDS
Parkinson’s disease, α-synuclein, TFEB

PUBLICATIONS 2018


RESEARCH PROJECTS 2018

Code: PI2016/06.
Title: Identificacion de vias fisiopatologicas y biomarcadores candidatos en la fase pre-diagnóstica de la enfermedad de Parkinson.
Principal investigator: Miquel Vila Bover.
CIBERNED's collaboration: Yes.
CIBERNED groups: G109 ; G601; G207; G410. Other CIBER's collaboration: No.
Type: Intramurales.
Funding agency: CIBERNED.

Code: SAF2016-77541-R.
Title: Diagnostic and therapeutic potential of neuromelanin in Parkinson’s disease using novel humanized preclinical in vivo model.
Principal investigator: Miquel Vila Bover.
CIBERNED's collaboration: No.
CIBERNED groups: G109 . Other CIBER's collaboration: No.
Type: Nacional.
Funding agency: MICINN.

Code: COEN4016.
Title: Focused ultrasound modulation of neuromelanin accumulation in a humanized rat model of Parkinson’s disease.
Principal investigator: Miquel Vila Bover.
CIBERNED's collaboration: No.
CIBERNED groups: G109 . Other CIBER's collaboration: No.
Type: Europeo.
Funding agency: Comision Europea.

Code: 2017 SGR 1806.
Title: Grup de Recerca Consolidat-Malalties Neurodegeneratives.
Principal investigator: Miquel Vila Bover.
CIBERNED's collaboration: No.
CIBERNED groups: G109 . Other CIBER's collaboration: No.
Type: CCAA.
Funding agency: Generalitat de Catalunya.

Code: P17/00496.
Title: La disfuncion autofagica/lisosomal en la enfermedad de Parkinson: caracterizacion y desarrollo de nuevas estrategias traslacionales con el lisosoma como diana terapeutica.
Principal investigator: Marta Martinez Vicente.
CIBERNED's collaboration: No.
CIBERNED groups: G109 . Other CIBER's collaboration: No.
Type: Nacional.
Funding agency: Instituto de Salud Carlos III.
Code: Fundacio Marato de TV3-Malalties del cor (320/U/2015).
Title: New molecular functions of apoptotic genes in cardiac development and stress.
Principal investigator: Daniel Sanchis Morales.
CIBERNED’s collaboration: No.
CIBERNED groups: G109 . Other CIBER’s collaboration: No.
Type: Privado.
Funding agency: Fundacio La Marato de TV3.

Code: SAF2015-73997-JIN.
Title: The Gut-Brain axis in Prodromal Parkinson’s disease: new possibilities for risk/diagnostic biomarkers and therapeutic interventions.
Principal investigator: Ariadna Laguna Tuset.
CIBERNED’s collaboration: No.
CIBERNED groups: G109 . Other CIBER’s collaboration: No.
Type: Nacional.
Funding agency: MICINN.

Title: Therapeutic target of GCase enzyme in Parkinson’s disease with novel pharmacological chaperones.
Principal investigator: Marta Martinez Vicente.
CIBERNED’s collaboration: No.
CIBERNED groups: G109 . Other CIBER’s collaboration: No.
Type: Internacional.
Funding agency: Michael J Fox Foundation.

Code: PMP15/00025.
Title: A precise approach for nucleoside-based therapy of neuromuscular disorders with defects in mitochondrial dna.
Principal investigator: Miguel Angel Martin Casanueva.
CIBERNED’s collaboration: No.
CIBERNED groups: G109 . Other CIBER’s collaboration: CIBERER.
Type: Nacional.
Funding agency: MICINN.

PHD DISSERTATIONS 2018

Author: Sandra Franco Iborra.
Title: Mitochondrial quality control in neurodegenerative diseases: focus on Parkinson’s disease and Huntington’s disease.
PROGRAM 3

AMYOTROPHIC LATERAL SCLEROSIS AND OTHER NEUROMUSCULAR DISORDERS
Neuromuscular diseases (NMDs) form a heterogeneous group of pathologies affecting the spinal cord and its tracts, nerve roots as well as motor and sensitive peripheral nerves, the neuromuscular junction and the muscles. Diagnosis involves using sophisticated methods covering: neurophysiological studies, muscle or nerve biopsy with the use of immunohistochemical techniques and some others, metabolic analysis and tests, MRI studies, quantitative muscle assessment, and in many cases, genetic studies.

Just a few epidemiological studies are available in Spain, from which it can be inferred that the prevalence of chronic neurodegenerative and/or hereditary pathology would account for around 60,000 patients throughout the whole country.

The main research topics in this line focus on the following aspects:

- Clinical characterization of neuromuscular pathologies and correlation between the clinical phenotype and their genotype (or proteomic characterization).
- Development of animal models based on the genotypically identified dystrophies.
- Research on the physiopathology of neuromuscular diseases.
- Development of new therapeutic strategies.

Program 3 is coordinated by Drs. Rafael Fernández Chacón (University of Seville) and Adolfo López de Munain Arregui (Biodonostia Research Institute, San Sebastián).
Our research project is focused on the investigation of the molecular mechanisms involved in the maintenance of the structure and function of synaptic terminals which integrity can be compromised in neurodegenerative diseases. Most of our studies are based on the generation and/or phenotypic analysis of genetically modified mice with modifications in genes that encode for co-chaperones (CSPα, CSPγ), proteins of the synaptic vesicle cycle or express proteins with pathogenic mutations in humans such as mutations L115R and L116Del in Dnajc5 (that encodes for CSPα) which cause adult neuronal ceroidal lipofuscinosis or the G2019S mutation in LRRK2 associated with Parkinson’s disease. Our molecular, structural and functional studies are normally carried out in primary cultures of different cell types and slices of mouse brain. An important part of our recent investigations are based on a new line of mice in which Dnajc5 is floxed. This novel mouse line is allowing us to study the function of CSPα in specific neuronal and cell types by using different mouse lines that express cre-recombinase protein under specific promoters. One of these lines (Sox2CreERT2) has allowed us to show in vivo that the absence of CSPα in neural stem cells of the hippocampus interferes with the quiescence of these cells, increases the percentage of proliferating cells and compromises the size of the stem cell pool (submitted to Proc Natl Acad Sci USA).
This line of research is being reinforced by our collaboration with Dr. Isabel Fariñas. Our observations in neurogenesis have led us to investigate the molecular mechanisms of a previously unsuspected relationship between CSPα and the mTOR pathway (mechanistic target of rapamycin), a key route in the regulation of cell growth and nutrient-dependent metabolism and growth factors and involved in autophagy and cell proliferation. Within our CIBERNED project, we have also considered the use of new viral vectors that cross the blood-brain barrier to investigate the possibilities of therapeutic intervention to rescue neurodegenerative phenotypes associated with the absence of CSPα. Part of this project has been selected by the Tatiana Perez de Guzman el Bueno Foundation in a proposal that also includes the use of two-photon microscopy (2P) to monitor functional changes in neural circuits in the context of the dysfunction / synaptic degeneration and recovery after rescue in lines in which CSPα has been eliminated in specific neurons. On the other hand, we have also designed new constructions based on fluorescent reporters to monitor brain synaptic activity with 2P in vivo. Importantly, this year our collaboration with the group of Dr. Lucas Lozano has advanced very well leading to the publication of findings of great interest related to the molecular basis of autistic spectrum disorder (ASD) (Parras et al., Nature, 560:441-446 (2018)).

**KEYWORDS**

Synapse, synaptic vesicle cycle, hippocampus, neurogenesis, neuronal ceroid lipofuscinosis, single-cell sequencing, transcriptomic, skeletal muscle.

**PUBLICATIONS 2018**


RESEARCH PROJECTS 2018

Code: PI2015-2/06.
Title: Molecular mechanisms of brain and muscle stem cell function in aging and neurodegeneration.
Principal investigator: Pura Munoz Canoves.
CIBERNED’s collaboration: Yes.
CIBERNED groups: G604; G102; G606; G111; G306.
Other CIBER’s collaboration: No.
Type: Intramurales.
Funding agency: CIBERNED.

Code: BFU2016-76050-P.
Title: Mecanismos Moleculares del Mantenimiento a Largo Plazo de las Sinapis Glutamatergicas in Vivo.
Principal investigator: Rafael Fernandez-Chacon.
CIBERNED’s collaboration: No.
CIBERNED groups: G606. Other CIBER’s collaboration: No.
Type: Nacional.
Funding agency: MICINN.

PHD DISSERTATIONS 2018

Author: José Antonio Martínez López.
Title: Presynaptic calcium dynamics, neuronal excitability and synaptic vesicle cycle in central synapses lacking Cysteine String Protein-alpha (CSP-alpha).
Date: 22/9/2018. Supervisor: Rafael Fernández Chacón.
601 | Jon Infante Ceberio

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Peripheral Neuropathies

Our investigation has continued been focused on Charcot-Marie-Tooth disease (CMT) and Guillain-Barré syndrome (GBS), which will be analyzed separately. In a collaborative paper, we have defined the phenotype associated with homozygous MME mutations, which is characteristically included in AR-CMT2 of adult onset. Our contributions to intermediate CMT have resulted in a significant revision of the syndrome in the OMIM catalogue (cf. Cassandra L. Kniffin: 02/20/2018), and in the phenotypic re-definition of CMT associated to heterozygous GNB4 mutations causing not an intermediate but an axonal syndrome. We have reported the potential pathogenic role of endoneurial inflammatory oedema in CMT1A.

We have established that the physiological background of normorreflexia in CANVAS (Cerebellar ataxia, neuropathy, vestibular areflexia syndrome) is preservation of fibres Ia in the hallmark of a severe somatic sensitive deficit. Likewise, selective involvement of Ia fibres may be of help for detecting reversible conduction failure in early GBS. We have updated the pathophysiology of axonal damage and the role of proximal nerve trunk lesions in early GBS; this allowed us to revisit the great legacy by Haymaker and Kernohan (Medicine 1949; 28: 50-141). We have proposed a new mechanism of nerve trunk pain that might be an inaugural manifestation in any GBS subtype. Our interpretation of initial semeiology of Franklin Delano Roosevelt’s acute paralytic disease, August 1921, has been helpful in establishing that the future US President suffered from not paralytic polio but GBS. We have proposed that in acute flaccid myelitis (AFM) there may be distal motor axonopathy, a fact suggesting the pathogenic relationship between AFM and GBS. We have continued collaborating in the IGOS study (International Guillain-Barré Outcome Study).

Parkinson’s disease

We have replicated in a multicentric study, together with the Hospital Clinic in Barcelona, the association of a SNP in SNCA gene with the penetrance of the LRRK2 G2019S mutation in Spanish population. This polymorphism has an influence in the age of onset of this form of genetic Parkinson’s disease (PD), unlike the SNP rs2421947 of DMN3 gene, as it had been reported previously by other authors. In collaboration with the International Parkinson’s Disease Genomic Consortium an exome sequencing of 2835 PD patients, 5343 controls and 111 pathologically confirmed cases of Lewy body dementia (LBD) has been carried out. This study doesn’t support a pathogenic role of genetic variants in LRP10 in PD or LBD. We are undertaking an ambitious project searching for multimodal biomarkers in a large cohort of carriers of the LRRK2 G2019S mutation to deepen knowledge in prodromal Parkinson’s disease.

Ataxias

The results of survival at 10 years from the EUROSCA longitudinal cohort, a multicentric international study that includes 525 patients with the most frequent forms of dominant ataxias (SCA1, 2, 3 and 6) have been recently published, yielding the following figures: 57%, 74%, 72% y 87%, respectively. Within the same study, after a follow-up of 8 years, patients’ reported outcome measures have been evaluated, showing that they provide relevant complementary information to that obtained from neurological scales. The results from both studies have a direct application for the design of coming clinical trials.

Alzheimer’s disease

We have started the project “Valdecilla Cohort for Memory and Brain Aging” whose purpose is to set up a cohort with a large sample of volunteers cognitively healthy volunteers.
Neuropsychology: During 2017 we carried on the neuropsychological description of one of the largest series of right semantic dementia patient. Three manuscripts have been written based on these data, as part of Ana Pozueta’s doctoral thesis.

Genetics: Within the multicenter project PI16/01652. “Study of rare variants in genes associated with Alzheimer’s disease in the Spanish population” we have gathered a population of 772 DNA samples from Spanish patients with early-onset Alzheimer’s, which is one of the main samples studied to date. The study, funded by the Instituto de Salud Carlos III and whose PI and coordinator is Pascual Sánchez-Juan, is the first large project of DEGESCO (DEmentia gEnetics Spanish COnsortium) for a large-scale genomic study of dementias in the Spanish population. Within the international study of Alzheimer’s genomics IGAP, it is worth mentioning our participation in its latest publication in Nature Genetics: “Genetic meta-analysis of diagnosed Alzheimer’s disease identifies new risk loci and implicates Aβ, tau, immunity and lipid processing.

Biomarkers: In 2018, a manuscript was published in the Journal of Alzheimer’s Disease in which we evaluated the extensive experience of the Cognitive Impairment Unit in the clinical use of amyloid PET. Also during this year it is worth mentioning an editorial in the journal N Engl J Med in connection with our project “MicroRNA Profile in Patients with Alzheimer’s Disease” funded by CIBERNED, for the study of the diagnostic value of the determination of these structures in CSF both free and exosomes and whose results were published in 2017 in the Journal of Alzheimer’s Disease.

Amyotrophic lateral sclerosis (ALS)

Regarding ALS epidemiology, we have published two reviews discussing the role of environmental factors (Riancho et al, Int J Biomet 2018) and infectious agents (Castanedo-Vazquez et al, J Neurol 2018) in the disease. We have continued with our scientific collaborations: i) Professor Ana Maria Cuervo (Albert Einstein College of Medicine, New York) focused on the role of autophagy in ALS; ii) Biopharma-University of Santiago de Compostela devoted to the identification of new Retinoid X Receptor agonists as a new potential therapy for ALS (Riancho et al, JAMA Neurol 2018) and iii) Professor Adolfo López de Munain (Biodonostia Research Institute-CIBERNED, San Sebastian) focused in the investigation of new biomarkers for ALS. In this line we have identified several lipidomic disturbances in ALS patients (Fernandez de Eulate G et al, Neurology, submitted). Our group has recently collaborated in the creation of the first Spanish ALS consortium (ALSGESCO)

Cell neurobiology

Our work has focused in two research topics: i) dysfunction of RNA metabolism in motor neurons (MNs) of the murine SMNΔ7 model of Type I spinal muscular atrophy (SMA), and ii) DNA damage processing in neurons and its relevance in neurodegeneration. Regarding the first point, survival motor neuron (SMN) deficiency in MNs from the SMA mice interferes with mRNA processing, particularly pre-mRNA splicing. As a result, intron-containing and incorrectly processed polyadenylated mRNAs are retained in poly(A) RNA granules that also concentrate the splicing regulator Sam68. As a consequence, MNs undergo an important déficit in mRNA processing and translation that severely impacts on SMA pathogenesis. Concerning the second point, we have demonstrated in rat cortical neurons exposed to 4Gy of ionizing radiation that DNA damage processing takes place in a specific chromatin compartment and identified DNA sequences more vulnerable to DNA damage or refractory to DNA repair. Interestingly, some of these sequences are specifically involved in human neurodegenerative disorders.
KEYWORDS
CMT, Guillain Barré syndrome, LRRK2, ataxia, Spinal muscular atrophy, Alzheimer’s disease, Parkinson’s disease, ALS, Cajal bodies, nucleolus.

PUBLICATIONS 2018


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**RESEARCH PROJECTS 2018**

**Code:** PI2016/06.  
**Title:** Identificacion de vias fisiopatologicas y biomarcadores candidatos en la fase pre-diagnostica de la enfermedad de Parkinson.  
**Principal investigator:** Miquel Vila Bover.  
**CIBERNED’s collaboration:** Yes.  
**CIBERNED groups:** G109 ; G601; G207; G410.  
**Other CIBER’s collaboration:** No.  
**Type:** Intramurales.  
**Funding agency:** CIBERNED.  
**Funding:** 196000. **Duration:** 2016-2018.

**Code:** PREVAL 17/03 Carmen Lage Martinez.  
**Title:** Contrato Predoctoral IDIVAL-UC.  
**Principal investigator:** Sanchez Juan, Pascual Jesus.  
**CIBERNED’s collaboration:** No.  
**CIBERNED groups:** G601. **Other CIBER’s collaboration:** No.  
**Type:** Intramurales.  
**Funding agency:** IDIVAL.  
**Funding:** 65688. **Duration:** 2017-2021.
Title: Diseño de estructuras biopolímericas funcionalizadas con grafeno para el desarrollo de cultivos neuronales en modelos celulares de patología de la motoneurona.
Principal investigator: Olga Tapia Martinez.
CIBERNED’s collaboration: No.
CIBERNED groups: G601. Other CIBER’s collaboration: No.
Type: Intramurales.
Funding agency: IDIVAL.

Code: NVAL16/21.
Title: Diseño de nuevas moléculas para el tratamiento de la esclerosis lateral amiotrófica-Innopharma.
Principal investigator: Javier Riancho.
CIBERNED’s collaboration: No.
CIBERNED groups: G601. Other CIBER’s collaboration: No.
Type: Intramurales.
Funding agency: IDIVAL.

Code: NVAL17/22.
Title: Efecto del déficit del factor de supervivencia de las neuronas motoras (SMN) sobre la organización estructural y molecular de los compartimentos nucleares implicados en la biogénesis de RNPs espicesomales y en el procesamiento de RNAs: estudio experimental.
Principal investigator: Olga Tapia Martinez.
CIBERNED’s collaboration: No.
CIBERNED groups: G601. Other CIBER’s collaboration: No.
Type: Intramurales.
Funding agency: IDIVAL.

Code: NVAL 16/21.
Title: Enfermedad de Alzheimer y síndrome de Down. Una aproximación clínica y experimental.
Principal investigator: Javier Riancho.
CIBERNED’s collaboration: No.
CIBERNED groups: G601. Other CIBER’s collaboration: No.
Type: Intramurales.
Funding agency: IDIVAL.

Code: PI17/00936.
Title: Estudio de biomarcadores motores, genéticos y de imagen en la enfermedad de Parkinson prodromica asociada a la mutación G2019S de LRRK2.
Principal investigator: Jon Infante.
CIBERNED’s collaboration: No.
CIBERNED groups: G601. Other CIBER’s collaboration: No.
Type: Nacional.
Funding agency: Instituto de Salud Carlos III.
**Code:** PI16/01652.
**Title:** Estudio de variantes raras en genes asociados a Enfermedad de Alzheimer en población española.
**Principal investigator:** Pascual Sanchez Juan.
**CIBERNED’s collaboration:** No.
**CIBERNED groups:** G601. **Other CIBER’s collaboration:** No.
**Type:** Nacional.
**Funding agency:** Instituto de Salud Carlos III.
**Funding:** 139150. **Duration:** 2017-2019.

**Code:** ESMI.
**Title:** European Spinocerebellar Ataxia Type 3/Machado Joseph disease initiative.
**Principal investigator:** Thomas Klockgether.
**CIBERNED’s collaboration:** No.
**CIBERNED groups:** G601. **Other CIBER’s collaboration:** No.
**Type:** Europeo.
**Funding agency:** JPND.
**Funding:** 3000. **Duration:** 2016-2019.

**Code:** IGOS.
**Title:** International Guillain-Barre syndrome outcome study (IGOS).
**Principal investigator:** Bart Jacobs.
**CIBERNED’s collaboration:** No.
**CIBERNED groups:** G601. **Other CIBER’s collaboration:** No.
**Type:** Internacional.
**Funding agency:** Erasmus Medical Center.
**Funding:** ND. **Duration:** 2012-2019.

**Code:** BFU2017-84046P.
**Title:** Papel del dano en el DNA y de la reorganización epigenética del DNA y de las histonas como determinantes del destino de las células progenitoras del esqueleto de las extremidades.
**Principal investigator:** Juan Antonio Montero Simón y Juan Hurle González.
**CIBERNED’s collaboration:** No.
**CIBERNED groups:** G601. **Other CIBER’s collaboration:** No.
**Type:** Nacional.
**Funding agency:** MICINN.
**Funding:** 199650. **Duration:** 2018-2020.

**Code:** COOPADIS.
**Title:** Proyecto COOPADIS (Cohort of patients with Parkinson’s disease in Spain, 2015).
**Principal investigator:** Diego Santos.
**CIBERNED’s collaboration:** No.
**CIBERNED groups:** G601. **Other CIBER’s collaboration:** No.
**Type:** Privado.
**Funding agency:** ABBVIE, ACEBRE, ALTER, ASOCIACIÓN PARKINSON ARAGÓN, ASOCIACIÓN PARKINSON PALENCIA, ASOCIACIÓN PARKINSON VALENCIA, AYUNTAMIENTO DE A CORUÑA, CLIMANOSA, CONSTRUDECO NORTE, FEDERACION GALLEGOS ATLETISMO, ESTEVE, LUND-BECK, QUALIGEN, UCB PHARMA, VALENCIA CONCIE.
**Funding:** 2557,38. **Duration:** 2016-2021.
Code: SMA Europe Call 8 grant application.
Title: Regulation of the survival motor neuron (SMN) protein by acetylation and its importance in snRNP biogenesis and molecular assembly of Cajal bodies.
Principal investigator: Olga Tapia Martinez.
CIBERNED’s collaboration: No.
CIBERNED groups: G601. Other CIBER’s collaboration: No.
Type: Europeo.
Funding agency: SMA Europe.

Code: Tau Consortium (UCSF, USA) 2016.
Title: Tau Consortium.
Principal investigator: Suzee Lee.
CIBERNED’s collaboration: No.
CIBERNED groups: G601. Other CIBER’s collaboration: No.
Type: Internacional.
Funding agency: UCSF.
**PRINCIPAL INVESTIGATOR**
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ABSTRACT

PARKINSON DISEASE

Main research lines:
1. Genetics and pre-motor markers of PD. The studies are focused on patients with the LRRK2 R1441G mutation (frequent in the Basque Country) and asymptomatic carriers, which allows to know pre-motor biomarkers of PD: clinical, molecular and imaging (DATSCAN and RM) as well as its evolutional behavior.
2. Design of compounds with kinase inhibitory activity and drug testing models
3. Clinical trials
4. Frontotemporal dementia. The group continues working on the cohort of patients with DT secondary to mutations in progranulin as well as on carriers, focusing their study on the search for progression biomarkers as well as the study of lysosomal function whose alteration seems to be the cause of the clinical manifestations. The group studies various known targets and works in the design of their modulators using as models immortalized cells of patients and Drosophila.

NEUROMUSCULAR DISORDERS

The group is composed by neurologists, neuropsychologists and biologists who develop a comprehensive approach to neuromuscular pathology from a clinical and basic aspect (including ELA and hereditary-based muscular diseases), as well as on the role of the muscle in the metabolic control and its influence on the development of central phenomena associated with aging (brain proteinopathies and aging).

Main research lines:
1. Myotonic dystrophy. The group continues studying aging mechanisms linked to the disease and its clinical consequences. There is an established collaboration to develop chemical compounds to act on the disease and to design phase I clinical trials and test them along with other groups.
2. Duchenne dystrophy. Study of alterations in calcium homeostasis and its rescue with compounds targeting ryanodine receptor stability. The study has resulted in a patent for a serial of compounds called generically AHULKEN. A company has been created for its preclinical development: MIRAMOON PHARMA (www.miramoonpharma.com). This study has been extended to test the therapeutic potential on the cardiac manifestations of the disease.
3. Facioscapulohumeral dystrophy. The group continues collaborating with other groups in the clinical characterization of cases with scapuloperoneal syndrome and methylation patterns. A researcher based in London will soon join the group to promote this line using CRISPR / Cas13 editing techniques in this disease.
4. Limb Girdle Dystrophy type 2 A. Study of the influence of calpain 3 in proliferation, differentiation and replacement of muscle satellite cells mechanisms, as well as the relationship with the extracellular matrix proteins. The group continues working on the study of calcium homeostasis and RER and also on the potential of CRISPR mediated gene editing, for both using corrected cells as a therapy and creating a pig animal model in collaboration with the University of Murcia. The group is also developing strategies for searching targets related to the functioning of myogenesis in the body as well as in the regulation of the Wnt pathway.
5. Amyotrophic Lateral Sclerosis. Recent incorporations have strengthened the current intraciber network. The group has already completed an intraciber research
The group will present another project in the next call. The results of this line will be published throughout 2019 and have opened multiple collaboration possibilities with other groups of CIBERER, as well as the design of therapeutic strategies whose development will be done together with the startup MIRAMOON Pharma. The group has joined ENCALS and takes part actively in other international ALS consortiums.

**KEYWORDS**

Parkinson Disease, frontotemporal dementia, cognitive impairment, LRRK2, progranulin, neuroinflammation, muscular dystrophies, calpain, biomarkers, neurogenetics, ALS, drug design.

**PUBLICATIONS 2018**


Etxeberria A, Iribar J, Rotaecho R, Vrotsou K, Barral I, Barral I. et al. Evaluation of an educational inter-


RESEARCH PROJECTS 2018

Code: PI2016/04. 
**Title:** The ALS CIBERNED Challenge: Accelerating New Drug Discovery. 
**Principal investigator:** Adolfo Lopez De Munain. 
**CIBERNED’s collaboration:** Yes. 
**CIBERNED groups:** G609 ; G303; G503; G408. **Other CIBER’s collaboration:** No. 
**Type:** Intramurales. 
**Funding agency:** CIBERNED. 
**Funding:** 200000. **Duration:** 2016-2018.

Code: DTS15/00141. 
**Title:** Evaluacion del impacto de la imagen PET de amiloide en el diagnostico de los pacientes con deterioro cognitivo evaluados por sospecha de Alzheimer. 
**Principal investigator:** Dr. Javier Arbizu. 
**CIBERNED’s collaboration:** Yes. 
**CIBERNED groups:** G504 ; G502; G609. **Other CIBER’s collaboration:** No. 
**Type:** Nacional. 
**Funding agency:** Instituto de Salud Carlos III. 
**Funding:** 59139. **Duration:** 2016-2018.

**Title:** Desarrollo de agentes terapeuticos basados en acidos nucleicos para el tratamiento de enfermedades neuromotoras y neuromusculares. 
**Principal investigator:** Ruben Lopez Vales. 
**CIBERNED’s collaboration:** Yes. 
**CIBERNED groups:** G607 ; G609. **Other CIBER’s collaboration:** No. 
**Type:** Nacional. 
**Funding agency:** MICINN. 
**Funding:** 204315. **Duration:** 2015-2018.

Code: ASAP. 
**Title:** Aligned and Standardized Neuroimaging in Atypical Parkinsonism. 
**Principal investigator:** Thilo Van Eimeren.
CIBERNED's collaboration: No.
CIBERNED groups: G609. Other CIBER's collaboration: No.
Type: Europeo.
Funding agency: Comision Europea.

Code: 2018222031.
Title: Alteraciones metabólicas y perturbaciones de orgánulos celulares en la fisiopatología de la esclerosis lateral amiotrófica.
Principal investigator: Ian Holt.
CIBERNED's collaboration: No.
CIBERNED groups: G609. Other CIBER's collaboration: No.
Type: CCAA.
Funding agency: Gobierno Vasco.

Code: BIO/ER/022.
Title: Análisis del papel de la Calpaina 3 en la regulación de las células satélite musculares.
Principal investigator: Adolfo Lopez De Munain.
CIBERNED's collaboration: No.
CIBERNED groups: G609. Other CIBER's collaboration: No.
Type: Privado.
Funding agency: Eitb Maratoia.

Code: FPU/04677.
Title: Beca Formacion de Profesorado Universitario (FPU) 2015.
Principal investigator: Irene Navalpotro.
CIBERNED's collaboration: No.
CIBERNED groups: G609. Other CIBER's collaboration: No.
Type: Nacional.
Funding agency: MECD.

Code: DPPE17/001.
Title: Compuestos Ahulken: Nuevos moduladores de calcio como tratamiento para la distrofia muscular de Duchenne.
Principal investigator: Ainara Vallejo.
CIBERNED's collaboration: No.
CIBERNED groups: G609. Other CIBER's collaboration: No.
Type: Internacional.
Funding agency: Duchenne Parent Project.

Code: CM16/00033.
Title: Contrato Rio Hortega.
Principal investigator: Irene Navalpotro Gomez.
CIBERNED's collaboration: No.
CIBERNED groups: G609. Other CIBER's collaboration: No.
Type: Nacional.
Funding agency: MICINN.
Code: 2018222021.
Title: Desarrollo preclínico de una terapia combinada frente a la distrofia miotonica con rycals y compuestos anti-envejecimiento.
Principal investigator: Adolfo Lopez de Munain.
CIBERNED’s collaboration: No.
CIBERNED groups: G609 . Other CIBER’s collaboration: No.
Type: CCAA.
Funding agency: Gobierno Vasco.

Title: Envejecimiento en la distrofia miotonica tipo 1: Analisis multifactorial desde una perspectiva biologica, neuropsicologica y neurorradiologica.
Principal investigator: Andone Sistiaga Berrondo.
CIBERNED’s collaboration: No.
CIBERNED groups: G609 . Other CIBER’s collaboration: No.
Type: Nacional.
Funding agency: Instituto de Salud Carlos III.

Title: Estudio de la capacidad regenerativa de los progenitores musculares derivados del ipss del pacientes con distrofia de cinturas tipo 2e. Estudio in vitro y en un modelo murino de dano tisular.
Principal investigator: Adolfo Lopez De Munain.
CIBERNED’s collaboration: No.
CIBERNED groups: G609 . Other CIBER’s collaboration: No.
Type: Nacional.
Funding agency: Instituto de Salud Carlos III.

Title: Funcion de la calpaina 3 en las celulas satelite durante la regeneracion muscular y su modulacion farmacologica como posible tratamiento de la LGMD2A.
Principal investigator: Adolfo Lopez de Munain.
CIBERNED’s collaboration: No.
CIBERNED groups: G609 . Other CIBER’s collaboration: No.
Type: Nacional.
Funding agency: Instituto de Salud Carlos III.

Title: Generation of “Lab-on-chip” systems to investigate neuromuscular disorders.
Principal investigator: Francisco Javier Gil Bea.
CIBERNED’s collaboration: No.
CIBERNED groups: G609 . Other CIBER’s collaboration: No.
Type: Nacional.
Funding agency: MICINN.

Title: Implicacion de la calpaina 3 en la senescencia prematura de las celulas satelite musculares: Estudio del ciclo celular en progenitores musculares derivados de IPSs de pacientes con LGMD2A.
**Principal investigator:** Adolfo Lopez De Munain.  
**CIBERNED collaboration:** No.  
**CIBERNED groups:** G609.  
**Other CIBER’s collaboration:** No.  
**Type:** CCAA.  
**Funding agency:** Gobierno Vasco.  
**Funding:** 53920.  
**Duration:** 2016-2018.  

**Title:** Metabolic distrubancer and organelle erturbations in the PAT.  
**Principal investigator:** Francisco Javier Gil Bea.  
**CIBERNED collaboration:** No.  
**CIBERNED groups:** G609.  
**Other CIBER’s collaboration:** No.  
**Type:** Privado.  
**Funding agency:** Eitb Maratoia.  
**Funding:** 81115.  
**Duration:** 2018-2020.  

**Title:** Modulacion de SERCA como diana terapeutica para el tratamiento de la distrofia muscular LGMD2A.  
**Principal investigator:** Ainara Vallejo.  
**CIBERNED collaboration:** No.  
**CIBERNED groups:** G609.  
**Other CIBER’s collaboration:** No.  
**Type:** CCAA.  
**Funding agency:** Gobierno Vasco.  
**Funding:** 67310.  
**Duration:** 2018-2019.  

**Title:** Papel de SOX2 en la remodelacion dermica y en el deficit de cicatrizacion cutanea asociado al envejecimiento.  
**Principal investigator:** Ander Izeta.  
**CIBERNED collaboration:** No.  
**CIBERNED groups:** G609.  
**Other CIBER’s collaboration:** No.  
**Type:** Nacional.  
**Funding agency:** Instituto de Salud Carlos III.  
**Funding:** 183315.  
**Duration:** 2017-2019.  

**Title:** Pharmacological modulation of ryanodine receptor in Duchenne and Becker muscular dystrophies.  
**Principal investigator:** Ainara Vallejo.  
**CIBERNED collaboration:** No.  
**CIBERNED groups:** G609.  
**Other CIBER’s collaboration:** No.  
**Type:** Nacional.  
**Funding agency:** Instituto de Salud Carlos III.  
**Funding:** 99220.  
**Duration:** 2018-2021.  

**Title:** Plasticidad sinaptica y actividad de los ganglios basales en un modelo de parkinsonismo e impulsividad.  
**Principal investigator:** Maria Cruz Rodriguez Oroz.  
**CIBERNED collaboration:** No.  
**CIBERNED groups:** G609.  
**Other CIBER’s collaboration:** No.
Type: CCAA.
Funding agency: Gobierno Vasco.

Code: P16/01325.
Title: Regulacion de la expresion de FRZB in vitro e in vivo, para el restablecimiento de la homeostasis en la fibra muscular de pacientes con distrofia de cinturas tipo 2A (LGM-D2A).
Principal investigator: Amets Saenz Pena.
CIBERNED's collaboration: No.
CIBERNED groups: G609. Other CIBER's collaboration: No.
Type: Nacional.
Funding agency: Instituto de Salud Carlos III.

Code: DFG17/003.
Title: Terapia combinada con tioredoxinas ancestrales y nuevos compuestos rycals para tratar desequilibrios calcio-redox en enfermedades neurodegenerativas.
Principal investigator: Adolfo Lopez De Munain.
CIBERNED's collaboration: No.
CIBERNED groups: G609. Other CIBER's collaboration: No.
Type: CCAA.
Funding agency: Gobierno Vasco.

Code: HR17-00268.
Title: Therapeutic targeting of MBNL microRNAs as innovative treatments for myotonic dystrophy.
Principal investigator: Ruben Artero.
CIBERNED's collaboration: No.
CIBERNED groups: G609. Other CIBER's collaboration: No.
Type: Privado.
Funding agency: Fundacio La Caixa.

PHD DISSERTATIONS 2018

Author: Neia Naldaiz Gastezi.
Title: Caracterización celular y molecular de la miogénesis dérmica de ratón y su posible traslación al humano.

Author: Leire Casas Fraile.
Title: doctoral defendida en 2018: Title: FRZB gene expression regulation in vitro to restore muscle fibre homeostasis in limb-girdle muscular dystrophy type 2A (LGMD2A) and Frzb-/- murine model muscle analysis.
ABSTRACT

Muscle stem cells are subjected to circadian regulation, and this regulation is altered during aging.

1. Our group showed for the first time that muscle stem cells, despite being quiescent, are subject to a strict circadian control throughout the 24 hour day/night cycle, and this circadian regulation is altered with aging.

Based on these findings from the group, we have addressed our research this year to answer two fundamental questions:

1.1. What are the long-term molecular and epigenetic consequences of muscle stem cell clock dampening during aging? These results will help us to identify which clock genes and their targets show aberrant epigenetic modifications that might affect their expression during aging. Since the enzymes responsible for regulating these chromatin marks are known, identifying changes in these may point toward strategies to re-establish normal clock function in aged muscle stem cells.

1.2. Does disruption of the clock machinery affect satellite cell quiescence and regenerative ability? The synchronization of physiological and metabolic processes to the appropriate time of the day is achieved by the regulation of systemic factors, and by the regulation of local tissue specific gene expression. We have characterized how both
clocks coordinate (systemic and tissue specific) and how each clock de-regulation affects muscular stem cells during aging.


2. Studying the heterogeneity of quiescent muscular stem cells.

Several studies based on transgenesis have probed that muscular stem cells is not a homogeneous population. Our group has developed a cellular sorting strategy by flux citometry (FACS) able to screen two different populations of satellite cells with different myogenic properties and we have demonstrated that the transcription factor FoxO3a is a regulator of both populations divergence.

- Submitted work (García Prat L, Perdiguero E and Muñoz-Cánoves P).

3. Additional studies in stem cells show their autophagic activity loss during aging and the entrance in senescence.

We have demonstrated that caloric restriction during three months in aged mice is able to restitute autophagy in their satellite cells and increase their regenerative capacity.


4. Studying Sestrins capacity to prevent muscular atrophy.

We have demonstrated that Sestrins over-expression protects muscle from mass and strength loss caused by disuse, by 1) mTORC1 inhibition, which up-regulates autophagy, and 2) AKT activation which inhibits muscular proteolysis. These results have a potential implication in sarcopenia treatment.


Additional studies and reviews:

- Baar MP, Perdiguero E, Muñoz-Cánoves P, de Keizer PL. Musculoskeletal senescence: a moving target ready to be eliminated. Curr Opin Pharmacol. 40:147-155, 2018

KEYWORDS

Skeletal muscle, regeneration, muscle stem cells, sarcopenia, aging, inflammation, fibrosis.
PUBLICATIONS 2018


RESEARCH PROJECTS 2018

Code: PI2015-2/06.
Title: Molecular mechanisms of brain and muscle stem cell function in aging and neurodegeneration.
Principal investigator: Pura Munoz Canoves.
CIBERNED’s collaboration: Yes.
CIBERNED groups: G604; G102; G606; G111; G306.
Other CIBER’s collaboration: No.
Type: Intramurales.
Funding agency: CIBERNED.

Code: TV3.
Title: New stem cell therapies for Duchenne Muscular Dystrophy.
Principal investigator: Antonio Serrano Sanchez.
CIBERNED’s collaboration: No.
CIBERNED groups: G604. Other CIBER’s collaboration: No.
Type: Privado.
Funding agency: Fundacio La Marato de TV3.

Code: ERC.
Title: Tissue regeneration and aging: the decisive quiescent stem-cell state.
Principal investigator: Pura Munoz Canoves.
CIBERNED’s collaboration: No.
CIBERNED groups: G604. Other CIBER’s collaboration: No.
Type: Europeo.
Funding agency: Comision Europea.

Title: Understanding and reversing muscle stem cell regenerative decline in DMD.
Principal investigator: Pura Munoz Canoves.
CIBERNED’s collaboration: No.
CIBERNED groups: G604. Other CIBER’s collaboration: No.
Type: Internacional.
Funding agency: Muscular Dystrophy Association (MDA)-USA.

Code: La Caixa.
Title: Understanding muscle regenerative decline with aging.
Principal investigator: Pura Munoz Canoves.
CIBERNED's collaboration: No.
CIBERNED groups: G604. Other CIBER's collaboration: No.
Type: Privado.
Funding agency: Fundacio La Caixa.

Code: SAF2015-67369-R.
Title: Understanding skeletal muscle regenerative decline with aging.
Principal investigator: Pura Munoz Canoves.
CIBERNED's collaboration: No.
CIBERNED groups: G604. Other CIBER's collaboration: No.
Type: Nacional.
Funding agency: MICINN.

PHD DISSERTATIONS 2018
Author: Pedro Maseres Javaloy.
Title: Regulation of cell proliferation and differentiation by p38MAPK in distinct physiological processes.
Date: 12/3/2018. Supervisor: Pura Muñoz Cánoves.
PRINCIPAL INVESTIGATOR
Navarro Acebes, Xavier

LIST OF PERSONNEL
Amo Aparicio, Jesús. Bachelor degree.
Badía Casahuja, Jordi. Bachelor degree.
Baylo Marín, Olaia. Bachelor degree.
Bosch Merino, Assumpció. PhD.
Bruna Escuer, Jordi. Bachelor degree.
Calls Cobos, Aina. Bachelor degree.
Casas Louzao, Caty. PhD.
De la Oliva Muñoz, Natalia. Bachelor degree.
del Valle Maciá, Jaume. PhD.
Gaja Capdevilla, Nuria. Bachelor degree.
García Alias, Guillermo. PhD.
Hernández Martín, Joaquín. PhD.
Hernández Solanes, Neus. Technician.
Herrando Grabulosa, Mireia. PhD.
Jaramillo Rodríguez, Jessica. Technician.
Leiva Rodríguez, Tatiana. Bachelor degree.
López Serrano, Clara. Bachelor degree.
López Vales, Rubén. PhD.
Martínez Muriana, Anna. Bachelor degree.
Módol Caballero, Guillem. Bachelor degree.
Penas Pérez, Clara. PhD.
Puigdomènech Poch, Maria. Bachelor degree.
Rodríguez Cañón, Maria. Bachelor degree.
Romeo Guitart, David. Bachelor degree.
Rubio Pérez, Miguel Angel. Bachelor degree.
Sánchez Fernández, Alba. Bachelor degree.
Udina Bonet, Esther. PhD.
Velasco Fargas, Roser. Bachelor degree.

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ABSTRACT

The Group of Neuroplasticity and Regeneration of the UAB is a multidisciplinary research group working on repair, regeneration and functional recovery after peripheral nerve and spinal cord lesions and in neurodegenerative diseases. The research activities of the Group of Neuroplasticity and Regeneration have focused on the study of physiopathological mechanisms of neural lesions, neuropathic pain and neurodegeneration, and on the application of novel therapeutic strategies for promoting neuroprotection and regeneration in traumatic and degenerative lesions of the nervous system. The active research lines include:

• Cellular and molecular mechanisms implicated in motoneuron degenerative diseases in experimental models. Search for biomarkers. Neuroprotective strategies based on gene and pharmacological therapy.

• Cell therapy by transplantation of mesenchymal stem cells and neural stem cells for the repair of spinal cord injuries and motoneuron degenerative diseases.

• Repair of spinal root avulsion injuries by surgical reimplantation and pharmacological neuroprotection.

• Etiopathogenic role of lipid mediators and modulators of the neuroinflammatory response in neurodegeneration induced by central nervous system lesions.

• Activity-dependent therapies for enhancing axonal regeneration and functional recovery after peripheral nerve lesions and for preventing neuropathic pain.

• Physiopathologic mechanisms in neuropathic pain induced by nerve and spinal cord lesions. Study of the relationship between neuroinflammation and hyperexcitability.

• Study of etiopathogenic mechanisms and potential neuroprotective treatments in peripheral neuropathies induced by diabetes and by antitumoral agents.

• Gene therapy using viral vectors for diseases affecting both the central (mucopolysaccharidosis type VII, megalencephalic leukodystrophy, amyotrophic lateral sclerosis) and peripheral nervous system (diabetic neuropathy, nerve regeneration).

• Neuromodulation of neural plasticity for promoting functional restitution in spinal cord injuries.

• Design and evaluation of neural interfaces for the development of neuroprostheses applied to neurorehabilitation. Study of new intraneural electrodes for the selective stimulation and recording of neural activity.

KEYWORDS

Neurodegeneración, regeneración nerviosa, lesión de médula espinal, dolor neuropático, enfermedades de motoneuronas, neuropatías periféricas, neuroplasticidad, interfases neuronales, terapia génica
PUBLICATIONS 2018


Romeo-Guitart D, Leiva-Rodriguez T, Espinosa-Alcantud M, Sima N, Vaquero A, Dominguez-Martin H. et al. SIRT1 activation with neuroheal is neuroprotective but SIRT2 inhibition with


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**RESEARCH PROJECTS 2018**

**Code:** TV32016-GG.

**Title:** Recuperacion de los movimientos del brazo y de la mano en pacientes con lesion de la medula espinal cervical mediante la neuromodulacion electrica espinal asistida con un exoesqueleto de brazo.

**Principal investigator:** Guillermo Garcia-Alias.

**CIBERNED's collaboration:** No.

**CIBERNED groups:** G607.

**Other CIBER's collaboration:** CIBER-BBN.

**Type:** Privado.

**Funding agency:** Fundacio La Marato de TV3.

**Funding:** 399945. **Duration:** 2018-2021.

**Code:** RTC-2015-3750-1.

**Title:** Desarrollo de agentes terapeuticos basados en acidos nucleicos para el tratamiento de enfermedades neuromotoras y neuromusculares.

**Principal investigator:** Ruben Lopez Vales.

**CIBERNED's collaboration:** Yes.

**CIBERNED groups:** G607; G609.

**Other CIBER's collaboration:** No.

**Type:** Nacional.

**Funding agency:** MICINN.

**Funding:** 204315. **Duration:** 2015-2018.

**Code:** E10668.

**Title:** eBIONERVE: personalized nerve grafts for treating human nerve injuries.

**Principal investigator:** Xavier Navarro.

**CIBERNED's collaboration:** No.

**CIBERNED groups:** G607.

**Other CIBER's collaboration:** No.

**Type:** Europeo.
Funding agency: Comision Europea.

Code: SAF2016-79774-R.
Title: Estudio de los mecanismos de accion de la interleucina-37 en el sistema nervioso central lesionado.
Principal investigator: Ruben Lopez-Vales.
CIBERNED's collaboration: No.
CIBERNED groups: G607 . Other CIBER's collaboration: No.
Type: Nacional.
Funding agency: MICINN.

Code: PI15/01303.
Title: Estudio exploratorio sobre la etiopatogenia, biomarcadores de riesgo y mecanismos implicados en la regeneracion de la neuropatia inducida por platinos.
Principal investigator: Jordi Bruna.
CIBERNED's collaboration: No.
CIBERNED groups: G607 . Other CIBER's collaboration: No.
Type: Nacional.
Funding agency: Instituto de Salud Carlos III.

Code: PI15/01271.
Title: Estudio molecular y tratamiento de la Mucopolisacaridosis tipo VII.
Principal investigator: Assumpcio Bosch.
CIBERNED's collaboration: No.
CIBERNED groups: G607 . Other CIBER's collaboration: No.
Type: Nacional.
Funding agency: Instituto de Salud Carlos III.

Code: CI17-00019.
Title: Immunoresolvent lipids for multiple sclerosis and amyotrophic lateral sclerosis.
Principal investigator: Ruben Lopez-Vales.
CIBERNED's collaboration: No.
CIBERNED groups: G607 . Other CIBER's collaboration: No.
Type: Privado.
Funding agency: Fundacio La Caixa.

Code: WFL-ES-14-17.
Title: Interleukin-37: a novel therapeutic approach for the treatment of spinal cord injury.
Principal investigator: Ruben Lopez-Vales.
CIBERNED's collaboration: No.
CIBERNED groups: G607 . Other CIBER's collaboration: No.
Type: Internacional.
Funding agency: Wings for Life Foundation.

Code: SAF2016-79279-R.
Title: Neuromodulacion electrica del conectoma cortico-medular para facilitar la recuperacion de la destreza manual tras una lesion medular.
Principal investigator: Guillermo Garcia-Alias.
CIBERNED's collaboration: No.
CIBERNED groups: G607. Other CIBER's collaboration: No.
Type: Nacional.
Funding agency: MICINN.

Code: AC16/00050.
Title: Non-invasive electrical stimulation of the cervical spinal cord to facilitate arm and hand functional recovery in incomplete traumatic cervical spinal cord injured patients (CERMOD).
Principal investigator: Guillermo Garcia-Alias.
CIBERNED's collaboration: No.
CIBERNED groups: G607. Other CIBER's collaboration: No.
Type: Europeo.
Funding agency: Comision Europea.

Title: Promoting plasticity of reticulospinal axons to recover skilled hand function after spinal cord injury.
Principal investigator: Guillermo Garcia-Alias.
CIBERNED's collaboration: No.
CIBERNED groups: G607. Other CIBER's collaboration: No.
Type: Nacional.
Funding agency: MICINN.

Title: Reprogramacion neuronal para promover los mecanismos endogenos de neuroproteccion usando biologia sintetica en un modelo de degeneracion retrograda de motoneuronas.
Principal investigator: Caty Casas.
CIBERNED's collaboration: No.
CIBERNED groups: G607. Other CIBER's collaboration: No.
Type: Nacional.
Funding agency: MICINN.

Code: CA15138.
Title: TRANSAUTOPHAGY: European network for multidisciplinary research and translation of autophagy knowledge.
Principal investigator: Caty Casas.
CIBERNED's collaboration: No.
CIBERNED groups: G607. Other CIBER's collaboration: No.
Type: Europeo.
Funding agency: Comision Europea.
PHD DISSERTATIONS 2018

**Author:** Natalia de la Oliva Muñoz.  
**Title:** Biological response to implanted intraneural electrodes.  
**Date:** 9/2/2018.  
**Supervisor:** Xavier Navarro Acebes.

**Author:** Anna Martínez Muriana.  
**Title:** Modulation of the inflammatory response in amyotrophic lateral sclerosis.  
**Date:** 26/7/2018.  
**Supervisor:** Rubén López Vales.

**Author:** Tatiana Leiva Rodríguez.  
**Title:** Investigation of the role and modulation of autophagy for neuroprotection and nerve regeneration using models of peripheral nerve injury.  
**Date:** 9/11/2018.  
**Supervisor:** Caty Casas Louzao.
COOPERATIVE RESEARCH
COOPERATIVE RESEARCH

The cooperative research program continues to be viewed as an essential scientific tool for planning CIBERNED future actions. This program is one of the cornerstones of the Center’s activities, and aims to encourage collaborative research between the various research groups, joining forces and exploiting synergies and complementary skills. It is intended to identify collaborative research projects with a marked innovative and translational nature where the cooperative effort significantly increase the added value of the research activity. Proposals, although subject to final approval by the Steering Committee, are externally reviewed by the National Evaluation Agency (ANEP), so that the allocation of funds is independent and transparent.

The cooperative research program has so far launched nine calls for projects overall. The first four (2010, 2011, 2013 and 2014) has already included seventeen completed projects and a total accumulated budget allocation of 5,422,174 €.

In 2015, the fifth and sixth calls were launched. The fifth call included three collaborative projects with a total allocation of 690,000€ and was finished by the end of 2017. The sixth call included two collaborative projects with a total allocation of 700,000€ which, due to an extension that did not involve additional funding, ended during 2018.

In 2016, the seventh call for cooperative projects was approved with a total allocation of 1,016,000€. This seventh call included five projects that ended in late 2018.

In 2017, the eighth call was launched with the concession of three new projects with a total allocation of 650,000€.

Finally, during the last semester of 2018, the ninth call was launched with the concession of three additional projects with a budget allocation of 600,000€.
## 2010 CALL

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<tr>
<th>CODE</th>
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<tbody>
<tr>
<td>PI2010/05</td>
<td>Generating a dopaminergic neuronal model from induced pluripotent stem cells from patients with Parkinson's disease associated to mutations in the LRRK2 gene</td>
<td>Tolosa Sarró, Eduardo</td>
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<td>PI2010/06</td>
<td>Neuroprotection in Huntington's disease</td>
<td>García de Yébenes Prous, Justo</td>
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<tr>
<td>PI2010/07</td>
<td>Reelin and GSK3 as therapeutic targets in Alzheimer's disease</td>
<td>Ávila de Grado, Jesús</td>
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<tr>
<td>PI2010/08</td>
<td>Glial activation during the neuroinflammatory process: a potential therapeutic target for Alzheimer's disease</td>
<td>Vitorica Ferrández, Francisco Javier</td>
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<tr>
<td>PI2010/09</td>
<td>BESAD-P: Biomarkers of early stages of Alzheimer disease - prevention</td>
<td>Ferrer Abizanda, Isidro</td>
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<td>PI2010/11</td>
<td>Consortium to generate a common database aimed at implementing clinical and basic research on neuromuscular diseases</td>
<td>Illa Sendra, Isabel</td>
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## 2011 CALL

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<td>PI2011/01</td>
<td>The Nrf2 transcription factor as a new therapeutic target for Parkinson's disease</td>
<td>Cuadrado Pastor, Antonio</td>
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<tr>
<td>PI2011/02</td>
<td>Onset and progression of Parkinson's disease. Vulnerability of the nigrostriatal pathway, events at origin and destination</td>
<td>Obeso Inchausti, José Ángel</td>
</tr>
<tr>
<td>PI2011/03</td>
<td>Generation of dopaminergic neurons from somatic cells of parkinsonian patients with cognitive failure</td>
<td>Moratalla Villalba, Rosario</td>
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<tr>
<td>PI2011/04</td>
<td>Multicenter study on LCR and neuroimaging biomarkers in the continuum preclinical- prodromal Alzheimer's disease (SIGNAL Study)</td>
<td>Lleó Bisa, Alberto</td>
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## 2013 CALL

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<tr>
<td>PI2013/01</td>
<td>Emergent properties of the neuron-glia relationship underlying neurodegeneration and dementia in Alzheimer's disease</td>
<td>Torres Alemán, Ignacio</td>
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<tr>
<td>PI2013/05</td>
<td>Identification and molecular characterization of cannabinoid receptors subpopulations in poliglutaminopatías</td>
<td>Guzmán Pastor, Manuel</td>
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<tr>
<td>PI2013/07</td>
<td>Role of GSK-3β in the cortical circuits alterations occurring in Alzheimer's disease</td>
<td>Iglesias Vacas, Teresa</td>
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<tr>
<td>PI2013/08</td>
<td>Mitochondrial dynamics and mitophagy as therapeutic targets in Parkinson's and Huntington's diseases</td>
<td>Soriano García, Eduardo</td>
</tr>
<tr>
<td>PI2013/09</td>
<td>Degeneración sináptica y desregulación de la neurogénesis del adulto en modelos murinos de neurodegeneración</td>
<td>Fernández Chacón, Rafael</td>
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### 2014 CALL

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<tr>
<td>PI2014/02</td>
<td>Epigenetic mechanisms involved in the etiology and progression of rapidly progressive neurodegenerative dementias</td>
<td>Calero Lara, Miguel</td>
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<tr>
<td>PI2014/06</td>
<td>Onset and progression of Parkinson's disease: role of glial activation</td>
<td>Rodríguez Oroz, Mª Cruz</td>
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### 2015-I CALL

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<tr>
<td>PI2015/01</td>
<td>Neuregulin gene therapy aimed at the treatment of motor neuron degeneration in ALS</td>
<td>Navarro Acebes, Xavier</td>
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<td>PI2015/02</td>
<td>Validation of new therapeutic targets and biomarkers in Parkinson’s disease</td>
<td>Labandeira García, José Luís</td>
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<tr>
<td>PI2015/03</td>
<td>Differential metabolic profiles in Parkinson's disease</td>
<td>Fuentes Rodríguez, José Manuel</td>
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### 2015-II CALL

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<tr>
<td>PI2015-2/02</td>
<td>Pathological potential of astrocytes: a new perspective on Alzheimer's disease</td>
<td>Comella Carnicé, Joan Xavier</td>
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<tr>
<td>PI2015-2/06</td>
<td>Molecular mechanisms of brain and muscle stem cell function in aging and neurodegeneration</td>
<td>Muñoz Cánoves, Pura</td>
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### 2016 CALL

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<tr>
<td>PI2016/01</td>
<td>Alterations of gluco-lipid metabolism and development of Alzheimer's dementia</td>
<td>Torres Alemán, Ignacio</td>
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<tr>
<td>PI2016/02</td>
<td>Monitoring the Onset and Evolution of Neuronal Dysfunctions in Propagative Neural Disorders using Microfluidic Devices and Translational approaches</td>
<td>Del Río Fernández, José Antonio</td>
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<td>PI2016/04</td>
<td>The ALS CIBERNED Challenge: Accelerating New Drug Discovery</td>
<td>López de Munain Arregui, Adolfo</td>
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<tr>
<td>PI2016/05</td>
<td>Dream inhibitors and Alzheimer’s Disease</td>
<td>Naranjo Orovio, José Ramón</td>
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<tr>
<td>PI2016/06</td>
<td>Identification of pathophysiological pathways and candidate biomarkers in the prediagnostic phase of Parkinson’s disease</td>
<td>Vila Bover, Miquel</td>
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These twenty-seven projects, which have been already finished, have actively involved up to 57 CIBERNED research groups, as well as other external ones, representing 90.4% of the existing groups.

During the year 2018, the sixth and seventh calls for CIBERNED cooperative projects were completed, and the groups involved presented the results obtained in the corresponding final reports that were delivered to the CIBERNED scientific management.

Below is a brief description of the results obtained by each of the projects during these calls:

**Project PI2015-2/02 Pathological potential of astrocytes: a new perspective on Alzheimer’s disease**

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<td>Comella Carnicé, Joan Xavier</td>
<td>CIBERNED, Vall d’Hebron University Hospital, Barcelona</td>
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<td>Vitorica Ferrández, Francisco Javier</td>
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<td>Gutiérrez Pérez, Antonia</td>
<td>CIBERNED, University of Malaga</td>
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<td>Vicario Abejón, Carlos</td>
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<td>Moratalla Villalba, Rosario</td>
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Although astrocytes have well characterized roles related with trophic support, homeostasis, elimination of toxic molecules, production of cytokines, vascularization, extracellular matrix reshaping and control of synaptic activity, it is unknown their specific role in the development of AD. It has been characterized that astrocytes activate and accumulate around b-amyloid plaques, but it is unknown the detailed changes in their genetic expression patterns, or how their secreted factors contribute to the development of the disease. In this project, we have tried to go deeper in the knowledge of the role of astrocytes in the development of Alzheimer’s disease. To achieve this goal, we have started different experimental approaches to study the role of astrocytes in the development of the disease, such as the generation of iPS cells from fibroblasts and differentiated into astrocytes. We have also generated a model that should allow modifying in vivo the levels of neuronal FAIM-L, a protein that could play an interesting role in the protection of neurons against the disease, and also in the cross-talk neuron/glia.

Our results show that in murine models, as well as in Alzheimer’s patients, reactive astrocytes associated to the amyloid plaques, but nor activated microglia, have phagocytic activity, selectively eliminating axonal and presynaptic distrophies. In addition, when analyzing samples from different stages of Alzheimer’s disease, we observed that this phagocytic component is altered in the development of the disease, thus constituting a likely therapeutic target for the disease, since the functional impairment of astrocytes seems a key component in the progression of Alzheimer’s disease.

Regarding the in vivo models of FAIM, we have characterized that the FAIM KO mouse has an epileptic phenotype, with recurrent attacks induced by manipulation, which are age-dependent, and characterized by electrophysiological alterations, locomotor hyperexcitability, deficits in social interaction, and an altered behavior in nest building, as well as some general deficits in learning and memory. We have additionally
generated adeno-associated viruses which will allow us to explore if neuronal altered expression levels of FAIM may induce changes in the development of the disease in different murine models.

We have also explored the effects of ApoE polymorphisms, which clearly induce alterations in cholesterol homeostasis and autophagy, alterations that are systemic, because do not only affect neurons, but also peripheral cells, pointing to higher levels of cholesterol esters in patients fibroblasts as an useful metabolic trait to further explore in cellular models of the disease. In addition, fibroblasts from AD patients show dramatic alterations in lysosomes and mitochondria.

**Project PI2015-2/06: Molecular mechanisms of brain and muscle stem cell function in aging and neurodegeneration**

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<td>Muñoz Cánoves, Pura</td>
<td>CIBERNED, Pompeu Fabra University, ICREA, Barcelona</td>
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<td>Fariñas Gómez, Isabel</td>
<td>CIBERNED, University of Valencia</td>
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<td>Lucas Lozano, José Javier</td>
<td>Center for Molecular Biology &quot;Severo Ochoa&quot; CSIC-UAM, Madrid</td>
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<td>Fernández Chacón, Rafael</td>
<td>CIBERNED, University of Seville</td>
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<td>Iglesias Vacas, Teresa</td>
<td>CIBERNED, Institute of Biomedical Research CSIC-UAM, Madrid</td>
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The functional decline of the Nervous and the musculoskeletal systems is a major factor determining the quality of life in elderly populations. Neural and muscular stem cells must remain active throughout life for the functional maintenance of both tissues. However, these cells are sensitive to aging and, possibly to the pathogenic factors that cause neurodegeneration as well, thus progressively losing their regenerative potential by unknown molecular mechanisms. Our consortium has identified possible mechanisms that would affect both neural and muscular stem cells as a result of both aging and neurodegeneration. These include: (1) the aging-dependent inhibition of autophagy in stem cells mediated by target-of-rapamycin (mTOR) signaling pathway; (2) the premature exhaustion of stem cell pools due to cell cycle and cell division mode dysregulation; and (3) stem cell dysfunctions due to alterations in alternative splicing such as those occurring in neurodegenerative diseases associated to polyglutamine repeats.

The coordinator of the consortium Dr. Munoz-Cánoves has recently described key molecular pathways underlying the functional decline and senescence of satellite cells that impair muscle rejuvenation (Sousa-Victor, 2014). The transcriptomic analysis included in this study also points to the mTOR signaling pathway as an additional mechanism as well as to three key genes that are the central subject of study in the consortium laboratories: (a) Cysteine String Protein-alpha (CSP-alpha), a synaptic co-chaperone that prevents presynaptic degeneration (Garcia-Junco et. al, 2010) that, unexpectedly, maintains the postnatal quiescence of neural stem cells through inhibition of mTOR (unpublished work from Dr. Fernandez-Chacon’s group); (b) Kinase D interacting substrate (Kidins220), a major effector of multiple receptor signaling pathways regulating cellular responses in nervous, vascular and skeletal muscle systems (Iglesias, 2000; Neubrand, 2012) present in neural stem cells of the subventricular
zone (SVZ) and regulates them (unpublished data from the collaboration between the groups Dr. Teresa Iglesias and Dr. Isabel Fariñas); (c) Rbfox1, a specific splicing factor from neurons and skeletal muscle previously linked to myotonic dystrophy DM1 and that is decreased in Huntington’s disease, resulting in a pathogenic splicing of CPEB4 (unpublished work by Dr. José Lucas’s group). Although satellite cells are the main focus of the study, the SVZ neural stem cells will be studied in parallel, easier to approach methodologically and better known thanks to the pioneering work of Dr. Isabel Fariñas.

Our consortium brings together groups with ample expertise in the biology of stem cells and neural development, the role of satellite cells in muscle fiber maintenance and the molecular basis of neurodegenerative diseases and synaptic dysfunction. Our laboratories will synergistically interact to maximize multidisciplinary methodological resources and expertise which include a highly specialized knowledge in the cell biology of neural stem and satellite cells, yet-unpublished biological resources, i.e. mouse models, and first-hand understanding of specific signaling molecules and pathways. We expect that our project will throw light on key mechanisms involved in the functional maintenance of adult stem cells, an essential point for the potential regeneration of muscle fibers and specific neuronal types.

**Project PI2016/01: Alterations of gluco-lipid metabolism and development of Alzheimer’s dementia**

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<td>CIBERNED, Center for Molecular Biology “Severo Ochoa” CSIC-UAM, Madrid</td>
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<td>Camins Espuny, Antonio</td>
<td>CIBERNED, University of Barcelona</td>
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<td>Carro Díaz, Eva</td>
<td>CIBERNED, Doce de Octubre University Hospital, Madrid</td>
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<td>Cantero Lorente, José Luis</td>
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The aim of the Project was to determine along time, possible metabolic disturbances associated to progressive cognitive alterations in Alzheimer’s disease (AD) patients. We carried out a parallel study in AD patients and animal models. We first analyzed the serum glyco-lipid pattern in an AD cohort encompassing the entire natural history of the disease. Brain imaging analysis in the same patients was conducted to obtain structural/functional data potentially associated with peripheral metabolism that could ideally characterize each of the stages of the disease. The results show no relationship between changes in glyco-lipid metabolism and structural/functional alterations seen in the brain along the different stages of AD, at least in our patient population. However, we observed a correlation between serum homocysteine and oxidative stress, seemingly mediated by sleep quality, in mild cognitive impairment (MCI) patients. Thus, we propose a multi-factorial model to predict cognitive deterioration based in the relationship between adiposity and quality of sleep. Further, and emphasizing the known sexual dimorphism of the disease, we found that cholinergic denervation in temporal cortex from the basal nuclei of Meynert is more pronounced in MCI women than in men. In asymptomatic subjects we observed changes in diverse miRNAs that predict cerebral atrophy together with a decrease in brain metabolism, suggesting that affected miRNAs may serve as biomarkers of brain vulnerability dur-
ing aging. We have also determined, in a parallel study carried out in an additional AD cohort, that serum lactoferrin, an immunomodulator regulated by metabolic status, may constitute a new peripheral biomarker.

In AD animal models, we examined how metabolic disturbances associated to high fat diet or to brain glucose alterations (typically found in AD patients) impact in the development of the disease. We determined amyloidosis, tauopathy, lipid disturbances and insulin resistance. We found a profound cognitive loss in obese JNK2-/- . In addition, we also found a relationship between obesity, the JNK1 isoform, cognitive improvement, and increased synapse numbers. Our results indicate that this isoform, together with inhibitory drugs, would potentiate cognitive processes. We also obtained the lipid profile of APP/PS1 mice and their controls after submitting them to a high fat diet. We used diets with n-6/n-3 fatty acids in intact, ovariectomized, and ovariectomized plus estradiol female mice. In these groups we have determined diverse neural markers. In megalin-deficient mice showing cognitive deterioration, obesity, and neuroinflammation, we analyzed the relationship between altered metabolism, amyloid levels and cognitive loss. Specifically, we determined whether metabolic disturbances are sufficient to trigger cognitive loss or whether the underlying amyloidosis is essential.

In a fourth type of experiments, we analyzed the influence of altered glucose metabolism in the development of AD (using APP/PS1 mice lacking either insulin or IGF-I receptors in astrocytes) and found in both cases changes in disease progress. Furthermore, we observed dysfunctional brain perfusion and abnormal angiogenesis by merely deleting the insulin receptor in astrocytes, which leads to brain insulin resistance.

Collectively, our results indicate that glyco-lipid metabolism plays a role in development of the pathology in animal models. However, the results obtained in AD patients make us to be cautious, even though a potential relationship could be envisaged. Indeed, more human studies are required.

Project PI2016/02: Monitoring the Onset and Evolution of Neuronal Dysfunctions in Propagative Neural Disorders using Microfluidic Devices and Translational approaches

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<td>Del Río Fernández, José Antonio</td>
<td>CIBERNED, Catalanian Institute de Bioengineering, Barcelona</td>
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<td>Ávila de Grado, Jesús</td>
<td>CIBERNED, Center for Molecular Biology “Severo Ochoa” CSIC-UAM, Madrid</td>
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<td>Canela Campos, Enric Isidre</td>
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Numerous aged-related neurodegenerative diseases (END) are characterized by the slow but inexorable advance of neuronal dysfunctions in brain patients that progress though anatomically linked regions. This evolution of the disease shared with the progressive accumulation of abnormally folded proteins in affected neurons that stem for gradual neuronal dysfunction, which involves synaptic transmission abnormalities, axonal damage and cell death. However, in some cases the observed spread though brain parenchyma failed to follow the “classical” progression illustrated in seminar studies, e.g., in Alzheimer’s (AD) or Parkinson’s (PD) diseases. For example, some elderly individ-
uals without diagnostics showed Lewy bodies in the olfactory bulb, amygdala or cortex which should seem to violate the theory of progression and perhaps fit better with a multicentric disease process. In addition, anatomically connected regions of the brain (e.g., entorhino-hippocampal formation) showed different p-tau burden in AD and other tauopathies. In conclusion, these data suggested both an area-specific and a differential neuronal vulnerability during disease progression. Factor/s modulating this differential neuronal vulnerability are unknown. The goal of the present project is to recreate in vitro using microfluidic devices (MFDs) normal and diseased neuronal networks of selected neural pathways susceptible to suffer neurodegeneration by using mice disease models or differentiated human pluripotent stem cells. We would like to focus on α-synuclein and Tau. In particular, MFDs in our project will allow us for i) the recreation of specific neuronal networks of neuroanatomical relevance in neurodegenerative diseases in vitro; ii) to investigate factors mediating the propagation of the neurodegenerative process in models of ND and iii) to monitor early/late physiological changes mediated by amyloid proteins. Due that α-synuclein and Tau behave as “prion-like” elements we will study in our culture platforms whether crucial neural functions (e.g., neuronal networks dynamics) or the onset and progression of neuronal dysfunctions appeared during the spreading of deleterious signals triggered by these “prion-like” elements in order to understand their propagation and neuron specific effects in vivo in parallel experiments.

**Project PI2016/04: The ALS CIBERNED Challenge: Accelerating New Drug Discovery**

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<td>López de Munain Arregui, Adolfo</td>
<td>CIBERNED, Biodonostia Research Institute, San Sebastian</td>
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<td>Ferrer Abizanda, Isidro</td>
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<td>Soriano García, Eduardo</td>
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Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder characterized by progressive weakness and atrophy of skeletal muscles until paralysis and death. Multi-factorial and multi-systemic neurotoxic mechanisms are the cause of a common pathological entity: motor neuron (MN) degeneration in central nervous system (CNS). The disease may spread to frontal cortex and other regions leading to frontotemporal lobar degeneration (FTLD) and dementia. The enormous heterogeneity in the patterns of clinical symptoms, anatomical onset, disease progression and survival among patients suggests that pathogenic pathways for MN degeneration are variable at topographical and pathophysiological levels. Moreover, involvement of the frontotemporal cortex in ALS and the motor system in FTLD-TDP-43 links ALS and FTLD-TDP-43 within the spectrum of TDP-43 proteinopathies. This complex scenario for ALS would explain the unfavorable outcomes collected in clinical trials.

Future research must consider:

1) Identification of clinico-pathological markers in brain, CSF and blood specific of ALS subtypes, which will allow the design of individual intervention treatments.

2) Identification of new altered molecular pathways in different CNS regions to unveil
common and specific profiles of regional vulnerability.

3) Identification of converging pathways of MN and frontal cortex degeneration, which will allow the generation of neuroprotective strategies to halt MN degeneration.

The present collaborative project integrates 4 CIBERNED clinical/basic research groups (Adolfo López-de-Munain, Isidro Ferrer, Eduardo Soriano and Javier Fernández-Ruiz), with the purpose to address these 3 hot points in ALS/FTLD-TDP43 complex. Collaborative efforts will be extended to other CIBERNED groups.

The first part of the project will create a unique Spanish ALS cohort by unifying several Spanish individual registries with standardization of clinical data and methods of biological sample collection. Large ALS cohort provides necessary potency to achieve the following milestones:

a) Identification of novel clinical and molecular signatures categorizing different ALS subtypes.

b) Identification of new altered molecular pathways in the motor system and frontal cortex in post-mortem brains of ALS (in comparison with FTLD-TDP-43).

c) Discovery of novel biomarkers in brain, CSF, blood and striate muscle for diagnosis and prognosis.

d) Drawing a pathophysiological map of the disease to detect potential targets for treatment.

These objectives will be accomplished by carrying out combined ‘omics and computational integrative analyses in samples from alive ALS patients and post-mortem tissues.

The second part of the project is aimed at exploring neuroprotective targets following the hypothesis of a crosstalk between TDP-43 proteinopathy and mitochondrial defects as a common pathogenic pathway to MN degeneration (and probably frontal/temporal cortex degeneration). Three main points will be analyzed:

a) Efficacy of patented compounds as novel inhibitors of RyR Ca2+ channel as a way to protect neuromuscular system from cytosolic Ca2+ overload induced by pathological TDP-43-mediated mitochondria defects.

b) Study of pharmacological targets within the endocannabinoid system against TDP-43-mediated mitochondria defects.

c) The role of Eutherian Armcx proteins on mitochondrial dynamics in relation to TDP-43 pathology as a promising target for MN neuroprotection.

Both parts of the project are interconnected and will be carried out by the collaborative work of the four group members of the proposal.
Deregulated protein and Ca2+ homeostasis underlie synaptic dysfunction and neuronal death in neurodegenerative diseases including Huntington’s (HD) and Alzheimer’s disease (AD). Early symptoms of synaptic dysfunction in AD are characterized by a reduced response to external stimuli and a progressive loss of post-synaptic dendritic spines in excitatory synapses, which correlates strongly with AD symptoms and memory loss. Previous to spine loss, atrophy of the spine apparatus, a synaptopodin-positive ER-associated membranous structure, is particularly relevant since the spine apparatus has an essential role in regulating the fate of calcium entering the spine upon synaptic activation and could be considered the structural base for synaptic plasticity. Dendritic failure in AD is also largely related to the accumulation of pathogenic protein aggregates that have been related to a defective unfolded protein response (UPR) and to changes in actin polymerization as a result of increased cofilin de-phosphorylation in AD.

DREAM, also known as calsenilin or KChIP3, is a Ca2+ binding protein that regulates Ca2+ homeostasis and neuronal survival through transcriptional control of target genes and through protein-protein interactions. DREAM was originally associated with AD because of its interaction with presenilins. Preliminary results from our group show changes in the expression of DREAM in cerebral cortex and hippocampus in J20 and Tg2576 mice, two murine models of AD, as well as in frontal cortex from AD patients. Genetic manipulation of DREAM levels or chronic repaglinide treatment modified cognition in Tg2576 and J20 mice.

These data support the idea that, like in HD, an early down regulation of DREAM level in neurons during the pre-symptomatic phase of the AD, is part of a neuroprotective mechanism and suggest that DREAM could be a novel and wide spectrum target for therapeutic intervention in AD. The aim of this collaborative research program is to investigate whether cognition improvement in AD mouse models after repaglinide restores the early response to neuronal activation (induction of immediate-early genes Npas4, Nr4a1 and Arc) and is related to changes in synaptopodin-positive dendritic spines, in cofilin dephosphorylation and/or in increased ATF6 processing and UPR activation in hippocampal neurons.
Mutations in the leucine-rich repeat kinase 2 (LRRK2) gene are the most common genetic cause of Parkinson’s disease (PD). Like idiopathic PD (iPD), it is believed that the onset of PD associated with mutations in LRRK2 (LRRK2-PD) occurs before the onset of motor symptoms, but information on the prodromal phase is scarce. The subjects with mutations in LRRK2 who do not show motor symptoms (LRRK2-NMC), but who present a higher risk of developing LRRK2-PD, represent a unique opportunity to investigate the early pathophysiology of LRRK2-PD and to identify molecular profiles that could be candidate biomarkers associated with the prodromal and/or manifest phases of LRRK2-PD.

To address these fundamental issues, we have used four different and complementary approaches to analyze the biological samples of selected patients. In the first year of this collaborative project we carried out the first discovery phase, in which we studied LRRK2-NMC subjects (subdivided according to whether they present normal/abnormal DAT-SPECT), LRRK2-PD patients, iPD patients and the healthy controls. In these five groups, we have studied the metabolic profiles in serum and we have characterized the epigenome in peripheral blood to determine the metabolic and epigenomic changes that occur in the prodromal and manifest phases of LRRK2-PD. In addition, we have studied the number of copies of mitochondrial DNA (mtDNA) and its release in fibroblasts derived from patients.

Our data show a significant alteration in the lipid metabolism of subjects with mutations in LRRK2 and point to certain metabolites as potential biomarkers of PD status. We have also identified significant epigenetic changes in the peripheral blood of patients with overt PD in incipient stages of motor disease. Finally, the results obtained up to now in fibroblasts indicate that the alteration of mtDNA replication and transcription is a common factor underlying idiopathic and familial PD, supporting the hypothesis that transcription and replication are alternative processes and that its regulation is altered in PD.

To conclude, up to now we have identified some candidate biomarkers of different nature that may be useful as biomarkers of the prediagnostic phase of PD. Throughout the second year of this collaborative project we expect to complement the studies of the discovery phase, as well as to use an integrative approach using systems biology for the identification of the physiopathological pathways and the molecular profiles associated with the prodromal and manifest phases of LRRK2-PD. We will also carry out the validation phase of those markers of greatest interest identified in the first phase of discovery.

Finally, during the second semester of 2017, the eighth call was launched, which was again evaluated by the ANEP and resolved at the end of that same year with the granting of three new projects:
The funding approved for this eighth call was 325,000€ per year for 2 years, which meant a total allocation of 650,000€ to the eleven participating CIBERNEd research groups. Below is a brief description of the scientific activity carried out by each of the projects during their first year of execution:

**Project PI2017/1: Study of the microRNA in the cerebrospinal fluid exosomal compartment as a biomarker of frontotemporal dementia and a tool for understanding the biological basis of the disease.**

Frontotemporal degeneration (FTD) is a clinical, genetic and pathologically heterogeneous neurodegenerative disease, characterized by atrophy of the frontal and temporal lobes, resulting in a progressive alteration of behavior and/or language. Neuropathological studies indicate that 50% of cases present brain aggregates of the TDP43 protein (FTD-TDP), which has a pivotal function in the RNA metabolism. There is no specific biomarker for FTD, nor any that could distinguish between patients with DFT-TDP from the rest (typically with Tau: FTD-Tau). Exosomes are vesicles of 50-100nm in diameter that act as intermediaries in intercellular communication and can alter the transcriptional metabolism of the recipient cells through the microRNAs (miRNA) contained within. Due to their presence in most of the body fluids, exosomes have become a novel and attractive source for the study of biomarkers in peripheral tissues. Preliminary results obtained by the PI’S group have allowed us to elucidate for the first time part of the miRNA content that is found in the exosomal compartment of the cerebrospinal fluid (CSF; see Annex). From a large panel containing 752 different miRNAs we were able to identify 130 that are stably expressed in the CSF. Our analysis has elucidated differences in some of these microRNAs among patients with the semantic variant of DFT (characterized by presenting aggregates of TDP43) and healthy controls. Objective: The present project intends to examine (i) the impact of candidate miRNAs on global gene expression pattern, (ii) the consequences of these miRNAs on synaptic function and neuronal survival and (iii) their sensitivity and specificity as a diagnostic biomarker for FTD and / or the FTD-TDP
subtype. Design: To analyze the sensitivity and specificity of these miRNAs as biomarkers of DFT, as well as their ability to distinguish the DFT-TDP variant of DFT-Tau, a total of 144 subjects have been included (30 controls, 20 with Alzheimer’s disease, 28 with FTD (behavioral variant), 32 with semantic dementia and 34 with PSP / DCB). Results: The study has shown 4 species of miRNAs that are differentially expressed in the subgroup of patients with PSP / DCB. These are miR-146, miR-15, miR-361 and miR-708. Conclusions: The conclusions of this first phase of the study are that there are expression profiles of miRNAs in the exosomal CSF compartment that could be used as possible biomarkers for the in vivo diagnosis of the pathological subtype of the PSP / DCB group, within the spectrum of the DFT.

During the second half of the study (second year) the functional / mechanistic studies of these 4 miRNAs will be carried out, from neuronal cultures in which the levels of the miRNAs of interest will be modulated, analyzing the expression pattern by means of high density microarrays, neuronal viability and functionality and synaptic density, as well as its role in different autophagy functions.

**Proyecto PI2017/2: Glucocerebrosidase and Neurodegenerative Proteinopathies.**

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<td>Kulisevsky Bojarski, Jaime</td>
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It has only been recently uncovered a link between GBA 1 mutations (the gene coding for glucocerebrosidase) and the development of synucleinopathies such as Parkinson’s disease (PD) and dementia with Lewy bodies (DLB). Studies performed on patients suffering from Gaucher disease (a lysosomal storage disorder caused by GBA1 mutations) revealed that GBA1 mutations are the most common genetic risk for PD and DLB. PD patients carrying GBA1 mutations develop PD earlier than non-carriers and are more frequently affected by cognitive decline and neuropsychiatric symptoms, as shown in studies performed by clinical researchers from the applicant team. Furthermore, it is worth noting that the aggregation of alpha-synuclein (SYN) per se induces a GCase loss-of-function. In other words, both types of PD patients (e.g., with and without GBA1 mutations) are indeed susceptible of being treated with GCase. This also applies to patients suffering from dementia with Lewy bodies. Moreover, how exactly the aggregation, degradation and subcellular processing of SYN and GCase activity are coupled together—and vice versa— still is an open question with limited experimental evidence to date. Preliminary studies carried out in our laboratory showed that neurons from the nucleus basalis of Meynert, substantia nigra pars compacta and locus ceruleus are the ones showing the highest GCase baseline levels of expression than any other brain area. Finally, it is also well known that the earliest neurodegenerative phenomena in Alzheimer’s disease (AD) were typically found in cholinergic neurons from the basal forebrain. Accordingly, the main aims of this project are summarized as follows:

1. To evaluate whether a viral vector-mediated increase of GCase activity in the substantia nigra could slow down/stop the progressive SYN-induced dopaminergic neurodegeneration.
2. To evaluate whether a viral vector-mediated increase of GCase activity in the nucleus basalis of Meynert could slow down/stop the progressive Tau-induced cholinergic neurodegeneration.

3. To disclose whether patients with mild cognitive impairment (MCI) carrying GBA1 mutations are progressing towards AD quicker than non-carriers.

Neurospecific adenoassociated viral vectors (AAVs) will be used to overexpress either mutated SYN or Tau proteins into the substantia nigra pars compacta or in the nucleus basalis of Meynert, respectively. Experiments will be carried out in rats (AAV9-SynA53T) and in NHPs (AAV9 SynA53T and AAV9-Tau301L). Next, a GBA1-coding AAV5 will be used to increase GCase activity to further induce SYN and Tau clearance. In parallel, genetic studies will be conducted looking for a potential association between GBA1 mutations and the incidence of AD in patients. Besides the strong translational focus of this project, it is expected that the experiments described here will provide new clues elucidating the crossroads between GCase and SYN homeostasis as well as in tau-related neurodegenerative proteinopathies.

**Project PI2017/4: Glial dysfunction in Alzheimer’s disease: pathogenic implications and clinical potential.**

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<thead>
<tr>
<th>PRINCIPAL INVESTIGATOR</th>
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<tr>
<td>Vitorica Ferrández, Francisco Javier</td>
<td>CIBERNED, Universidad de Seville</td>
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<tr>
<td>Gutiérrez Pérez, Antonia</td>
<td>CIBERNED, Universidad de Malaga</td>
</tr>
<tr>
<td>Cuadrado Pastor, Antonio</td>
<td>CIBERNED, Autonomous Universidad, Madrid</td>
</tr>
<tr>
<td>Sáez Valero, Javier</td>
<td>CIBERNED, Miguel Hernández University, Elche</td>
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<tr>
<td>Comella Carnice, Joan Xavier</td>
<td>CIBERNED, Vall d’Hebron University Hospital, Barcelona</td>
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In the present project, we propose a new pathogenic scenario in Alzheimer’s disease, where microglial dysfunction would suppose an astroglial hyperactivation. This hyperactivation could be involved in the neurodegenerative process and, therefore, it would be necessary to reproduce this dysregulation of the innate brain immune system, in animal models, to increase its predictive value and ensure greater success of human therapies.

To emulate this microglial dysfunctionality, we are developing genetic models that allow us to reduce the number of microglia in Abeta (APPsl) or Tau (TauP301S) models. In the same way, we are also developing a genetic model that allows the elimination of active microglia. With these models, we hope to determine the microglial role on the pathology and, in parallel, their impact on astroglial activation. The study of the possible microglial and / or astroglial “signature” in cerebrospinal fluid (CSF) collections of subjects with amnestic-type mild cognitive impairment (prodromal stages), to Alzheimer’s subjects characterized with classic CSF markers has also stated during this year.

Finalmente, durante el último semestre de 2018, se lanzó la novena convocatoria que fue de nuevo evaluada por la ANEP y resuelta a finales de ese mismo año con la concesión de 3 nuevos proyectos:
2018 CALL

<table>
<thead>
<tr>
<th>CODE</th>
<th>TITLE</th>
<th>COORDINATOR</th>
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<tbody>
<tr>
<td>PI2018/01</td>
<td>CB1R-GRP78 interaction: a new mechanism regulating the neuroprotective activity of cannabinoids ?</td>
<td>Guzman Pastor, Manuel</td>
</tr>
<tr>
<td>PI2018/02</td>
<td>Cellular and molecular analysis of seeding and progression of tau in animal and cell models of different human tauopathies</td>
<td>Ferrer Abizanda, Isidro</td>
</tr>
<tr>
<td>PI2018/06</td>
<td>Targeting CPEB-dependent impaired mitochondrial metabolism and synaptic and stem cell function in Huntington's disease</td>
<td>Lucas Lozano, José Javier</td>
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</tbody>
</table>

The funding approved for this eighth call was 300,000€ per year for 2 years, which meant a total allocation of 600,000€ to the twelve participating CIBERNED research groups. Below is a brief description of the scientific activity carried out by each of the projects during their first year of execution:

Project PI2018/01: CB1R-GRP78 interaction: a new mechanism regulating the neuroprotective activity of cannabinoids ?.

PRINCIPAL INVESTIGATOR | INSTITUTION
-----------------------|-------------------
Guzman Pastor, Manuel  | CIBERNED, Complutense University of Madrid
Ginés Padrós, Silvia   | CIBERNED, University of Barcelona
Fernández Ruiz, Javier | CIBERNED, Complutense University of Madrid
Mengod Los Arcos, Guadalupe | CIBERNED, Institute of Biomedical Research IDIBAPS-CSIC, Barcelona

Understanding the processes of neuron survival/death is a pivotal issue for characterizing the aetiology and progression of neurodegenerative diseases and, therefore, for designing rational therapies for their treatment. In this context, since CIBERNED was funded, groups in the present consortium have been collaborating in the study of how type-1 cannabinoid receptor (CB1R), the main molecular target of endocannabinoids and cannabis active components, confers neuroprotection in preclinical models of neurodegeneration. Of note, two cannabinoid-based medicines have already been approved by EMA to palliate symptoms of neurodegenerative diseases as spasticity in multiple sclerosis (Sativex®) and seizures in refractory epilepsies (Epidiolex®). However, the assessment of the physiopathological relevance and therapeutic potential of CB1R-evoked neuroprotection is still hampered, at least in part, by the lack of knowledge on the neuron-subpopulation selectivity of CB1R action. CB1R action may be modulated in different manners, being conceivably one of them its association to intracellular proteins through its large cytoplasmic C-terminal domain. Recently, we have purified the CB1R C-terminal domain and have conducted wide-scale proteomic analyses and yeast two-hybrid experiments aimed at finding receptor interactors. The combination of these two approaches has rendered a list of potential CB1R-interacting proteins, among which there is one that clearly stands out: glucose-regulated protein 78 (GRP78/BiP/Hspa5). Hence, the general objective of this project is to characterize in detail the neurobiological and neuropathological role of GRP78 as a potential CB1R interactor. Our initial hypothesis is that CB1R, through its C-terminal domain, is capable of binding GRP78 in a spatiotemporally-selective manner; this modulates CB1R-mediated signalling on specific neuron subpopulations; and this, in
turn, tunes CB1R neuroprotective action. We will appraise this issue through the following specific objectives:

1. Characterizing CB1R-GRP78 interaction in cultured cells.
2. Characterizing CB1R-GRP78 interaction in mouse brain.
3. Defining the functional relevance of CB1R-GRP78 interaction in mouse models of neurodegeneration.
4. Mapping CB1R-GRP78 interaction in post-mortem brain samples from human neurodegenerative diseases.

These studies, which will put together the experience and complementary abilities of the 4 groups in the consortium, will provide a better understanding of the contextual features of CB1R-coupled neuronal signalling, which may thus contribute to (i) developing more selective neuroprotective strategies targeting the endocannabinoid system, and (ii) gaining deeper insight into unwanted effects of cannabinoid-based medicines used in the management of neurodegenerative diseases.
Project PI2018/02: Cellular and molecular analysis of seeding and progression of tau in animal and cell models of different human tauopathies.

**PRINCIPAL INVESTIGATOR**

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<tr>
<th>Name</th>
<th>INSTITUCIÓN</th>
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<tbody>
<tr>
<td>Ferrer Abizanda, Isidro</td>
<td>CIBERNED, Bellvitge Institute of Biomedical Research, Barcelona</td>
</tr>
<tr>
<td>Del Río Fernández, José Antonio</td>
<td>CIBERNED, Catalan Institute de Bioengineering, Barcelona</td>
</tr>
<tr>
<td>Ávila de Grado, Jesús</td>
<td>CIBERNED, Center for Molecular Biology &quot;Severo Ochoa&quot; CSIC-UAM, Madrid</td>
</tr>
</tbody>
</table>

Tauopathies are clinically, biochemically and anatomically heterogeneous neurodegenerative diseases, identified by the deposit of excessively phosphorylated tau protein, abnormally folded and forming aggregates in neurons, astrocytes and oligodendrocytes with particular characteristics for each disease. Neurons and glial cells have an active and interactive role in the pathogenesis. These diseases have a progressive character with selective affection that extends over time to the entire brain and manifests itself with certain neurological deficits once a threshold of damage has been reached. The present project has the following objectives:

**Objective 1:** To determine specific disease differences in the seeding and spreading of tau species using microfluidic devices with primary cultures of neurons, astrocytes and mixed, with different species of tau derived from human taupathies, as well as organotypic cultures with barriers. In a second phase, neural or mixed cultures derived from iPSc will be used. The neurons or glial cells cultured from I) wild mice (C57BL6 / J), II) mutant mice (P301S) or iii) iPSc, will be treated with sarkosil-insoluble fractions from human brain homogenates or with recombinant tau.

**Objective 2:** To determine the role of microglia cells in the propagation of pathological tau. Specifically, to study potential receptors and mechanisms involved in the propagation of tau in these cells.

**Objective 3:** To determine the specific differences in seeding and spreading of tau pathology after intracerebral inoculations (hippocampus) in wild-type mice of tau-enriched homogenates from pure and combined neuronal and glial human taupathies that accumulate 3Rtau or 4Rtau or 4Rtau + 3Rtau: Primary age-related tauopathy (PART), Aging related tau astroglialopathy (ARTAG), globular glial tauopathy (GGT), Pick disease (PiD), Argyrophilic grain disease (AGD) and Gerstmann-Sträussler-Scheinker syndrome (GSS). Assessment of the involvement of neurons and glial cells as effectors and as targets of taupathy.

**Objective 4:** To analyze in vitro, possible changes in the activity of neural networks between the interconnected areas subjected to tau seeding, and to quantify the variations of the individual neuronal activity and the general alterations of the network. We will use genetically-encoded calcium indicators to monitor the evolution of the network over several days. In addition, we will modulate the neuronal activity of the network by using in vitro optogenetic techniques. The data of spontaneous activity at cellular resolution will be analyzed using advanced and customized software NETCAL or FLUOSNNAP. Ca2+ waves, spontaneous activity frequency, activity patterns that cover the network (network bursts) and their alteration during the process of seeding and spreading will be investigated. Then, theoretical information algorithms will be used among all the pairs of neurons registered to identify functional alterations of the network; and Objective 5: To determine the effect on seeding and spreading after combined inoculation in wild mice of taupathy homogenates (PART, ARTAG) and α-synucleinopathy (Lewy body disease: LBD and multisystem atrophy: MSA); and use of inoculates in P301S and snca transgenic mice, for analysis of co-morbidity which is common in human pathology above sixty-five years.
Project PI2018/06: Targeting CPEB-dependent impaired mitochondrial metabolism and synaptic and stem cell function in Huntingtons disease.

PRINCIPAL INVESTIGATOR

Lucas Lozano, José Javier

Iglesias Vacas, Teresa

Muñoz Cánoves, Pura

Fernández Chacón, Rafael

Fariñas Gómez, Isabel

Mir Rivera, Pablo

INSTITUTION

CIBERNED, Center for Molecular Biology “Severo Ochoa” CSIC-UAM, Madrid

CIBERNED, Institute of Biomedical Research CSIC-UAM, Madrid

CIBERNED, Pompeu Fabra University, ICREA, Barcelona

CIBERNED, University of Seville

CIBERNED, University of Valencia

CIBERNED, Virgen del Rocío University Hospital, University of Seville

Huntington’s disease (HD) and multiple inherited spinocerebellar ataxias are caused by polyQ-encoding expanded CAG repeats in different genes. Cytoplasmic Polyadenylation Element Binding Proteins (CPEB1-4) regulate translation of specific mRNAs by modulating the length of their poly(A)-tail. Interestingly, the CPEB Drosophila orthologue Orb2 was identified in an enhancer/suppressor screening as one of the few genes that modify both CAG mRNA- and polyQ-induced toxicity. However, a role of CPEBs in neurodegenerative disorders had not been fully explored until we recently analyzed the status of CPEBs in brain of HD patients and mouse models. We found increased CPEB1 and decreased CPEB4 levels (Parras et al., manuscript in preparation). Since neuronal mitochondrial function depends on proper CPEB1 mediated translation and CPEB1/CPEB4 crosstalk plays a key role in mitotic cell cycle progression, here we hypothesize that imbalanced CPEBs in HD leads to altered mitochondrial function and defective tissue homeostasis due to impaired stem cell function. In support of this hypothesis, we have recently reported that 9% of the transcripts in HD mouse brains are aberrantly deadenylated (Parras et al. Nature in press) and these include genes that are essential for mitochondrial function such as SLC19A3, several NDUFVs, and PRKD1, as well as CPEB4 itself -which controls FoxO3/4 translation- and is therefore expected to affect proper renewal of both neural and muscle stem cells. In this collaborative proposal we take advantage of the unique expertise of the participants to tackle specific aims that require multidisciplinary approaches. In the first objective, we aim to target mitochondrial deficit by: a) characterizing the role of the thiamine transporter SLC19A3 (hTHTR2) in HD pathogenesis and b) promoting a clinical trial of vitamin supplementation in collaboration with Dr. Pablo Mir at Hosp. Virgen del Rocío. In the second objective we will further characterize the effect of decreased expression of PRKD1, a kinase that preserves mitochondrial function and potentiates the elimination of mitochondrial reactive oxygen species (ROS) and neuronal survival in an excitotoxic environment as we have recently reported (Pose-Utrilla et al. Nat. Commun. 2017). We will also perform rescue experiments with AAVs for the neurospecific expression of a neuroprotective form of the kinase in HD models where synaptic activity will also be evaluated. Finally, in the third objective we will explore whether CPEB4 modulation may be used to enhance adult neural and muscle stem cell function as we have evidence to believe that the role of CPEBs in the division of adult neural stem cells (NSCs) from subventricular or subependymal zone (SVZ/SEZ) can be key to the maintenance and potential of these cells in normal and HD brains. On the other hand, regarding muscle stem cells (MuSCs), FoxO3/4 polyadenylation changes
in CPEB4 modified mice (Parras et al. Nature in press) and we have preliminary evidence of FoxO transcription factors are potential regulators of both basal autophagic activity required for renewal of stem cells and for defining the cellular heterogeneity of satellite cells. We will therefore also analyze whether CPEB4 modification attenuates the sarcopenia of HD-mice and their MuSC functional abnormalities.

The cooperative activity program of CIBERNED has so far involved a global budget of approximately 9,078,174€ distributed in the thirty-three cooperative projects mentioned above. A total of 59 CIBERNED research groups have actively participated at least in one cooperative project, which represents 93.6% of all the groups belonging to CIBERNED during this period, in addition to ten associated external groups. In addition, 51 groups (80.9%) have participated in more than one cooperative project and projects from the 2017 and 2018 calls are still active, with the involvement of 23 CIBERNED research groups (46%).

By analyzing previous calls, and considering that some are already closed and others still ongoing, an estimation of the budget invested can be made by individual project and participating group. Thus:

<table>
<thead>
<tr>
<th>Call</th>
<th>Budget</th>
<th>Duration in years</th>
<th>Number of groups</th>
<th>Number of projects</th>
<th>Average budget for project and year</th>
<th>Average budget for project and group</th>
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</thead>
<tbody>
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<td>2010</td>
<td>2.322.100 €</td>
<td>3</td>
<td>40</td>
<td>6</td>
<td>129.005,56 €</td>
<td>19.350,83 €</td>
</tr>
<tr>
<td>2011</td>
<td>1.192.000 €</td>
<td>2</td>
<td>26</td>
<td>4</td>
<td>149.000,00 €</td>
<td>22.923,08 €</td>
</tr>
<tr>
<td>2013</td>
<td>1.376.000 €</td>
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<td>23</td>
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<td>137.600,00 €</td>
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<td>2014</td>
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<td>8</td>
<td>2</td>
<td>133.018,50 €</td>
<td>33.254,63 €</td>
</tr>
<tr>
<td>2015-I</td>
<td>690.000 €</td>
<td>2</td>
<td>11</td>
<td>3</td>
<td>115.000,00 €</td>
<td>31.363,64 €</td>
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<tr>
<td>2015-II</td>
<td>700.000 €</td>
<td>2</td>
<td>10</td>
<td>2</td>
<td>175.000,00 €</td>
<td>35.000,00 €</td>
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<tr>
<td>2016</td>
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<td>19</td>
<td>5</td>
<td>101.600,00 €</td>
<td>26.736,84 €</td>
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<tr>
<td>2017</td>
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<td>11</td>
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<td>29.545,45 €</td>
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<tr>
<td>2018</td>
<td>600.000 €</td>
<td>2</td>
<td>12</td>
<td>3</td>
<td>100.000,00 €</td>
<td>33.333,33 €</td>
</tr>
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INTERNATIONAL RELATIONS
International scientific collaboration increases more and more, not only because of the availability of international funding and the drive of modern communication technologies, but also because science itself has become a truly international collaborative activity. In particular, the scope and scale of the problem of neurodegenerative diseases in today’s society require a global response to confront this great challenge and thus has been recognized by various international institutions such as the European Union (EU), the Organization for Economic Cooperation and Development (OECD), the World Health Organization (WHO), etc., and the industrialized countries that constitute the G8. This global concern has led to the creation of the World Dementia Council (WDC) with the aim of collectively spur action against dementia worldwide in the areas of research, clinical care and social awareness.

The leaders of governments, businesses and academia also recognize the need for a coordinated strategy to address this major global challenge for health systems. There is consensus among all stakeholders on the need to build capacities, infrastructures and R&D resources in the field of neurodegenerative diseases. As a result, WHO has decided to establish a global observatory on dementia to monitor the prevalence of the condition and resources to care for patients in Member States as well as to track the establishment of national plans and policies against dementia.

There is also a pressing need for global participation and a commitment to a significant increase in investment in skills and resources to reduce the duration of these chronic brain pathologies and/or the number of people at risk. This budgetary effort should be accompanied by sound policies and legislative initiatives to encourage public-private partnerships. History has shown that collaboration between academic researchers, government agencies and pharmaceutical and biotechnology companies is an essential ingredient in promoting this type of ambitious initiatives, especially when resources are limited.

In this context, in recent years CIBERNED, has given a boost to its relations with international organizations in the area of research in neurodegenerative diseases such as the EU Joint Programme for Research in Neurodegenerative Diseases (JPND) and the Network of Centres of Excellence in Neurodegeneration (COEN), among other initiatives.
The EU Joint Programming for Research in Neurodegenerative Diseases (JPND) is an innovative collaborative research initiative created to address the growing challenges posed by these disorders. The JPND is a pioneering example of joint programming for the promotion of research within the European Union aimed at scientific challenges requiring a response that exceeds the capacity of a single country, based on the alignment of national research programs devoted to these challenges. Its objective is to enhance the impact of research by aligning existing national research programs and the identification of common objectives whose scope would benefit from joint action. The JPND Scientific Advisory Committee has significant participation of two CIBERNED researchers, Drs. Jesús Avila and Jesús de Pedro, as well as Dr. Angel Cedazo-Minguez, from the Karolinska Institute in Stockholm and member of the CIBERNED Scientific External Advisory Committee.

The Research Strategy designed by JPND provides a framework for future investments and shows that the research effort within the European Union can be leveraged to improve care on prevention, diagnosis and treatment of patients suffering from these diseases.

To achieve impact there is a need to encourage novel as well as multidisciplinary approaches, and to strengthen and extend existing capabilities across the full spectrum of basic, clinical, health and social care, and translational research. To that end, a number of priority areas for future research have been identified: The origins of neurodegenerative diseases; Disease mechanisms and models; Disease definition and diagnosis; Treatment and prevention; Health and social care.

This Research Strategy also provides a framework of opportunities for countries involved in JPND and willing to participate in joint actions, which will be implemented through co-operative activities that realign or link national investments to achieve increased impact, and the provision of new funding. A guiding principle for its delivery will be that the research to be supported is of the highest scientific quality.

In this regard, during 2011 took place the first call for European research projects JPND. Under the theme “Optimization of biomarkers and harmonization of their use in the clinic”, four transnational projects were awarded for the period 2012-2015. Subsequently, in late 2012 a new call under the topic “Identifying protective factors and genetic and epigenetic risk in neurodegenerative diseases” was launched, resulting in five approved projects for the period 2014-2017. During 2018, there have been no CIBERNED research groups involved in active projects within the joint European Union program for research on neurodegenerative diseases (JPND).

Unfortunately, despite repeated attempts from CIBERNED to modify this situation, the decrease in the budget dedicated to the JPND calls and the restrictions on the participation of the CIBERNED groups (especially the strict requirement of doing so only as a coordinating group) imposed in recent years by the ISCIII as the funding agency have ended up discouraging the participation of the CIBERNED groups in the JPND calls, with a gradual but very significant decrease in the number of applications submitted to these calls in recent years. From CIBERNED, as
the only Research Center specifically focused on the study of neurodegenerative
diseases, we will continue to demand the possibility of participating in equal con-
ditions with other institutions, so that it is the evaluation of the scientific merits
of each application that determines the approval of the corresponding projects
on a competitive basis.

CENTERS OF EXCELLENCE IN NEURODEGENERATION (COEN)

A major obstacle to the advancement of research on neurodegenerative diseases is the
relative lack of common standards and mechanisms for validation of potentially relevant
results in preclinical studies, and clinical studies based on population. One approach to
deal with these challenges on a large scale is through a more effective use of large centers
and institutes, where there is already the necessary critical mass of resources and exper-
tise. Increased collaboration between national centers of excellence should also provide
the opportunity to accelerate progress in understanding the basic mechanisms of disea-
se, and the identification of new therapeutic approaches.

To this end, on June 10, 2010, the Canadian Institutes of Health Research (CIHR), the Ger-
man Centre for Neurodegenerative Diseases (DZNE, Germany) and the Medical Research
Council (MRC, UK) launched a funding initiative to establish a collaborative approach to
research in neurodegenerative diseases, called “Centers of Excellence in Neurodegene-
ration (COEN)”. These founding members were later joined by other European institu-
tions and thus, in December 2011 the COEN membership application by CIBERNED-CIEN
Foundation was approved, recognizing the scientific excellence in both basic and clinical
science of the institution which became part of the COEN Oversight Group.

In 2012, CIBERNED and CIEN Foundation joined this Committee to participate actively in
the design of the future COEN scientific strategy. Both institutions are represented by
Dr. Miguel Medina, CIBERNED Deputy Scientific Director and member of the CIEN Founda-
tion Scientific Advisory Board. During 2015 the French Agence Nationale de la Recherche
(ANR) has also been acknowledged as a new COEN member.

Current COEN members are:

• Canadian Institutes of Health Research (CIHR)
• Deutsche Zentrum für Neurodegenerative Erkrankungen (DZNE, Germany)
• Medical Research Council (MRC, United Kingdom)
• Flanders Institute of Biotechnology (VIB Flanders, Belgium)
• Health Research Board (HRB) / Science Foundation Ireland (SFI), Ireland
• Ministero della Salute (MDS, Italy) Centre of Excellence for Brain Research (MES-
RS), Slovakia
• CIBERNED-Fundación CIEN, Spain
• Agence Nationale de la Recherche (ANR), France

The overlapping of the COEN group members with those of the JPND will ensure that
their complementary objectives progress in close cooperation with each other. This is
accomplished through a two-step process, involving expert workshops for the analysis
of needs, followed by a call for proposals for collaborative teams between PIs within the
participating national Centers of Excellence.

The first phase of the COEN initiative began at the end of 2010 and was intended to esta-
blish common resources and methodological approaches to support future studies. Some of the key issues addressed have been: the refinement and validation of cellular and animal disease models; the development of new measures to define patient subgroups for clinical trials; the identification of new biomarkers to support translational research; the development and harmonization of cognitive test batteries for diagnosis and follow-up of disease progression; and the establishment of common computer platforms to improve data analysis and exchange.

Phase II of the initiative was launched during the year 2013, with the aim of catalyzing collaborative research between centers with a critical mass of resources and expertise to thus promote a radical change in research on neurodegeneration. To do this, the countries participating in COENs contributed a total amount of 5.5 million € (of which Spain has provided 600,000 €) in this call to establish an innovative and progressive research program to address the major challenges in this field. The call was intended to encourage the community to think outside the pre-established frameworks and stimulate new and creative approaches and solutions to the challenges of research in neurodegeneration.

This call of Pathfinder projects intends to combine the strengths of research groups through Centers of Excellence in at least two partner countries to provide a truly collaborative effort and value that will advance our approach to research neurodegeneration. The projects would address issues that are not easily financed through standard grant mechanisms from COEN partners, and is expected to further collaboration between Centers of Excellence, the projects would also serve to provide a platform for future collaboration with industry.

The approved projects with the participation of CIBERNED that have been active during 2018 is described below:

**COEN4016: Focused ultrasound modulation of neuromelanin accumulation in a humanized rat model of Parkinson’s disease.**

**Project partners:** Miquel Vila (Spain), Stéphane Lehericy (France).

Parkinson’s disease (PD) is a common neurodegenerative disorder which incidence is increasing due to the progressive aging of the world’s population. Despite the availability of symptomatic treatments, PD remains incurable, as current treatments do not halt nor slow the progressive loss of neurons in these patients. In PD there is a selective degeneration of neurons containing the pigment neuromelanin (NM), especially dopamine-producing neurons of the substantia nigra, which leads to the classical motor symptoms of the disease. In humans, NM appears in early childhood and accumulates progressively with age, since neurons cannot degrade or eliminate this pigment. We have recently demonstrated, using a novel rat model genetically engineered to produce human-like NM up to levels reached in elder humans, that age-dependent intracellular NM accumulation ultimately compromises neuronal function and triggers PD pathology when reaching a certain threshold. Here we will determine whether transcranial focused ultrasound (tFUS), an emerging non-invasive technology, is able to lower NM levels below their pathogenic threshold in NM-producing PD rats and prevent, halt or delay neuronal dysfunction and degeneration. If successful, this proposal will lay the groundwork for the development of a novel disease-modifying therapy for PD based on the modulation of NM levels with tFUS.
COEN4017: Developing preclinical and clinical biomarkers of NRF2 pathway activation for therapeutic application in neurodegenerative diseases.

Project partners: Pamela Shaw (UK), Antonio Cuadrado (Spain)

Neurodegenerative diseases such as Alzheimer’s (AD) and motor neuron disease (ALS/MND) cause cell death of different populations of nerve cells. These conditions are very distressing for sufferers and their families. There is a severe lack of treatments available to slow disease progression and clinical trials have had high failure rates partly because there is no way to demonstrate that a drug is reaching the nervous system in the right amounts to protect the nerve cells from injury. Although the underlying causes that trigger these diseases are complex (multiple genes and environmental factors), there is substantial overlap in the cell pathways that lead to neurodegeneration. This project is focused on a master cellular pathway (sometimes called the programmed cell-life pathway) controlled by a molecule NRF2 that promotes cell survival in the face of stresses such as oxidative stress, inflammation, and failure of the energy-generating and protein quality-control pathways within neurons which are known to contribute to neurodegeneration. Our aim is to develop MRI imaging and body fluid markers to show NRF2-activating drugs working in the body. These results will be applied later in clinical trials to test the effectiveness of NRF2 activators for patients with MND and AD.

INTERNATIONAL CONGRESS FOR RESEARCH AND INNOVATION IN NEURODEGENERATIVE DISEASES (CIIEN)

During 19th to 21st September 2018, it was held in Alicante, Spain the VI International Congress on Research and Innovation in Neurodegenerative Diseases (CIIEN), promoted by the Queen Sofia Foundation in collaboration with CIEN Foundation and CIBERNED. The main objective of CIIEN is providing a forum in which to share progress and information of interest on neurodegenerative diseases among the scientific community.

The CIIEN, created in 2013, definitely consolidates the two major scientific conferences on neurodegenerative diseases organized in Spain: the International Symposium on Advances in Alzheimer’s Disease, promoted annually by the Queen Sofia Foundation and CIEN Foundation, and the CIBERNED Scientific Forum, which brought together every year the research groups constituting the CIBER in Neurodegenerative Diseases. Unifying both congresses was a first step in creating a new operating structure in the two main institutions devoted to research on neurological and neurodegenerative diseases in Spain: the CIEN Foundation and CIBERNED, both dependent on the Ministry of Science, Innovation and Universities through the Carlos III Institute of Health. This new structure seeks greater effectiveness and efficiency in research, favoring an interaction between the different research groups.

This sixth edition of CIIEN was held at the Faculty of Medicine of the University of Santiago de Compostela and during three intense days of presentations and sharing of knowledge, gathered well over a hundred international experts. Organized by the Queen Sofia Foundation, CIEN Foundation (Foundation Center for Research in Neurological Diseases) and CIBERNED (Network Center for Biomedical Research in Neurodegenerative Diseases), the VI Congress CIIEN is a forum for exchange on the main advances in research and treatment of Alzheimer’s, Parkinson’s, Huntington’s, and other neurodegenerative diseases.

The invited speakers included world leaders such as Harald-Jürgen Hampel (University of the Sorbonne, France), who spoke about the developments in precision medicine for
Alzheimer’s disease in his inaugural lecture; Michael T. Heneka (Medical Research Center of the University of Bonn, Germany), who focused on the relationship between the innate aspects of the immune system and Alzheimer’s disease; and Adriano Chiò (University of Turin, Italy), who delved into the role of cognitive phenotypes. In addition to the intervention of the scientific director of CIBERNED, Jesús Ávila, and the deputy scientific director, Miguel Medina, the Congress included internationally recognized speakers, including Isabel Fariñas (University of Valencia), whose presentation focused on the effects of certain extracellular proteins in the stem cells; Ángel Carracedo (University of Santiago de Compostela), with a work on the search of genes involved in neurodegenerative diseases, and José Luis Labandeira-García.

Likewise, and responding to the vocation to promote the training of young researchers of CIBERNED, the Young Researcher Award was awarded during the congress to Julia Pose Utrilla, who made presented the study which has been granted such recognition.

In short, this event is consolidated in its sixth edition as a meeting point for the best national and international leading experts in neurodegenerative diseases, enabling sharing of knowledge, working methods, new advances and discoveries, in a field in which international cooperation between institutions is decisive for obtaining optimal results in research.
OTHER INTERNATIONAL ACTIVITIES

H2020 MARIE SKŁODOWSKA-CURIE ACTIONS: INNOVATIVE TRAINING NETWORKS

The Innovative Training Networks (ITN) are actions created by the European Union (within the Horizon 2020 program framework) to support research in the European Research Area and are aimed to form, through an international network of public and private centers, a new generation of creative and innovative researchers, capable of transforming knowledge and ideas into products and services for the economic and social benefit of the European Union. During 2018, the CIBERNED groups have participated in two of these actions:

1. **Blood Biomarker-based Diagnostic Tools for Early-stage Alzheimer’s Disease – BBDiag**

   The main objective of this project carried out within the international network “Innovative Training Networks” of the EU (ITN-BBDiag research project) is the development of a new non-invasive methodology aimed at the identification and validation of blood biomarkers with diagnostic value, in preclinical models of Alzheimer’s disease (AD). To do this, we will analyze AD biomarker levels in blood, related to the main changes that appear in the brain in animals with AD and in different disease stages (starting from the prodromal state). For this we have established 7 experimental groups (2, 3, 4, 6, 9, 12 and 15 months-old animals) according to the presymptomatic and postsymptomatic characterization of AD in these animals. Additionally, we have standardized a non-invasive method of taking plasma samples from the different age groups of AD transgenic mice. This non-invasive blood collection protocol was optimized and cross-validated with other researchers in the field.

   We have also carried out several immunocytochemical and immunohistochemical analyzes to examine the specific load of beta-amyloid (Aβ) plaques in correlation with neuroinflammation and neurogenesis during the progression of pathology both in cortical and the hippocampal areas. Next, we have pre-validated, in collaboration with other laboratories members of the consortium, possible biomarkers that will finally be validated using technology based on the use of biosensors.
As an added value, we have analyzed in vitro neurogenesis in 2D cultures, and also in vivo. We have managed to establish primary cultures from our prodromal animal model and also in late stages. One of the main challenges in this regard is to find in vitro and in vivo the relationship between neurogenesis and the appearance of biomarkers. In addition, we are using new neuroprotective agents developed in the laboratory to discover how to improve the progression of the disease in preclinical models of Alzheimer’s disease. We are currently performing an in vitro analysis of factors involved in such neuroprotection for once the in vitro results have been obtained, to carry out a complete study in vivo.

The development of a new model 2-3D in vitro to study neurodegenerative pathology, especially in AD, is mandatory in the understanding of the pathophysiological pathways involved in the disease and could lead to an advance in drug development and subsequent treatment of this disorder.

2. Interdisciplinary training network on the purinergic P2X7 receptor to control neuroinflammation and hyperexcitability in brain diseases - PurinesDX

PurinesDX encompasses global leaders in translational research on purinergic signaling, clinical specialists in a wide range of brain disorders and industry partners specializing in the drug development and biomarkers. Throughout this first year of the PurinesDX Project, we have focused on the study of the P2X7 receptor status in patients with Huntington’s disease in relation to its messenger RNA isoforms and protein levels. Regarding the activities related to interdisciplinary training, our Early Stage Researchers (ESR) have participated in several meetings and symposia in which they improve the collaborations with the other participants of the consortium. Starting in April, we attended the Introduction Program and the Mini-Symposium on Nervous Diseases: New Approaches in Diagnosis and Therapeutics. Our ESR also participated in the First Transferable Skills Course where they were able to learn about statistics, the importance of social networking in research and scientific writing skills, among others. In October, we attended the PurinesDX Project Follow up Meeting where the EU commission reviewed our work during the first months of project execution. Our ESR also participated in the Second Transferable Skills Course where they learned about 3D imaging, business plan organization and resource management, among others.

ALZHEIMER’S ASSOCIATION

The Alzheimer’s Association is a non-for-profit organization that focuses on the care and support for patients with Alzheimer’s disease, and also funds research through competitive calls for research projects on Alzheimer’s disease. During the year 2018, CIBERNED researchers have received funding from the Alzheimer’s Association through 2 research projects:

1. A multicenter, randomized, double-blind, placebo-controlled, 4-arm, 26 week parallel-group study to evaluate the safety, tolerability and anti-inflammatory effect of three oromucosal doses of Sativex® in patients with mild cognitive impairment of Alzheimer type or early Alzheimer dementia (Sat-CIEN-02)

During 2018 we continued with the activities of this clinical trial, included in an open and competitive call of the Alzheimer’s Association that was approved and financed by it to be developed in Spain during the period of Sept-2016 to Oct-2018.

The primary end-point of the trial is to prove the safety and tolerability of the cannabinoids in these patients; in addition some hints about their potential therapeutic
effect are expected and will be useful for the design of future efficacy studies. The selected doses in accordance with previous experimental animal studies are low and without psychoactive effects. The indication of these drugs in the Alzheimer’s disease is based on their modulatory action on the synaptic activity and their potent anti-inflammatory and neuroprotection effect.

2. **AARG-17-528125: Novel Methods to Interrogate the Subcellular Machinery of AD Models in Vivo**

The hippocampus is one of the few brain regions that experience the existence of neurogenesis throughout life (1). In this brain area, a population of neurons that plays an important role in the acquisition of new memories, granular neurons, are severely damaged in patients suffering from Alzheimer’s disease (2). These alterations are also reflected in an animal model of the disease, the mouse that over-expresses the protein glycogen synthase kinase 3β (GSK-3β). This mouse shows a reduction in the maturation of the new neurons in the hippocampus, which could be related to the loss of hippocampal-dependent memory that is observed in these mice. The main objective of this project is to analyze in depth the causes of the malfunction that these cells undergo in the mouse that over-expresses GSK-3β, in order to be able to test two novel therapeutic strategies in these mice. To date, we have found important alterations in several of the cellular components that are part of these neurons (we are currently preparing two research articles summarizing these findings). Throughout the duration of this project, we intend to continue analyzing these alterations, as well as propose some of the strategies we are testing to slow down the progress of the pathology observed in mice.

SCIENTIFIC PRODUCTIVITY AND OTHER ACTIVITIES
ANALYSIS OF CIBERNED SCIENTIFIC PRODUCTIVITY IN 2018

The table below summarize the bibliometric indicators related to the scientific activity from years of 2017 and 2018. A quick analysis shows a consolidation of the improved scientific production in 2018 (in line with the ongoing historical improvement observed in the last years since the creation of the Centre), not only in quantity but particularly in quality (number of publications overall, within the first quartile, number of publications led by CIBERNED groups within quartiles 1 and 2; number of international publications in Q1 and Q2; or ).

<table>
<thead>
<tr>
<th>INDICATOR</th>
<th>2017</th>
<th>2018</th>
<th>CHANGE %</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A) Total number of publications</td>
<td>571.00</td>
<td>613.00</td>
<td>7.36</td>
</tr>
<tr>
<td>(B) Number of publications in quartiles (Q) 1 y 2</td>
<td>470.00</td>
<td>497.00</td>
<td>5.74</td>
</tr>
<tr>
<td>(C) Number of publications in Q1 y Q2 as percentage of total (A)</td>
<td>82.31</td>
<td>81.08</td>
<td>-1.50</td>
</tr>
<tr>
<td>(E) Number of publications in 1st decile</td>
<td>189.00</td>
<td>167.00</td>
<td>-11.64</td>
</tr>
<tr>
<td>(F) Number of publications (1st decile) as percentage of total (A)</td>
<td>33.10</td>
<td>27.24</td>
<td>-17.69</td>
</tr>
<tr>
<td>(G) Number of publications in Q1 (includes 1st decile)</td>
<td>372.00</td>
<td>402.00</td>
<td>8.06</td>
</tr>
<tr>
<td>(H) Number of publications in Q1 as percentage of total (A)</td>
<td>65.15</td>
<td>65.58</td>
<td>0.66</td>
</tr>
<tr>
<td>(I) Number of publications in Q1 as percentage of total Q1 and Q2 (B)</td>
<td>79.15</td>
<td>80.89</td>
<td>2.19</td>
</tr>
<tr>
<td>(J) Number of publications in Q2</td>
<td>98.00</td>
<td>95.00</td>
<td>-3.06</td>
</tr>
<tr>
<td>(K) Number of publications in Q2 as percentage of total (A)</td>
<td>17.16</td>
<td>15.50</td>
<td>-9.70</td>
</tr>
<tr>
<td>(L) Number of publications (Q1+Q2) led by CIBERNED groups (1st author or corresponding author)</td>
<td>267.00</td>
<td>273.00</td>
<td>2.25</td>
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<tr>
<td>(M) Number of publications in Q1 and Q2 led by CIBERNED groups as percentage of total (B)</td>
<td>56.81</td>
<td>54.93</td>
<td>-3.31</td>
</tr>
<tr>
<td>(N) Number of publications (Q1 and Q2) not led by CIBERNED groups (1st author or corresponding author)</td>
<td>203.00</td>
<td>224.00</td>
<td>10.34</td>
</tr>
<tr>
<td>INDICATOR</td>
<td>2017</td>
<td>2018</td>
<td>CHANGE %</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------</td>
<td>-------</td>
<td>-------</td>
<td>----------</td>
</tr>
<tr>
<td>(O) Number of publications in Q1 and Q2 not led by CIBERNED groups as percentage of total (B)</td>
<td>43,19</td>
<td>45,07</td>
<td>4,35</td>
</tr>
<tr>
<td>(P) Number of publications in Q1 and Q2 in which “CIBERNED” appears in the affiliation (as percentage of total (B))</td>
<td>81,70</td>
<td>84,71</td>
<td>3,68</td>
</tr>
<tr>
<td>(Q) Number of publications in Q1 and Q2 led by CIBERNED groups in which “CIBERNED” appears in the affiliation (as percentage of total (L))</td>
<td>90,26</td>
<td>90,11</td>
<td>-0,17</td>
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<tr>
<td>(R) Number of publications in Q1 and Q2 not led by CIBERNED groups in which “CIBERNED” appears in the affiliation (as percentage of total (N))</td>
<td>70,44</td>
<td>78,13</td>
<td>10,90</td>
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<tr>
<td>(S) Number of publications in Q1 and Q2 with international groups</td>
<td>260,00</td>
<td>282,00</td>
<td>8,46</td>
</tr>
<tr>
<td>(T) Number of publications in Q1 and Q2 with international groups (S) as percentage of total number of publications (B)</td>
<td>55,32</td>
<td>56,74</td>
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<tr>
<td>(U) Number of publications in Q1 and Q2 with international groups, and led by CIBERNED groups</td>
<td>123,00</td>
<td>118,00</td>
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<td>(V) Number of publications in Q1 and Q2 with international groups, and led by CIBERNED groups as percentage of all international publications (S)</td>
<td>47,31</td>
<td>41,84</td>
<td>-11,55</td>
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<tr>
<td>(W) Number of publications in Q1 and Q2 with other CIBERS</td>
<td>18,00</td>
<td>19,00</td>
<td>5,56</td>
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<tr>
<td>(X) Percentage of publications in Q1 and Q2 with other CIBERS led by CIBERNED groups</td>
<td>27,78</td>
<td>31,58</td>
<td>13,68</td>
</tr>
<tr>
<td>(Y) Number Percentage of published in Q1 y Q2</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(Z) Percentage of Percentage of led by CIBERNED groups</td>
<td>40,00</td>
<td>50,00</td>
<td>25,00</td>
</tr>
<tr>
<td>(A2) Addition of impact factors of journals (Q1 y Q2) in which articles have been published</td>
<td>2859,70</td>
<td>3345,81</td>
<td>17,00</td>
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<tr>
<td>(B2) Average of impact factors of journals (Q1 y Q2) in which articles have been published</td>
<td>6,08</td>
<td>6,18</td>
<td>1,59</td>
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<td>(C2) Number of publications in journals with impact factor &gt;15</td>
<td>44,00</td>
<td>61,00</td>
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</tr>
<tr>
<td>Number of publications in Q1 and Q2 with 2 CIBERNED groups</td>
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<td>48,00</td>
<td>-15,79</td>
</tr>
<tr>
<td>Number of publications in Q1 and Q2 with 3 CIBERNED groups</td>
<td>20,00</td>
<td>12,00</td>
<td>-40,00</td>
</tr>
<tr>
<td>Number of publications in Q1 and Q2 with 4 CIBERNED groups</td>
<td>1,00</td>
<td>7,00</td>
<td>600,00</td>
</tr>
<tr>
<td>Number of publications in Q1 and Q2 with 5 CIBERNED groups</td>
<td>-</td>
<td>1,00</td>
<td>-</td>
</tr>
<tr>
<td>Number of publications in Q1 and Q2 with 6 CIBERNED groups</td>
<td>2,00</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Number of publications in Q1 and Q2 with 7 CIBERNED groups</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Number of publications in Q1 and Q2 with 8 CIBERNED groups</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cooperative projects – Program 1</td>
<td>68,00</td>
<td>96,00</td>
<td>41,18</td>
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CIBERNED 2018 ANNUAL REPORT

### Table: Bibliometric Indicators

<table>
<thead>
<tr>
<th>INDICATOR</th>
<th>2017</th>
<th>2018</th>
<th>CHANGE %</th>
</tr>
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<tbody>
<tr>
<td>Cooperative projects – Program 2</td>
<td>157,00</td>
<td>147,00</td>
<td>-6,37</td>
</tr>
<tr>
<td>Cooperative projects – Program 3</td>
<td>-</td>
<td>62,00</td>
<td>-</td>
</tr>
<tr>
<td>Projects with other CIBERs/REITCs/CIEN networks</td>
<td>36,00</td>
<td>15,00</td>
<td>-58,33</td>
</tr>
<tr>
<td>Basic Research-type projects</td>
<td>79,00</td>
<td>74,00</td>
<td>-6,33</td>
</tr>
<tr>
<td>Translational research-type projects</td>
<td>146,00</td>
<td>175,00</td>
<td>19,86</td>
</tr>
<tr>
<td>Projects with other national research groups</td>
<td>121,00</td>
<td>163,00</td>
<td>34,71</td>
</tr>
<tr>
<td>Projects with international research groups</td>
<td>45,00</td>
<td>50,00</td>
<td>11,11</td>
</tr>
<tr>
<td>Projects with industry</td>
<td>82,00</td>
<td>92,00</td>
<td>12,20</td>
</tr>
</tbody>
</table>

The following are a few figures that summarize some of the main bibliometric indicators in relation to the scientific production of CIBERNED, including the total production (indexed and not indexed in PubMed and Scopus), during the year 2018 and its evolution since 2011:

**FIGURE 1.** Percentage of indexed CIBERNED 2018 publications distributed by quartiles. Q1 stands for publications in the 1st quartile; Q2 stands for publications in the 2nd quartile; Q3 stands for publications in the 3rd quartile; Q4 stands for publications in the last quartile. No IF stands for publications for which no impact factor is available.
FIGURE 2. CIBERNED 2011-2018 production by quartiles/1st decile. Q1+Q2 stands for the sum of publications in 1st and 2nd quartiles; D1 stands for publications in the 1st decile.

FIGURE 4. Number of CIBERNED 2011-2018 publications within 1st and 2nd quartiles and 1st decile.

FIGURE 5. Evolution of the impact factor from 2011 to 2018. IF stands for impact factor.
FIGURE 7. Scientific journals with 5 or more CIBERNED publications in 2018.
FIGURE 8. Most frequent SUBJECT categories (according to WoS-JCR) in CIBERNED 2018 publications.
CROSS-NETWORK PROGRAMS

NEUROLOGICAL TISSUE BANKS
1. Neurological Tissue Bank and Biological Samples of the IDIBELL Institute of Neuropathology, Bellvitge Hospital (Head: Dr. Isidro Ferrer).
2. CIEN Foundation Tissue Bank for Neurological Research (BT-CIEIN) (Head: Dr. Alberto Rábano).
3. Neurological Tissue Bank (BTN) at the University of Barcelona (Head: Dr. Eduardo Tolosa)

OTHER PLATFORMS
• DNA Analysis Service (Head: Dr. Jordi Pérez Tur).
• Electron Microscopy Service (Head: Dr. José Manuel García Verdugo).
• Neuroimaging Service (Head: Dr. Jose Luis Cantero Llorente)
• Dementia Genetics Spanish Consortium (DEGESCO) (Coordinator: Dr. Jordi Clarimón)
EVENTS AND OTHER ACTIVITIES

CIBERNE D has held several meetings throughout the year, including the VI Conference on Research and Innovation in Neurodegenerative Diseases (CIIIEN) which took place in Santiago de Compostela on September 19-21 and the Second DEGESCO Symposium on Genetics of Dementia (held on May 23 in the CosmoCaixa auditorium in Barcelona), in addition to other scientific, dissemination and international cooperative events described below.

VI INTERNATIONAL CONFERENCE ON RESEARCH AND INNOVATION IN NEURODEGENERATIVE DISEASES (CIIIEN)

In 2018 CIBERNE D held its annual Scientific Forum. This event, which has been held year after year since 2007, is essential for the proper functioning of CIBERNE D, as it allows the principal investigators, the members of their groups, as well as all the attendees, to meet to discuss the findings of their research, present new data and establish collaborations. In 2013, a new format as an International Conference on Research and Innovation in Neurodegenerative Diseases (CIIIEN) was established with great success, which has been consolidated in the successive editions (2014, 2015, 2016, 2017 and 2018).

Coinciding with the week in which World Alzheimer’s Day is celebrated, on September 19-21, the VI Conference on Research and Innovation in Neurodegenerative Diseases - CIIIEN was held in Santiago de Compostela, which, during three intense days of presentations and knowledge exchanges, brought together well over a hundred international experts. Organized by the Queen Sofia Foundation, CIEN (Neurological Diseases Research Center Foundation) Foundation and CIBERNE D (Network Center for Biomedical Research in Neurodegenerative Diseases), the VI CIIIEN Conference is an exchange forum on the main advances in research and treatment of Alzheimer’s, Parkinson’s, Huntington’s, and other neurodegenerative diseases.

In short, this event is consolidated in its fifth edition as a meeting point for the greatest national and international experts in neurodegenerative diseases, allowing to share knowledge, work methods, new advances and discoveries, in a field in which international cooperation and between institutions is decisive for obtaining optimal results in research.
SECOND DEGESCO SYMPOSIUM ON GENETICS OF DEMENTIA

DEGESCO (Dementia Genetics Spanish Consortium) is a nation-wide consortium of scientific and technical nature jointly promoted by eleven founding research centers under the institutional umbrella of CIBERNED. DEGESCO was constituted in 2013 with the general aim of promoting and strengthen the development of genetic studies in order to understand the genetic architecture of neurodegenerative dementias in the Spanish population through the implementation of collaborative projects and actions among its members. DEGESCO philosophy is inclusive, that is, it is open to the incorporation of new research groups, whether public or private, that show their capacity and interest to conduct research on dementias. DEGESCO is a coordination structure for sample repositories that share information and processing protocols. The samples selected by the participants for DEGESCO must be characterized by both scientific-technical and ethical quality, complying with the Biomedical Research Law (Law 14/2007) and the Royal Decree of Biobanks (RD 1716/2011). The transfer of samples between the members of the consortium will be carried out in accordance with the requirements of the Royal Decree of Biobanks.

At the end of 2018, DEGESCO is composed of 24 fully-fledged research groups with the institutional coverage of CIBERNED (Center for Biomedical Research in Neurodegenerative Diseases Network). Those member groups are the following:

DEGESCO (DEmentia GEnetics Spanish COnsortium)
Continuing with the consortium dissemination activities, the Second DEGESCO (Dementia Genetics Spanish Consortium) Symposium on Genetics of Dementia was held at the CosmoCaixa Auditorium in Barcelona on May 23, 2018. This symposium, which was organized for the first time as part of the XI edition of the Barcelona-Pittsburgh Conference, which Fundació ACE has organized during the last 20 years for its commitment to training and research, and aimed to bring together the best national experts on genetics of neurodegenerative diseases to address a key research area by thoroughly reviewing the genetic aspects of the different types of dementia and their implications in the Spanish population.

EXCELLENCE IN NEURODEGENERATION SEMINAR SERIES

During 2018 CIBERNED has continued to carry out the series of lectures “Excellence in Neurodegeneration Seminar Series”, offering presentations by leading international experts in their areas of research on all aspects of frontier research in neurodegenerative diseases (molecular, cellular, genetic, cognitive, clinical, animal models, biomarkers, imaging, etc.) and related areas.

Below there is a list of the seminars held during 2017 within this series:

- **Speaker:** Harald-Jürgen Hampel, Sorbonne University, France.
  **Title:** Development of Precision Medicine for Alzheimer Disease.

- **Speaker:** Michael T. Heneka, University of Bonn Medical Center, Germany.
  **Title:** Does innate immune activation drives Alzheimer disease?.

- **Speaker:** Adriano Chiò, University of Turin, Italy.
  **Title:** The determinants of motor and cognitive phenotypes in ALS.

- **Speaker:** Werner Poewe, Innsbruck Medical University, Austria.
  **Title:** Novel therapeutic targets for Parkinson’s Disease.

- **Speaker:** Ángel Carracedo, University of Santiago de Compostela, Spain.
  **Title:** The search for genes involved in neurodegenerative diseases: Challenges and new strategies

YOUNG INVESTIGATOR OF THE YEAR AWARDS

To promote research excellence, CIBERNED annually awards a prize to an emerging scientific involved in clinical or basic research, and on a biennial basis, a prize to an emerging scientist involved in clinical research in neurodegenerative diseases.

The candidates for the 2018 Young Investigator of the Year Award must be under 35 years old, members of a CIBERNED research group and main authors of an article published in an indexed scientific journal during 2017.

The call remit was announced by email addressed to all personnel belonging to CIBERNED as well as through the Center’s website.

Once the deadline for submitting applications had elapsed, a total of 8 applications were received that met the specifications of both calls in an appropriate and timely manner.

For both calls, the selection committee was made up of members of the Steering Committee and of Senior Researchers from outside the Committee, who assessed the scientific quality and impact of the publications, as well as the candidate's specific contribution.
Once the evaluation process for the submitted applications was completed, the CIBERNED Scientific Directorate agreed to award the Young Investigator Award to Julia Pose Utrilla for her work “Excitotoxic inactivation of constitutive oxidative stress detoxification pathway in neurons can be rescued by PKD1”, published in Nature Communications (2017); 8 (1): 2275.

OTHER RELEVANT EVENTS

UNIVERSITY OF EXTREMADURA (UEX) SUMMER-AUTUMN COURSE

Between 20th and 22nd June, 2018 the Course “Advances in neurobiology and neurodegenerative diseases” was held in Cáceres, as part of the XIX edition of the International Summer Courses of the University of Extremadura, led by Dr. José Manuel Fuentes Rodriguez, Principal Investigator of CIBERNED and member of the Department of Biochemistry and Molecular Biology and Genetics of the Faculty of Nursing and Occupational Therapy of the University of Extremadura.

This Course was focused on knowing the most current advances at the molecular and cellular level of the Nervous System, with special emphasis on what refers to neurodegenerative disorders, given its growing importance at the social, health and scientific level. It was also intended to integrate this knowledge to address aspects such as its understanding, its prevention, or its treatment; to allow an improvement in the acquisition of skills for future professional training, especially if it has to do with scientific research or clinical practice in relation to these or other diseases of the Nervous System; to obtain scientific training in the biomedical field that bridges basic and clinical research, and acquire cross-cutting knowledge to ensure a multidisciplinary vision of the neuroscientist activities.

Among other specialists, the following CIBERNED Principal Investigators participated in the Course: Drs. José Ramón Naranjo, Isidre Ferrer, Rosario Moratalla, José Luis Labandeira, Rafael Fernández Chacón, Adolfo López de Munain and Jordi Pérez Tur.

PURINESDX MINI-SYMPOSIUM – BRAIN DISEASES: NEW APPROACHES ON DIAGNOSTICS AND THERAPEUTICS

On April 24, a symposium of the European project PurinesDX entitled “Brain Diseases: New Approaches on Diagnostics and Therapeutics” was held at the Royal College of Surgeons in Ireland (RCSI) in Dublin, where the main objectives of the project and the specific aims of each of the partners of the consortium were addressed.

The PurinesDX project is part of the European Union’s Horizon 2020 research and innovation program, collaborates with leading research leaders in purinergic signaling, brain pathologies and in the development of biomarkers and therapies.

The symposium was attended by Dr. Jose J. Lucas, Principal Investigator of CIBERNED, and Dr. Miguel Medina, Deputy Scientific Director of CIBERNED.
II EUROTAU MEETING 2018

On April 26 and 27, 2018, the second edition of the Eurotau Meeting took place in Lille. This event, hosted by Dr. Luc Bueé, brought together the main European specialists involved in Tau research and constitutes a reference forum to share new ideas and hypotheses about the physiological and pathological roles of Tau proteins and the so-called tauopathies.

Like last year, Drs. Jesús Ávila and Miguel Medina, who also participated as a speaker, were part of the scientific committee of the event. In addition, the program had the intervention of Drs. Lastres-Becker and Sánchez-Juan, both members of CIBERNED.

The organizers and the scientific committee of the Eurotau Meeting aim to make the annual meeting one of the reference events for scientists and researchers around the world, especially as a forum for discussing alternative approaches to tauopathies in a context of disparate results in drug development.

I MOLECULAR NEUROPATHOLOGY DAY

On February 16, 2018, the First Molecular Neuropathology Day was held at the Center of Molecular Biology Severo Ochoa (CBMSO, for its acronym in Spanish) in Madrid. This event was organized jointly between the Department of Molecular Neuropathology of the Center of Molecular Biology Severo Ochoa and CIBERNED, along with other institutions.

The event aimed to share the results of projects related to neurological pathologies and researchers from other research institutions and centers with research lines in this field were invited to participate. In addition, the participation of young researchers in the field was promoted and encouraged.

XI NEUROBIOLOGY SYMPOSIUM: FUTURE TECHNICAL ADVANCES

This Symposium is a biennial scientific event organized by the Experimental Neurobiology section of the Catalan Society of Biology and on this occasion was held on November 12-13, 2018 in Barcelona.

The objective of the Symposium was to present recent scientific advances in the field of neuroscience from the research groups of our community.

In this event, topics such as development, neurogenesis and stem cells, glial cells and neuroinflammation, neurotransmission, neuropharmacology, receptors and cell signaling or death mechanisms and neuronal regeneration, among others, were discussed.

The organizing committee was formed by two members who belong to the CIBERNED network since its inception, Drs. Carles Saura and Silvia Ginés.
FINANCIAL REPORT
The Network Center for Biomedical Research in Neurodegenerative Diseases (CIBERNED) is a research organization with its own legal personality, according to Article 6.5 of Law 30/1992 of November 26, on the Legal Regime of Public Administrations and the Common Administrative Procedure, whose mission is the broadly defined monographic research on neurodegenerative diseases. It is composed of research groups, without physical contiguity, belonging to different Administrations, Institutions and Regions, from the public and private sector with research lines and goals focused on the specific common area of neurodegenerative diseases and coordinating for the achievement of objectives, which could hardly be envisaged in a more restricted context of implementation.

CIBERNED became part of the State Public Administrative Sector on May 14, 2010. Since January 1, 2011, it has been subject to the Public Accounting General Plan, approved by Order EHA/1037/2010, as an accounting standard, taking into account the Adaptation of the PGCP for Public Entities whose expenditure budget are estimated.


CIBERNED is a virtual Research Center consisting of research groups belonging to different Administrations and Institutions in partnership: the member Principal Investigators work in the institutions to which they belong by participating actively and simultaneously in CIBERNED's own cooperative research agenda. It is therefore the result of the collaboration and association of entities as well as the sum of research groups.

In 2018, it consisted of 50 groups, an average of 120.32 hired staff that add up to 119 by December 31, 2018.
Average staffing for the year 2018:

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>WOMEN</th>
<th>MEN</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administrative assistant</td>
<td>4.93</td>
<td>-</td>
<td>4.93</td>
</tr>
<tr>
<td>Undergraduate</td>
<td>2.42</td>
<td>-</td>
<td>2.42</td>
</tr>
<tr>
<td>Doctor (PhD)</td>
<td>26.17</td>
<td>13.89</td>
<td>40.06</td>
</tr>
<tr>
<td>Graduate (BSc, MSc)</td>
<td>24.82</td>
<td>16.28</td>
<td>41.10</td>
</tr>
<tr>
<td>Technician</td>
<td>26.88</td>
<td>4.93</td>
<td>31.81</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>85.22</strong></td>
<td><strong>35.32</strong></td>
<td><strong>120.32</strong></td>
</tr>
</tbody>
</table>

Staff personnel at year end:

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>WOMEN</th>
<th>MEN</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administrative assistant</td>
<td>6</td>
<td>-</td>
<td>6</td>
</tr>
<tr>
<td>Undergraduate</td>
<td>3</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Doctor (PhD)</td>
<td>26</td>
<td>16</td>
<td>42</td>
</tr>
<tr>
<td>Graduate (BSc, MSc)</td>
<td>26</td>
<td>18</td>
<td>44</td>
</tr>
<tr>
<td>Technician</td>
<td>19</td>
<td>4</td>
<td>23</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>80</strong></td>
<td><strong>38</strong></td>
<td><strong>118</strong></td>
</tr>
</tbody>
</table>

The Scientific Head Office is located at the Center for Molecular Biology “Severo Ochoa” in Madrid. The headquarters and the Manager Office are located at Valderrebollo 5 in Madrid within the premises of the Alzheimer Center of the Queen Sofia Foundation.

**FUNDING**

The Resolution of March 30, 2006 from the Carlos III Health Institute, which calls for grants to fund stable cooperative research structures in the area of biomedicine and health sciences within the framework of the initiative Ingenio 2010, Consolider program, and CIBER actions, establishes the conditions of the grants under point 13.

In that point, it is indicated that the ISCIII assistance may reach a maximum of 80% of the budget of the Consortium’s activities. This budget will be used to cover expenses directly related to the development and execution of CIBERNED activities. In determining the total budget the corresponding expenditure to fund salaries for researchers that are part of the CIBERNED and do not have a working contract with the consortium, but rather with the associated institutions is considered included, but not eligible and therefore allocated in the 20% not funded by the grant.

In this financial year, the contribution of the Associated Institutions accounted for 2,185,041.12€.

During 2018, the Consortium counts on the funding from the Carlos III Institute of Health as a promoter organization for the execution of the activities and general objectives already described.
On March 2, 2018, the Resolution of the Carlos III Institute of Health was approved, which regulates the conditions for the license to CIBER in the thematic area of Neurodegenerative Diseases of the nominative assignments provided for in the Statement of Expenditure of the 2017 Expanded Budget for 2018 of the Carlos III Institute of Health. That resolution was issued respecting the limits imposed by the seventh paragraph of the Ministerial Agreement of December 29, 2017, which decided:

To assign to CIBERNED the following nominative contributions foreseen in the Statement of Expenditure of the Carlos III Institute of Health Budget for the year 2017:

- **1,961,620 euros** from budget heading 27.107.465A.44605
- **81,690 euros** from budget heading 27.107.465A.74605

Corresponding to 50% of the total credit existing in the aforementioned budgetary headings, leaving the remaining 50% of the credit subject to the approval of the General State Budget Law for 2018.

Once the General State 2018 Budget Law 6/2018 of July 3 was approved, the amounts initially allocated were adjusted and by resolution of July 31, 2018, the amounts granted were increased:

- **1,826,620 euros** from budget heading 27.107.465A.44605
- **81,690 euros** from budget heading 27.107.465A.74605

Other sources of income for the development of the activity and general objectives of the Consortium are:

- Contributions that may be obtained as a result of research, technical assistance or advice that is performed.
- Income from private law and any other income or consideration authorized by current legislation.

**BASIS OF PRESENTATION OF THE ACCOUNTS**

**True and fair view**

The financial statements have been prepared from the accounting records of the Entity following the accounting principles and standards established in the General Public Accounting Plan (PGCP, for its acronym in Spanish), showing the true and fair view of the net worth, changes in the same, financial situation, budget execution, statement of cash flows and results.

The accounting principles and valuation criteria are applied in accordance with the registration and valuation rules of the PGCP, Order EHA / 1037/2010 of April 13 and the adaptation of the PGCP for public bodies whose expenditure budget is estimated, approved by Resolution of July 28, 2011 of the General Intervention of the State Administration and other legal provisions in force regarding accounting matters.

These financial statements have been prepared by the Managing Director of the Institution and will be submitted to approval by the Governing Council.
### Balance sheet year 2018

<table>
<thead>
<tr>
<th>ASSETS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A) Non-current assets</strong></td>
<td><strong>1,320,631,82</strong></td>
</tr>
<tr>
<td>I. Intangible assets</td>
<td><strong>40,239,20</strong></td>
</tr>
<tr>
<td>1. Investment in research and development</td>
<td>-</td>
</tr>
<tr>
<td>2. Industrial and intellectual property</td>
<td>-</td>
</tr>
<tr>
<td>3. IT applications</td>
<td><strong>40,239,20</strong></td>
</tr>
<tr>
<td>4. Investments in assets used under lease or assignment</td>
<td>-</td>
</tr>
<tr>
<td>5. Other intangible assets</td>
<td>-</td>
</tr>
<tr>
<td>II. Material assets</td>
<td><strong>1,279,789,92</strong></td>
</tr>
<tr>
<td>1. Lands</td>
<td>-</td>
</tr>
<tr>
<td>2. Buildings</td>
<td>-</td>
</tr>
<tr>
<td>3. Infrastructures</td>
<td>-</td>
</tr>
<tr>
<td>4. Historic heritage assets</td>
<td>-</td>
</tr>
<tr>
<td>5. Other material assets</td>
<td><strong>1,279,789,92</strong></td>
</tr>
<tr>
<td>6. Fixed assets under construction and advances</td>
<td>-</td>
</tr>
<tr>
<td>III. Real state investments</td>
<td>-</td>
</tr>
<tr>
<td>IV. Long-term financial investments in group companies, joint ventures and associates</td>
<td>-</td>
</tr>
<tr>
<td>V. Long-term financial investments</td>
<td><strong>602,70</strong></td>
</tr>
<tr>
<td>1. Financial investments in equity</td>
<td>-</td>
</tr>
<tr>
<td>2. Credit and debt securities</td>
<td>-</td>
</tr>
<tr>
<td>3. Financial derivatives</td>
<td>-</td>
</tr>
<tr>
<td>4. Other financial investments</td>
<td><strong>602,7</strong></td>
</tr>
<tr>
<td>VI. Debtors and other long-term accounts receivables</td>
<td>-</td>
</tr>
<tr>
<td><strong>B) Current assets</strong></td>
<td><strong>3,404,044,99</strong></td>
</tr>
<tr>
<td>I. Assets assigned for sale</td>
<td>-</td>
</tr>
<tr>
<td>II. Inventory</td>
<td>-</td>
</tr>
<tr>
<td>III. Debtors and other accounts receivable</td>
<td><strong>932,560,35</strong></td>
</tr>
<tr>
<td>1. Debtors from management operations</td>
<td><strong>534,764,17</strong></td>
</tr>
<tr>
<td>2. Other accounts receivable</td>
<td>-</td>
</tr>
<tr>
<td>3. Public Administrations</td>
<td><strong>397,796,18</strong></td>
</tr>
<tr>
<td>IV. Short-term financial investments in group companies, joint ventures and associates</td>
<td>-</td>
</tr>
<tr>
<td>V. Short-term financial investments</td>
<td><strong>4,285,76</strong></td>
</tr>
<tr>
<td>1. Financial investments in equity</td>
<td>-</td>
</tr>
<tr>
<td>2. Credits and debt securities</td>
<td><strong>4,285,76</strong></td>
</tr>
<tr>
<td>3. Financial derivatives</td>
<td>-</td>
</tr>
<tr>
<td>4. Other financial investments</td>
<td>-</td>
</tr>
<tr>
<td>VI. Accrual</td>
<td><strong>14,342,99</strong></td>
</tr>
<tr>
<td>VII. Cash and cash equivalents</td>
<td><strong>2,452,855,89</strong></td>
</tr>
<tr>
<td>1. Treasury</td>
<td><strong>2,452,855,89</strong></td>
</tr>
<tr>
<td><strong>TOTAL ASSETS (A+B)</strong></td>
<td><strong>4,724,676,81</strong></td>
</tr>
</tbody>
</table>
## EQUITY AND LIABILITIES

### A) Equity

<table>
<thead>
<tr>
<th>Description</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Contributed equity</td>
<td>-</td>
</tr>
<tr>
<td>II. Generated equity</td>
<td>1,111,824,39</td>
</tr>
<tr>
<td>1. Results from previous years</td>
<td>1,436,086,28</td>
</tr>
<tr>
<td>2. Results in the year</td>
<td>-324,261,89</td>
</tr>
<tr>
<td>3. Reserves</td>
<td>-</td>
</tr>
<tr>
<td>III. Valuation adjustments</td>
<td>-</td>
</tr>
<tr>
<td>IV. Other assets increases pending allocation to results</td>
<td>130,264,58</td>
</tr>
</tbody>
</table>

### B) Non-current liabilities

<table>
<thead>
<tr>
<th>Description</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Long-term provisions</td>
<td>60,466,86</td>
</tr>
<tr>
<td>II. Long term debts</td>
<td>356,893,52</td>
</tr>
<tr>
<td>1. Debentures and other marketable securities</td>
<td>-</td>
</tr>
<tr>
<td>2. Debts with credit institutions</td>
<td>-</td>
</tr>
<tr>
<td>3. Financial derivatives</td>
<td>-</td>
</tr>
<tr>
<td>4. Other debts</td>
<td>356,893,52</td>
</tr>
<tr>
<td>5. Debtors for long-term capital leasing agreements</td>
<td>-</td>
</tr>
<tr>
<td>III. Debts with group companies, joint ventures and associates</td>
<td>-</td>
</tr>
<tr>
<td>IV. Creditors and other long-term payables</td>
<td>-</td>
</tr>
<tr>
<td>V. Adjustments for long-term accrual</td>
<td>-</td>
</tr>
</tbody>
</table>

### C) Current liabilities

<table>
<thead>
<tr>
<th>Description</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Short-term provisions</td>
<td>38,240,05</td>
</tr>
<tr>
<td>II. Short-term debts</td>
<td>1,346,782,32</td>
</tr>
<tr>
<td>1. Debentures and other marketable securities</td>
<td>-</td>
</tr>
<tr>
<td>2. Debts with credit institutions</td>
<td>-</td>
</tr>
<tr>
<td>3. Financial derivatives</td>
<td>-</td>
</tr>
<tr>
<td>4. Other debts</td>
<td>1,346,782,32</td>
</tr>
<tr>
<td>5. Debtors for short-term capital leasing agreements</td>
<td>-</td>
</tr>
<tr>
<td>III. Debts with group companies, joint ventures and associates</td>
<td>-</td>
</tr>
<tr>
<td>IV. Accrual</td>
<td>507,823,87</td>
</tr>
<tr>
<td>1. Creditors from management operations</td>
<td>305,676,47</td>
</tr>
<tr>
<td>2. Other accounts payable</td>
<td>16,13</td>
</tr>
<tr>
<td>3. Public Administrations</td>
<td>202,131,27</td>
</tr>
<tr>
<td>V. Adjustments for accrual</td>
<td>-</td>
</tr>
</tbody>
</table>

**TOTAL EQUITY AND LIABILITIES (A+B+C)** 4,724,676,81
## 2018 Economic Assets Income Statement

<table>
<thead>
<tr>
<th>Description</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Income tax and social contributions</td>
<td>-</td>
</tr>
<tr>
<td>2. Transfers and subsidies received</td>
<td>6,564,336.41</td>
</tr>
<tr>
<td>a) Del ejercicio</td>
<td>6,416,950.54</td>
</tr>
<tr>
<td>a.1) Subsidies received to finance expenditures for the year</td>
<td>442,169.42</td>
</tr>
<tr>
<td>a.2) Transfers</td>
<td>5,974,781.12</td>
</tr>
<tr>
<td>b) Allocation of subsidies for non-financial assets</td>
<td>147,385.87</td>
</tr>
<tr>
<td>3. Net sales and services</td>
<td>240,131.19</td>
</tr>
<tr>
<td>4. Changes in inventory of finished and in progress of manufacturing goods and impairment loss</td>
<td>-</td>
</tr>
<tr>
<td>5. Work by the company for its fixed assets</td>
<td>-</td>
</tr>
<tr>
<td>6. Other income from ordinary management</td>
<td>-</td>
</tr>
<tr>
<td>7. Provisions surpluses</td>
<td>4,781.36</td>
</tr>
<tr>
<td><strong>A) Total Revenues from Ordinary Management (1+2+3+4+5+6+7)</strong></td>
<td>6,809,248.96</td>
</tr>
<tr>
<td>8. Personnel costs</td>
<td>-3,502,828.43</td>
</tr>
<tr>
<td>a) Wages and salaries and similar expenses</td>
<td>-2,642,824.19</td>
</tr>
<tr>
<td>b) Social security costs</td>
<td>-860,004.24</td>
</tr>
<tr>
<td>9. Transfers and grants awarded</td>
<td>-2,257,329.11</td>
</tr>
<tr>
<td>10. Procurements</td>
<td>-728,435.40</td>
</tr>
<tr>
<td>a) Consumption of goods and other supplies</td>
<td>-728,435.40</td>
</tr>
<tr>
<td>11. Other ordinary management expenses</td>
<td>-474,724.70</td>
</tr>
<tr>
<td>a) Supplies and other external services</td>
<td>-474,622.69</td>
</tr>
<tr>
<td>b) Taxes</td>
<td>-102.01</td>
</tr>
<tr>
<td>c) Others</td>
<td>-</td>
</tr>
<tr>
<td>12. Depreciation of fixed assets</td>
<td>-149,906.44</td>
</tr>
<tr>
<td>Description</td>
<td>Amount</td>
</tr>
<tr>
<td>----------------------------------------------------------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td><strong>B) TOTAL COSTS OF ORDINARY MANAGEMENT (8+9+10+11+12)</strong></td>
<td>-7,113,224,08</td>
</tr>
<tr>
<td>I Results (surplus or deficit) of ordinary management (A+B)</td>
<td>-303,975,12</td>
</tr>
<tr>
<td>13. Impairment loss and results on disposals of non-financial assets and selling state assets</td>
<td>-5,420,57</td>
</tr>
<tr>
<td>14. Other non-ordinary items</td>
<td>827,67</td>
</tr>
<tr>
<td>a) Income</td>
<td>827,99</td>
</tr>
<tr>
<td>b) Expenditure</td>
<td>-0,32</td>
</tr>
<tr>
<td>II results of non-financial operations (I +13+14)</td>
<td>-308,568,02</td>
</tr>
<tr>
<td>15. Financial income</td>
<td>713,41</td>
</tr>
<tr>
<td>a) participations in equity instruments</td>
<td>-</td>
</tr>
<tr>
<td>b) marketable securities and loans of fixed assets</td>
<td>713,41</td>
</tr>
<tr>
<td>16. Financial expenses</td>
<td>-</td>
</tr>
<tr>
<td>17. Financial expenses charged to assets</td>
<td>-</td>
</tr>
<tr>
<td>18. Change of fair value of financial assets and liabilities</td>
<td>-</td>
</tr>
<tr>
<td>19. Exchange differences</td>
<td>-16,407,28</td>
</tr>
<tr>
<td>20. Impairment loss, retirements and disposals of financial assets and liabilities</td>
<td>-</td>
</tr>
<tr>
<td>21. Grants to fund financial operations</td>
<td>-</td>
</tr>
<tr>
<td>III Result of financial operations (15+16+17+18+19+20+21)</td>
<td>-15,693,87</td>
</tr>
<tr>
<td>IV Net surplus (or deficit) in the year (II + III)</td>
<td>-324,261,89</td>
</tr>
<tr>
<td>(++) Adjustments to the account of the outcome of the prior year</td>
<td>-</td>
</tr>
<tr>
<td>Adjusted profit for the prior year</td>
<td>-</td>
</tr>
</tbody>
</table>
IDENTIFICATION OF PROGRAMS

Programs and other activities have the following breakdown of financial resources for their implementation, the description of each, as well as data and information is detailed in the scientific section of this report:

<table>
<thead>
<tr>
<th>Personnel</th>
<th>Implementation Costs</th>
<th>Amortization</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration, management and coordination</td>
<td>122,210,10</td>
<td>138,170,29</td>
<td>11,763,62</td>
</tr>
<tr>
<td>Program 1 “Alzheimer’s disease and other degenerative dementias”</td>
<td>795,168,85</td>
<td>141,776,13</td>
<td>58,464,60</td>
</tr>
<tr>
<td>Program 2 “Parkinson’s disease and other degenerative motor disorders”</td>
<td>1,307,412,44</td>
<td>258,920,21</td>
<td>65,923,03</td>
</tr>
<tr>
<td>Deputy Scientific Director / Cross-network platforms</td>
<td>234,352,42</td>
<td>36,273,37</td>
<td>278,53</td>
</tr>
<tr>
<td>Training / Young Investigator Award / Mobility</td>
<td>-</td>
<td>26,383,18</td>
<td>-</td>
</tr>
<tr>
<td>Media service, internationalization, and transfer of knowledge</td>
<td>14,265,49</td>
<td>56,937,77</td>
<td>-</td>
</tr>
</tbody>
</table>

COOPERATIVE RESEARCH

<p>| Cooperative projects, 4th call (PI2014/2013) | 0,00 | 431,00 | 1,219,31 | 1,650,31 |
| Cooperative projects, 54th call (PI2015) | 156,327,46 | 49,312,62 | - | 205,640,08 |
| Cooperative projects, 6th call (PI2015-2) | - | 936,85 | - | 936,85 |
| Cooperative projects, 8th call (PI2016) | 356,218,49 | 211,838,94 | 855,21 | 568,912,64 |
| Cooperative projects, 8th call (PI2017) | 184,587,31 | 20,953,04 | - | 205,540,35 |
| Coordination and management of call for projects | 12,187,97 | - | - | 12,187,97 |</p>
<table>
<thead>
<tr>
<th>Project Description</th>
<th>Personnel</th>
<th>Implementation Costs</th>
<th>Amortization</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COMPETITIVE PROJECTS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI11/03028</td>
<td></td>
<td></td>
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<tr>
<td>COEN Projects - 2013</td>
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<td></td>
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<tr>
<td>COEN Projects - 2017</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BBVA Research Projects</td>
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<tr>
<td>RTC-2014-1877-1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>InDIWIP/ Ramon Areces Foundation</td>
<td>15,600,70</td>
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<td>ALZ.ASSOC/SATIVEX</td>
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<td>-</td>
<td>-18,533,71</td>
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<td>HEMP SOLUTION</td>
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<td>FGCSIC</td>
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</table>

**TOTAL**

3,502,828,43
3,460,489,21
149,906,44
7,113,224,08
The data in the table below show that CIBERNEd has allocated 2,627,655.26€ for implementing research programs, which represents 53% of the ordinary operating expenses, excluding taxes and without taking into account the contribution of Associated Institutions.

<table>
<thead>
<tr>
<th></th>
<th>2017</th>
<th>2018</th>
<th>VARIACIÓN %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research programs expenditure</td>
<td>2,534,372,53</td>
<td>2,627,655,26</td>
<td>+3,68%</td>
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</tbody>
</table>

The amount allocated in 2018 to cover the costs of the internal calls for cooperative projects adds to 994,868.20€, representing 20% of the overall budget. Without considering the contribution from the Associated Institutions.

<table>
<thead>
<tr>
<th></th>
<th>2017</th>
<th>2018</th>
<th>VARIACIÓN %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cooperative research expenditure</td>
<td>1,073,770,34</td>
<td>994,868,20</td>
<td>-7,35%</td>
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</tbody>
</table>

The total expenditure allocated to fund internal research activities, either through the CIBERNEd research groups or through the calls for cooperative projects, amounts to a total of 3,622,533,46€, which represents 73.5% of the year’s expenditure, without taking into account the contribution of the associated institutions.

<table>
<thead>
<tr>
<th></th>
<th>2017</th>
<th>2018</th>
<th>VARIACIÓN %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research programs/Cooperative research expenditure</td>
<td>3,608,142,87</td>
<td>3,622,533,46</td>
<td>+0,40%</td>
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</table>

The expenditure on personnel dedicated to stable research structures (groups and cooperative projects) represents 56.64% of total expenditure, excluding the contribution of the associated institutions.

<table>
<thead>
<tr>
<th></th>
<th>2017</th>
<th>2018</th>
<th>VARIACIÓN %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal costs Research groups/Cooperative</td>
<td>2,791,727,22</td>
<td>2,811,902,52</td>
<td>+0,72%</td>
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</table>

The resources allocated to the Administration department decrease compared to previous years, representing 5.52% of the total of ordinary expenses, excluding the valuation of the contribution of the associated institutions.

<table>
<thead>
<tr>
<th></th>
<th>2017</th>
<th>2018</th>
<th>VARIACIÓN %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration</td>
<td>346,822,60</td>
<td>272,144,01</td>
<td>-21,50%</td>
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## ACQUISITION OF FIXED ASSETS

The acquisition of assets made during the year are as follows:

<table>
<thead>
<tr>
<th>PURCHASE ORDER</th>
<th>EQUIPMENT DESCRIPTION</th>
<th>DATE</th>
<th>COST</th>
</tr>
</thead>
<tbody>
<tr>
<td>0012171885</td>
<td>LAPTOP HP 250 G6</td>
<td>12/01/2018</td>
<td>598,04</td>
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<td>0012171886</td>
<td>NETGEAR CABIN CAPACITY 48 TB</td>
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<td>0012171887</td>
<td>HP PROBOOK 640 G3</td>
<td>11/01/2018</td>
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<tr>
<td>0012171888</td>
<td>HP PROBOOK 640 G3</td>
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<tr>
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<td>QX200 DROPLET PCR READER</td>
<td>24/01/2018</td>
<td>88,198,11</td>
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<tr>
<td>4102141890</td>
<td>C1000 TOUCH CYCLER THERM CYCLER BASE</td>
<td>24/01/2018</td>
<td>8,788,23</td>
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<tr>
<td>2042171892</td>
<td>LAPTOP ASUS SENBOOK UX4900UA</td>
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<td>1,784,08</td>
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<td>SHAKER GRANT BIO PS-3D</td>
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<tr>
<td>5032171894</td>
<td>COMPUTER HP BUNDLE22_260-P10979 + MONITOR</td>
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<tr>
<td>4092171895</td>
<td>COMPUTER HP PAVILION</td>
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<td>ULTRAMICROTOME</td>
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<tr>
<td>4092141897</td>
<td>CYTOMETER</td>
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<tr>
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<td>VERTICAL FREEZER - 80 MODEL EXF32086</td>
<td>29/01/2018</td>
<td>9,196,00</td>
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<tr>
<td>6072141899</td>
<td>MICROSCOPE WITHPHOTOMICROGRAPHY SYSTEM</td>
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<td>APPLE AIRPORT TIME CAPSULE-2TB</td>
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<td>ROCKER VARIABLE SPEED ROCKER II 230V</td>
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</tbody>
</table>
HUMAN RESOURCES

During 2018, the number of people who have been part of the consortium’s research groups has totaled 458, of which 310 have been personnel assigned to the research groups and 148 have been staff hired by CIBERNED at some point of the year. Below we detail the personnel segmented by each research group.

<table>
<thead>
<tr>
<th>GROUP</th>
<th>PRINCIPAL INVESTIGATOR</th>
<th>INSTITUTION</th>
<th>ASSIGNED</th>
<th>HIRED</th>
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</thead>
<tbody>
<tr>
<td>101</td>
<td>Cuadrado Pastor, Antonio</td>
<td>Autonomous University of Madrid</td>
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<tr>
<td>102</td>
<td>Fariñas Gómez, Isabel</td>
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<td>103</td>
<td>Fuentes Rodríguez, José Manuel</td>
<td>University of Extremadura</td>
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<td>López Barneo, José</td>
<td>Andalusian Public Foundation for Health Research Management in Seville</td>
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<td>106</td>
<td>Ceña Callejo, Valentín</td>
<td>University of Castilla La Mancha</td>
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<td>108</td>
<td>Vicario Abejón, Carlos</td>
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<tr>
<td>109</td>
<td>Vila Bover, Miquel</td>
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<tr>
<td>111</td>
<td>Iglesias Vacas, Teresa</td>
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<td>García Verdugo, José Manuel</td>
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<tr>
<td>114</td>
<td>Del Río Fernández, José Antonio</td>
<td>Bioengineering Institute of Catalonia (IBEC)</td>
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<tr>
<td>201</td>
<td>Canela Campos, Enric Isidre</td>
<td>University of Barcelona</td>
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<tr>
<td>204</td>
<td>Moratalta Villalba, Rosario</td>
<td>Higher Council of Scientific Research</td>
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<tr>
<td>205</td>
<td>Obeso Inchausti, José Angel</td>
<td>HM – Hospitals of Madrid</td>
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<tr>
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<td>Rodríguez Díaz, Manuel</td>
<td>University of La Laguna</td>
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<tr>
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<td>Barcelona Clinical and Provincial Hospital</td>
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<tr>
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<td>Labandeira García, José Luis</td>
<td>University of Santiago de Compostela</td>
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<tr>
<td>209</td>
<td>Pérez Tur, Jordi</td>
<td>Higher Council of Scientific Research</td>
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<tr>
<td>301</td>
<td>Alberch Vié, Jordi</td>
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<td>2</td>
<td>4</td>
</tr>
<tr>
<td>GROUP</td>
<td>PRINCIPAL INVESTIGATOR</td>
<td>INSTITUTION</td>
<td>ASSIGNED</td>
<td>HIRED</td>
</tr>
<tr>
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<td>------------------------</td>
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<tr>
<td>303</td>
<td>Fernández Ruiz, Javier</td>
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<tr>
<td>305</td>
<td>Guzmán Pastor, Manuel</td>
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<tr>
<td>306</td>
<td>Lucas Lozano, José</td>
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<tr>
<td>307</td>
<td>Naranjo Orovio, José Ramón</td>
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<td>401</td>
<td>Ávila de Grado, Jesús</td>
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<tr>
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<td>403</td>
<td>De Felipe Oroquieta, Javier</td>
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<tr>
<td>404</td>
<td>Matute Almua, Carlos</td>
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<tr>
<td>406</td>
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<td>408</td>
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<td>Torres Aleman, Ignacio</td>
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<td>Trullas Oliva, Ramón</td>
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<tr>
<td>411</td>
<td>Vitorica Ferrández, Francisco Javier</td>
<td>University of Sevilla</td>
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<td>Comella Carnice, Joan Xavier</td>
<td>Foundation Research Institute of the University Hospital Valle de Hebron</td>
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<td>415</td>
<td>Gutiérrez Pérez, Antonia</td>
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<td>502</td>
<td>Carro Díaz, Eva María</td>
<td>Foundation for Biomedical Research of the 12 de Octubre University Hospital</td>
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<td>503</td>
<td>Ferrer Abizanda, Isidro</td>
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<td>Pablo de Olavide University</td>
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</table>
Comparing these data with those collected in 2017, we can observe a stabilization of personnel, producing small variations compared to the immediately previous year. Specifically, there has been an increase of 12 assigned researchers and a decrease of 10 hired workers. The distribution of these personnel by the different Regions is as follows.

### Distribution of personnel by Region

<table>
<thead>
<tr>
<th>Region</th>
<th>Assigned</th>
<th>Hired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andalucía</td>
<td>12</td>
<td>33</td>
</tr>
<tr>
<td>Cantabria</td>
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<td>13</td>
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<tr>
<td>Castilla-La Mancha</td>
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<td>3</td>
</tr>
<tr>
<td>Cataluña</td>
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<td>113</td>
</tr>
<tr>
<td>Com. de Madrid</td>
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<td>74</td>
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<tr>
<td>Com. foral de Navarra</td>
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<td>2</td>
</tr>
<tr>
<td>Com. Valenciana</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Extremadura</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Galicia</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Islas Canarias</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Pais Vasco</td>
<td>5</td>
<td>43</td>
</tr>
</tbody>
</table>

**Total**

- **Assigned**: 310
- **Hired**: 148
INCORPORATION OF NEW TALENT

Maintaining our quest to attract the greatest amount of talent to CIBERNED’s research, during the year 2018 a total of 12 call for personnel have been published, in which 33 job positions have been posted. This year we have increased the dissemination of our job calls through different social networks in order to reach the largest number of potential candidates, whether they are located in the national territory or not.

<table>
<thead>
<tr>
<th>CALL YEAR</th>
<th>NUMBER OF CALLS</th>
<th>AVAILABLE POSITIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
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<td>47</td>
</tr>
<tr>
<td>2016</td>
<td>8</td>
<td>37</td>
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<tr>
<td>2017</td>
<td>10</td>
<td>36</td>
</tr>
<tr>
<td>2018</td>
<td>12</td>
<td>33</td>
</tr>
</tbody>
</table>

All jobs posted are defined with a specific profile, required qualifications, job requirements and roles to be developed space as well as the working hours and location of the workplace.

Out of the 33 positions filled-in during 2018, thirteen people had a PhD degree, fourteen were graduates with Higher Degree, one graduate with Middle Degree, and five were advanced technicians.

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>2017</th>
<th>2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doctor (PhD)</td>
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<td>13</td>
</tr>
<tr>
<td>Graduate (Higher Degree)</td>
<td>22</td>
<td>14</td>
</tr>
<tr>
<td>Graduate (Middle Degree)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Advanced technician</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

Another interesting fact that we can highlight from these results is that of the 33 job profiles that have been posted in 2018, 25 of them have been filled in by women and 8 have been filled in by men, which means that 76% of the job postings called had a woman as the best candidate.

New incorporations by gender
INCORPORATION AND ORIENTATION OF NEW PERSONNEL

CIBERNED is a consortium for research, with its own legal personality, without physical contiguity, and this can be a stumbling block for the incorporation and orientation of new staff in research groups. To facilitate this quickly and efficiently, a Welcome Handbook was written that is provided to workers from day one. This guide contains all the information that will be useful in providing the new personnel with an overview of our organization, as well as some basic guidelines that facilitate their working relationship. Its contents includes a brief presentation of CIBERNED, its origin and its objectives, job classification, organization of work, leaves and vacations, a summary of Occupational Risk Prevention (ORP) and templates to handle vacations and ORP. Likewise, they are provided with a Safety and Health Handbook with the information related to their job position.

In order to guarantee the health and safety of all its researchers in all activities undertaken at the workplace, CIBERNED provides a health-friendly work environment in accordance with the highest standards of reliability, hygiene and safety. The Human Resources department ensures the safety of each worker and compliance with the Occupational Health and Safety protocols, seeing it as an opportunity to detect room for improvement in those areas most closely linked to work procedures, professional development, competences, training and communication with researchers.

To improve all this type of information and facilitate the procedures that CIBERNED workers may need, this 2018 we have been working on improving our intranet so that from the first day our workers can obtain all the information related to the Consortium, they can already access and perform all work procedures in a simple and efficient way.

Distribution of personnel in the research groups during 2018

During 2018 the distribution of personnel by type of contract was 27 permanent hirings and 121 part-time ones.

Types of work contracts

![Chart showing the distribution of personnel by contract type: 82% permanent and 18% part-time.](image)
During 2018 the distribution of personnel according to their degree was 53 Doctors (PhD), 51 graduates Higher Degree, 4 graduates Middle Degree, 34 advanced technicians, and 6 administrative assistants.
TRAINING PROGRAM

During 2018, the activities included in the CIBERNED’s Training Program have continued to be promoted and semi-annual grants have been called for the realization of short secondments in other research centers, as well as for attending courses or training activities that contribute to the training of our researchers in the field of neurodegenerative diseases.

In 2018, two semi-annual calls were launched that included the following actions:

- Grants for the realization of short stays in other research centers.
- Grants for carrying out training activities

Below are both the number of applications received, and those granted throughout this year:

Applications 2018

<table>
<thead>
<tr>
<th></th>
<th>1st. Call</th>
<th>2nd. Call</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mobility</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Training</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Budget requested</td>
<td>€12,817,00</td>
<td>€5,980.00</td>
</tr>
</tbody>
</table>
Grants awarded 2018

<table>
<thead>
<tr>
<th></th>
<th>1st. Call</th>
<th>2nd. Call</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mobility grants awarded</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Training grants awarded</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Budget approved</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

€ 8 017,00
€ 4 790,00
PREVENTION OF OCCUPATIONAL RISKS

During the management period analyzed, the following preventive activities have been carried out:

- Coordination of the visits to the research centers with the External Prevention Service and the different associated Institutions, for data collection related to personnel risk assessment.
- Management of the training of employees in Prevention of Occupational Hazards, requesting the Prevention Service the specific training schedule for existing job positions.
- Delivery of laboratory, offices and health sector handbooks to inform workers of the risks of their jobs and preventive measures to be observed for safe work.
- The monitoring of individual health has been carried out for more than 73% of the workforce. The medical examinations carried out were 93, subject to specific protocols according to the risks to which the employees are exposed.

Finally, the objectives of improving the safety and health conditions of employees and reducing accident rates taken as a reference by the Mutual Insurance Company for Occupational Accidents and Disease have been met, keeping those indexes to zero and therefore below the performance benchmarks of the Research and Development sector:

<table>
<thead>
<tr>
<th>CNAE REFERENCE</th>
<th>LIMIT VALUE OF ACCIDENT RATE</th>
<th>CIBERNED</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VALUE</td>
<td>ACCIDENT RATE</td>
</tr>
<tr>
<td>INDEX 1</td>
<td>5,98</td>
<td>0</td>
</tr>
<tr>
<td>INDEX 2</td>
<td>0,54</td>
<td>0</td>
</tr>
<tr>
<td>INDEX 3</td>
<td>0,33</td>
<td>0</td>
</tr>
</tbody>
</table>

QUALITY

In 2018, the transition to the new version of ISO 9001:2015 standard was made; as well as the renewal of the certificate of said quality standard.

For this purpose, we worked on the evaluation, administration, elimination and/or minimization of risks and opportunities and measures were taken to ensure the reduction of the effects of said risks; opportunities were also effectively addressed and monitored.

The understanding of needs and expectations established the way in which the CIBERNED responded to these measures.

CIBERNED Management Office of the is open to any improvement proposal, where it will be the organization’s own leaders who promote and develop a quality culture and adaptation to the organization’s change.
## COLLABORATION AGREEMENTS

In 2018, the following agreements have been kept in force by the institution:

<table>
<thead>
<tr>
<th>SIGNING PARTNER INSTITUTIONS</th>
<th>SUBJECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRTA (PERSONNEL IDIBELL)-CIBERNED</td>
<td>Establishing a cooperation framework to perform joint activities in the field of neurodegenerative diseases, including prion disorders or transmissible spongiform encephalopathies</td>
</tr>
<tr>
<td>STATE GENERAL ADMINISTRATION (MINISTRY OF JUSTICE, STATE’S ATTORNEY, DIRECTORATE OF THE LEGAL SERVICE OF THE STATE)-CIBERNED</td>
<td>Legal assistance</td>
</tr>
<tr>
<td>RAMÓN ARECES FOUNDATION-CIBERNED</td>
<td>XVIII National call for research grants on life and materials sciences</td>
</tr>
<tr>
<td>BIOCROSS- CIEN FOUNDATION-CIBERNED</td>
<td>Collaboration agreement for the implementation of public-private cooperation actions within the call RIS3 2016</td>
</tr>
<tr>
<td>BIOCROSS- CIEN FOUNDATION-CIBERNED</td>
<td>Collaboration agreement for the implementation of public-private cooperation actions within the call retos colaboración 2017</td>
</tr>
<tr>
<td>CIBER ISCIII-CIBERNED</td>
<td>Regulate the participation of the research groups of ciberned in the Vallecas project (Cohortes p. Vallecas)</td>
</tr>
<tr>
<td>UNIVERSITY OF BARCELONA</td>
<td>Assignment of use to the university of barcelona</td>
</tr>
<tr>
<td>CLÍNIC FOUNDATION FOR BIOMEDICAL RESEARCH, CLINICAL HOSPITAL OF BARCELONA, UNIV. OF BARCELONA, CSIC AND CIBERNED</td>
<td>Co-ownership agreement related to patent “Method for the subclassification for patients suffering from parkinson disease”</td>
</tr>
<tr>
<td>BIOCROSS-ISCIII-CIBERNED</td>
<td>Co-ownership agreement related to patent “A fast and cost-effective method for apolipoprotein e isotyping as an alternative to apoe genotyping”</td>
</tr>
<tr>
<td>NATIONAL EVALUATION AND PROSPECTIVE AGENCY (ANEP)-CIBERNED</td>
<td>Scientific-technical evaluation of ciberned cooperative projects</td>
</tr>
<tr>
<td>CSIC-AUTONOMOUS UNIVERSITY OF MADRID-CIBERNED</td>
<td>Co-ownership agreement related to patent nº 201431898 “Compuestos modulares del sensor neuronal de calcio dream y sus usos terapéuticos”</td>
</tr>
<tr>
<td>CSIC-UAM-CIBERNED</td>
<td>Co-ownership agreement related to patent nº201431898 “Compuestos moduladores del sensor neuronal de calcio dream y sus usos terapéuticos”</td>
</tr>
<tr>
<td>SECRETARIAT OF STATE OF UNIVERSITIES MINISTRY OF EDUCATION, CULTURE AND SPORTS -CIBERNED</td>
<td>Management of training and mobility grants from the promotion of talent program and its employability of the state plan of scientific and technical research and of innovation 2013-2016 and other actions of grants calls for the mobility of students and college teachers</td>
</tr>
<tr>
<td>UNIVERSITY OF EXTREMADURA-CIBERNED</td>
<td>Curricular and extracurricular practices of students</td>
</tr>
<tr>
<td>COMPLUTENSE UNIVERSITY OF MADRID-CIBERNED</td>
<td>Co-ownership agreement related to patent &quot;Regulación de receptores CB1 de cannabionoides para la generación de neuronas corticospinales a partir de células troncales embrionarias murinas&quot;</td>
</tr>
<tr>
<td>SIGNING PARTNER INSTITUTIONS</td>
<td>SUBJECT</td>
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<td>----------------------------</td>
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<tr>
<td>UNIVERSITY OF EXTREMEADURA - CIBERNED</td>
<td>Curricular and extracurricular practices of students</td>
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<tr>
<td>CIBERNED ASSOCIATED INSTITUTIONS</td>
<td>Establish a framework for the development of relations with institutions that are integrated in the consortium</td>
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<tr>
<td>HOSPITALES DE MADRID FOUNDATION - CIBERNED</td>
<td>Establish a framework for the development of relations with institutions that are integrated in the consortium</td>
</tr>
<tr>
<td>MIGUEL HERNÁNDEZ UNIVERSITY OF ELCHE - FOUNDATION FOR THE PROMOTION OF HEALTH AND BIOMEDICAL RESEARCH OF THE REGION OF VALENCIA - CIBERNED</td>
<td>Co-ownership agreement related to patent P201130290 &quot;Método de diagnóstico y/o pronóstico de la enfermedad de alzheimer&quot;</td>
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<tr>
<td>FIBIO 12 DE OCTUBRE HOSPITAL - CIBERNED</td>
<td>Co-ownership agreement related to patent pct/ es2013/070693 &quot;Modelo animal de déficit cognitivo, procedimiento de obtención y aplicaciones&quot;</td>
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<tr>
<td>CSIC - CIEN - FOUNDATION CIENBERED</td>
<td>Co-ownership agreement related to patent ep13382108.2 “Methods for the prognosis and diagnosis of neurodegenerative diseases”</td>
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<tr>
<td>BIOCROSS – CIEN FOUNDATION - CIBERNED</td>
<td>Non-disclosure agreement related to patent ep13382108.2 “Methods for the prognosis and diagnosis of neurodegenerative diseases”</td>
</tr>
<tr>
<td>CSIC - NEURON BIO-CIBERNED</td>
<td>Co-ownership agreement related to patent P201231654 &quot;Proteína viral recombinante SGG2/y/o complejos binarios SGG2-FNS para su uso en crecimiento y/o regeneración axonal&quot;</td>
</tr>
<tr>
<td>CSIC-CIBERNED</td>
<td>Co-ownership agreement related to patent p201231654 &quot;Proteína viral recombinante SGG2/y/o complejos binarios SGG2-fns para su uso en crecimiento y/o regeneración axonal&quot;</td>
</tr>
<tr>
<td>FUNDACIÓN ACE-CIBERNED</td>
<td>Collaboration framework agreement</td>
</tr>
<tr>
<td>TEOFILO HERNANDO INSTITUTE (UAM)-CIBERNED</td>
<td>Collaboration framework agreement to promote and strengthen study, research, and teaching activities, as well as the dissemination and holding of events of scientific, academic and cultural interest</td>
</tr>
<tr>
<td>CSIC-CIBERNED</td>
<td>Co-ownership agreement related to patent &quot;ADN mitocondrial como marcador para el diagnostico de enfermedades neurodegenerativas&quot;</td>
</tr>
<tr>
<td>FIBIO RAMÓN Y CAJAL HOSPITAL - CIBERNED</td>
<td>Co-ownership agreement related to patent &quot;Medio condicionado de glía como agente neuroprotector&quot;</td>
</tr>
<tr>
<td>MIGUEL HERNÁNDEZ UNIVERSITY OF ELCHE - CIBERNED</td>
<td>Co-ownership agreement related to patent &quot;método para determinar la enfermedad de alzheimer mediante la detección de glicoproteínas portadoras del glicopéptido HNK-1&quot;</td>
</tr>
<tr>
<td>CIEN FOUNDATION - CSIC - CRG - CIBERNED</td>
<td>Co-ownership agreement related to patent p201130033 &quot;Compuestos para el tratamiento de enfermedades neurodegenerativas&quot;</td>
</tr>
<tr>
<td>CIEN FOUNDATION (UIPA. ALZHEIMER PROJECT RESEARCH UNIT) - CIBERNED</td>
<td>Establish an association agreement in the framework of art. 29 of the ciberned statutes for the development of scientific-technological research on neurodegenerative diseases</td>
</tr>
<tr>
<td>ISCIII-ASSOCIATED INSTITUTIONS</td>
<td>Collaboration agreement for the creation of the CIBER consortium for the thematic area of neurodegenerative diseases</td>
</tr>
</tbody>
</table>
INVESTIGATORS INDEX
**ALPHABETICAL INDEX**

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<thead>
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<th>Page</th>
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<th>Group</th>
</tr>
</thead>
<tbody>
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<td>Alberch Vié, J</td>
<td>2 - 301</td>
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<td>Ávila de Grado, J</td>
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<td>Guzmán Pastor, M</td>
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249 | Navarro Acebes, X - Program 3 - Group 607
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192 | Pérez Tur, J - Program 2 - Group 209
082 | Rodríguez Álvarez, J - Program 1 - Group 406
198 | Rodríguez Díaz, M - Program 2 - Group 206
085 | Sáez Valero, J - Program 1 - Group 407
089 | Soriano García, E - Program 1 - Group 408
201 | Tolosa Sarró, E - Program 2 - Group 207
093 | Torres Alemán, I - Program 1 - Group 409
096 | Trullás Oliva, R - Program 1 - Group 410
211 | Vicario Abejón, C - Program 2 - Group 108
214 | Vila Bover, M - Program 2 - Group 109
099 | Vitorica Ferrández, JV - Program 1 - Group 411
102 | Wandosell Jurado, F - Program 1 - Group 412