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ANNUAL REPORT

Fundación Centro Investigación Enfermedades Neurológicas

INSTITUTO ALZHEIMER FUND



FUNDACIÓN CIEN

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Enfermedades Neurológicas

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PROFILE AND PRESENTATION



1.1.

Who we are

A foundation from the public sector

The Research Center for Neurologic Diseases (CIEN, for its acronym in Spanish) Foundation was established on December 27, 2002 by virtue of a resolution of the Council of Ministers. It is defined as a non-profit public sector Foundation, with State-wide scope and competence. Currently, it depends on the Ministry of Science, Innovation and Universities through the Carlos III Institute of Health.



Among its founding objectives are supporting, promoting and coordinating research in neurological diseases, especially neurodegenerative disorders. It also highlights its unifying and coordinating role of leading Spanish research groups in this field.

The CIEN Foundation is based at the Queen Sofia Foundation Alzheimer Center, whose construction was called the Alzheimer Project. Once the Alzheimer Center was built, it was divided into a residence for healthcare and follow-up of the patients and an Alzheimer Project Research Unit of the (UIPA, for its acronym in Spanish), whose main project is the Vallecas Project.



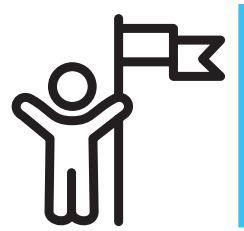
Collaboration with the Queen Sofia foundation

Since its establishment, the CIEN Foundation manages and coordinates the Alzheimer Project Research Unit (UIPA), created by the Queen Sofia Foundation and located in the Alzheimer Center that bears her name.

The CIEN Foundation is a pioneer center in Spain in which to comprehensively address the consequences that Alzheimer's disease causes both on patients and their family environment. Since its opening in 2007, the CIEN Foundation, located at the neighborhood of Vallecas, Madrid, seeks to respond to the social health project proposed by the Alzheimer Project of the Queen Sofia Foundation.

A reference center in Europe on Alzheimer's disease research

Only two institutions in Spain participate in the European Union Joint Programming for Disease Neurodegenerative Diseases (JPND): CIEN Foundation and CIBERNED. Its excellent infrastructures, modern methodologies and cutting edge technologies at their disposal as well as the available critical mass of researchers were the criteria most valued by representatives of this organization after being proposed by the Carlos III Institute of Health.



In addition, both CIEN Foundation as CIBERNED are integrated into the international Network of Centers of Excellence in Research on Neurodegeneration (COEN), mostly composed by European research centers.

An innovative, integrated vision of the fight against Alzheimer's disease



The CIEN Foundation and the Queen Sofia Foundation share a common perspective on action in relation to Alzheimer's disease: This disease requires a comprehensive approach model where research should be one of the fundamental pillars. The leading exponent of this integrative model is the Queen Sofia Foundation Alzheimer Center, where the main backbones of Alzheimer Project converge.

- A live-in residence for 156 Alzheimer's patients.
- A day-care outpatient center for 40 Alzheimer's patients.
- An Alzheimer's research center: the so-called Alzheimer's Project Research Unit (UIPA), managed by the CIEN Foundation.
- A training center for healthcare staff, relatives and volunteers.

The management model implemented by the Queen Sofia Foundation Alzheimer Center has sought to summon the will and interests of all parties involved: Administration (State, Regional and Local) and civil society. For this reason, the management of UIPA, devoted to research, was assigned to the CIEN Foundation, while the Ministry of Family and Social Affairs of the Region of Madrid is responsible for healthcare and training activities.

Focused on research in neurodegenerative diseases

The CIEN Foundation is in charge of the following tasks: implement a model of translational research that allows to effectively and efficiently transfer the scientific advances achieved in basic research to clinical practice; promote the continuous training of professionals involved with the research in neurodegenerative diseases through seminars, lectures and doctoral theses; disseminate the calls launched by funding agencies, both nationally and internationally, promoting participation; and encourage the implementation of coordinated research projects in neurodegenerative diseases.



From the administrative point of view, the CIEN Foundation is also responsible for managing other centers related to research in neurodegenerative diseases such as the Network Center for Biomedical Research in Neurodegenerative Diseases (CIBERNED, for its acronym in Spanish), maintaining collaboration agreements with the Carlos III Institute of Health for carrying out those management activities.

A sustainable center for the benefit of research



Until December 2019, the Queen Sofia Foundation Alzheimer Center has avoided emitting a total of 133,529 kg of CO₂ since its inauguration in 2007 thanks to the power generation from its solar thermal and photovoltaic panels. In total, they have produced 251,941 kWh, which has saved 124,816.06€ that have been allocated to research on this disease.

In its design and construction 17 years ago at the initiative of Her Majesty Queen Sofia, "special care" was taken that the project maintained a "deep respect for the environment", incorporating bioclimatic measures, an orientation adapted to its location, actions against the overheating, natural ventilation, water treatment or use of ecological covers. For this reason, it was recognized with the "Green Light" emblem of the European Commission, and obtained the highest qualification in its energy certification by the Institute for Diversification and Energy Savings (IDEAE, for its acronym in Spanish).

CAFRS PHOTOVOLTAIC ENERGY

Billing since the opening of the Center	124.816,06 €
Accumulated production	251.941 kWh
CO ₂ emissions avoided	133.529 kg

1.2.

The CIEN Foundation in 2019

- During 2019, CIEN Foundation researchers published 20 scientific papers in specialized journals, of which 18 (90%) were in journals classified within the first and second quartiles, with an average impact factor of 8.326, an 39.06% increase over the previous year.
- At the beginning of 2019, the project "Family history of Alzheimer's disease in older people: influence of subjective cognitive impairment (ERAD)" started, funded by the Ministry of Science, Innovation and Universities through the 2018 call for R&D projects. D + i "Research Challenges" of the State Program of R + D + i Oriented to the Challenges of Society (RTI2018-098762-A-C32).
- The international research project entitled "Spain-Portugal Longevity Research Program +90 (PILEP+90)" was launched at the beginning of the year, funded by the General Foundation of the University of Salamanca (0348_CIE_6_E).
- In September 2019, the CIEN Foundation formalizes the hiring of Dr. Javier Quilis under the ImageH subproject belonging to PILEP + 90.
- The II Conference of Neuroscientists Today: Sowing references, was held on the occasion of the World Day of Women and Girls in Science.
- Inauguration of the traditional "Christmas Tree of Memories" which in 2019 was installed once again in the Madrid City Council and the Villa de Vallecas Market.
- For the seventh consecutive year, the already institutionalized Vallecas Project Volunteer's Day was celebrated, in recognition of the collaboration of these people in favor of research.
- During 2019, the CIEN Foundation maintained its co-ownership in one active patent application, in national phases at various countries, both licensed to Raman Health Technologies.
- The CIEN Foundation 2019 Seminar Series included 12 sessions of scientific seminars with the participation of speakers, both from the CIEN Foundation, as well as related, national and international institutions.
- The Annual Conference of the National Network of Biobanks was held on February 2019 at the CIEN Foundation, with the participation of all biobanks in the Network.
- Launch of the Neurological Tissue Banks Working Group within the National Network of Biobanks. Holding of the GT-BTN pre-congress meeting at the X National Congress of Biobanks (Valencia, October 2019).

- Creation of the Iberian Neuropathology Working Group, in which the Spanish Neuropathology Club (Coordinated by Dr. Alberto Rábano) and the Portuguese Neuropathology Society participate jointly (Salamanca, October 2019).
- Initiation of the determinations of salivary Lactoferrin as an Alzheimer's disease marker in Down syndrome.
- Collaboration agreement with the Dementia Unit of the Princess Leonor Hospital for the creation of a cohort of patients with mild cognitive impairment with clinical study and markers in plasma and cerebrospinal fluid of patients.
- Collaboration with the "Severo Ochoa" Molecular Biology Center for the study of microRNAs and proteins in tear fluid from patients with mild cognitive impairment and dementia.
- VII Edition of the International Congress on Research and Innovation in Neurodegenerative Diseases (CIIIEN) in collaboration with the Queen Sofia Foundation and CIBERNED. This annual event, consolidated as the International Congress of reference in our country in the area of neurodegenerative diseases, was held in Valencia on September 17-20 with It was held in this edition in Valencia from September 17 to 20 with great media coverage. There were many media that echoed the development of this international congress, with broadcasts on TV such as Antena 3, publications in agencies such as Europa Press or EFE; specialized media in health and research such as ConSalud.es; and on national daily press such as La Razón.
- Planning, organization and launch of the 1st edition of the Memorables Film Festival, the first short film festival dedicated to Alzheimer's disease, whose main objective is to show and promote the creation and dissemination of short films that have Alzheimer's disease as a common thread. 15 candidate short films participated. A dissemination campaign was also developed on social networks, through the hashtag #MemorablesFilmFestival.
- Collaboration with Hard Rock Café Madrid in the Hard Rock Memory Series initiative in favor of Alzheimer's research on the occasion of its 25th anniversary, in which 25 national and international musicians and bands participated. This initiative was complemented by a campaign on social networks through the hashtags # NEURO2020 and # HARDROCKCAFE25.
- Launch of the meetings of the Governing Commission for the event of exceptional public interest "Neurodegenerative Diseases 2020. International Year of Research and Innovation", established in March 2019, in order to comply with the provisions of the Additional Provision Ninety-seventh of Law 6/2018, of July 3, on General State Budgets for the year 2018.
- In June 2019, an agreement was signed to establish a framework for developing relationships to carry out scientific and training activities between the CIEN Foundation, the Carlos III University, the Carlos III Health Institute, and the Carlos III National Cancer Research Center foundations (CNIO, for its

acronym in Spanish) and the Carlos III National Center for Cardiovascular Research (CNIC, for its acronym in Spanish).

- In March 2019, the winner of the Queen Sofía Foundation- Mapfre 2019 Fellowship was hired. This year, the fellowship is divided into stays between our Center and the Neurology department of the University Hospital in Jena, Germany.
- Until December 2019, the Queen Sofia Foundation Alzheimer Center has avoided emitting a total of 133,478 kg of CO₂ since its inauguration in 2007 thanks to the power generation of its solar thermal and photovoltaic panels. In total, they have produced 251,845 kWh, which has saved 124,816.06€ that has been allocated to the CIEN Foundation for research on this disease.
- In collaboration with the Hospital and University Center of Coimbra, Portugal, the secondment of a resident from the Pathological Anatomy Service, in the Pathological Anatomy area of the CIEN Foundation, was approved.
- To increase the knowledge and experience in the area of pathological anatomy of Medical Intern residents (MIR), during 2019 the rotations of MIR personnel from the 12 de Octubre University Hospital and the Son Espases University Hospital were approved.



1.3.

Presentation

The CIEN Foundation was established with the objective of supporting, promoting and coordinating research in all fields of basic, clinical and epidemiological neurology, with special emphasis on issues related to neurodegenerative diseases.

Throughout its course, the Foundation has carried out various tasks, standing out for its unifying and coordinating role of prominent Spanish research groups in this field, thus being entrusted with the management of the Network Center for Biomedical Research for Neurodegenerative Diseases.

At the same time, it was assigned the management of the Alzheimer Project Research Unit once the Queen Sofia Foundation assigned use of the building to the CIEN Foundation.

On January 18, 2006, H.M. The Queen Sofia of Spain, President of the Queen Sofia Foundation and Ms. Elena Salgado Méndez, Minister of Health and Consumer Affairs and President of the CIEN Foundation Board of Trustees signed an agreement whereby the former ceded the premises and equipment devoted to the Research of the Alzheimer Project Complex to the latter, the CIEN Foundation committing itself to the management of the Research Unit, strictly adhering to the mission of said Unit and establishing the appropriate objectives, actions and actions based on it.

The Research Unit of the Alzheimer Project allows priority research on Alzheimer's disease and other dementias with studies such as the "Vallecas Project" or the "Research Program of the Queen Sofia Foundation Alzheimer Center", and in a complementary way, research on other neurodegenerative diseases.

The Unit currently consists of five areas: a Neuroimaging area with a 3T Magnetic Resonance; a Neuropathology area whose nuclear activity corresponds to the CIEN Tissue Bank (BT-CIEN), for the extraction, processing, classification and distribution of tissue; an area of Biochemistry and Molecular Genetics, for the processing and analysis of biological samples; a Neurology area and a Neuropsychology area, which carry out the assessment and clinical follow-up of both the patients treated at the Complex, as well as those volunteers from research projects that attend to the Center.

1.4.

Organizational structure

1.4.1. Governing and Management Bodies

The CIEN Foundation is composed of three bodies, one of management, represented by Mrs. M^a Ángeles Pérez Muñoz, manager of the CIEN Foundation; another one of scientific management, represented by Professor Jesús Ávila de Grado, and a third governing body, the Board of Trustees:

- Board of Trustees: is responsible for the government and representation of the CIEN Foundation as well as for the fulfillment of the Foundation objectives, administration and management of its capital assets. Board members represent all sectors involved in neurological diseases research: public institutions related to the field of health, research, social and industrial policy, technology, business and education.
- Scientific Director: represented by Prof. Jesus Ávila de Grado.
- Managing Director: represented by Ms. M. Ángeles Pérez Muñoz.

1.4.2. Advisory and participation bodies

External Scientific Advisory Committee

In the Board meeting held on March 10, 2014 the composition of the CIEN Foundation External Scientific Advisory Committee it is presented and approved. It is aimed at improving the scientific quality of the activities, optimizing the available resources and exploiting the singularities of the Queen Sofia Foundation and the Alzheimer Center. Since that date, the Committee is formed by the following members:

Mr. Joaquín Arenas Barbero. BSc in Pharmacy and PhD in Clinical Biochemistry by Faculty of Medicine of Complutense University of Madrid. He has held the positions of General Director and Deputy General Director of Networks and Cooperative Research Centers within the Carlos III Institute of Health (ISCIII). He is currently Director of the 12 de Octubre Hospital Research.

Mr. Javier De Felipe Oroquieta. PhD in Biological Sciences by the Complutense University of Madrid. Neurobiologist at the Cajal Institute. He leads the Spanish team of the Blue Brain international project (Cajal Blue Brain) integrated by scientists from the Technical University of Madrid and CSIC. He belongs to CIBERNED and collaborates actively with the CIEN Foundation.

Mr. Miguel Medina Padilla. PhD in Biochemistry and Molecular Biology from the Autonomous University of Madrid. Deputy Scientific Director of CIBERNED and principal Investigator of the Vallecas Project.

Mr. José Ramón Naranjo Orovio. PhD in Pharmacy from the Complutense University of Madrid. Neurobiologist at the National Center for Biotechnology (CSIC). He belongs to CIBERNED and collaborates actively with the CIEN Foundation.

Mr. Fernando Rodríguez Artalejo. Doctor in Medicine and Surgery from the Autonomous University of Madrid. Professor of Preventive Medicine and Public Health at the Autonomous University of Madrid.



The Board of Trustees will function in plenary session and as a Delegated Commission.

At the end of 2019 the Board of Trustees has the following members:

HONORARY PRESIDENT

Mr. Pedro Duque Duque. Minister of Science, Innovation and Universities

Chair:

Mr. Rafael Rodrigo Montero. State Secretary of Coordination of Science Policy.

Vice-chair:

Ms. Raquel Yotti Álvarez. Director of the Carlos III Institute of Health.

Ex-officio members:

Ms. Rosa Menéndez López, President of the Higher Council for Scientific Research State Agency

Mr. Faustino Blanco González, General Secretary of Health and Consumer Affairs

Representative from the Ministry of Economy, Industry and Competitiveness with a Director General rank (to be appointed)

Mr. Borja Luis Cabezón Rojo, Director of the Department of National Affairs of the Office of the Prime Minister. Registered termination effective on 04-13-2019

Ms. Pilar Aparicio Azcárraga, Director General of Public Health, Quality and innovation, Ministry of Health, Social Services and Consumer Affairs

Mr. Cristóbal Belda Iniesta, Deputy Director General of Evaluation and Promotion of Research, Carlos III Institute of Health. Pending

Ms. Margarita Blázquez, Deputy General Director of Cooperative Research Networks and Centers, Carlos III Institute of Health.

Elected members:

Mr. Manuel García León. General Director of Research and Transfer of Knowledge, Government of the Region of Andalusia. Registered termination effective on 02-21-2019.

Ms. Ana M^a Ávila Peñalver. Director General for Research, Innovation, Technology and Quality, Government of the Region of Valencia. Registered termination effective on 10-18-2019.

Mr. Pablo Cortés Achedad (General Director of Research and Transfer of Knowledge, Government of the Region of Andalusia.). Pending acceptance.

Mr. Javier Santos Burgos, Director General of Research and High Health Inspection of the Council of Universal and Public Health, Government of the Region of Valencia. Pending acceptance.

Secretary:

Ms. Margarita Blázquez Herranz, Deputy General Director of Cooperative Research Networks and Centers, Carlos III Institute of Health.

Legal advisor

Mr. José Luis Beotas López. State Attorney.

Invited guests

CIENTIFIC FOUNDATION

Mr. Jesús Ávila de Grado. Scientific Director.

Ms. María Ángeles Pérez Muñoz. Managing Director.

QUEEN SOFIA FOUNDATION

Mr. José Luis Nogueira Guastavino

DIRECTOR OF THE TECHNICAL CABINET OF THE SECRETARIAT
FOR SCIENTIFIC POLICY COORDINATION

Ms. Petra Fernández Álvarez

ASSISTANT TO THE SECRETARY

Ms. M^a Dolores Donoso Menciao

The following members will also form part of the Executive Committee:

- The General Director of Public Health, Quality and Innovation of the MSSI.
- The Deputy Director General of Evaluation and Promotion of Research of the Carlos III Institute of Health.
- The General Director of Scientific and Technical Research of the Ministry of Science, Innovation and Universities.
- The Secretary will be the same as that of the Plenary.

Research Ethics Committee of the Carlos III Institute of Health

Since June 2010, the CIEN Foundation's research activity is supervised for clinical projects and for the activity of the Tissue Bank, by the Research Ethics and Animal Welfare Committee (CEIYBA, for its acronym in Spanish) of the ISCIII. The CEIYBA of the Carlos III Institute of Health is a collegiate body, according to what is described in Article 12 of Law 14/2007 of July 3, on Research.

As of 2016, starting with RESOLUTION R-119/16 of Management, when the subcommittees that had been operating as CEIYBA were separated into the Research Ethics Committee and the Animal Welfare Ethics Committee. From this moment on, the requests for reports will be processed to the corresponding committee.

With regard to the functions described in Law 14/2007 on Biomedical Research, the Committee provides services to the Centers and Units of the Carlos III Institute of Health, to the Foundations promoted by it and to mixed or associated Centers recognized by the Carlos III Institute of Health.

Thus, the CIEN Foundation requests a report on any study carried out with human beings, their samples or their data through the Research Ethics Committee (CEI, for its acronym in Spanish).



1.5

Future outlook

At the end of 2013, the Vallecas Project concluded the recruitment phase, finally constituting a cohort of 1,213 volunteers of both sexes aged between 69 and 85 years. Once included in the study, an annual follow-up of the volunteers was carried out in order to assess the evolutionary profile of all the participants, specifically identifying those people who have developed mild cognitive impairment, incipient dementia or advanced dementia. The objective of the Vallecas Project is mainly focused on the early detection of Alzheimer's disease with a multidisciplinary approach, based on the conjunction of sociodemographic, clinical, neurological, neuropsychological, genetic, biochemical and neuroimaging data.

Additionally, the Vallecas Project cohort represents a unique and invaluable research resource that allows addressing complementary research objectives such as the study of the factors involved in healthy aging, the analysis of the etiopathogenic mechanisms of Alzheimer's disease or the definition of new therapeutic targets. In this regard, the Vallecas Project cohort is one of the Foundation's main resources for establishing national and international collaborations. As a result of these collaborations, work of high impact and international relevance is already being carried out.

Likewise, the availability of multidisciplinary data and a repository of longitudinal biological samples that cover all stages of the evolution of the disease from normality to dementia constitutes a future value that transcends the present usefulness of the Vallecas Project. This scope is increased when combined with the BT-CIEN biobank structure that guarantees the availability of data and samples for the scientific community once the Vallecas Project reaches the end of its follow-up phase, thus providing a high added value to the effort carried out in recent years within the Vallecas project.

Due to the fact that during the years of development of the project there has been a significant attrition of the cohort of volunteers for various reasons (loss

of interest, fatigue, illness, change of address, death, etc.), in order to enhance all the work already carried out (once the epidemiological situation makes it possible to resume the follow-up visits safely), in the short term it is proposed to recover the largest possible number of volunteers for at least one last visit, so that their evolution can be recorded, especially in the area of cognition. Likewise, given that one of the limitations of the cohort is the lack of cerebrospinal fluid biomarkers (the protocol does not include performing lumbar punctures) that allow us to increase the precision of clinical diagnoses, the measurement of disease markers is proposed in blood using ultrasensitive cutting-edge techniques. All of this will allow us to continue with the definition of markers of Alzheimer's disease with greater precision and scientific relevance.

Finally, it is worth highlighting another important ramification of the current study of this cohort that is related to the low rate of conversion to dementia observed throughout the eight years of development of the project, and the supra-normalization of the cohort. In this sense, a study of "superagers" is being carried out, focused on determining the factors of resilience to neurodegeneration.







**MANAGEMENT
REPORT**

2024

2.1.

General management

CIEN Foundation is a State wide public sector Foundation supervised by the Carlos III Institute of Health under the Ministry of Economy, Industry and Competitiveness.

The CIEN Foundation is governed by its Statutes; by Law 50/2002, of December 26, on Foundations; by Royal Decree 1337/2005, of November 11, which approves the Regulations of the Foundations of State competence; by the provisions of the National Budget Law, in everything that refers to the Foundations of the State Public Sector; by Royal Decree 384/1996, of March 1, on the Registry of Foundations of State Competence; by Law 49/2002, of December 23, on the Tax Status of Non-Profit Organizations and Tax Incentives to Patronage; and for the rest of the legal provisions of an administrative, civil, mercantile or labor nature that apply to it.

The purpose of the CIEN Foundation is to promote research in all fields of basic, clinical and epidemiological neurology, aspiring to become a Center of national and international reference on research in Alzheimer's disease and other dementias. The CIBERNED-CIEN Foundation consortium is the only Spanish institution recognized as a Center of Excellence in Neurodegeneration within the Centers of Excellence in Neurodegeneration Network (COEN), a complementary initiative to the JPND to establish a common approach to research in neurodegenerative diseases, promoting collaborative research between recognized national Centers of Excellence in neurodegeneration in order to accelerate progress in understanding the mechanisms of the disease, as well as the identification of new therapeutic approaches.

Particular aims include fostering scientific advances to have an impact on the healthcare system and the well-being of patients. To this end, an offer of ser-

VICES carried out by various Consultation Units and Research Groups of the CIEN Foundation has been articulated and made available to users outside the Center:

- Cerebral tissue sample request service
- Magnetic resonance Imaging acquisition service
- Diagnostic consultation service

2.2.

Management of financial and economic resources

The CIEN Foundation is funded by specific subsidies granted by the State and other local or institutional public entities, as well as by income derived from European and national research projects, contracts for the provision of services and patronage activities.

The annual accounts are prepared from the accounting records of the Entity, having applied the legal provisions in force in accounting matters in order to show the true image of the assets, the financial situation and the results of the CIEN Foundation.

Income statement for the year 2019

INCOME STATEMENT	NotEs	2019	2018
A) Surplus for the year			
1. Income from own activity	-	1.792.403,96	1.762.213,63
d) Subsidies, donations and legacies attributed to the surplus for the year	10.1	1.792.403,96	1.762.213,63
2. Sales and other income from commercial activity	10.1	150.155,95	73.981,80
3. Expenses for grants and others	-	-45.242,70	-16.000,00
a) Monetary aid	10.2	-45.242,70	-16.000,00
4. Variation in inventories of finished products and in manufacturing process	-	-293,41	-2.358,58
6. Supplies	10.2	-175.725,59	-106.165,92

7. Other income from the activity	10.2	1.298,46	6.033,97
8. Personnel expenses	10.2	-835.432,52	-802.162,35
9. Other expenses of the activity	10.2	-592.332,23	-623.160,17
10. .Amortization of fixed assets	5.1-5.2	-524.958,84	-537.836,69
11. Subsidies, donations and bequests of capital transferred to the surplus for the year.	11.1-11.2	526.203,18	530.588,86
13. Other results	-	-5.318,89	-
A.1) SURPLUS OF THE ACTIVITY (1+2+3+4+5+6+7+8+9+10+11+12)		290.757,37	285.134,55
16. Financial income	10.1	233,66	250,56
19. Exchange differences	-	0	52,47
A.2) SURPLUS FROM FINANCIAL OPERATIONS (16+19)	-	233,66	303,03
A.3) SURPLUS BEFORE TAXES (A.1+A.2)	-	290.991,03	285.437,58
A.4) Variation in equity recognized in the surplus for the year (A.3+18)	-	290.991,03	285.437,58
B)) Income and expenses charged directly to equity	-	-	-
1. Grants received	11	50.000,00	6.499,21
2. Donations and bequests received	11	505.403,96	438.255,84
B.1) Variation in equity due to income and expenses recognized directly in equity (1+2+3+4)	-	555.403,96	444.755,05
C) Reclassifications to the surplus for the year	-	-	-
1. Grants received	11	-35.617,90	-40.003,58
2. Donations and bequests received	11	-1.007.989,24	-908.841,12
C.1) Variation in equity due to reclassifications to the surplus for the year (1+2+3+4)	-	-1.043.607,14	-948.844,70
D) Variations in equity due to income and expenses charged directly to equity (B.1+C.1)	-	-488.203,18	-504.089,65
F) Adjustments for errors	-	-	-
G) Variations in the initial endowment	-	-	-
H) Other variations	-	-	-
I) TOTAL RESULT, VARIATION IN EQUITY IN THE YEAR (A.4+D+E+F+G+H)	-	-197.212,15	-218.652,07

Revenues

In 2019, the CIEN Foundation managed an income budget of over 2.4 million euros. The main source of income comes from the nominative assignment of the Carlos III Institute of Health, which amounts to € 1.275,000 (representing 52% of total income), aimed at achieving the specific goals and objectives that are materialized in the promotion of research in health sciences, and develop and offer scientific-technical services of the highest quality, aimed at the National Health System and the whole of society.

The breakdown of total revenues obtained in 2018 and 2019 has been as follows:

DESCRIPTION	2018	2019
Grants, donations and legacies charged to surplus for the year	1.762.213,63	1.792.403,96
Reimbursement of grants and subsidies	73.981,80	150.155,95
Sales and other income from commercial activity	6.033,97	1.298,46
Other income	530.588,86	526.203,18
Grants, donations and legacies transferred to capital surplus for the year	250,56	233,66
Financial income	108,32	-
Total	2.373.177,14	2.470.295,21

Revenues of the institution consist mainly of grants, donations and operating legacies and capital received from Public Administrations and other institutions, companies and individuals.

GRANTS, DONATIONS AND LEGACIES CHARGED TO SURPLUS FOR THE YEAR	Amount
ISCIII 2018 nominative allocation current expenses	1.275.000,00
Other donations charged to surplus	88.089,44
Vallecas 2 project - queen sofia foundation	300.000,00
Queen sofia foundation --mapfre fellowships	44.000,00
PEJ-2016-MED-AI/ CAM	10.602,84
Ciiien 2018 conference/ queen sofia foundation	14.650,50
PT17-0015-0015/ ISCII	41.001,41
PEJ-2017-TL-BMD	19.000,00
RTI2018-098762-A-C32	59,77
	1.792.403,96

The Carlos III Institute of Health, in the exercise of its functions of planning, promotion and coordination of biomedical and health research and innovation, resolves to grant the CIEN Foundation a nominal allocation for current expenses of the year 2019 of 1,275,000 euros.

Resolution, of April 10, 2019, of the Directorate of the OAMP Carlos III Institute of Health, which regulates the conditions for the concession to the Neurological Diseases Research Center Foundation of the nominative allocations provided in the Statement of Budget Expenditures of the Carlos III Institute of Health for the year 2019.

The Neurological Diseases Research Center Foundation is a foundation of the State public sector supervised by the ISCIII, whose specific aims and objectives can be summed up in the promotion of research in the neurological field and the creation and maintenance of the referred Center. For the fulfillment and development of these purposes, the Statement of Expenditure of the ISCIII Budget extended from 2018 to 2019 approves the granting of the following nominative contribution:

- The amount of 1,275,000 euros charged to the budget application 28.107.465A.445, provided that there is adequate and sufficient credit in the general General Budget for 2019.

These contributions will be compatible with subsidies, grants, income or resources for the same purpose, coming from any Administration or public or private, national, coming from the European Union or international organizations.

The purpose of such transfers is to cover the maintenance and operation of the scientific, research and dissemination tasks of the activity carried out by the CIEN Foundation.

The contribution of the Queen Sofia Foundation in 2019 focuses on the funding of three main activities:

- I) collaboration in carrying out the Vallecas-2 Project, early detection of Alzheimer's disease. Risk factors and prevention;
- II) collaboration in the VI edition of the International Congress of Research and Innovation in Neurodegenerative Diseases CIIIEN, held in Valencia between September 17 and 20;
- III) call for the Queen Sofia Foundation-MAPFRE Foundation fellowship.

The rest of the amount corresponding to the subsidies, donations and legacies allocated to the surplus for the year is identified with the projects financed by the ISCIII (Biobank Platform-PT17), by the Region of Madrid (Youth Employment Program, PEJ2016/PEJ2017) and other research projects identified in the table above.

The item of sales and other revenues from the activity correspond to the provision of research services, based on contracts signed with other public and private research centers.

Revenues from provision of services during 2018-2019

DESCRIPTION	2018	2019
Energy production	11.149,59	9.421,77
Revenues from performing MRIs and collaborative research projects	62.832,21	140.734,18
TOTAL	73.981,80	150.155,95

In the subsidies, donations and capital legacies item transferred to the surplus of the year (526,203.18 €), a contribution from the Queen Sofia Foundation of 490,585.28 € is recorded, corresponding to the rights of use of the building, equipment and furniture of the Alzheimer's Project Research Unit (UIPA, for its acronym in Spanish). The remaining amount until reaching the total of this item corresponds to the official capital grants received from the ISCIII financing of capital expenditures, € 35,617.90.

Expenditure

The expenses are used for the development of the CIEN Foundation's own activities, which basically correspond to the research and management activities of the Alzheimer's Project Research Unit (UIPA), which is part of the Queen Sofia Foundation Alzheimer Project Complex. The Queen Sofia Foundation and the CIEN Foundation formally signed in January 2006, renewed in January 2016, an agreement whereby the former cedes the use of the premises and their equipment, and the CIEN Foundation is committed to the maintenance of the dependencies and equipment, replacing and repairing the one that is necessary. The use of facilities will be used as a priority for the research of Alzheimer's disease and other dementias, and in a complementary manner to other types of research on diseases that are part of the CIEN Foundation's mission.

Distribution of CIEN Foundation revenues

YEAR	2018	%	2019	%
Monetary aid and others	16.000,00	0,77%	45.242,70	2,08%
Variation of existences of merchandise	2.358,58	0,11%	293,41	0,01%
Supplies	106.165,92	5,09%	175.725,59	8,06%
Staff costs	802.162,35	38,42%	835.432,52	38,33%
Other operating expenses	623.160,17	29,85%	592.332,23	27,18%
Depreciation and amortization	537.836,69	25,76%	524.958,84	24,09%
Impairment and gains on disposal fixed assets	0,00	0,00%	5.318,89	0,24%
Exchange differences	55,85	0,00%	0,00	-
TOTAL EXPENDITURE	2.087.739,56		2.179.304,18	

2.3.

Research projects and grants

CIEN Foundation aims to support, promote and coordinate research in neurological diseases. In order to do this, it focuses its efforts especially in neurodegenerative diseases and in coordinating prominent Spanish research groups. Research projects managed by the Foundation seek to foster research and study in these fields, especially Alzheimer's disease and related disorders.

2.3.1 Research projects

The CIEN Foundation was created with the aim of promoting the creation of a network center that supports, promotes and coordinates research activities. The objectives of the CIEN Foundation are specified in six fundamental activities:

- The Vallecas project
- BT-CIEN Tissue Bank.
- Alzheimer Program
- Other research projects
- Service provisions
- Training

Vallecas-2 Project: Research aimed at identifying individuals with a higher risk of developing Alzheimer's type dementia (AD), based on the combination of sociodemographic, clinical, neurological, neuropsychological, genetic, biochemical and neuroimaging data, within the framework of the project called "Vallecas-2, early detection of Alzheimer's disease. Risk and protection factors". The Queen Sofia Foundation, signatory of the agreement dated on February 14, 2018, undertakes to contribute during each of the 4 years of planned duration of the project, the successive amounts that are agreed annually by its Board of Trustees, corresponding to the first year 2018 a total amount of three hundred thousand euros (€ 300,000.00). An equal amount has been allocated for 2019.

YEAR	2018	2019
Queen Sofia Foundation Contribution	300.000,00	300.000,00

The **Vallecas Project** is one of the main research project carried out by the CIEN Foundation, both in terms of resources used and its social impact. In parallel, the CIEN Foundation is engaged in other research projects on neurodegenerative diseases, among which the **Alzheimer Center Project** and the **Biobank Platform** stand out.

Tissue-Bank (BT-CIEN): Through the Department of Neuropathology of the CIEN Foundation, a biobank of neurological tissue is managed (CIEN Tissue Bank). Contributions to BT-CIEN come, in addition to those obtained in the CAFRS (Internal

Donation Program), from donors from the Community of Madrid and other Regions (External Donation Program). In turn, the BT-CIEN, after processing, diagnosis and classification, maintains the biological material in long-term archive conditions and distributes it to researchers and institutions that require it for research projects, in accordance with the application and transfer of biobank samples protocols.

Research Program of the Queen Sofia Foundation Alzheimer Center: Systematic evaluation, by means of a protocol adapted and agreed upon, of the patients institutionalized in the Queen Sofia Foundation Alzheimer Center (CAFRS, for its acronym in Spanish) and attendants to the Day Care Center, after signing a proper informed consent. This evaluation includes the following:

- Neurological evaluation
- Neuropsychological assessment
- Psychiatric evaluation
- Functional evaluation
- Magnetic resonance imaging
- Blood sampling and analysis of genetic risk factors
- Extraction and neuropathological study of brains donated by deceased patients

Other research projects granted in competitive competition in force in 2019:

RTI2018-098762-A-C32. Call for projects with resolution date on August 26, 2019, from the Secretary of State for Universities, Research, Development and Innovation and the Presidency of the State Research Agency, approving the call for early processing for the year 2018 of the procedure for granting support to R+D+i Projects "Research Challenges", corresponding to the State R+D+i Program aimed at Society Challenges, within the framework of the State Plan for Scientific and Technical Research and Innovation 2017-2020. Funded by the Ministry of Science, Innovation and Universities. Project title: Family history of Alzheimer's disease in older people: influence of subjective cognitive impairment. Principal Investigator: Dr. Miguel Ángel Fernández.

Duration: 01/01/2019 - 12/31/2021. With a total budget of 108,900 €. The budget for 2019 has been 52,272.00 €.

PT17/0015/0014: Biobank Platform. Principal Investigator: Dr. Alberto Rábano Gutiérrez. Project funded by Resolution of the Director of the Carlos III Institute of Health, of December 4, 2017, by which grants are awarded for support research Platforms in health sciences and technologies of the 2017 call for Strategic Action in Health, with a total budget of 135.300 euros, distributed in 3 annuities of 45,100 € each.

Collaboration agreement signed with King's College London, University of Pennsylvania and University College London, for carrying out the project entitled "**Phases 2b-4 Field Validation of the MDS-NMS, the International Parkinson's and Movement Disorders Society Non Motor Scale for Parkinson's disease**" funded by The International Parkinson and Movement Disorders Society. Budget: 39,375€.



Specific collaboration agreement Established between CIBER and CIBERNED for the execution of the project "**Search for biomarkers for the early detection of Alzheimer's disease in the Vallecas project cohort**", with the active participation of the Neuroimaging department and the CIEN Foundation Tissue Bank..

Actions funded within the framework of Law 18/2014, of October 15, of approval of urgent measures for growth, competitiveness and efficiency and of the *Youth Employment Operative Program*:

PEJ16-MED-AI-1963. Granting of support for hiring a research assistant in the framework of the call for Grants for the Recruitment of Research Assistants and Laboratory Technicians, call 2016. The contract was formalized on 02/13/2017, and on September 27, 2018 an extension was granted until July 3, 2019. The grant was terminated with the presentation of the final report.

PEJ-2017-TL-BMD. Order 4606/2017 of December 14 for which grants are given for the execution of contracts for laboratory technicians corresponding to the 2017 call. Granting of support for the employment of a laboratory technician during 2018. The CIEN Foundation, as the grant beneficiary, formalized the corresponding contract on 03/08/2018, with a duration of two years, until 03/07/2020.

2.3.2 Fellowships and grants

During 2019 the CIEN Foundation has awarded/carried out the following fellowships and grants:

MAPFRE-Queen Sofia Foundation Fellowship 2017-2018. The fellowship program resolved to grant in this new call to Dr. Linda Zhang. Project title: "Internal and external validation of a statistical model for predicting conversion from normal cognition to mild cognitive impairment in elderly populations". Six months stay, extended for additional six months. Research program focused on the study of neurodegenerative disorders using an approach that combines mathematical modelling and computational simulation, in order to achieve the characterization of predictive algorithms, including a stay at the Eastern University of Finland in Kuopio.

MAPFRE-Queen Sofia Foundation Fellowship 2018-2019. This call is declared void on January 9, 2019, finally being awarded in favor of Ms. Marta Garo on February 25, 2019.

2.4.

Management of Human Resources

Since its inception, the CIEN Foundation has worked to maintain a highly qualified team whose levels of technical skills, knowledge and attitudes conform to the qualitative parameters that identify the Foundation. In order to achieve this, in 2018 we have made two new additions: a graduate in Biology and a senior technician in Pathology. These positions have been convened by the CIEN Foundation through an open competition procedure, under criteria of capacity, merit and publicity, being published on the website of the CIEN Foundation, ISCIII and CIBERNED, always respecting the principle of free concurrence and objectively valuing the merits of the applicants.

To carry out its research work throughout this year, the CIEN Foundation has had a total of 51 professionals, of which 25 are hired from both subsidized and competitive grants, 8 have been students interested in carrying out internships in our center, 2 medical intern residents that have made a rotation in our department of Neuropathology, another 2 students have stayed at our center during their training period, 1 Fullbright scholarship in the neuroimaging department, 2 volunteers who have selflessly collaborated in the activities of the CIEN Foundation, 7 professionals have developed their activity under collaboration agreements and 4 professionals who have been hired through a service provision contracts.

CIEN Foundation staff also includes the research and technical supporting staff funded through CIBERNED and the collaboration agreements for research signed by the CIEN Foundation.

CIEN Foundation Organization Structure

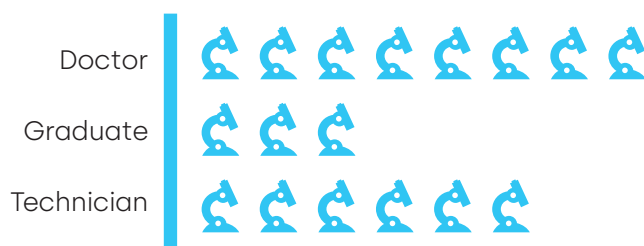
The different departments in which the human resources that make up the CIEN Foundation are located and where our professionals have developed their work are the following:

- Department of Management and Administration
- Department of Neuroimaging
- Department of Neuropathology and Tissue Bank
- Department of Molecular Genetics
- Department of Neurology
- Department of Neuropsychology

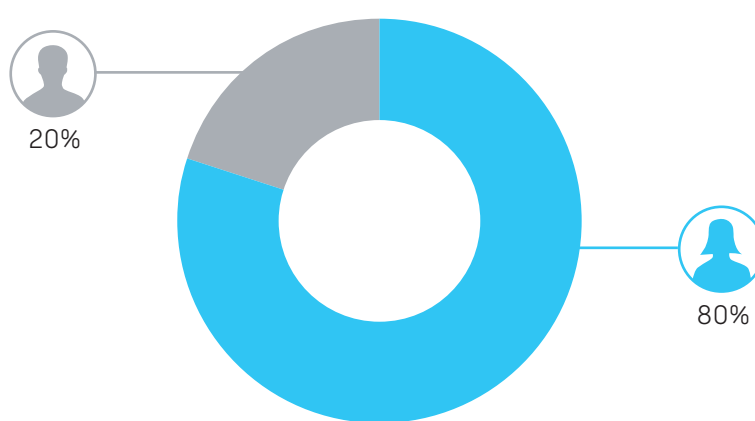
The following table shows a list of CIEN Foundation staff in 2019, distributed in the different departments:



Research Staff



Personnel by gender



2.4.1. Training program

Continuous training and updating of professional knowledge and skills have been configured as a training system intended to accompany workers in their personal development and professional promotion capacity. It constitutes a fundamental support to the competitive and innovative capacity of organizations based on quality human resources.

The main objective of the CIEN Foundation through the training program is to provide adequate means for the development of professional skills, in order to effectively manage the challenges that each job entails. Training is an integral part of our culture as an organization and we are aware of the need to permanently improve the knowledge and skills of our professionals.

In 2019 the CIEN Foundation has offered or participated in the following training activities:

Training courses and actions carried out by our staff

TRAINING ACTIVITY	CENTER/INSTITUTION
28th Annual Computational Neuroscience Meeting	CNS
Acreditación de biobancos normas ISO 20387	Colegio Oficial de químicos DE Madrid

Alzheimer's & Parkinson's Diseases Congress	Alzheimer's & Parkinson's Diseases Congress
CONY 2019: the 13th World Congress on Controversies in Neurology	World Congress on Controversies in Neurology
Curso Inmunohistoquímica	Asociación Zamorana de Técnicos de Anatomía Patológica y Citología
Curso Microcopia y aplicaciones	Instituto de Óptica
Curso Múltiples aspectos de su actividad en los servicios de anatomía patológica	IFAPES
Día Mundial del ICTUS	SEN, Freno al Ictus, GEECV
FCIEN-PurinesDX Symposium on <i>Advances in clinical techniques and challenges faced in the treatment of neurological disorders</i>	Fundación CIEN y Marie Skłodowsk-Curie Innovative Training Network
I Encuentro de investigadores CNIE	CNIE
Inteligencia Artificial en Radiología oportunidad o amenaza	Servicio de Radiodiagnóstico del Hospital Universitario de la Zarzuela
Primeros auxilios	QUIRÓN PREVENCIÓN
Procesado automático de imagen microscópica	Universidad de Castilla la Mancha
Responsible Innovation in smart homes and smart health virtual summit	Living Innovation
Reunión de la Sociedad Española de Neurología en Sevilla	Sociedad Española de Neurología
World Congress on Controversies in Neurology	COMTECMED
X Congreso Nacional Biobancos	Red Nacional de Biobancos, Centro de Investigaciones Biomédicas en Red de Enfermedades Respiratorias, Generalitat Valenciana, Red Valenciana de Biobancos
VII Congreso Internacional de Investigación e Innovación en Enfermedades Neurodegenerativas	Fundación CIEN, CIBERNED y Fundación Reina Sofía

Internships

Tutoring of external internships for students in the Department of Neuropsychology:

- 1 student from the Autonomous University of Madrid
- 1 student from the Rey Juan Carlos University

Tutoring of external internships for students in the Department of Neuropathology:

- 2 students from the IES Moratalaz
- 1 Final Master project the Complutense University of Madrid



- 1 Final Master project from Master on Translational Medicine Research, Autonomous University of Madrid
- 1 student from the Autonomous University of Madrid
- 1 Medical Intern resident from the Son Espases University Hospital.
- 1 Medical Intern resident from the 12 de Octubre University Hospital

Tutoring of external internships for students in the Department of Neuroimaging:

- 1 Final Master project from the Autonomous University of Madrid. Master on Neuroscience
- 1 Final Master project from the Technical University of Madrid.

Fellowships

- MAPFRE-Queen Sofia Foundation Fellowship 2017-2018
- MAPFRE-Queen Sofia Foundation Fellowship 2018-2019
- Fullbright Fellowship

2.4.2. Prevention of Occupational Hazards

Following the establishment of the CIEN Foundation's Occupational Health and Safety Policy, which is intended to promote respect for occupational safety and health in the development of our activities, the commitment of the organization expressed is established in the following terms:

- Comply with applicable regulations in the field of occupational health and safety, within the European, national, regional and local regulatory framework.
- Advance in the continuous improvement of our behavior in occupational health and safety.
- Guarantee the protection of the safety and health of workers
- Promote training and communication both internally and externally.

To guarantee the protection of occupational health and safety, CIEN Foundation has carried out, in coordination with the Prevention Service, various preventive activities during the year 2018, among which the following stand out:

- Emergency and evacuation drill, in coordination with the Queen Sofia Alzheimer Center.
- Review of the Initial Risk Assessment
- Review of the Prevention Plan

On June 20, 2019, two training sessions were held for the entire staff of the company on EMERGENCY TRAINING.

Management of the Occupational Risk Prevention training of staff: the specific training on prevention is renewed with the External Prevention Service for all existing job positions.

In terms of health surveillance, through the External Prevention Service a total

of 15 medical examinations were carried out between January 2018 and January 2019. The health exams have included a work history with detailed description of the job, the time spent in it, the risks detected in the analysis of working conditions and the prevention measures taken, anamnesis data, clinical exploration, biological control and complementary studies, directed and chosen according to the risks inherent in the work performed.

Finally, the accident rate data issued by the Mutual Insurance for Accidents in the Workplace and Professional Illness in 2019 is summarized below

- Number of records of accidents in the workplace without sick leave: 1
- Number of records of accidents in the workplace with sick leave: 0
- Number of records of occupational diseases without sick leave: 0
- Number of records of occupational diseases with sick leave: 0
- Number of records of relapse of accidents in the workplace: 0

2.5.

Quality Policy

The main milestone regarding the Quality Management System in 2019 has been the updating of the scope of the ISO 9001: 2015 Certificate, so that as of this year it comprises:

- The diagnosis of neurodegenerative diseases
- The transfer of tissue samples
- Research projects related to neurodegenerative diseases

On the other hand, work has remained on the continuous improvement of the Management System and specifically on aspects such as the improvement of the maintenance management of laboratory equipment, improvements in databases, filing system, and in the conditions of conservation of samples.

In addition, we continue to use both internal and external audits as tools to detect possible areas of improvement.



2.6.

Data Protection Law and Guarantee of Digital Rights (LOPDGDD)

The purpose of the LOPDGDD is to protect the privacy and integrity of the individual, in compliance with article 18.4 of the Spanish Constitution. Likewise, it regulates the obligations of the individual in any data transfer process to guarantee the security of the exchange.

The CIEN Foundation has files containing personal data, for which it is responsible and must be protected in accordance with the provisions of the current regulations on Personal Data Protection (LOPD, for its acronym in Spanish) and the new General Data Protection Regulation (GDPR) in force since May 2018.

The purpose of the LOPDGDD is to protect the privacy and integrity of the individual, in compliance with article 18.4 of the Spanish Constitution.


Likewise, it regulates the obligations of the individual in any data transfer process to guarantee the security of the exchange.

This information is contained in the Security Document, as well as the people involved in their treatment and the premises where they are located, located at C\ Valderrebollo nº 5. 28031 in Madrid.

To exercise your rights, any request or query must be addressed to lopd@fundacioncien.es

As the sole data controller, the CIEN Foundation is committed to fulfilling with its obligation of confidentiality of personal data.



A laboratory setting with various pieces of equipment. In the foreground, there is a white microplate with several small, clear test tubes, some with yellow caps. To the right, a blue microplate rack holds several larger, clear test tubes. The background is slightly blurred, showing more laboratory equipment. The entire image has a blue color overlay.

**SCIENTIFIC
ACTIVITY**

3



3.1. Overview

On January 18, 2006, the CIEN Foundation signed an agreement with the Queen Sofia Foundation, under which the former assumes the management of the Alzheimer Project Research Unit (UIPA, for its acronym in Spanish). The context in which the UIPA is framed is the Alzheimer Project, promoted by the Queen Sofia Foundation. The main exponent of this project is the Queen Sofia Foundation Alzheimer Center (Alzheimer Complex), located in the Vallecas neighborhood (Madrid), which in 2017 has celebrated its 10th Anniversary. One of the most outstanding aspects of the Alzheimer Complex is that there is a Healthcare Center (formed by a Residence and a Day Center) for Alzheimer's patients and related diseases as well as a Training Center, in addition to the UIPA. This Unit began its activity in April 2007, while the healthcare activity began at full capacity in the second half of that year.

Currently, the UIPA consists of five departments with a clear multidisciplinary approach and with specific objectives, among which are the following: the monitoring and periodic evaluation of patients at the Alzheimer Center; the development of clinical, epidemiological, genetic, research projects as well as on biomarkers in biological samples or neuroimaging, in the field of neurodegenerative diseases, with special focus in Alzheimer's disease and related dementias.

Through this series of studies, new knowledge in genetics and molecular biology that have different applications is generated, that teach the researchers about the pathogenic mechanisms of the disease which can be in turn implemented into the field of diagnosis and, desirably, can result in the development of better treatments.

However, far from promising a simple solution to the problem of neurodegenerative dementias, these advances anticipate an increasingly complex picture, in which the remedies will be achieved through small goals, and only by the complementary and synergistic work of many research groups. This complexity is the

main feature of neurodegenerative diseases since they affect both the biological aspect as well as the clinical and personal level. Thus, the psychological and social aspects involved in dementia need to be taken into account and be aware that ethical and legal issues such as the right to information and participation in medical decisions are increasingly gaining prominence every day.

3.2.

Department Structure

The scientific activity of UIPA is structured around four complementary research areas:

- Department of Neurology
- Department of Neuropsychology
- Department of Neuroimaging
- Department of Neuropathology
- Department of Biochemistry and Molecular Genetics

From the clinical perspective, the UIPA counts with personnel from the **Departments of Neurology and Neuropsychology**, who are in daily contact with patients who come to the Queen Sofia Foundation Alzheimer Center (CAFRS, for its acronym in Spanish) and with the staff at the healthcare Residence, as well as with the cohort of volunteers from the Vallecas Project (see section 4), playing a role of mediation between basic researchers, relatives and caregivers. This role is critical in making patients, relatives and caregivers aware of the research purpose of the UIPA, give consent and collaborate with the research projects. One of the research activities of these departments consists in carrying out a clinical, syndromic and etiological diagnosis of the patients from the CAFRS, either in the resident regime (Units of Life) or in daycare (Day Center). In addition, a set of clinical data is obtained that will be very useful for the other UIPA scientific areas studies.

Patients with dementia require specific attention, consisting of an accurate and early diagnosis, an assessment of the affected cognitive areas and its severity, as well as applying and monitoring the treatment. It is essential that various medical disciplines be involved, due to the need to follow the progression, the specific treatment, the overseeing of complications, the application of measures to neutralize them, and the corresponding practice of social health resources. Hence, UIPA responds to a translational vocation to investigate the progression of clinical knowledge in dementias. It is established as an intermediary between



basic sciences and the fields of clinical and social sciences related to health, to promote knowledge about neurodegenerative dementias and its application. A team of specialists in Neurology, Psychiatry and Neuropsychology, together with the participation of geriatricians, occupational therapists, physiotherapists and social workers from the Center's healthcare area make up this part of the Unit. The evaluations carried out in these areas composed the clinical and sociological database that, in addition to its intrinsic interest for research purposes, supports the biological samples and neuroimaging data obtained systematically in the Center.

In addition to the clinical departments, the UIPA has a translational perspective in its original project, made up of the departments of **Biochemistry and Molecular Genetics, Neuropathology and Neuroimaging**. These three areas bring together the most promising fields of research on the biological processes underlying dementia.

The UIPA is characterized by its marked **multidisciplinary approach**, so that both clinical and **basic aspects** are in continuous contact, through those five departmental areas, elaborating and contrasting hypotheses, and jointly carrying out various research projects. On the other hand, it is from reinforcing these two perspectives, how concepts such as translational research in Medicine have been developed. The scientific activity of the CIEN Foundation is based on this idea: to transfer to the clinical field the advances obtained with basic research.

3.2.1. Department of Neurology

Neurology as a medical-scientific discipline aims to study the structure and function of the nervous system, the identification, description and analysis of its numerous and varied pathologies, the diagnosis of its clinical alterations and the treatment of patients who suffer them. In the field of cognitive impairment, the neurologist must characterize the numerous types and variants of this syndrome through a systematic clinical evaluation of the patient and his/her environment, collaborate with other specialists in psychology, radiology, laboratory, genetics, neurophysiology, etc. make a diagnosis and prescribe and monitor a treatment. In a research group such as the Queen Sofia Foundation Alzheimer Center (CAFRS, for its acronym in Spanish), the Neurology team offers basic clinical support to all studies carried out with volunteers and patients, generates and implements clinical research hypotheses and collaborates with the other teams of specialists in clinical and basic research, in the early detection, prevention and treatment of Alzheimer's disease and other related pathologies. The Department of Neurology develops the following activities:

- General and neurological medical evaluation, and clinical diagnosis of the Vallecas Project participants
- Detection and management of possible clinical complications of the Vallecas Project participants.
- Preparation of clinical reports
- Evaluation and diagnosis of patients attending the Center



- Neurological monitoring of patients admitted to the Residence
- Management and curation of databases.
- Statistical analysis and preparation of scientific reports.
- Teaching and mentoring of graduate and PhD students who collaborate in some research projects
- Communication in scientific forums of research work carried out in the department.
- Development of research projects on neurodegenerative diseases, especially focused on Alzheimer's disease.
- Dissemination to society of the progress of the investigation.

Main lines of research

The activities of this department focus on the following main areas:

1. The Vallecas Project cohort: (due to its size, a complete section in this report is dedicated to this study, see section 4 of this Report). In this project, it is carried out an annual systematic clinical and neurological evaluation of the more than one thousand volunteers participating in the study cohort. This information, together with the data from the neuropsychological assessment, allows establishing the evolutionary diagnosis of each subject and is stored in a large database for carrying out various research projects.

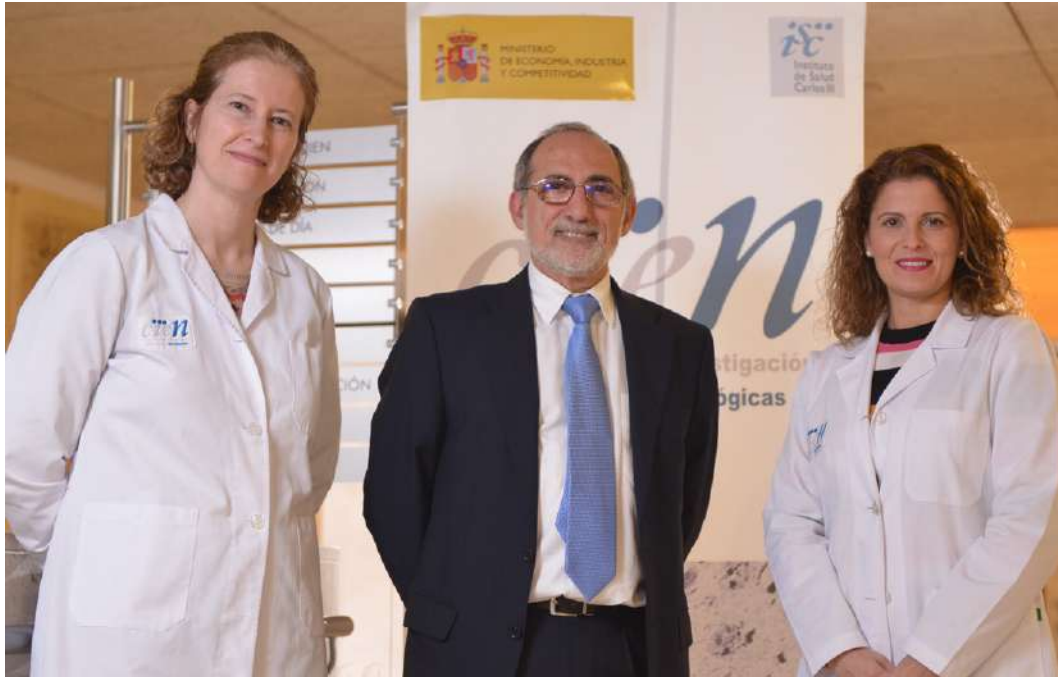
2. Queen Sofia Foundation Alzheimer Center Research Program (CAFRS) cohort: it consists on the systematic clinical evaluation, every six months, of the patients who are in the CAFRS, both in internment regime (Units of Life) and in day care (Day Center). This evaluation, carried out together with the rest of the staff from the Center and healthcare professionals leads to the syndromic and etiological diagnosis and to the protocolled collection of neurological, psychiatric, neuropsychological, demographic, analytical, therapeutic and neuroimaging data. This systematic gathering of information, from the moment the patient enters the study until it is transferred to another Day Center or passes away, allows for the generation of a large database of clinical data that can be exploited in itself or in relation to the neuroimaging and/or neuropathological data.

In 2019, there were 16 new admissions in the Day Care Center and in the Residence, all of them signed the consent to participate in the multidisciplinary periodic evaluations. On top of the baseline evaluations, a total of 973 clinical evaluations (semi-annual frequency), 32 brain MRI studies (annual frequency) and 210 analytical studies were carry out.

3. Other ongoing research projects: The Department of Neurology, with its own resources or, more often than not, in collaboration with other CAFRS or external groups, is carrying out several other research projects. Most of them are mainly based on information o from the Vallecas Project or the Queen Sofia Foundation Alzheimer Center Research Program databases. In other instances, information provided by various collaborators is used.



Neurology Team.



- Components and effects of cognitive reserve in a cohort of cognitively normal elderly
- Clinicopathological study of early Alzheimer's disease patients
- Salivary lactoferrin in Down syndrome
- Validation of salivary lactoferrin as a marker of Alzheimer's disease
- Adapted diet in advanced stage of dementia
- Psychotic symptoms and vascular risk factors in Alzheimer's disease
- Behavioral disorders and neuropathological findings in Alzheimer's disease

4. Other collaborative projects with other departments:

- PILEP+90 nonagenarians study (Dpt. Of Neuropsychology)
- CONNECT-AD cohort study, (Dpt. Of Neuropsychology)

5. Other collaborative projects with other institutions:

- Master of Methodology from the Faculty of Psychology, Complutense University of Madrid,
- Mild Cognitive Impairment case registry with biological samples (blood and CSF) (Neurology Service, Infanta Leonor Hospital).

Team

This department is composed by the following staff:

Teodoro del Ser Quijano, Dr. Medicine, Neurology. Head of department
Merixell Valentí Soler, Dr. Medicine, Neurology
María Ascensión Zea Sevilla, Dr. Medicine, Neurology

Periodic multidisciplinary assessments during 2019

Admissions in Day Centre and Residence	16
Informed Consents	16
Baseline Assessments	32
Clinical Evaluations	973
Brain MRI Studies	32
Blood testing	210

3.2.2. Department of Neuropsychology

Neuropsychology is a scientific field that aims to describe, diagnose and treat cognitive, behavioral and emotional changes that appear as a result of a possible functional or structural impairment of the Central Nervous System. Within the field of dementias Neuropsychology not only allows to characterize in an accurate way the cognitive state of an individual, but also helps to guide the diagnostic decision, to determine which subjects present a higher risk of developing a future neurodegenerative disorder and propose the appropriate therapeutic intervention.

Given the multidisciplinary nature of the CIEN Foundation, the purpose of the Neuropsychology department is to contribute to the proper development of ongoing research projects through proper coordination with the rest of the departmental areas. In addition, among its objectives are also the conceptualization and implementation of new research hypotheses in the context of early detection and prevention of Alzheimer's disease.

Among the specific tasks carried out by the Department of Neuropsychology, the following activities are noteworthy:

- Neuropsychological assessment and cognitive diagnosis
- Preparation of clinical reports.
- Management and curation of databases.
- Statistical analysis and preparation of scientific reports.
- Teaching and mentoring of the external training practices of students from the last year of the Psychology Degree at the Autonomous University, the Rey Juan Carlos University and the Complutense University of Madrid.
- Communication in scientific forums of the research work carried out in the department.
- Dissemination to society of the progress of the investigation.
- Development of research projects on neurodegenerative diseases, especially focused on Alzheimer's disease.

Main lines of research

The interests of the Neuropsychology department focus on four well defined lines of research in the area of its competence. In particular, the following priority research lines can be identified, which are described below.



1. Cognitive markers for the early detection of the prodromal phase of Alzheimer's disease.

The professional figure of the neuropsychologist usually handles the application of different evaluation instruments. These include various types of tests, scales and questionnaires useful to measure both the objective cognitive performance and the subjective perception of an individual with respect to aspects such as memory complaints, mood or coping styles. To meet the challenges posed in the context of the Vallecas Project, the neuropsychological test battery focuses especially on the evaluation of memory processes, attention and executive functions as potential early markers of Alzheimer's disease. In addition, the neuropsychological profile of each participant is completed by gathering information related to other cognitive domains such as language, visuospatial ability and visuoconstruction, as well as emotional variables. This is particularly important because it allows identifying the strengths and weaknesses in the cognitive profile and characterize, if appropriate, the type of cognitive impairment that an individual presents. Moreover, the neuropsychological evaluation protocol includes various questionnaires in order to collect information complementary to the cognitive profile. Specifically, we obtain data about the assessment of possible cognitive complaints, as well as different aspects of them such as the time of appearance, the concern generated or the profile of these complaints. In essence, the study of all these cognitive variables, both objective and subjective, together with the rest of the biographical and clinical data, will allow us to establish what role each cognitive parameter plays in the appearance and course of Alzheimer's disease.

1.1. Usefulness of subjective cognitive complaints as an early marker.

This is perhaps the most consolidated line of research in the department that has even led to the publication of a doctoral thesis. Subjective Cognitive Impairment (SCI) appears in preclinical stages of Alzheimer's disease. Cognitive complaints may appear in preclinical phases of Alzheimer's disease; even a person can often experience this type of complaint though their cognitive performance in a formal neuropsychological examination is within normal parameters. For this reason, there has been renewed scientific interest in recent years for the study of subjective cognitive complaints as a possible marker of future objective cognitive impairment.

The Department of Neuropsychology has carried out different studies to analyze the role of cognitive complaints as a predictor of cognitive impairment in a sample of elderly people from the general population. Specifically, the focus is placed on studying which specific aspects and what type of cognitive complaints show a greater relationship with the development of cognitive impairment. In general, the following conclusions can be drawn from all the research work carried out:

- The SCI rate in the Vallecas Project cohort (~ 70%) is slightly higher than that obtained in other research studies. This can be explained by the fact that our cohort has a higher mean age.
- Our results are consistent with the accumulated evidence: SCI is more strongly associated with subjective variables (i.e. depression, anxiety, quality of life, etc.)

than with objective cognitive performance in neuropsychological tests.

- Not all cognitive complaints have the same specific weight when differentiating between cognitively healthy people and patients with Mild Cognitive Impairment (MCI). More specifically, complaints related to forgetting recent events, with things that we must remember in the future or with the ability to manage ourselves effectively on a day-to-day basis, allow us to differentiate between those two groups.
- Using the criteria of the International SCI Working Group, it is possible to classify individuals in preclinical stages of AD into three groups: non-SCI, SCI and SCI-Plus. This last group is considered the one with the highest risk of conversion based on a series of evidence-based parameters. Our results support the clinical interest of the classification proposed by the International Working Group: SCI-Plus has a 4 times higher risk of developing MCI in just one year compared to non-SCI. Although there are no significant differences between non-SCI and SCI, there is a higher conversion rate in SCI. Perhaps the one-year follow-up is not enough to show greater differences.
- A comprehensive protocol proposal for collecting SCI-related information has been described and published. An operational definition has also been provided to classify individuals into the above three groups, namely non-SCI, SCI and SCI-Plus.
- An opinion paper has been published related to the need to demonstrate that the SCI classification is stable over time. This is a prerequisite to be able to consider SCI as a variable of interest in the field of early detection of MCI.
- Our results have shown that when an assessment protocol is used systematically and rigorous operational criteria are employed, the SCI classification is sufficiently stable.
- After analyzing the temporal dynamics of the DCS groups during 3 years, the following sequential transition is observed that fits perfectly with the hypothesis of the different stages of AD: non-SCI SCI SCI-Plus MCI. The risk of developing MCI therefore increases progressively in the SCI and SCI-Plus groups respectively.
- In the future, although we have not yet been allowed access to neuroimaging data, our interest is to combine the available cognitive data with fMRI data. The objective is to determine if there are significant differences between control subjects and individuals with SCI-Plus with respect to the pattern of brain connectivity (a greater hyperconnectivity associated with SCI-Plus would be expected, as the literature has already shown in later phases of mild cognitive impairment).

1.2. Usefulness of various cognitive parameters as early markers

Numerous studies have shown that there are certain cognitive variables that allow the identification of subjects at higher risk of developing Alzheimer's disease years before their diagnosis. With this idea in mind, we investigate whether certain parameters of the neuropsychological protocol, in the context of a longitudinal research project such as the Vallecas Project, are useful to identify individuals at risk of cognitive impairment. These parameters are analyzed in an evolutionary way together with the rest of clinical and genetic information of each volunteer in

order to obtain a classification algorithm that could eventually be generalized to daily clinical practice.

In addition, the Department of Neuropsychology is interested in developing new assessment tools that allow examining the role of other cognitive markers not studied in standard neuropsychological evaluations. It is expected that the identification of these markers increase sensitivity and specificity when detecting individuals at risk of dementia. Among the most important results obtained over the years in this line of research, the following are noteworthy:

- Cognitive tests, and in particular the Free and Cued Selective Reminding Test (FCSRT) verbal episodic memory test, are the most sensitive tools for identifying subjects at risk of conversion to MCI. Its discriminating capacity is above other variables of interest such as APOE genotyping.
- The predictive capacity of the FCSRT has been shown to be high even in a 4-year follow-up. Especially useful is the parameter of immediate free recall, in which an individual's score below 18 is considered risk for conversion in the next 4 years.
- Processing speed (i.e. mental alertness) is another cognitive parameter that has been revealed as an early marker of interest for MCI although we still need to carry out additional analysis in this regard.
- The analysis of the possible effect of drugs on cognitive performance in the Vallecas Project cohort has been examined. The two-year cross-sectional and longitudinal results have not identified any effects of interest and, when any association has been found, it is inseparable from the underlying pathology of the drug itself.
- A pilot study has been carried out with an attentional blinking task among the subjects of the Vallecas Project. The attentional blink task is a classic paradigm in Experimental Psychology whose use has not been extended to clinical samples. It allows obtaining first-order cognitive parameters not explored in conventional evaluations that may be of interest as early markers. Our preliminary results show a high correlation between performance in the attentional blink task and classical cognitive parameters. It is pending to investigate whether differences at the fMRI level exist.
- Given that the experience in applying the State-Trait Anxiety Inventory (STAI) test during the Vallecas Project baseline visit raised serious doubts about its suitability for our reference population, a psychometric study was carried out and published to reduce test items and categories of response. As a result, a much more useful reduced scale was obtained, but just as precise as the original one, which we have incorporated into the Vallecas Project as of the evaluation visit 6. The same was also done with the inventory of cognitive symptoms (MFE-11).

2. The relationship between cognitive reserve and socioeconomic status with the onset of cognitive impairment

The cognitive reserve is a theoretical construct that formulated several decades ago to explain the lack of correspondence between the degree of brain damage and clinical symptoms sometimes observed among patients. It is presumed as an individual capacity that develops throughout the life cycle fundamentally through formal education, the type of professional activity performed and the intellectual activity developed. Numerous studies have supported the protective role played by the cognitive reserve in modifying the course of different neurodegenerative pathologies, including Alzheimer's disease. Likewise, the socioeconomic status associated with a person's area of residence can be understood as an environmental factor that determines to some extent the probability of developing a possible cognitive impairment.

The interest of the department of Neuropsychology for this construct focuses on analyzing different variables that apparently have the capacity to confer cognitive reserve and therefore could play a protective role against cognitive impairment. Within the Vallecas Project, this set of variables is being studied individually and as groups, with special emphasis on the activities of daily life performed during mid-life. Likewise, different variables of lifestyle are examined in order to classify them as risk or protective factors against the appearance of dementia. The results have shown that both the variables associated with the individual socioeconomic level and those associated with the neighborhood of residence play a complementary role in the conversion to cognitive impairment.

3. Spain-Portugal Longevity Research Program (PILEP + 90)

PILEP + 90 is a research project designed to examine the role of biological and environmental determinants associated with longevity and, more specifically, dementia-free longevity. For this, the study analyzes different variables associated with cognition, health, lifestyles and brain structure in two cohorts of people over 90 from Madrid and Braga.

The research program is led by the CIEN Foundation Neuropsychology department and it includes researchers from four different institutions in Spain (CIEN Foundation, Madrid Health Autonomous Organization, Complutense University of Madrid, and Biomedical Technology Center), Portugal (University of Minho) and Denmark (University of Southern Denmark) throughout three research subprojects:

- "Factors associated with healthy and pathological aging in a sample of people over 90 years from the city of Madrid (MADRID+90)", led by Dr. Miguel Ángel Fernández-Blázquez, head of the Department of Neuropsychology of the CIEN Foundation.
- "Factors associated with healthy and pathological aging in a sample of people over 90 years of age in the Braga region (BRAGA+90)", led by Dr. Nadine Correia Santos from the University of Minho.
- "Application of data mining techniques for the identification of factors of healthy

and pathological aging (ImageH)", led by Dr. Jaime Gómez-Ramírez, Neuroimaging department of the CIEN Foundation. In addition, in September 2019, Javier Quilis Sancho (Dr. in Physics) was hired under this PILEP+90 subproject.

The results of PILEP+90 will allow obtaining reliable data on the prevalence of cognitively healthy and cognitively impaired long-lived people, as well as validating a battery of clinical tests to study the elderly. In addition, thanks to the combination and exploitation through machine learning techniques of demographic, lifestyle, clinical, cognitive and neuroimaging data collected in the study, PILEP+90 is expected to help delay the effects of cognitive aging, to reduce the risk of developing dementia, promote the level of functional independence and increase the quality of life of all older people

4. Study of non-pharmacological therapies for the prevention and modification of the course of Alzheimer's disease

Non-pharmacological interventions have usually three specific objectives: to stimulate cognitive processes, promote the level of autonomy and, ultimately, increase the quality of life of individuals. These interventions can be carried out both in healthy elderly people, in order to prevent the onset of cognitive impairment, as well as in patients with cognitive impairment, to try to modify the course of the disease. Among the most used non-pharmacological interventions, changes in lifestyle, especially regarding diet, physical exercise, and cognitive training stand out.

Neuropsychology
Team.



Although scientific evidence has shown that non-pharmacological therapies have a protective effect against cognitive impairment, there are still some unresolved issues related to this topic. For example, determine what type of intervention is most beneficial or what clinical variables are associated with a better prognosis of the therapy. Taking advantage of the knowledge accumulated throughout the Vallecas Project, the objective of the Department of Neuropsychology is to study the impact that these non-pharmacological interventions have on subjects at risk of developing mild cognitive impairment. Thus, the department is associated to a consortium made up of various research groups from the Complutense University of Madrid (UCM, for its acronym in Spanish), the technical University of Madrid (UPM, for its acronym in Spanish) and the San Carlos Clinical University Hospital of Madrid through the joint research project "Study of the functional connectome modulations in young and elderly relatives of AD patients: assessment of the influence of an intervention and SCI" (RTI2018-098762-B-C31) funded by the Ministry of Science, Innovation and Universities through the Research Challenges call 2018 of the R+D+i National Plan. Specifically, within this project the department of neuropsychology leads the subproject entitled "Elderly Relatives of Alzheimer Disease (ERAD): influence of the Subjective Cognitive Decline".

Both PILEP ≥ 90 and ERAD can be considered as two natural extensions of the Vallecas Project. This is so because, throughout the last waves of the Vallecas Project, a bias towards over-representation of older people with a higher physical, cognitive and functional level has been observed in the cohort. Due to this bias, at present the cohort cannot be considered as representative of the rest of the target population. In fact, due to the appearance of this bias, the initial idea of the Vallecas Project to find early markers of cognitive deterioration could be changing in favor of the identification of protective factors that favor healthy cognitive aging.

PILEP ≥ 90 allows investigating the variables associated with longevity in a sample of cognitively healthy people over 90 years of age. The data obtained in this research program will in turn complement the data collected in the Vallecas Project. For its part, ERAD can also be conceptualized as a continuation of the Vallecas Project to the extent that, once we are able to identify the subjects at risk of cognitive impairment, we will try to intervene on modifiable lifestyle patterns - diet, physical exercise and cognitive training - that help reduce the risk of developing eventual cognitive decline.

Future lines of research

Using the available data from the Vallecas Project, at least five studies are proposed that already have produced preliminary results:

- Study of the variables associated with the reversion of the MCI state to that of cognitive normality. The objective of this work is to identify those lifestyle variables that could be playing an essential role in the reversion and, later, propose possible interventions on them in another sample of subjects.
- Obtain a probabilistic and predictive algorithm, through the use of artificial intelligence techniques, that allows quantifying the risk of developing cognitive impairment in the short and medium term. This algorithm will allow the identification of subjects at risk of conversion at least 5 years before the evolution takes place. Consequently, it is expected to be able to intervene on these subjects through interventions of all kinds in order to prevent or modify the course of the disease.
- Analysis of discrepancies and unreliability in the collection of educational level within the Vallecas Project. Fortuitously, the self-reported data regarding the educational level of the subjects has been collected during three consecutive visits to the Vallecas Project. The results show a completely unexpected finding: the reliability in the collection of this variable, which is highly relevant in this field, is highly questionable since 1 in 3 subjects do not report consistently on their actual educational level.
- Longitudinal normative data and reliable change index in a selection of cognitive tests from the Vallecas Project. To carry out this work, we will collaborate with partners of the consortium that emerged under the project financed within the 2018 call of the National Plan.
- Study of the association between SCI-Plus and functional connectivity measured through fMRI. Over the last few years we have repeatedly requested access to neuroimaging data from both the head of the department and the PI of the Vallecas Project. Despite the fact that this access has never materialized, in the neuropsychology department we do not lose hope of being able to carry out this study that can have a high impact: there are hardly any similar studies in the scientific literature, and much less considering that we have longitudinal data.

Team

Miguel Ángel Fernández Blázquez (Dr. Psychology, Neuropsychology). Head of Neuropsychology.

Marina Ávila Villanueva (Dr. Psychology, Neuropsychology).

Belén Frades Payo (Grad. Psychology, Neuropsychology).

NEUROLOGY-NEUROPSYCHOLOGY ADMINISTRATION

Francisca Martínez Lois (Administrative Assistant)

Beatriz Salado Martínez (Administrative Assistant)



3.2.3. Department of Neuroimaging

Knowledge of the morphological variations occurring in brain structure throughout life is essential to assess the corresponding pathological changes that occur in neurodegenerative diseases. Currently, neuroimaging in any form, and combined, is one of the areas of greatest progress in the understanding of various aspects of Alzheimer's disease and other neurodegenerative diseases: etiology, early diagnosis and differential functioning of brain areas, metabolism, neurotransmission.

In this regard, neuroimaging techniques such as magnetic resonance imaging (MRI) have led to significant progress in understanding brain changes associated with age. MRI is a noninvasive tool that allows the study of normal aging individuals at different times of his life. However, conventional MRI techniques are unable to detect and quantify microstructural changes dependent on age who have been described in post-mortem studies of brain tissue.

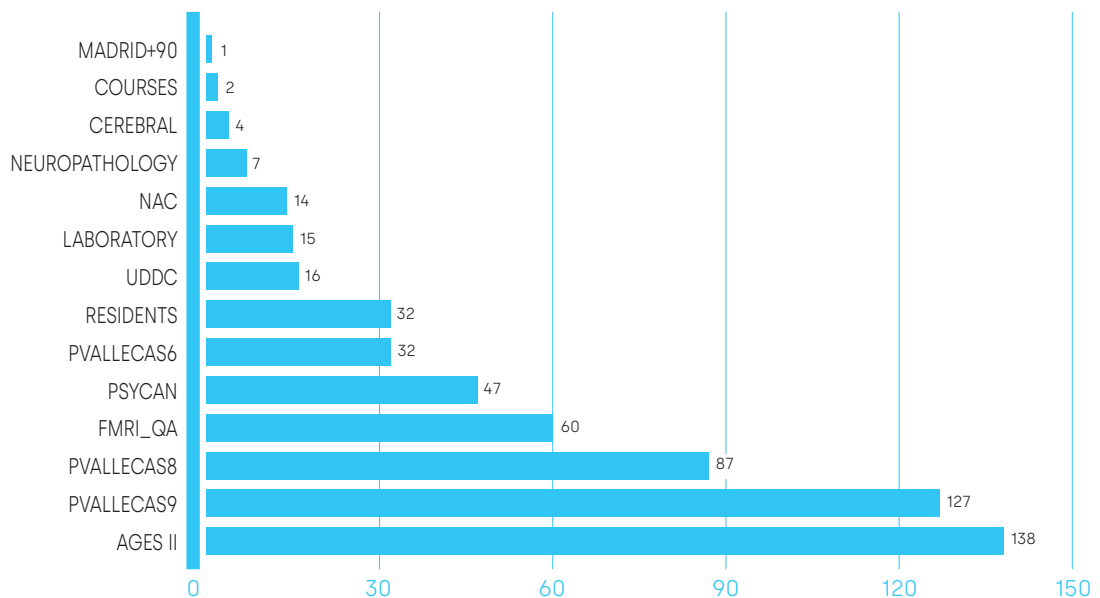
For this reason, the Department of Neuroimaging has a state-of-the-art 3 Tesla (T) MRI equipment as well as a collaboration agreement for research with the supplier: General Electric.

The main objectives Department of Neuroimaging are:

- Promotion and development of neuroimaging research projects in the field of neurodegenerative diseases with special interest in AD and related dementias
- Acquisition and postprocessing of MR images for UIPA ongoing research projects
- Dissemination of knowledge on neuroimaging techniques related to neurodegenerative diseases
- Personnel training related to obtaining, postprocessing or interpretation of advanced neuroimaging techniques

Department activities

Number of studies by Project 2019



UIPA's Department of Neuroimaging primarily deals with the acquisition of MR data (and, where appropriate, the performance of other imaging techniques such as PET or CT through external collaborations) and post-processing and analysis of the data obtained. All studies are monitored and reported by a neuroradiologist.

In addition, the Department provides technical assistance to both the rest of the scientific areas of the UIPA and external research groups. It also searches for new resources and promotes the UIPA research projects and the post-processing of images service among other research groups.

This activity complements the internal seminars and external courses, both national and international, on specific neuroimaging techniques.

During 2019, the Department of Neuroimaging has participated in MRI studies in the following clinical trials:

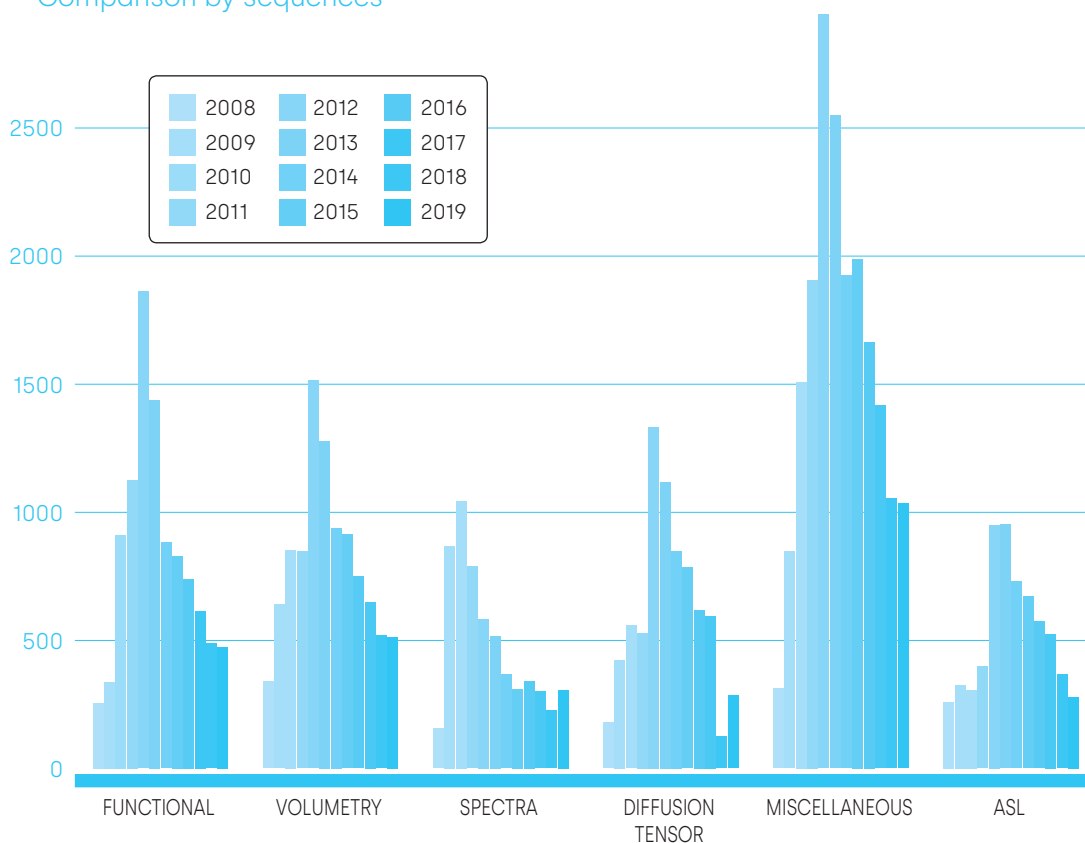
- **"NAC II"**. "Combination of N-Acetyl Cysteine (NAC) Treatment and Cognitive Training to Promote Changes in Behavioral and Neural Activation Patterns Underlying Cognitive Deficit in Adolescent Psychosis." (Exp/n. FAK182018). Dr. Marta Rapado Castro. Child and Adolescent Psychiatry Service, Gregorio Marañón University General Hospital, Faculty of Medicine, Complutense University, CIBERSAM
- **"Effect of 48-Week N-Acetylcysteine Treatment on Gray Substance Loss and Oxidative Metabolism in Patients with Early-Onset First Psychotic Episodes: Randomized, Double-Blind, Placebo-Controlled Clinical Trial."** (Exp/n. SAM18PI02/2019). Dr. Celso Arango López. Child and Adolescent Psychiatry Service, Department of Psychiatry. Gregorio Marañón University General Hospital.

- **“Observational study in young people with high-risk mental states. Differential profiles and influence of traumatic experiences and biological variables in the development of psychosis”.** (Exp/n. PI17-00481). Dr. María Mayoral Aragón. Child and Adolescent Psychiatry Service, Department of Psychiatry. Gregorio Marañón University General Hospital.
- **“Longitudinal Study of Oxidative and Neuroinflammatory Markers of Cognitive Function in First Episodes of Adolescent Psychosis”.** (Exp / n° PI18/00753). Dr. Marta Rapado Castro. Child and Adolescent Psychiatry Service, Gregorio Marañón General University Hospital, Faculty of Medicine, Complutense University, CIBERSAM.
- **“Effect of 48-Week N-Acetylcysteine Treatment on Gray Substance Loss and Oxidative Metabolism in Patients with Early-Onset First Psychotic Episodes: Randomized, Double-Blind, Placebo-Controlled Clinical Trial.”** (Exp/n° SAM-18PI02/2019). Dr. Celso Arango López. Foundation for Biomedical Research of the Gregorio Marañón Hospital.
- **PSYSCAN project:** “Translating neuroimaging findings from research into clinical practice”. PI: Dr. Celso Arango.

During 2019 the acquisition of MR images from 568 subjects has been completed. Overall, 3,178 MRI studies have been performed distributed among the different research projects.

58,589 MRI sequences have been conducted since the creation of the department, distributed by year and type of sequence, as it is shown in the next graph:

Comparison by sequences



	FUNCTIONAL	VOLUME-TRY	ESPECTRA	DIFFUSION TENSOR	MISCELLANEOUS	ASL
2008	255	339	156	178	312	259
2009	337	638	866	423	845	326
2010	910	852	1042	556	1506	305
2011	1124	845	786	528	1904	398
2012	1858	1512	583	1330	2938	949
2013	1436	1276	516	1116	2544	950
2014	880	937	367	847	1920	729
2015	828	912	309	783	1985	669
2016	739	749	341	618	1661	572
2017	614	648	299	594	1415	523
2018	487	519	226	124	1051	367
2019	473	513	306	285	1033	278

Provision of services

The Department of Neuroimaging has a 3T MR scanner (GEHC, HDxt) system equipped with dual gradient system of up to 50mt/m, 3 antennas for brain studies (transmitter/receiver quadrature antenna, receiving 8 channels antenna and 16 channels receiving antenna) and small antennas for rats and mice. Data is stored in PACS with direct recovery capacity for five years of work.

For Functional MRI studies, the Department has an audio/video system compatible with 3T MRI.

A variety of software packages is used, mainly SPM12, FSL and Freesurfer.

Sequences

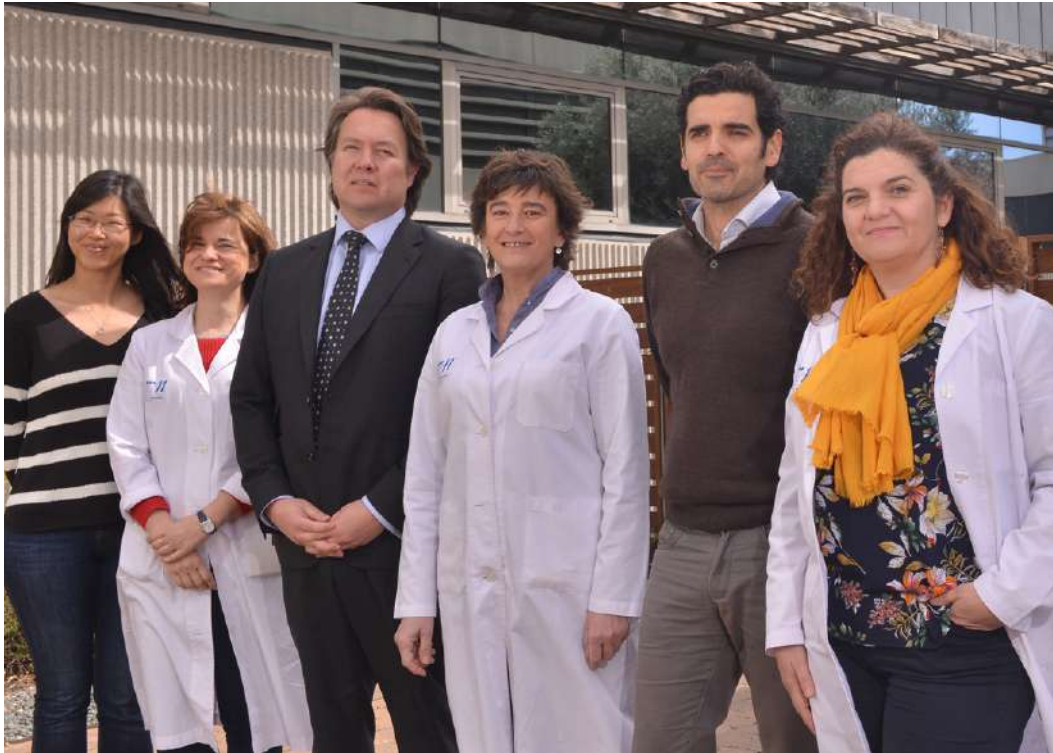
Image acquisition of 3D isotropic studies with T1 sequences for VBM.

Image acquisition of T2 sequences, DWI, ASL, BOLD and spectroscopy.

The service provision data are publicly available on the CIEN Foundation website: (https://www.fundacioncien.es/documentos/Tarifas-resonancia-magnetica_FCIEN.pdf)

Team

The Department of Neuroimaging team, led by Dr. Bryan Strange (MD, PhD, Clinical Neuroscience), has a highly multidisciplinary nature and consists of the following personnel:



Neuroimaging team.

RESEARCH FELLOWS

Jaime Gómez Ramírez. (PhD, Computer Engineering, Automatics and Robotics).
Linda Zhang (PhD Radiological Imaging. Graduate in Psychology). Queen Sofia Foundation-Mapfre Scholarship until July 2019, then hired by the CIEN Foundation.

Marta Garo (Master in Neuroscience, UAM). Queen Sofia Foundation-Mapfre Scholarship since March 2019.

Pablo Gómez del Campo del Bosque. (Master Biomedical Engineering, UPM). Until June 2019.

Kimberly Bress. Graduate in Neuroscience and Mental Health (Institute of International Education, Fulbright Scholar, USA). Until June 2019.

Darya Frank. PhD Cognitive Neuroscience (UPM Agreement). Since October 2019.

RADIODIAGNOSTICS

Mabel Torres Llacsá (MD, Radiodiagnostics)

IMAGE ACQUISITION

Eva Alfayate Sáez (Technical Coordinator Technician in Radiodiagnostics)

Felipe García Fernández (Advanced Technician in Diagnostic Imaging)

Carmen Rojas Obregón (Technician in Radiodiagnostics)

Marta Molero ((Advanced Technician in Diagnostic Imaging). From May to October 2019.

MANAGEMENT

Arantza Narciso Perianes (Administrative Assistant)

Corina Ghinea Radu (Administrative Assistant)

3.2.4. Department of Neuropathology

Neuropathology of neurodegenerative disorders is a specialty in continuous progress with capacity for contrasting clinical judgment and performance of any diagnostic test, including the most recent biomarkers, with the final diagnosis that is still neuropathology (“gold standard”). However, in the field of basic research, neuropathology plays an additional role, providing critical information about the molecular components of the characteristic lesions of each disease, the pathogenic mechanisms and the potential biomarkers.

The post-mortem neuropathological findings observed in donations of brain tissue from patients with neurodegenerative diseases, especially in the case of dementias, have allowed to know in recent decades the epidemiological reality of these diseases in the population, and among other evidences, have revealed the high prevalence of combined pathology (mainly Alzheimer’s pathology, Vascular pathology, Lewy pathology, and TDP-43 pathology).

The neuropathology of dementia landscape has dramatically changed in recent years. The incorporation to the neuropathological diagnosis of new antibodies for immunostaining and new molecular techniques has helped establishing the boundaries and internal heterogeneity of entities such as dementia with Lewy bodies and frontotemporal dementia, and has also led to the discovery of new entities in this area (DFT-TDP. DFT-FUS, etc.). The neuropathological study of an increasing number of patients with neurodegenerative pathology has allowed identifying new genetic causes of these diseases, thus helping to define new molecular targets for possible therapeutic approaches. In addition, the definition of diagnostic criteria from large series of brains (in biobanks of neurological tissue or brain banks) has allowed us to address the problem of combined and mixed pathology, specifically regarding Alzheimer’s disease. The evolution of the diagnostic criteria themselves (e.g. the new criteria for the diagnostic classification of Alzheimer’s disease proposed by the National Institute of Aging - Alzheimer’s Association, 2012) and molecular techniques are converting the histological diagnosis into an fundamental element in the process of classifying dementias, definitive or quasi-definitive in some cases, but partial or probabilistic in many others. As repeatedly demonstrated in clinical-pathological sessions, made possible in most cases thanks to the donation of brain tissue by patients or their families and the close collaboration of clinicians, the final classification of a case requires the integration of all clinical, neuroradiological, neuropathological and molecular information, when available.

Thanks to the joint work of neuropathologists from various continents, all of them associated with brain tissue donation programs, in recent years the precise characterization of histological brain lesions that until now had not been interpreted as defined pathological entities has been achieved. This has led to the description of new tauopathies, such as PART (Primary Age Related Tauopathy) and ARTAG (Aging-Related Tau Astrogliopathy) and of a new entity with TDP pathology, LATE (Limbic-Predominant age-related TDP-43 encephalopathy), all of which occur frequently in combination with the most prevalent patholo-

gies that produce dementia in elderly subjects.

A need for dementia research is the availability of well-diagnosed, classified and long-term preserved brain tissue. Brain banks (biobanks of neurological samples) respond to this need, and the CIEN Foundation has one of the main brain banks in the country, the CIEN Tissue Bank (BT-CIEN, for its acronym in Spanish).

Neuropathology also provides significant support for studies based on animal models of neurological diseases, both for the histological evaluation of transgenic animals and for the search for natural models of the disease. The Department of Neuropathology of the CIEN Foundation participates regularly in the histological evaluation of animal models of different neurodegenerative diseases developed by CIBERNED researchers, as well as in the neuropathological study of elderly mammals of the Madrid Zoo.

Department activities

The core activity of the UIPA's Department of Neuropathology corresponds to the BT-CIEN, both to its organizational and logistical components as well as the neuropathological diagnostic work and the management of biological samples.

The Department also participates in numerous collaborations in external research projects, mainly with CIBERNED research groups, and carries out its own internal projects, mainly based on series of cases from post mortem donation. Among the active lines of research in the Department are the following:

- **Neuropathological and molecular study of tauopathies, including Alzheimer's disease.** Pathogenic significance and spread of associated cellular lesions. Argyrophilic grains disease and other recently described tauopathies (PART, ART-AG) as models of tauopathy with predominant involvement of the medial temporal lobe. Lewy pathology limited to the amygdala. Hippocampal sclerosis and associated TDP-43 pathology (LATE).
- **Clinicopathological profiles in advanced dementia.** Characterization of the combined and mixed pathology and its impact on the clinical trajectories of the patients, with special attention to disease progression rate and survival time (project based mainly on the patient cohort from the residency of the Queen Sofia Foundation Alzheimer's Center Research Program).
- **Pathological role of fungal colonization and the polymicrobial infection of the Central Nervous System in Alzheimer-type pathology.** Risk factors and clinical impact. Impact of neuroinflammation associated with polymicrobial infection on the origin and progression of neurodegenerative pathology.
- **Distinctive features of Alzheimer-type pathology in nonagenarians and centenarians.** Neuropathological findings in subjects without cognitive disorder above 90 years of age.
- **Advance age-associated changes in Central Nervous System and cerebral pathology in mammals and non-human primates.** Search for natural models of Alzheimer in primates and other mammalian groups.



Provision of services

The range of activities undertaken by the department derives from the ability of its members to collect, process, evaluate and diagnose brain tissue sample from human or animal origin. All the services listed below provided by the BT-CIEN are accessible to donors and researchers through the website.

- **Performing neuropathological autopsies** in brain tissue donors, both in the Region of Madrid and neighboring Regions, as well as in other Regions that do not have a brain bank.
- **Management of a biobank of neurological samples.** Transfer of samples to researchers according to the BT-CIEN standard operating protocols together with biobank external committees.
- **Prospective collection of special biological samples for research projects**, at the request of the researchers, once approved in compliance with BT-CIEN protocols (and by the scientific and ethical external committees).
- **Diagnostic consultations of neuropathological cases.** Among the external consultations, those carried out as support of other biobanks of neurological samples with which BT-CIEN maintains a regular collaboration (Murcia, Salamanca, Leon and Cordoba) stand out. Consultations are also received from different public hospitals and from the Anatomical Forensic Institute of Madrid
- **Performing neurohistological and immunohistochemical techniques** in neurological samples of human and experimental origin.
- **Incorporation in the biobank of samples collections** (usually, biological fluids, blood and CSF) from clinical research projects.
- **Organization of informative lectures and visits to the biobank** for the dissemination and promotion of brain tissue donation among patients and relatives, health professionals and the general population.
- **Participation in formal training programs** for Pathological Anatomy Technicians, Laboratory Technicians, and Pathological Anatomy and Neurology resident physician interns.

CIEN Foundation Tissue Bank (BT-CIEN)

Since its opening in May 2010, the CIEN Foundation Tissue Bank (BT-CIEN) has traveled a path of growth and consolidation in the field of Spanish Neuroscience, supporting national and international research groups and maintaining close contact with neurological disease patients and relatives associations.

The number of registered donors in the BT-CIEN registry has continued to grow every year, as has the tissue donations made at our Center within our Internal Donation Program, which involves residents of the Queen Sofia Foundation Alzheimer Center (CAFRS), and the External Donation Program, that involves donors from the Region of Madrid and other Regions.

There is also an increasing number of research groups applying for biological samples from BT-CIEN, especially groups from the Center for Networked Research in Neurodegenerative Diseases (CIBERNED).

One of the missions of BT-CIEN is to promote the creation of new neurological samples biobanks whenever donors and researchers demand them. The Region of Murcia Brain Bank (BCRM), the Neurological Tissue Bank from the Institute of Neuroscience of Castilla y León (BTN-CyL) and the of Queen Sofia University Hospital Biobank from Cordoba are active examples of this commitment. At the present time, support is being provided for the creation of a new NTB in Ciudad Real, as a reference biobank for the Community of Castilla-La Mancha, and a NTB in Zaragoza.

In 2013, the BT-CIEN has been accredited by the Council of Health of the Region of Madrid, according to what is established in the Royal Decree 1716/2011 on Biobanks, and registered in the National Registry of Biobanks of the Carlos III Institute of Health.

In January 2014 the Biobanks National Network Platform (PRNBB, for its acronym in Spanish), promoted and funded by the Carlos III Institute of Health (2014-2017) was constituted, with participation of the main biobanks in the country, both hospital and non-hospital, including BT-CIEN. PRNBB mission is to create a stable organizational structure that allows the coordinated activity of participating biobanks in the collection, management and transfer of biological samples of human origin. Before concluding its period of activity in December 2017, the PRNBB renewed its commitment to the ISCIII for a new funding period, 2018-2020. The BT-CIEN has played a prominent role in the R&D&I Program of the PRNBB and in the new phase of the platform, initiated in January 2018, has assumed the coordination tasks of the R+D+i program as a whole. Moreover, since 2012 the BT-CIEN has the ISO 9001/2008 quality certification, renewed in 2016, and that was also renewed in 2018 under the ISO 9001/2015 standard.

In September 2018, the 1st Symposium on Neurological Tissue Banks was held in Salamanca, organized by BT-CIEN and the Castilla y León Institute of Neurosciences. As agreed there, the Neurological Tissue Banks Working Group (NTBWG) was set up within the RNBB at the beginning of 2019, with the participation of the 15

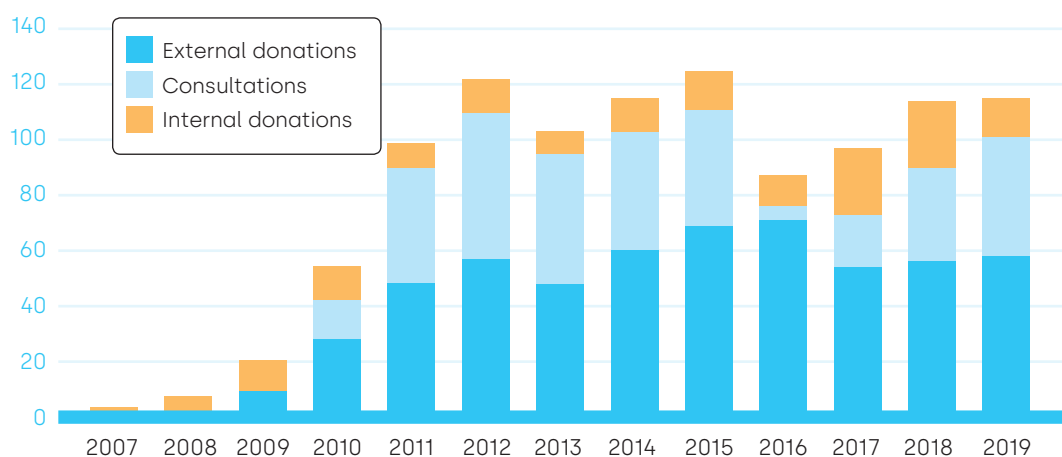
NTB active in Spain. The BT-CIEN has been very much involved in the creation and in the annual tasks of the NTBWG, and also participated in the organization of the NTBWG satellite Conference during the X National Congress of Biobanks (Valencia, October 2019).

In October 2019, the first joint meeting of the Spanish Neuropathology Club (Spanish Society of Neurology and Spanish Society of Pathological Anatomy) and the Portuguese Society of Neuropathology was held in Salamanca. At the meeting, it was decided to create the Iberian Neuropathology Neuropathology Working Group (INPWG), and a roadmap of activities for the coming years was drawn up.

The BT-CIEN registry had 708 registered donors by December 31, 2019.

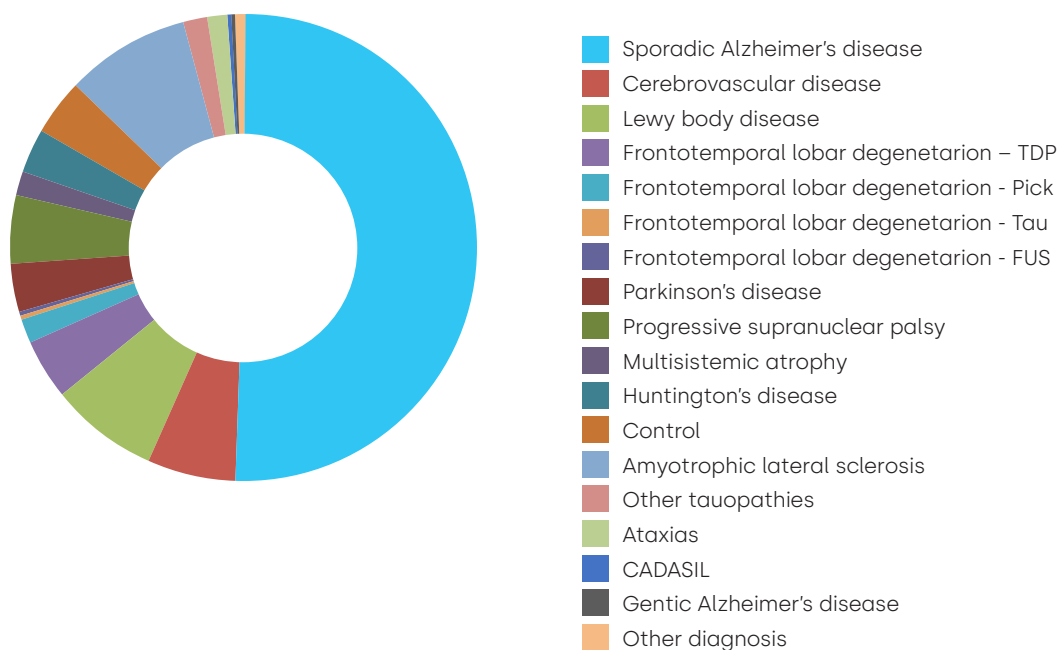
Up to 115 cases were processed in the Neuropathology laboratory during 2019, with the following distribution depending on the origin::

- 58 donations from the External Program (depicted in blue in the graph)
- 14 donations from the Internal Program (depicted in red in the graph)
- 43 consultation cases (not included in the graph)



According to these data, the number of donation cases extracted and processed entirely in the UIPA in 2019 amounted to 72.

Regarding the cases accumulated since the beginning of BT-CIEN activity, the distribution by main neuropathological diagnosis is the one shown in the following figure, with approximately 50% of Alzheimer's cases, and extensive representation of the rest of neurodegenerative diseases.



The research centers that have received samples from BT-CIEN during 2019 have been:

- Institute of Biomedical Research "Alberto Sols". IIBm (CSIC-UAM)
- Hertie Institute for Clinical Brain Research, University Clinic Tübingen, Germany
- Center for Molecular Biology "Severo Ochoa", CSIC, Madrid
- Carlos III Institute of Health
- Faculty of Veterinary Medicine, Complutense University of Madrid
- Navarra Health Research Institute Foundation, IDISNA
- Vall d'Hebron Research Institute (VHIR) -ICREA
- General University Hospital of Valencia
- Teófilo Hernando Institute Foundation - Autonomous University of Madrid
- Cajal Institute, CSIC
- 12 de Octubre Hospital Research Institute

Research projects

During 2019, the Department of Neuropathology has been involved in the following research projects:

National Biobank Network (RNBB), Platform funded by ISCIII, 2018-2020, which has



Neuropathology Team.



the BT-CIEN as one of its nodes. Alberto Rábano is co-coordinator of Program 3 (R+D+i) while Laura Saiz performs tasks to support the Coordination. Within the Program 3 research lines, Ana Belén Pastor participates in Working Group 3.2 dedicated to the study of microRNAs as new types of biological sample, and Valentina González collaborates in line 2.1 dedicated to the study of quality markers in tissue samples (OPTIMARK multi-center research project, funded by FIS, ISCIII).

Team

During 2019, the Department of Neuropathology staff was composed of the following personnel:

Dr. Alberto Rábano (Neuropatólogo), (neuropathologist), Head of Neuropathology and BT-CIEN Scientific Director.

Laura Sáiz Auz (sample management technician)

Valentina González Álvarez (biologist, quality program and special samples).
Until July 2019.

Eugenia Hitt Rech (Pathology Technician).

COLLABORATORS (24 h autopsies team):

Luis Javier Martín Lentijo (Pathology Technician)

M^a Cruz Santiago San Marcos (Técnica de Neuropatología)

3.2.5. Department of Biochemistry and Molecular Genetics

The aging of the population and the growing epidemic of Alzheimer's disease (AD) highlight the importance of research in the molecular mechanisms of pathology, as well as in the development of methods for the early detection of the disease to carry out an adequate evaluation of risk and to be able to implement early and effective therapies. Currently, it is widely accepted that changes at the cellular level associated with AD, including the formation of neurofibrillary plaques and tangles, begin many years before clinical symptoms are evident or the existence significant cell death in the brain. Therefore, the development of biomarkers that allow the identification of patients with incipient AD or asymptomatic people at risk is of great importance, so that treatments aimed at stopping neurodegeneration can be initiated before it becomes irreversible.

The most extensively studied biochemical markers are the tau protein (total levels and different phosphorylated isoforms) and the amyloid peptide in cerebrospinal fluid (CSF), that are both directly related to neurofibrillary and amyloid pathology, respectively. However, the drawbacks derived from obtaining CSF, together with a limited precision of these assays in early phases, highlight the need to identify new markers, in particular in more accessible biological fluids such as blood. Currently, many researchers believe that both the development of neurofibrillary and amyloid pathologies in AD represent relatively late events in the evolution of the disease, which may or may not reflect the fundamental biochemical-molecular dysfunctions that give rise to the disease. The clinical manifestations of AD are preceded by an asymptomatic preclinical phase, after which the first symptoms appear in the prodromal phase of the disease characterized by mild cognitive impairment (MCI). In this sense, AD can be understood as a continuous process that evolves from the asymptomatic phases to the dementia phase. This evolution is largely determined by genetic risk variants and is associated with biochemical changes that can ideally serve as early markers of the disease.

Department activities

The activity of the Molecular Genetics Department focuses mainly on the search for biomarkers of early diagnosis of Alzheimer's disease and the study of genetic susceptibility factors of AD and other neurodegenerative disorders. This activity has the following objectives: to deepen the molecular basis of the disease and develop predictive algorithms that combine information on genetic and biochemical markers with diagnostic, prognostic or response value to modifying therapies.

For this purpose, multidisciplinary research with the rest of the CIEN Foundation departments, together with the CIEN Tissue Bank (BT-CIEN), are decisive for working on the two main projects of the CIEN Foundation-Queen Sofia Foundation: the Vallecas Project for the early detection of Alzheimer's disease and the Alzheimer's Center of the Queen Sofia Foundation Research Program.



• The Vallecas Project

It is currently known that the pathological processes that determine Alzheimer begin many years before the disease leads to the first noticeable symptoms in patients. Years before that future drug treatments preventing or slowing down disease progression could be applied to the “population at risk” who has developed these subclinical lesions, or has a higher risk of developing it than the rest of the population. In this context it is framed the Vallecas Project, which is constituted as a 5-year longitudinal study specifically aimed at discovering the factors that would allow us to detect this “population at risk” in a phase of potentially treatable pathology.

During 2019, 300 volunteers were studied, with the following distribution: 1 volunteer from the fifth follow-up visit of the study, 33 volunteers from the sixth visit, 142 from the seventh visit and 124 from the eighth visit.

Of all volunteers recruited in the study and having an informed consent, a blood sample is collected and immediately transferred to the laboratory for fractionation into aliquots following the so-called Vienna Institute of Neurology protocol, which allow different types of analysis, as well as classification and storage (see Figure below). Additionally, one blood tube (BD-CPT citrate Vacutainer) for the isolation of mononuclear leukocytes, together with another tube lacking anticoagulant to obtain serum are processed.

[Vienna Institute of Neurology Protocol for blood processing in various fractions for the search for biomarkers and susceptibility genes.](#)

Within the Molecular Genetics department, the activity of the Vallecas Project is shown in the table on the following page:

EVALUATION	1 ST	2 ND	3 RD	4 TH	5 TH	6 TH	7 TH	8 TH	TOTAL
N° SAMPLES	1169	767	755	699	662	414	172	7	4645
2019 SAMPLES	-	-	-	-	1	33	142	124	300
TOTAL	1169	767	755	699	663	447	314	131	4945
N° ALIQUOTS	16366	10738	10570	9786	9282	6258	4396	1834	69230

The type of primary aliquots that are obtained in duplicate are the following:

- Whole blood (ST, for its acronym in Spanish)
- Platelets-rich plasma (PRP)
- Platelets-free plasma (PFP)
- Buffy Coat (BC)
- Red blood cells (RBC)
- Serum (Suero, in Spanish)
- Mononucleate leukocytes (LM, for its acronym in Spanish)

Genomic DNA was extracted from whole blood of all participants who have signed informed consent to it and the APOE gene, an important marker of genetic risk for Alzheimer's disease, was analyzed. The comparison of the frequency of APOE allele $\epsilon 4$ carriers between CAFRS patients and Vallecas Project volunteers confirms the risk to suffer from Alzheimer's disease with an OR = 3.53 ($p < 0.001$). In addition, in order to define different subpopulations of genetic risk, other possible genetic susceptibility genes have also been analyzed in a subset of participants (see below).

Distribution of genotypes of APOE gene in the population of volunteers from the Vallecas Project.

APOE GENOTYPES	N
e2/e2	5
e2/e3	118
e2/e4	10
e3/e3	848
e3/e4	195
e4/e4	12

It is also important to emphasize that the samples obtained from Vallecas Project volunteers aged between 70 and 85 years (at the baseline evaluation) that include a comprehensive assessment of cognitive, sociological and neuroimaging state are optimal for its use as a control population in various projects related to neurodegenerative diseases, especially Alzheimer's disease. The monitoring for a period of 5 years will allow us to detect early, even before clinical symptoms manifestation, susceptibility factors and biomarkers associated with Alzheimer's disease.

Queen Sofia Foundation Alzheimer Center Research Program

The **Queen Sofia Foundation Alzheimer Center Research Program**, focuses on regular and protocol-based monitoring of a cohort of CAFRS patients with dementia, either as residents at the Center or attendants at the Day Center, with the main objective of investigating the final stages of Alzheimer's disease. A family member or guardian recruits patients into the monitoring program after signing an Informed Consent. The Alzheimer Project program consists of i) a biannual clinical and neuropsychological assessment by the Multidisciplinary Support Unit (UMA, for its acronym in Spanish), ii) a biannual blood sampling, coincident with the usual one taken at the residence, iii) conducting an annual cranial MRI if the patient's condition allows it, and iv) donation of brain tissue after patient's death.

The CAFRS takes care of 156 patients in residence, and 40 patients in the Day Centre. The Alzheimer project-monitoring program includes obtaining a blood sample biannually coinciding with the one routinely performed at the Center for conven-

tional analytics. Thus, performing a venipuncture in the patient for research purposes only is avoided. After extraction, each blood sample is processed at once, resulting in 14 aliquots comprising various hematologic derivatives (whole blood, plasma, serum, etc.), including extraction of DNA for genetic studies.

Aliquots obtained from blood samples are incorporated into the CIEN Tissue Bank (BT-CIEN, for its acronym in Spanish) collection according to the protocols of the biobank. The total number of samples incorporated to the BT-CIEN so far, corresponding to the Alzheimer project monitoring program, adds up to 2,420 (14.0% patients corresponding to the Day Centre), which have resulted in a total of 33,880 aliquots of different fractions derived from blood samples.

Samples obtained up to December 31, 2019 according to the number of semiannual evaluations. Above: samples obtained in 2019. Below: samples accumulated since the beginning of the CAFRS Research program

2019																					
EVALUATION	1ª	2ª	3ª	4ª	5ª	6ª	7ª	8ª	9ª	10ª	11ª	12ª	13ª	14ª	15ª	16ª	17ª	18ª	T		
Residence	16	24	19	18	33	16	6	7	11	8	7	8	3	3	1	1	2	1	184		
Day Center	1	5	2	0	9	3	2	1	1	0	0	0	1	0	0	1			26		

ACUMULATED																							
EVALUATION	1ª	2ª	3ª	4ª	5ª	6ª	7ª	8ª	9ª	10ª	11ª	12ª	13ª	14ª	15ª	16ª	17ª	18ª	19ª	20ª	21ª	22ª	TOTAL
Residence	349	320	281	234	224	178	154	142	141	128	97	88	72	68	45	39	35	27	202	14	8	2	2848
Day Center	133	102	77	58	44	29	15	10	6	4	4	4	3	1	1	1	0	0	26	0	0	0	518

Consistent with other studies, the analysis of the APOE gene polymorphism in CAFRS patients revealed a high presence of allele $\epsilon 4$, which in this population appears to be more prevalent in men. In addition, the phenomenon of advancement of the age of onset of Alzheimer's disease associated with the $\epsilon 4$ allele observed in other cohorts, is noted, as it is the reverse phenomenon of delayed age of onset associated with the $\epsilon 2$ allele.

Distribution of APOE genotypes in the CAFRS patients cohort

APOE GENOTYPES	N
e2/e2	0
e2/e3	19
e2/e4	5
e3/e3	214
e3/e4	168
e4/e4	35

Other projects

Currently, several lines of study are being followed up based on the combined use of biochemical markers and genetic data.

- **MicroRNAs and lipid metabolism markers as potential links between vascular dysfunction and Alzheimer's physiopathology.**

During 2019, the project initiated in 2017 and entitled "MicroRNAs and lipid metabolism markers as potential links with vascular dysfunction and Alzheimer's disease pathology", funded by MINECO (RETOS Projects), whose principal investigators are Drs. Miguel Medina and Miguel Calero, has continued. The main objective of this proposal is to explore the possible role of miRNAs and markers of lipid metabolism as possible links between peripheral vascular dysfunction and the pathophysiology of AD. The design of the project is based on a double approach with complementary aims related to the existing cohorts (Vallecas Project and Research Program of the Vallecas Research Center (PICAV) and the CIEN Foundation Brain Bank. The central working hypothesis builds upon the existence of circulating miRNAs and molecules of lipid metabolism in plasma that could differentiate cognitively normal individuals from people with mild cognitive impairment or dementia, either alone or in combination with other parameters being collected from the same individuals (elderly volunteers) within the Vallecas Project, as well as patients with confirmed AD after autopsy. To this end, we propose to carry out a complementary and synergistic approach to evaluate, validate and standardize the identification, monitoring, quantification and functional validation of miRNAs in plasma samples taken from elderly subjects who are cognitively normal, show deterioration cognitive mild or moderate dementia, in the presence or absence of peripheral vascular pathology. Following a multidisciplinary approach, the analysis of the data obtained will benefit from the availability of other data generated within the Vallecas project (sociodemographic data, clinical history, annual neurological evaluation, neuropsychological evaluation, structural and functional brain MRI, genotyping, etc.) in order to identify molecular, clinical, or neuroimaging signals that may serve to define populations at higher risk of developing dementia in the future.

Dementia Genetics Spanish Consortium (DEGESCO).

Also, during this year, the CIEN Foundation has continued participating in Dementia Genetics Spanish Consortium (DEGESCO) in which a number of Spanish research groups share genetic data within this consortium to achieve greater study power in dementia genetics and especially in the Alzheimer's disease. In the context of DEGESCO, during 2019, research activities continued to be carried out oriented towards the definition of new genetic risk factors and the participation of the national consortium in international proposals (see below).

In addition to the study of the APOE gene, using samples from the Vallecas Project (controls) and samples from the Alzheimer Project (AD cases), genetic associa-



tion studies of the main genes associated with AD have been carried out, including SORL1, LDLR, BIN1, CLU, ABCA7, CR1, PICALM, BACE1 and PRNP. These association studies, in addition to serving as a replication in a Spanish population of studies carried out in other populations, will allow us to determine the most important genetic factors in the development of cognitive dysfunction in our population of the Vallecas Project. It will also allow defining endophenotypes based on genetic variations as well as concrete and measurable characteristics of the patients and controls based on clinical neuroimaging, biochemical or pathological measurements (see figure).

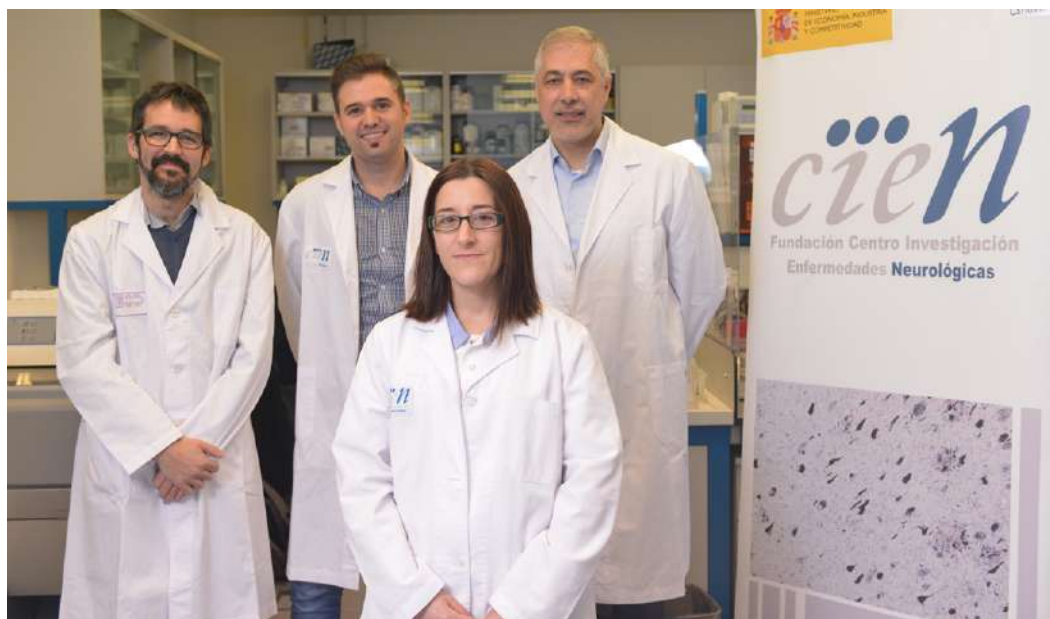
Illustration of the concept of endophenotypes for defining homogenous populations based on certain genetic variants and biomarkers in Alzheimer's disease (modified from Doring et al. 2011)

- A European DNA bank for deciphering the missing heritability of Alzheimer's disease - EADB (European AD DNA Bank) and GR@ACE project (Genomic Research at Fundació ACE)

This project is an international collaboration initiative carried out through DEGESCO that aims at significantly increasing the generation of data based on GWAS (Genome-Wide Association Studies), through the creation of a European DNA biobank of Alzheimer's disease (EADB). In this study, over 30,000 AD cases and 40,000 controls in 11 countries will be analyzed. GWAS and complementary statistical analyses will be carried out (based on genotype and imputation data) in order to identify the missing heritability and pathophysiological mechanisms of the disease.

This initiative will increase the number of AD samples available in Europe more than four times and around the world by almost two-fold. Carrying out this project will allow us to understand the genetics of AD thus improving our knowledge of the underlying pathophysiological processes in the disease; since the genetic factors seem to represent up to 80% of the attributable risk in AD. In parallel, the EADB will collect DNA samples from the largest European longitudinal cohort of cases of mild cognitive impairment, with the aim of identifying genetic markers that modulate the rate of disease progression and cognitive decline. From a translational perspective, the identification of genetic factors in the pathways that modulate AD risk and increase the rate of disease progression/cognitive decline will be critical for the development and testing of therapeutic approaches. Additionally, in the context of the DEGESCO consortium, collaboration has begun with the GR@ACE project, led by the ACE Foundation, which will be carried out in three years, and whose objective is the application of high resolution genomic technologies for the identification of a new generation of genes that contribute data in the design of new treatments to deal with Alzheimer's disease.

In relation to the study of biomarkers and the collaborative context with the company Biocross SL and with various Spanish hospitals, we continue with the plasma metabolomic studies of people with Alzheimer's disease, mild cognitive impairment or without cognitive dysfunction. In addition, we also continue with the de-



Biochemistry
and Molecular
Genetics Team.

velopment of a non-genetic test adapted to the hospital diagnostic routine for measuring blood ApoE4 as a marker for determining the AD risk and that has currently obtained the CE label.

Other collaborations

- Assessment of lactoferrin levels in saliva as a marker of Alzheimer's disease in collaboration with Drs. Eva Carro and Félix Bermejo from the 12 de Octubre Hospital
- Study of the role of lipofuscin in neurodegeneration in collaboration with Dr. A Kun from the University of the Republic, Uruguay
- Study of the participation of the A β peptide in gliogenesis and proliferation in human neural stem cells with Dr. I. Liste from the Carlos III Health Institute.

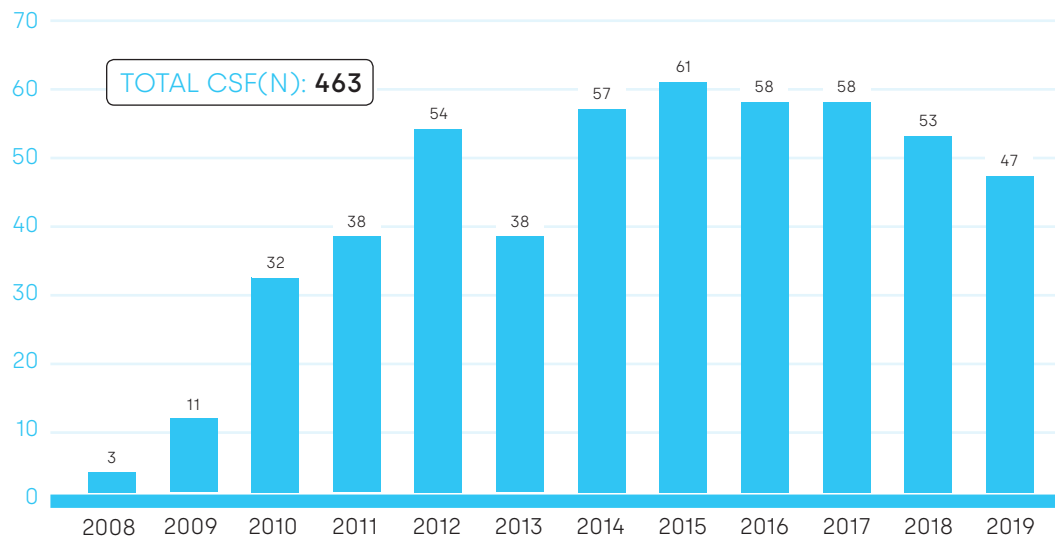
Contribution to BT-CIEN

The Biochemistry and Molecular Genetics department also contributes to the BT-CIEN with processing of various samples, and collaborates on several external projects focused on Alzheimer's disease and other neurodegenerative diseases.

In the context of research focused on the study of biomarkers and genetic susceptibility factors, the UIPA Laboratory department is responsible for collecting, processing and storing biological samples for research related to various projects or for its deposit in the BT CIEN, whose ultimate purpose is to use in different research areas on neurodegenerative diseases.

Currently, the department contributes to BT-CIEN with various biological samples including 520 CSF samples from donor's brain, 315 skin samples, and 258 saliva samples.

Samples of cerebrospinal fluid (CSF) obtained post-mortem since 2008.



Team

During 2019, the team of the biochemistry and Molecular Genetics Department was composed of the following personnel:

Miguel Calero Lara (PhD, Chemistry), Head of Department

Ana Belén Pastor López (Laboratory Technician)


COLLABORATORS

Olga Calero Rueda (PhD, Biology)

Andrés Rodríguez Martín (Laboratory Technician, CIEN Foundation-Biocross agreement)

Sergio Veiga Herrero (PhD, Biology CIEN Foundation-Biocross agreement)





**THE VALLECAS
PROJECT**

4



4.1.

Introduction

Aging is one of the major risk factors for some of the most prevalent diseases such as cancer, cardiovascular disorders or neurodegenerative diseases, but while the number of cases of the first two tends to stabilize, the number of patients with neurodegenerative pathologies, particularly dementia, continues to grow exponentially. According to the demographic estimates of the National Institute of Statistics, in 2019 there are 8.9 million people in Spain aged 65 or over (19.4% of the population) and it is estimated that in 2050 about 15 million Spaniards (approximately one third of our population) will be over 65 years old. In fact, the combination of one of the highest life expectancies in the world and one of the lowest birth rates make the Spanish population the oldest in Europe and one of the oldest in the world after South Korea and Japan.

Dementia is a clinical syndrome characterized by a progressive cognitive impairment severe enough to affect personal and social functioning of an individual. Alzheimer's disease (AD) is the leading cause of dementia in our environment. According to the National Epidemiology Center, 7.3% of the population over 65 years could suffer from this disease nowadays. In total, AD constitutes about 75% of the etiology of dementias, either alone or in combination with cerebrovascular disease. Because of increased life expectancy and the progressive aging of the population in Western countries, dementia represents a huge challenge for public health systems. In our country, it is estimated that approximately one million Spaniards could have dementia by 2050.

According to the Survey of Disability, Personal Autonomy and Dependency Situations developed by the National Institute of Statistics, the rate of disability stands at ninety dementia cases per thousand inhabitants. However, the impact of dementia is not only produced directly on the patient, but also has a great influence his/her family and social environment concerning affective, organiza-

tional and economic aspects. In this sense, dementia should be understood as a social problem that must be approached in a comprehensive manner.

The transition from a cognitively healthy stage to an AD-type dementia is a continuum in which some intermediate stages, preclinical and prodromal can be recognized. These stages are characterized by the presence of an incipient cognitive impairment that increases the probability of conversion to dementia in the future. An effective therapeutic intervention in these phases prior to AD could eventually slow the progression of deterioration and thus reduce the prevalence of the disease. For this reason, one of the challenges currently faced by research is the development of useful tools that allow early diagnosis of AD.

Currently, there is no reliable method to predict safely which individuals in these preclinical stages have an increased risk of converting to dementia. The emergence in the last decade of various diagnostic neuroimaging techniques (eg, brain PET amyloid) has led to considerable progress in research, although its use in regular clinical practice is not feasible due to its high cost.

The most recent descriptive epidemiological research on dementias is allowing us to investigate how prevalence and incidence are changing over time. To establish clear trends, these comparisons should be based on studies that use similar diagnostic and research methods consistently over time. It is important to bear in mind that the main non-genetic risk factors for the development of dementia are related to lifestyle, which makes it particularly important to carry out studies in the Spanish population. Important changes in our society and improvements in living conditions and education in recent decades can have a decisive influence not only on physical wellbeing, but also mental and cognitive health and therefore on the incidence of dementia in the elderly population. Thus, the analysis of risk factors related to the symptoms of dementia must be accompanied by a comprehensive phenotypic characterization in order to provide a better understanding of the underlying neurobiological mechanisms.

The concept of population studies - that is, the recruitment of participants from community environments to ensure good representations of the entire population - must be incorporated in future neurobiological and neuropathological investigations in dementia. The results of small clinical-based samples, which include only patients from memory clinics or other medical services, have inherently limited generalization and the considerable potential for bias due to highly selective recruitment. In particular, people who are socially disadvantaged are less likely to participate in that research. The integration of neuroscience with population studies and neuroscientific epidemiological approaches is of vital importance and provides the opportunity to integrate the understanding of brain health, neurobiology and neuropathology within the general population to support better prevention, care and cure of dementia.

The main objective of the population-based study "Vallecas Project" for Early Detection of Alzheimer's Disease, is to elucidate, through tracking of progres-



sion, the best combination of clinical parameters and complementary tests (imaging and laboratory) that allow deciphering at medium- and long-term features that distinguish those who will develop memory impairment (MCI and dementia) from those who will not. Thus, it intends to identify various markers to determine eventually the potential risk that each individual could have to develop the disease in the future.

4.2

Background: Pilot project

A pilot study was conducted between June 2010 and February 2011, prior to the final project, whose first preliminary results are presented in this report. The aims of this study were:

- To verify the feasibility of the working procedure, the cooperation of the target population and the adequacy of screening protocols to the study objectives.
- To obtain early and sufficient information on the characteristics of the recruited volunteers and those that could not be recruited, as well as the limitations of the actual sampling compared to the intended one.
- To get experience in the implementation of the different elements of the protocol and to estimate the burden of the evaluator and the evaluated.
- To promote the Project to achieve the participation of volunteers and attracting enough funds to carry out the Vallecas Project.

175 volunteers were involved in this phase of the project, of which:

- 95 people were able to participate in the project.
- 80 people were unable to participate because they met at least one exclusion criterion.



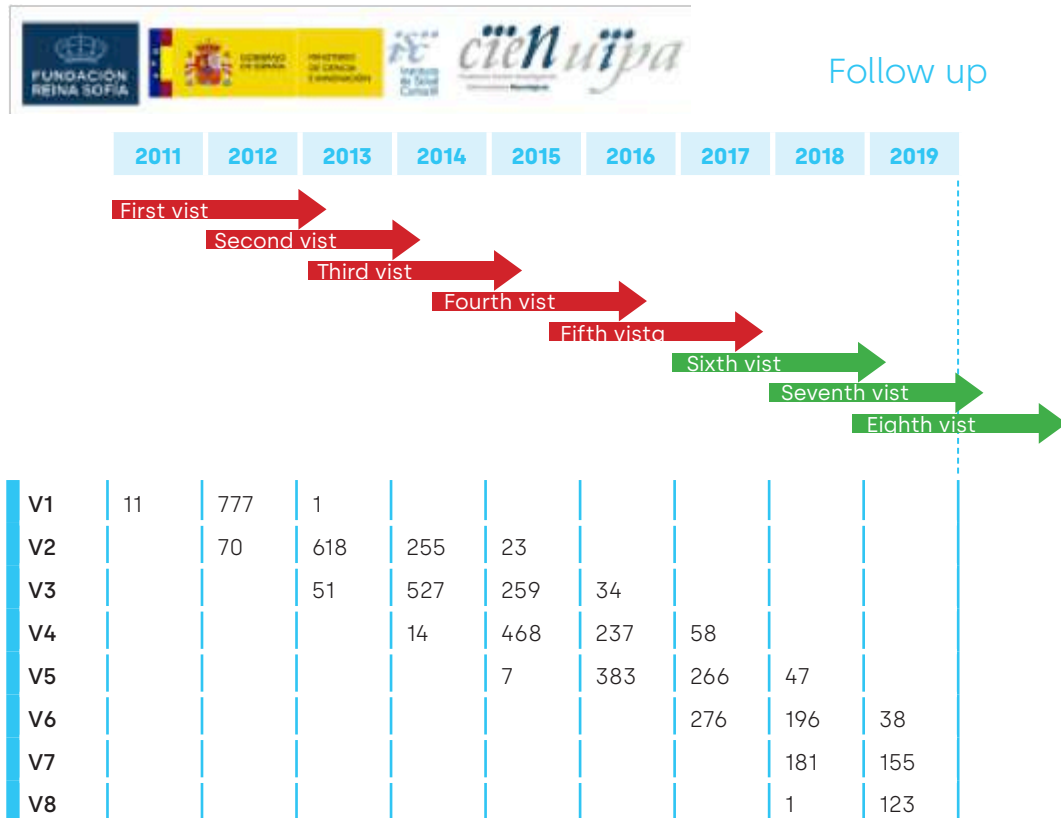
4.3.

The Vallecas Project

Following the completion and analysis of the pilot study the protocol was amended based on the experience gained and a volunteer recruitment strategy was established (social awareness campaign in the media, visits to centers for seniors, contact pensioner's organizations, etc.). In September 2011, after the "Global Summit on Alzheimer Disease Research" held in Madrid and with the financial support of the Queen Sofia Foundation.

The Vallecas Project is being carried out in the Queen Sofia Foundation Alzheimer Center Research Unit by researchers from the CIEN Foundation (Carlos III Institute of Health). It aims to develop a probabilistic algorithm to identify individuals at risk for AD-type dementia over the course of a few years. Such an algorithm will be based on a combination of socio-demographic, historical, clinical, neurological and neuropsychological, biological (from blood tests) and neuroimaging (various forms of 3T MRI).

The participant recruitment phase for the Vallecas project lasted from October 2011 to December 2013. By then, 1,213 individuals of both genders, aged 70-85 years were recruited and evaluated at baseline. Once included in the study, the project conducts an annual follow-up for five years in order to assess the evolution profile of all participants, specifically identifying those that develop cognitive impairment and/or dementia. At the beginning of 2018, an agreement was signed between the CIEN Foundation and the Queen Sofia Foundation to extend the duration of the Vallecas Project beyond the five years of follow-up originally planned. This second phase covered by the new agreement will allow the cohort to be followed for an additional four-year period. At the end of 2019 we have completed the sixth visit for the whole cohort, being towards the end of the seventh and mid-way through the eighth.



4.3.1. Baseline evaluation

Before entering the study, volunteers interested in participating in it were subjected to an initial assessment to determine whether they meet the criteria for inclusion and/or whether an exclusion criterion exists. Overall, all volunteers were required to meet four inclusion criteria in order to be considered for entering the study:

- Signing an informed consent.
- Be aged between 70 and 85 years old.
- Availability and ability to reach the Alzheimer Centre for visits.
- Visual and hearing abilities that allow conducting the study tests.

In addition, a number of exclusion criteria were established, including the following: i) suspected or diagnosed dementia; ii) inability to perform neuroimaging studies; iii) alcohol abuse; iv) mental retardation; or v) history of certain psychiatric or neurological diseases (e.g. schizophrenia, stroke, severe head trauma, Central nervous system infections, uncorrected vitamin deficiencies, etc.).

In the table below some global data from the cohort of approximately 1,213 individuals evaluated to date are indicated.

THE VALLECAS PROJECT IN FIGURES

Recruited sample	1.213
Excluded at baseline	47 (3,87%)
AGE	
Sample mean	74,46 años
Age group 69-74	671 (55,32%)
Age group 75-79	379 (31,24%)
Age group > 80	163 (13,44%)
GENDER	
Females	780 (64,30%)
Males	433 (35,70%)
EDUCATION	
Sample mean	10,35 años
Illiteracy	4 (0,34%)
Read/Write	60 (5,11%)
Minimum studies mínimos (numeracy skills)	154 (13,11%)
Primary Education	389 (33,11%)
Senior High School / Professional Training	282 (23,99%)
University Education	286 (24,34%)

4.3.2. Sociodemographic profile

The following variables are collected through semi-structured interview: gender, date of birth, marital status, number of children, type and amount of income, primary occupation and education level, hobbies and leisure activities, etc.

In addition, each year volunteers also must complete a scale of quality of life and subjective well-being (mobility, personal care, daily activities, pain/discomfort, anxiety/depression, and perceived health status) as well as various questionnaires to gather information related to lifestyle.

4.3.3. Clinical evaluation

At each visit relevant information is collected from each volunteer by applying a semi-structured clinical interview:

- Vascular risk factors: blood pressure, diabetes mellitus, smoking, heart disease, stroke
- Neurological history: mental retardation, head injuries, etc.
- Consumption and/or toxic addiction: alcoholism/level of regular alcohol intake, addiction/consumption of other psychotropic substances.
- Psychiatric pathology: depression, dysthymia, bipolar disorder, psychotic disorders, anxiety syndromes.

- Other relevant systemic diseases: hepatic failure, renal failure, Obstructive Sleep Apnea Syndrome (OSA)...
- Family history with special attention to the history of dementia or movement disorders, developmental delay or psychiatric disorders.
- Regular drug treatment during the last 5 years.
- From 2017 to 2019, all volunteers who consent to carry an accelerometer device (Actigraph®), similar to a wrist watch, are being provided with it for the recording of physical activity and sleep for a week. During that period, the following records have been registered:
 - 2017: 251 records
 - 2018: 375 records
 - 2019: 181 records

Distributed as follows:

- Volunteers with only 1 record: 249
- Volunteers with 2 records: 262
- Volunteers with 3 records: 12

Hence, we have a sample size of 523 volunteers with at least one record already registered, and 274 volunteers with a second record after one year follow up.

This information must be processed to obtain a number of variables related to light, moderate or intense activity, as well as indicators of sleep duration and pattern.

4.3.4. General examination

All subjects undergo a general and neurological standard examination: cranial nerves, muscle balance, coordination, extrapyramidal system, gait, osteotendinous reflexes, midline release reflexes, etc. The following parameters are analyzed in a special way:

- Gait disturbance
- Handwriting
- Instrumental activities of daily living

4.3.5. Neuropsychological Examination

The neuropsychological evaluation allows to explore in a holistic way the various cognitive domains (gnosias, attention, memory, language, praxis and executive functions), as well as a series of variables related to affectivity, behavior and level of autonomy in the daily life of an individual. To do this, the neuropsychologist can use different assessment instruments, including clinical interviews, behavioral observation, cognitive tests and different questionnaires that allow for collecting information from both the individual and a reliable informant.

The Vallecas Project neuropsychological examination protocol has been designed to comprehensively assess neuropsychological functioning of study participants, as well as their progression during the longitudinal follow-up. Specifically, although the neuropsychological battery focuses especially on the evaluation of memory processes, attention and executive functions as potential early markers of Alzheimer's disease, the neuropsychological profile is completed by getting information related to other cognitive domains such as language, visuospatial ability and visuoconstruction. All these data allow identifying the strengths and weaknesses in the cognitive profile and characterizing, if necessary, the type of cognitive impairment that an individual presents. Table below lists the different tests that make up the neuropsychological battery of the Vallecas Project, as well as the visit number in which they have been applied to all study participants:



		VISITAS							
		1	2	3	4	5	6	7	8
Cognitive performance	Reading test to evaluate premorbid intelligence								
	Mini Mental State Examination (MMSE)								
	Clock Drawing Test								
	Free And Cued Selective Reminding Test (FCSRT)								
	Semantic Lexical Evocation (P, M, R)								
	Semantic Verbal Fluency (Animals, Fruits and Vegetables, Kitchen Utensils)								
	Number Key (WAIS-III)								
	Rey-Osterreith Complex Figure Test								
	Forward and reverse digits (WAIS-III)								
	Symbolic gesture and Imitation of bilateral postures (TBR)								
	Rules Change (BADs)								
	Test of the five points								
	Boston Naming Test (BNT-15)								
Cognitive complaints	Interview for the assessment of cognitive complaints								
	Memory Failures in Everyday (MFE)								
Depression and anxiety	Geriatric Depression Scale (GDS-15)								
	State-Trait Anxiety Inventory (STAI)								
Functional scales	Functional Activities Questionnaire (FAQ)								

4.3.6. Determination of biomarkers

It is currently widely accepted that the molecular changes associated with AD, including the formation of amyloid plaques and neurofibrillary tangles begin many years before the appearance of clinical symptoms. In recent years, the need to define and develop new early biomarkers of AD that allow us to assess the risk and early diagnosis of the disease has become clear. Thus, blood sam-

ples will be collected within the Vallecas Project for the study of genetic and biochemical markers. Samples are obtained according to the protocol "Collection and Processing of Human Blood Samples in the Vallecas Project" and processed to obtain the various fractions indicated in the protocol, which are stored at -80°C . On one hand, DNA is extracted from blood cells to determine, by PCR and sequencing techniques, genetic markers associated with the various polymorphisms in the following genes: APOE, CR1, BIN1, CLU, PICALM, ABCA7, SORL1, PRNP, GRM8, and BACE1. These genes are studied using DNA obtained from the extraction of samples from the first visit.

Also, in the context of the project funded by the MINECO (Projects RETOS) entitled "miRNA and lipid metabolism markers as potential links between vascular dysfunction and Alzheimer's pathophysiology", and whose main researchers are Drs. Miguel Medina and Miguel Calero, in collaboration with the group of Dr. Tobias Engel (Royal College of Surgeons, Dublin, Ireland) plasma-derived microRNAs are being analyzed as potential biomarkers, as well as molecules related to vascular dysfunction, lipid metabolism and inflammation: Adiponectin/Acrp30, P-Selectin, ICAM-1, IL-6, MMP-9, Serpin E1/PAI-1, TNF-alpha, VCAM-1, CCL2/MCP-1, IL-1 beta, CXCL8/IL-8, E-Selectin, MMP-3, and CRP. The usefulness of these biomarkers is complementary with the information derived from the study of genetic risk markers already mentioned and can define risk factors already revealed in previous studies.

Samples collected and processed to date are summarized in the table below:

EVALUATION	TOTAL
1 st Visit	1169
2 nd Visit	767
3 rd Visit	755
4 th Visit	699
5 th Visit	663
6 th Visit	447
7 th Visit	314
8 th Visit	131
TOTAL	4945

4.3.7. Neuroimaging Studies

Knowing the morphological variations occurring in brain structure throughout life is essential to assess the corresponding pathological changes that occur in neurodegenerative diseases. In this context, neuroimaging techniques such as magnetic resonance imaging (MRI) have led to significant progress in understanding brain changes associated with age.

MRI is a noninvasive tool that allows the study of normal aging individuals at different moments of his life. However, conventional MRI techniques are unable to detect and quantify age-dependent microstructural changes who have been described in post-mortem studies of brain tissue. Accordingly, the project aims to conduct a series of studies based on various MRI modern techniques that can provide volumetric quantitative indexes of the morphological changes.

In this regard VBM (voxel-based morphometry techniques), based on creating statistical comparisons of gray and white matter patterns are the method of choice in research. The discriminatory power of volumetry in degenerative pathologies such as Alzheimer's disease (volumetric reduction in amygdala, hippocampus, entorhinal cortex, etc.) decreases if age-dependent morphological changes are not well established in control samples, so that it is critical to have large, well quantified samples.

Structural Study (3D volumetry, T2 and FLAIR)

Determining the progressive loss of brain volume during aging, especially in white matter provides volumetric quantitative indexes of the morphological aging-associated changes. In this sense, the VBM (Voxel-Based Morphometry) techniques, based on creating statistical comparisons of gray and white matter patterns constitute the method of choice, and allows us to determine the volume reduction of the amygdala, hippocampus, entorhinal cortex, etc.

Diffusion Study (b: 800)

White matter, partly due to Wallerian degeneration and partly to reduced connectivity by decreased cortical activity, presents ultrastructural changes that can be detected with diffusion techniques (DTI).

Brain Perfusion Study

LCerebral perfusion related to cortical activity may be assessed -without needing to inject contrast-through MR sequences (Arterial Spin Labelling, ASL) and therefore hypofunctioning areas will present decreased perfusion.

Throughout 2015 all Neuroradiology reports from every subject and each of the visits from the 'Vallecas Project' have been incorporated in the single project database. Text reports have been encoded, incorporating each item to the database, as well as attaching the report of each visit in pdf format, enabling viewing and downloading to all researchers who have access to the database.

On the other hand, we have organized MRI data corresponding to the 'Vallecas Project' and Queen Sofia Foundation Alzheimer Center subjects, converting the data obtained directly from MRI equipment into the appropriate format for analysis.

A collaborative project with CESVIMA (Supercomputing and Visualization Center of Madrid), a center from the UPM (Technical University of Madrid) has also been established.

As a result, a VBM analysis of T1 sequences from visits 1 and 2 of the subjects 'Vallecas Project' has been performed. The results of this analysis form the basis of a new project awarded to Dr. Bryan Strange by the Alzheimer's Association ("The healthy elderly brain: MRI predictors for developing MCI"), which has allowed the hiring of a new team member, Dr. Linda Zhang. Dr. Zhang, expert in analysis of structural MR images, has examined the white matter in visit 1 of the subjects of the Vallecas Project.

In 2019, Dr. Linda Zhang continued working on the predictive algorithm in Dr. Jussi Tohka's laboratory at the University of Eastern Finland in Kuopio, Finland, as part of her Queen Sofia Foundation-MAPFRE scholarship. Dr. Tohka is specialized in machine learning and assisted in the validation of the predictive algorithm, both through validation in an internal sample (subjects of the Vallecas Project with mild cognitive impairment-MCI beyond visit 2), as well as in an external sample (subjects with DCL from the ADNI cohort).

Dr. Zhang has also focused on investigating the effects that the $\epsilon 4$ allele of the APOE gene has on the hippocampal volume of cognitively healthy elderly from the Vallecas Project, as this is a genetic risk factor for Alzheimer's disease. These effects were investigated both transversally and longitudinally from visit 1 to visit 5. In addition, she identified subjects carrying the $\epsilon 4$ allele who experienced MCI during the Vallecas Project follow-up and performed a longitudinal analysis between these subjects and a control group with an allelic combination $\epsilon 3/\epsilon 3$ of the APOE gene and who had also developed MCI.

In 2019, Marta Garo Pascual was a recipient of the Queen Sofia Foundation-MAPFRE scholarship. The objective of the scholarship was to further study the superagers population that had been identified the previous year within the Vallecas Project cohort. Superagers respond to people over 80 with an episodic memory at least as good as that of a healthy person in their 50s and 60s.

The first period of the scholarship was dedicated to refining the selection criteria for both the superagers and the control group, extending them from visit 2 to visit 6 of the Vallecas Project. In addition, she studied demographic, lifestyle, and medical factors that may be associated with superaging. The second half of this scholarship was developed at the University Hospital of Jena, Germany, together with Dr. Christian Gaser. During this period, he carried out a cross-sectional and longitudinal structural analysis of superagers and controls, implementing the CAT12 tool that Dr. Gaser himself has developed and for which his help has been essential.



In 2019, Dr Strange was awarded a 'Consolidator Grant' in neuroscience from the European Research Council (ERC). As part of this project, he has launched new functional resonance acquisition sequences to study memory formation in humans

4.3.8. Current status

The Vallecas Project is the main research project conducted at CIEN Foundation, both in terms of resources and social impact. In late 2013, the project completed the recruitment phase and the baseline first visits of volunteers. During 2019, parts of the fifth, sixth and seventh follow-up visits of the project volunteers have been done simultaneously.

VALLECAS PROJECT ACTIVITIES DURING 2019	
Number of sixth visit assessments	38
Number of seventh visit assessments	155
Number of eighth visit assessments	123

The following table shows the status of clinical evaluations conducted to date:

VALLECAS PROJECT CLINICAL EVALUATIONS (OCTOBER 2011-DECEMBER 2019)	
First visit	1,176
Excluded at baseline	47
Second visit	967
Third visit	870
Fourth visit	778
Fifth visit	703
Sixth visit	511
Seventh visit	336
Eighth visit	124
Drop outs	857
Do not comply with inclusion criteria	35
Deceased	38
Diagnosis of neurological disease	59
Volunteer withdrawal	725



INTERNATIONAL RELATIONS

3E



5.1

Introduction

The world population is aging. Improvements in health care in the last century have helped people to have longer and healthier lives. However, this has resulted in an increase in the number of people with age-related diseases, including neurodegenerative diseases. Neurodegenerative diseases are responsible for mitigating states, largely untreated and are closely linked with age. Among these disorders, dementias are responsible for the greatest burden of disease, with Alzheimer's disease and related disorders the causes of impairment of approximately seven million people in Europe. This figure is expected to double every 20 years, as the population ages.

Currently, care and treatment of patients with some form of dementia in Europe accounts for a cost of around 130,000 million euros a year, according to estimates by the Joint Programme of the European Union for Research in Neurodegenerative Diseases (JPND). This comes to show that age-related neurodegenerative disorders are one of the leading medical and social challenges facing our society.

Although primarily affecting older people, dementia is not a normal part of aging. Dementia is a syndrome mainly of chronic or progressive nature, caused by a variety of brain illnesses that affect memory, thinking, behavior and the ability to perform activities of daily life. Dementia is devastating not only for those who suffer from it but also for their caregivers and family. Worldwide, it is one of the leading causes of disability and dependence among the elderly. In most countries somehow there is a lack of awareness and understanding of dementia, causing stigmatization, barriers to diagnosis and care, and impacts on caregivers, family and society, both from the physical as well as psychological and economic point of view.

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.

Supporting research in Alzheimer's disease and related disorders has been and is one of the working priorities of the Queen Sofia Foundation since 2002, the year that promoted the construction of the Queen Sofia Foundation Alzheimer Center (CAFRS, for its acronym in Spanish), and from which it has continued to support the work of the institutions related to this dementia, both financially as well as with the invaluable drive and personal interest of Queen Sofia. In this context, in recent years CIEN Foundation together with the Network Center for Biomedical Research in Neurodegenerative Diseases (CI-BERNED, for its acronym in Spanish) 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 Centers of Excellence in Neurodegeneration (COEN), among other initiatives. These and other internationalization activities carried out during 2018 by CIEN Foundation are detailed below

5.2.

European Union Joint Programming on Neurodegenerative Disease Research (JPND)

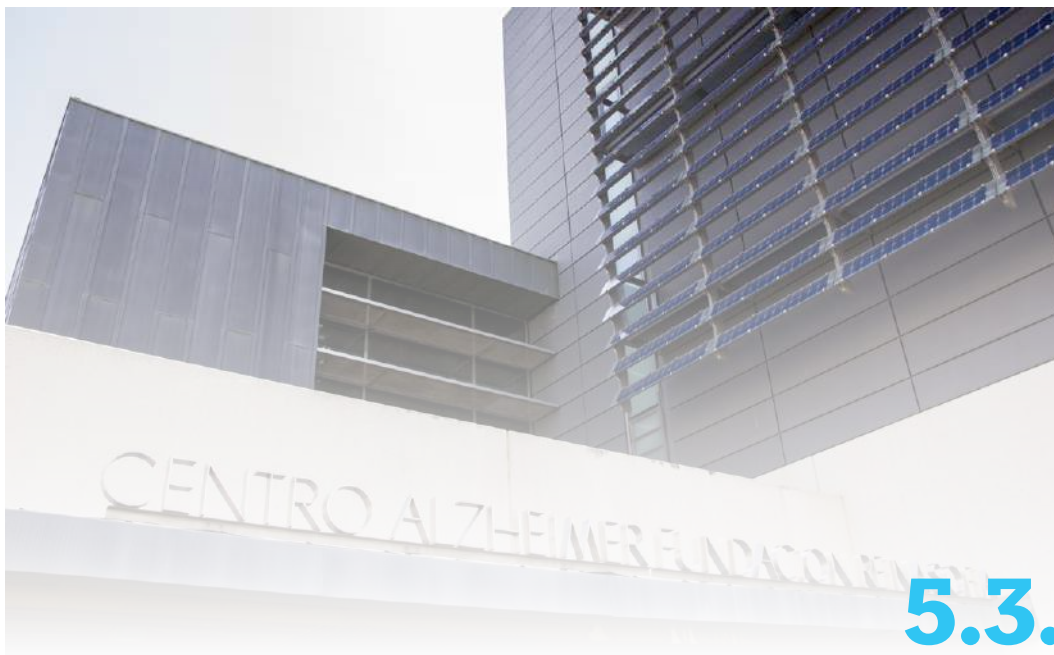
The EU Joint Programming for Research in Neurodegenerative Diseases (JPND) is an innovative collaborative research initiative created to address the growing challenges posed by these disorders. The JPND is a pioneering example of joint programming for the promotion of research within the European Union 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-Mínguez, 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, with participation of the CIEN Foundation in one of them, the DEMTEST Project: "Biomarker based diagnosis of rapid progressive dementias-optimization of diagnostic protocols".



5.3.

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 expertise. Increased collaboration between national centers of excellence should also provide the opportunity to accelerate progress in understanding the basic mechanisms of disease, and the identification of new therapeutic approaches.

To this end, on June 10, 2010, the Canadian Institutes of Health Research (CIHR), the German 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 Neurodegeneration (COEN)". These founding members were later joined by other European institutions 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 Foundation 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 (MESRS), Slovakia
- CIBERNED-Fundación CIEN, Spain
- Agence Nationale de la Recherche (ANR), France

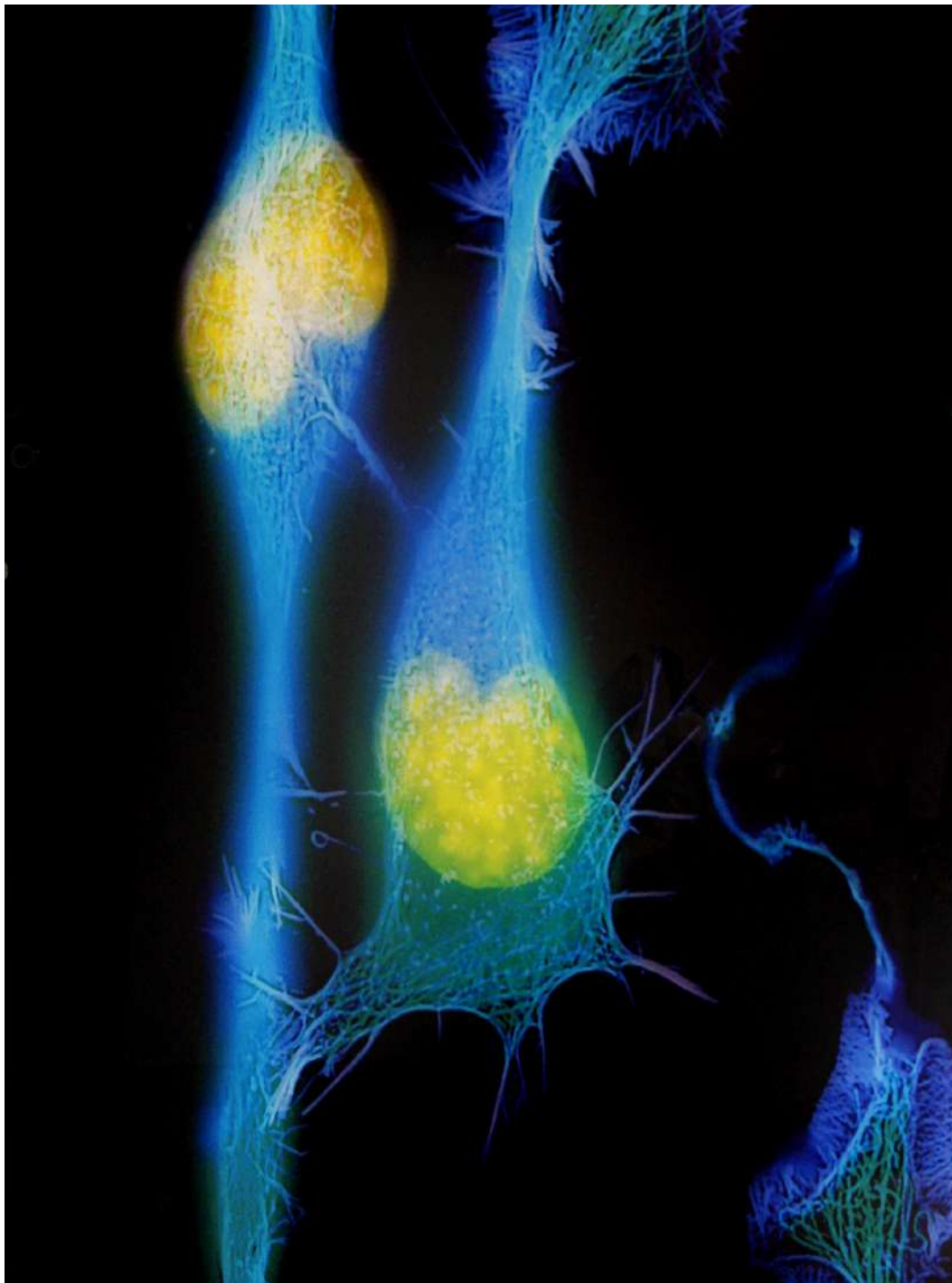
The global objective of this initiative is to create a collaborative research framework in the field of neurodegeneration that transcends national borders, with special emphasis on critical mass and excellence. COEN is aligned with the JPND, although it functions as an independent entity. The overlapping of the members of the COEN group with those of the JPND ensures that their complementary objectives are developed in close cooperation with the rest. This has been carried out through a two-phase process: first conducting expert workshops to determine the scope of the needs, followed by a call for proposals to establish collaborative teams among the PIs assigned to the participating National Centers of Excellence.

The first phase of the COEN initiative began at the end of 2010 and was intended to establish 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 launch of the 1st call for projects called "Pathfinder." In the years 2015 and 2017, the subsequent 2nd and 3rd calls were launched, whereas the 4th call was launched during 2019.

These calls for "Pathfinder" research projects aim to catalyze collaborative research between the different centers with a critical mass of resources and knowledge to drive a radical change in research in the field of neurodegeneration. Pathfinder project calls aim to encourage the scientific community to think outside the pre-established frameworks, to stimulate new unconventional approaches and thus reach creative solutions to the challenges of neurodegeneration research, carrying out high-risk/high-reward projects and welcoming unconventional and innovative applications.

The scientific scope of the "Pathfinder" projects is very broad and applications may include studies to improve our understanding of neurodegenerative mechanisms or create technological advances to support new diagnostic or therapeutic approaches. Joint nominations of researchers from identified Centers of Excellence are invited, and projects must include researchers from two or more countries. The projects address issues that would not be easily funded through the standard grant mechanisms of COEN partners, and it is expected that, in addition to collaborations between Centers of Excellence, the projects will also serve to provide a platform for future collaboration with the industry.



5.4.

International Congress for Research and Innovation in Neurodegenerative Diseases (CIIEN)

During 17th to 20st September 2019, it was held in Valencia, Spain the VII 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 seventh edition of CIIEN was held at the Santiago Grisolia Auditorium in the Principe Felipe Science Museum 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 VII 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 speakers included world leaders such as Agneta Nordberg (Karolinska Institute, Sweden), who in her Opening Lecture spoke about the importance of early diagnosis for the development of new treatments and preventive therapies. It also had the participation of Hilal Lashuel (Federal Polytechnic School of Lausanne, Switzerland), who presented his discoveries in the process of the formation of Lewy bodies in the formation of Parkinson's, or Jorge J. Palop (Gladstone Institute of Neurological Diseases of San Francisco, Unit-



ed States), whose presentation centered around network alterations and interneuronal dysfunction in Alzheimer's.

In addition to the intervention of the Scientific Director of CIEN Foundation and CIBERNED, Jesús Ávila, the Congress had internationally recognized Spanish speakers, including Jordi Pérez-Tur and Isabel Fariñas (University of Valencia), Rosario Osta (University of Zaragoza), or Abraham Acevedo (University Hospital of the Canary Islands, Tenerife).

Likewise, and responding to the vocation to promote the training of young researchers of CIBERNED, the Young Researcher and the Young Clinical Researcher Awards were awarded during the congress to Alberto Parras (University of Lausanne, Switzerland) and Raul Martinez (CINAC, HM Foundation and San Pablo CEU University), respectively, who presented the studies for which they have 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.

For more information about this and other events in which the CIEN Foundation has participated during 2019, please check Section 7 of this Report.

5.5.

Other international activities

5.5.1. H2020: MARIE SKŁODOWSKA-CURIE ACTIONS (MSCA): INNOVATIVE TRAINING NETWORKS (ITN)

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. The CIEN Foundation actively participates as Associated Partner in the following ITN:

Targeting the purinergic P2X7 receptor to treat Alzheimer's disease

Brain disorders affect some 180 million people and their families in Europe alone, with an annual cost to the taxpayer estimated at 800 billion €, an economic burden greater than cardiovascular disease and cancer combined. Despite diverse etiologies, the overlap in clinical symptoms and comorbidities among brain disorders suggests shared pathogenic mechanisms. In particular, hyperexcitable states driven by glial activation and neuroinflammation appear almost ubiquitous in these disorders. With advances in understanding the function of the purinergic ionotropic P2X7 receptor (P2X7R), the highly promising effects demonstrated by its antagonists in models of brain disease, and the large investment in P2X7R-related drug development programs, now is the perfect time to pool resources. Studying these mechanisms offers the potential to improve symptoms and reverse dis-



ease progression in a wide range of brain disorders. Through its role in regulating neuroinflammation and the mechanistic link between neuronal hyperexcitability and glial activation, P2X7R with ATP is one of the most promising molecular targets for pharmacological intervention in the neuroinflammation-hyperexcitability pathway. PurinesDX brings together world leaders in translational research on purinergic signaling, leading European clinical specialists in a wide range of neurological diseases and industry partners specialized in drug and biomarker development. The ability to share unique genetic tools, newly developed diagnostic devices and novel, selective and stable P2X7R antagonists in the brain, along with the synergy facilitated by the PurinesDX consortium will be extended to the training of a new generation of highly skilled, innovative scientists, creative and entrepreneurs that are urgently needed. Along with the provision of this interdisciplinary, international and cross-sector environment, original and high-level training in cutting-edge neuroscience will be provided, nurturing a highly competitive cohort of researchers with the potential to drive a new era of neuroscience research.

Caterina Di Lauro, is a biomedical PhD student at the Complutense University of Madrid and part of the PurinesDX program, an innovative MSCA training network focused on understanding the role of the P2X7 purinergic receptor in a variety of brain disorders, including neurodegenerative diseases and psychiatric disorders. Her project focuses on studying the role of P2X7R in Alzheimer's disease and its potential as a pharmacological target to improve this pathological condition.

As part of her doctoral training, Di Lauro completed a clinical assignment at the CIEN Foundation in 2019 under the supervision of Dr. Miguel Medina. During the time he spent at the Center, she had the opportunity to follow one by one, all the steps of the Vallecas Project.

First, she joined the neurologists and neuropsychologists in evaluating the volunteers. This showed her how to carry out and interpret the various protocols aimed at obtaining a complete evaluation of the cognitive domains, as well as the behavioral variables of the individuals.

Subsequently, she observed the acquisition and analysis of brain images through neuroimaging techniques, a very powerful tool to assess the connection between brain morphological changes and cognitive dysfunctions associated with neurodegenerative diseases.

Finally, she had the opportunity to visit the CIEN Tissue Bank and follow Dr. Alberto Rábano in the collection, processing, classification and diagnosis of human brain samples. In addition, she was able to benefit from the service that BT-CIEN offers to researchers who request it: the possibility of obtaining brain samples, in this case, from patients with Alzheimer's and Pick's disease for her research project.

In the words of Di Lauro herself, "following the Vallecas Project has been very useful to me because it has allowed me to better understand the aspects of Alzheimer's disease in human patients and have a clearer idea about the parameters to be considered and evaluated in the study of this disease when using mouse models".



For more information you can go to the PurinesDX program website: <http://purinesdx.eu/>

In relation to this program, during 2019 the CIEN Foundation has organized the following event at its headquarters:

FCIEN-PurinesDX Symposium: Clinical techniques and challenges in patient treatment

The CIEN Foundation and the ITN Marie Skłodowska-Curie PurinesDX have organized the Symposium "Clinical techniques and challenges in patient treatment", which was held on October 24 and 25 at the Queen Sofia Foundation Alzheimer Center in Madrid. During the symposium, the importance of the confluence of basic, translational and clinical research was emphasized, in order to promote the translation of new scientific findings in therapeutic advances.

Through eight lectures and two practical workshops (brain magnetic resonance and neuropathological diagnosis), speakers from the CIEN Foundation, CIBERNED, the ISCIII or the San Carlos Clinical Hospital, among other institutions, provided participants with an understanding of some of the most relevant clinical challenges in brain disorders, as well as the most innovative techniques that are being developed for the treatment of these diseases.

To see the full program, you can visit our website:

https://www.fundacioncien.es/media/58355/diptic_fcien-purinesdx-symposium_web_fv.pdf



**SCIENTIFIC
PRODUCTIVITY**

6

6.1.

Bibliometric analysis

The CIEN Foundation maintains a strong commitment to the development of research, as well as to generate and promote scientific knowledge in improving the diagnosis and treatment of neurodegenerative diseases both within and outside our borders. Translating to society and the scientific community the progress made in the knowledge about neurological diseases in general, and about Alzheimer's disease in particular, is a fundamental task.

The scientific production of the CIEN Foundation researchers during 2019 has reached a total of 20 publications, of which 25 have been published in nationally and internationally recognized scientific journals (23 original articles and two reviews), one book and one book chapter.

The analysis of these publications has allowed studying, through a series of quantitative indicators, both the CIEN Foundation scientific activity as the production, subject, and degree of collaboration and impact of scientific publications. Through this analysis we can note, for instance, that the average impact factor of publications within the first and second quartiles has gone from 5.074 in 2018 up to 8.326 in 2019, an 39.06% increase over the previous year.

In addition, during this year the CIEN Foundation has continued its national and international collaborations, so that 44% of the articles corresponded to studies carried out in collaboration with international institutions, 72.22% with Spanish ones, and the remaining 5.56% were performed exclusively by CIEN Foundation researchers. Also noteworthy is the high proportion of collaborative publications with other CIBERS and research networks in the first and second quartiles (50%).

The following table shows output indicators of production (number of publications), quality (publications in journals ranked within the first and second quartile

of their subject category), impact (determined by the accumulated and average impact factor of the journals in which it has been published) and degree of collaboration at national and international level.

2019 INDICATORS	
Total number of publications	20
Number of publications in scientific journals	20
Total number of publications in the ISI citation index within the first and second quartile	18
Cumulative impact factor of publications within the first and second quartile	149,87
Average impact factor of the publications of the first and second quartile	8,326
Number of collaborative publications of all kinds (CIBERNED, other national groups, international groups) within the first and second quartile	17
Number of international collaborative publications within the first and second quartile	8
Number of national collaborative publications within the first and second quartile	13
Number of collaborative publications with other CIBERs and networks within the first and second quartile	9

In summary, during 2019 the CIEN Foundation researchers have published 20 scientific papers, of which 19 (95%) have been in journals included in the Journal Citation Report (JCR), accessible through the Web of Science portal (WoS, Clarivate Analytics) and 18 (90%) have been published in journals ranked within the first and second quartile in their category. Considering the type of document, 90% of the publications in scientific journals (18) correspond to original articles.

Moreover, according to their scientific subject category 55.56% of the publications within the first and second quartiles have focused on the following categories: Neurosciences, Clinical Neurology, Multidisciplinary Sciences, and Geriatrics and Gerontology.

With regards to scientific dissemination activities in meetings and national and international events during the year 2019, there have been a total of 29 participations at scientific conferences, 23 of which correspond to lectures and oral presentations, and 6 correspond to written communications in the form of posters. These communications have been presented at national (19) and international scientific conferences and meetings (10).

6.2.

Publications

References of the 20 scientific publications from CIEN Foundation scientists are listed below according to type of publication: 20 publications in scientific journals (18 original articles and two reviews).

6.2.1. Journal articles

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Number of publications by subject category in 2019

Neurosciences	6
Multidisciplinary Sciences	4
Clinical Neurology	1
Behavioral Sciences	1
Biochemical Research Methods	1
Biochemistry & Molecular Biology	1
Cell Biology	1
Genetics & Heredity	1
Medicine, Research & Experimental	1
Pharmacology & Pharmacy	1

6.2.2. Communications to Conferences

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6.3.

CIEN Foundation Seminar Series

The CIEN Foundation has organized this Seminar Series since the beginning of 2015, in which, every Monday afternoon, speakers from both the Foundation and guests from other related institutions, present their work and then the issues are debated. The following are the seminars developed in our Alzheimer Center of Vallecas during 2019:

- January 14 - Dr. Alberto Rábano (Head of Neuropathology and Director of the CIEN Foundation Tissue Bank): "Amygdala-predominant Lewy pathology: background, materials and methods for a project".
- January 28 - Prof. Jesús Ávila (Scientific Director, CIEN Foundation -CIBERNED): "The Vallecas project"
- February 4 - Dr. Miguel Medina, Deputy Scientific Director of CIBERNED, PI Vallecas project: "Update on biomarker studies in the Vallecas Project"
- February 11 - Dr. Teodoro del Ser (Coordinator, Neurology Area CIEN Foundation): "What cognitive reserve is?"
- February 18 - Prof. Bryan Strange (responsable del Dpto. de Neuroimagen de la Fundación CIEN): "Memory loss and memory preservation in Vallecas"
- February 25 - Dr. Miguel Ángel Fernández, coordinator of the CIEN Foundation Neuropsychology Department: "Longevity Research Program Spain-Portugal +90 (PILEP + 90)"
- March 11 - Dr. Miguel Calero, coordinador del departamento de Biología Molecular de la Fundación CIEN: "Molecular basis of neurodegenerative diseases"
- April 1 - Dr. José María Galván (La Princesa Biomedical Research Institute; Internal Medicine Service; University Hospital of the Princess): "Down Syndrome"
- April 8 de - Dr. Alberto Rábano (Head of Neuropathology at CIEN Foundation and Director of the CIEN Tissue Bank) and Valentina González (biologist, quality and special samples program in the Area of Neuropathology at CIEN Foundation): "A new tauopathy in a new context. ARTAG associated with frontotemporal lobar degeneration due to a new GRN mutation "
- April 29 - Belén Frades, neuropsychologist at CIEN Foundation: " Characterization of language and executive functions in volunteers with MCI from the Vallecas project "
- May 20 - Jesús Ávila, Scientific Director at CIEN Foundation and CIBERNED: " Neuronal Regeneration "
- June 17 - Kimberly Bress, Predoctoral Fellow, Fullbright Grant (Institute of International Education), at CIEN Foundation: "Pathological gradients along the longitudinal axis of the human hippocampus in Alzheimer's Disease".



6.4.

Funded projects

During 2019 the CIEN Foundation researchers have participated in five scientific research projects granted through various national and international competitive calls and funded by different institutions as well as in two research service provisions.

Funded research projects are cited below:

- **Code: Vallecas 2**

Principal Investigator: Dr. Miguel Medina

Title: Vallecas 2 – Early detection of Alzheimer's disease. Risk and protection factors

Funding agency: Queen Sofia Foundation

Duration: 2018-2021

Budget 2018-2019: 600,000 € (The Queen Sofia Foundation undertakes to contribute during each of the 4 years of planned duration of the project, the successive amounts that are agreed annually by its Board of Trustees, corresponding to the first two years a total amount of six hundred thousand euros (300,000 in 2018 and 300.000 in 2019).

In February 2018, a new collaboration agreement was signed with the Queen Sofia Foundation, with an expected duration of 4 years. This agreement governs the framework of cooperation to carry out the research oriented to the identification of individuals with greater risk of developing Alzheimer's type dementia (AD) within the project called "Vallecas 2, early detection of Alzheimer's disease. Risk and protection factors".

- **Code: RTI2018-098762-A-C32**

Principal Investigator: Dr. Miguel Ángel Fernández

Title: Antecedentes familiares de enfermedad de Alzheimer en personas mayores: influencia del deterioro cognitivo subjetivo. (CONNECT-AD)

Funding agency: Ministerio de Ciencia, Innovación y Universidades

Duration: 2019-2022

Total budget: 108.900 €

2018 budget: 52.272,00€

2019 budget: 10.890,00 €

2020 budget: 45.738,00 €

CALL: Resolution of the Secretary of State for Universities, Research, Development and Innovation and the Presidency of the State Research Agency, approving the call for early processing for the year 2018 of the procedure for allocating grants to R&D&i Projects on «Research Challenges» corresponding to the State Program of R&D&i Oriented to the Challenges of Society, within the framework of the State Plan for Scientific and Technical Research and Innovation 2017-2020.

- **Code: PT17/0014/0015**

Principal Investigator: Dr. Alberto Rábano

Title: Biobanks Platform

Funding agency: Carlos III Institute of Health

Duration: 2018-2020

Total budget: 135,300 €

2018 budget: 45,100 €

2019 budget: 45,100 €

Call for the year 2017 of grants within the Strategic Health Action 2013-2016. These grants are co-funded by the European Regional Development Fund, Intelligent Growth Operational Program 2014-2020

- **PEJ16/MED/AI-1963**

Principal Investigator: Dr. Alberto Rábano

Title: Grants for hiring research assistants and laboratory technicians.

Funding agency: Council of Education, Youth and Sports, Region of Madrid

Duration: 2017-2019

Total budget: 45,000 €

Call for grants to hire research assistants and laboratory technicians through the Youth Employment Operational Program and the Youth Employment Initiative (YEI) (2016). These grants will be co-funded by the European Social Fund (FSE, for its acronym in Spanish) through the Youth Employment Operational Program. In February 2018, the execution of the 2nd annuity of the awarded grant within the framework of the 2016 call for the execution of contracts for research assistants and laboratory technicians begins, which will be valid until July 2019.

- **PEJ-2017-TL-BMD**

Principal Investigator: Dr. Alberto Rábano

Title: Grants for hiring research assistants and laboratory technicians.

Funding agency: Council of Education, Youth and Sports, Region of Madrid

Duration: 2018-2020



Total budget: 38,000 €

2018 budget: 19,000 €

2019 budget: 19,000 €

Call for grants to hire research assistants and laboratory technicians through the Youth Employment Operational Program and the Youth Employment Initiative (YEI) (2017). These grants will be co-funded by the European Social Fund (FSE, for its acronym in Spanish) through the Youth Employment Operational Program.

SERVICE PROVISIONS / RESEARCH SERVICES

- **Code: MDS-NMS_ Rating Scales Program**

Principal Investigator: Dr. Pablo Martínez

Title: MDS-NMS_ Rating Scales Program

Funding agency: International Parkinson and Movement Disorders Society

Duration: 2017-2019

Total budget: 75,000 €

- **Contract for the provision of services and use of facilities between the Center for Research in Neurologic Diseases Foundation and BIOCROSS, S.L.**

Principal Investigators: Miguel Calero / Matt Mittino

Title: Development of an early non-invasive Alzheimer's diagnostic test: development of a new biomarker of high sensitivity and specificity for the early determination of Alzheimer's disease through molecular analysis of β -amyloid peptides in biological fluids.

Funding entity: Biocross SL

2019 budget: 9407.75 €

In December 2018, two contracts were signed for the provision of multidisciplinary research services on aging within the framework of the International Center on Aging Project (CENIE) that have been launched during 2019:

- **Project Code 0348_CIE_6_E**

Funding agency: University of Salamanca General Foundation (FGUSAL)

Call: International Center on Aging Project (CENIE)

Code: PILEP +90

Title: Factors associated with healthy and pathological aging in the sample of people over 90 years of the city of Madrid "

Principal Investigator: Miguel Ángel Fernández-Blázquez

Starting date January 1, 2019

End date: December 31, 2019

Budget: 39,875 € (VAT excluded)



- **Project Code 0348_CIE_6_E**

Funding agency: University of Salamanca General Foundation (FGUSAL)

Call: International Center on Aging Project (CENIE)

Code: ImageH

Title: Application of data mining techniques for the identification of factors of healthy and pathological aging (ImageH)

Principal Investigator: Jaime D. Gómez Ramírez

Starting date January 1, 2019

End date: December 31, 2019

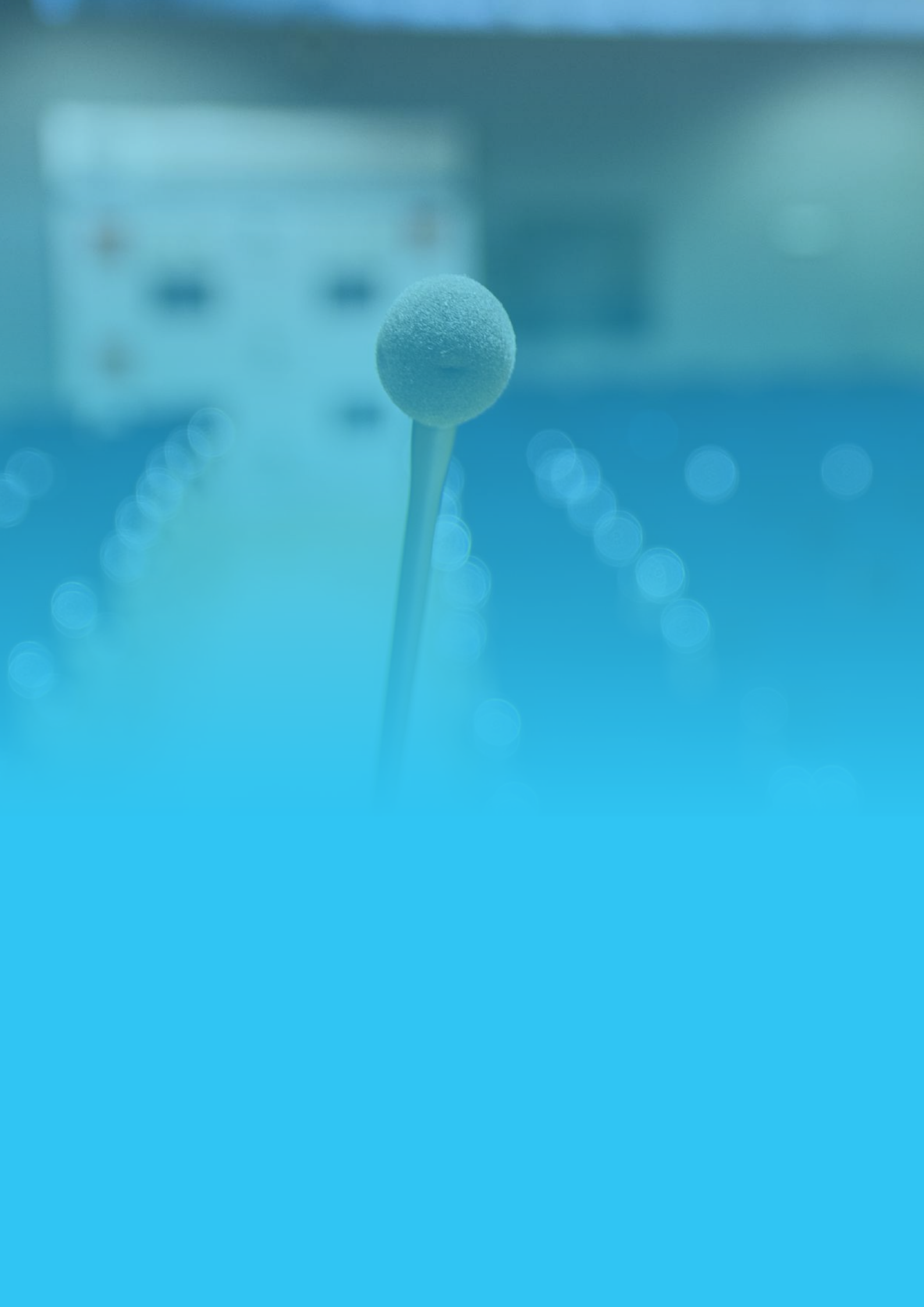
Budget: 33,000 € (VAT excluded)

6.5.

Patents

During 2019 one patent applications remain active at national and international stages, which have currently a co-ownership agreement with participation of CIEN Foundation and a licensing agreement with Raman Health Technologies:

- Inventors: **Pablo Martínez Martín**, Pedro Carmona Hernández, Adolfo Toledano Gasca, **Miguel Calero Lara**, Félix Bermejo Pareja, Marina Molina Santos.
Title: Raman analysis, infrared or Raman-infrared of plasma protein structure from peripheral blood and its relationship to the cognitive development in Alzheimer's disease.
Registration N°: EP123823304 PCT/EP/2013/067304.
Application date: 20/08/2012.
Type: National/European.
Licensing agreement Raman Health Technologies.



**DISSEMINATION
ACTIVITIES**





7.1

Dissemination activities

One of the founding goals of the CIEN Foundation is to translate to society in an easy and accessible manner the advances and progress made in the research in neurological diseases.

In this sense, the CIEN Foundation department heads have organized, as every year, various activities that allow the dissemination of the research work carried out by its professionals. This allows them to bring the scientific field to society in a kinder way, while translating results and relevant information on the various neurological diseases under study. During 2019 the CIEN Foundation has continued to develop dissemination actions of different types, among which we highlight the following.

Educational talks

With the aim of contributing to the welfare of society, from the CIEN Foundation, we want to raise awareness, through the translation of a series of fundamental aspects in the fight against Alzheimer's disease, of the importance of its prevention, the value of donation of tissues for research, or the latest achievements obtained from the study of this condition.

That is why CIEN Foundation professionals, in addition to communications of a purely scientific nature in congresses or seminars, annually schedule informative talks in hospitals, nursing homes or other institutions in different parts of the Spanish geography. A good example of this is the conference that Dr. Miguel Ángel Fernández, head of the Neuropsychology Area, and Dr. Marina Ávila, neuropsychologist at the CIEN Foundation, organized and gave on April 8 at the Carlos III University of Madrid. "Latest advances in Alzheimer's disease research", which was attended by many people, mostly students from the UC3M University for the

Elderly, who, after the presentation, were able to clarify and discuss some issues with the neuropsychologists.

Regarding donations, Dr. Alberto Rábano, director of the Tissue Bank and head of the CIEN Foundation's Neuropathology Area, continues to promote the work carried out at BT-CIEN. Proof of this is that on September 11, he participated in the round table "Brain donation. Why and what for ", an event organized by the Foundation for a Tomorrow without Alzheimer's at the León Unicaja Assembly Hall. In his intervention, Dr. Rábano explained that currently brain banks "have found their place, being one more type of biobank such as the blood ones." And it is that, "brains contribute something very important such as human disease, research in recent years has been based on animal models, so the researchers have seen that they only partially reproduce the human situation". Some of the leading experts on brain donation in Spain, such as Ana Cuesta, director of the León University healthcare Complex Biobank, and Javier Herrero, scientific director of the Castilla y León Institute of Neuroscience Neurological Tissue Bank. In addition, Dr. Rábano emphasized the work of family members, who "have been key in spreading the donation programs" and have helped reinforce the work of the biobanks.

Meetings with Associations of relatives of Alzheimer's patients and other neurodegenerative disorders

During 2019, CIEN Foundation organized and participated in a series of meetings with associations of relatives of Alzheimer's and other neurodegenerative disorders patients, developing joint actions to disseminate advances in the Foundation research activities.

An example of this is the celebration on the occasion of World Parkinson's Day on April 11, of a dissemination session on this disease, organized by the CIEN Foundation, CIBERNED (including its representative research group in Galicia, the Neurobiology Group Cellular and Molecular of Parkinson's Disease from the University of Santiago de Compostela) and the patient associations of Santiago de Compostela (ASPAC) and Vigo (PARKVIGO), which took place in the Galician capital.

The objective of the session was to contribute to making visible the real impact of Parkinson's disease in the population and to inform, especially patients and their families, about the disease and current advances in its treatment. To know first-hand its social and emotional impact, representatives of the patient associations participated, who showed the work of this type of associations. A fundamental task in the day-to-day life of patients, but also their families. In addition, the attendees were able to enjoy the performance of the Parkinson Canta choir, from the Vigo Parkinson Association.

The event was attended by the mayor of the city, Martiño Noriega, representatives of the Department of Health and the University of Santiago de Compostela, patient associations, M^a Ángeles Pérez, managing director of the CIEN Foundation and CIBERNED, as well as Prof José Luis Labandeira García, who leads the repre-

sentative research group of CIBERNED in Galicia, whose research focuses on Parkinson's disease and its treatment.

The event included five presentations in which Parkinson's disease was approached from different perspectives. The speakers were: Professor José Luis Labandeira and researchers Ángel Sesar from the University Hospital of Santiago de Compostela, Diego Santos from the University Hospital of La Coruña, and Carmen Labandeira, from the Álvaro Cunqueiro University Hospital in Vigo.



Queen Sofia Foundation – MAPFRE Foundation Scholarships Award Ceremony

Her Majesty Queen Sofia and Antonio Huertas, president of MAPFRE Foundation, awarded two research grants to young scientists in the field of neurodegenerative diseases, within the framework of a meeting held at the Queen Sofia Foundation Alzheimer Center, on occasion of the commemoration of the 10 years of the program resulting from the collaboration between the two institutions and CIEN Foundation. Since its creation, more than a decade ago, the Queen Sofia Foundation – MAPFRE Foundation program has supported more than 10 applied clinical research and scientific training projects at an international level through financial contributions worth over 350,000 euros. The grants are awarded to young researchers in biomedical specialties, aimed towards applied clinical research in neurodegenerative diseases and early diagnosis of dementia and Alzheimer's disease. With an annual endowment of 32,000 euros and strict evaluation criteria, the scholarship has allowed young Spanish neuroscientists to consolidate their academic and scientific training in world-renowned centers. On this occasion, scholarships were formally awarded to Linda Zhang, a psychologist specializing in human biology and PhD in Diagnostic Radiology, who will carry out her stay at the University of Eastern Finland, and to Marta Garo Pascual, a biologist and neuro-

scientist, who will spend six months at the University Hospital of Jena in Germany. The award ceremony was also attended by M^a Ángeles Pérez, manager of the CIEN Foundation, José Luis Nogueira, secretary of the Queen Sofia Foundation, María Dolores Moreno, counselor for Social and Family Policies from the Region of Madrid, and Carlos González, general director of Attention to the Dependency and the Elderly.

During the award ceremony for the program grants, it was also announced the declaration of research on neurodegenerative diseases as an event of exceptional public interest for the years 2019 and 2020. The event "Neurodegenerative Diseases 2020. International Year of Research and Innovation "(Neuro 2020), promoted by the Queen Sofia Foundation and the CIEN Foundation, aims to raise public awareness of the importance of promoting research in neurodegenerative diseases, promoting fundraising activities to fund a series of initiatives , dissemination actions and applied research projects.

VII International Conference on Research and Innovation in Neurodegenerative Diseases

Coinciding with the week that World Alzheimer's Day is celebrated worldwide, the VI International Conference on Research and Innovation in Neurodegenerative Diseases – CIIEN - was held in Valencia, which gathered more than 100 international experts with the aim of sharing the latest advances in Alzheimer's research and other neurodegenerative diseases such as Parkinson's, ALS or Huntington's. Together with H.M. Queen Sofia, participated in the inauguration of the CIIEN Ximo Puig, president of the Generalitat of Valencia; Pedro Duque, Minister of Science, Innovation and Universities; Ana I. Lima Fernández, Secretary of State for Social Services; and the mayor of Valencia, Joan Ribó.

The Congress was held from September 17 to 20, at the Príncipe Felipe Science Museum, whose Santiago Grisolia auditorium hosted the opening ceremony and



plenary sessions. As has been customary in recent years, within the framework of the VII International Congress on Research and Innovation in Neurodegenerative Diseases (CIIIEN), on September 17, the symposium "Social and health research in Alzheimer's disease and other dementias" again had its space, organized by the State Reference Center for the care of people with Alzheimer's disease and other dementias of the IMSERSO (CRE Alzheimer), together with the Spanish Confederation of Associations of Alzheimer's Relatives (CEAFA), and with the support of the Queen Sofia Foundation. Alfonso J. Cruz-Jentoft, Head of the Geriatrics Service of the Ramón y Cajal Hospital in Madrid, was in charge of delivering the plenary lecture. This edition also included the intervention of several entities related to other neurodegenerative diseases, such as the Spanish Parkinson's Federation, the Spanish Association for Huntington's Korea and the Spanish Association for Amyotrophic Lateral Sclerosis, who shared their views on the future of the research social and health in this type of disease.

From the 18 th to 20th the Congress scientific program took place, organized in this case by the Queen Sofia Foundation, the CIEN Foundation (Center for Research of Neurological Diseases Foundation) and CIBERNED (Network Center for Biomedical Research in Neurodegenerative Diseases). The VII The CIIIEN Congress had world leading experts such as Agneta Nordberg (Karolinska Institute, Sweden), whose opening lecture focused on the importance of early diagnosis for the development of new treatments and preventive therapies. It also had the participation of Hilar Lashuel (Federal Polytechnic School of Lausanne, Switzerland), who presented his discoveries in the process of formation of Lewy bodies in Parkinson's or Jorge J. Palop (Gladstone Institute of Neurological Diseases of San Francisco, United States), whose presentation revolved around network alterations and interneuronal dysfunction in Alzheimer's.

In addition to the intervention of CIBERNED scientific director, Jesús Ávila, the Congress had other Spanish speakers of international prestige, among them Jordi Pérez-Tur and Isabel Fariñas (University of Valencia), Rosario Osta (University of Zaragoza), or Abraham Acevedo (University Hospital of the Canary Islands, Tenerife). Researchers Alberto Parras (University of Lausanne, Switzerland) and Raúl Martínez (HM CINAC Foundation and San Pablo CEU University) received the Young Researcher Awards and presented their respective research works for which they were awarded.

The Congress was held within the framework of the event of exceptional public interest, as stated in the General State Budget for 2018, "Neurodegenerative Diseases 2020. International Year of Research and Innovation." This event, which will be named as Neuro 2020, has been promoted by the Queen Sofia Foundation and the Center for Research in Neurodegenerative Diseases Foundation, and is aimed at raising public awareness on the importance of promoting research in neurodegenerative diseases to advance in our knowledge of the origin of its causes



Vallecas Project Volunteer's Day

The Queen Sofia Foundation and the CIEN (Neurological Diseases Research Center) Foundation, with the collaboration of the RTVE Orchestra and Choir, held on June 1 the seventh edition of the Vallecas Project Volunteer's Day. The Monumental Theater of Madrid hosted this tribute, in which the piece *Carmina Burana*, by the German composer Carl Orff, was performed by the public television Choir and Orchestra, and continued with the participation of the magician Andrés Madruga.

The journalist Irma Soriano presented the event, which was attended by the volunteers who make the Vallecas Project possible. José Luis Nogueira, secretary of the Queen Sofia Foundation, and M^a Ángeles Pérez, manager of the CIEN Foundation, welcomed the attendees and thanked the volunteers for their selfless contribution in favor of scientific research. José Luis Nogueira highlighted the "valuable contribution to science made by the project volunteers" and how "this type of action, which is social and scientific at the same time, makes it possible to progressively advance towards a solution for the disease." Along the same lines, the CIEN Foundation manager wanted to emphasize the importance of Alzheimer's research, which "would not be possible without the generosity of the volunteers who participate in this type of initiatives. The time they dedicate to us is invaluable, because it is time earned for science and research".

The journalist Irma Soriano, in charge of leading the event, stressed the importance of the contribution and selfless commitment of the volunteers, as well as the effort that both Foundations dedicate to the initiative: "we are proud of this collaboration between scientists and volunteers and of projects like this, which combine science and conscience". After the initial performance of the magician Andrés Madruga, the RTVE Orchestra and Choir performed the piece *Carmina Burana*, composed by Orff between 1935 and 1936, and which uses as its text some of the medieval poems in Middle German, Latin and Old Provençal. It is a work of great musical color that praises vital enjoyment and happiness as a basic value.

II Neuroscientists Women Today: Sowing Referents

The General Assembly of the United Nations approved in December 2015 a Resolution proclaiming on February 11 of each year the International Day of Women and Girls in Science with the purpose, according to the text, to promote through education and public awareness activities the full and equal participation of women and girls in education, recruitment, employment and decision-making processes in science. That is why the CIEN Foundation and CIBERNED, together with the Apadrina la Ciencia association, decided to organize the II Conference "Neuroscientists Today: sowing references". M^ª Ángeles Pérez, manager of the CIEN Foundation, presented the conference, during which the three organizing institutions proposed various activities to disseminate science and research in neurodegenerative diseases: the conferences "Altamira has a woman's name and also a mathematical one", by Prof. Francisco González Redondo from the UCM and "Animal Models of Alzheimer's disease" by Dr. Isabel Lastres-Becker, from CIBERNED. To bring the people who attended the research work closer together, a series of workshops were held by Drs. Rosario Fernández and Inés Antón, from Apadrina la Ciencia, Dr. Miguel Medina, CIBERNED Deputy Scientific Director, and Eva Alfayate, radiodiagnosis technician at the CIEN Foundation Neuroimaging department.

To close the day, the attendees, mostly students, had the opportunity to participate in the session "Ask a scientist", in which several researchers from the CIEN Foundation, CIBERNED and Apadrina la Ciencia, answered to the questions raised, with the aim of eliminating the still prevalent stereotypes and showing real references to other scientists, present and future.



The CIEN Foundation in the Brain Spanish Council

The Spanish Brain Council (CEC, for its acronym in Spanish), was founded in 2009 as a non-governmental organization that brings together scientific societies, patient associations and industry, with the main objective of promoting

brain research in Spain and thus expanding the knowledge of the functioning of the healthy brain, its diseases and their social impact. The CIEN Foundation is one of its founding members and participates as a Secretariat in its Board of Directors since November 2013. The CEC performs these tasks in permanent contact with the European Brain Council (EBC), participating in turn as a member observer in the Academy of the European Brain Council and as an alternate member of the representation of the Academy in the EBC General Assembly.

In 2019 the CEC has participated in the following activities:

- **Brain Awareness Week:** olfaction in Parkinson's disease, organized by the Spanish Brain Council, together with the Spanish Parkinson's Federation, the Cajal Institute-CSIC and the Spanish Olfactory Network. It took place on March 12 at the Cajal Institute and featured presentations by research professionals, both basic and applied, a practical olfaction workshop and a visit to the facilities where these research is carried out.
- **Proyecto Share4Brain: a European Erasmus+ project.** The Erasmus+ project, entitled "Sharing good practices for brain education in Europe" (Share4Brain), in which the CEC has participated since its inception in 2019, is aimed at the awareness of the academic and general public, as well as the relevant public institutions, on the importance of developing basic and clinical research in neuroscience to guarantee a better prevention, diagnosis and treatment of neurological and psychiatric disorders. The Share4Brain project aims to bring together patients, brain researchers, scientists, physicians, and caregivers and provide them with the skills and knowledge necessary to promote brain research and raise awareness about the social impact of brain diseases.
- **Publication of the document "Ten priorities for national brain and mental health plans".** . The European Brain Council, together with the National Brain Councils of France, Spain, Belgium and Serbia, has prepared this text with the aim of promoting Brain research. Bibliography: Croat Med J. 2019; 60: 152-5. <https://doi.org/10.3325/cmj.2019.60.152>.

Media campaigns

Neuro 2020: "Neurodegenerative Diseases 2020. International Year of Research and Innovation"

This year the meetings of the Governing Commission of the event of exceptional public interest "Neurodegenerative Diseases 2020. International Year of Research and Innovation", established in March 2019, have been launched in order to comply with the provisions of the Ninety-seventh additional provision of Law 6/2018, of July 3, on General State Budgets for the year 2018 with the heading: Tax benefits applicable to "Neurodegenerative Diseases 2020. Year of admission of Research and Innovation".



The event EN2020, promoted by the Queen Sofia Foundation and the Center for Research in Neurodegenerative Diseases (CIEN) Foundation, and promoted by the Ministries of Finance; Health, Consumption and Social Welfare; Science, Innovation and Universities, and the Carlos III Institute of Health, aims to raise public awareness on the importance of promoting research on neurodegenerative diseases to advance in the knowledge of the origin of their causes, the only way to reduce the number of people affected and stop the advance of these diseases; to promote the fundraising activities that will be used for the scientific and social purposes of both Foundations and as a platform for the generation of ideas and the exchange of experiences between experts and scientists in the field of neuroscience throughout the world. Numerous initiatives have been carried out around this event, such as the raffle dedicated to Neurodegenerative Diseases 2020. Last Saturday, September 28, 2019 State Lotteries and Betting dedicated its raffle to Neurodegenerative Diseases 2020 Research Year. Throughout Section 7 of this Report, we will see that many of the activities described are framed in the EN2020 event.

The main objectives of this initiative are:

- Contribute to Spain being among the leading countries in international scientific research on neurodegenerative diseases.
- Collaborate in the consolidation of the European program against these diseases.
- Raise funds from private and philanthropic origin for the social and research purposes of the Queen Sofia Foundation and the CIEN Foundation.

Christmas Tree of Memories

“Remember for those who can no longer” is the premise with which the Queen Sofia Foundation and the CIEN (Neurological Diseases Research Center) Foundation set up every year the “Christmas Tree of Memories” at the Cibeles CentroCentro in the capital, an initiative that has the support of the Madrid City Council, and which is aimed at raising awareness in society about the effects of Alzheimer’s disease in those who suffer from it, which in 2019 has been framed as one of the activities of the Event of Exceptional Public Interest NEURO 2020 .

The “Tree of Memories” could be visited last Christmas by the locals and visitors who passed through the CentroCentro, who has the opportunity hung their most precious Christmas memory on special cards prepared for the occasion, as well as through social networks with the hashtag #TreeofMemory.

The opening ceremony was attended by José Luis Nogueira, secretary of the Queen Sofia Foundation; M^a Ángeles Pérez, manager of the CIEN Foundation; José Anierte, councilor of the Madrid City Council and of the Family, Equality and Social Welfare area Government delegate, and Mercedes Montenegro, general director of the Elderly from the Madrid City Council.



In the words of the CIEN Foundation manager, M^a Ángeles Pérez, the “Tree of Memories” seeks to “value memory through positive emotions, which are the ones that most strongly fix memories in our brain”. The Christmas tree, with a firm trunk that supports hundreds of branches, symbolizes the endurance of emotions over time. It is also a metaphor for the social nature of this problem, and a call for the participation of all, essential to eradicate a disease that potentially affects society as a whole.

The initiative, part of NEURO2020 “Neurodegenerative Diseases 2020. International Year of Research and Innovation”, declared an Event of Exceptional Public Interest, also aims to raise public awareness on the importance of research in neurodegenerative diseases. And along this line, José Luis Nogueira, secretary of the Queen Sofia Foundation, stressed that “we continue working to improve the quality of life of patients suffering from Alzheimer’s and other neurodegenerative diseases, and those of the people who are by their side. We will never forget them and we will continue working for it”.

In addition, as in previous editions, the original tradition of the Vallecas “Tree of Memories” has been maintained, which since 2011 is set up every Christmas in that Madrid district. In the last edition, the Villa de Vallecas Municipal Market again welcomed this initiative, with the support of the Queen Sofia Foundation, the Villa de Vallecas District Board and the General Directorate of the Mayor of the Region of Madrid. One more year, the journalist and presenter Irma Soriano was also the god-mother, one more year, of both events.

Friends of the CIEN Foundation

On the occasion of World Alzheimer’s Day, last September we launched the Friends of the CIEN Foundation initiative, with which we can all help research, diagnosis and treatment of neurological diseases, especially Alzheimer’s and other dementias.





Friends of the CIEN Foundation is also a way to support and make visible the tireless work of scientists, families and caregivers, and contribute to improving the quality of life of those who suffer from a disease for which there is still no cure.

Through the form that can be found on our website (www.fundacioncien.es) any interested persons can fill in the corresponding fields and choose a way to collaborate: Collaborating Friend, Protective Friend or Benefactor Friend.

“Together we can achieve it” has been the motto chosen for this campaign that, at the end of 2019, already has more than 670 partners. From here, thanks to all our Friends. We would like to take this opportunity to thank our donor community, as well as all the followers in general, for their encouragement and support. After more than a year of the Friends of the CIEN Foundation initiative, we feel responsible for the trust they have placed in our institution and we are responding in the best way we know how: through Alzheimer's research.

Memorables Film Festival

The fight against Alzheimer's can inspire both scientific research and artistic creativity. In this case, the Queen Sofia Foundation and the CIEN (Center for Research in Neurodegenerative Diseases) Foundation called on audiovisual creators from all over Spain to portray the social reality of Alzheimer's. The 1st Edition of the Memorable Film Festival projected stories on the big screen that help the public to understand the impact of this disease on specific people: from the patients and their families, to researchers or professional caregivers.

M^{ra} Ángeles Pérez, manager of the CIEN Foundation, wanted to emphasize during her welcome address that “this event is a wonderful opportunity to bring two worlds closer together: that of science and creativity, which when they combine their efforts, are capable of creating great things”. In addition, she stressed the importance and effort of all the people behind this disease, family members, medical personnel, scientists and volunteers.



The short film *Imagine*, directed by Cindy Fuentes Marín from Granada, was the winner of the official section and received the golden little neuron, an award that represents the incidence of Alzheimer's disease on neuronal tissue. *Imagine* tells the story of a daughter's relationship with her mother, suffering from Alzheimer's. *My star*, by Sergio Barba Soler, and *Capitán Kinesis*, by Francisco Andrés Jiménez Céspedes, received the silver and bronze little neurons, respectively. In addition, the public could also appreciate the quality and message of the short films, a very special award that was awarded to *My name is Alba*, directed by Mar Estefanía Duarte. In addition, awards were distributed to the best actor and actress, best script, photography, editing and soundtrack.

In total, fifteen short films competed in the official section for the different awards, which are called Little Neurons, for the incidence of Alzheimer's on neuronal tissue, and whose trophy has been created by the sculptor and designer Eva González.

Raquel Yotti, director of the Carlos III Institute of Health and president of the jury, stressed that cinema "is an excellent vehicle to approach circumstances little known to society, and to make us understand that behind the figures there is a concrete human and social dimension". For Yotti, the short films that can be seen on the CIEN Foundation website since last December "reflect that we are facing a disease that changes people's lives, erasing many of the family memories that give meaning to their lives, but they also show that there is hope in science as well as in the affection and solidarity of those around them".

Thus, in this first edition, short films inspired by the personal and family history of some of the directors could be seen. Other works are narrated from the point of view of the patient himself, or also that of the scientists, doctors and caregivers of these people. According to the organizers, the image serves to recover those memories and also to express a growing commitment. The level of the short films presented, they affirmed, was very high, "which made it difficult to

choose the best ones, but the fact that they are in the official section is already a triumph not only for them, but for Alzheimer's research and for society as a whole".

To share ideas regarding this interesting meeting, Dr. Miguel Medina, CIBERNED Deputy Scientific Director, and the film director and screenwriter Alfonso Albacete, participated in the "Alzheimer's on the big screen" colloquium, in which they discussed the different ways to bring science and a social reality like Alzheimer's disease to the movies. The spokesperson for the Pasqual Maragall Foundation, Cristina Maragall, and the film and television director David Ulloa, who presented his short film "Naturales", also spoke about the impact of the disease on the lives of patients and their families.

This first edition of the Festival wanted to include among the members of the jury prominent personalities from both the scientific and cinematographic fields. Thus, the jury was chaired by Raquel Yotti, director of the Carlos III Institute of Health. Other members included : José Luis Nogueira, Secretary of the Queen Sofia Foundation; Alfonso Albacete, film director; Javier Elorrieta, film director, composer and screenwriter; Carmen Utrilla, casting director; Miguel Ángel Valero, actor who gave life to the mythical Piranha from the series 'Verano Azul'; M^ª Isabel González Ingelmo, managing director of CRE Alzheimer-Imsero (State Reference Center for care and intervention for people with Alzheimer's disease and other dementias and their families); Begoña Cortés, general director of Attention to the Elderly and to the Dependency of the CAM; Cheles Cantabrana, president of the Spanish Alzheimer's Confederation (CEAFA); M^ª Luisa San José, actress; and Milagros Martín-Lucas, communication consultant and writer..

Rock Memory Series

Last November, Hard Rock Café Madrid presented the "Hard Rock Memory Series", in which 25 great musicians joined the fight against Alzheimer's through a charity auction.



All of them personalized a guitar and added a memory to its back that they would never want to forget. The entire proceeds were donated to the CIEN Foundation for research.

The 25 artists and groups that made HARD ROCK MEMORY SERIES come true were: Amaral, Carlos Jean, Carlos Tarque, Cliff Cooper (guitarist and president of Orange), Dani Martín, Danny Gómez (A Night at the Opera, the best tribute to QUEEN, as endorsed by Brian May), David Otero, El Amir (Hanz Zimmer guitarist), Estopa, Hombres G, Ketama, La Oreja de Van Gogh, La Unión, Los Secretos, Mago de Oz, Malú, Manolo García, Marea, Nacho Cano, Rudy Sarzo (bassist for Ozzy Osborne, Whitesnake, DIO...), Rayden, Rulo y la Contrabanda, Sôber, Tequila and Tim Stewart (guitarist for Lady Gaga and Rihanna).

All of them had total freedom to customize the guitars and got down to work using paint, collage, drawing, graffiti, etc. In this way, Amaral invited us to travel with a guitar that has a world map stamped on it, Marea opted for the drawing and on his instrument appears a caricature of its five members, David Otero sculpted in braille one of his most personal themes, Dance, which he performs with Rozalén, Sôber pays tribute with his piece to Alberto Madrid, a former member of the band, and Rayden wrote small fragments of his most representative songs.

In the sentences there is also a great variety of memories and winks. For example, Mägo de Oz chose a verse from Sleepless Dreams, a song that Txus dedicated to his grandfather, who suffered from the disease. The same line of inspiration was followed by Rulo y la Contrabanda, transcribing the lyrics of La Reina Del Barrio, written by Rulo for two very special people who fought against Alzheimer's: his grandmother and his mother-in-law. However, Malú chose to use a quote that always accompanies her: "Where words fail, music speaks". Carlos Jean also made reference to music with the following wish: "I want the songs that make me smile, cry, discover, think, fly..." to always remain in my mind.

Those interested in collaborating in the project and acquiring these unique pieces could bid on todocoleccion.net until November 24. In addition, to encourage the countdown, the guitars were exhibited at Hard Rock Cafe Madrid, and Mägo de Oz, one of the participants, offered a free showcase on November 19 in the main room of the restaurant.

On Monday, November 25, 2019, the Hard Rock Cafe in Madrid put the finishing touch to the celebrations for its 25th anniversary. It was exactly the same day, twenty-five years later, that the place opened its doors in the capital in 1994. Sôber and Rulo y La Contrabanda participated in the party, performing the songs they composed about Alzheimer's: La Escalera and La Reina del Barrio respectively. During the event, the CIEN Foundation received 24,000 €, the proceeds from the HARD ROCK MEMORY SERIES solidarity auction.

HARD ROCK MEMORY SERIES, an initiative framed within the 25th anniversary of Hard Rock Cafe Madrid, was launched with the aim of helping to raise awareness in society about Alzheimer's disease, disseminate the activities developed by the Queen Sofia Foundation's Alzheimer Project and raise funds for its research center,



in order to continue promoting its grant programs that respond to the needs of people suffering from this disease.

Hard Rock Cafe Madrid has shaped this project thanks to the support of Hard Rock Heals, the foundation that oversees and activates the philanthropic actions of Hard Rock Cafe and whose mission is to improve people's lives through music.

From the CIEN Foundation, we want to thank Hard Rock Cafe, the 25 participating bands and all the people and entities that have launched and participated in this initiative, which is both necessary and urgent for society as a whole.

I Villa de Madrid Ham Solidarity Fair

Gastronomy and solidarity came together on Sunday October 20 to support research on neurodegenerative diseases at the 1st Villa de Madrid Ham Solidarity Fair, an action promoted by the Madrid Associations of Ham Cutters and Always United Solidary Cutters together with the CIEN (Center for Research in Neurological Diseases) Foundation.

More than 120 ham cutters from all over Spain gathered at the Railway Museum to participate in this macro-tasting of ham and, in turn, collaborate with research on neurodegenerative diseases. From 11:00 a.m. to 3:00 p.m., the people of Madrid enjoyed the fair where they could taste dishes of different hams cut by some of the best cutters in our country and, in addition, they could visit the Railway Museum, an iconic place of the city and the scene of a multitude of film shoots. Both the Railway Museum and the Spanish Railway Foundation collaborate with the CIEN Foundation in a solidarity initiative to stop neurodegenerative disorders. The event also featured a performance by magician Andrés Madruga, with presenter Irma Soriano as master of ceremonies.

The 1st Villa de Madrid Ham Solidarity Fair was framed within the "NEURO2020: Neurodegenerative Diseases 2020. International Year of Research and Innovation" with the aim of raising awareness among citizens about the importance of research in neurodegenerative diseases, promoting fundraising for a series of initiatives, dissemination actions and applied research projects.

V Esquivias Solidary League

During Sunday October 27, the "V LEGUA DE ESQUIVIAS" was held in the municipality of Esquivias, Toledo, which sold out its numbers several days before the race and which in this edition allocated its earnings to the CIEN Foundation.

With an itinerary of just over a league (equivalent to 5,572 m), the race, organized by the La Montera de Esquivias Bullfighting Cultural Association with the official timing and oversight of the Evedeport company, and the collaboration of the Excmo. Esquivias City Council, the Local Police and Civil Protection, was a race open to the participation of all athletic fans, both male and female, whether they were



federated or not. Trials for minor categories were also held jointly, aimed at promoting athletics in the municipality in the Meta area.

In parallel, a race called 'free modality' by the organizers was also held, in which the participants did not compete to do a great time, but to join a charitable cause of notable importance. This second modality took on special importance since the numbers were exhausted in the competitive modality, and also allowed nobody to be left without collaborating with the initiative in favor of CIEN. In fact, the organization has also enabled a Row 0, where everyone who wanted could leave their contribution, even if they did not attend the race in person.

Likewise, the support of well-known personalities through social networks has been essential to obtain this excellent response from athletes in terms of participation. And it is that there have been many who have shared in their profiles videos of support to the race, as in the case of, among others, the national record holder of the marathon Julio Rey, the television chef Pepe Rodríguez, the presenter Irma Soriano or Ana del Alto, the first patient diagnosed with genetic Alzheimer's in Spain who, in addition to carrying out a great dissemination campaign with her husband, exhibited her pictorial work in the Esquivias Cervantes House Museum. This remarkable endorsement for a popular race that continues to demonstrate how, with the little push of many, very great things can be accomplished.

Charity Concert from the Choir of the Spanish Railways Foundation

Various studies suggest that music is one of the most efficient therapies for the treatment of Alzheimer's disease. For this reason, the Choir of the Spanish Railway Foundation has wanted to support Alzheimer's research with a charity concert on June 19, the funds of which have been allocated entirely to the projects and initiatives developed by the CIEN (Center for Research in Neurological Diseases) Foundation.

The Madrid Railway Museum, managed by the Spanish Railway Foundation and which recreates an old train station scene of multiple film shoots, has hosted the performance. The Spanish Railways Foundation Choir is made up of 30 mixed voices and led by Joan Borrás have performed a repertoire of 10 songs, including "New York, New York", by J. Kander and F. Ebb , or "¡Viva Madrid!", by P. Sorozábal.

The concert has also been part of the activities of "NEURO2020: Neurodegenerative Diseases 2020. International Year of Research and Innovation. In this way, these types of actions bring society closer to the reality of neurodegenerative diseases, which in many cases have important social consequences for the families and caregivers of patients.

The concert was attended by José Luis Nogueira, secretary of the Queen Sofia Foundation (in whose Alzheimer Center the CIEN Foundation is headquartered), M^{ra} Ángeles Pérez, manager of the CIEN Foundation, and Francisco Polo, director of the Railway Museum from Madrid. José Luis Nogueira affirmed that this type of action "helps to make citizens aware of the importance of the work that is carried out every day in the field of research, such as that carried out by scientists from the Queen Sofia Foundation Alzheimer Center to achieve a solution to the disease ". Along these lines, M^{ra} Ángeles Pérez wanted to emphasize the "great help that charitable actions like this represent, which are an important boost to continue developing different research projects in neurodegenerative pathologies such as Alzheimer's disease". For his part, Francisco Polo stressed the importance of showing this type of social action through cultural activities such as music.



7.2.

Presence in media

As every year, during 2019, the Communication Area of the CIEN Foundation developed a communication plan, which has been carried out. Constant communications and regular meetings have been maintained with the CIEN Foundation Management regarding media appearances, press releases, reports, programmed initiatives, organization, etc.

For the formulation and achievement of the objectives for the year 2019, the annual CiiiEN congress was held, which took place in September in Valencia. The organization and carrying out of this event focused on the conception and strategy of the 2019 communication plan, although several other communication actions and initiatives were also executed.

Indeed, communication actions referred not only to CiiiEN, but also to the activity of the CIEN Foundation and other actions. In addition, the constant flow of press releases reflects the updated information on the CIEN Foundation and the "Vallecas Project", its most important research project. During 2019, a significant impact was achieved in the press, radio, television and online media, both in terms of dissemination and range of the network of contacts with researchers in national and international neurodegenerative diseases.

Work has also been performed on the dissemination of other events, already classics at the CIEN Foundation, such as the Vallecas Project Volunteers's Day, at the Monumental Theater of Madrid, which had the collaboration of the RTVE Symphony Orchestra and Choir, or a new edition of the Christmas Tree of Memories, in collaboration of the Madrid City Council, an initiative aimed at raising awareness about the problem of neurodegenerative diseases, and which was set up in December at the CentroCentro Cibeles of the capital and the Vallecas Market, or ceremony award of the Queen Sofia Foundation – MAPFRE Foundation scholarships, which in 2019 commemorated the 10th anniversary of the program as a result of the collaboration between the two institutions, together with the CIEN Foundation. As a novelty, in 2019 the 1st edition of the Memorable Film Festival was held, the first short film festival dedicated to Alzheimer's disease that brought together audiovisual creatives from all over Spain at the Queen Sofia Foundation Alzheimer Center to portray the social reality of the disease.

Within the collaboration with other organizations and institutions, during 2019 different initiatives have been developed such as the "Hard Rock Memory Series" project, a charity auction in collaboration with Hard Rock Cafe Madrid, in favor of the research work carried out by the CIEN Foundation at the Queen Sofia Foundation Alzheimer Center, with the participation of 25 national and international filmmakers.

Regarding the impact on the press, the diffusion of the activities and projects of the CIEN Foundation has been maintained and increased.



In addition to press releases, reports and information generated around the CIIEN, there have been press appearances and online and audiovisual media that include extensive reports in media such as RTVE, TVE Internacional, Antena 3, El País, El Mundo, ABC, Cadena COPE, Telemadrid, La Razón, Cadena SER, Diario Médico, ConSalud, El Español and Acta Sanitaria, as well as regular dissemination through the main news agencies.

Six elements have focused the press interventions and appearances:

- The "Vallecas Project"
- The volunteers of the "Vallecas Project"
- The CIEN Foundation Tissue Bank
- Queen Sofia Foundation – MAPFRE Foundation scholarships Award Ceremony
- The International Conference on Research and Innovation in Neurodegenerative Diseases CIIEN, in Valencia
- The I Edition of the Memorables Film Festival

Regarding press statements, the control and prior informative consent protocol introduced in 2017 was followed during 2019, by which journalists are informed in detail of the CIEN Foundation's affiliation with the Carlos III Institute of Health and the Ministry of Science, Innovation and Universities.

The number of impacts during 2019 in media, in terms of scope and represented as the estimated number of readers/people reached, arrived at 98 million readers, which, expressed as ROI, was 1,613,961 €.

7.3.

Presence in social media

The CIEN Foundation has continued to implement its promotion strategy, which has been rewarded both in the results obtained in social media as well as in the recognition and prestige it has at the national and international level as an organization.

Throughout 2018, the community has received the support and advice of numerous experts who have solved their doubts and queries in real time through social media.

Several campaigns have been promoted from the official accounts of the CIEN Foundation, highlighting above all that which aimed to increase the visibility of Alzheimer's disease in society through the contribution of data and new discoveries (#Alzheimer), the one referred to the campaign of "Friends of the CIEN Foundation" (#AmigosdelaFundacionCIEN) or the "Vallecas Project" (#ProyectoVallecas).

Sporadic campaigns and events have also been covered and disseminated. These events include the coverage of the 1st edition of the Memorables Film Festival (#MemorablesFilmFestival), the "Hard Rock Memory Series" project, the initiative of the "Tree of Memories" (#ÁrbolDeLaMemoria), the campaign carried out for the CiiiEN 2019 organized in Valencia (#CIIIEN2019) or the coverage provided to the CIEN Foundation 2019 Seminars Series (#CicloSeminariosFCIEN).

Analyzing the status of the various official accounts of the CIEN Foundation, we can observe the evolution they have experienced during 2019:

- **Facebook:** 2019 ended with 5,294 followers, who have been increasing progressively and whose positive trend continues constant. This figure represents a 9% increase over the previous year.
- **Twitter:** By the end of 2019, the profile counted on 13,2769 followers with whom it has constant interaction, receiving numerous comments, retweets and likes. The number of followers have experienced an increase of 3.8% compared with the previous year.



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