

The logo for Fundación Centro Investigación Enfermedades Neurológicas (cièn) is displayed in a white circular frame. The text 'cièn' is written in a blue, lowercase, sans-serif font.

Fundación Centro Investigación
Enfermedades **Neurológicas**



2018
Annual Report

CIEN FOUNDATION
Research Center for
Neurological Diseases Foundation

Centro Alzheimer Fundación Reina Sofía
C/ Valderrebollo, 5. 28031 Madrid
Tel.: (+34) 91 385 22 00 Fax: (+34) 91 385 21 18
www.fundacioncien.es
info@fundacioncien.es



Annual Report 2018



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C/ Valderrebollo, 5. 28031 Madrid
Tel.: (+34) 91 385 22 00 Fax: (+34) 91 385 21 18
www.fundacioncién.es

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Profile and presentation

The CIEN Foundation is a reference entity in the field of neurodegenerative diseases scientific research, especially in Alzheimer's disease. Supported by the Carlos III Institute of Health and the Queen Sofia Foundation, it proposes an integral model based, mostly, on research translatable for the benefit of society.





1.1. Who we are

A FOUNDATION FROM THE PUBLIC SECTOR

The CIEN 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.

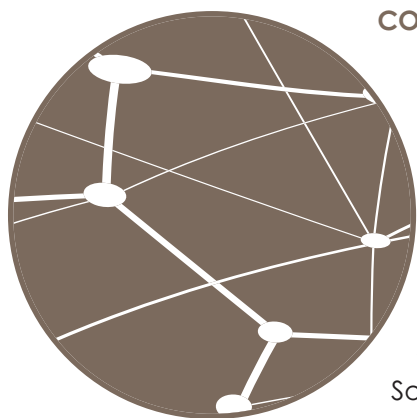
The CIEN Foundation is based at the Queen Sofia Foundation Alzheimer Center, whose construction was called the Alzheimer Project. Once the Alzheimer Center was built, it was divided into a residence for healthcare and follow-up of the patients and an Alzheimer Project Research Unit of the (UIPA, for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

As indicated, the headquarters of the CIEN Foundation are located in the Queen Sofia Foundation Alzheimer Center, a pioneering 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, at the neighborhood of Vallecas, Madrid, seeks to respond to the social health project proposed by the Alzheimer Project of the Queen Sofia Foundation.

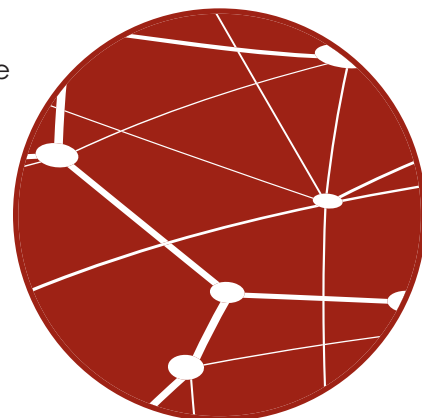


A REFERENCE CENTER IN EUROPE ON ALZHEIMER'S DISEASE RESEARCH

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.



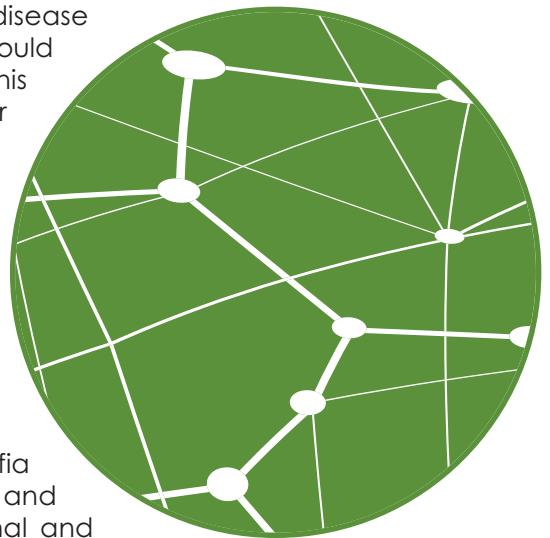
1. PROFILE AND PRESENTATION

AN INNOVATIVE, INTEGRATED VISION OF THE FIGHT AGAINST ALZHEIMER'S DISEASE

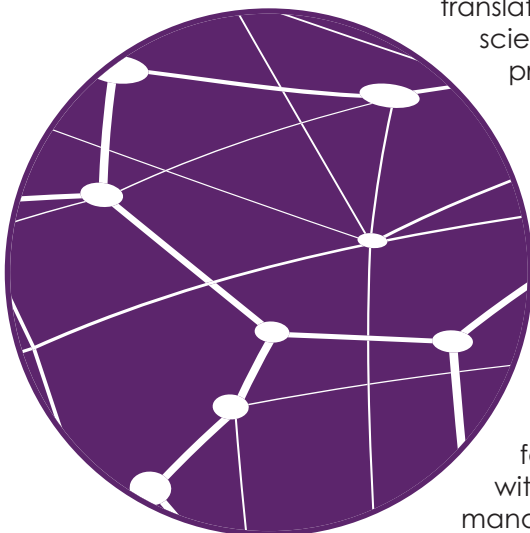
The CIEN Foundation and the Queen Sofia Foundation share a common perspective on action in relation to Alzheimer's disease: This disease requires a comprehensive approach model where research should be one of the fundamental pillars. The leading exponent of this integrative model is the Queen Sofia Foundation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

1. A live-in residence for 156 Alzheimer's patients.
2. A day-care outpatient center for 40 Alzheimer's patients.
3. An Alzheimer's research center: the so-called Alzheimer's Project Research Unit (UIPA), managed by the CIEN Foundation.
4. 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.

But its function does not end here. 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.



1.2. The CIEN Foundation in 2018

- During 2018, CIEN Foundation researchers published 27 scientific papers, 25 original articles in specialized journals, of which 20 (80%) were in journals classified within the first and second quartiles, with an average impact factor of 5.074.
- Resolution of the General Foundation of the University of Salamanca that selects and finances the international research project entitled "Spain-Portugal Longevity Research Program +90 (PILEP+90)".
- Launch of the "Friends of CIEN Foundation" campaign in September 2018, coinciding with World Alzheimer's Day.
- Beginning of the eighth follow-up visit of the Vallecas Project for the early detection of Alzheimer's disease.
- Celebration of the VI Edition of the International Congress on Research and Innovation in Neurodegenerative Diseases (CIIEN) in Santiago de Compostela, established as the International Congress of reference in our country in the area of neurodegenerative diseases.
- Celebration of the First "Women Neuroscientists Today: Sowing referents", on the occasion of the World Day of Women and Girls in Science.
- Inauguration of the traditional "Christmas Tree of Memories" which in 2018 was installed again in the Madrid City Council and the Villa de Vallecas Market.
- For the sixth consecutive year, the already institutionalized Vallecas Project Volunteer's Day was celebrated, in recognition of the collaboration of these people in favor of research.
- Dr. Bryan Strange, Head of the CIEN Foundation Neuroimaging department, received the 2018 European Research Council (ERC) Consolidator Grant entitled "Human Subcortical-Cortical Circuit Dynamics for Remembering the Exceptional".
- The Cognitive Impairment Diagnostic Unit was started up, with the objective of making a diagnostic approach in patients with suspected Cognitive Impairment or Degenerative Dementia.
- During 2018, the CIEN Foundation maintained its co-ownership in two active patent applications, in national phases at various countries, both licensed to Raman Health Technologies.
- Launch of the YO RECUERDO (I remember) Campaign, an initiative joined by some celebrities and with which funds were raised to support Alzheimer's research. Journalists such as Irma Soriano, Mercedes Milá, Nieves Herrero, Quico Taronjé or the renowned singer Diana Navarro have collaborated in the initiative. A social media support campaign was also developed, through the hashtag #YoRecuerdo.
- Incorporation of physical activity records through accelerometers in the Vallecas Project cohort.
- In June 2018, the winner of the 2017 Queen Sofia Foundation-MAPFRE Scholarship grant was



1. PROFILE AND PRESENTATION

recruited for stays at our Center and at the University of Eastern Finland in Kuopio.

- Throughout 2018, the CIEN Foundation maintained its commitment to the Youth Employment Operational Program of the Council of Education, Youth and Sports of the Region of Madrid, by formalizing a new contract for the promotion of young employment and implementation of the Youth Guarantee in R+D+I.
- During 2018, three new collaboration agreements were signed between the CIEN Foundation and the Queen Sofia Foundation, among which we highlight the "Neurodegenerative Diseases 2020. International Year of Research and Innovation", which regulates the relationship between the parties to its implementation, with the objective of obtaining financial resources for the purposes of both foundations and that of "Vallecas 2, early detection of Alzheimer's Disease. Risk and protection factors", intended to establish the collaboration framework to carry out research aimed at the identification of individuals at greater risk of developing Alzheimer's type dementia (AD), based on the conjunction of sociodemographic, clinical, neurological, neuropsychological data, genetic, biochemical and neuroimaging biomarkers.
- In 2018, a total of 559 visits were carried out in Magnetic Resonance and a total of 3,227 studies were conducted to these subjects.
- Validation of our predictive algorithm of mild cognitive impairment with a new group of individuals from the Vallecas Project. This work has been carried out by Linda Zhang, recipient of the MAPFRE-CIEN Foundation Grant.
- In 2018, the CIEN Tissue Bank reached registration number 900.
- Work began on the National Biobank Network Platform (2017 Call), which will be active between 2018 and 2020, and in which the CIEN Tissue Bank acts as Coordinator of the R&D Program.
- The director of the CIEN Foundation Tissue Bank, Alberto Rábano, received in 2018 the Alzheimer Award (Scientific Section) from the Spanish Society of Neurology.
- The CIEN Foundation Tissue Bank organized, together with the Tissue Bank from the Institute of Neurosciences of Castilla y León, the First Symposium of Neurological Tissue Banking in Salamanca on September 27-28, 2018.
- Five members of the CIEN Foundation Tissue Bank (oral communications, lectures, round tables, etc.) participated during the IX National Congress of Biobanks, Oviedo, 7-9 November 2018.
- The CIEN Foundation 2018 Seminar Series included 21 sessions of scientific seminars with the participation of speakers, both from the CIEN Foundation, as well as related, national and international institutions.





■ 1.3 Letter from the Managing Director M^a Ángeles Pérez



The year 2018 has been an exercise in progress and consolidation. The ongoing projects and our research work devoted to the benefit of society continue moving forward to find solutions to one of the main threats of the 21st century: Alzheimer's disease. Therefore, it is an honor for me to address you, one

more year, to take stock of the activity of the CIEN Foundation and highlight the milestones that have marked this year.

The CIEN Foundation is a reference in basic, clinical and epidemiological neurology, both due to our translational research projects as well as to the internationalization of our activities. After more than 10 years developing our work at the Queen Sofia Foundation Alzheimer Center, we lead the investigation in neurodegenerative diseases, something that would not be possible without the unconditional support of Queen Sofia Foundation and the Carlos III Institute of Health (ISCIII).

Thus, one of the most important milestones achieved during 2018 has been the signing of a collaboration agreement between the CIEN Foundation and the Queen Sofia Foundation to raise public awareness about the importance of promoting research in neurodegenerative diseases. Under the name Neuro2020: "Neurodegenerative diseases 2020. International Year of Research and Innovation", both institutions also seek to create a platform for the generation of ideas and the exchange of experiences between experts from around the world and contribute to Spain being among the leading countries in international scientific research in this field.

Regarding the scientific productivity of the CIEN Foundation in 2018, the conscientious research work carried out by our team of professionals has led to the publication of 25 original articles in specialized journals, 80% of them in journals ranked first and second quartile. Together with the publication of new articles, the CIEN Foundation has promoted the expansion of scientific knowledge through the organization, jointly with the Queen Sofia Foundation and the Network Center for Biomedical Research in Neurodegenerative Diseases (CIBERNED), of the VI edition of the International Congress of Research and Innovation in Neurodegenerative Diseases

María Ángeles Pérez Muñoz
CIEN Foundation Managing Director

1. PROFILE AND PRESENTATION

(CIIEN) held in Santiago de Compostela. A reference meeting in this area of study that counted, one more year, with the presence of H.M. Queen Sofia.

Throughout 2018, the prominence of the "Vallecas Project", our most ambitious initiative launched in 2011, which seeks to identify markers for the early detection of Alzheimer's disease has continued. In 2018, the "Vallecas Project" has been one of the research lines that has grown the most. We have started the eighth follow-up visit of volunteers and have launched the Cognitive Impairment Diagnostic Unit with the aim of making a diagnostic approach in patients with suspected dementia. Applied research that responds to the needs of patients and their relatives. Moreover, we have begun to make physical activity records to the cohort of volunteers of the "Vallecas Project" using accelerometers. In this way we have a new set of data that allow us to improve our knowledge of people at-risk of developing Alzheimer's disease.

These advances and the promising results of the project have led us, thanks to the help of the Queen Sofia Foundation, to the implementation of a second phase of the study aimed at the detection of individuals at higher risk of developing Alzheimer's disease.

For its part, the CIEN Foundation Tissue Bank also continues to grow in number of samples, renown and visibility. In 2018, registration number 900 was reached, a milestone achieved thanks to the generosity and awareness of our donors. In order to expand the knowledge of the scientific and medical community, the CIEN Foundation Tissue Bank organized for the first time, together with the Tissue Bank from the Institute of Neurosciences of Castilla y León, a Symposium on Neurological Tissue Banking. The success of the meeting held in Salamanca is a sign of the important role that biobanks play in the progress

of research in Alzheimer's and other neurodegenerative diseases.

The development of these projects has been possible thanks to the support of society and those who support the work of the CIEN Foundation. From the volunteers of the "Vallecas Project", a key piece for the development of cognitive studies and to whom we pay tribute to celebrating the "Vallecas Project" Volunteer's Day, to the new "Friends of the CIEN Foundation", anonymous donors who support neurodegenerative disease research. In 2018, we also started the "Yo recuerdo" (I remember) campaign, a call to increase the visibility of Alzheimer's disease and raise funds for research.

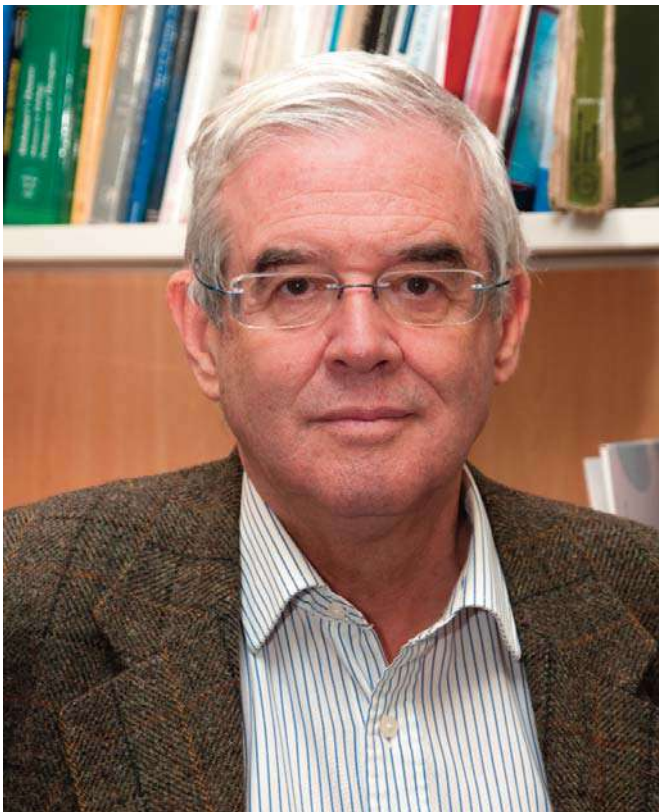
Also fulfilling our commitment towards the promotion and training of young talent, during 2018 we have formalized a new agreement with the Youth Employment Operational Program of the Council of Youth and Sports Education of the Region of Madrid for the implementation of the Youth Guarantee in R+D+i. A collaboration through which we promote the interest of young people in scientific research, and we awaken their vocations to contribute new ideas and points of view.

And talking about talent, I cannot finish without praising the effort and dedication shown by those who make up the CIEN Foundation, involved in increasing the knowledge of Alzheimer's disease with the aim of improving people's lives. Among all, we are taking small steps towards the future.





1.4. Letter from the Scientific Director Jesús Ávila



During 2018, the CIEN Foundation has done a good job, given our scarcity of resources. 27 papers have been published, with a good average impact index, not only in collaboration with other groups but we also started publishing papers carried out in our Center with the first and last author from the CIEN Foundation.

Jesús Ávila de Grado
Scientific Director of CIEN Foundation

New research grants have been obtained in competitive calls and the Director of the Neuroimaging Area, Dr. Strange has received an ERC grant. There has been a good progress in the Tissue Bank Service, which has been provided with the necessary resources for its proper functioning. The Cognitive Impairment Diagnostic Unit has been launched and collaboration with DEGESCO has continued.

From the point of view of training activities, a new Doctoral Thesis has been defended, and a new FCIEN Research Scholar has been incorporated, thanks to the Queen Sofia Foundation and the MAPFRE Foundation. In addition, the Seminar Series has continued throughout the year.

In collaboration with CIBERNED and the Queen Sofia Foundation, the annual Congress was held in Santiago de Compostela.

Before finishing, I would like to take this opportunity to thank the Institutions that support us financially the most: the Queen Sofia Foundation, with which we have signed in 2018 three new collaboration agreements and the Carlos III Institute of Health (ISCIII) that has commissioned us a study on the reorganization of CIEN Foundation in order to develop and improve further our Institution.

I would like to conclude, thanking the work of all the members of our CIEN Foundation who are responsible for the work we perform.

1. PROFILE AND PRESENTATION





1.5. Organizational structure

1.5.1. Governing and Management Bodies

The CIEN Foundation is composed of three bodies, one of management, represented by Mrs. M^o 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.

The CIEN Foundation 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.

At the end of 2018 the Board of Trustees has the following members:

► CHAIR:

- Mr. Rafael Rodrigo Montero, State Secretary of Coordination of Science Policy from the Ministry of Science, Innovation and Universities

► 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
- Mr. Borja Luis Cabezón Rojo, Director of the Department of National Affairs of the Office of the Prime Minister
- 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 accept
- Ms. Margarita Blázquez, Deputy General Director of Cooperative Research Networks and Centers, Carlos III Institute of Health

► SECRETARY:

- 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
- Ms. Ana M^o Ávila Peñalver, Director General for Research, Innovation, Technology and Quality, Government of the Region of Valencia



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► LEGAL ADVISOR:

State Attorney
Mr. José Luis Beotas López

► INVITED GUESTS:

- CIEN FOUNDATION
Scientific Director: Mr. Jesús Ávila de Grado
Managing Director: Ms. María Angeles Pérez Muñoz
- QUEEN SOFIA FOUNDATION
Mr. Jose Luis Nogueira Guastavino
- ADVISOR TO THE OFFICE OF THE SECRETARY OF STATE FOR RESEARCH
Mr. Agustín Larrañaga Elorriaga
- ASSISTANT TO THE SECRETARY
Ms. M^a Dolores Donoso Mencía

1.5.2 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. The Committee is formed by the following members:

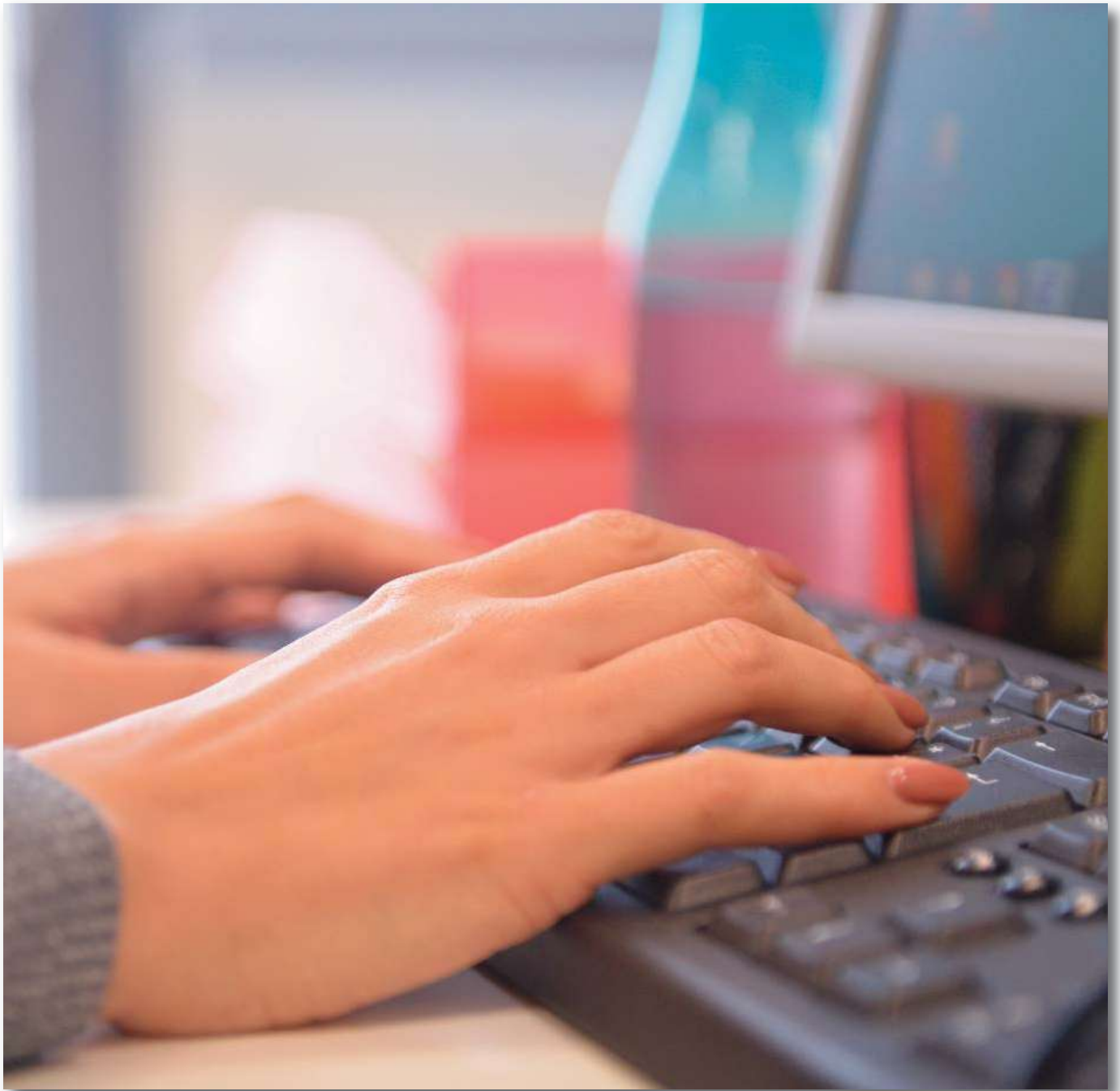
- Mr. Joaquín Arenas Barbero. BSc in Pharmacy and PhD in Clinical Biochemistry by Faculty of Medicine of Complutense University of Madrid. He has held the positions of General Director and Deputy General Director of Networks and Cooperative Research Centers within the Carlos III Institute of Health (ISCIII).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



Mänagement *re*port

The continuous training of its researchers and the promotion of young talent are two of the pillars on which the progression experienced by the CIEN Foundation has been based upon. Both aspects, together with an efficient management of resources and the promotion of a cooperative research model and with a clear international focus, are a guarantee for the future to establish the reference position of the CIEN Foundation in the research of neurodegenerative diseases such as Alzheimer's.





2. MANAGEMENT REPORT

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 services carried out by various Consultation Units and Research Groups of the CIEN Foundation has been arti-

culated 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.

Revenues

In 2018, the CIEN Foundation managed an income budget of over 2.3 million euros. The main source of income comes from the nominative assignment of the Carlos III Institute of Health, which amounts to € 1.325,000 (representing 56% 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 the total income/revenue obtained in 2018 and 2017 is shown in the table on the following page.

Revenues of the institution consist mainly of grants, donations and operating legacies and capital re-





ceived from Public Administrations and other institutions, companies and individuals.

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 2018 of 1,325,000 euros.

Resolution of July 31, 2018, by which the following nominative contribution provided in the Statement of Expenditure of the ISCIII Budget for the year 2018 is destined for the CIEN Foundation:

- 412,500 euros from the budget application 27.107.465A.445 corresponding to 50% of the total credit existing in the aforementioned budget applications.

Once Law 6/2018, of July 3, on General State Budgets has been approved for the year 2017:

- 912,500 euros from the budget application 27.107.465A.445.

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 2018 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 CIEN, held in Santiago de Compostela between September 19 and 21; and iii) call for the Queen Sofia Foundation-MAPFRE Foundation fellowship.

The rest of the amount corresponding to the subsidies, donations and bequests allocated to the surplus of the year is identified with the projects funded by ISCIII (National Network of Biobanks Platform-PT13 and Biobanks Platform-PT17), by the Region of Madrid (Youth Employment Program, PEJ2016 / PEJ2017) and other research projects identified in the table above.

The breakdown of total revenues obtained in 2018 and 2017 has been as follows:

	2018	2017
Grants, donations and legacies charged to surplus for the year	1,762,213.63 €	1,206,348.64 €
Reimbursement of grants and subsidies	73,981.80 €	97,694.11 €
Sales and other income from commercial activity	6,033.97 €	5,866.66 €
Other income	530,588.86 €	524,630.33 €
Grants, donations and legacies transferred to capital surplus for the year	250.56 €	11.64 €
Financial income	108.32 €	13,925.68 €
TOTAL	2,373,177.14 €	1,848,477.06 €



2. MANAGEMENT REPORT

Breakdown of grants, donations and legacies charged to surplus for the year

	2018
ISCIII 2018 NOMINATIVE ALLOCATION	1,325,000.00 €
VALLECAS 2 PROJECT - QUEEN SOFIA FOUNDATION	300,000.00 €
CIIIEEN CONFERENCE 2018/ QUEEN SOFIA FOUNDATION	35,178.90 €
PT17-0015-0015/ ISCIIE	28,322.51 €
OTHER DONATIONS CHARGED TO SURPLUS	23,457.00 €
PEJ-2017-TL-BMD	15,463.89 €
PEJ-2016-MED-AI/ CAM	13,397.92 €
QUEEN SOFIA FOUNDATION - MAPFRE FELLOWSHIP 2017	12,000.00 €
PT13-0010-0045/ ISCIIE	7,044.85 €
IN-KIND DONATIONS	2,000.00 €
KING'S COLLEGE/MDS	348.56 €
TOTAL	1,762,213.63 €

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.

In the subsidies, donations and capital legacies item transferred to the surplus of the year (€ 530,588.86), a contribution from the Queen Sofia Foundation of € 473,427.65 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 ISCIIE financing of capital expenditures, € 51,202.68.

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



Revenues from provision of services during 2018

	2018	2017
Energy production	11,149.59 €	11,374.38 €
Revenues from performing MRIs and collaborative research projects	62,832.21 €	86,319.73 €
TOTAL	73,981.80 €	97,694.11 €

other dementias, and in a complementary manner to other types of research on diseases that are part of the CIEN Foundation's mission.

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 five fundamental activities:

Distribution of CIEN Foundation revenues

	2018	%	2017	%
Monetary aid and others	16,000.00 €	0.77%	40,253.30 €	1.82%
Variation of existences of merchandise	2,358.58 €	0.11%	2,696.60 €	0.12%
Supplies	106,165.92 €	5.09%	154,130.42 €	6.97%
Staff costs	802,162.35 €	38.42%	890,134.41 €	40.27%
Other operating expenses	623,160.17 €	29.85%	577,060.15 €	26.10%
Depreciation and amortization	537,836.69 €	25.76%	532,435.17 €	24.09%
Impairment and gains on disposal fixed assets	0.00 €	0.00%	0.00 €	0.00%
Exchange differences	55.85 €	0.00%	13,843.41 €	0.63%
TOTAL EXPENDITURE	2,087,739.56 €		2,210,553.46 €	



2. MANAGEMENT REPORT

- The Vallecas project
- BT-CIEN Tissue Bank.
- Alzheimer Program and 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).

The **Vallecas Project** is 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: 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 2018:

- **PT13 / 0010/0045:** Biobank Platform. Principal investigator: Dr. Alberto Rábano Gutiérrez. Project funded by the ISCIII with a budget of €44,478.26 for the year 2017-2018. An extension of execution has been approved by the General Subdirectorate of Evaluation and Promotion of Research of the Carlos III Institute of Health, extending its execution period until December 31, 2018 with no additional funding.
- **PT17 / 0015/0014:** Biobank Platform. Principal investigator: Dr. Alberto Rábano Gutiérrez. Project funded through Resolution of the Director of the Carlos III Institute of Health, of December 4, 2017 awarding grants for platforms supporting research in health sciences and technologies of the 2017 call for the Strategic Health Action, with a final budget of €135,300 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 financed 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.
- **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.

2.3.2 Fellowships and grants

During 2018 the CIEN Foundation has awarded/carried out the following fellowships and grants:

- **MAPFRE-Queen Sofia Foundation Fellowship 2016-2017.** On December 27, 2016, the Selection Committee decided to grant the scholarship to Mrs. Susana Navas Rutete. A 6-months stay, extendable for the same period, in the Dementia/Alzheimer's disease research

program at the Royal College of Surgeons in Ireland (RCSI), Dublin, Ireland, during the first 5 months. The remaining 7 months were held at the Queen Sofia Foundation Alzheimer Center until January 31, 2018.

- **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 52 profes-



2. MANAGEMENT REPORT

nals, of which 23 are hired from both subsidized and competitive grants, 12 have been students interested in carrying out internships in our center, 1 medical doctor intern that has made a rotation in our department of neuropathology, 1 Fullbright scholarship, 3 volunteers who have collaborated selflessly in the activities of the CIEN Foundation, 8 professionals have developed their activity thanks to collaboration agreements and 4 professionals who have been hired through a service provision contract.

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.

Incorporation of young talent

As every year, CIEN Foundation has continued with its commitment to young researchers and collaboration with public and private institutions. During 2018 has participated in the program "CAM Call for grants to hire research assistants and laboratory technicians funded by the European Social Fund, through the Youth Employment Operative Program (YEI) PEJ-2017-TL/BMD/7518" with one formalized hiring. With the aim that young researchers can start their careers and develop their potential, the CIEN Foundation participates in the theoretical and practical training of university students, both in Spain and in other European Union countries, through collaboration agreements carrying out university hands-on training.

One more year, the Call for Grants of the MAPFRE-Queen Sofia Foundation Fellowship will allow the incorporation of a specialist in biomedical sciences within the Alzheimer Project Research Unit.

CIEN Foundation Organization Structure

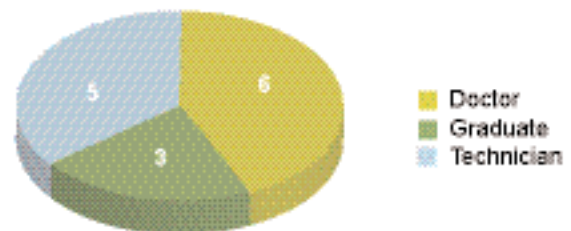
The different departments in which the human resources that make up the CIEN Foundation are lo-

cated and where our professionals have developed their work are the following:

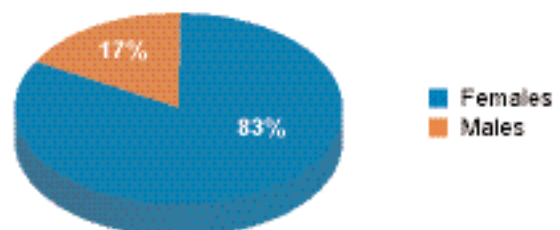
- Department of Management and Administration
- Department of Neuroimaging
- Department of Neuropathology and Tissue Bank
- Department of Molecular Genetics
- Department of Neurology
- Department of Neuropsychology

The following table shows the relationship of CIEN Foundation staff in 2018, 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 2018 the CIEN Foundation has offered or participated in the following training activities:

- Intensive Course on "Survival and Linear, Logistics and Cox Regression with SPSS". ICOMEM
- "Pathology of Sleep: From Neurobiology to Systemic Manifestations". Ramón Areces Foundation.
- I Symposium of Neurological Tissue Banks. Institute of Neurosciences of Castilla y León (INCYL), University of Salamanca.
- "EEG and EEG video. Advanced level". LXX Annual Meeting of the Spanish Society of Neurology. Seville Renaissance.
- Course on "European Patent Law Higher Program", School of Industrial Organization (EOI) and Center for International Studies of Intellectual and Industrial Property (CEIPI).
- VI International Conference on Research and Innovation in Neurodegenerative Diseases (CIIEN). CIEN Foundation, CIBERNED and Queen Sofia Foundation. University of Santiago School of Medicine.
- V Edition of the "Good laboratory practices" Course. Andalusian Government.
- Conference "An update on the contractual management of research centers upon the enforcement of Law 9/2017 of Public Sector Agreements". Secretariat of State for Research, Development and Innovation (SEIDI).
- Conference "The Strategic Action in Health 2018". Carlos III Institute of Health.
- Higher University Course on "Senior management secretariat". Rey Juan Carlos University and Organizational Business Initiatives.
- Office automation: "Computer Applications Management".
- Continuing education course on "New approaches to cognitive and behavioral disorders". La Paz University Hospital.
- Course on "Supervision on implementing a quality management system in accordance with the ISO 9001:2015 standard in biobanks and other biological sample management laboratories". Center for Continuous Training, University of Salamanca.
- Course on "R&D on demand and collaborative: modalities and instruments. Technology transfer agreements". Madrid R&D Foundation for Knowledge.
- Course on "Industrial and intellectual property rights in Horizon 2020". Madrid R&D Foundation for knowledge.
- "ALS Infoday" Day. Francisco Luzon Foundation.



2. MANAGEMENT REPORT

INTERNSHIPS

- ▶ Tutoring of external internships for students in the Department of Neuropsychology:
 - 1 student from the Autonomous University of Madrid
 - 2 students from the Complutense University of Madrid
 - 1 student from the Rey Juan Carlos University
- ▶ Tutoring of external internships for students in the Department of Neuropathology:
 - 2 student2 from the IES Moratalaz
 - 1 Final Master project from the Complutense University of Madrid. Master on Translational Medicine Research
 - 1 Final Degree project from the University of Extremadura. Biology Degree
 - 1 student from the Autonomous University of Madrid
 - 1 students from the General University Hospital of Alicante
- ▶ Tutoring of external internships for students in the Department of Neuroimaging:
 - 1 student from the from the Autonomous University of Madrid
 - 1 Final Master project from the Autonomous University of Madrid. Master on Neuroscience
 - 1 Final Master project from the Complutense University of Madrid. Master on Biomedical Engineering

FELLOWSHIPS

- MAPFRE-Queen Sofia Foundation Fellowship 2016-2017
- MAPFRE-Queen Sofia Foundation Fellowship 2017-2018
- Fullbright Fellowship

DOCTORAL THESIS

- PhD Committee. Persistence of fMRI bold signal at rest and its use as physiological marker. Università Degli Studi di Torino
- PhD supervision. "Subjective cognitive impairment as a reliable preclinical marker in Alzheimer's disease". Complutense University of Madrid
- PhD in Neurosciences by the Complutense University of Madrid (UCM). Degree of Doctor in Psychology with the thesis entitled "Subjective cognitive impairment as a reliable preclinical marker in Alzheimer's disease"

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 emergency and evacuation drill, in coordination with the Queen Sofia Alzheimer Center, stands out.





On June 4, 2018, 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 9 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 objectives of improving the safety and health conditions of workers and reducing accident rates taken as a reference by the Mutual Society for Work-related Accidents and Professional Illness have been met, keeping said indexes to zero and, therefore, below of the benchmarks of the Research and Development sector.

2.5. Quality Policy

In 2018, the transition to the new version of the ISO 9001: 2015 standard was made; as well as the renewal of the certificate of said standard.

For this purpose, the evaluation, administration, elimination and/or minimization of risks and opportunities were worked on and measures were taken to ensure the reduction of the effects of said risks. Opportunities were also effectively addressed and monitored.

The understanding of needs and expectations established the way in which the CIEN Foundation-CIBERNED responded to those measures. The CIEN Foundation-CIBERNED Management Office is open to any proposal for improvement, where it will be the organization's own leaders, who promote and develop a quality culture, and adaptation to the organization's changes.

2.6. Data Protection Law

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

	CNAE REFERENCE NUMBER	CIEN FOUNDATION	
	Accident rate limit	Value	Accident rate
INDEX 1	5.98	0	0
INDEX 2	0.54	0	0
INDEX 3	0.33	0	0



2. MANAGEMENT REPORT

its acronym in Spanish) and the new General Data Protection Regulation (GDPR) in force since May 2018.

This information is contained in the Safety Document, as well as the people involved in their handling and the premises in which they are placed, located at 5 Valderrebollo street, 28031-Madrid.

As the sole responsible for the files, the CIEN Foundation is committed to fulfilling its obligation of secrecy of personal data and its duty to save them, and to adopt the necessary measures to prevent their alteration, loss, or unauthorized access, taking into account at all times the state of the technology, and guaranteeing compliance with the GDPR at all times.



Staff from CIBERNED and CIEN Foundation Management and Deputy Scientific Director departments.



Scientific activity

The CIEN Foundation-managed Alzheimer Project Research Unit (IUPA, for its acronym in Spanish) has a strong multidisciplinary approach characterized by the continued collaboration between its five departments: three mostly devoted to basic research (Neuropathology, Neuroimaging and Molecular Genetics, previously called Laboratory) and two focused on the clinic (Neurology and Neuropsychology). Among its objectives are the following: varying out research projects in the field of neurodegenerative diseases, especially in Alzheimer's disease, and the periodic evaluation and monitoring of CAFRS patients.





3. SCIENTIFIC ACTIVITY

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

La actividad científica de la UIPA se estructura alrededor de cinco áreas de investigación con funciones complementarias:

- **Department of Neurology**
- **Department of Neuropsychology**
- **Department of Neuroimaging**
- **Department of Neuropathology**
- **Department of 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.

From the basic research side, UIPA's original project contemplated the creation of departments of 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 develo-

ped. 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.



3. SCIENTIFIC ACTIVITY

- 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.
- 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 (due to its size, a complete section in this report is dedicated to this study, see

block 4). 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): 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 eva-





luation, 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 2018, there were 35 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 1084 clinical evaluations (semi-annual frequency), 34 studies of brain MRI (annual frequency) and 250 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 Foun-

ation Alzheimer Center Research Program databases. In other instances, information provided by various collaborators is used.

- Detection of biomarkers of Alzheimer's disease in tear fluid
- Influence of the regular intake of drugs on cognitive performance in the Vallecas Project cohort (published article)
- Psychotic symptoms and vascular risk factors in Alzheimer's disease
- Behavioral disorders and neuropathological findings in Alzheimer's disease
- Components and effects of cognitive reserve in a cohort of the elderly

4. Other collaborative projects:

- Metabolomic study in patients with Alzheimer's disease or Mild Cognitive Impairment
- PET study with and amyloid tracer in patients with Alzheimer-type Mild Cognitive Impairment

5. Collaboration with the Master of Methodology from the Complutense University of Madrid Faculty of Psychology

Periodic multidisciplinary assessments during 2018

Admissions in Day Centre and Residence	35
Informed Consents	35
Baseline Assessments	70
Clinical Evaluations	1,084
Brain MRI Studies	34
Blood testing	250



3. SCIENTIFIC ACTIVITY

Team

This department is composed by the following staff:

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



Neurology team





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



3. SCIENTIFIC ACTIVITY

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.

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 es-

pecially 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:

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.

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.

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 Alzhei-

mer'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 in groups, with special emphasis on the activities of daily life performed in the middle stages of life.

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



3. SCIENTIFIC ACTIVITY

(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 of the Neuroimaging department of the CIEN Foundation. The euroimagen de la Fundación CIEN.

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 el-

derly. 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 therapies are a set of interventions that are set in place with 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 therapies, cognitive stimulation, physical exercise, occupational activity, music therapy and even diet control stand out.

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.

Team

- Miguel Ángel Fernández Blázquez. Dr. Psychology, Neuropsychology. Head of department.
- 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. SCIENTIFIC ACTIVITY



Department of Neuropsychology





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

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 nationals and internationals, on specific neuroimaging techniques.

During 2018, the Department of Neuroimaging has participated in MRI studies in the following clinical trials:

- **"Pilot clinical trial to evaluate the efficacy and safety of deep brain stimulation in Alzheimer's disease"**. ECP-EA. PI: Dr. Aurora Viloría Jiménez. San Carlos Clinical Hospital.
- **"NAC"**. Phase III study: "Effect of Adjuvant treatment with N-acetylcysteine for 48 weeks over the loss of gray matter and oxidative metabolism in patients with early onset psychotic episodes". Randomized, Double-blind, placebo-controlled Clinical Trial Code: FIBHGM-ECNC002-2012, EudraCT Number: 2012-005435-87. Promoter Center: Foundation for Biomedical Research Gregorio Marañón Hospital. PI: Celso Arango.
- **Clozapine** in First Outbreaks of Schizophrenia as Possible Preventive Treatment of Cerebral and Clinical Impairment". Code protocol:



3. SCIENTIFIC ACTIVITY

CLOZAPINA-1, N° EudraCT: 2006-00200-34. PI: Dr. Francisco Javier Sanz Fuentenebro. 2010-2013. CIBERSAM.

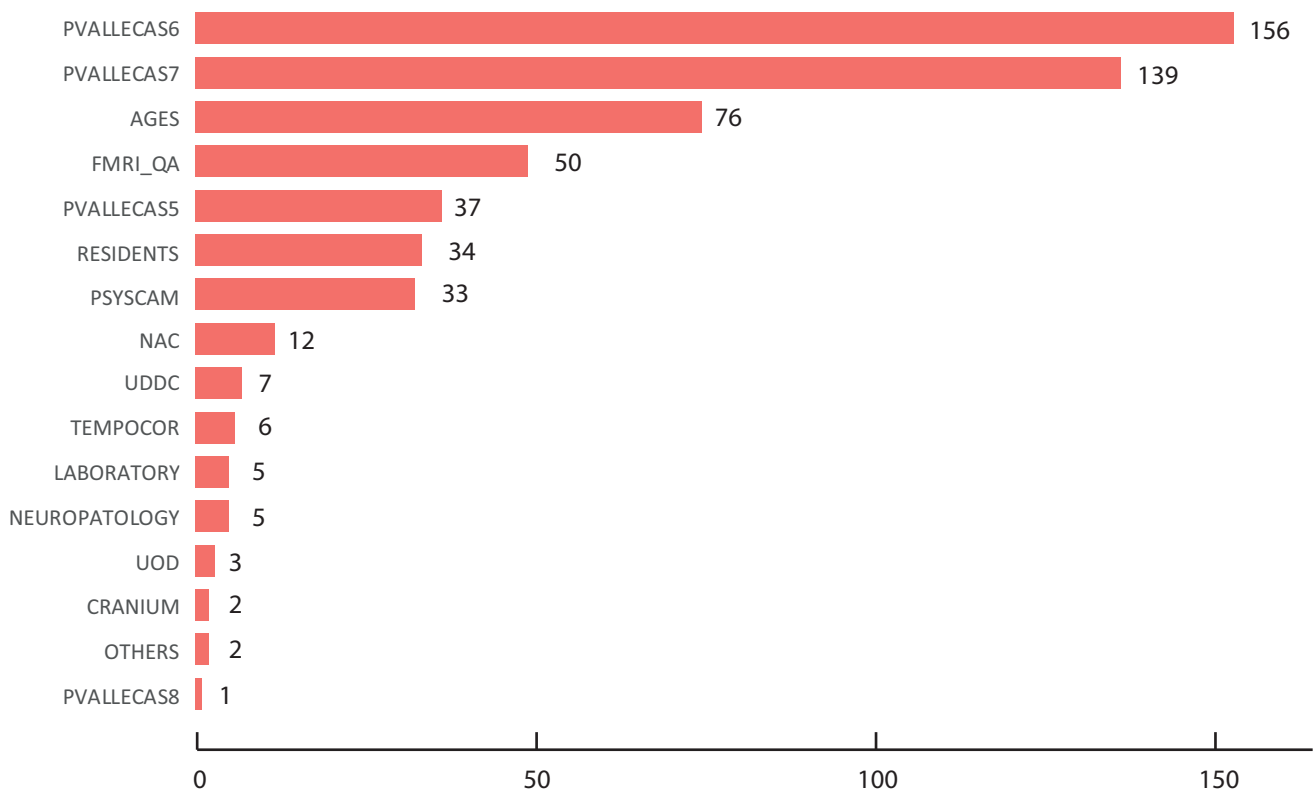
- **Project "Environment and genes in schizophrenia"**. Funding agency: Region of Madrid, in the framework of the Research Groups Program of the region of Madrid. Reference number: AGES-S2010 / BMD-2422. Duration 1-2-2012 / 12-31-2015. CIBERSAM.
- **PSYSCAN project:** "Translating neuroimaging findings from research into clinical practice". PI: Dr. Celso Arango.

- **TEMPACOR project:** "Dysfunction of the Temporo-Parietal Cortex as an Endophenotype of Depression". PI. Dr. Stephan Moratti, Prof. of Basic Psychology I.

During 2018 the acquisition of MR images from a 568 subjects has been completed. Overall, 3,178 MRI studies have been performed distributed among the different research projects.

55,411 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:

Number of studies by project 2018





	FUNCTIONAL	VOLUMETRY	SPECTRA	DIFUSSION TENSOR	MISC.	ASL
2008	255	339	156	178	312	259
2009	337	638	866	423	845	326
2010	910	852	1,042	556	1,506	305
2011	1,124	845	786	528	1,904	398
2012	1,858	1,512	583	1,330	2,938	949
2013	1,436	1,276	516	1,116	2,544	950
2014	880	937	367	847	1,920	729
2015	828	912	309	783	1,985	669
2016	739	749	341	618	1,661	572
2017	614	648	299	594	1,415	523
2018	487	519	226	124	1,051	367

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.

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:

Research fellows

- Linda Zhang (PhD in Radiological Imaging. Grad. Psychology).
- Jaime Gómez-Ramírez (PhD, Computer Engineering, Automatics and Robotics).
- Marta Garo (Master in Neurosciences). Since July 2018.
- Pablo Gómez del Campo del Bosque (Master in Biomedical Engineering). Since November 2018.
- Kimberly Bress (Fullbright Scholar, USA). Since September 2018



3. SCIENTIFIC ACTIVITY

Radiodiagnostics

- Mabel Torres Llacsca (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)

Administration

- Arantza Narciso
(Administrative Assistant)
- Corina Ghinea
(Administrative Assistant)



Neuroimaging team





3. SCIENTIFIC ACTIVITY

3.2.3. 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 (Alzheimer's pathology, Vascular pathology and Lewy pathology, mainly).

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.

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, ARTAG) as models of tauopathy with predominant involvement of the medial temporal lobe.
- 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.
- Distinctive features of Alzheimer-type pathology in nonagenarians and centenarians. Neuropathological findings in subjects without cognitive disorder above 90 years of age.
- Clinical-pathological and molecular characterization of other focal neurodegenerative pathologies (in addition to tauopathies) with a predominance in the medial temporal lobe: hippocampal sclerosis

associated with dementia and Lewy pathology limited to the amygdala.

- 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 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



3. SCIENTIFIC ACTIVITY

- 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.

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.

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.

The BT-CIEN registry had 660 registered donors by December 31, 2018.

Up to 107 cases were processed in the Neuropathology laboratory during 2018, with the following distribution depending on the origin (see right)

According to these data, the number of donation cases extracted and processed entirely in the UIPA in 2018 amounted to 73, which is slightly lower than

that obtained in 2017. As in the previous year, the increase in donations from the Internal Donation Program is noteworthy, with 152 total donations until the end of 2018.

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 2018 have been:

- Karolinska Institutet. Center for Alzheimer Research (Estocolmo)
- Research Functional Unit in Chronic diseases, ISCIII, Madrid.
- Medical School, University of La Laguna, Tenerife,
- Medical School, University of Castilla-La Mancha, Ciudad Real
- Cajal Institute, CSIC
- Center for Molecular Biology "Severo Ochoa", CSIC, Madrid
- Institute of Biomedical Research "Alberto Sols"
- Oslo University Hospital
- 12 de Octubre Hospital Research Institute
- Center of Applied Medical Research (CIMA), University of Navarra
- Royal College of Surgeons in Ireland
- Universität Göttingen, Deutsches Zentrum für Neurodegenerative Erkrankungen

Research projects

"Use of hyperoxia combined with vasculature normalizing agents for the treatment of Alzheimer's disease, a proof of concept." Project funded by the Domingo Martínez Foundation. Principal investigator: Alberto Pascual, Seville Biomedicine Institute

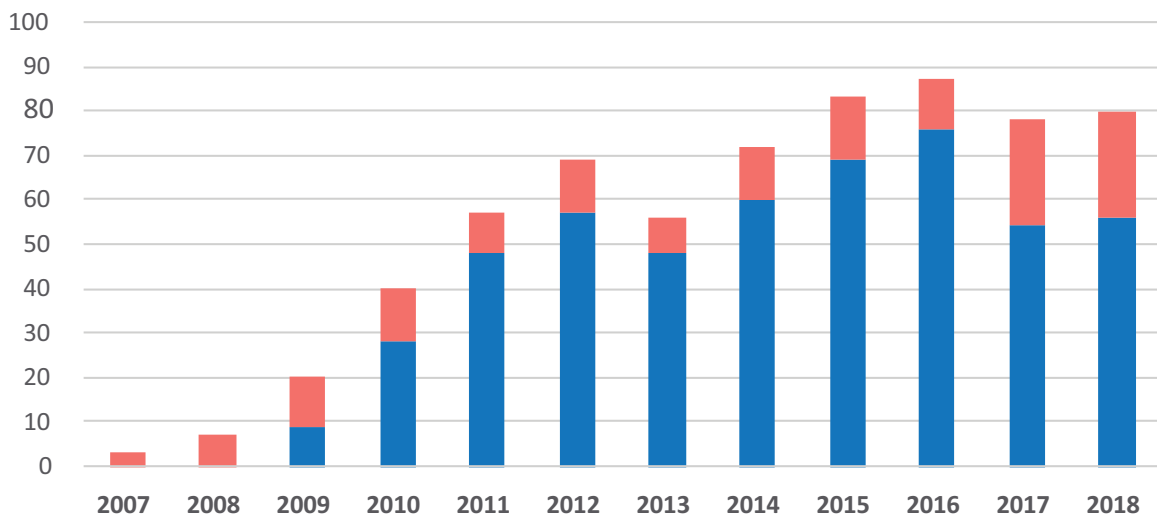


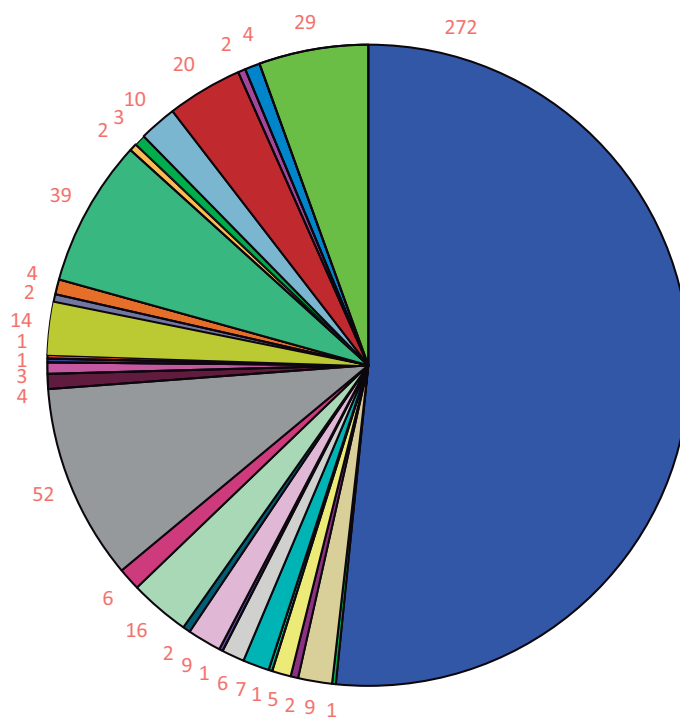
3. SCIENTIFIC ACTIVITY

(IBiS)/CSIC. Alberto Rábano and Valentina González, members of the research team. Duration: 2018

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

55 donations from the External Program ■
18 donations from the Internal Program ■
34 consultation cases
(not included in the graph)





- Sporadic Alzheimer's disease
- Inherited Alzheimer's disease
- Multi System Atrophy
- ARTAG
- Degenerative ataxias
- CADASIL
- Control brains
- Corticobasal degeneration
- Frontotemporal lobe degeneration-FUS
- Frontotemporal lobe degeneration-Pick
- Frontotemporal lobe degeneration-Tau
- Frontotemporal lobe degeneration-TDP
- Argyrophilic grain disease
- Amyotrophic Lateral Sclerosis
- Encephalitis
- Hippocampal sclerosis
- Multiple sclerosis
- Normal pressure hydrocephalus
- Huntington's disease
- Non-specific findings
- Leukoencephalopathy
- Lewy body disease
- Central Nervous System malformations
- Metabolic disorders
- Parkinson's disease
- Progressive Supranuclear Palsy
- Tauopathies (other)
- Tumors
- Cerebrovascular disorder



3. SCIENTIFIC ACTIVITY

Team

During 2018, the Department of Neuropathology staff was composed of the following personnel:

- Dr. Alberto Rábano (MD, PhD, Pathology), Head of Department and BT-CIEN
- Izaskun Rodal González (Pathology Technician)
- Laura Sáiz Auz (sample management technician)
- Valentina González Álvarez (biologist, quality program and special samples)

- Eugenia Hitt Rech (Pathology Technician). Since March 2018

Collaborators (autopsies):

- Luis Javier Martín Lentijo (Pathology Technician)
- Ana Sánchez de Castro (Pathology Technician)
- M^a Cruz Santiago San Marcos (Técnica de Neuropatología).



Neuropathology team





3.2.5. Department of 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 β 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 pre-clinical 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 de-

mentia 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.

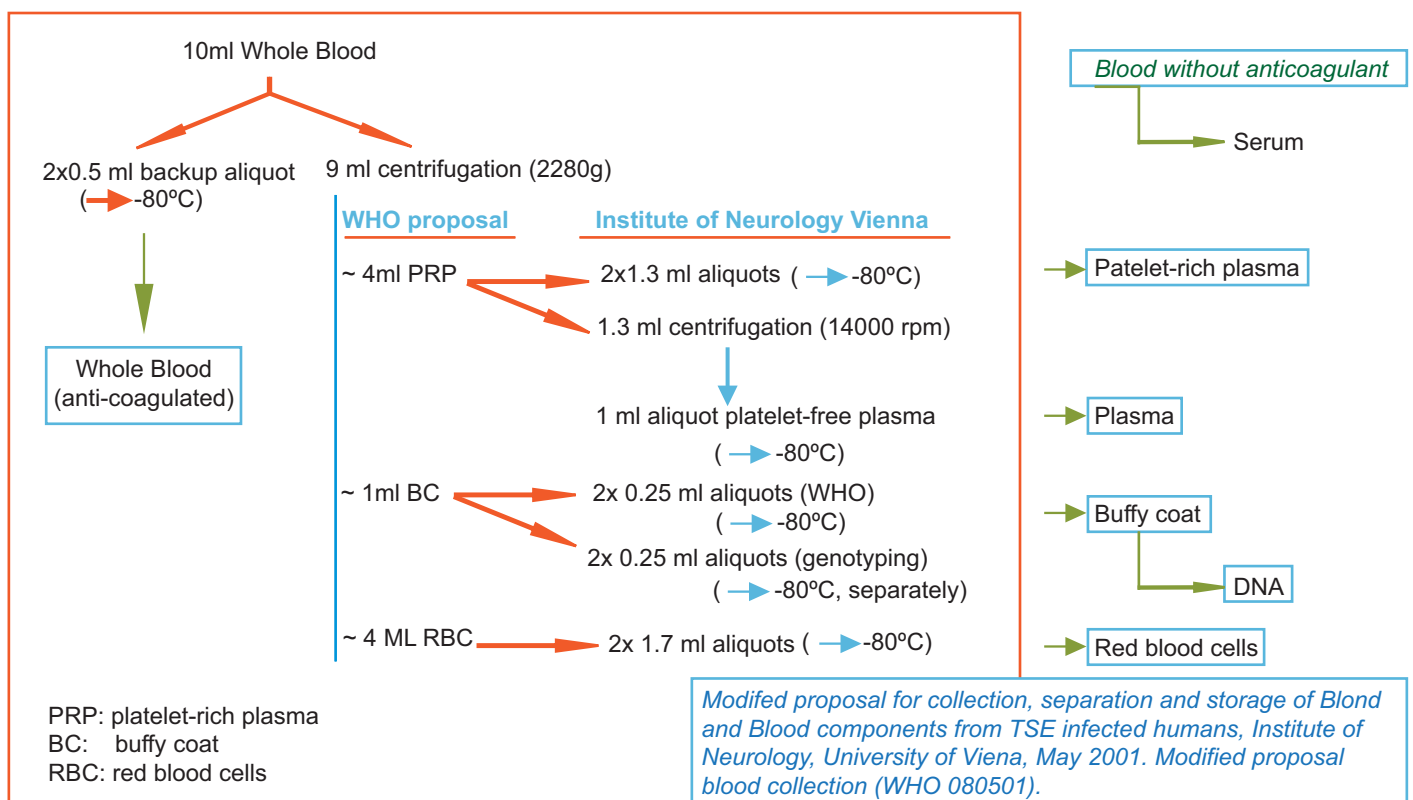


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The phase of recruiting volunteers for participation in the study was finished in December 31, 2013, with its corresponding baseline assessment (n=1,169). The project includes activities from the five research areas of the CIEN Foundation. During 2018, 388 volunteers were studied, distributed in 44 volunteers from the fifth follow-up visit of the study, 165 volunteers from the sixth visit, 172 from the seventh visit and 7 from the eighth visit.

Of all patients 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

Protocol for blood fraction collection, separation and storing



Vienna Institute of Neurology Protocol for blood processing in various fractions for the search for biomarkers and susceptibility genes.





lacking anticoagulant to obtain serum are processed.

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).

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.

Research Program of the Queen Sofia Foundation Alzheimer Center

This program focuses on regular and protocol-based monitoring of a cohort of CAFRS patients with dementia, either as residents at the Center or atten-

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

Evaluation	1st	2nd	3rd	4th	5th	6th	7th	8th	TOTAL
N° samples	1,169	767	755	699	618	249	0	0	4,257
2018 samples	0	0	0	0	44	165	172	7	388
Total	1,169	767	755	699	662	414	172	7	4,645
N° Aliquots	16,366	10,738	10,570	9,786	9,268	5,796	2,408	98	65,030



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dants 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 conventional

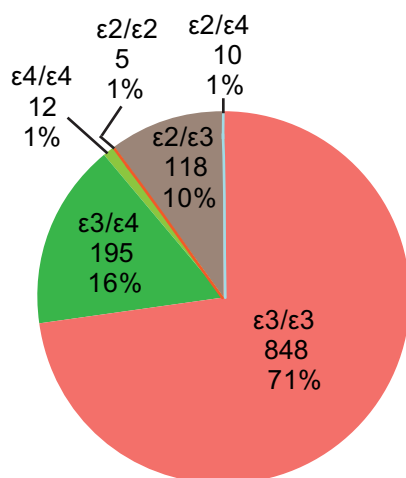
analytics. Thus, performing a venipuncture in the patient for research purposes only is avoided. After extraction, each blood sample is processed at once, resulting in 14 aliquots comprising various hematologic derivatives (whole blood, plasma, serum, etc.), including extraction of DNA for genetic studies.

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 2,946 (15.8% patients corresponding to the Day Centre), which have resulted in a total of 41,244 aliquots of different fractions derived from blood samples.

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

APOE genotypes



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 pathophysiology

During 2018 the project entitled "miRNA and lipid metabolism markers as potential links between vascular dysfunction and Alzheimer's pathophysiology" has continued, funded from MINECO (RETOS call for

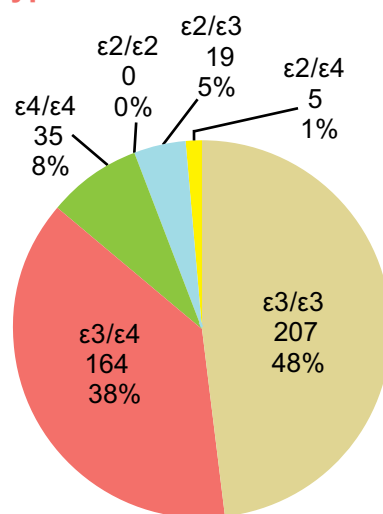




projects), whose main investigators are Drs. Miguel Medina and Miguel Calero. The main objective of this proposal is to explore the possible role of miRNAs and markers of lipid metabolism as possible links between peripheral vascular dysfunction and the pathophysiology of AD. The design of the project is based on a double approach with complementary aims related to the existing cohorts (Vallecas Project and Research Program of the Vallecas Research Center (PICAIV) 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

Distribution of APOE genotypes in the CAFRS patients cohort

APOE genotypes



3. SCIENTIFIC ACTIVITY

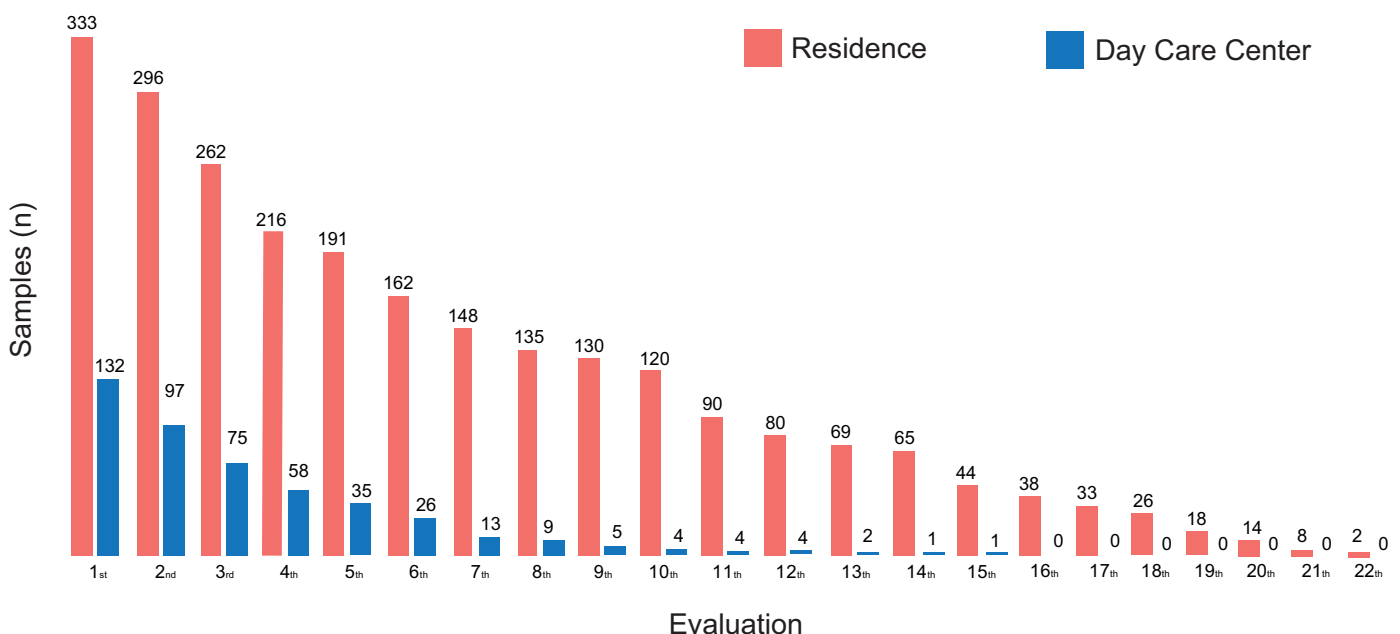
carry out a complementary and synergistic approach to evaluate, validate and standardize the identification, monitoring, quantification and functional validation of miRNAs in plasma samples taken from elderly subjects who are cognitively normal, show deterioration cognitive mild or moderate dementia, 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 mo-

lecular, 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 2018, research activities continued to be carried out orien-

Samples obtained up to December 31, 2018 according to the number of semiannual evaluations





ted towards the definition of new genetic risk factors and the participation of the national consortium in international proposals.

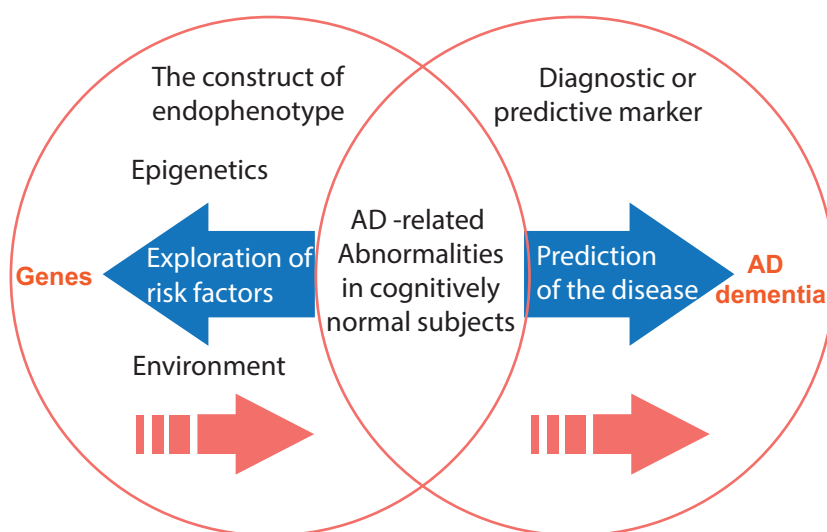
In addition to the study of the APOE gene, using samples from the Vallecas Project (controls) and samples from the Alzheimer Project (AD cases), genetic association studies of the main genes associated with AD have been carried out, including SORL1, LDLR, BIN1, CLU, ABCA7, CR1, PICALM, BACE1 and PRNP. 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 defi-

ning 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 below)

An 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

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



3. SCIENTIFIC ACTIVITY

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 development 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 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 463 CSF samples from donor's brain and 315 skin samples.





Team

Collaborators

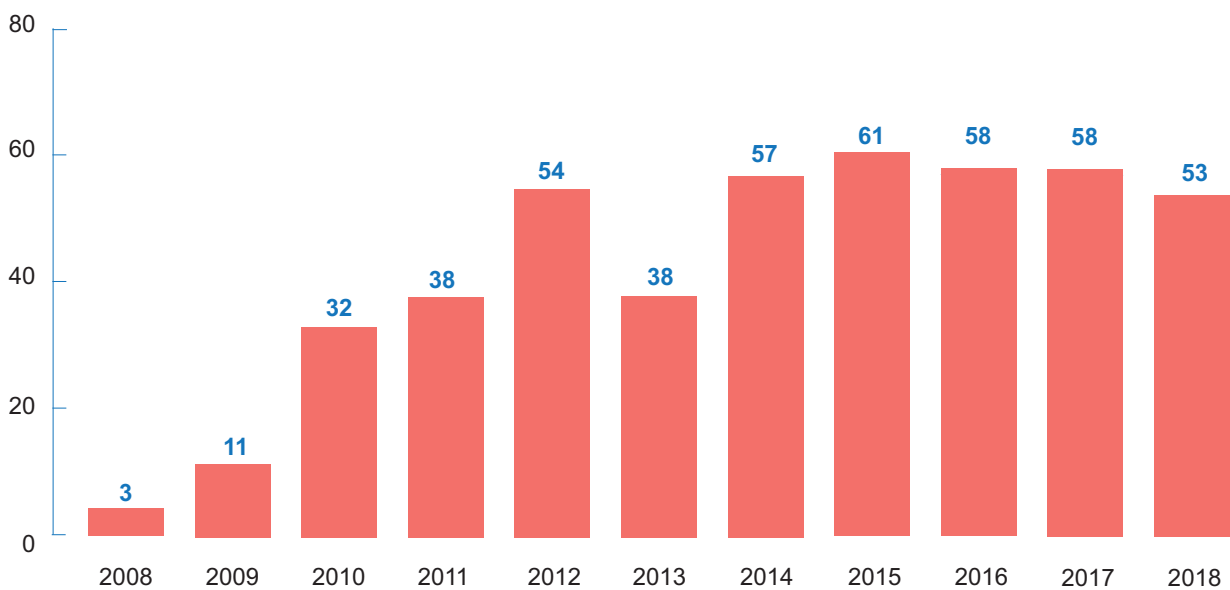
During 2018, the team of the Molecular Genetics Department was composed of the following personnel:

- Miguel Calero Lara (PhD, Chemistry)
Head of Department
- Ana Belén Pastor López (Laboratory Technician)

- Olga Calero Rueda (PhD, Biology)
- Andrés Rodríguez Martín (Laboratory Technician, CIEN Foundation-Biocross agreement)
- Sergio Veiga Herrero (PhD, Biology CIEN Foundation-Biocross agreement)

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

(LCR) post-mortem (n=463)



3. SCIENTIFIC ACTIVITY



Molecular Genetics team



The Vallecas Project

Aging is one of the biggest risk factors for some of the most prevalent diseases, such as neurodegenerative diseases. In 2018, the CIEN Foundation and the Queen Sofia Foundation have signed an agreement to extend the duration of the Vallecas Project. This longitudinal study that seeks to detect early Alzheimer's disease has a horizon of ten years, compared to the five initially planned. During the year, the fifth, sixth and seventh follow-up visits of the volunteers participating in the study have been carried out simultaneously.





4. THE VALLECAS PROJECT

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 2017 there are 8.7 million people in Spain aged 65 or over (18.87% 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 by 2050 a third of the population will be over 65 years, so that approximately one million Spaniards could have dementia by then.

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, organizational 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

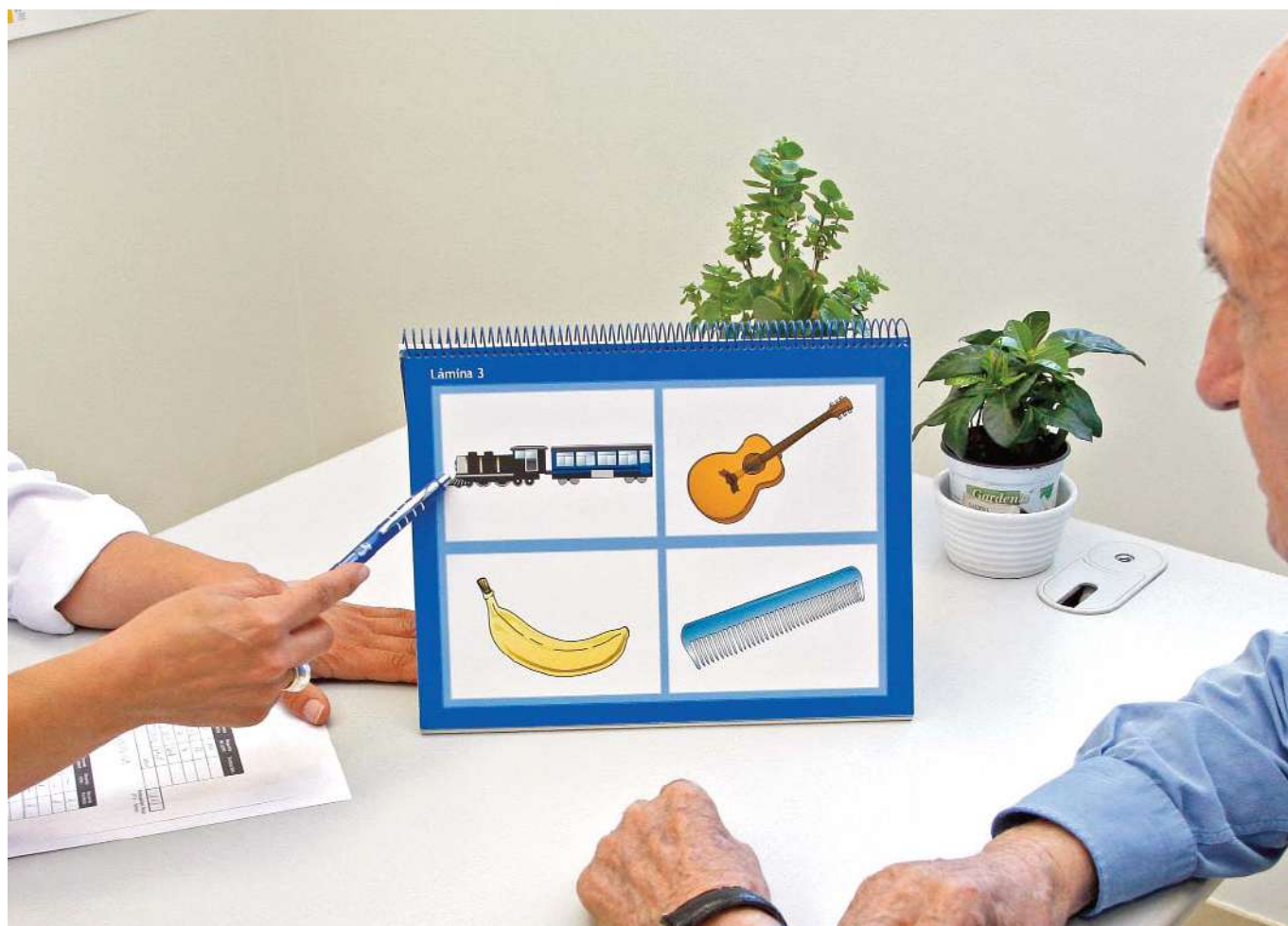




wellbeing, but also mental and cognitive health and therefore on the incidence of dementia in the elderly population. Thus, the analysis of risk factors related to the symptoms of dementia must be accompanied by a comprehensive phenotypic characterization in order to provide a better understanding of the underlying neurobiological mechanisms.

The concept of population studies - that is, the recruitment of participants from community environ-

ments 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



4. THE VALLECAS PROJECT

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 progression, 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 2018 we are at finishing the sixth visit for the whole cohort, towards the middle of the seventh and just started the eighth (see figure in section 1.6 of this Report).

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:

THE VALLECAS PROJECT IN FIGURES

Recruited sample	1,213
Excluded at baseline	47 (3.87%)
Age	
Sample mean	74.46 years
Age gorup 69-74	671 (55.32%)
Age gorup 75-79	379 (31.24%)
Age gorup > 80	163 (13.44%)
Gender	
Females	780 (64.30%)
Males	433 (35.70%)
Education	
Sample mean	10.35 years
Illiteracy	4 (0.34%)
Read/Write	60 (5.11%)
Minimum studies (numeracy skills)	154 (13.11%)
Primary Education	389 (33.11%)
Senior High School / Professional training	282 (23.99%)
University Education	286 (24.34%)



4. THE VALLECAS PROJECT

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

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.
- Since 2018, 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

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 neu-

	VISITS						
	1°	2°	3°	4°	5°	6°	7°
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)	✓	✓	✓	✓	✓	✓	✓
Clinical Dementia Rating (CDR)	✓	✓	✓	✓	✓	✓	✓



4. THE VALLECAS PROJECT

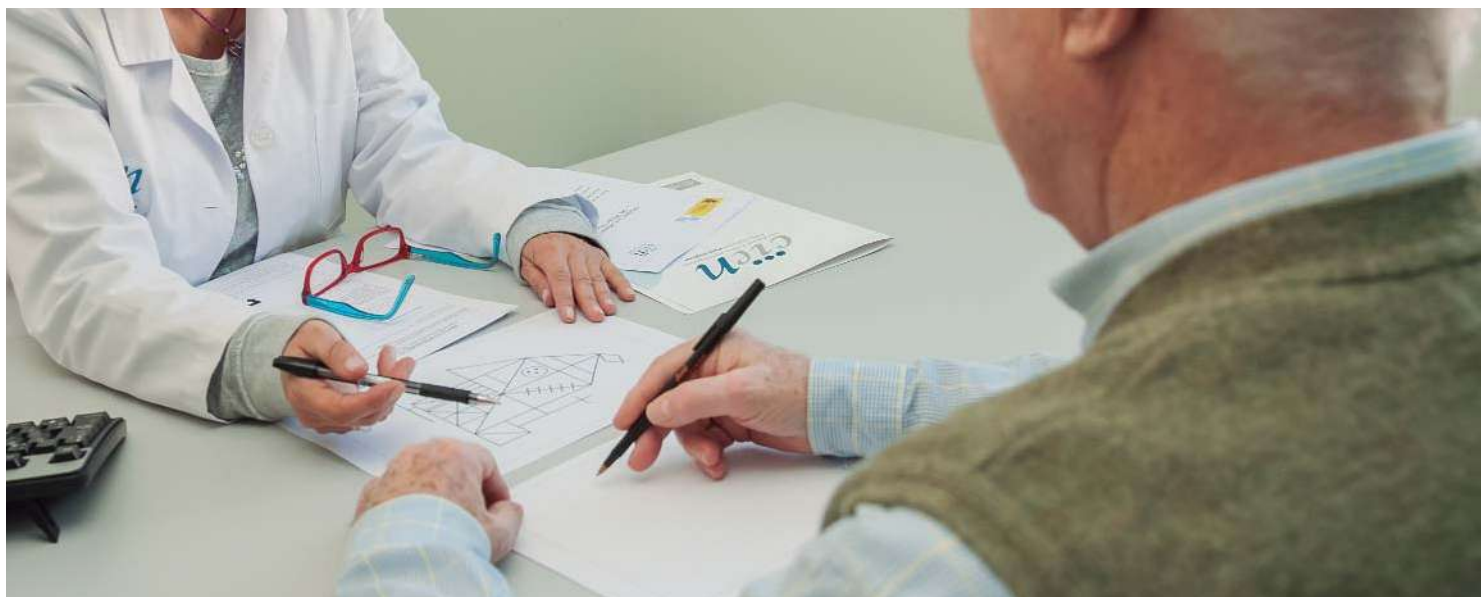
ropsychological profile is completed by getting information related to other cognitive domains such as language, visuospatial ability and visuoconstruction. All these data allow identifying the strengths and weaknesses in the cognitive profile and characterizing, if necessary, the type of cognitive impairment that an individual presents. Table XXX 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.

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 samples 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:

1st Visit	1,169
2nd Visit	767
3rd Visit	755
4th Visit	699
5th Visit	662
6th Visit	414
7th Visit	172
8th Visit	7
TOTAL	4,645

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 microstruc-

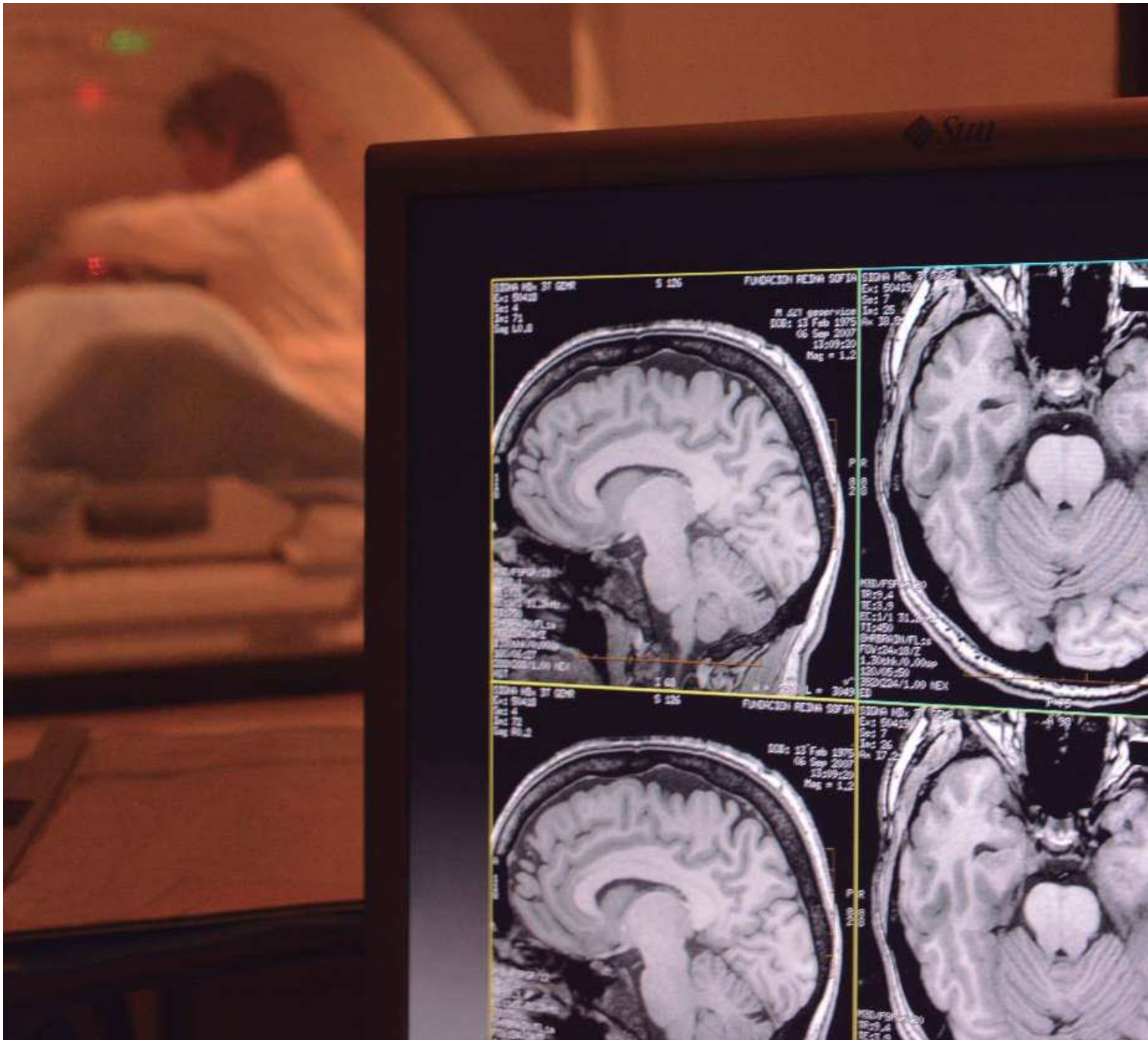
tural changes who have been described in post-mortem studies of brain tissue. Accordingly, the project aims to conduct a series of studies based on various MRI modern techniques that can provide volumetric quantitative indexes of the morphological changes.

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**
 Cerebral 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.



4. THE VALLECAS PROJECT





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 2018, Dr. Zhang received the Queen Sofia Foundation-MAPFRE Scholarship. The objective of his scholarship has been the extension of the analysis of the T1 sequences of all the visits of the Vallecas Project. This step has allowed us to verify, with an independent sample, an algorithm that predicts MCI in healthy people developed from the data of visits 1 and 2. With the same purpose, additional analyses have also been carried out on the Alzheimer's Disease Neuroimaging Initiative (ADNI) public database. The Vallecas Project not only allows us to investigate risk factors for the loss of cognitive abilities, but also

allows us to look for the parameters associated with those abilities that are maintained over time in some individuals. These are the so-called "Superagers", whose definition according to researchers at the Northwestern University in Chicago includes people over 80 years of age and with an episodic memory equal to or greater than of healthy people 50 to 60 years old. In June 2018, Marta Garo Pascual, student of the Neurosciences master's degree at UAM, as part of her final master's work has identified a sample of "Superagers" in visit 2 of the Vallecas Project. During her study, she made a structural analysis of the MT images from these subjects, as well as the analysis of some demographic factors that could be associated with this condition of "super aging."

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 2018, parts of the fifth, sixth and seventh follow-up visits of the project volunteers have been done simultaneously.

Percentage of visits in the Vallecas project during the year 2018

VALLECAS PROJECT ACTIVITIES DURING 2018

Number of fifth visit assessments	47
Number of sixth visit assessments	196
Number of seventh visit assessments	181
Number of eighth visit assessments	1



4. THE VALLECAS PROJECT

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

VALLECAS PROJECT CLINICAL EVALUATIONS OCTOBER 2011 - DECEMBER 2018

First visit	1,176
Excluded at baseline	47
Second visit	967
Third visit	870
Fourth visit	778
Fifth visit	703
Sixth visit	473
Seventh visit	181
Eight visit	1
Drop outs	728
Do not comply with inclusion criteria	34
Deceased	30
Diagnosis of neurological disease	53
Volunteer withdrawal	611



International *re*lations

During 2018, the CIEN Foundation has reinforced and consolidated its international cooperation activities. To its participation in the European Union Joint Programming for Research on Neurodegenerative Diseases (JPND) and in the Network of Centers of Excellence in Neurodegeneration (CoEN), it must be added the participation of its researchers in the Innovative Training Networks (ITN), actions created by the EU under the H2020 program, as well as the implementation of research projects supported by the Alzheimer's Association. To complete the international activity of the year, the sixth edition of CIIEN was held in Santiago de Compostela.





5. INTERNATIONAL RELATIONS

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 in-

ternational 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 (CIBERNED, 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 Neurodegene-



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ration (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 for Research in Neurodegenerative Diseases (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 num-

ber 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". Currently, the CIEN Foundation does not have any active research projects through the JPND, but its researchers will continue to participate actively in the program.

■ 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 acce-





lerate 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,



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whereas the 4th call is expected to be 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 19th to 21st September 2018, it was held in Alicante, Spain the VI International Congress on Research and Innovation in Neurodegenerative Diseases (CIIEN), promoted by the Queen Sofia Foundation in collaboration with CIEN Foundation and CIBERNED. The main objective of CIIEN is providing a forum in which to share progress and information of interest on neurodegenerative diseases among the scientific community.

The CIIEN, created in 2013, definitely consolidates the two major scientific conferences on neurodegenerative diseases organized in Spain: the International Symposium on Advances in Alzheimer's Disease, promoted annually by the Queen Sofia Foundation and CIEN Foundation, and the CIBERNED Scientific Forum, which brought together every year the research groups constituting the CIBER in Neurodegenerative Diseases. Unifying both congresses was a first step in creating a new operating structure in the two main institutions devoted to research on neurological and neurodegenerative diseases in Spain: the CIEN Foundation and CIBERNED, both dependent on the Ministry of Science, Innovation and Universities through the Carlos III Institute of Health. This new structure seeks greater effectiveness and efficiency in research, favoring an interaction between the different research groups.

This sixth edition of CIIEN was held at the Faculty of Medicine of the University of Santiago de Compostela and during three intense days of presentations and sharing of knowledge, gathered well over a hundred international experts. Organized by the Queen Sofia Foundation, CIEN Foundation (Foundation Center for Research in Neurological Diseases) and CIBERNED (Network Center for Biomedical Re-

search in Neurodegenerative Diseases), the VI Congress CIIEN is a forum for exchange on the main advances in research and treatment of Alzheimer's, Parkinson's, Huntington's, and other neurodegenerative diseases.

The invited speakers included world leaders such as Harald-Jürgen Hampel (University of the Sorbonne, France), who spoke about the developments in precision medicine for Alzheimer's disease in his inaugural lecture; Michael T. Heneka (Medical Research Center of the University of Bonn, Germany), who focused on the relationship between the innate aspects of the immune system and Alzheimer's disease; and Adriano Chiò (University of Turin, Italy), who delved into the role of cognitive phenotypes. In addition to the intervention of the scientific director of CIEN Foundation and CIBERNED, Jesús Ávila, and the deputy scientific director, Miguel Medina, the Congress included internationally recognized speakers, including Isabel Fariñas (University of Valencia), whose presentation focused on the effects of certain extracellular proteins in the stem cells; Ángel Carracedo (University of Santiago de Compostela), with a work on the search of genes involved in neurodegenerative diseases, and José Luis Labandeira-García.

Likewise, and responding to the vocation to promote the training of young researchers of CIBERNED, the Young Researcher Award was awarded during the congress to Julia Pose Utrilla, who made presented the study which has been granted such recognition.

In short, this event is consolidated in its sixth edition as a meeting point for the best national and international leading experts in neurodegenerative diseases, enabling sharing of knowledge, working methods, new advances and discoveries, in a field in which international cooperation between institutions is decisive for obtaining optimal results in research.



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5.5. Other International Activities

5.5.1. H2020: MARIE SKŁODOWSKA-CURIE ACTIONS: 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. During 2018, the CIBERNED groups have participated in two of these actions in collaboration with CIEN Foundation:

1. Blood Biomarker-based Diagnostic Tools for Early-stage Alzheimer's Disease – BBDiag

The main objective of this project carried out within the international network "Innovative Training Networks" of the EU (ITN-BBDiag research project) is the development of a new non-invasive methodology aimed at the identification and validation of blood biomarkers with diagnostic value, in preclinical





models of Alzheimer's disease (AD). To do this, we will analyze AD biomarker levels in blood, related to the main changes that appear in the brain in animals with AD and in different disease stages (starting from the prodromal state). For this we have established 7 experimental groups (2, 3, 4, 6, 9, 12 and 15 months-old animals) according to the presymptomatic and postsymptomatic characterization of AD in these animals. Additionally, we have standardized a non-invasive method of taking plasma samples from the different age groups of AD transgenic mice. This non-invasive blood collection protocol was optimized and cross-validated with other researchers in the field. We have also carried out several immunocytochemical and immunohistochemical analyzes to examine the specific load of beta-amyloid (A β) plaques in correlation with neuroinflammation and neurogenesis during the progression of pathology both in cortical and the hippocampal areas. Next, we have pre-validated, in collaboration with other laboratories members of the consortium, possible biomarkers that will finally be validated using technology based on the use of biosensors.

As an added value, we have analyzed in vitro neurogenesis in 2D cultures, and also in vivo. We have managed to establish primary cultures from our prodromal animal model and also in late stages. One of the main challenges in this regard is to find in vitro and in vivo the relationship between neurogenesis and the appearance of biomarkers. In addition, we are using new neuroprotective agents developed in the laboratory to discover how to improve the progression of the disease in preclinical models of Alzheimer's disease. We are currently performing an in vitro analysis of factors involved in such neuroprotection for

once the in vitro results have been obtained, to carry out a complete study in vivo. The development of a new model 2-3D in vitro to study neurodegenerative pathology, especially in AD, is mandatory in the understanding of the pathophysiological pathways involved in the disease and could lead to an advance in drug development and subsequent treatment of this disorder

2. Interdisciplinary training network on the purinergic P2X7 receptor to control neuroinflammation and hyperexcitability in brain diseases - PurinesDX

PurinesDX encompasses global leaders in translational research on purinergic signaling, clinical specialists in a wide range of brain disorders and industry partners specializing in the drug development and biomarkers. Throughout this first year of the PurinesDX Project, we have focused on the study of the P2X7 receptor status in patients with Huntington's disease in relation to its messenger RNA isoforms and protein levels. Regarding the activities related to interdisciplinary training, our Early Stage Researchers (ESR) have participated in several meetings and symposia in which they improve the collaborations with the other participants of the consortium. Starting in April, we attended the Introduction Program and the Mini-Symposium on Nervous Diseases: New Approaches in Diagnosis and Therapeutics. Our ESR also participated in the First Transferable Skills Course where they were able to learn about statistics, the importance of social networking in research and scientific writing skills, among others. In October, we attended the PurinesDX Project Follow up Meeting where the EU commission reviewed our work during the first months of project execution. Our ESR also participated in the Second Transferable Skills



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Course where they learned about 3D imaging, business plan organization and resource management, among others.

5.5.2. Alzheimer's Association

The Alzheimer's Association is a non-for-profit organization that focuses on the care and support for patients with Alzheimer's disease, and also funds research through competitive calls for research projects on Alzheimer's disease. During the year 2018, CIEN Foundation researchers in collaboration with CIBERNED and the Technical University of Madrid have received funding from the Alzheimer's Association through 2 research projects:

1. **A multicenter, randomized, double-blind, placebo-controlled, 4-arm, 26 week parallel-group study to evaluate the safety, tolerability and anti-inflammatory effect of three oromucosal doses of Sativex® in patients with mild cognitive impairment of Alzheimer type or early Alzheimer dementia (Sat-CIEN-02)**

Principal Investigator: Dr. Isidro Ferrer (CIBERNED)

During 2018 we continued with the activities of this clinical trial, included in an open and competitive call of the Alzheimer's Association that was approved and financed by it to be developed in Spain during the period of Sept-2016 to Oct-2018.

The primary end-point of the trial is to prove the safety and tolerability of the cannabinoids in these patients; in addition some hints about their potential therapeutic effect are expected and will be useful for the design of future efficacy studies. The selected doses in accordance with previous experimental animal studies are low and without psychoactive effects. The indication of these drugs in the Alzheimer's disease is based on their modulatory action on

the synaptic activity and their potent anti-inflammatory and neuroprotection effect.

2. **The healthy elderly brain: MRI predictors for developing MCI.**

Principal Investigator: Dr. Bryan Strange (UPM, FCIEN)

The problem addressed in this project is the current lack of techniques to predict whether or not a healthy elderly person will develop Alzheimer's disease (AD). This is important, since treatment for this progressive neurodegenerative disorder is more likely to succeed if it is administered as soon as possible in the development of the disease. The funded project investigates data from a large sample: that of the 1,213 volunteers who are part of the Vallecas Project (aged 70-85 years, men and women), followed in a 5-year longitudinal study. At each annual visit, volunteers undergo a detailed neuropsychological and clinical evaluation, blood tests and a complete cerebral magnetic resonance imaging (MRI) protocol. During follow-up, some volunteers move from a cognitively healthy state to a state of mild cognitive impairment (MCI). The objective of the project is to retrospectively identify biomarkers in healthy individuals who predict the subsequent development of DCL. In contrast to the extensive research effort to determine MRI parameters as a prediction of the conversion of MCI into AD, much less is known about specific brain biomarkers that predict the previous step: moving from healthy to MCI. The novelty of this proposal, and the significant progress, is to identify the changes in the brain present in healthy elderly groups that are clinically indistinguishable, and that differ only later in the development of MCI. Structural MRI (T1, T2 weighted), weighted



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diffusion (DWI), functional (resting state magnetic resonance) and perfusion studies (ASL) have been performed in approximately 1,000 volunteers. The first goal of this proposal is to examine MRI in healthy elderly individuals who can predict the subsequent development of MCI. A first analysis of whole brain gray matter density (GMD) in these "converters" in relation to a matched control group selected from the entire cohort - on visit 1 (when both groups are healthy) - has already shown fascinating specific differences in the entorhinal cortex. The same type of analysis will now be extended to measures of white matter integrity, perfusion and functional resting networks to provide a complete picture of the brain abnormalities present before MCI onset. While the first analyses show differences between groups in the MR data, this proposal aims to develop a method that - for a given healthy individual - provides predictive value as to whether that person will subsequently develop MCI. For this, demographic, neuropsychological, biochemical and genetic data are used in our analyses, in addition to MR data of all the sequences described above. A machine learning approach is being followed to generate a statistical algorithm to determine the probability of a healthy individual converting to MCI in a given period of time. In addition, some volunteers are expected to move from MCI to AD, thus providing a measure of whether these biomarkers could be extended to predict the developed AD from a healthy state.

The determination of brain imaging biomarkers that in healthy people predict the development of MCI will have a significant impact on the field of dementia. Data acquired on a relatively routine basis can give an individual a risk index for the future development of MCI that will

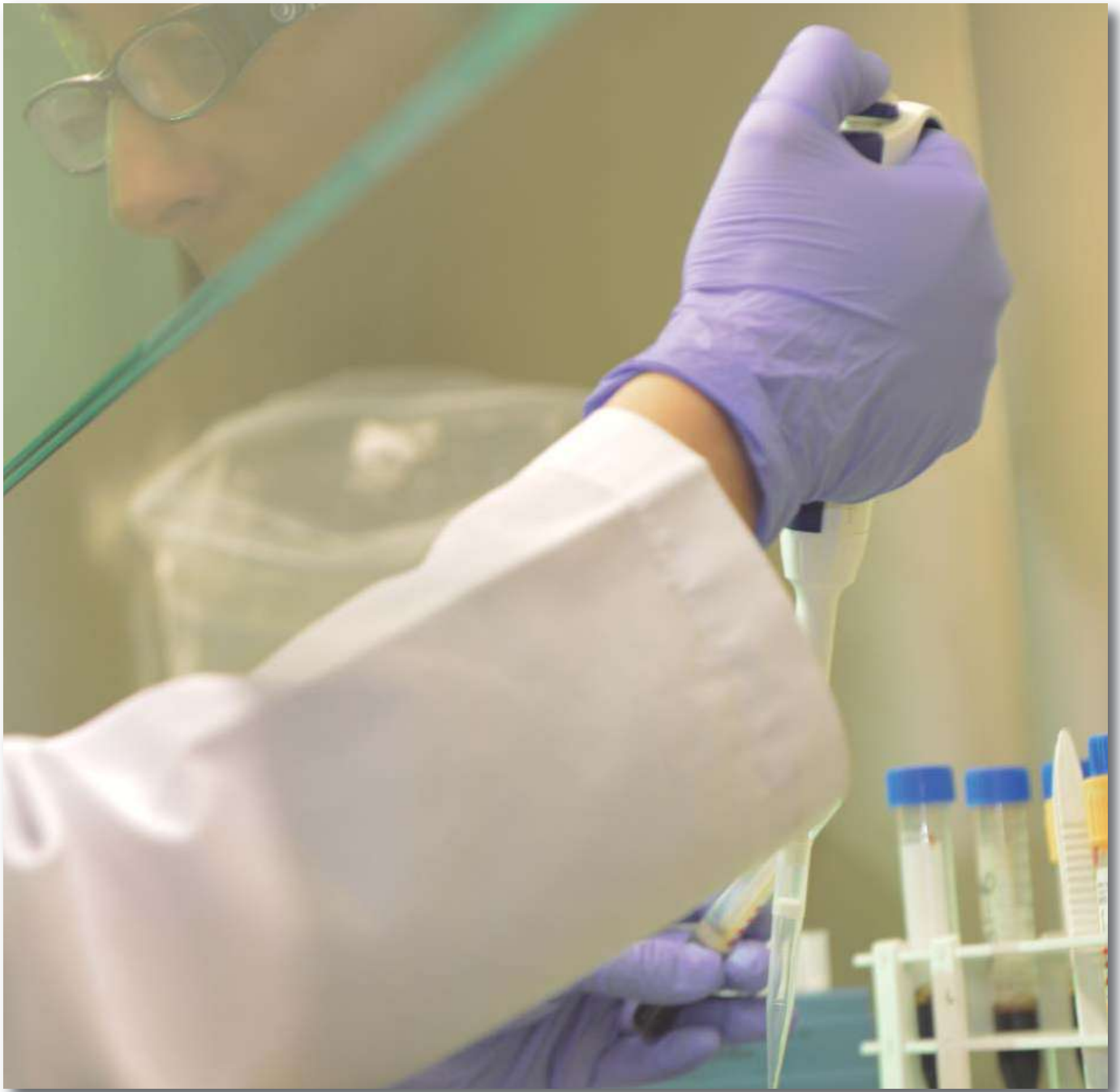
provide immediate motivation to control modifiable risk factors for dementia (for example, quitting smoking, reducing alcohol intake, reduce cholesterol, etc.). In addition, in the hopeful situation that new treatments for dementia will be available soon, it is most likely to increase therapeutic efficacy if this treatment is started as soon as possible in the neurodegenerative process. Therefore, if we manage to identify people at risk of dementia while they are in the preclinical asymptomatic state, treatment could begin at this stage. Moreover, the same approach we developed to classify biomarkers for AD in our longitudinal study could be applied to similar studies investigating other dementias.



Scientific productivity

The research work carried out by the CIEN Foundation throughout 2018 has resulted in the publication of 25 peer-reviewed original papers in specialized journals of recognized national and international prestige. Among them, the publications carried out in collaboration with foreign institutions stand out. 80% of the articles have been included in journals classified within the first and second quartiles in their categories.





6. SCIENTIFIC PRODUCTIVITY

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 2018 has reached a total of 27 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 5.074 in 2018.

In addition, during this year the CIEN Foundation has continued its national and international collabora-

tions, so that 44% of the articles corresponded to studies carried out in collaboration with international institutions, 52% with Spanish ones, and the remaining 4% 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 (47.37%).

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.

In summary, during 2018 the CIEN Foundation researchers have published 25 scientific papers, of which 22 (88%) have been in journals included in the Journal Citation Report (JCR), accessible through the Web of Science portal (WoS, Clarivate Analytics) and 20 (90.91%) have been published in journals ranked within the first and second quartile in their category. Considering the type of document, 92% of the publications in scientific journals (23) correspond to original articles.

Indicators 2018

Total number of publications	27
Number of publications in scientific journals	25
Total number of publications in the ISI citation index within the first and second quartile	20
Cumulative impact factor of publications within the first and second quartile	101,49
Average impact factor of the publications of the first and second quartile	5,07
Number of collaborative publications of all kinds (CIBERNED, other national groups, international groups) within the first and second quartile	19
Number of international collaborative publications within the first and second quartile	7
Number of national collaborative publications within the first and second quartile	12
Number of collaborative publications with other CIBERS and networks within the first and second quartile	10





Moreover, according to their scientific subject category 60% 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 2018, there have been a total of 41 participations at scientific conferences, 31 of which correspond to lectures and oral presentations, and 10 correspond to written communications in the form of posters. These communications have been presented at national (28) and international scientific conferences (13).

6.2. Publications

References of the 27 scientific publications from CIEN Foundation scientists are listed below according to type of publication: 25 publications in scientific journals (23 original articles and two reviews), one book and one book chapter.

6.2.1. Journal articles

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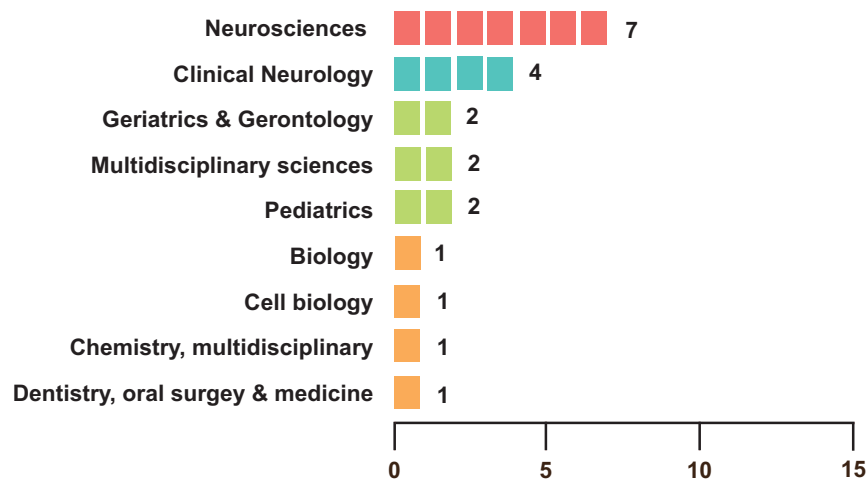
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- Prof. José Manuel Ramírez (Instituto Castroviejo) and Prof. Luis Jáñez (Faculty Psychology, UCM): "Retina y visión en pacientes con enfermedad de Alzheimer". Monday, January 15.
- Dr. Pascual Sánchez-Juan (CIBERNED, Neurologist, Marqués de Valdecilla University Hospital): "Utilidad del PET de amiloide en el mundo real". Monday, January 22.
- Susana Navas (Queen Sofia Foundation–MAPFRE Fellowship 2016-2017): "Influence of genetics and age on spatial navigation". Monday, January 29.
- Prof. Antonia Gutiérrez (CIBERNED, University of Malaga, Cell Biology, Genetics and Physiology Department): "Exploring microglial and astroglial responses in Alzheimer's disease: evidences from transgenic models and human brains". Seminar framed with the activities organized on the occasion of the "International Day of Women and Girls in Science". Monday, February 12.
- Drs. Isabel Campillo and Yolanda Sanz (Microbial Ecology Group of the Department of Nutrition and Health of Food Sciences of the Institute of Agrochemistry and Food Technology, CSIC): "Estudio de la microbiota intestinal en la enfermedad de Alzheimer". Monday, February 19.
- Dr. Alberto Fernández (Psychiatry and Medical Psychology Department, UCM). UPM-UCM Cognitive and Computation Neuroscience Laboratory: "Magnetoencefalografía en la enfermedad de Alzheimer: evidencias en fase preclínica y prodrómica". Monday, February 26.
- Prof. Bryan Strange, Prof. José A. Obeso, Prof. Antonio Hernando and Prof. Fernando Maestú: "What does MEG offer for understanding the development of Neurodegenerative Diseases?". Monday, May 21.
- Prof. María A. Moro: "Deterioro cognitivo vascular: estudio experimental de los mecanismos implicados". Monday, May 28.
- Dr. Miguel Díaz-Hernández, Biochemistry and Molecular Biology Department, Veterinary School, UCM: "Blood purines as novel diagnostic

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 2018:





- for pre-clinical AD and identification of P2X7R-dependent down-stream targets in AD". Monday, July 2.
- Seminar serie on "Spatial navigation - a window to understanding cognitive decline in ageing and dementia": 1. "Revealing an embodied neural representation of space through changes in imagined head direction and first-person point-of-view" (Mario B. Pérez-López. Aging & Cognition Research Group, German Center for Neurodegenerative Diseases (DZNE) Magdeburg, Germany); 2. "Investigating path integration as a function of age and APOE-genotype" (Anne Bierbrauer. Institute of Cognitive Neuroscience. Department of Neuropsychology, Ruhr University Bochum, Germany); 3. "Stimulating the nucleus accumbens to improve spatial navigation in humans" (Bryan Strange. Director, Laboratory for Clinical Neuroscience, CTB-UPM and Department of Neuroimaging, CIEN Foundation). Monday, July 9.
 - Dr. Liset Menéndez de la Prida (Director of the Neuronal Circuits Laboratory, Cajal Institute, CSIC): "Deep-superficial structure of hippocampal oscillations in health and disease". Monday, July 16.
 - Dr. Lidia Blázquez (UPM, UNED), Dr. Lidia Alonso-Nanclares (CTB-UPM, Cajal Institute, CSIC): "Three-dimensional analysis of synapses in mesial cortex of Alzheimer's disease patients". Monday, July 23.
 - Alexandra Moreno (Carlos III Institute of Health and CIBERNED): "Role of neuromelanin in neuronal degeneration". Monday, September 10.
 - Dr. Jaime Gómez-Ramírez (Neuroimaging Department, CIEN Foundation): "Identificación de factores de riesgo en Deterioro Cognitivo Leve con técnicas de Inteligencia Artificial". Monday, October 8
 - Dr. Linda Zhang (Neuroimaging Department, CIEN Foundation): "The Vallecas Project: Study Updates". Monday, October 22.
 - Dr. María A. Zea-Sevilla (Department of Neurology, CIEN Foundation): "Salud bucodental en pacientes con enfermedad de Alzheimer". Monday, October 29.
 - Marina Ávila (Departament of Neuropsychology, CIEN Foundation): "Deterioro Cognitivo Subjetivo como marcador preclínico fiable en enfermedad de Alzheimer". Monday, November 5.
 - Monday, November 12- Oral communications to the S.E.N. Annual Meeting:
 - "Educación y nivel socioeconómico como determinantes del deterioro cognitivo leve". Miguel Ángel Fernández-Blázquez.
 - "Utilidad del parpadeo atencional en la evaluación del deterioro cognitivo: resultados preliminares de un estudio traslacional". Miguel Ángel Fernández.
 - "Estudio de la relación entre el ortostatismo y el deterioro cognitivo en una muestra de personas mayores". Meritxell Valentí.
 - "Cambios asociados al envejecimiento cerebral en mamíferos". Alberto Rábano.
 - "Identificación de factores de riesgo en deterioro cognitivo leve con aprendizaje automático: hacia una ayuda al diagnóstico multifactorial y autoinformada". Jaime Gómez Ramírez.
 - Prof. Félix Bermejo Pareja (Alzheimer's Extraordinary Chair, Department of Medicine, Complutense University of Madrid, emeritus professor of CIBERNED and consultant neurologist of the 12 de Octubre Hospital Research Institute): "Lactoferrina, demencia y enfermedad de Alzheimer". Monday, November 19
 - Dr. Meritxell Valentí (Neurology Department, CIEN Foundation): "El Consejo Español del Cerebro". Monday, December 10.
 - Alberto Rábano (Departament of Neuropathology, CIEN Foundation, BT-CIEN): "Vacuolización cortical en patología de Lewy: una aproximación a la diversidad molecular de las sinucleinopatías". Monday, December 17



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6.4. Funded projects

During 2018 the CIEN Foundation researchers have participated in nine 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 year 2018 a total amount of THREE HUNDRED THOUSAND EUROS (300,000 €))

In February 2018, a new collaboration agreement was signed with the Queen Sofia Foundation, with an expected duration of 4 years, and a contribution of 300,000 € for the 2018 financial year. This agreement regulates 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".

- **Código: PT13/0010/0045**

Principal Investigator: Dr. Alberto Rábano
Title: Biobank Platform
Funding agency: Instituto de Salud Carlos III
Duration: 2014-2018
Total budget: 179,934.78 €
2017 budget: 44,478.26 €

Call corresponding to the year 2013 of grants from the Strategic Action in Health. Grant co-funded by the European Regional Development Fund (FEDER, for its acronym in Spanish). In 2018, the extension approved by the Subdirector General for Evaluation and Promotion of Research of the Carlos III Health Institute was executed, with the deadline for execution on December 31, 2018.

- **Código: 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 €

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 €
2018 budget: 22,500 €

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 €

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.

- **Code: K. COLLEGE-MDS-NMS**

Principal Investigator: Dr. Pablo Martínez
 Title: Phases 2b-4 Field Validation of the MDS-NMS, the International Parkinson's and Movement Disorders Society Non Motor Scale for Parkinson's disease
 Funding agency: International Parkinson and Movement Disorders Society
 Duration: 2016-2018
 Budget: 39,347.65€

**Services 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. Enfermedades Neurológicas y 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
 Duration: 2016-2019
 Budget: 27,990 €

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):

- **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



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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 2018 two patent applications remain active in 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.
Title: Infrared analysis of fractions obtained from peripheral blood to indicate cognitive development.
Registration N°: EP128217460,
PCT/ES2012/070613.
Application date: 08/08/2011.
Type: Europea/Internacional.
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.



Social outreach activities

In 2018, the Neuro2020 agreement was signed in collaboration with the Queen Sofia Foundation with the aim of raising public awareness about the importance of research in neurodegenerative diseases. In addition, among the social activities of the CIEN Foundation, the implementation of new initiatives such as the #YoRecuerdo campaign or the "Friends of the CIEN Foundation" project stands out. Activities of great relevance for the Foundation have been maintained, such as the "Christmas Tree of Memories", the "Vallecas Project Volunteer's Day" or the VI International Conference on Research and Innovation in Neurodegenerative Diseases (CIIEN).





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7. SOCIAL OUTREACH

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 2018 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. Good examples of this are two of the lectures delivered by Prof. Jesús Ávila, Scientific Director of the CIEN Foundation and CIBERNED, the first of them at the Academy of Science of the Region of Murcia in January, which was entitled "Alzheimer's disease: cure, prevent or delay" and, in the month of November participated in the Lecture Series "What do we know about ...?" organized by the CSIC with "How to cure, prevent or delay Alzheimer's disease", held at the Museum of Science in Valladolid.

Dr. María Ascensión Zea, a researcher in the Neurology area of the CIEN Foundation, participated on June 7 in an important meeting on Innovations in Dementia organized by Sanitas since, according to Pedro Cano, Director of Medical Innovation and Management System in Sanitas Mayores, "in dementias it is essential to be able to offer all possible tools to people living with the disease". On that occasion, Dr. Zea participated in the Round Table "New trends in medical innovation", where some of the innovations provided by new digital technologies and improvements in treatment, diagnosis and prevention to improve the quality of life of this people were discussed.

In December 2018, Dr. Miguel Ángel Fernández Blázquez, coordinator of the neuropsychology area of the CIEN Foundation, gave a conference on "Contributions of neuropsychology to early detection of Alzheimer's disease" at the State Center for Alzheimer's Reference (CRE, for its acronym in Spanish) in Salamanca, in which he disserted in detail about the importance of early diagnosis, the different types of disease markers, the neuropsychological tools for the early detection of Alzheimer's disease, as well as the Vallecas Project of the CIEN Foundation for the identification of early markers of Alzheimer's disease and finally discussed about future challenges. The lecture, aimed at professionals, caregivers and people interested in Alzheimer's disease and other dementias, aimed to disseminate the latest advances related to the early diagnosis of Alzheimer's disease, with special emphasis on cognitive markers. This informative action could also be followed in live streaming through the CRE Alzheimer's website.

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

During 2018, 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.

This was the case of the participation in the XVI FAGAL Interdisciplinary Days, held at the Faculty of Psychology of the University of Santiago de Compostela on June 9, in which M^a Ángeles Pérez, manager of CIEN Foundation and CIBERNED, delivered a talk entitled "CIBERNED-CIEN Foundation: Lines of work". These training days in Alzheimer's and other neurodegenerative dementias, brought together staff from the Galician Alzheimer's associations, professionals from the social and health sector and researchers in dementias.

At the end of June, representatives of the Association of Alzheimer's relatives from Valencia (AFAV, for its acronym in Spanish) visited the Queen Sofia Foundation Alzheimer Center facilities. Ms. Ana M^a Ruiz Cano, recently appointed president of the Association and Ms. Ana Morón, manager of AFAV, were able to meet through Ms. M^a Ángeles Pérez, manager of the CIEN Foundation, the Alzheimer Project Research Unit and the Residence Care Center. For the CIEN Foundation, it is always an honor to participate, whenever there is an opportunity, in the search for the identification of common spaces and objectives for action with the different Associations of Relatives of Alzheimer's patients and other neurodegenerative diseases that exist in Europe.

As usual in recent years, in the prelude to the VI International Congress of Research and Innovation in Neurodegenerative Diseases (CIIEN) (to which we devote the next Section of this Report) on Tuesday, September 18, it was held also in the Faculty of Medicine of the University from Santiago de Compostela, the Symposium on social-health research in Alzheimer's disease and other dementias, organized by the State Reference Center for people with Alz-

heimer's disease and other dementias of the IM-SERSO (CRE Alzheimer) together with the Spanish Confederation of Associations of Relatives of Alzheimer's (CEAFA) and with the support of the Queen Sofia Foundation.

Another meeting worth to highlight during 2018 was the participation of the CIEN Foundation, on November 16, in the 10th meeting between health professionals, Alzheimer's associations and caregivers "Ten Years of Advances in Alzheimer's disease". Diagnoses and treatments, the result of the work and collaboration between the Federation of Associations of Huelva and the Infanta Elena Hospital. M^a Ángeles Pérez, manager of CIEN Foundation and CIBERNED, was in charge of delivering the talk "The role of the CIEN Foundation and CIBERNED at the Alzheimer Center Queen Sofia Foundation: an integrative vision". Pérez talked about how our Research Center makes the Vallecas Alzheimer Complex a unique model in Spain.

VI 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 Santiago de Compostela, which gathered more than 100 international experts during three days of presentations and knowledge exchanges.

Organized by the Queen Sofia Foundation, CIEN Foundation (Center for Research in Neurological Diseases Foundation) and CIBERNED (Network Center for Biomedical Research in Neurodegenerative Diseases), the VI CIIEN Conference served as an exchange forum on the main advances in research and treatment of Alzheimer's, Parkinson's, Huntington's and other neurodegenerative disorders. This meeting had the collaboration of the City of San-



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tiago de Compostela and was held at the Faculty of Medicine of the University of Santiago, whose auditorium hosted the opening ceremony and plenary sessions.

Among the speakers were world research leaders such as Harald-Jürgen Hampel (Sorbonne University –France-), Michael T. Heneka (Medical Research Center of the University of Bonn –Germany), which discussed on the relationship between innate aspects of the immune system and Alzheimer's disease, and Adriano Chiò (University of Turin –Italy-), who deepened into the role of cognitive phenotypes.

In addition to the intervention of the Scientific Director of the CIEN Foundation and CIBERNED, Jesús Ávila, and the Deputy Scientific Director, Miguel Medina, the Congress had Spanish speakers of international prestige, including Isabel Fariñas (University of Valencia), whose lecture focused on the effects of certain extracellular proteins in stem cells; Ángel Carracedo (University of Santiago de Compostela),

with a talk on the search for genes involved in neurodegenerative diseases, and Prof. José Luis Labandeira-García.

During the Opening Session, chaired by Her Majesty Queen Sofia, She was accompanied by the Secretary of State for Universities, Research, Development and Innovation, Ángeles Heras; the President of the Xunta de Galicia, Alberto Núñez Feijóo; the President of the Parliament of Galicia, Miguel Ángel Santalices; the Delegate of the Government in the Region of Galicia, Javier Losada; the fFirst Deputy Mayor of the City of Santiago de Compostela, María Rozas; and by the Magnificent Rector of the University of Santiago de Compostela, Antonio López Díaz, among other personalities.

After the interventions of the Magnificent Rector and the authorities, Jesús Ávila, Scientific Director of CIEN Foundation and CIBERNED, introduced the lecture by Harald-Jürgen Hampel, from the Sorbonne University (France), who disserted on the progress in precision medicine for Alzheimer's disease.



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In the afternoon, after the II scientific session, at the headquarters of the ABANCA Social Work Foundation, those attending the Congress visited the exhibition "Alzheimer's: the Path of Memory". Upon arrival, Her Majesty Queen Sofia, was received by the President of the Xunta de Galicia, Alberto Núñez and the curators of the exhibition. The exhibition gathered objects that belonged to the Nobel Prize in Medicine Santiago Ramón y Cajal and photographs that illustrated the trip from Malaga to Santiago de Compostela by journalist Antonio Ortín (Diario Sur) and photographer Alejandro Hurtado (Photography); and was curated by Antonia Gutiérrez, Ana Grande, Enrique Viguera, Antonio Ortín and Alejandro Hurtado.

The next day, at the Faculty of Medicine of Santiago, two other new scientific sessions and a plenary session were held, attended by H.M. Queen Sofia and in which were delivered the lectures "New therapeutic objectives for Parkinson's disease", by Werner Poewe, from the University of Medicine of Innsbruck, and "The search for genes involved in neurodegenerative diseases: challenges and new strategies", by Ángel Carracedo, from the University of Santiago de Compostela.

In the evening, Queen Sofia presided over at the Pabellón de Santiago de Compostela, the concert and subsequent Reception offered to the authorities of Galicia, Xunta, Santiago City Council and researchers on the occasion of the VI CIEN Congress. The day ended with a dinner commemorating the "World Alzheimer's Day", which was attended by all participants in the Congress.

The Congress ended on Friday, September 21, coinciding with World Alzheimer's Day. Dr. Miguel Calero Lara, coordinator of the Molecular Biology Area of the CIEN Foundation, was in charge of closing the VI and last scientific session with the conference "Epidemiological, clinical and molecular basis of neuro-

degenerative diseases: Towards an integrated model of neurodegeneration".

Vallecas Project Volunteer's Day

One more year the tribute to the 1,200 volunteers of the Vallecas Project has been celebrated, an event that had the participation of the Madrid Coral Alliance in a zarzuela concert.

The Queen Sofia Foundation and the CIEN (Neurological Disease Research Center) Foundation, in collaboration with LA ONCE, have organized the sixth edition of the Vallecas Project Volunteer's Day, in which the protagonists have been the more than 1,200 volunteers aged between 70 and 85 years that are part of this project of early detection of Alzheimer's disease, since it began its journey in 2012.

The Vallecas Project, which is being carried out at the Queen Sofia Foundation Alzheimer's Center, aims to identify biological and psychological markers that allow an early diagnosis of the disease. With the follow-up of the volunteers, who annually go through a series of neurological tests, analyzes, interviews and neuroimaging studies, we try to identify factors and variables that allow us to predict the possibility that a person develops Alzheimer's disease, and thus implement programs of prevention and early diagnosis.

The Duque de Pastrana Auditorium hosted this act in which the Manager of the CIEN Foundation, and the Secretary of the Queen Sofia Foundation, acknowledged the volunteers on behalf of both organizations for their selfless participation in the project and highlighted the commitment of Her Majesty Queen Sofia, who was unable to attend due to agenda reasons but who closely follows the Project and appreciates the efforts of the volunteers, in addition to boosting the support of her Foundation to the project, having just approved the continuation



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of the funding to the Second phase of the Vallecas Project, which started in 2018, which made this tribute act take place in an even more special way. The honorees were able to enjoy the show of the magician Andrés Madruga and the main performance of the Madrid Coral Alliance, which has among its members one of the volunteers who are part of the project, the tenor José Martín. With Rostislav Fedorov in the direction, they interpreted a wide repertoire of well-known pieces of zarzuela as "The Waltz of the Knight of Grace" from La Gran Vía, "La Paloma" from El Barberillo de Lavapiés or "El Chotis de Madrid" by Agustín Lara.

I 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 decided to join this initiative by organizing on Monday, February 12 the Meeting "Neu-





roscientists Women Today: Sowing Referents" and a Scientific Seminar delivered by one of the main CIBERNED researchers.

The first edition of "Neuroscientists Today: Sowing Referents", was a day aimed at any interested person, but especially to students and professionals from these areas as well as students from last years of high school who are considering developing their career in the field of Science. In it, the researchers from the CIEN Foundation, Marina Ávila, and CIBERNED, Diana Furcila, made a historical tour, until they reached the current situation of women in science. Afterwards, a colloquium was held around the issue "The role of women in Science: sowing references for the new generations", chaired by Dr. Eva Carro (CIBERNED PI, Research Institute of the 12 de Octubre Hospital), with the participation of Dr. M^o Jesús Bullido (CIBERNED PI, Center for Molecular Biology "Severo Ochoa" CSIC-UAM), Dr. Antonia Gutiérrez (Professor of the UMA, Department of Cell Biology, Genetics and Physiology), Dr. Teresa Iglesias (CIBER-

NED PI, CSIC senior scientist, Biomedical Research Institute "Alberto Sols", CSIC-UAM), Dr. María Llorens-Martín (CIBERNED researcher, Center for Molecular Biology "Severo Ochoa"), Dr. Ana Pérez- Castillo (CIBERNED PI, Biomedical Research Institute, CSIC-UAM), Alba Ruiz (UNEX student, carrying out her End of Master's project in the CIEN Foundation Neuropathology Department) and Dr. María Ascensión Zea (researcher in the Neurology Department of the CIEN Foundation). They told us about their experience throughout their career, successes and difficulties, with the aim of serving as a reference to other scientists, present and future.

In addition, during the afternoon Dr. Antonia Gutiérrez (CIBERNED PI, Professor at the Department of Cell Biology, Genetics and Physiology, University of Malaga), delivered a scientific seminar with the results of the latest work of her research group entitled "Exploring microglial and astroglial responses in Alzheimer's disease: evidences from transgenic models and human brains".



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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 2018 the CEC has participated in the following activities:

- **Survey on the current state of care for patients suffering from brain diseases**

The CEC participates in the survey on the current state of care for patients with brain diseases promoted by the National Brain Councils and the EBC during the spring of 2018.

- **National Workshop on Off-label Use of Medicines: Declaration on good practices of the use of medicines outside the technical data sheet in Spain.**

The objective of this EBC campaign was to raise awareness about the conditions necessary to correctly implement the prescription for the use of medicines outside the technical data sheet, to promote its discussion and to support the 'Declaration on good practices of the use of medicines outside the technical data sheet'. In Spain, the CEC organized an event at the Cajal Institute, together with the EBC, in which medical societies, patient associations and industry participate to present and debate this controversial issue.

- **The Brain on the Spanish National Radio Station**

The CEC participated in the radio program on the Brain in 'Open Future' on the Spanish National Radio Station broadcast on Sunday, June 3..

- **Joint statement 12%... 10%... 8%... Counting down to zero. Towards a future with underfunded health research?**

The CEC showed its support for the initiative led by the EBC to request an increase in the "Horizon Europe" budget and its redistribution to ensure that more funds in "Health" are allocated to the European Commission, the European Parliament and the Council.

The "Horizon Europe" proposal of June 2018 included a global budget of 94.1 billion euros, with only 7.7 billion euros for "Health" (8%). The EBC strongly believes that the proposed budget is insufficient to address social challenges effectively. It is estimated that the treatment of brain disorders alone will cost about €800 billion annually, instead the proposed budget for "Health" confirms a constant decrease in funding over time (12% during 2007- 2013, 10% during 2014-2020 and 8% during 2021-2027).

- **Event «The value of treatment: round table on the economic cost of Alzheimer's in Europe»**

The CEC attended last September 25 the event "The value of treatment: round table on the economic cost of Alzheimer's in Europe" presented by MEP Heinz K. Becker, moderated by Geoff Meade and chaired by the president of EBC, Prof. Monica Di Luca. Its objective was to gather experts from the value of treatment (VoT) project and the Alzheimer's field.

- **Let's add to normalize life with Multiple Sclerosis**

On Thursday, October 4, the "Sumemos" (Add) meeting to normalize life with Multiple Sclerosis took place at the Casa del Lector (Paseo de la Chopera, 14 Madrid). Merck, in its commitment to Multiple Sclerosis (MS), organized the Leadership Forum "SUMEMOS" to build among all the EM community a platform for continuous dialogue and





experiences with the goal of normalizing life with MS. Recently the conclusions of this act have been published.

• **Physical exercise as a treatment for Parkinson's**

The CEC participated in a conference organized by the Parkinson Madrid Association as well as in educational material in audiovisual format, to explain the importance of exercise from the earliest stages of the disease. October 16, 2018.

Media campaigns

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

During 2018, the Neuro 2020 collaboration agreement with the Queen Sofia Foundation was signed. The event EN2020, promoted by the Queen Sofia Foundation and the Neurodegenerative Diseases Research Center Foundation (CIEN) and the stimulus of 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 in neurodegenerative diseases to advance knowledge about the origin of their causes, the only way to reduce the number of people affected and stop the progress of these disorders; to promote raising of economic resources 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 from the field of neurosciences around the world.

The EN2020 event is included in the Ninety-seventh additional Provision of Law 6/2018, of July 3 of General State Budgets for 2018, with the heading: Tax benefits applicable to "Neurodegenerative Diseases 2020. Year of hospitalization Research and Innovation."

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

After the success of the previous campaign, the CIEN Foundation wanted to replicate its traditional "Christmas Tree of Memories" placed in the Centro-Centro building of the Madrid City Hall, located at Cibeles Square. This initiative, which also had the support of the City Council of the capital and the Queen Sofia Foundation, is aimed at raising awareness in society about the effects of Alzheimer's disease in those who suffer from it and giving value into memory through positive emotions, which are the strongest memories in our brain. This "Christmas Tree of Memories" planted on November 2018 could be seen during the Christmas period by thousands of locals who visited the center and hung their most precious Christmas souvenir in special cards prepared for the occasion as well as through social networks, with the hashtag #arboldelamemoria. The Christmas tree, with a firm trunk holding hundreds of branches, symbolized the idea of continuity of emotions over time, as well as a metaphor of the social nature of this problem and a call for everyone's involvement, essential to eradicate a disease that potentially affects society as a whole.

In addition, as in previous editions, the original tradition of the Vallecas "Tree of Memory" has been maintained, which since 2011 has been installed throughout Christmas in that district of Madrid. In the last edition, the Villa de Vallecas Market, again



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welcomed this initiative, with the support of the Queen Sofia Foundation, the Villa de Vallecas District Board of and the Region of Madrid General Directorate for the Elderly. The journalist and presenter Irma Soriano was, one more year, the patroness 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 sup-

port 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 2018, already has more than 600 partners. From here, thanks to all our Friends.





Yo recuerdo (I remember) campaign

During the summer of 2018, the CIEN Foundation promoted the "I remember" campaign, which was joined by a multitude of celebrities, such as the journalists Irma Soriano, Mercedes Milá, Terelu Campos or Nieves Herrero or the renowned singers Diana Navarro and Sagra Mielgo. Thousands of people have wanted to be part of this initiative, and thus contribute to research and, in addition, help improve the quality of life of patients, families and caregivers who live day by day with the disease. Thus, anyone can join with a contribution or by sharing the videos on social networks using the hashtag #YoRecuerdo.

Morè charity bracelets

Designer Eva González, through the Morè jewelry firm, has jointly created for the CIEN Foundation an exclusive edition of "I remember" bracelets in December 2018. With the purchase of these supportive bracelets, anyone can contribute to the research in Alzheimer's disease. Thanks to the firm Morè, we can allocate the full amount of this article to join efforts against Alzheimer's disease.

Exhibition "Alzheimer, pathway to memory"

Based on photographs by Alejandro Hurtado, texts by journalist Antonio Ortín and scientific panels pre-



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pared by researchers at the UMA, we wanted to show the clinical and neurological aspect of this type of dementia, counting on the vision of the patient, the caregivers and also their relatives. The exhibition made a visual tour of Alzheimer's disease, starting from the moment of diagnosis, to the effects it produces on the patient. The objective of this exhibition was to present this disease to society, considered the silent epidemic of the 21st century due to the serious cognitive deterioration that it carries and, also, to give visibility to the effort of researchers to understand the causes that originate it, the consequences that produce in the brain and the search for a pharmacological treatment, which currently does not exist. Thus, the exhibition dedicated a leading space to the father of modern Neuroscience, the Nobel Prize Ramón y Cajal. In addition, the showing contained a selection of photographs and texts of 'Camino de la Memoria', the book by Antonio Ortín and Alejandro Hurtado for the benefit of the Association of Relatives of Alzheimer's of Malaga (AFA Málaga). Last August, both made the Camino de Santiago by bicycle between Malaga and the Galician capital. During that trip, they learned firsthand the work done by the different Alzheimer associations that are along the route and reflected it in this book.

The exhibition was sponsored, among other institutions, by the CIEN Foundation, CIBERNED, the Queen Sofia Foundation, and the ISCIII. It was shown in two locations, coinciding with the cities of departure and arrival of Camino de la Memoria. It could be visited from January to March in the Cultural Area of El Corte Inglés in Malaga and from September to November at the headquarters of the ABANCA Social Work Foundation, in Santiago de Compostela.

Institutional visits

Throughout 2018, the Alzheimer Project Research Unit has received numerous institutional and non-ins-

titutional visits, with the aim of showing and disseminating the work carried out in it. For example, on July 19, we were honored to receive the Executive Director of the Queen Sofia Spanish Institute in New York, Mrs. Patrice Degnan, who attended with the Secretary of the Queen Sofia Foundation, Mr. José Luis Nogueira. Also accompanied by the Manager of the CIEN Foundation, Mrs. M^a Ángeles Pérez, Degnan had the opportunity to visit and learn about this unique model in which Alzheimer's disease is approached from three angles: research, training and care service for patients.

On September 5, we were also visited by the Director General of the Carlos III Health Institute, Dr. Raquel Yotti, who held a meeting of the Delegate Commission of the CIEN Foundation at the Queen Sofia Foundation Alzheimer Center. In addition, Yotti visited the facilities of the Center, accompanied by the Assistant Director General of Cooperative Research Networks and Centers, Mrs. Margarita Blázquez, the Scientific Director of the CIEN Foundation, Professor Jesús Ávila, the Manager Ms. M^a Ángeles Pérez and some researchers of the CIEN Foundation.

It is also worth mentioning the visit of the International Association of Diplomats of Spain (AIDE, for its acronyms in Spain) on November 24. AIDE representatives attended a lecture by Miguel Medina, Deputy Scientific Director of CIBERNED and Principal Investigator of the Vallecas Project, with the title "Challenges and opportunities in Alzheimer's Research", visited with great interest the Queen Sofia Foundation Alzheimer Center, the CIEN Foundation Tissue Bank and had the opportunity to exchange impressions with some of the Center's researchers.

7.2. Presence in media

As every year, during 2018, 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 2018, the annual CiiiEN congress was held, which took place in September in Santiago de Compostela. The organization and carrying out of this event focused on the conception and strategy of the 2018 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 2018, a significant impact has been achieved in the press, radio, television and online media, both in terms of dissemination and extension of the network of contacts with researchers in national and international neurodegenerative diseases.

Work has also been performed on the dissemination of other events, some of them are already classic ones at the CIEN Foundation, such as the Vallecas Project Volunteers's Day, held in the Auditorium of the ONCE Foundation, which had the collaboration of the Madrid Coral Association, or a new edition of the Christmas Tree of Memory, with the 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, as well as the campaign of supportive SMS "I remember", in which some personalities participated providing short videos supporting research on Alzheimer's disease.

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 CIIIEN, there have been press appearances and online and audiovisual media that include extensive reports in media such as RTVE, TVE Internacional, La 1 de TVE, El País, El Mundo, Cadena COPE, ABC, Telemadrid, La Razón, Cadena SER, Diario Médico, ConSalud, El Español and Acta Sanitaria, as well as regular dissemination through the main news agencies.

Five elements have focused the press interventions and appearances:

- Supportive SMS "Yo recuerdo" (I remember) campaign
- The "Vallecas Project", especially the results around the predictive algorithm and the virtual brain model for diagnosis.
- The volunteers of the "Vallecas Project".
- The CIEN Foundation Tissue Bank.
- The International Conference on Research and Innovation in Neurodegenerative Diseases CIIIEN, in Santiago de Compostela.

Regarding press statements, the control and prior informative consent protocol introduced in 2017 was followed during 2018, 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 2018 in media, in terms of scope and represented as the estimated number of readers/people reached, arrived at 73 million readers, which, expressed as ROI, was €923,000.



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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 the one referred to the supportive SMS campaign "I remember" (#YoRecuerdo), the "Vallecas Project" (#ProyectoVallecas), the campaign to encourage the donation of brain tissue and bring this possibility to users (#HazteDonante -Become a Donor-) and one that aimed to increase awareness of Alzheimer's disease among society through the provision of data and new discoveries (#Alzheimer). Sporadic campaigns and events have also been covered and disseminated. Among these events are worth mentioning the "Christmas Tree of Memory" (#ArbolDeLaMemoria) initiative, the DEGESCO Symposium that took place at the Queen Sofia Foundation Alzheimer's Center (#DEGESCO), the campaign carried out for the 2018 CiiiEN held in Santiago de Compostela, or the coverage provided to the CIEN Foundation 2018 Seminars Series (#Ciclo-SeminariosFCIEN).

Analyzing the status of the various official accounts of the CIEN Foundation, we can observe the evolution they have experienced during 2018:

Facebook:

2018 ended with 5,025 followers, who have been increasing progressively and whose positive trend continues constant. This figure represents a 4% increase over the previous year.

Twitter:

By the end of 2018, the profile counted on 13,260 followers with whom it has constant interaction, receiving numerous comments, retweets and likes. The number of followers have experienced an increase of 4.1% compared with the previous year.



5.025 followers
+4%



13.260 followers
+4,1%



Coordination and content management:

Miguel Medina Padilla

Aina Frontera Sánchez

José de Arriba-Enríquez

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Centro Alzheimer Fundación Reina Sofía
C/ Valderrebollo, 5. 28031 Madrid
Tel.: (+34) 91 385 22 00 Fax: (+34) 91 385 21 18
www.fundacioncién.es