



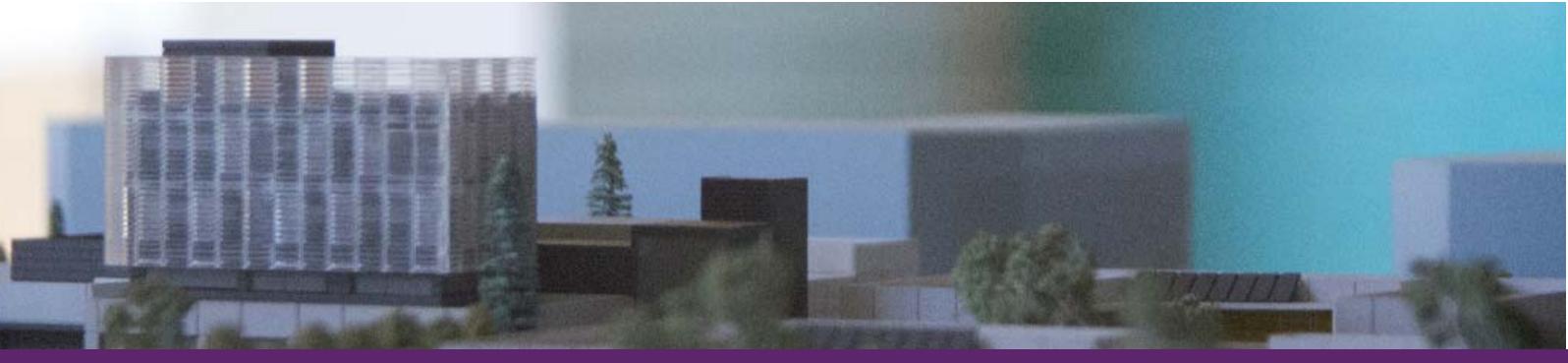
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Fundación Centro Investigación
Enfermedades **Neurológicas**

**Annual
Report
2016**

CIEN FOUNDATION
Research Center for
Neurological Diseases Foundation

Centro Alzheimer Fundación Reina Sofía
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Annual Report 2016



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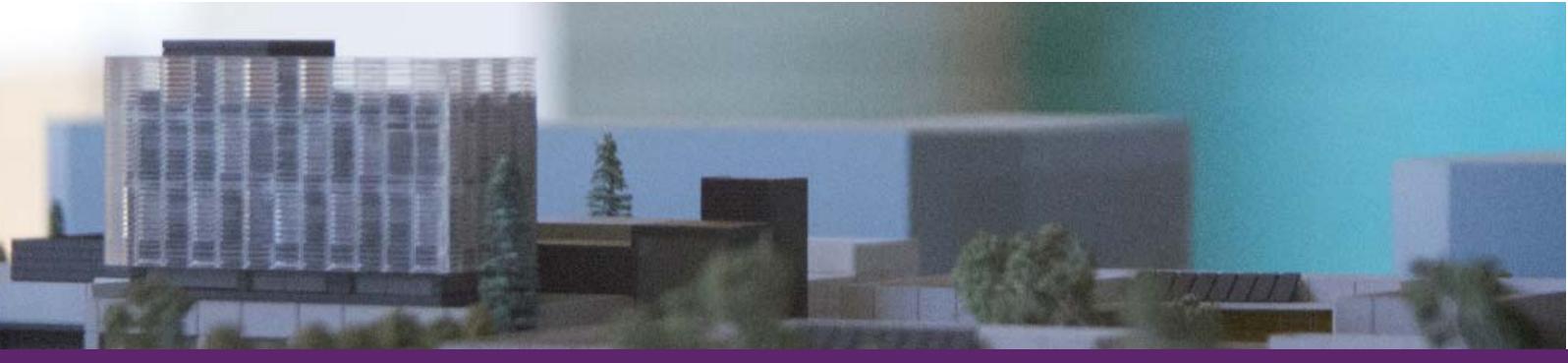


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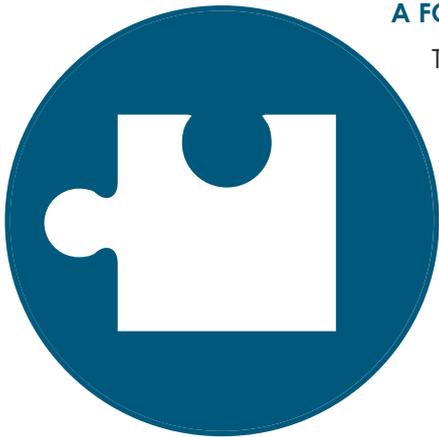
Profile *e* and presentation

The CIEN Foundation is a reference entity in the neurodegenerative diseases research area, predominantly in Alzheimer's. The support of the Carlos III Health Institute and the Queen Sofia Foundation allows the CIEN Foundation to promote and coordinate a high quality research program driven by a translational model for the benefit of our society.





1.1. Who we are



A FOUNDATION FROM THE PUBLIC SECTOR

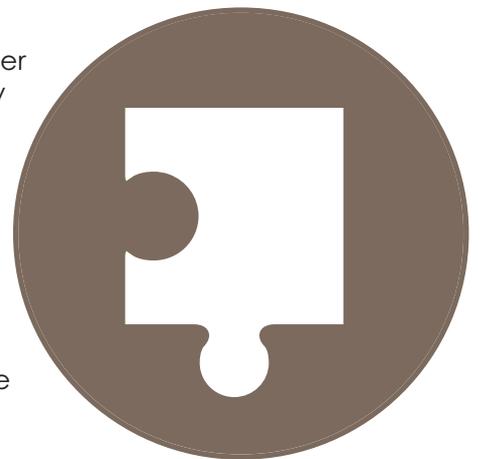
The CIEN Foundation was established by virtue of a resolution by the Council of Ministers on December 27, 2002. It is a non-profit public sector Foundation by definition, with state-wide scope and competence. Currently under the Ministry of Economy, Industry and Competitiveness through the Carlos III Institute of Health.

Support, promote and coordinate research in neurological diseases, but especially in neurodegenerative diseases, are among its founding objectives. Among its aims are also highlighted its unifying and coordinating role of leading research groups in this field.

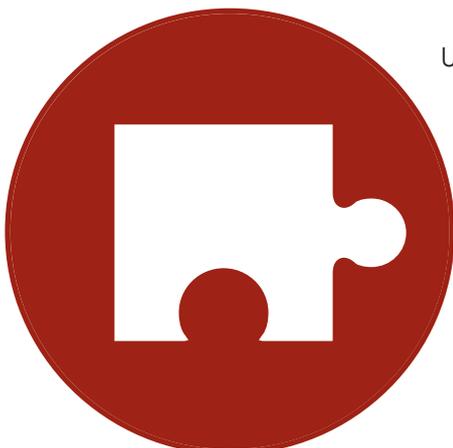
COLLABORATION WITH THE QUEEN SOFIA FOUNDATION

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

Since April 2007, CIEN Foundation headquarters are set at the Queen Sofia Foundation Alzheimer Center. This site located in the Madrid district of Vallecas, was conceived as a pioneer Center in Spain in which comprehensively address the impact that Alzheimer's disease causes on both patients and their family environment. It came to address the social health proposed by the Alzheimer Project of the Queen Sofia Foundation.



A CENTER OF REFERENCE IN SPAIN ON ALZHEIMER'S DISEASE RESEARCH



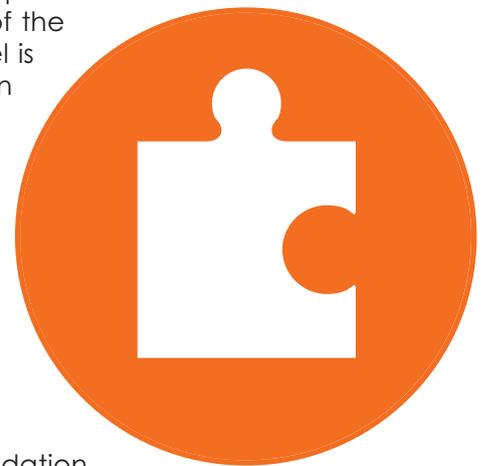
UIPA and CIBERNED are the only two institutions in Spain participating in the European Union Joint Programming for Disease Neudegenerative Diseases (JPND). Its excellent infrastructures, modern methodologies and cutting edge technologies at their disposal as well as the available critical mass of researchers 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).

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.

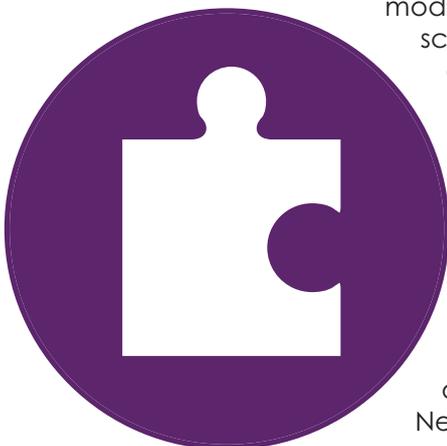


1. A live-in residence for 156 Alzheimer's patients.
2. A day-care outpatient center for 40 Alzheimer's patients.
3. An Alzheimer's research center: the so-called Alzheimer's Project Research Unit (UIPA), managed by the CIEN Foundation.
4. A training center for healthcare staff, relatives and volunteers.

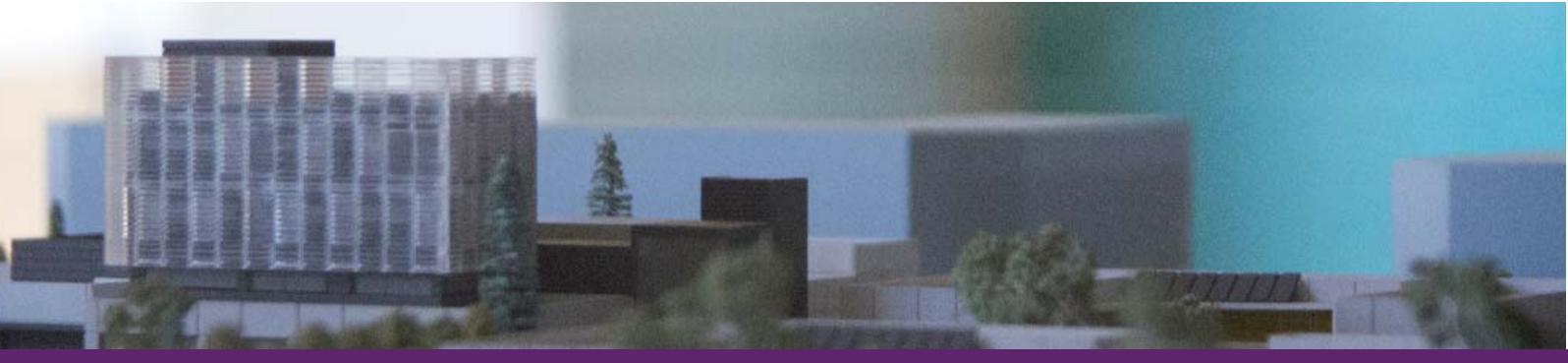
The management model implemented by the Queen Sofia Foundation Alzheimer Center has sought to summon the will and interests of all parties involved: Administration (Central, Regional and Local) and civil society. For this reason, the management of UIPA, devoted to research, was assigned to the CIEN Foundation, 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 tasks assigned to the CIEN Foundation include the following: implementing a model of translational research for conveying effectively and efficiently scientific advances in basic research into clinical practice; promoting continuous training of professionals involved with neurological diseases research by conducting seminars, lectures and doctoral theses; disseminating the calls made by funding agencies, both nationally and internationally; promoting participation; and fostering the implementation of coordinated research projects in neurological diseases.



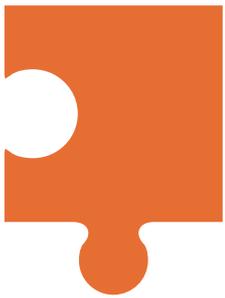
In addition, CIEN Foundation manages the Network Center for Biomedical Research in Neurodegenerative Diseases (CIBERNED), in collaboration with the Carlos III Institute of Health for the implementation of the strategic agenda of the European Union Joint Programming in Neurodegenerative Diseases (JPND).



1.2. The CIEN Foundation in 2016



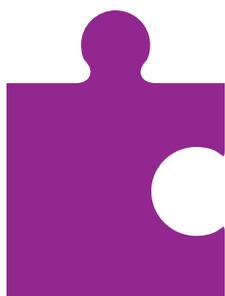
1. PROFILE AND PRESENTATION



The Vallecas Project

- In June 2016 the third visit of the Project concludes, with 866 participants.
- At the end of 2016, a total of 719 volunteers from the fourth visit and 390 from the fifth visit were assessed.
- Two articles were published with data from the Vallecas Project: "Specific Features of Subjective Cognitive Decline Predict Faster Conversion to Mild Cognitive Impairment" in *Journal of Alzheimer's Disease*, 52: 271-81; and "Clinical Relevance of Specific Cognitive Complaints in Determining Mild Cognitive Impairment from Cognitively Normal States in a Study of Healthy Elderly Controls" in *Frontiers in Aging Neuroscience*, 8: 233.
- Two oral communications entitled "Normative data from a population study for the early detection of Alzheimer's disease: Vallecas Project" and "Cognitive reserve and neuropsychological performance: results of a population study for the early detection of Alzheimer's disease. (Vallecas Project)" were presented in the First Ibero-American Congress of Neuropsychology.
- In May 2016, the Royal Academy of Medicine of Madrid presented the Best Poster Award shown at the LXVII Annual Meeting of the Spanish Society of Neurology (SEN) for the best poster to Miguel Ángel Fernández Blázquez, first author of "Usefulness of cognitive complaints as a marker of rapid conversion to mild cognitive impairment: results of a longitudinal research project"
- With occasion of the LXVIII Annual Meeting of the Spanish Society of Neurology (SEN) (November 15-18, 2016), the work of the CIEN Foundation was recognized. During the Plenary Session, Dr. Cristóbal Carnero Pardo presented the stellar communications section in Neurology of Conduct and Dementia, and Neuropsychology. The communications by Dr. Miguel Ángel Fernández Blázquez, "Neuropsychological markers for the early diagnosis of mild cognitive impairment: results of a longitudinal study" and Marina Avila Villanueva "Conversion profile to mild cognitive impairment in a sample of 1.090 elderly people for 24 months" were chosen among the top 10 in the congress.
- For the fourth consecutive year, the already institutionalized Vallecas Project Volunteer's Day was celebrated in recognition of the altruistic collaboration of these people in support of research.





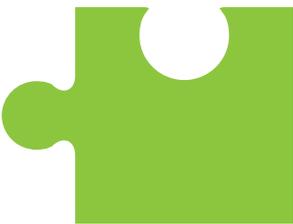
CIEN Foundation Tissue Bank

- The strategic position of the CIEN Foundation in the investigation of neurodegenerative diseases is reinforced by its central role (management and scientific collaboration) with regards to the Network Center for Biomedical Research in Neurodegenerative Diseases (CIBERNED), to which has contributed with the development since 2010 of a biobank of neurological samples in the Center (CIEN Tissue Bank), as part of the CIBERNED biobank platform. The cooperation between FCIEN and CIBERNED has been recognized by the European Union through the joint incorporation of both entities to the International Network of Centers of Excellence in Neurodegeneration Research (CoEN) within the Joint Program for Neurodegenerative Diseases.
- Particularly regarding the maintenance and management of the biological samples from the aforementioned CIEN Foundation projects, it is noteworthy the participation of the CIEN Tissue Bank in the National Biobank Network Platform, promoted by the ISCIII.
- In 2016, BT-CIEN reached a record number of total annual donations (including all programs) (87) as well as of donations from the external program (76).
- The internal donation program, corresponding to donations from the Alzheimer's Center Queen Sofia Foundation cohort, reached 100 donations in its history.
- The number of tissue samples donated was around 2,000, compared to 1,500 in 2015, which represents an increase of 75%.
- Among the publications made in 2016 with material from BT-CIEN, it can be highlighted an international study of a new gene involved in amyotrophic lateral sclerosis and frontotemporal dementia (Nat Commun., 2016 Apr 15; 7: 11253).
- In March 2016, the BT CIEN "Donor Card Handout" event was held at the Alzheimer Center of the Queen Sofia Foundation chaired by H.M. Queen Sofia, who attended the event. It is a symbolic act in recognition of people who give their brains to scientific research.
- Creation of the web page of the Tissue Bank of the CIEN Foundation, with useful and detailed information on its activity as well as its periodic updating.

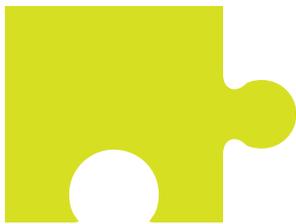


1. PROFILE AND PRESENTATION

Training



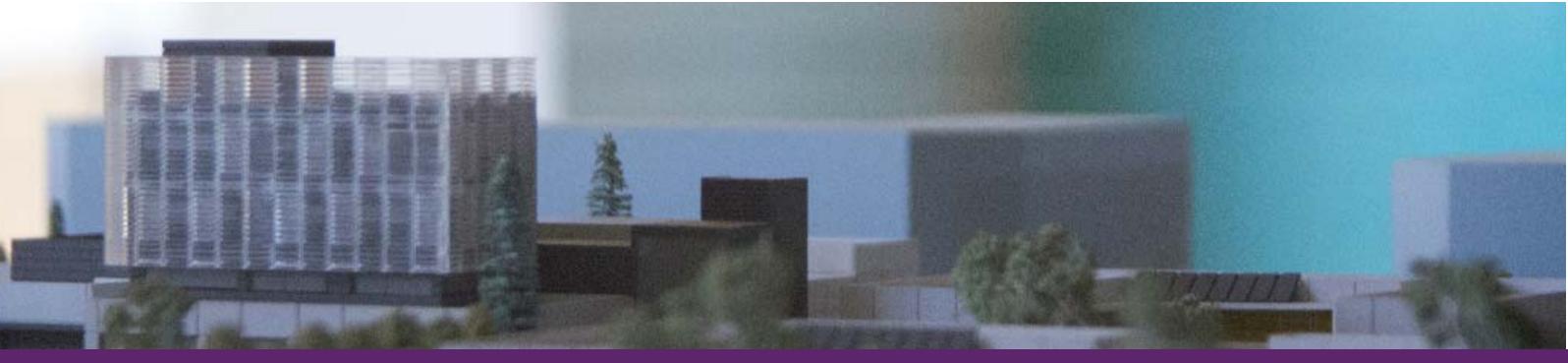
- The CIEN Foundation has collaborated during 2016 with some Spanish universities through student internships.
- After the first edition in 2015, the Seminar Cycle of the CIEN 2016 Foundation is consolidated with an almost weekly training activity in which speakers from both the Foundation and other institutions present their work and engaged in scientific discussion, in accordance with the training vocation that characterizes the CIEN Foundation.



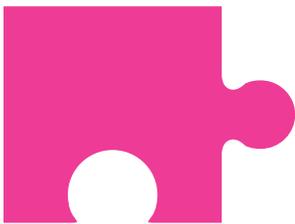
Hirings

- The CIEN Foundation maintains the four positions from the 2014 call for the promotion of young employment and the implementation of the Youth Guarantee in R+D+I initiated in December 2015 and extends its commitment to the Youth Employment Operative Program of the Ministry of Education, Education, Youth and Sports of the Region of Madrid, through the formalization of two new hirings, during 2016.
- Hiring of postdoctoral researcher Jaime Gómez Rodríguez, from the Department of Neuroscience and Mental Health, Hospital for Sick Children, University of Toronto, Canada.
- Call for MAPFRE-Queen Sofia Foundation Scholarship for the hiring of a researcher in a biomedical specialty with accredited specialization in research. The hiring will be effective in the CIEN Foundation and in a research center of international prestige.



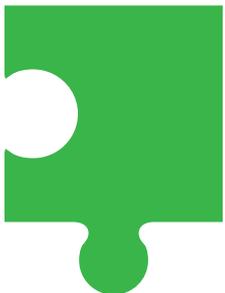


Funded Projects



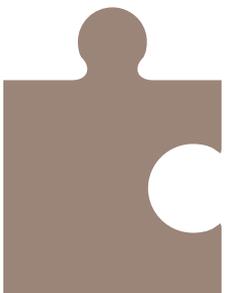
- Granting to Bryan Strange, Head of Neuroimaging at the CIEN Foundation, of the USA Alzheimer's Association Project New Investigator Research Grant" through the UPM and formalization of the hiring of Linda Zhang, from the University of Hong Kong .
- Signing of ISCIII-funded project "Search of biomarkers for the early detection of Alzheimer's disease in the Vallecas project cohort", with participation of CIBERNED and CIBERBBN. Much of this project will be carried out at the CIEN Foundation.

Communication



- The number of media impacts during 2016 was around 1,600, increasing by 46.39% compared to 2015. Thus, for example, only during the actions corresponding to the IV CiiEN -Congress of Innovation and Research in Neurodegenerative Diseases (Alicante, 21-23 September 2016)- more than 200 impacts were generated in the press (agencies and national media), 150 in online media (including the traditional digital publications) plus the notorious repercussion in social media, especially Twitter.

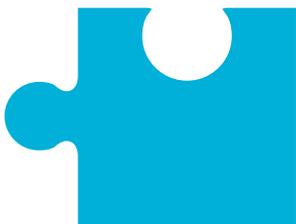
Clinical Trials



- Launch of the "Clinical Trials Program", a clinical research program that includes the design and organization of clinical trials. In 2016, two Clinical Trials were designed, one of which has been already launched.
- Presentation to the Spanish Agency of Medicines and Health Products of the Sat-CIEN-02 clinical trial, that has been approved by the AEMPS and by the Ethical Committee of the Belvitge Hospital.



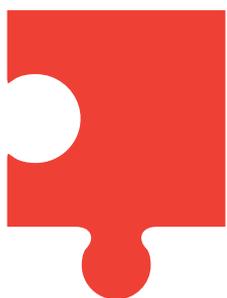
1. PROFILE AND PRESENTATION



Dissemination Activities

- In September 2016, it was held the fourth edition of the International Congress of Research and Innovation in Neurodegenerative Diseases (CIINEN), that has become fully established as the International Congress of reference in our country in the area of neurodegenerative diseases.
- We have expanded the scope of our traditional "Christmas Tree of Memories", promoted by the Queen Sofia Foundation. In December 2016, coinciding with the Christmas holidays, in addition to the 'Tree of Memories' in the Villa de Vallecas Municipal Market, a "Christmas Tree of Memories" was inaugurated in parallel at the Madrid City Hall, in the CentroCentro building located in the Plaza de Cibeles, through which thousands of people passed by, decorated with hundreds of paper balls with their Christmas memories.
- The SARquavitae Foundation and the CIEN Foundation joined efforts in the fight against neurodegenerative diseases by collaborating in the second edition of the "miles to remember" campaign, bringing together more than 2,000 participants.
- The CIEN Foundation, together with King's College London (University of London) and the National Parkinson Foundation, organized the meeting "Measuring Non-Motor Symptoms of Parkinson's Disease: 10 years since NMSQuest", held in the Ernest Lluch room (Carlos III Institute of Health, Madrid) on March 3-4, 2016.
- In October 2016, the traditional "Mano Amiga" (Friendly Hand) Awards Ceremony, held by Alzheimer Leon, was held. During the gala, public recognition went to H.M. Queen Sofia, for Her effort and personal dedication for decades to the fight against Alzheimer's disease, and the CIEN Foundation received nearly 12,000 euros raised through the Alzheimer León sponsors who collaborated with the Mano Amiga Awards with the Campaign "Invest in research to erase Alzheimer's together".

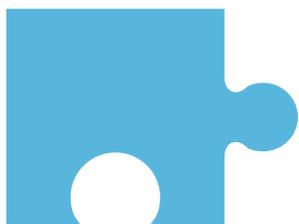




Collaboration Agreements

- The CIEN Foundation and Neuron Bio sign an agreement for the development of joint projects in the field of diagnosis of Alzheimer's disease with the aim of uniting the experience and knowledge of the specialists who are part of the Alzheimer Project Support Unit (UIPA), with scientists and developments recently reached by the biotechnological company Neuron Bio in the diagnosis field for this disorder.
- The CIEN Foundation signed in December 2016 a collaboration agreement with the University Hospital of Torrejón, an center integrated in the public network of hospitals in the Region of Madrid. This agreement will allow both institutions to advance in the research of neurodegenerative pathologies, to know how they affect the brain tissue and to develop new research lines that allow improving the early diagnosis and treatment of these diseases.

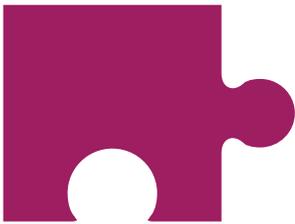
Publications



- During 2016, 29 original articles have been published in specialized journals, of which 24 (82.759%) are classified in first and second quartiles, with an average impact factor of 6.792, which represents a significant increase (43.959%) compared to 2015.
- During this year, the CIEN Foundation has increased its international collaborations, so that 53.6% of the articles were studies carried out in collaboration with foreign institutions and the rest with Spanish ones.



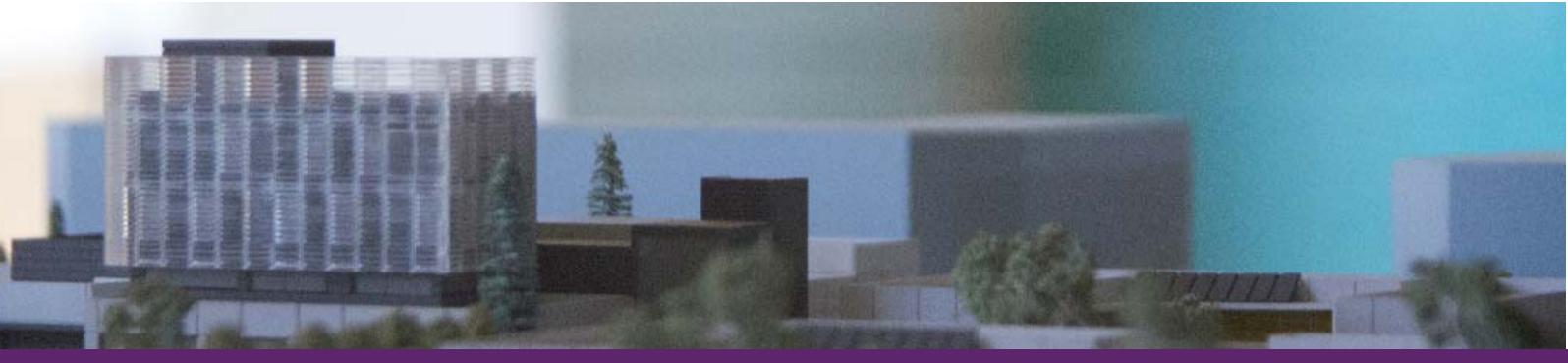
1. PROFILE AND PRESENTATION



Patents

- During 2016, the CIEN Foundation maintains its participation as co-owner in three active patents, both in national and international phases, two of which are licensed with Raman Health Technologies.





1.3. Letter from the Manager of the CIEN Foundation



After a productive and enriching year of work, I am writing to you once again to review the activity undertaken by the Center for Research in Neurological Diseases (CIEN, for its acronym in Spanish) during the past year 2016.

During the last few years, the CIEN Foundation path continues to be guided by our commitment to society and to research. This is demonstrated by the advancement of translational projects and the in-

ternationalization of our activities, organized around basic, clinical and epidemiological neurology. The evolution of the institution and the progress of the research work are due to the constant support of the Queen Sofia Foundation and to the dedication and commitment of those who are part of the CIEN Foundation. As well as the valuable contributions of the Carlos III Institute of Health (ISCIII, for its acronym in Spanish), involved in our research projects.

Nine years after the opening of the Center, the 'Vallecas Project' appears as one of our main drivers and one of the most ambitious studies carried out in Spain to advance the diagnosis of Alzheimer's and the main study with cognitively healthy volunteers in our research environment. At the end of 2016, a total of 1,109 volunteers have been assessed under the umbrella of this project.

The publication of the conclusions obtained in the framework of the 'Vallecas Project' has brought to the CIEN Foundation the recognition of the scientific community and a push to continue doing research. An example of this is the distinction of the Foundation's communications among the ten best presentations at the LXVIII Annual Meeting of the Spanish Society of Neurology. But undoubtedly, these advances in research would not be possible without the selfless participation of the volunteers. For all of them, we held for the fourth consecutive year the Vallecas Project Volunteer's Day, an institutionalized event that recognizes the value of this collaboration.

Following our translational research model, in 2016 we started the Clinical Trials Program, clinical research that includes the design and organization of trials. Two clinical trials have been designed this year and one of them has already been launched. At the same time, the CIEN Foundation continues to be the co-holder of three active patents, both nationally and internationally.

María Ángeles Pérez Muñoz
Manager of the CIEN Foundation

1. PROFILE AND PRESENTATION

The publication of 24 of the 29 articles from our research teams in specialized journals of the first and second quartiles demonstrates the quality and innovation of the research carried out. This represents an increase of more than 40% in the presence of the CIEN Foundation in the most prestigious journals with respect to 2015.

In addition to strengthening internal research activities, we continue at the Foundation to collaborate on national and international projects. This year specifically an agreement between the CIEN Foundation and Neuron Bio has been signed to develop new joint projects to advance the early diagnosis of Alzheimer's. We have also established a collaboration agreement with the Torrejon University Hospital to study how neurologic pathologies affect brain tissue and look for new lines of diagnosis and treatment.

The CIEN Foundation's collaboration with the Network Center for Biomedical Research in Neurodegenerative Diseases (CIBERNED, for its acronym in Spanish) reinforces the Foundation's strategic position in neurodegenerative diseases research based, among other aspects, in the Tissue Bank of the CIEN Foundation (BT-CIEN, for its acronym in Spanish). During 2016 the biobank of neurological samples reached a record number of 87 tissue donations.

Nevertheless, we are conscious that research must go hand in hand with dissemination, communication and outreaching. In the scientific environment, the fourth edition of the International Congress of Research and Innovation in Neurodegenerative Diseases (CIIIEN, for its acronym in Spanish) has raised the event to become an international reference conference in our country in the field of neurodegenerative diseases.

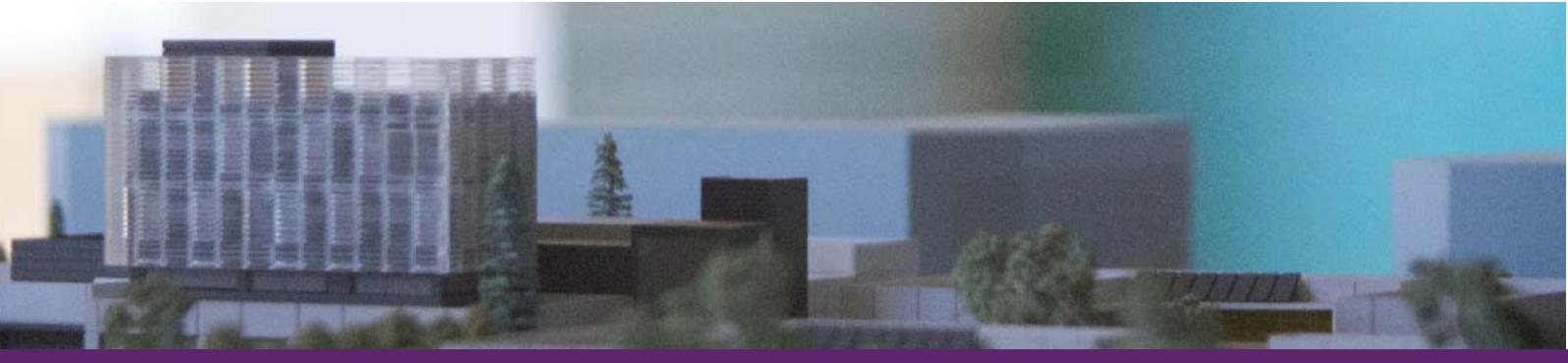
To bring society closer to our research activities, during 2016 we have carried out some social impact

initiatives such as the already well-known Tree of Memories. In addition, our Tree reached last year a greater diffusion thanks to having a twin displayed at the Madrid City Hall. Thousands of people participated with their Christmas memories. Donors of brain tissue have also gained prominence, and their work was recognized in March 2016 in a symbolic act to handle over their corresponding donor cards.

Finally, I would like to highlight the advances in the area of human resources, as the recruitment of new talent is key to the progression of the CIEN Foundation. We have maintained our commitment to employment of young people and expanded opportunities for them both through the Youth Guarantee System and through the Region of Madrid programs. The call for the MAPFRE-Queen Sofia Foundation Fellowship and the access of young university students to curricular practices enhances their vocation and training for future research projects.

The high quality of the work of our professionals and the unconditional collaboration of our patrons and benefactors allow us to continue searching for tools against one of the main challenges of the 21st century: Alzheimer's disease.





1.4. Letter from the Scientific Director of CIEN Foundation



The year 2016 has marked the ninth anniversary of the opening of the Queen Sofia Foundation Alzheimer Center and the first Vallecas Project is nearing completion, which is already bearing fruit in the form of publications and other scientific activities. This development of our Institution is due in large part to the constant support of the Queen Sofía Foundation and to the efforts of the people who work in the different Departments at our Vallecas Center. This task is beginning to be recognized nationally and internationally.

During the last year, ten scientific articles have been published from our Center and other collaborations have been carried out with other external groups in accomplishing five other publications. Various courses have been carried out, our personnel has participated in different scientific meetings and two new clinical trials have been designed, one of which has been already initiated. The FCIEN participates as co-holder in three active patents. In addition, collaboration agreements have been signed with different public and private institutions to develop new lines of research aimed at facilitating the early diagnosis of Alzheimer's disease.

Finally, I would like to congratulate those colleagues who have been awarded for their work, nationally and internationally and to thank the Vallecas Project volunteers for their participation and dedication.

Thank you all.

Jesús Ávila de Grado
Scientific Director of CIEN Foundation

1. PROFILE AND PRESENTATION



1.5. Organizational structure

1.5.1. Governing and Managing Bodies

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

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 2016 the Board of Trustees has the following members:

CIEN FOUNDATION BOARD OF TRUSTEES

POSITION	TITLE	NAME
Honorary chair	Minister of Economy and Competitiveness	Excmo. Sr. D. Luis de Guindos Jurado
Chair	State Secretary of Research, Development and Innovation	Excma. Sra. D ^a Carmen Vela Olmo
Vice-chair	Director of the Carlos III Institute of Health	Sr. D. Jesús Fernández Crespo
Ex-officio Members	General Secretary of Health and Consumer Affairs, Ministry of Health, Social Services and Equality	Sr. D. José Javier Castrodeza Sanz
Ex-officio Members	General Director of Scientific and Technical Research, Ministry of Economy and Competitiveness	Sra. D ^a . Marina Pilar Villegas Gracia*
Ex-officio Members	Director of the Technical Secretary, Executive Committee for Economic Affairs, President of the Government's Economics Office	Sra. D ^a . Cristina Ysasi-Ysasmendi
Ex-officio Members	Deputy Director General of Evaluation and Promotion of Research, Carlos III Institute of Health	Sra. D ^a Belén Bornstein Sánchez
Ex-officio Members	Director General of Public Health, Quality and innovation, Ministry of Health, Social Services and Equality	Sra. D ^a Elena Andradás Aragonés
Ex-officio Members	President of the Higher Council for Scientific Research	Sr. D. Emilio Lora Tamayo
Member And Secretary	Deputy General Director of Cooperative Research Networks and centers, Carlos III Institute of Health	Sra. D ^a . Margarita Blázquez Herraiz
Elected members Andalusia	General Director of Research, Technology and Business, Andalusian Government	Sr. D. Manuel García León
Elected members Valencia	Director General for Research, Innovation, Technology and Quality, Public Health Department	Mr. Óscar Zurriaga Lloréns
Elected members Canary Island	Director General of Welfare Programs, Canary Islands Health Service	Sr. D. Bernardo E. Macías Gutiérrez
Elected members Castilla-La Mancha	Secretary General of the Health Service of Castilla-La Mancha (SESCAM)	Sr. D. Fernando Sanz García
Legal advisor	State Attorney	Sr. D. José Luis Beotas López
Invited guests	Scientific Director	Sr. D. Jesús Ávila de Grado
Invited guests	Managing Director	Sra. D ^a María Ángeles Pérez Muñoz



1. PROFILE AND PRESENTATION

Invited guests	Queen Sofia Foundation	Sr. D. Jose Luis Nogueira Guastavino
Invited guests	Advisor to the Office of the Secretary of State for Research	Sr. D. Agustín Larrañaga Elorriaga
Invited guests	Assistant to the Secretary	Sra. D ^a M ^a Dolores Donoso Mencía

* Registration of resignations and new appointments in the composition of the CIEN Foundation Board of Trustees:

Ceases as a member in 2016:

D^a. Marina Pilar Villegas Gracia (General Director de Scientific and Technical Research, Ministry of Economy and Competitiveness).

Ceases as a member on November 21, 2016:

Region of Valencia: **Oscar Zurriaga Llorens** (General Director for Research, Innovation, Technology and Quality of the Department of Public Health of the Region of Valencia). Holds the position: D^a Ana María Ávila (pending processing, awaiting response from the Registry of Foundations).

1.5.2 Advisory and participation bodies

External Scientific Advisory Committee

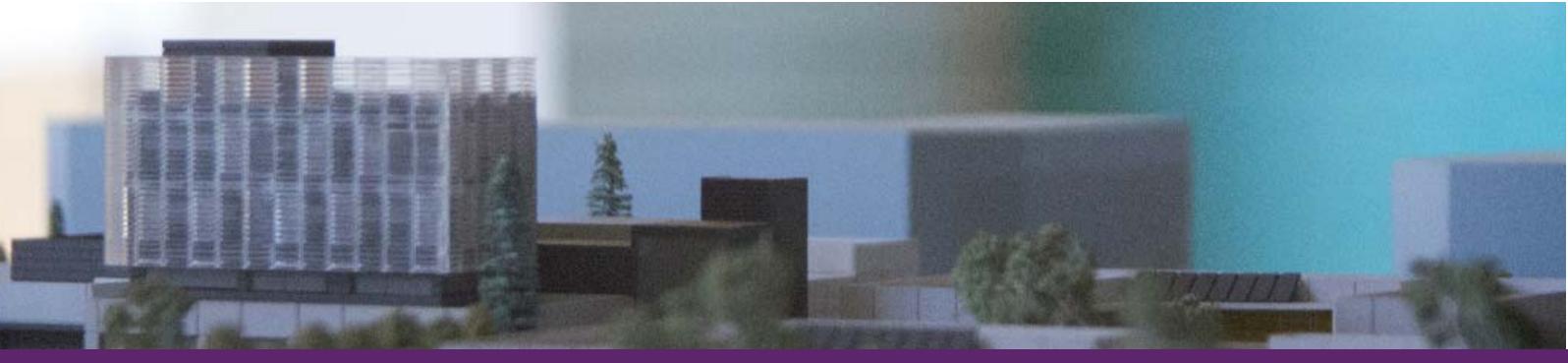
In the Board meeting held on March 10, 2014 the composition of the CIEN Foundation External Scientific Advisory Committee it is presented and approved. It is aimed at improving the scientific quality of the activities, optimizing the available resources and exploiting the singularities of the Queen Sofia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

- **Mr. 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. 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. 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. Miguel Medina Padilla**. Doctor in Biochemistry and Molecular Biology from the Autonomous University of Madrid. Deputy Scientific Director of CIBERNED.
- **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.

Meetings of the Scientific Advisory Committee with H.M Queen Sofia

Since its creation, several joint work meetings have taken place between UIPA researchers, members of the Scientific Advisory Committee of the CIEN Foundation and representatives of the Queen Sofia Foundation. In the last one, held in October 2016, H.M. Queen Sofia went to the Alzheimer Center Queen Sofia Foundation, headquarters of the CIEN Foundation, to meet with the External Scientific Advisory Committee.





The meeting focused on the exchange of news regarding the progress and state of research in Alzheimer's disease, one of the foundational and organizational pillars of the CIEN Foundation and the Queen Sofia Foundation, and a topic in which Queen Sofia has been personally involved since decades.

The meeting also served to share the main conclusions of the IV CiiEN (International Congress on Innovation and Research in Neurodegenerative Diseases, Alicante, September 21-23, 2016), organized by the Queen Sofia Foundation, the CIEN Foundation and CIBERNED and attended by more than 200 national and international scientists.

After the welcoming words from M^a Ángeles Pérez, manager of the CIEN Foundation and CIBERNED, the scientific director, Dr. Jesús Ávila, presented to the audience the main trends and recently published advances in international research on this pathology that affects millions of people, emphasizing the growing importance given to early detection and diagnosis. Avila also referred in his speech to the projects carried out in the Research Unit of the Alzheimer Center of the Queen Sofia Foundation, such as the Vallecas Project for biomarker research and cognitive impairment, in which 1,213 volunteers participate.

During the course of the meeting, H.M. Queen Sofia was interested in details of the research and spoke with some of the members of the External Scientific Advisory Committee of the CIEN Foundation, including Dr. Miguel Medina, and Drs. José Ramón Naranjo, Javier de Felipe and Fernando Rodríguez Artalejo.



1. PROFILE AND PRESENTATION



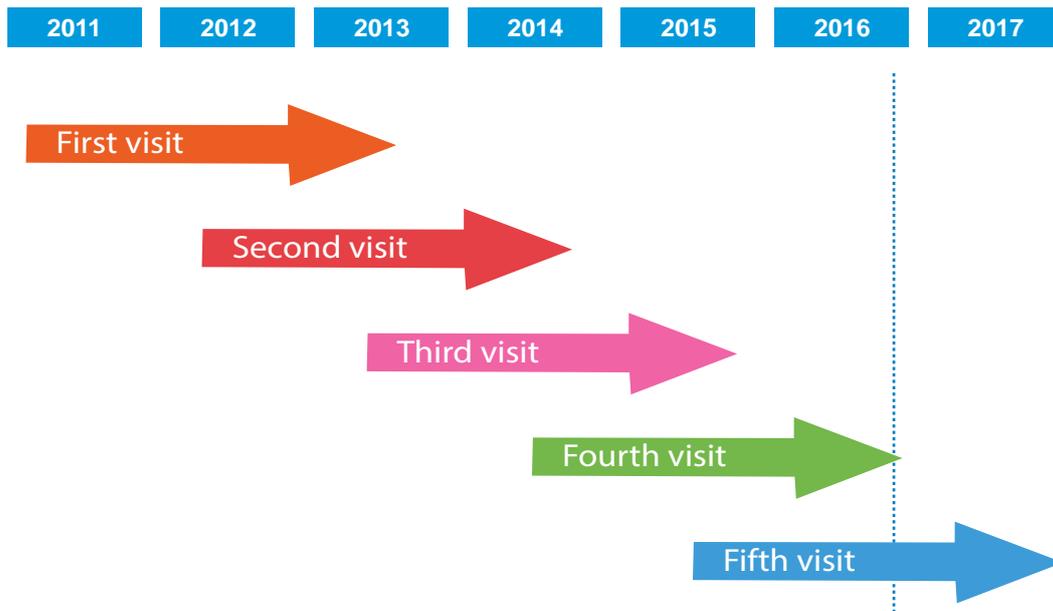
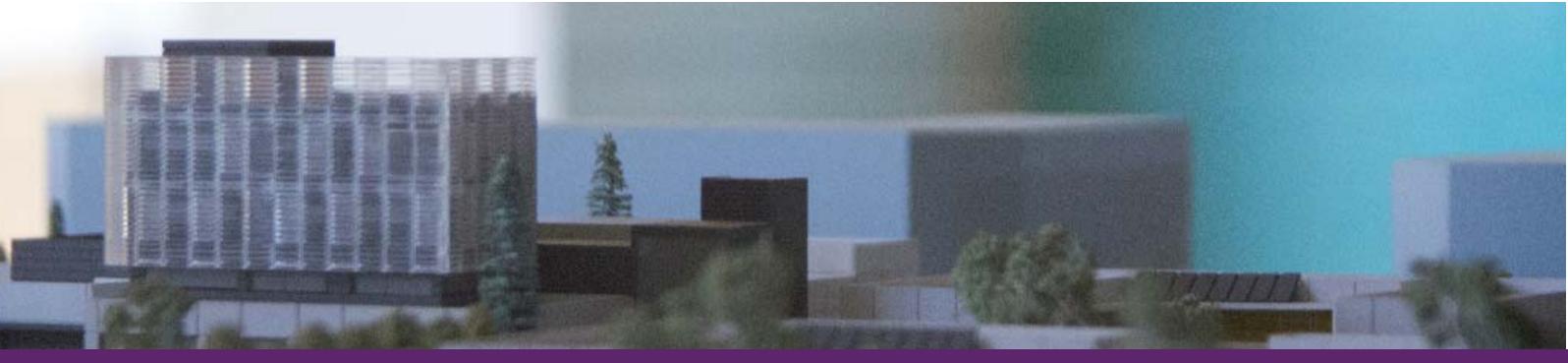
1.6. Vision

The Vallecas Project is the main research project being conducted at the CIEN Foundation, both in terms of resources employed as well as in terms of its social impact. At the end of 2013 the project concluded the recruitment and the phase of initial evaluation of the volunteers. The following figure shows the status of the clinical evaluations carried out up to December 31, 2016 (the exact figures can be looked up in section 4.3.8 of this report). During the first half of 2017, the fourth and fifth visits have been per-

formed simultaneously, and the sixth study visit has begun.

During this year, the validation of the historical data collected to date by the different departments has been completed and a single newly created, integrated and anonymized database has been established, with the aim of ensuring the reliability and security of the data and allowing at the same time, a more efficient analysis of them. The first analyses of the data from the first two visits have been presented to the Scientific Advisory Committee of the CIEN Foundation and to members of the Queen





Sofia Foundation. In addition to presenting our preliminary results in different congresses and scientific meetings, during 2016 the first two works with results generated entirely from the longitudinal analysis of the Vallecas project have been published in international scientific journals (see section 6.2.1.). The project is generating great interest among the scientific community and we hope to continue presenting our results in scientific journals, national and international congresses throughout the year 2017.

As the project progresses, a large volume of increasingly rich and relevant information is generated on the most initial phases of cognitive impairment in those subjects who develop it, as well as on the biomarkers (clinical, biochemical and neuroimaging) most suitable for its characterization and identification of the population at greater risk of developing it. In recent months, we have initiated the necessary contacts so that the information obtained from the assessments of the volunteers, their biological samples and the neuroimaging studies carried out inte-

grates with that of other national and international cohorts, which will significantly increase the potential of each of them as well as the Vallecas Project itself.

In addition to the Vallecas Project, the Alzheimer Project will continue to be a structural project of the Queen Sofia Foundation Alzheimer Center and the CIEN Foundation and a growing source of information (clinical, molecular, neuroradiological and neuropathological) on dementia in its moderate and advanced stages. This longitudinal study, initiated in 2007, aims to monitor the residents of the Alzheimer Center of the Queen Sofia Foundation and users of the Day Center.

In the coming months and years, the information collected since the beginning of the Project will provide important clues on how the two main pathologies that determine dementia in our environment, Alzheimer's pathology and cerebrovascular pathology, interact with each other and lead to



1. PROFILE AND PRESENTATION

defined evolutionary trajectories. A better understanding of the different forms of expression of these pathologies, when presented in isolation or, more frequently, in combination, will allow us to fully address their role in the origin of dementia, as well as to identify groups of patients that require care or can benefit from specific therapies.

The research model developed at the Alzheimer Center can also be applied to other institutions and

Day Centers of the Region of Madrid. In fact, the model of the Alzheimer Project in other social-health settings is already being applied to Day Centers of the Associations of Relatives of Alzheimer's patients (AFA, for its acronym in Spanish) of Soria and Leon, among others, with the intention of incorporating in future projects of the Foundation subjects diagnosed with mild cognitive impairment and mild dementia.



Mänagement *re*port

In 2016 CIEN Foundation management has continued to focus on its main objective of promoting research in the neurodegenerative field, with international participation and direct translation to the progress of our society. Under the auspices of the Carlos III Health Institute and the Queen Sofia Foundation, the CIEN Foundation maintains a quality management based on leadership, innovation and the responsibility of its professionals. The value of his team is further reinforced by a strong investment in training as a management tool for the acquisition of new knowledge.





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.

During 2016 CIEN Foundation continues to manage the following actions:

- Cooperation agreement between the ISCIII and CIEN Foundation for the development of the strategic agenda of the European Union Joint Program in Neurodegenerative diseases, particularly Alzheimer's disease (JPND) through the participation of CIEN Foundation in the European Network of Centers of Excellence (COEN). In 2016, the 3rd Pathfinder Project Call was resolved, resulting in one funded project with Spanish participation through a CIBERNED group.
- Collaboration agreement between the Foundation for Knowledge Madridmasd and CIEN Foundation to regulate the participation of the Foundation as host institution in the M+VISION program under the FP7-PEOPLE-2011-COFUND call as host institution. The project funded by the European Union provides for the participation of host institutions as legal entities in which the researchers selected for support within the M+VISION program conduct their training through Research.

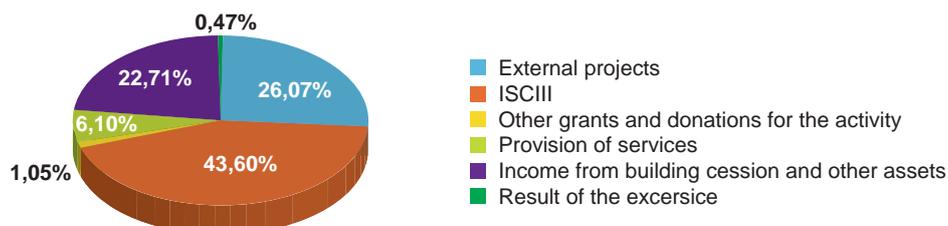
The M+VISION project includes two types of assistance depending on the type of mobility involving: incoming and outgoing. In the incoming grants researchers enjoy three years of funding in Spain. The project, financed by the European Union, envisages the participation of host institutions as legal entities in which the researchers selected for support of the project M+VISION conduct their training. The program offers grants of a total duration of three years, consisting of a year of scholarship and two-year contract plus contributions for research expenses and travel. The first year the researchers receive funding from the Region of Madrid and the scholarship takes place in a primarily academic environment, while the second and third years are directly employed by host organizations, making a more market-oriented research.

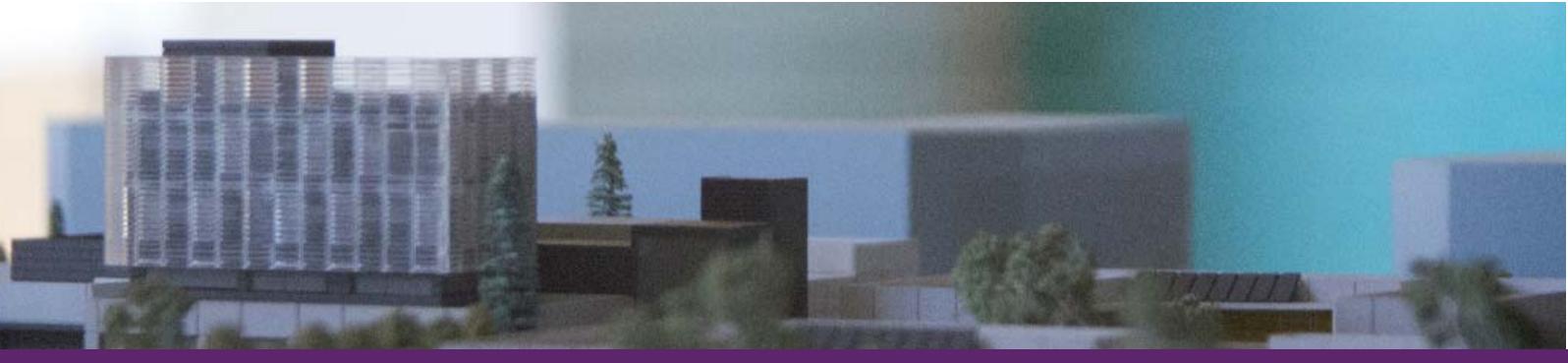
2.2. Management of financial and economic resources

Revenues

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

Percentage distribution of 2016 revenues





The breakdown of total revenues obtained in 2016 and 2015 has been as follows

	2016	2015
Grants, donations and legacies charged to surplus for the year	1.588.467,76	1.759.511,45
Reimbursement of grants and subsidies	0	45.074,96
Sales and other income from commercial activity	131.406,28	104.731,58
Other income	4.479,78	5.633,95
Grants, donations and legacies transferred to capital surplus for the year	506.781,77	658.091,90
Financial income	106,61	1.219,24
Positive exchange differences	227,85	13,83
TOTAL	2.231.470,05	2.574.276,91

CIEN Foundation's total revenue budget in 2016 exceeded 2.2 million euros. Considering the origin of the funds, the contribution of the ISCIII amounts to 972,968.52 €, the income from external projects adds up to 581,740.24 €, and the amount corresponding to services and other subsidies and donations received for the activity amount to 136,220.52 € and 23,380.44 €, respectively. The income corresponding to the transfer of the building is 506,781.77 €. The final result for the exercise is 10,378.56 €.

The allocation of grants, donations and bequests reflected in the table of total income obtained in 2016 includes the annual allocation of the ISCIII, aimed at achieving the specific aims and objectives of the CIEN Foundation; and the income from external projects (mainly the Vallecas Project, the Youth Employment Plan of the Ministry of Economy, Industry and Competitiveness, the Youth Employment Operative Program (YEI) of the Region of Madrid, the M + Vision project, and the Biobank Platform PT13/0010/0045).

Revenues from provision of services during 2016

	2016	2015
Energy production	10.378,56 €	12.982,68 €
Income from performing MRIs and collaborative research projects	121.027,72 €	91.748,90 €
TOTAL	131.406,28 €	104.731,58 €



Sales and other revenues from the activity correspond mainly to research services, based on contracts signed with other public and private research centers.

Expenditure

The expenditure executed by the CIEN Foundation is used for the development of activities in the Alzheimer Project Research Unit (UIPA) of the Queen Sofia Foundation Alzheimer Center.

Concerning the expenses executed by the CIEN Foundation in 2016, the item "Monetary aid" decreases due to the completion of the financing corresponding to the 2013 COEN call, in which three projects with Spanish participation were selected. In 2016, within the framework of the new COEN call, one project led by a CIBERNED researcher is funded.

The increase in "Staff costs" is explained by the formalization of new contracts framed in and funded by the Youth Employment initiative of MINECO and the Region of Madrid (section 2.3.2).

2.3. Management of Human Resources

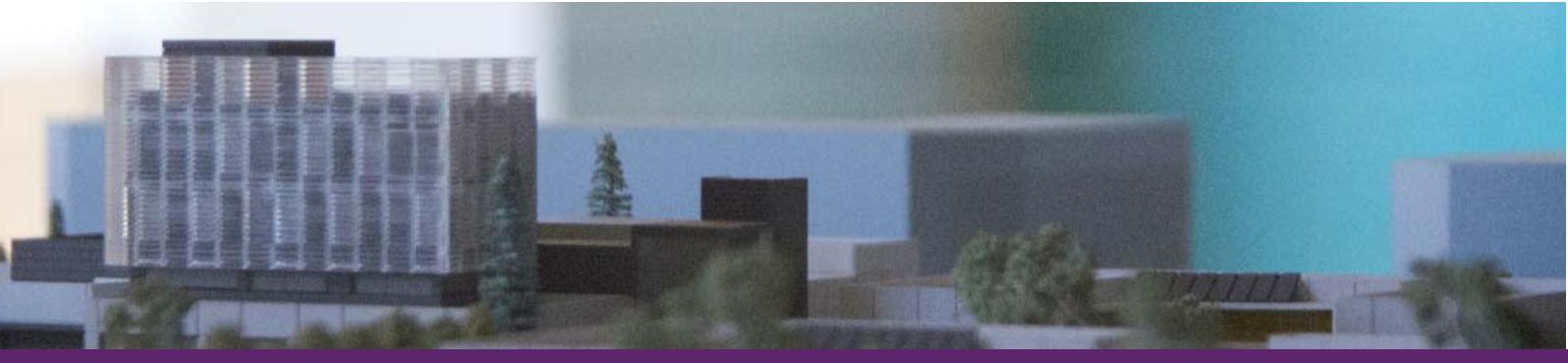
CIEN Foundation's commitment to society, research, scientific progress and quality management leads it to acquire new knowledge and innovate through leadership, responsibility and effort of its professionals. The progress of the results and the balance of the research of top level studies, such as the Vallecas Project, certify a great solidity and solvency of the research carried out by the professionals of the Foundation. These strategic projects provide maximum visibility and generate great social interest in the research carried out, guaranteeing the continuity of the CIEN Foundation as a national and international reference.

The CIEN Foundation has a competitive, professionally respected human team that is characterized by sharing our values, strategies and objectives. It offers its employees a solid project, continuous learning and a unique professional experience. It seeks to promote personal and collective commitment through the institutional mission, as well as the sense of belonging to the organization. The long-term suc-

Distribution of CIEN Foundation revenues

	2016	%	2015	%
Monetary aid and others	15.691,23 €	0,71%	341.349,65 €	13,34%
Variation of existences of merchandise	-12.708,72 €	-0,57%	-19.290,78 €	-0,75%
Supplies	164.432,45 €	7,40%	173.885,09 €	6,79%
Staff costs	930.045,89 €	41,87%	850.264,09 €	33,22%
Other operating expenses	616.438,80 €	27,75%	705.055,86 €	27,54%
Depreciation and amortization	506.470,99 €	22,80%	508.305,00 €	19,86%
Impairment and gains on disposal fixed assets	310,78 €	0,01%	0,00 €	0,00%
Exchange differences	410,07 €	0,02%	84,51 €	0,00%





cess of the CIEN Foundation depends on its ability to attract, motivate and train researchers capable of establishing research on a solid and constant basis. The know-how, skills and competences of our staff are decisive factors to accomplish the objectives of the Institution and that helps the research it develops to reach society through a permanent approach to excellence.

Human resources devoted to carrying out the activities of the Foundation

All positions offered by the CIEN Foundation have been procured through an open competition process under criteria of capacity, merit and publicity. Positions have been published on the CIEN Foundation, ISCIII and CIBERNED websites, having respected the principle of free competition and objectively assessed the applicants' merits. This procedure is in accordance with section 6.2 of ISO 9001:2008.

All positions offered are defined with a specific profile, required qualifications, requirements and functions to be performed.

During 2016, the CIEN Foundation has counted on a total of 51 professionals, including 30 hired from competitive grants, 11 fellows, 1 in-training Resident Medical Intern in neuropathology, 1 PhD in neuropathology, 2 volunteers who have collaborated selflessly with the CIEN Foundation, and 4 professionals who developed their activity under signed collaboration agreements.

CIEN Foundation has continued with its commitment to young researchers and collaboration with public and private institutions. During 2016 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) PEJ2015/BIO/AI-0615"

with one formalized hiring. Likewise, a CIEN Foundation researcher has participated in the "Call for grants aimed at attracting research talent to incorporate research groups from the Region of Madrid". In addition, continuing with its commitment to young people and future researchers, it participates in the theoretical and practical training of Spanish university students through collaboration agreements for carrying out university practices. One more year, the Call for Grants of the MAPFRE-Queen Sofia Foundation Fellowship has allowed the incorporation of a specialist in biomedical sciences within the Alzheimer Project Research Unit.

The multidisciplinary nature of our team defines the work of the departments that make up the CIEN Foundation. On a daily basis, the professionals of every department, formed by research, healthcare and management personnel, perform their functions with a high degree of commitment and cooperation. It is organized through the following areas:

- Department of Management and Administration
- Department of Neuroimaging
- Department of Neuropathology and Tissue Bank
- Department of Cell Biology Laboratory
- Department of Neurology
- Department of Neuropsychology

Human resources devoted to carrying out the activities of the Foundation are reflected in the following table.

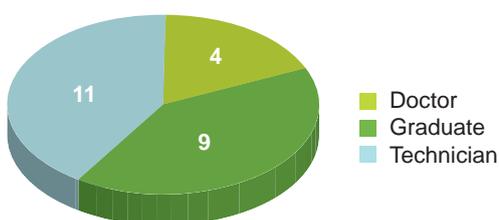
2.3.1. Training program

To achieve the goals and objectives of our organization, one of the main tools that the Foundation has defined is the development of a Training Program adapted to the needs of its staff, in a way that allows the development of their professional skills in the de-

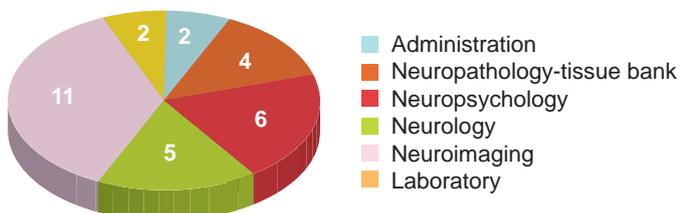


2. MANAGEMENT REPORT

Research staff by degree



CIEN Foundation staff in 2016



defined strategic lines and increases the quality of the activities carried out.

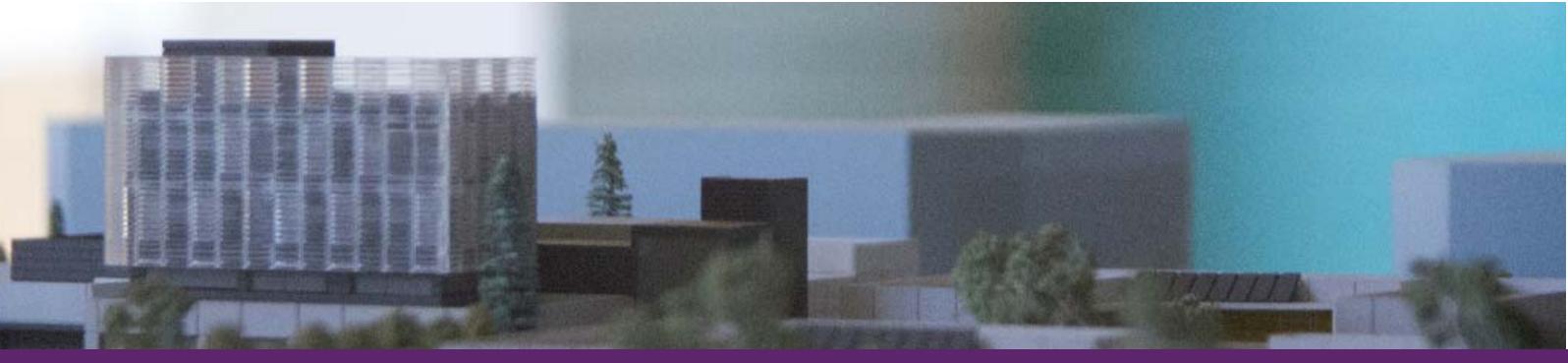
The CIEN Foundation has promoted the creation and development of the Training Program as a key piece to meet the requirements of competitiveness, efficiency and quality; and at the same time, satisfy the aspirations of professional and personal development of the employees.

Training must be understood as a management tool that allows the acquisition of knowledge that fosters the development of skills and contribute to our organization having professionals integrated into a common project to offer quality services.

Among the courses and training actions carried out by our staff during 2016, the following stand out:

- Course on "Written communication". CALAMO&CRAN
- Course on "Genetic analysis of critical samples". Complutense University of Madrid
- Workshop on "The importance of technology transfer in translating research results in Biomedicine". CIBER
- "I Multidisciplinary Day of Assistance Humanization. Care of the emotions". Prince of Asturias University Hospital of Alcalá de Henares
- Course on "European patent law". School of Industrial Organization
- Course on "Empowerment of patients as a first step towards participatory health". National School of Health-ISCIII
- Course on "Intensive English Course for Radiographers". University College Dublin, Ireland
- Course on "Evaluation of focal lesions and bile duct by MRI: the value of Primovits". Alcorcón University Hospital-BAYER
- Workshop on Quality Management Systems. NOVASOFT
- Course on "Applying fMRI to Study th Human Brain". Spanish Society of Psychophysiology and Cognitive and Affective Neuroscience
- Course on "Nutrition, genes y health". MiriadaX
- Course on "Study of the cerebrospinal fluid". Spanish Association of Laboratory Technicians
- Course on "Design and evaluation of social projects". ASISPA
- Workshop on SNOMED CT, 1st Edition". FISABIO
- Information Day "MSCA Actions, Innovate Training Networks (INT) Call 2017". ISCIII
- Course on "Statistical analysis applied to the Clinical Investigation". Official College of Physicians of Madrid.
- "Informative Day on the elaboration of the plan of action through the Application of annual accounts and plans of action ". Ministry of Education, Culture and Sports





2. MANAGEMENT REPORT

Internships

- Valentina Moschini and Jenifer González Herreros, students from the Psychology Degree of the Complutense University of Madrid supervised by Marina Ávila Villanueva and Miguel Ángel Fernández Blázquez (Apr-Jun 2016 and Jun-Oct 2016).
- María Ballesteros González, student from the Psychology Degree of the Rey Juan Carlos University supervised by Belén Frades Payo (Jan-May 2016).
- M^a Isabel Jaén Vicedo, student from the last year of the Psychology Degree of the Autonomous Universidad of Madrid supervised by Belén Frades Payo (Oct 2016-Jan 2017).
- Ilaria Giovanelli, neuropsychologist from the Italian program "Torno Subito" supervised by Miguel Ángel Fernández Blázquez (Oct 2015-Jun 2016).
- M^a Dolores Arrabal Ortiz, UAM PhD student supervised by Alberto Rábano at BT-FCIEN (Jul 2-Dec 2016).
- Joanna del Hierro Calderón, student from the Pathological Anatomy and Cytodiagnosis Higher Degree of the IES Moratalaz, supervised by Alberto Rábano (Jan-Jun 2016).
- Emily Lindemer PhD student from the Harvard/MIT Division of Health Sciences and Technology in the framework of a collaboration project between MIT and the Queen Sofia Foundation Alzheimer Center. Supervised by Bryan Strange and Christopher Long (Feb 2016).
- Alba Ruíz Herrero, student from the Biology Degree of the Extremadura University supervised by Alberto Rábano (Jul 2016).
- Linda Zhang, postdoctoral fellow from the University of Hong Kong supervised by Bryan Strange (Sep- Dec 2016).

End of master studies

- Valentina González Álvarez, Master in Neuroscience of the UAM. Department of Neuropathology. (Jun 2015-Jun 2016).

- Sara Enrile Lacalle, Master in Neuroscience of the UCM. Department of Neuropathology (Jul 2015-Jul 2016).

Rotations

- Lara Sanz Irene, Medical Intern Resident from La Paz University Hospital, Department of Neuropathology (Jan 2015-Feb 2016).

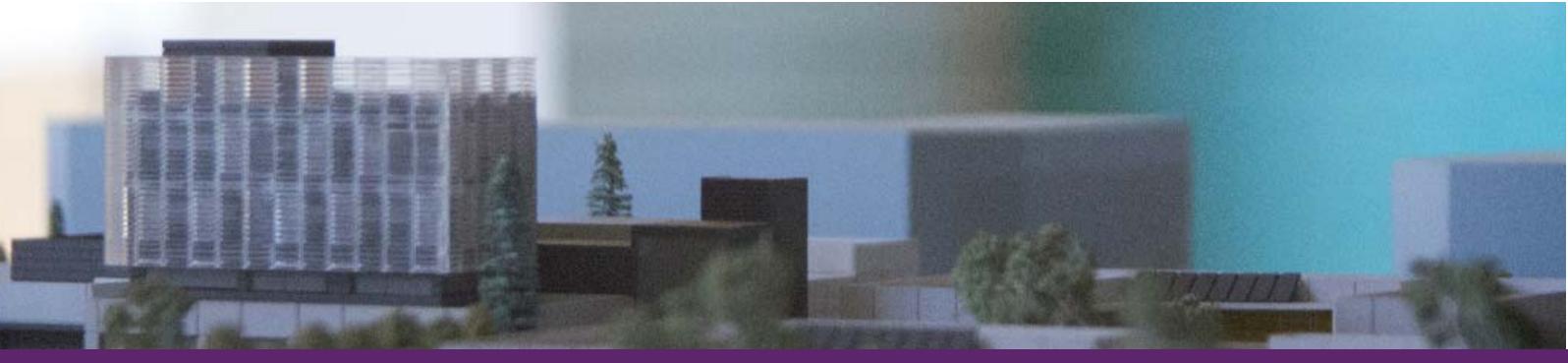
Fellowships

- Susana Navas Rufete, MAPFRE-Queen Sofia Foundation Fellowship 2016-2017.

Teaching

- Miguel Ángel Fernández Blázquez, Module on "Neuropsychological assessment: Attention, Gnosias, Praxis and Executive functions". Master in Clinical Neuropsychology organized by the Higher Institute of Psychological Studies (ISEP). (Jan 2016)
- Marina Ávila Villanueva, session on "Alzheimer's Disease", organized by Carlos III University (UC3M) of Madrid. (Mar 2016)
- Miguel Ángel Fernández Blázquez, Module on "Diagnosis of the main types of cognitive impairment through the neuropsychological tests" organized by the Madrid Society of Geriatrics and Gerontology. (May 2016)
- Miguel Ángel Fernández Blázquez, session on "Cognitive, emotional and behavioral processes in aging". Master in Aging and Dementia organized by the Higher Institute of Psychological Studies (ISEP) (Nov 2016)
- Marina Ávila Villanueva, session on "Alzheimer's Disease", organized by National University of Education at Distance (UNED). (Dec 2016)
- Eva Alfayate, organization and participation at the "Radiology International Day". CIEN Foundation and the Spanish Society of Graduates in Radiology. Event declared of Sanitary Interest by the Ministry of Health of





- the Community of Madrid (8 Nov 2016).
- “Applying fMRI to Study the Human Brain”, CIEN Foundation and Queen Sofia Foundation Alzheimer Center. Organized by the Spanish Society of Psychophysiology and Cognitive and Affective Neuroscience (SEPNECA) (29 Feb-1 Mar 2016)

2.3.2. Prevention of Occupational Hazards

The preventive activities carried out during 2016 have contributed to the proper implementation and application of the Occupational Hazards Prevention Plan established by the CIEN Foundation.

In the observation period, various preventive actions have been developed, together with educational and informative activities. Following the annual programming of the Prevention Service, the simulation of emergencies was carried out in the month of June, in coordination with the Queen Sofia Alzheimer Center.

Health Surveillance, through adequately validated procedures, aims at systematically and regularly detecting the symptoms and early signs of work-related harm, recognizing risk situations, and proposing the necessary preventive measures.

The medical examinations carried out in 2016 were 14, all subject to specific protocols based on the risks to which the workers are exposed. The protocols applied are:

The study sample of the 14 medical check-ups carried out consists mainly of women, who represent 85.7%. The most frequent age range is that of 25-34 years old, which represents 35.7%.

On the other hand, the accident objectives have been met, with no accidents occurring during work-days.

2.4. 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.

2.4.1 Research projects

The objectives of the CIEN Foundation are summarized in six fundamental activities:

- Research Program of the Alzheimer Center of Vallecas (PICAIV, for its acronym in Spanish): Systematic evaluation of the resident patients and attendants to the Day Center at the Queen Sofia Foundation Alzheimer Center
- The Vallecas project
- BT-CIEN Tissue Bank. Biobank of neurological samples

PROTOCOL	Nº
Data Display Screen	9
Biological Agents- Data Display - Strained positions- Chemicals	4
Biological Agents - Data Display Screen	1



2. MANAGEMENT REPORT

- Other research projects
- Service provisions/collaborations
- Training

Aware of the importance of research and collaboration between all levels of society, a great effort is made from CIEN Foundation to translate scientific progress in basic research to clinical practice, promoting carrying out of coordinated research projects in neurological diseases and fostering participation in calls for projects by national and international funding agencies. The main projects active during 2016 are the following:

- The Vallecas Project of early detection of Alzheimer's Disease: Multidisciplinary study of a cohort of 1,213 volunteers cognitively healthy at the beginning of the study. During five years, annual follow ups are carried out with the aim of assessing the progression of all participants, specifically identifying those who develop cognitive impairment and/or mild dementia. 2016 budget: 273,293.60 euros.
- Research Program of the Alzheimer Center of Vallecas (PICAV): social health project resulted in a healthcare complex in which Alzheimer's disease is approached from three angles: research, training and care services for patients. 2016 budget: 972,968.52 euros.
- Research projects awarded under competitive calls active during 2016:
 - PT13/0010/0045: Biobank Platform. Principal Investigator: Dr. Alberto Rábano. Project funded by the Carlos III Institute of Health with a budget of 44,478,26 € for 2015. On November 26, 2014 the Carlos III Institute of Health approved the continuity of funding for the years 2015, 2016 and 2017, always subject to the existence of appropriate and sufficient credit.

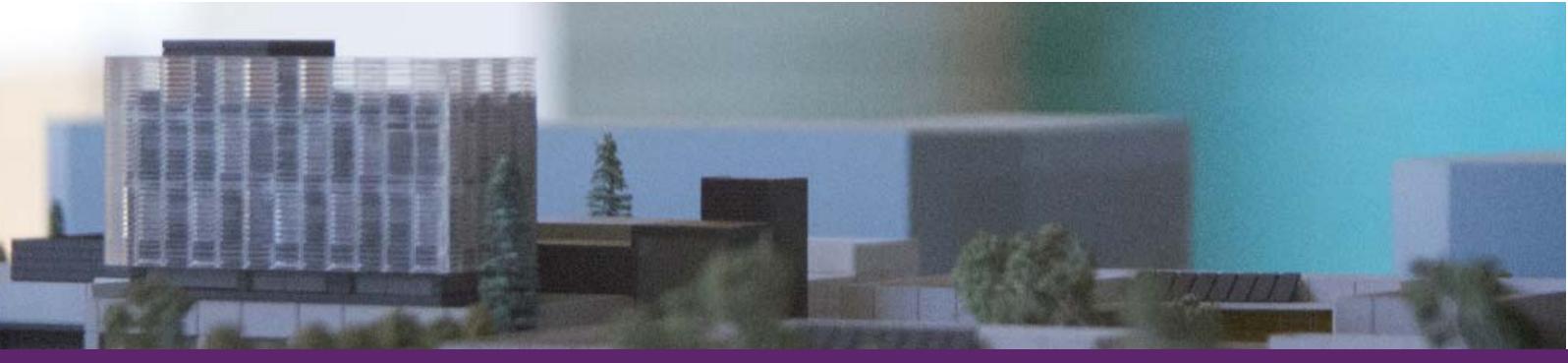
- Other projects:
 - M.J. Fox Foundation grant to the University of Maastricht to finance Parkinson's research, developed by P. Martínez Martín and AJ Leentjens, through the project "Assessing and diagnosing anxiety in patients with Parkinson's disease", with the objective of advancing in the design and validation of a new specific scale for the evaluation and diagnosis of anxiety disorders in the context of Parkinson's disease. Budget: 67,371.37 €.
 - Collaboration agreement between the Foundation for Knowledge Madridmasd and the CIEN Foundation to regulate the participation as a host institution of the latter in the M+VISIÓN project, within the framework of the FP7-People-2011-Cofund call. PI: Dr. Christopher Long.
 - Collaboration agreement signed with King's College London, University of Pennsylvania and University College London, for the development of the project "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 Disorder Society. PI: Dr. P. Martínez Martín. Budget: 39,375 €.
 - Specific collaboration agreement formalized between CIBER-CIBERNED for the development 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 Tissue Bank of the CIEN Foundation. PI: Dr. Miguel Medina. Co-PI: Drs. Bryan Strange and Alberto Rábano

2.4.2 Fellowships and grants

During 2016 the CIEN Foundation has awarded the following fellowships and grants:

- **MAPFRE-Queen Sofia Foundation Fellowship 2015-2016.** On March 18, 2015, the Selection





Committee decided to grant the scholarship to Ms. Ana Rebollo Vazquez, formalizing her hiring as provided in the call. In October of the same year, a 6-month extension was granted, ending in April 2016.

- **MAPFRE-Queen Sofia Foundation Fellowship 2016-2017.** On December 27, 2016, the Selection Committee decided to grant the scholarship to Mrs. Susana Navas Rutete. 7-months stay in (6 initials and one more, after the secondment in Germany) at the Queen Sofia Foundation Alzheimer Center and a 5-month stay at the RUHR-Universität Bochum (Germany) supervised by Prof. Nikolai Almacher, from the department of research in neurosciences. (Feb 2017-Feb 2018).
- **PEJ-2014-C-19788.** Grants for the promotion of young employment and implementation of the Youth Guarantee in R+D+I. Four actions were funded resulting in the recruitment of two university graduates and two technicians.
- **PEJ15/BIO/AI-0615.** 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, 2015 call.
- **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.
- **Call for project Pathfinder-CoEN.** Funding of a project with Spanish participation through a CIBERNED research group: "Protection of neurons in vitro and in vivo from synuclein toxicity by molecular tweezers". PI: Erwan Bezard (France), Carlos Matute (Spain), Richard Wade-Martins.

2.5. Quality Policy

During 2014 CIEN Foundation has successfully passed the certification follow up monitoring of the Quality Management System according to ISO 9001:2008 in the areas of management and the CIEN Foundation Tissue Bank.

The Quality Policy aims at guaranteeing and optimizing the processes related to: external and internal customer orientation, leadership, staff participation, process-based approach, continuous improvement and the incorporation of the process based on risks from the new ISO 9001: 2015 standard.

In this year, the procedures required by the new version of the UNE standard have been developed and the working tools have been adapted, providing greater predictive capacity for the evaluation, administration, mitigation and/or minimization of risks. The following measures stand out: the adoption of a process-based approach, the management of internal and external risks and the planning of quality objectives.

Annually, Quality Objectives are established in order to achieve continuous improvement in the processes and obtain higher levels of satisfaction in customer service, both externally and internally. The Quality Management System is carried out using the following tools:

- Audit reports, internal and external.
- Evaluation of suppliers.
- Complaints, suggestions and customer information.
- Results of studies of customer satisfaction.
- Evaluation of corrective and preventive actions.
- Indicators of quality of processes.
- Quality objectives.
- Internal or external modifications that influence the Quality System.



2. MANAGEMENT REPORT



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



Scientific activity

The Alzheimer Project Research Unit (UIPA), managed by the CIEN Foundation, is composed of five departments: Neurology, Neuropsychology, Neuroimaging, Neuropathology and Laboratory. Together they have as overall aims the monitoring and evaluation of Alzheimer's patients as well as the development of research projects to improve the diagnosis and treatment of neurodegenerative diseases. During 2016 the UIPA has continued working mostly on the 'Vallecas Project', in addition to providing samples to the BT-CIEN tissue bank, among other projects.





3. SCIENTIFIC ACTIVITY

3.1. Overview

The CIEN Foundation manages the Research Unit of the Alzheimer Project (UIPA, for its acronym in Spanish) since January 18, 2006 under an agreement signed with the Queen Sofia Foundation. The UIPA is part of the Alzheimer Project promoted by the Queen Sofia Foundation. The main exponent of this project is the Alzheimer Complex, located in the Vallecas neighborhood (Madrid), where there is an Healthcare Center (composed by a Residence and a Day Center) for Alzheimer's and related diseases patients and a Teaching Center, apart from the UIPA. This Unit started its activities in April 2007, while the healthcare facility began at full capacity in the second half of that year.

The UIPA currently 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. Departmental Structure

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

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

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 se-





verity, 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 Laboratory, Neuropathology, and Neuroimaging. These three areas bring together the most promising fields of research on the biological processes underlying dementia.

The UIPA has a marked multidisciplinary approach, so that both clinical and basic aspects are in continuous contact through those five departmental areas, elaborating and contrasting hypotheses, and developing various research projects. On the other hand, it is by combining these two aspects, how concepts such as translational research in Medicine have been developed. The scientific activity of the CIEN Foundation focuses on the idea of transferring the advances in basic research to the clinical arena. To achieve this it is necessary to establish communi-

cation links that help to focus and make efforts profitable.

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 dementia, Neurology faces the characterization and clinical diagnosis of numerous types and variants of this syndrome that can be caused by more than a hundred pathogenic agents. For this, the neurologist must apply a systematic clinical evaluation of the patient and their environment, collaborate with other specialists in Psychology, Radiology, Laboratory, Genetics, Neurophysiology, etc., in order to formulate a diagnosis as well as prescribe and monitor a treatment.

In a research team such as the one created at the CAFRS, the Neurology team offers basic clinical support to all studies carried out with volunteers and patients, it generates and implements clinical research hypotheses and collaborates with the other specialist teams in clinical and basic research, for the early detection, prevention and treatment of Alzheimer's disease and related pathologies.

Among the specific tasks developed by the Department of Neurology, the following are worth noticing:

- General and neurological medical evaluation, and clinical diagnosis of the Vallecas Project participants.
- Detection and management of possible clinical complications
- Preparation of clinical reports.
- Neurological monitoring of patients admitted to the Residence
- Management and curation of databases.



3. SCIENTIFIC ACTIVITY

- Statistical analysis and preparation of scientific reports.
- Teaching and mentoring of graduate and PhD students who collaborate in some research projects
- Communication in scientific forums of research work carried out in the department.
- Dissemination to society of the progress of the investigation.

In 2016 there were 40 admissions at the Day Center and Residence, all of whom signed consent to participate in regular multidisciplinary evaluations. Along with the 40 baseline assessments, a total of 480 clinical evaluations (every six months), 47 brain MRI studies (every year) and 289 blood tests were performed.

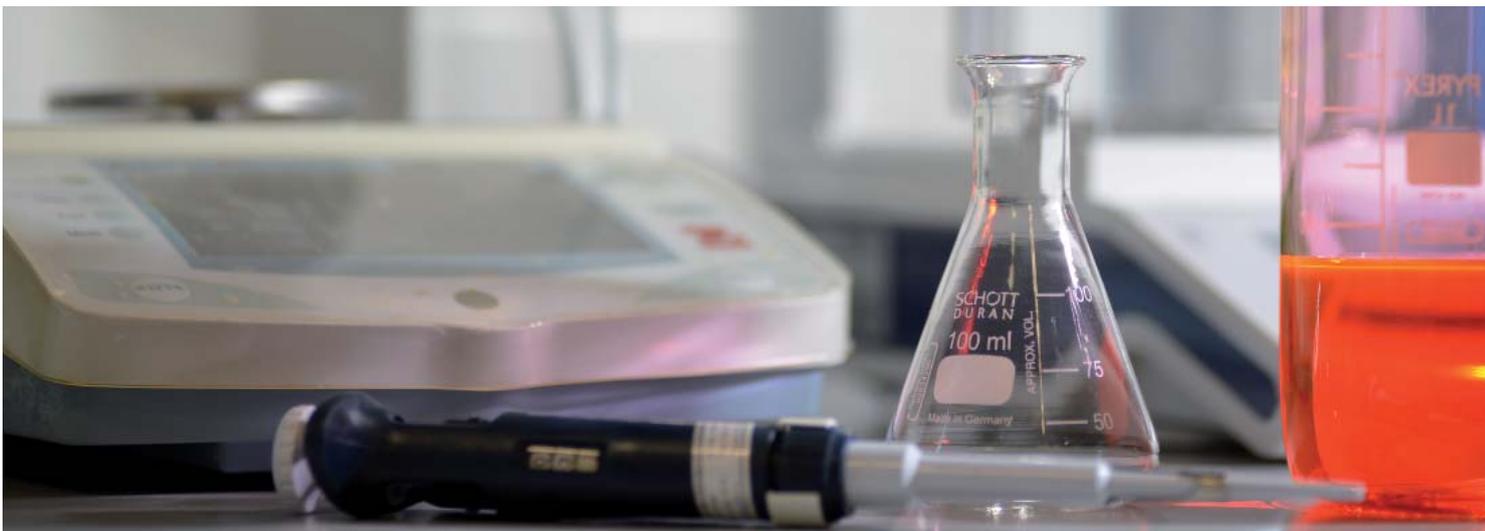
Main lines of research

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





3. Set up of a Clinical-Therapeutic research line.

The Sat-CIEN-02 project, an academic non-profit academic trial funded by the Alzheimer's Association USA, has been launched in 2016. The Principal Investigator is Dr. Isidre Ferrer and CIBERNED acts as promoter. The proposed clinical trial consists of the treatment for 26 weeks of a group of 60 patients with cognitive impairment or incipient dementia attributable to Alzheimer-type degeneration. The treatment will be controlled by double blindness and the patients will be randomized into four treatment sub-groups (one placebo and three doses of active medication). The product that will be evaluated is a cannabinoid mixture already registered in the Spanish market for a different indication (treatment of spasticity in patients with multiple sclerosis). The trial will be carried out in nine Spanish healthcare centers (five in Madrid, two in San Sebastián, one in Barcelona and one in Santander). The trial application was submitted at the beginning of December 2016 and has already been approved by the Ethics Committee and the Spanish Agency for Medicines and Health Products.

4. 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 PICA V databases. In

other instances, information provided by various collaborators is used. These projects are listed below: • Detección de proteínas en la lágrima como biomarcadores de la enfermedad de Alzheimer.

- Detection of proteins in the tear as biomarkers of Alzheimer's Disease
- Project REGISTRY. International multi-center observational study conducted by the European Huntington's Disease Group (EHDN).
- Influence of the regular intake of drugs on cognitive performance in the Vallecas Project cohort
- Replication of previous findings on the importance of vascular pathology in the cerebral and cognitive reserve ("brain battering" hypothesis). Parallel clinical-pathological study in two databases (Alzheimer Project and National Alzheimer's Coordinating Center)
- Psychotic symptoms and vascular risk factors in Alzheimer's disease
- Behavioral disorders and neuropathological findings in Alzheimer's disease

5. Collaboration with other CAFRS groups in other 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

PERIODIC MULTIDISCIPLINARY ASSESSMENTS DURING 2016

Admissions in Day Centre and Residence	40
Informed Consents	40
Baseline Assessments	40
Clinical Evaluations	480
Brain MRI Studies	47
Blood testing	289



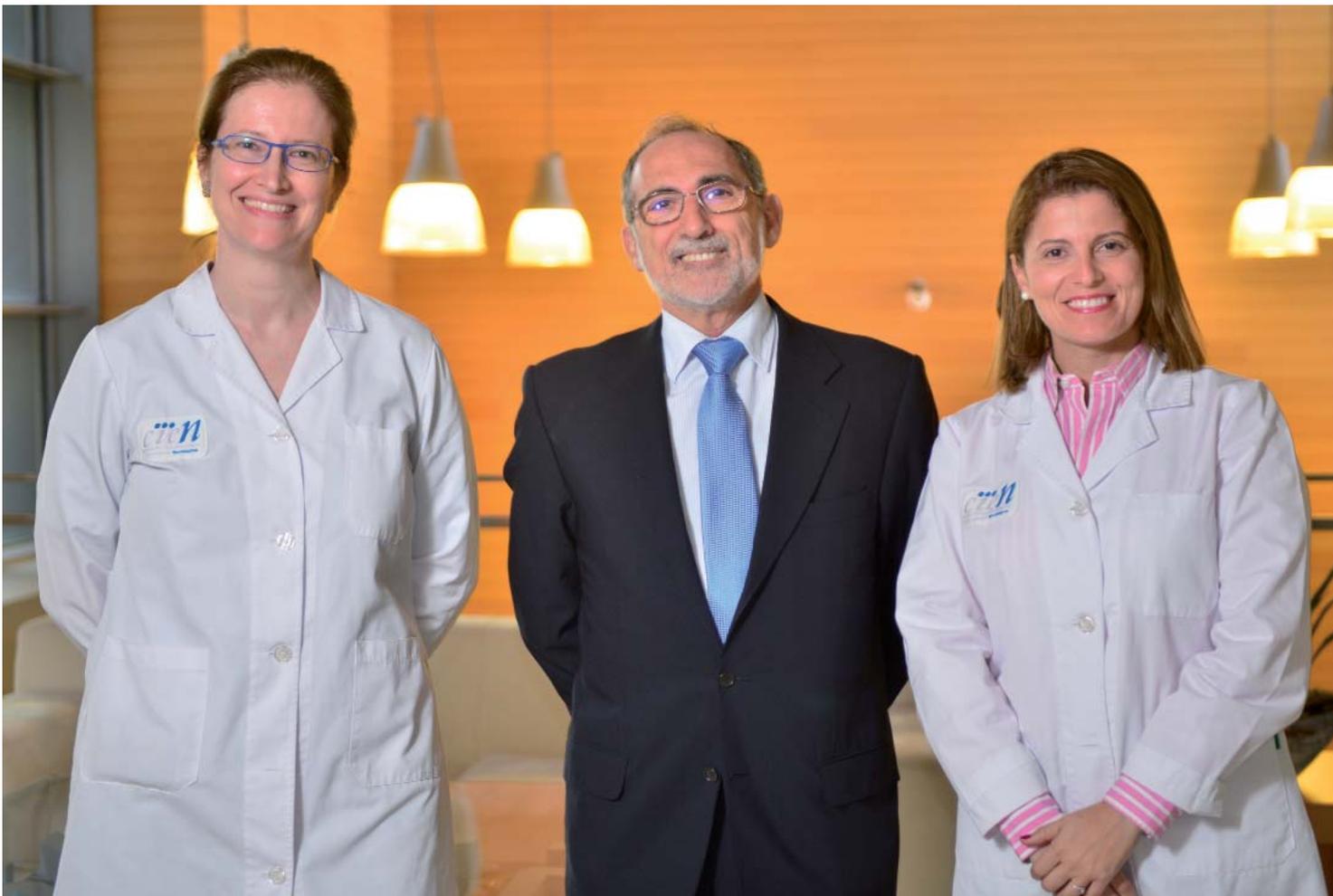
3. SCIENTIFIC ACTIVITY

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

- Early and late components of the cognitive reserve
- Data mining in the Vallecas Project
- Data mining in the neuropathological database from the CIEN Foundation Tissue Bank.

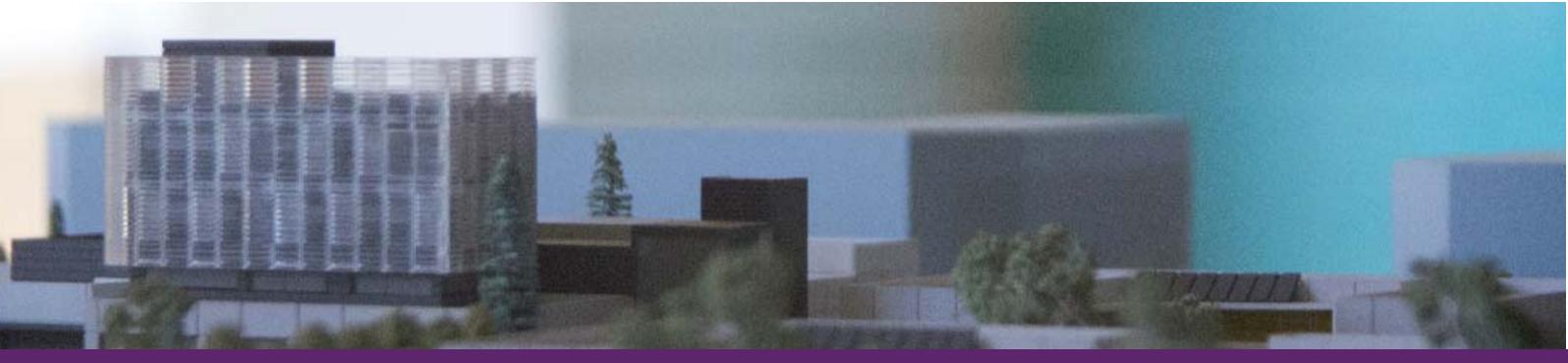
Team

- Teodoro del Ser Quijano, Dr. Medicine, Neurology. Head of department.
- Meritxell Valentí Soler, Grad. 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 Cen-

tral Nervous System. In its basic and applied aspects, Neuropsychology is located at the crossroads between the basic neurosciences, medicine, cognitive psychology and clinical psychology. More specifically, within the field of dementias Neuropsychology not only allows to characterize in an accurate way



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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.

The purpose of the Neuropsychology Department is to generate and launch new research hypotheses in the context of early detection and prevention of Alzheimer's disease. In addition, given the multidisciplinary nature of the CIEN Foundation, another of its missions is to contribute to the proper development of ongoing research projects through proper coordination with the rest of the departmental areas. Among the specific tasks carried out by the Department of Neuropsychology, the following activities are noteworthy:

- Neuropsychological assessment and cognitive diagnosis of the Vallecas Project participants.
- 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 in 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

Apart from its own activity, the interests of the Neuropsychology Department focus on three well-defined lines of research in the area of its competence. More specifically, four priority lines of research can be identified, which are described below.

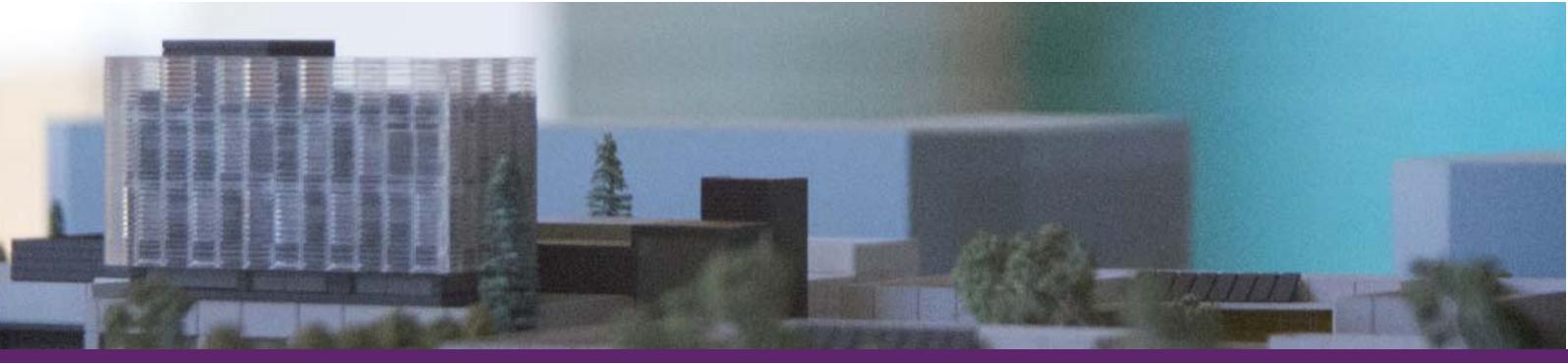
1. Cognitive markers for the early detection of the prodromal phase of Alzheimer's disease:

The professional figure of the neuropsychologist usually handles the application of different evaluation instruments. These include various types of tests, scales and questionnaires useful to measure both the objective cognitive performance and the subjective perception of an individual with respect to aspects such as memory complaints, mood or coping styles. To meet the challenges posed in the context of the Vallecas Project, the neuropsychological test battery focuses especially on the evaluation of memory processes, attention and executive functions as potential early markers of Alzheimer's disease. In addition, the neuropsychological profile of each participant is completed by gathering information related to other cognitive domains such as language, visuospatial ability and visuoconstruction, as well as emotional variables. This is particularly important because it allows identifying the strengths and weaknesses in the cognitive profile and characterize, if appropriate, the type of cognitive impairment that an individual presents. Moreover, the neuropsychological evaluation protocol includes several brief 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 prior to the presence of 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 are the most related to the development of a future 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 role of cognitive and functional reserve in the prevention of cognitive impairment:

The cognitive reserve is a theoretical construct that formulated se-

veral decades ago to explain the lack of correspondence between the degree of brain damage and clinical symptoms sometimes observed among patients. It is presumed as an individual capacity that develops throughout the life cycle fundamentally through formal education, the type of professional activity performed and the intellectual activity developed. Numerous studies have supported the protective role played by the cognitive reserve in modifying the course of different neurodegenerative pathologies, including Alzheimer's disease. 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 the middle stages of life. Likewise, different lifestyle variables are examined in order to classify them as risk or protection factors against dementia onset.

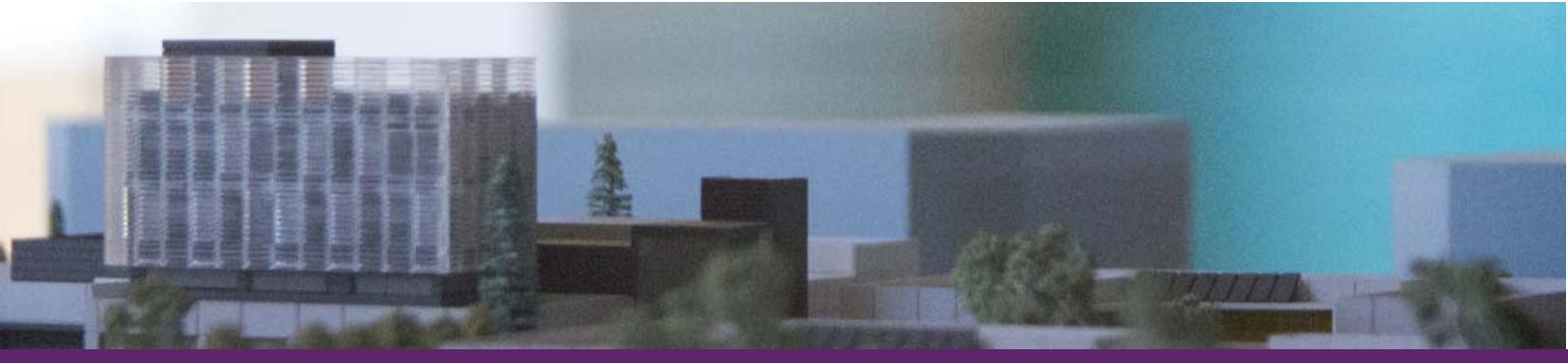
3. Clinical and physiopathological mechanisms common to Down syndrome and Alzheimer's disease:

A new line of research is envisaged in collaboration with the Madrid Social Care Agency (AMAS, for its acronym in Spanish) of the Region of Madrid and with the Complutense University of Madrid (UCM). In this research project, a specific protocol will be designed for the longitudinal cognitive assessment of a cohort of people with Down syndrome. The purpose of this study is twofold. On the one hand, to characterize this population group clinically and cognitively, adapting and designing new tools and protocols for the evaluation and early diagnosis of cognitive impairment in these individuals. On the other hand, the prevalence rate of Alzheimer's disease in Down syndrome will be examined and the association between certain biological and biographical variables with the disease will be studied. Ultimately, the impact of this study is expected



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to improve the social healthcare and the quality of life of people with intellectual disabilities who begin to manifest the first signs of cognitive impairment.

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 Neuropsychology.
- Marina Ávila Villanueva (Grad. Psychology, Neuropsychology).
- Belén Frades Payo (Grad. Psychology, Neuropsychology).

- Ana Rebollo Vázquez (Grad. Psychology, Neuropsychology; until April 2016)
- María García Otero (Grad. Psychology, Neuropsychology, Postgraduate in Neuropsychology)
- Virginia Guerra Martín (Grad. Psychology, Neuropsychology, Postgraduate in General Clinical Psychology).

Neurology-Neuropsychology Administration

- Francisca Martínez Lois (Administrative Assistant)
- Beatriz Salado Martínez (Administrative Assistant)

CAFRS Collaborators

The following CAFRS staff also collaborated during 2016:

- Irene Rodríguez Pérez (Occupational therapist, Residence)
- Almudena Pérez (Occupational therapist, Residence)
- Inmaculada Barrero Rodríguez (Occupational therapist, Day Center) (until April 2016)
- Rocío Rodríguez Casas (Occupational therapist, Centro de Día) (from April 2016)
- Cynthia Pérez Muñoz (Training technician and Occupational therapist)
- Emma Osa Ruiz (Physiotherapist, Residence)
- Álvaro Sanabria Luque (Physiotherapist, Residence) (from March 2016)



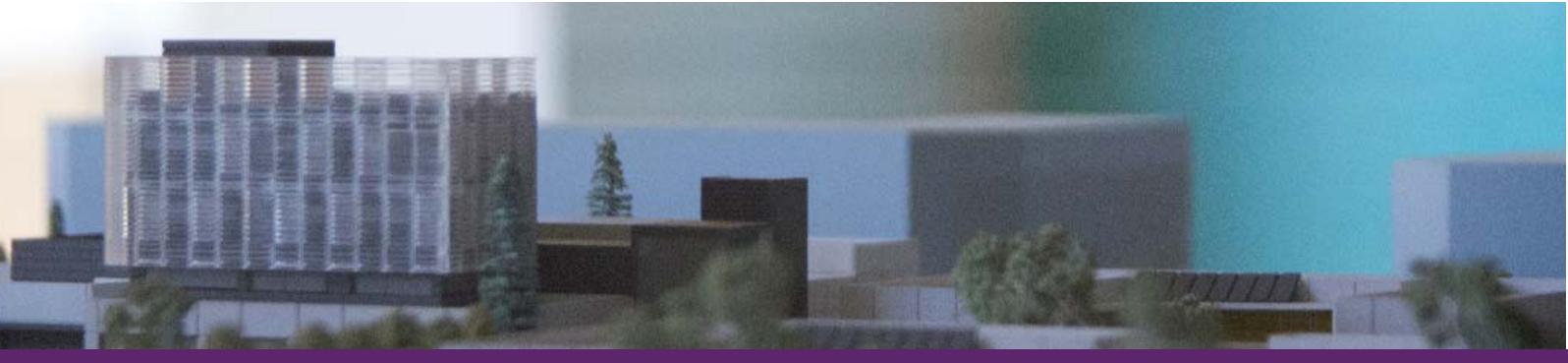
3. SCIENTIFIC ACTIVITY

- Juan García Ordoñez
Physiotherapist, Residence)
(from March until November 2016)
- Sara Esteban Prior
(Physiotherapist, Residence)
(From November 2016)
- Irene Gamarro García
(Physiotherapist, Day Center)
- Carolina Mendoza Rebolledo (Grad.
Psychology, Neuropsychology, Day Center)
- Gema Melcón Borrego
(Grad. Social Work, Day Center)
- Lidia Espada Raboso
(Grad. Social Work, Residence)
- Belén González Lahera
(MD, Geriatrics)



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 national and international, on specific neuroimaging techniques.

During 2016, the Department of Neuroimaging has participated in MRI studies in the following clinical trials:

- **"Lilly"** (Multicentric, European). Extension "Eli Lilly Protocol H8A-MC-LZAO". Effect of passive immunization on the evolution of Alzheimer's disease: LY2062430 against placebo. Sponsor: Eli Lilly.
- **"Optimise"**. Optimization of Treatment and Management of Schizophrenia in Europe. PI: R. Kahn. University Medical Center Utrecht. 2011-2013. CIBERSAM.
- **ABE_4869g**" A phase II randomized, double-blind, placebo-controlled, parallel group, multicenter to evaluate the efficacy and safety of MABT5102A in patients with



3. SCIENTIFIC ACTIVITY

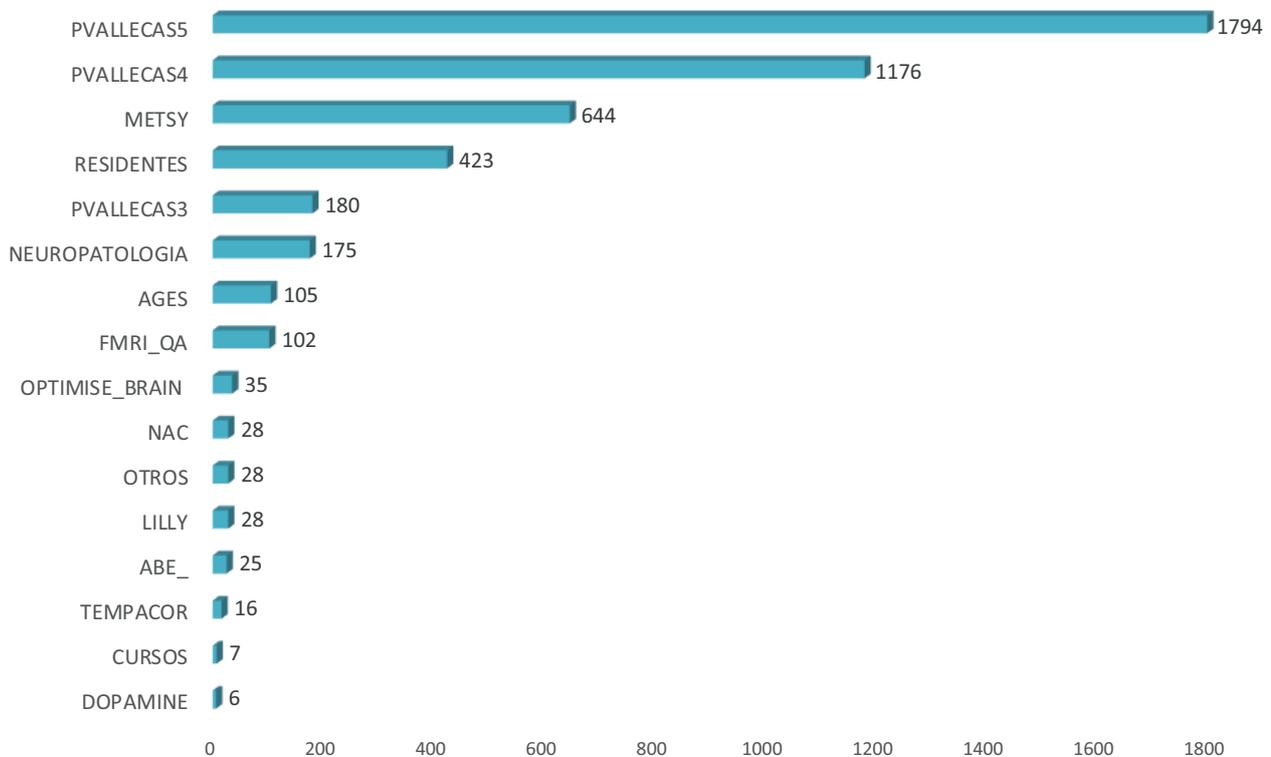
moderate Alzheimer's disease". Code EudraCT: (2010-021926-37). GENENTECH, Inc.

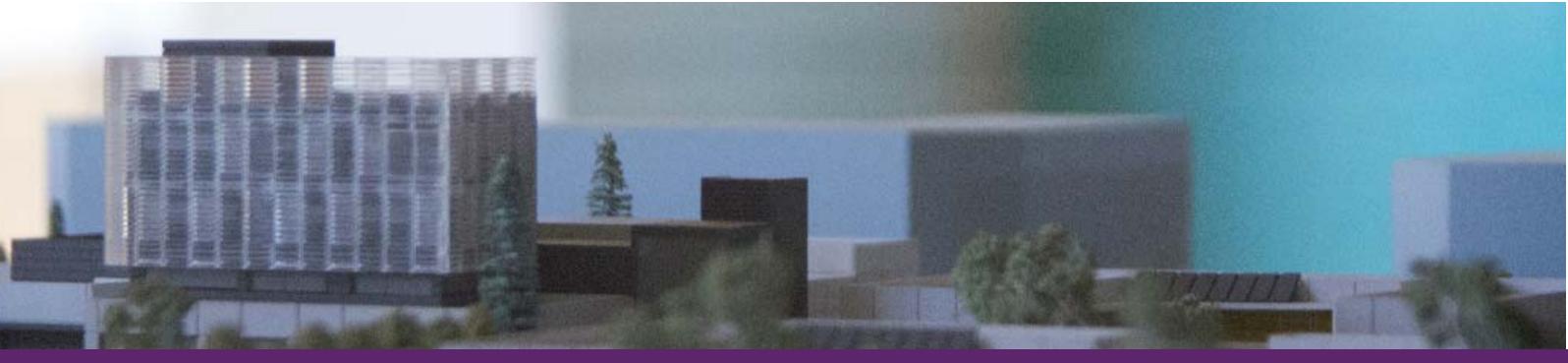
- **"NAC"** Phase III study: "Effect of Adjuvant treatment with N-acetylcysteine for 48 weeks over the loss of gray matter and oxidative metabolism in patients with early onset psychotic episodes". Randomized, Double-blind, placebo-controlled Clinical Trial Code: FIBHGM-ECNC002-2012, EudraCT Number: 2012-005435-87. Promoter Center: Foundation for Biomedical Research Gregorio Marañon Hospital. PI: Celso Arango.

During 2016 the acquisition of MR images from a 795 subjects has been completed. Overall, 4,772 MRI studies have been performed distributed among the different research projects.

48,544 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 2016





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

- Alba Sierra-Marcos (MD, Neurology). Until April 2016.
- Dr. Christopher Long (PhD, Engineering, Specialist in Biomecical Imaging, Madrid-Massachusetts Institute of Technology Vision Program).
- Eva Dueñas Moreno (BSc, Biology).
- María Molina Matas (BSc, Physics).
- Jaime Gómez Ramírez (PhD, Computer Engineering, Automatics and Robotics). Since August 2016.
- Linda Zhang (PhD in Radiological Imaging. Grad. Psychology). Since September 2016.

Radiodiagnostics

- Mabel Torres Llacsá (MD, Radiodiagnostics)

	FUNCTIONAL	VOLUMETRICS	SPECTRA	DIFUSSION TENSOR	MISC.	ASL
2008	255	339	156	178	312	259
2009	337	638	866	423	845	326
2010	910	852	1042	556	1506	305
2011	1124	845	786	528	1904	398
2012	1858	1512	583	1330	2938	949
2013	1436	1276	516	1116	2544	950
2014	880	937	367	847	1920	729
2015	828	912	309	783	1985	669
2016	739	749	341	618	1661	572



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Image Acquisition

- Eva Alfayate Sáez
(Technical Coordinator Técnico 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)

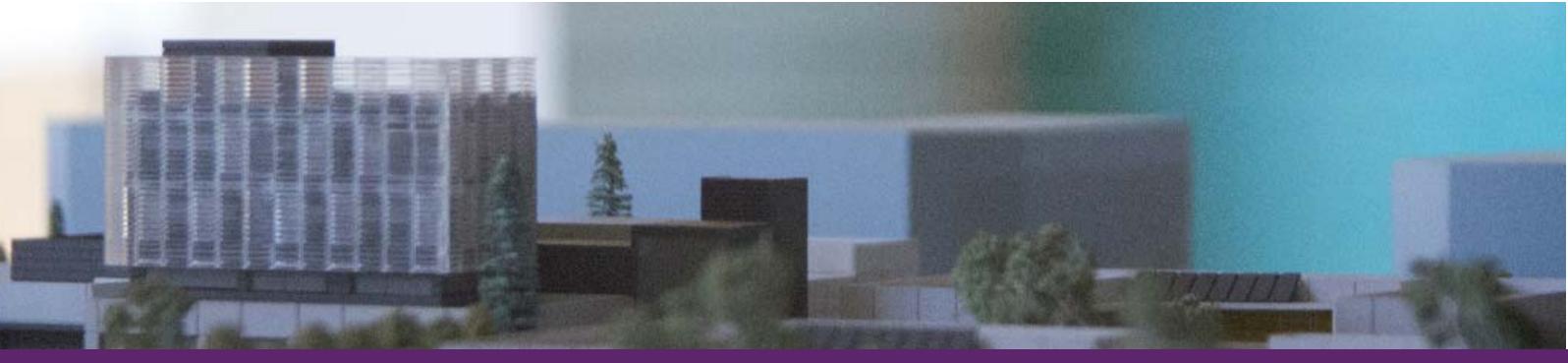
Other Collaborators

- Roberto García Álvarez (PhD, Physics)



Neuroimaging team





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3.2.4. Department of Neuropathology

Neuropathology of neurodegenerative disorders is a specialty in continuous progress with capacity for contrasting clinical judgment and performance of any diagnostic test, including the most recent biomarkers, with the final diagnosis that is still neuropathology ("gold standard"). However, research wise their scope goes beyond that and provides essential information about the molecular components of the characteristic lesions, the pathogenic mechanisms of the disease, and potential biomarkers. Neuropathological findings observed in post mortem brain tissue from donors suffering from neurodegenerative diseases, particularly dementia have allowed in the last decades to further understand the epidemiologic reality of these disorders and their frequent combinations in the population.

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 or tissue banks) has allowed addressing the problem of combined and mixed pathology, specifically regarding Alzheimer's disease. The evolution of the diagnostic criteria (eg, new diagnostic classification criteria for Alzheimer patients, National Institute of Aging, 2012) and molecular techniques are turning the histological diag-

nosis in a critical element in the process of classifying dementia, definite or quasi-definite in some cases, but partial or probabilistic in many others. As demonstrated by the clinicopathological sessions, the final classification of a case requires integration of all clinical, neuroradiological, neuropathological and molecular, when available.

A need for research in dementia is the provision of brain tissue perfectly diagnosed, classified and preserved. Meeting this need is one of the purposes of the brain banks, with CIEN Foundation having one of the major brain banks in the country, the BT-CIEN. Neuropathology also provides significant support to studies of neurological diseases based on animal models, both for histological evaluation of transgenic animals as well as to search for natural models of disease.

Department activities

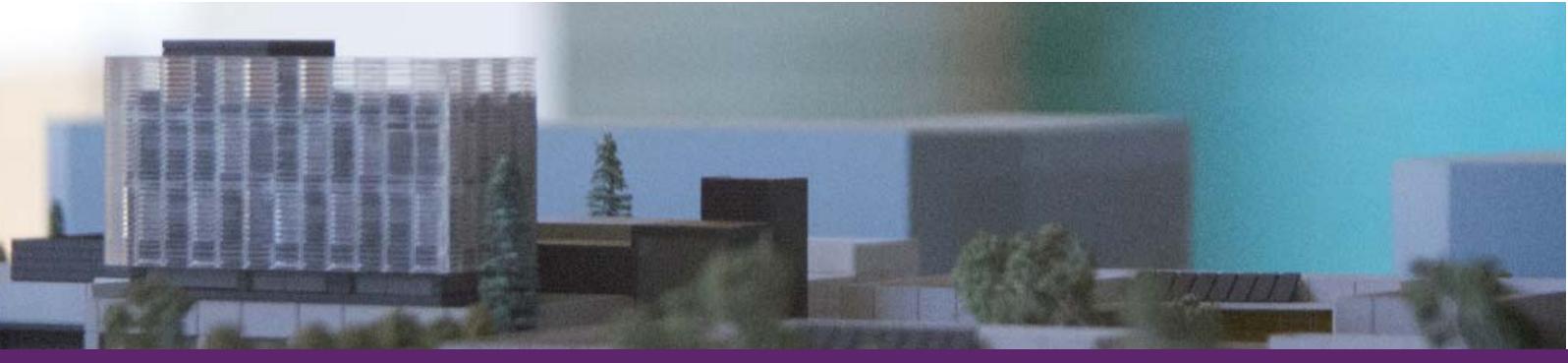
The core activity of the UIPA's Department of Neuropathology corresponds to the BT-CIEN, both to its organizational and logistical components as well as the neuropathological diagnostic work and the management of biological samples.

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.
- 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.

- Pathological role of fungal colonization of the Central Nervous System in Alzheimer-type pathology.
- Distinctive features of Alzheimer-type pathology in nonagenarians and centenarians.
- Characterization and pathogenic study of dementia-associated hippocampal sclerosis.
- Advance age-associated changes in Central Nervous System and cerebral pathology in other animal species. 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.
- Prospective collection of special biological samples for research projects, at the request of the researchers, and once compliance with BT-CIEN protocols has been approved.
- 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 and Cordoba) stand out. Consultations are also received from different public hospitals and from the Anatomical Forensic Institute of Madrid

- Performing neurohistological and immunohistochemical techniques in neurological samples of human and experimental origin.
- Incorporation in the biobank of samples collections (usually, biological fluids, blood and CSF) from clinical research projects.
- Organization of informative lectures and visits to the biobank for the dissemination and promotion of brain tissue donation among patients and relatives, health professionals and the general population.

CIEN Foundation Tissue Bank (BTCIEN)

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.



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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. Moreover, since 2012 the

BT-CIEN has renewed its ISO 9001/2008 quality certification.

The BT-CIEN registry had around 675 registered donors by December 31, 2016.

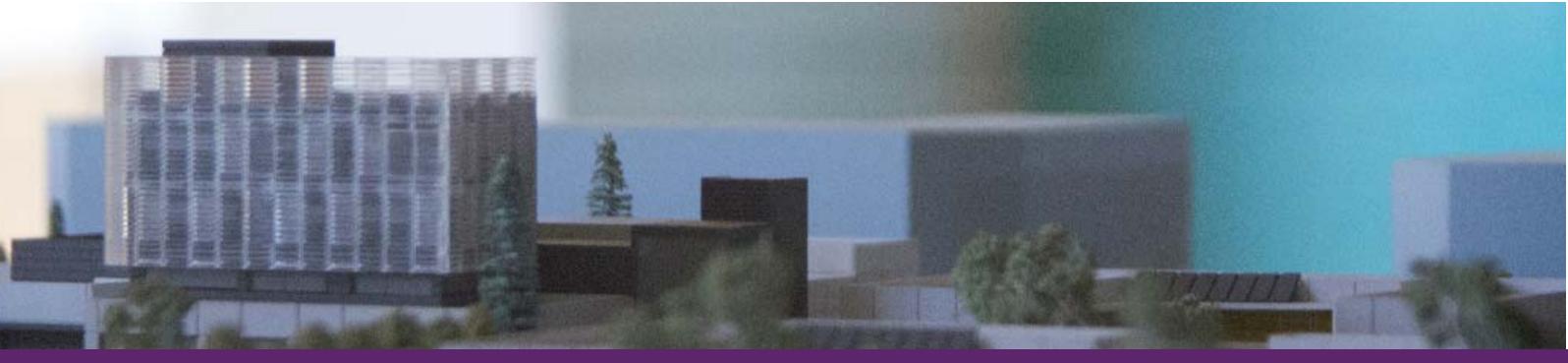
Up to 87 cases were processed in the Neuropathology laboratory during 2016, with the following distribution depending on the origin:

- **71 donations from the External Program.**
- **11 donations from the Internal Program**
- **5 consultation cases**

According to these data, the number of donation cases extracted and processed entirely in the UIPA in 2016 amounted to 82, which is an increase over

Distribution of donation cases by origin in 2016





previous years. However, there is a decrease in 2016 of the total cases studied annually in the BT-CIEN due to a lower demand for consultations.

In 2016, the average post-mortem interval obtained is 5.35 hours, a 25 min reduction compared to previous years.

The research centers that have received samples from BT-CIEN during 2016 have been:

- Center of Biomedical Technology (Technical University of Madrid).
- Faculty of Medicine, University of Castilla-La Mancha, Ciudad Real.
- Institute of Neuroscience - Autonomous University of Barcelona.
- University of Alicante
- Complutense University of Madrid
- Institute of Biomedical Research August Pi i Sunyer (IDIBAPS)
- Institute of Neurosciences of Castilla y León - University of Salamanca
- University of La Laguna

By the end of 2016, the accumulated number of the BT-CIEN donations was 489, of which about 50% are cases of Alzheimer-type pathology.

Team

During 2016, the Department of Neuropathology staff was composed of the following personnel:

- Dr. Alberto Rábano (MD, PhD, Pathology), Head of Department and BT-CIEN
- Elena Gómez Blázquez (Pathology Technician)
- Izaskun Rodal González (Pathology Technician)
- Mario Lozano Enguita (Pathology Technician)



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Collaborators (autopsies)

- Luis Javier Martín Lentijo
(Pathology Technician)
- Ana Sánchez de Castro
(Pathology Technician)



Neuropathology team





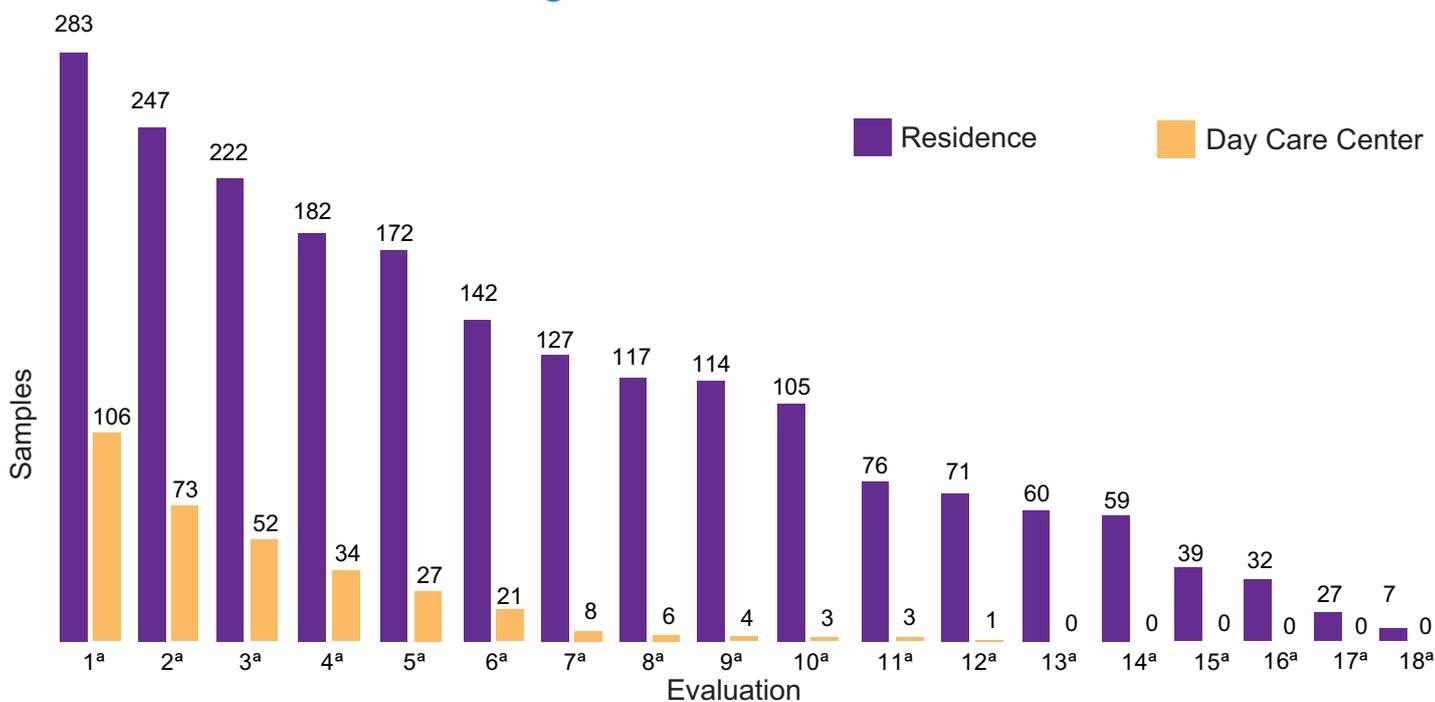
3.2.5. Department of Laboratory

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.

From a neuropathological point of view, Alzheimer's disease (AD) is a neurodegenerative disease that affects specific areas of the brain, altering the circuits involved in the catecholaminergic, serotonergic and cholinergic transmission. AD pathophysiology includes the presence of neuritic amyloid plaques, neurofibrillary tangles, neuronal loss and neurochemical abnormalities. In this sense, biochemical changes reflecting the presence of disease-related pathology, mainly neurofibrillary and amyloid pathology, can potentially serve as biomarkers of AD, even during the earliest stages of the disease. Thus, the most ex-

Samples obtained up to December 31, 2016 according to the number of semiannual evaluations



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tensively studied biochemical markers are the tau protein (total levels and phosphorylated isoforms) and the β -amyloid peptide in cerebrospinal fluid (CSF). However, the drawbacks derived from obtaining CSF, together with a limited precision of these tests in early phases, highlight the need to identify new markers.

Currently, many researchers believe that both the development of amyloid plaques and NFT formation represent relatively late events in the progression of the disease, which may or may not reflect the fundamental biochemical-molecular dysfunctions that trigger the disease. The clinical manifestations of AD are preceded by an asymptomatic preclinical phase, after which the first symptoms appear in the prodromal phase of the disease characterized by mild cognitive impairment (MCI). In this regard, AD can be viewed as an ongoing process that evolves from the asymptomatic phase to the dementia stages. This progression is largely determined by genetic risk variants and is associated with biochemical changes that may ideally serve as early markers of the disease. In this sense, the activity of the Laboratory Department focuses mainly on the search for biomarkers of early diagnosis of Alzheimer's disease and the study of genetic susceptibility factors for AD and other neurodegenerative diseases.

Department activities

The current objectives of the Laboratory Department are focused on the study of biomarkers and susceptibility genes of Alzheimer's disease. This study has the following aims: 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, the Department's research is connected with the activities of the Multidisciplinary Sup-

port Unit, and the Departments of Neuroimaging, Neuropathology and BT-CIEN on the two main research projects in the CIEN Foundation and Queen Sofia Foundation: the Vallecas project for early detection of AD and the Basic research project at the Alzheimer Healthcare Center from the Queen Sofia Foundation.

Research Program of the Vallecas Research Center (PICA V)

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

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

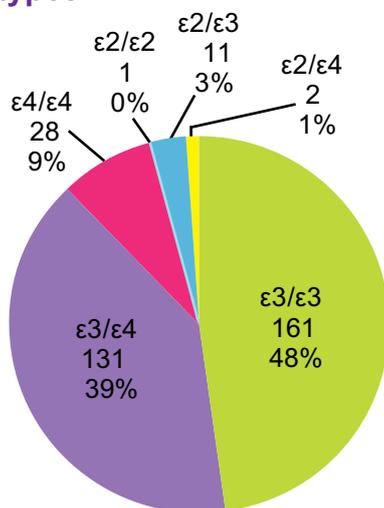
Aliquots obtained from blood samples are incorporated into the CIEN Tissue Bank (BT-CIEN, for its acronym in Spanish) collection according to the pro-





Distribution of APOE genotypes in the CAFRS patients cohort

APOE genotypes



protocols of the biobank. The total number of samples incorporated to the BT-CIEN so far, corresponding to the Alzheimer project monitoring program, adds up to 2,420 (14.0% patients corresponding to the Day Centre), which have resulted in a total of 33,880 aliquots of different fractions derived from blood samples.

Consistent with other studies, the analysis of the APOE gene polymorphism in CAFRS patients revealed a high presence of allele ε4, 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 ε4 allele observed in other cohorts, is noted, as it is the reverse phenomenon of delayed age of onset associated with the ε2 allele.

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.

The phase of recruiting volunteers for participation in the study was finished in December 31, 2013, with its corresponding baseline assessment (n=1,213). The project includes activities from the Multidisciplinary Support Unit (UMA), Neuroimaging, and Laboratory. During 2016, we have studied 28 volunteers to complete the third follow-up study, 191 volunteers on the fourth visit, 377 on the fifth visit.

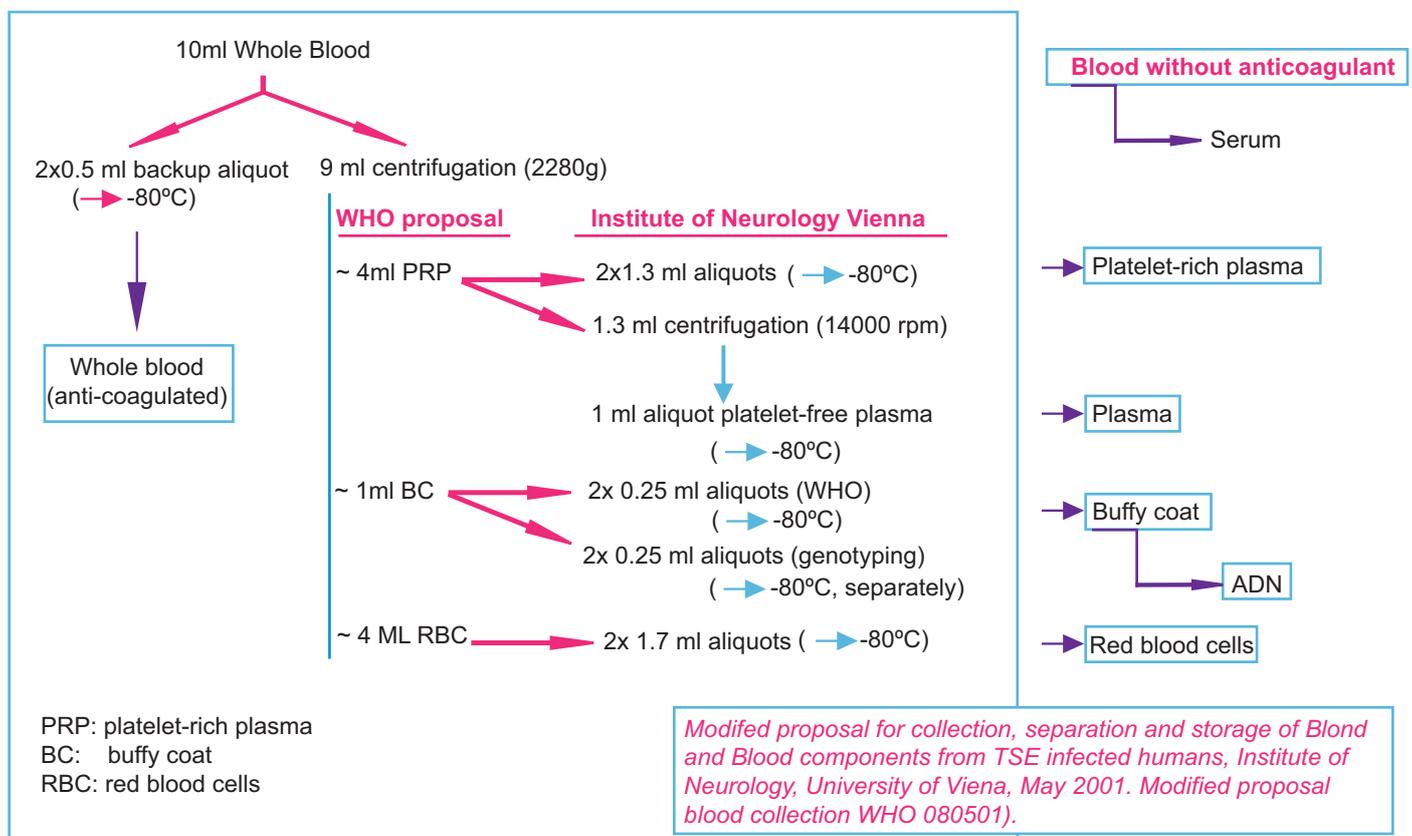
Of all patients recruited in the study and having an informed consent, a blood sample is collected and immediately transferred to the laboratory for fractionation into aliquots following the so-called Vienna Institute of Neurology protocol, which allow different types of analysis, as well as classification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

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



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



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 ε4 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 suscep-





tibility genes have also been analyzed in a subset of participants.

It is also important to emphasize that the samples obtained from Vallecas Project volunteers aged between 70 and 85 years 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.

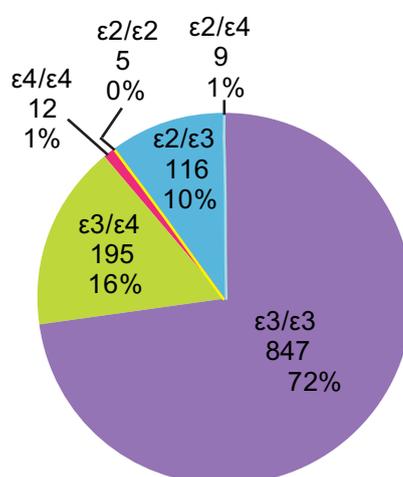
Other projects

We are currently working on three different research projects based on the joint use of biochemical markers and genetic data. In 2016, funding has been obtained for the following research lines:

- Vascular dysfunction associated with Alzheimer's disease (FIS project)
- Epigenetic mechanisms involved in the etiology

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

APOE genotypes



The Vallecas Project activity in figures

Evaluation	1°	2°	3°	4°	5°	TOTAL
Total samples	1.169	767	727	457	7	2.633
2016 samples	0	0	28	191	377	596
Total	1.169	767	755	648	384	3.723
N° Aliquotas	16.366	10.738	10.570	9.072	5.376	52.122



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and progression of rapidly progressive neurodegenerative dementias (CIBERNED cooperative project)

During 2016, several lines of work have been initiated that continue and complement the work focused on biomarkers for the early diagnosis of AD and the analysis of genetic risk factors.

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

During 2016, the study of microRNA as potential biomarkers of AD has begun, in collaboration with Dr. Tobias Engel (Royal College of Surgeons, Dublin, Ireland). In this context, funding has been obtained from MINECO (RETOS call for projects) for carrying out the project entitled "miRNA and lipid metabolism markers as potential links between vascular dysfunction and Alzheimer's pathophysiology", 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 (PICA) and the CIEN Foundation Brain Bank. The central working hypothesis builds upon the existence of circulating miRNAs and molecules of lipid metabolism in plasma that could differentiate cognitively normal individuals from people with mild cognitive impairment or dementia, either alone or in combination with other parameters being collected from the same individuals (elderly volunteers) within the Vallecas Project, as well as patients with confirmed AD after autopsy. To this end, we propose to carry out a complementary and synergistic approach to evaluate, validate and standardize the identification, monitoring,

quantification and functional validation of miRNAs in plasma samples taken from elderly subjects who are cognitively normal, show deterioration cognitive mild or moderate dementia, in the presence or absence of peripheral vascular pathology. Following a multidisciplinary approach, the analysis of the data obtained will benefit from the availability of other data generated within the Vallecas project (socio-demographic data, clinical history, annual neurological evaluation, neuropsychological evaluation, structural and functional brain MRI, genotyping, etc.) in order to identify molecular, clinical, or neuroimaging signals that may serve to define populations at higher risk of developing dementia in the future.

Dementia Genetics Spanish Consortium (DEGESCO)

Also, during this year, the CIEN Foundation has continued participating in Dementia Genetics Spanish Consortium (DEGESCO). 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. Because of these collaborations, an interesting study on the association of the H1 haplotype of the MAPT gene in non-carriers of the APOE ϵ 4 allele has been published. In the context of DEGESCO, during 2016 several research actions were carried out aimed at defining 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 stu-





dies carried out in other populations, will allow us to determine the most important genetic factors in the development of cognitive dysfunction in our population of the Vallecas Project. It will also allow defining endophenotypes based on genetic variations as well as concrete and measurable characteristics of the patients and controls based on clinical neuroimaging, biochemical or pathological measurements (see figure).

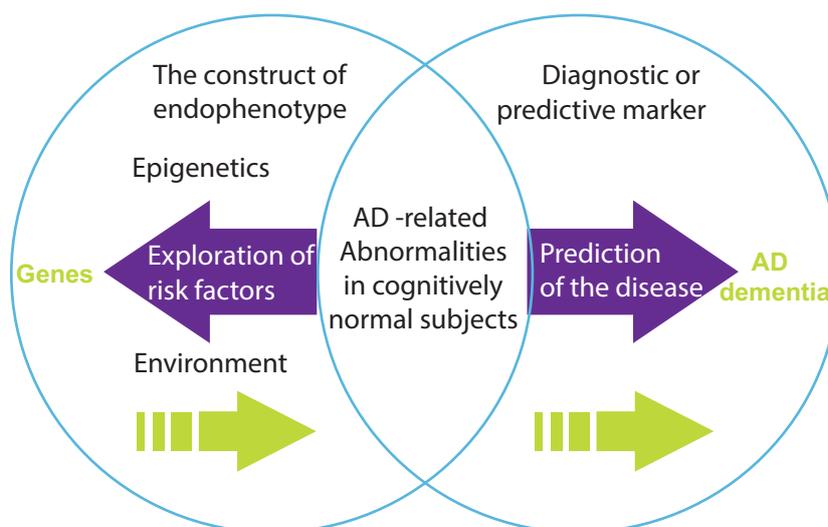
An European DNA bank for deciphering the missing heritability of Alzheimer's disease - EADB (European AD DNA Bank)

This project is an international collaboration initiative carried out through DEGESCO that aims at significantly increasing the generation of data based on

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

This initiative will increase the number of AD samples available in Europe more than four times and around the world by almost two-fold. Carrying out this project will allow us to understand the genetics of AD thus improving our knowledge of the underlying pathophysiological processes in the disease; since the genetic factors seem to represent up to

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)



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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.

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

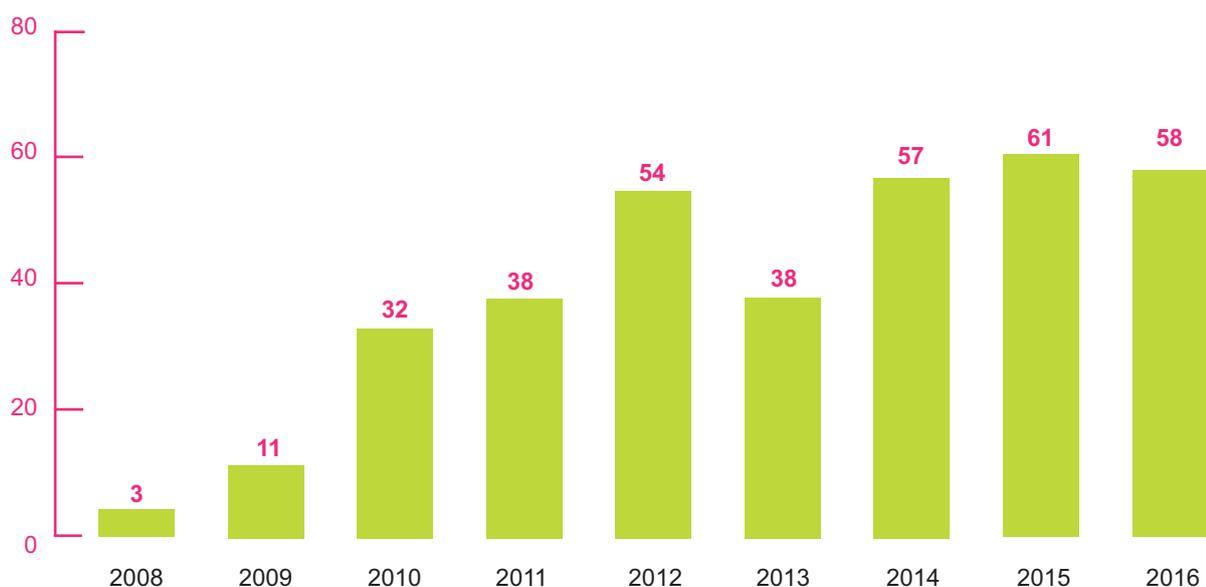
cognitive dysfunction. In addition, we also continue with the development of a non-genetic test adapted to the hospital diagnostic routine for measuring blood ApoE4 as a marker for determining the AD risk.

Contribution to BT-CIEN

The Laboratory 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

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



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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 352 CSF samples from donor's brain and 294 skin samples.

Team

During 2016, the team of the Laboratory Department was composed of the following personnel:

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

Collaborators

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



Lab team





3.3. Collaboration with other entities

3.3.1. Signing agreement with NeuronBio

In April 2016, CIEN Foundation and Neuron Bio reached an agreement for the development of joint projects in the field for diagnosis of the Alzheimer's disease.

The framework agreement, the first one signed by CIEN Foundation with private company, aims to unite the experience and knowledge of specialists, who are part of the Research Support Unit of the Alzheimer Project, located in the Vallecas (UIPA), a complex managed by the CIEN Foundation, with the experience and knowledge of scientists and developments recently achieved by the biotech company Neuron Bio in the diagnosis field of this disease, and more concretely with the AlzTest®.

Javier S. Burgos, the CEO of Neuron Bio stated, "CIEN Foundation is a global pioneer in the research of Alzheimer's disease, thus the collaboration agreement with this institution will allow Neuron Bio to accelerate research projects in the diagnosis field of this dementia. The Vallecas Project has samples of more than a thousand individuals from the early stages of the disease. Due to this, it is one of the most interesting collections in the world for the design and evaluation of diagnostic and predictive tools for Alzheimer's disease".

The agreement also provides the implementation of reciprocal training programs to enable teams of both entities deepen both, the mechanisms of disease and their evolution after the diagnosis.

3.3.2.- Signing agreement with the i+12 Foundation

The CIEN Foundation and the Foundation for Biomedical Research of the 12 de Octubre University Hospital (i + 12 Foundation) agreed, in June 2016, to launch a joint program of excellence in healthcare and clinical research to be carried out in the two ins-

titutions. Both Foundations have a common interest in cooperating to consolidate a Unit of Excellence and configure a multidisciplinary research program combining the resources, experience and health-care, clinical, technological, logistical and human efforts of the signatory institutions. The ultimate goal is to shorten the distance between basic research and the clinical care received by patients and effectively address the health and social challenge posed by Alzheimer's disease and other dementias. The main objective of the agreement is to coordinate the efforts of both institutions to start up:

- a) A Clinical Program of Excellence in Alzheimer's disease and other dementias (PACAD, for its acronym in Spanish) for developing and applying new and better diagnostic methods, testing new treatments, creating devices and resources to support the clinic and the research, implementing prevention plans and coordinating with other national and international agents.
- b) A Clinical Research Program in Alzheimer's disease and other dementias (PICAD, for its acronym in Spanish) that enhances the current and future research lines of the signatory institutions, facilitates their coordination with other national and international agencies and has a relevant impact on their scientific productivity in this area.

Both programs will mutually reinforce each other, taking advantage of the accumulation of the critical mass of the signatory institutions and channeling the multiple synergies that will occur. These programs aim to achieve a series of specific objectives:

- **Improve the quality of care for patients** treated in the southern area of Madrid by increasing diagnostic and therapeutic resources; more efficient management of the demand for care; the coordination of numerous specialists, interdisciplinary collaboration; the implementation of new technologies; access to



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new pharmacological and non-pharmacological therapies in early phases; the development of preventive strategies and the accumulation of clinical information, biological samples, neuroimaging and brain tissue.

- **Integrate the resources of the Clinical Research**
Units of the signatory institutions devoted to Alzheimer's disease and other dementias to:
 1. Improve its competitive level in the national and international context
 2. Promote research projects, public and private, national and international
 3. Generate large series of patients and special cohorts of patients and controls that facilitate carrying out studies of impact
 4. Share infrastructure, knowledge, personnel resources and technologies that facilitate the achievement of competitive funding for research in this field and the execution of projects of relevant impact.
- Implement interdisciplinary programs for high-quality comprehensive care of Alzheimer's disease and dementia in general (prevention, early diagnosis, pharmacological and non-pharmacological treatment, cohorts monitoring), and the offer of new experimental or advanced therapies through clinical trials promoted by external agents or by the Institutions themselves.
- Consolidate established lines of collaboration and promote the scientific activity of the Institutions within the framework of a translational model in which the interaction of basic and clinical research predominates.
- Promote competitive research projects, public or private, national or European: The possibility of managing large series of patients as well as having more infrastructures, personnel and knowledge, should give the groups and researchers involved in this agreement a greater competitive capacity to obtain resources that finance research.

3.3.3.- Signing agreement with the Torrejón Hospital

The CIEN Foundation signed in December 2016 a collaboration agreement with the University Hospital of Torrejón, integrated in the public network of hospitals in the Region of Madrid. This agreement will allow both institutions to advance in the research of neurodegenerative pathologies, to know how they affect the brain tissue and to develop new research lines that allow improving the early diagnosis and the early treatment of these diseases.

The Foundation works jointly with the Hospital in the study of mild cognitive impairment through biomarkers in blood and cerebrospinal fluid for the creation of a sample repository.

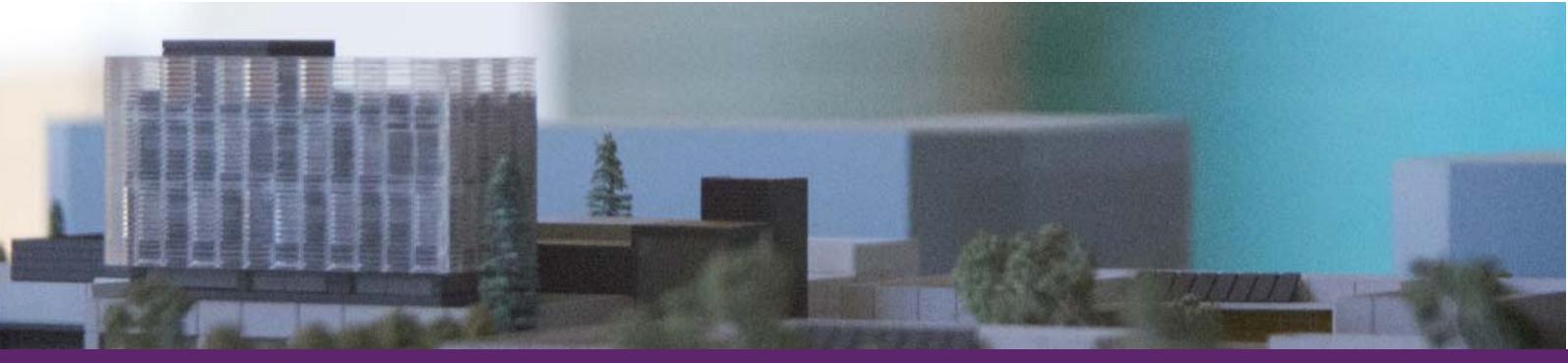
On the other hand, the Hospital works on the promotion of brain tissue donation both from people free of neurological disease as well as from people with neurodegenerative pathologies who decide to donate their brain post mortem through an agreement established with BT-CIEN (Tissue Bank of the CIEN Foundation). This allows developing research techniques to find effective treatments for Alzheimer's and other dementias, such as Parkinson's disease, Amyotrophic Lateral Sclerosis and other neurodegenerative disorders.



The *e* Vallecas Project

The continuation of the 'Vallecas Project' has made possible the publication in 2016 of research papers that have received recognition from the scientific community. Continuing with its goal of early detection of Alzheimer's disease, during the past year the evaluations of the third, fourth and fifth visits, as appropriate, of the 1,213 volunteers of the "Vallecas Project" have been carried out. Through the evolutionary follow-up of the volunteers in the Research Unit of the Queen Sofia Foundation Alzheimer Center we seek an integral approach to the social problem that the Alzheimer presently means.





4. THE VALLECAS PROJECT

4.1. Introduction

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.

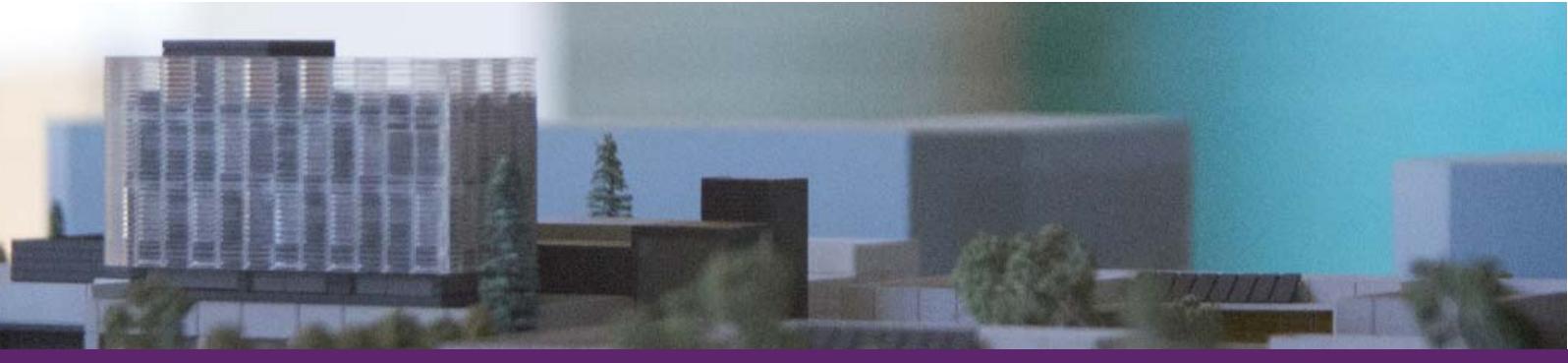
The main objective of the population-based study "Vallecas Project" for Early Detection of Alzheimer's Disease, is to elucidate, through tracking of progression, the best combination of clinical parameters and complementary tests (imaging and laboratory) that allow deciphering at medium- and long-term 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 end of 2016, we are at the end of the fourth visit for the entire cohort, about the middle of the fifth visit and just starting the sixth one (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::

- 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 (eg schizophrenia, stroke, severe head trauma, Central nervous system infections, uncorrected vitamin deficiencies, etc.).

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



4. THE VALLECAS PROJECT

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, perceived health status).

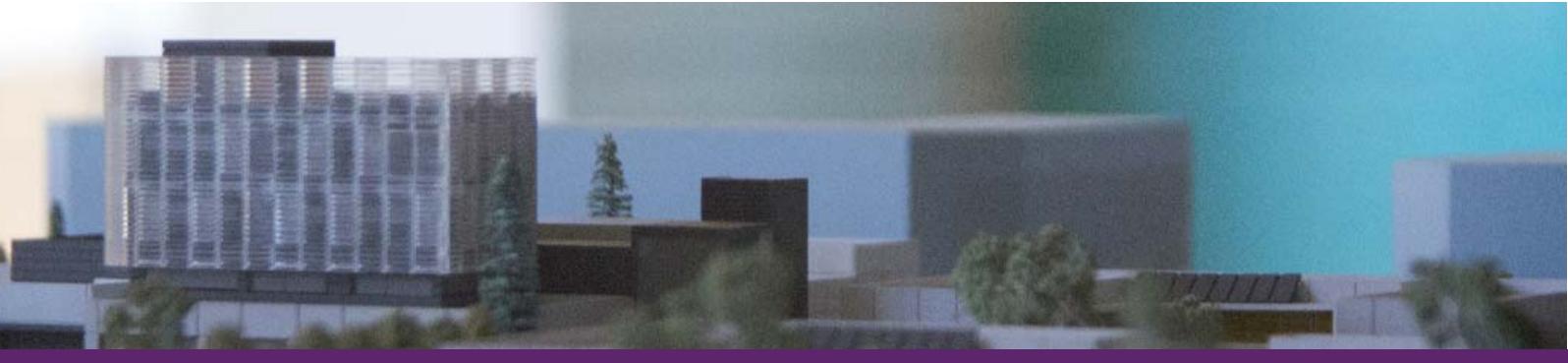
4.3.3. Clinical evaluation

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

THE VALLECAS PROJECT IN FIGURES

Recruited sample	1.213
Excluded at baseline	47 (3,87%)
Age	
Sample mean	74,46 años
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%)
Schooling	
Sample mean	10,35 años
Illiteracy	4 (0,34%)
Read/Write	60 (5,11%)
Minimum studies mínimos (numeracy skills)	154 (13,11%)
Primary Education	389 (33,11%)
Senior High School / Proffesional Training	282 (23,99%)
University Education	286 (24,34%)





- 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.

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 is a procedure that allows to explore in a holistic way the various cognitive (gnosias, attention, memory, language, praxis and executive functions), affective and behavioral domains of an individual, as well as their level of autonomy in everyday life. To do this, the neuropsychologist can use different assessment instruments, including clinical interviews, behavioral observation, cognitive tests and different question-

naires that allow for collecting information from both the individual and a reliable informant.

The Vallecas Project neuropsychological examination protocol has been designed to comprehensively assess neuropsychological functioning of study participants, as well as their progression during the longitudinal follow-up.

Specifically, although the neuropsychological battery focuses especially on the evaluation of memory processes, attention and executive functions as potential early markers of Alzheimer's disease, the neuropsychological profile is completed by getting information related to other cognitive domains such as language, visuospatial ability and visuoconstruction. All these data allow identifying the strengths and weaknesses in the cognitive profile and characterizing, if necessary, the type of cognitive impairment that an individual presents. Table 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. Identification 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. It has been a great interest of the scientific community during recent years in the development of new biomarkers of AD and its utility in risk assessment and early diagnosis of the disease. Thus, blood samples will be collected within the Vallecas Project for the study of a number 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 fractions indicated in the protocol, which will be stored at -80°C. On one hand, DNA is extracted from blood cells to deter-



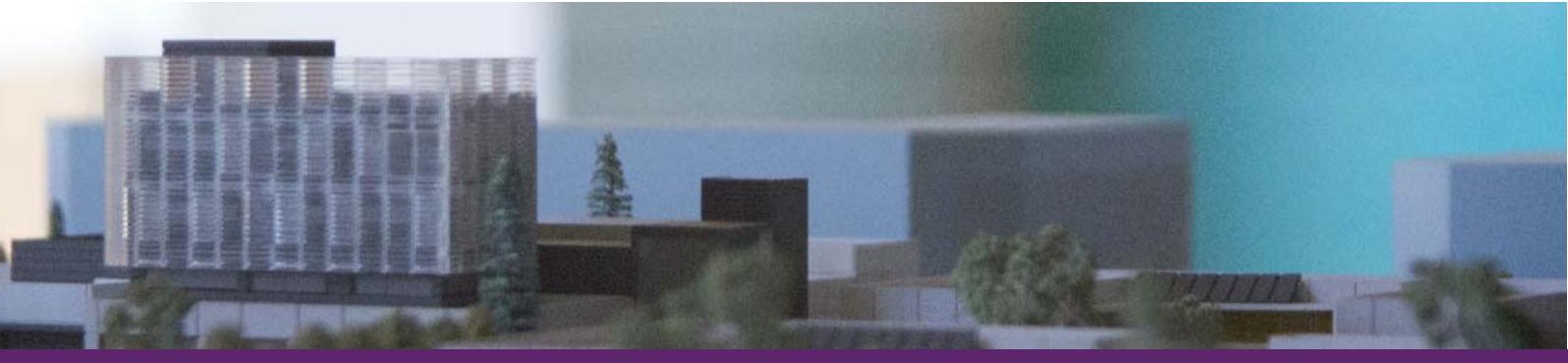
4. THE VALLECAS PROJECT

mine, by PCR and sequencing techniques, genetic markers associated with the various polymorphisms of the following genes: APOE, CR1, BIN1, CLU, PI-

CALM, ABCA7, SORL1, PRNP, GRM8, BACE1. These genes are studied using DNA obtained from the extraction of samples from the first visit.

	VISITS				
	1 ^o	2 ^o	3 ^o	4 ^o	5 ^o
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)	✓	✓	✓	✓	✓





On the other hand, a selection of plasma samples are being used to determine markers of vascular damage, cytokines and human chemokines involved in lipid metabolism and inflammation: MMP-9, serpin E1/PAI-1, E-Selectin, ICAM-1, VCAM-1, IL-1 beta, IL-6, CXCL8/IL-8, CCL2/MCP-1, TNF-alpha, Adiponectin/Acrp30, CRP, P-Selectin and MMP-3.

Likewise, we have begun the collection of samples for the analysis of microRNA collaboration with the group of Dr. Tobias Engel (Royal College of Surgeons, Dublin, Ireland). This set of markers represent the working basis for the application of a project funded by the MINECO (RETOS Projects) entitled "miRNA and lipid metabolism markers as potential links between vascular dysfunction and Alzheimer's pathophysiology", and whose principal investigators are Drs. Miguel Medina and Miguel Calero.

The utility of these biomarkers complements the information derived from the study of genetic risk markers mentioned above and can define risk factors made evident in previous studies.

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

First visit	1.169
Second visit	767
Third visit	755
Fourth visit	648
Fifth visit	384
Total	3.723

4.3.7 Neuroimaging Studies

Knowing the morphological variations occurring in brain structure throughout life is essential to assess

the corresponding pathological changes that occur in neurodegenerative diseases. In this context, neuroimaging techniques such as magnetic resonance imaging (MRI) have led to significant progress in understanding brain changes associated with age.

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

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

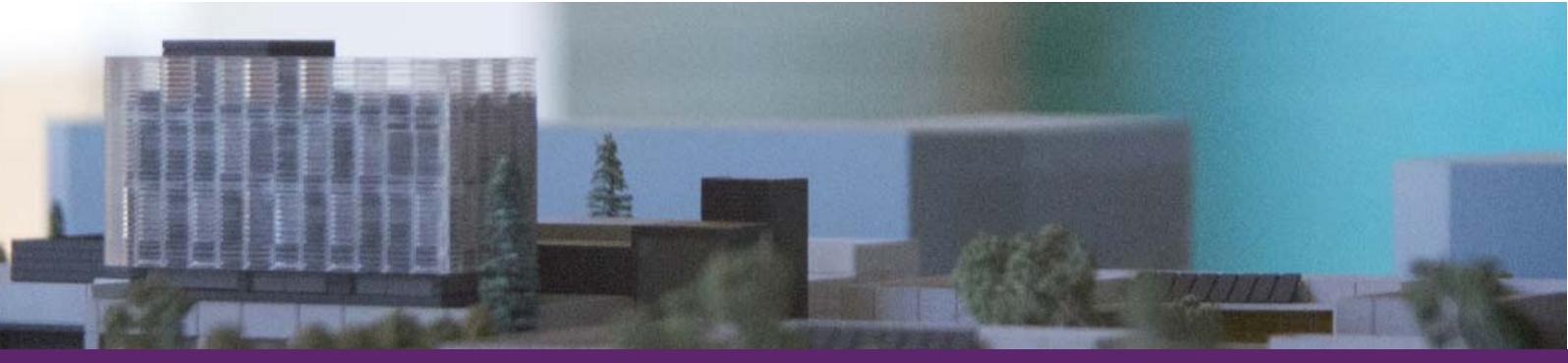
- **Structural Study (3D volumetry, T2 and FLAIR)**

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



4. THE VALLECAS PROJECT





- **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. 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.

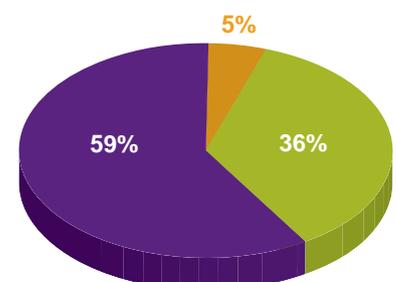
4.3.8. Current State

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 2016 we have combined the third, fourth and fifth follow-up visits from volunteers.

VALLECAS PROJECT ACTIVITIES DURING 2016

Number of third visit assessments	33
Number of fourth visit assessments	238
Number of fifth visit assessments	382

- Third visit
- Fourth visit
- Fifth visit



4. THE VALLECAS PROJECT

VALLECAS PROJECT CLINICAL EVALUATIONS (OCTOBER 2011-DECEMBER 2016)

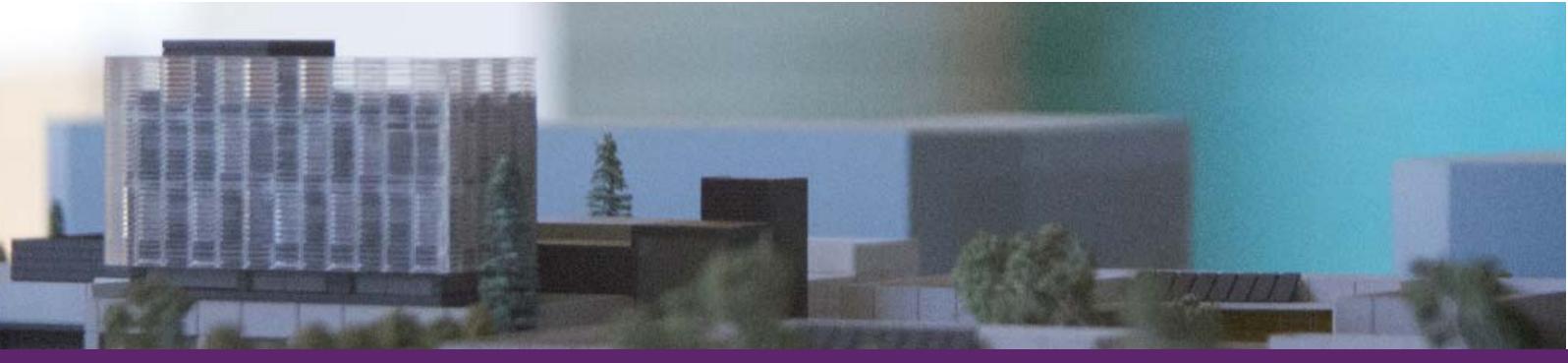
First visit	1.175
Excluded at baseline	47
Second visit	967
Third visit	870
Fourth visit	720
Fifth visit	388
Drop outs	465
Do not comply with inclusion criteria	27
Deceased	17
Diagnosis of neurological disease	33
Volunteer withdrawal	387



International *re*lations

The CIEN Foundation is well aware of the importance of international cooperation and thus it has continued during 2016 tied in with European organizations. The CIBERNED-CIEN Foundation partnership is involved in projects from the EU Joint Programming for Research in Neurodegenerative Diseases and the Network of Centers of Excellence in Neurodegeneration. Furthermore, the collaboration agreement with the Champalimaud Foundation has been kept and also takes part of a project from the Alzheimer's Association. The Foundation has organized, once again, in collaboration with the Queen Sofia Foundation and CIBERNED, the International Congress of Research and Innovation in Neurodegenerative Diseases.





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.

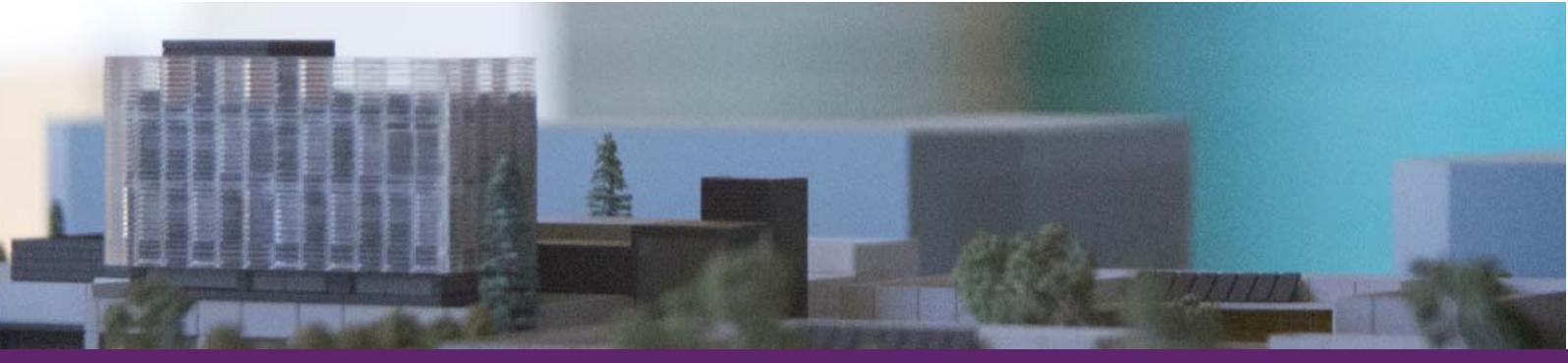
International scientific collaboration increases more and more, not only because of the availability of international funding and the drive of modern com-

munication 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 Neurodegeneration (COEN), among other initiatives. These and other internationalization activities carried out during 2016 by CIEN Foundation are detailed below.



5. INTERNATIONAL RELATIONS

5.2. EU Joint Programming on Neurodegenerative Disease Research (JPND)

The EU Joint Programming for Research in Neurodegenerative Diseases (JPND) is an innovative collaborative research initiative created to address the growing challenges posed by these disorders. The JPND is a pioneering example of joint programming for the promotion of research within the European Union aimed at scientific challenges requiring a response that exceeds the capacity of a single country, based on the alignment of national research programs devoted to these challenges. Its objective is to enhance the impact of research by aligning existing national research programs and the identification of common objectives whose scope would benefit from joint action. The JPND Scientific Advisory Committee has significant participation of the CIEN Foundation Scientific Director, Dr. Jesús Ávila.

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

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

This Research Strategy also provides a framework of opportunities for countries involved in JPND and wi-

ling 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.

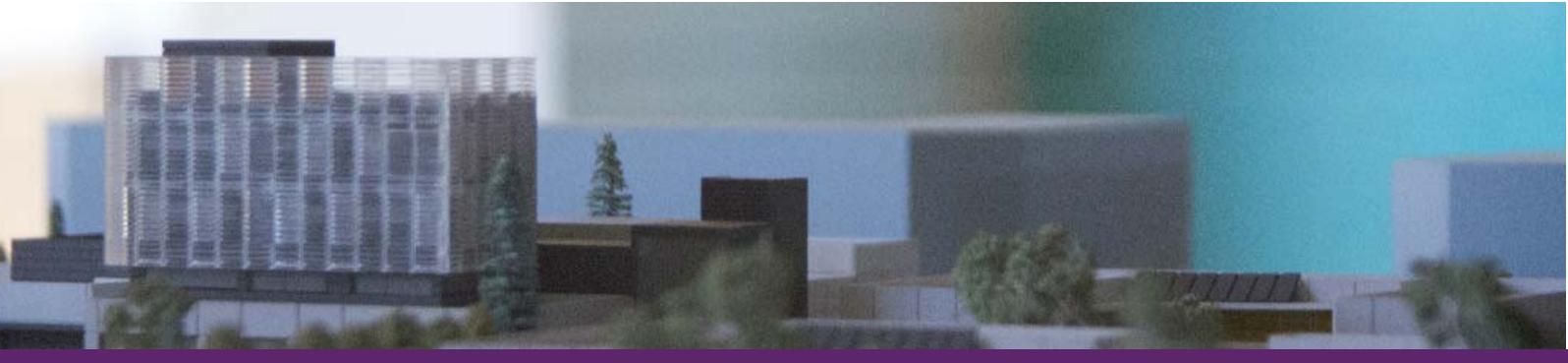
In this regard, during 2011 took place the first call for European research projects JPND. Under the theme "Optimization of biomarkers and harmonization of their use in the clinic", four transnational projects were awarded for the period 2012-2015, one of which has the participation of CIEN Foundation: the DEMTEST project on "Biomarker based diagnosis of rapid progressive dementias-optimization of diagnostic protocols". At present, the CIEN Foundation participates and will continue to participate actively in the JPND.

5.3. Network of Centers of Excellence in Neurodegeneration (COEN)

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

To this end, on June 10, 2010, the Canadian Institutes of Health Research (CIHR), the German Centre for Neurodegenerative Diseases (DZNE, Germany) and the Medical Research Council (MRC, UK) launched a funding initiative to establish a collaborative ap-





proach 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, CIEN Foundation and CIBERNED joined this Committee to participate actively in the design of the future COEN scientific strategy. Both institutions are represented by Dr. Miguel Medina, member of the CIEN Foundation Scientific Advisory Board and CIBERNED Deputy Scientific Director. 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- CIEN Foundation, Spain
- Agence Nationale de la Recherche (ANR), France

The overall objective of the COEN initiative is to create a collaborative research activity in the field of neurodegeneration beyond national borders, focusing on critical mass and excellence. COEN is aligned with the JPND, although it functions as an independent entity. The overlapping of the COEN

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

Phase I of the initiative was launched by 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.

Phases II and III of the initiative, termed as "Pathfinder", were launched in 2013 and 2015, respectively, with the aim of catalyzing collaborative research between centers with a critical mass of resources and expertise to thus promote a radical change in research on neurodegeneration. Pathfinder calls for projects are intended to encourage the community to think outside the pre-established frameworks and stimulate new and creative approaches and solutions to the challenges of research in neurodegeneration, carrying out high risk/high benefit projects and welcoming novel, non-conventional 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.

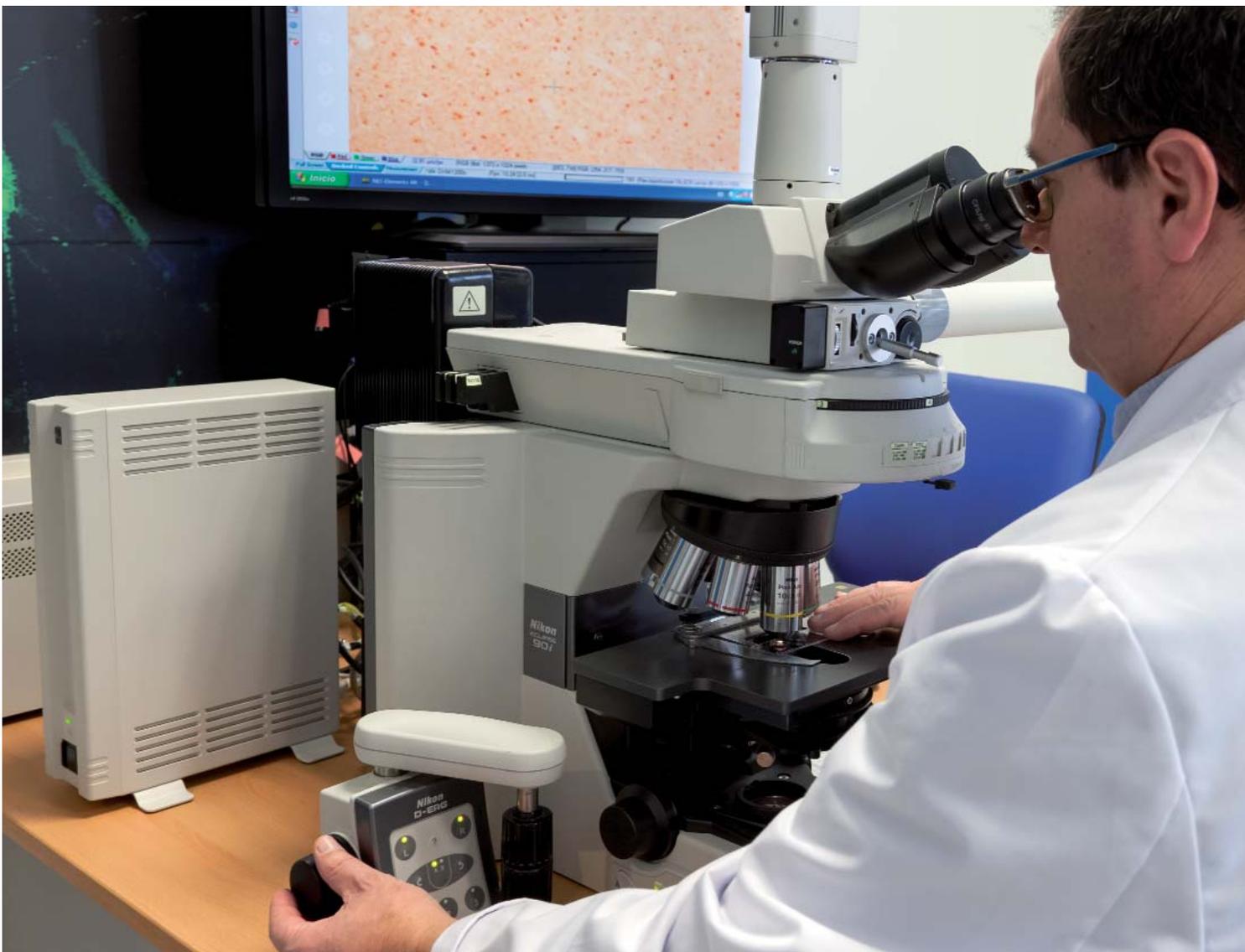


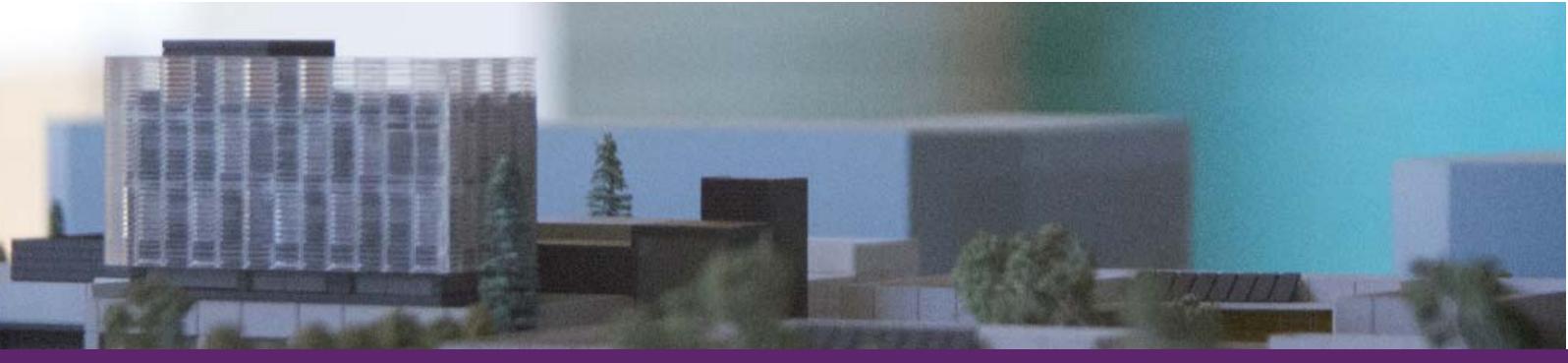
5. INTERNATIONAL RELATIONS

Joint nominations of researchers from recognized Centers of Excellence are invited, and projects must include researchers from two or more countries. The projects should address issues that would not be easily funded through the standard grant mechanisms of COEN partners, and it is expected that, in addi-

tion to the collaboration between Centers of Excellence, the projects will also serve to provide a platform for future collaboration with the industry.

In addition to the collaboration between Centers of Excellence, COEN also aims at providing a mecha-





nism for the industry to link to its Centers of Excellence and to develop novel and effective partnerships with the industry in precompetitive research. As a first step towards commitment to the industry, a working meeting was held in November 2013, attended by more than 40 researchers from the COEN centers and representatives of the biopharmaceutical and diagnostic sector.

5.4. International Congress in Research and Innovation on Neurodegenerative Diseases (CIIEN)

During 21st to 23rd September 2016, it was held in Alicante the Fourth 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.

CIIEN was created in 2013 and consolidates the merger of the two major scientific conferences on neurodegenerative diseases in general and Alzheimer's disease in particular, organized in Spain: the XI International Symposium Advances in Alzheimer's Disease, promoted annually by the Queen Sofia Foundation and CIEN Foundation, and the 9th CIBERNED Scientific Forum, which brought together every year more than the 58 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: CIEN Foundation and CIBERNED, both under the Ministry of Economy and Competitiveness through the Institute of Health Carlos III. This new structure seeks greater effectiveness

and efficiency in research, promoting the interaction of the different research groups.

This fourth edition of CIIEN was held at the headquarters of the Intellectual Property Office of the European Union (EUIPO) in Alicante, which accentuated the international nature of the event, chaired once again by Her Majesty the Queen Sofia. The scientific program consisted of an opening session, two plenary sessions and five scientific sessions. Among the invited speakers who participated in the Congress there were some international researchers who are a global reference in their field of research such as: Bengt Winblad (Karolinska Institute, Stockholm, Sweden), who spoke about present and future treatments and strategies for Alzheimer's disease; Anthony Schapira (UCL London, Great Britain), who addressed the latest advances in the treatment of Parkinson's disease; Eckhard Mandelkow (DZNE, Bonn, Germany), who delved into the role of Tau protein in the development of Alzheimer's disease and other neurodegenerative disorders; or Luc Buè (University of Lille, France-) who focused on the experimental models of Tau protein and therapeutic strategies.

5.5. Other activities of international cooperation

5.5.1. Collaboration with the Champalimaud Foundation

The CIEN Foundation continues to actively partner with the Champalimaud Foundation in accordance with the collaboration agreement signed in December 2015. This agreement aims to establish the framework of collaboration between the Champalimaud Foundation, the Queen Sofia Foundation and the CIEN Foundation, for the organization of the Global Summit on Research in Neurodegenerative Diseases, to be held on 21, 22 and 23 September 2017 in Lisbon, under the chair-



5. INTERNATIONAL RELATIONS

manship of HM Queen Sofia. As a result of this agreement, all the parties involved have carried out throughout 2016 a series of organizational meetings, both in Lisbon and in Madrid, focused on jointly planning the Global Summit with the intention of promoting the knowledge in both countries on a field still as unknown as that of neuroscience.

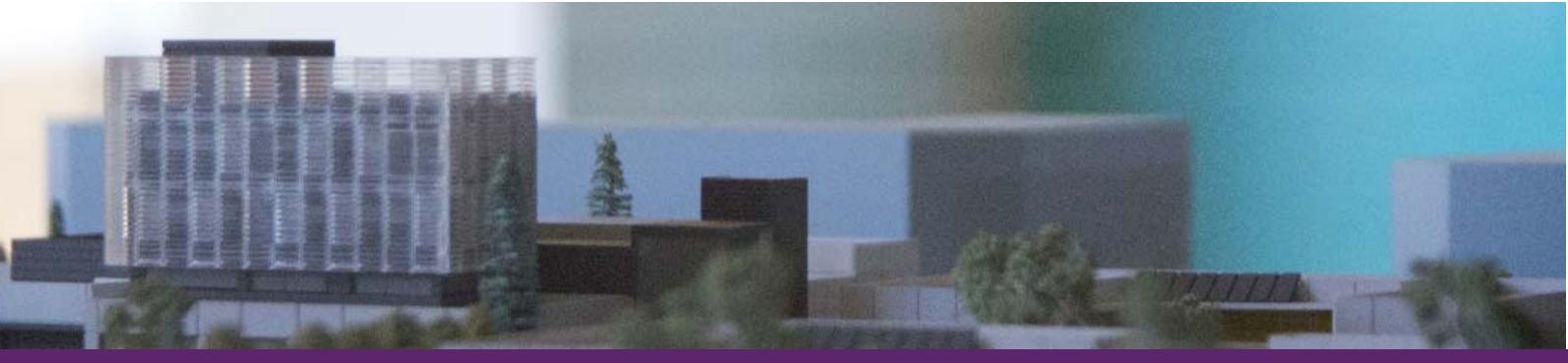
5.5.2. Alzheimer's Association

The Alzheimer's Association is a non-profit organization that focuses on the care and support of patients with Alzheimer's disease, and which also finances re-

search projects on this field through competitive calls. During 2016, CIEN Foundation researchers received funding from the Alzheimer's Association for a Research Project awarded to the Head of the Neuroimaging Department, Bryan Strange, entitled "The healthy elderly brain: MRI predictors for developing MCI".

The problem addressed in this proposal is the current lack of a technique to predict whether a healthy elderly individual will develop AD. This is important, given that any treatment for this progressive neurodegenerative disorder is more likely to be successful





if administered as early as possible in the disease process. The proposed project will interrogate data from a large sample of 1,213 healthy elderly individuals (70-85 yrs; male and female) as they are followed up in a 5-year longitudinal study. At each yearly visit, volunteers undergo detailed neuropsychological and clinical evaluation, serum biochemistry analysis, as well as a comprehensive magnetic resonance imaging (MRI) protocol, with genetic data acquired on visit 1. On follow-up, some volunteers go from healthy to a state of mild cognitive impairment (MCI).

The goal of the project is to retrospectively determine biomarkers in healthy individuals which predict subsequent development of MCI. By contrast to the extensive research effort into determining MRI parameters predicting conversion of MCI to AD, much less is known about specific brain biomarkers that predict the preceding step: going from healthy to MCI. The novelty of this proposal, and the significant advance, is that we will identify changes in the brain present in groups of healthy elderly people that are indistinguishable in the clinical setting, and that differ only subsequently in the development of MCI.

We have acquired structural (T1, T2 weighted), diffusion-weighted (DWI), functional (resting state functional MRI) and perfusion scans (arterial spin-labeling, ASL) in approximately 1,000 volunteers. The first goal of this proposal is to examine the MRI parameters in healthy elderly individuals that predict later development of MCI. A first analysis comparing whole-brain grey-matter density (GMD) in these “converters” relative to a matched control group selected from the large sample – at visit 1 (when both groups are healthy) – has already shown fascinating differences specific to the entorhinal cortex. The same type of analysis will now be extended to measures of white matter integrity, perfusion and resting functional networks to provide a comprehensive picture of brain abnormalities present before MCI develops.

Whereas the first analyses speak to group differences in MRI data, this proposal aims to develop a method that – for a given healthy elderly individual – provides predictive value regarding whether that person will subsequently develop MCI. For this purpose, we will include demographic, neuropsychological, biochemical and genetic data in our analyses, in addition to MRI data from all sequences described above. We will adopt a “machine learning” approach to generate a statistical algorithm to determine the likelihood (or odds ratio) of a healthy individual developing MCI in a given time period. Furthermore, it is expected that some volunteers will progress from MCI to AD, thus furnishing a test of whether these biomarkers extend to predicting AD development from the healthy state.

Determining the brain imaging biomarkers that in healthy people predicts development of MCI will have significant impact on the field of dementia. That relatively routinely acquired data can give an individual an index of risk of MCI development will provide that individual with immediate motivation for addressing modifiable risk factors for dementia (e.g. smoking cessation, reduced alcohol intake, cholesterol reduction).

Furthermore, in the hopeful situation that novel dementia treatments will be available soon, it will most likely increase therapeutic efficacy if this treatment is started as early as possible in the neurodegenerative process.

Thus, if we can identify those at risk of dementia while they are in the pre-clinical asymptomatic state, treatment could be started at this stage. Furthermore, the same approach we develop for classifying biomarkers for AD in our longitudinal study can then be applied to similar studies investigating other dementias.



5. INTERNATIONAL RELATIONS



Scientific productivity

During 2016 the scientific productivity of the CIEN Foundation has maintained a constant growth in quality and internationalization. The publication of scientific papers in prestigious journals has realized in a 44% increase in the average impact factor of the original articles within the first and second quartile with respect to the previous year. There has been also an increase in the percentage of publications in collaboration with foreign and national institutions.





6. SCIENTIFIC PRODUCTIVITY

6.1. Bibliometric analysis

During the last few years, a steady and significant growth is being consolidated, not so much in quantity as in quality and internationalization of the scientific productivity of the CIEN Foundation. This is largely due to the strong commitment of the Foundation to research development, as well as to generate and promote scientific knowledge to improve the diagnosis and treatment of neurodegenerative diseases both inside and outside our borders.

During 2016, researchers CIEN Foundation have produced a total of 29 publications, of which 28 have been published in scientific journals of national and international recognition (24 original articles, three reviews, and one meeting abstract) 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 quartile has increased from 4.718 in the year 2015 to 6.792 in 2016, which means a significant increase (44%)..

In addition, during this year the CIEN Foundation has increased its international collaborations, so that

53.6% of the articles corresponded to studies carried out in collaboration with international institutions and the rest with Spanish ones. Also noteworthy is the high proportion of collaborative publications with other CIBERS and networks in the first and second quartiles (66.7%).

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:

Among 2016 milestones we can highlight that the CIEN Foundation researchers have published 29 scientific papers, of which 26 (89.7%) have been in journals under the coverage of the Science Citation Index Expanded, accessible through the Web of Science portal (WoS, Thomson Reuters) and 24 (82.1%) have been published in journals ranked within the first and second quartile in their category. Considering the type of document, 85.7% of the publications in scientific journals (24) correspond to original articles.

Moreover, according to their scientific subject category 66.7% of the publications within the first and second quartiles, have focused on the following

2016 Indicators

Total number of publications.....	29
Total number of publications in the ISI citation index within the first and second quartile.....	24
Cumulative impact factor of publications within the first and second quartile.....	163.19
Average impact factor of the publications of the first and second quartile.....	6.792
Number of collaborative publications of all kinds (CIBERNED, other national groups, international groups) within the first and second quartile.....	24
Number of international collaborative publications within the first and second quartile.....	14
Number of national collaborative publications within the first and second quartile.....	10
Number of collaborative publications with other CIBERS and networks within the first and second quartile.....	16





categories: Neurosciences, Clinical Neurology, Geriatrics and Gerontology, Medicine, Research and Experimental, and Psychiatry.

As scientific dissemination activities in meetings and national and international events during the year 2016 there have been a total of 22 participations at scientific conferences, 12 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 (15) and international scientific conferences (7).

6.2. Publications

References of scientific publications from CIEN Foundation professionals are listed below according to type of publication: 28 publications in scientific journals (24 original articles, 3 reviews, and one meeting abstract) and one book chapter..

6.2.1. Journal articles

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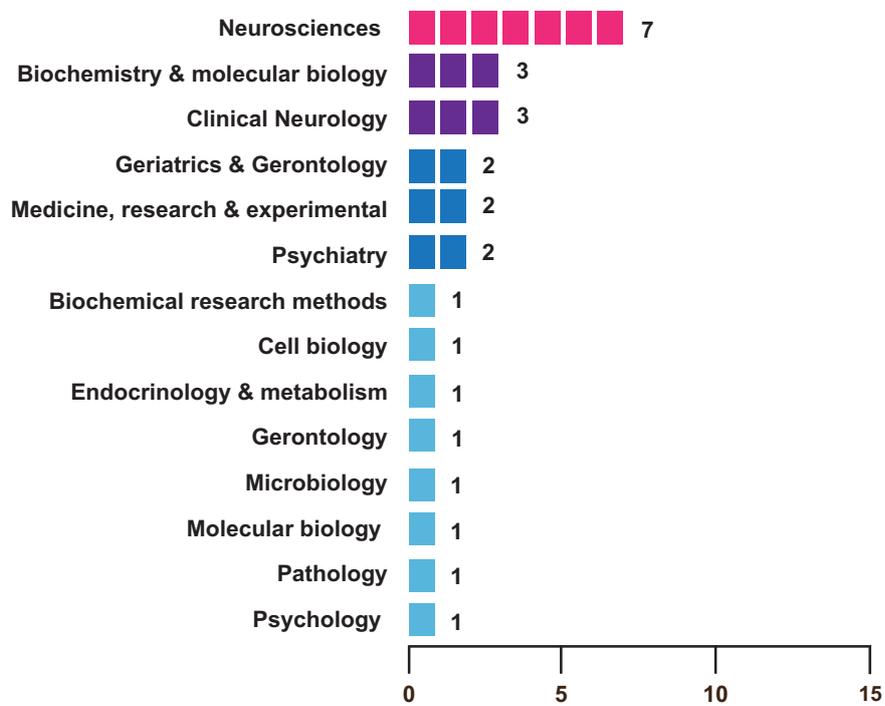
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6.2.3. Communications to Congresses

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- Villena C, Artiga MJ, Bahamonde O, Belar O, Bermudo R, Castro E, De la Puente R, Escámez T, Fraga M, Jauregui L, Novoa I, Peiró-Chova L, Piñero E, Rejón JD, Ruiz-Miró M, Vieiro P, Zazo S, Villar V y Rábano A. Optimización de muestras de tejido para el desarrollo y la validación de biomarcadores de enfermedad: proyecto OPTIMARK. Oral Communication.

6.2.4. Awards

In the seventh edition of the National Congress of Biobanks and the 1st Latin American Congress of Biobanks held in Santiago de Compostela from 16th to 18th of November, the work entitled "Optimization of tissue samples for the development and validation of disease biomarkers: project Optimark", was awarded the prize for best oral communication in the congress. The work, coordinated by Cristina Villena (CIBERES) and Alberto Rábano (Center for Research on Neurological Diseases, CIEN), summarizes the study carried out so far over a year and a half by the multi-center collaborative group on R&D&I on tissue quality from the National Biobanks Network Platform.

In May 2016, the Best Poster Award of the LXVII Annual Meeting of the Spanish Society of Neurology

(SEN) was presented at the National Academy of Medicine of Madrid to Miguel Ángel Fernández Blázquez, the first author of the poster "Usefulness of cognitive complaints as a marker of rapid conversion to mild cognitive impairment: results of a longitudinal research project".

The CIEN Foundation's work was recognized at the LXVIII Annual Meeting of the Spanish Society of Neurology (SEN) (November 15-18, 2016). During the Plenary Session, Dr. Cristóbal Carnero Pardo presented the stellar communications of the section of Behavioral Neurology and Dementias, and Neuropsychology. The lectures "Neuropsychological markers for the early diagnosis of mild cognitive impairment: results of a longitudinal study" by Dr. Miguel Ángel Fernández Blázquez, and "Conversion profile to mild cognitive impairment in a sample of 1090 elderly people during 24 months" Marina Ávila Villanueva were highlighted.

6.3. CIEN Foundation Seminar Series

The CIEN Foundation has been organizing 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 discuss the topics treated. Below are the seminars that have been developed in our Center of Vallecas within CIEN Foundation Seminar Series :

- María C. García Otero, neuropsychologist at CIEN Foundation. Proyecto Alzheimer: revisión del protocolo cognitivo y de psiquiatría". 11th January, 2016.
- Emily Lindermer, visiting PhD student from MIT. Quantitative methods for white matter analysis in aging and cognitive decline. 15th February, 2016.
- José Ramón Naranjo, CIBERNED and CSIC. Early neuroprotection in Huntington disease through ATF6 activation. 14 th March, 2016.





- Jaime González Ramírez, Associate Investigator, Department of Neuroscience and Mental health, The Hospital for Sick Children, University of Toronto, Canada. Exploring the network degeneration hypothesis in AD". 11th April, 2016.
- Juan Eugenio Iglesias, Basque Center on Cognition, Brain and Language. Probabilistic atlasing and segmentation of hippocampal structures using ex vivo MRI. 25th April, 2016.
- María Molina, CIEN Foundation Research Fellow. "Música y Alzheimer". 9th May, 2016.
- Alberto Rábano, Head of Neuropathology and Director of the CIEN Foundation Tissue Bank. Enfermedad de Alzheimer e infección microbiana". 30th May, 2016.
- Juan Antonio Barcia, Head of Neurosurgery, Hospital Clínico San Carlos and Professor of Neurosurgery, Complutense University of Madrid. "Estimulación cerebral profunda como tratamiento en la enfermedad de Alzheimer". 27th June, 2016.
- Eva Dueñas, CIEN Foundation Research Fellow. Efecto de la estimulación transcraneal por corriente directa (ETCD) en pacientes con enfermedad de Alzheimer. Estudio preliminar sobre mejoría de la memoria. 11th July, 2016.
- Marta del Campo, VUmc Amsterdam: Research at the NL Lab: Biomarkers for neurodegenerative disorders. 17th October, 2016.
- Marina Ávila, neuropsychologist at Fundación CIEN: Quejas cognitivas, rendimiento neuropsicológico y marcadores biológicos asociados al deterioro cognitivo debido a enfermedad de Alzheimer. 24th October, 2016.
- Linda Zhang, CIEN Foundation Postdoctoral Research Fellow: Effect of ethnicity on cortical grey matter volumes in cognitively normal elderly subjects. 31st October, 2016.
- Jesús Ávila: Los análisis en y del CAFRS. 7th November, 2016.
- Communications to SEN 2016, 14th de November:
 - o Virginia Guerra: Correlación entre síntomas neuropsiquiátricos y patología neurodegenerativa.
 - o Ana Rebollo: Bilingüismo como protección frente al deterioro cognitivo.
 - o Belén Frades: Envejecimiento saludable: análisis de actividades cotidianas y de ocio.
 - o Miguel Ángel Fernández: Estabilidad de las quejas de memoria.
 - o Isabel Faro - Meritxell Valentí: Dermatoglifos en la enfermedad de Alzheimer
 - o M^o Asunción Zea: Factores de riesgo vascular en los síntomas psicóticos de la EA.
 - o Miguel Ángel Fernández: Marcadores neuropsicológicos para la detección precoz del deterioro.
 - o Alberto Rábano: Esclerosis del hipocampo asociada a demencia.
- Marta del Campo, VUmc Amsterdam.- SPPL2b: a novel protein related to Tau pathology in Alzheimer's disease? 21st November, 2016.
- Bryan Strange, Head of Neuroimaging at CIEN Foundation: Human intracranial studies on processing salient stimuli". 28th November, 2016.
- Stephan Moratti. Associate Professor of Psychology, Department of Basic Psychology, UCM: "Is right cortical temporo-parietal dysfunction a potential endophenotype of depression". 5th December, 2016.

6.4. Funded projects

During 2016 the CIEN Foundation researchers have participated in six scientific research projects obtained through various national and international competitive calls and funded by different institutions.

Funded research projects are cited below:

- **Código FCIEN-005/11**

Principal Investigator: Dr. Miguel Medina
Title: Proyecto Vallecas – Early detection of Alzheimer's disease
Funding agency: Queen Sofia Foundation
Duration: 2011-2017
Total budget: 1,800.000 €
2016 budget: 273,293.60€

- **Code: Código: PT13/0010/0045**

Principal Investigator: Alberto Rábano



6. SCIENTIFIC PRODUCTIVITY

Title: Biobanks Platform
Funding agency: Carlos III Institute of Health
Duration: 2014-2017
Total budget: 179,934.78 €
2016 budget: 44,178.26 €

- **Code: MDSNMS**

Principal Investigator: Dr. Pablo Martínez
Title: Validación de las escalas de ansiedad en la enfermedad de Parkinson
Funding agency: Michael J. Fox Foundation
Duration: 2016
Budget: 67,371.37 €

- **Code: PEJ-2014-C-19788**

(Youth Employment Plan)
Principal Investigator: Dr. Alberto Rábano
Title: Grants for Promoting Youth Employment and Implementation of the Youth Guarantee in R+D+i within the framework of the National Plan of Incorporation
Funding agency: Ministry of Economy and Competitiveness / Secretary of State for Research, Development and Innovation
Duration: 2015-2017
Total budget: 150,000 €
2016 budget: 75,000 €

- **Code: PEJ2015/BIO/AI-0615**

Principal Investigator: Dr. Alberto Rábano
Title: Grants for hiring research assistants and laboratory technicians.
Funding agency: Ministry of Education, Youth and Sports, Region of Madrid
Duration: 2016-2018
Total budget: 45,000 €
2016 budget: 22,500 €

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

Principal Investigator: Dr. Alberto Rábano
Title: Ayudas para la realización de contratos para ayudantes de investigación y técnicos de laboratorio.
Funding agency: Consejería de Educación, Juventud y Deporte Comunidad de Madrid
Duration: 2017-2019
Total budget: 45,000 €
2016 budget: 22,500 €

6.5. Patents

During 2016 three patent applications remain active, active at national and international stages, which have currently a co-ownership agreement with participation of CIEN Foundation:

- **Inventors: Pablo Martínez Martín**, Pedro Carmona Hernández, Adolfo Toledano Gasca, Miguel Calero Lara, Félix Bermejo Pareja
Título: Infrared analysis of fractions obtained from peripheral blood to indicate cognitive development.
Registration N°: P201131370 PCT/ES2012/070613
Application date: 08/08/2011
Type: National/European
Licensing agreement with Biocross

- **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°: EP12382330.4
PCT/EP/2013/067304
Application date: 20/08/2012
Type: National/European
Licensing agreement with Biocross
National phases for this patent to the following countries have been initiated during 2015: Australia, Brazil, Canada, China, USA, Israel, New Zealand, South Africa, Japan and Russia.

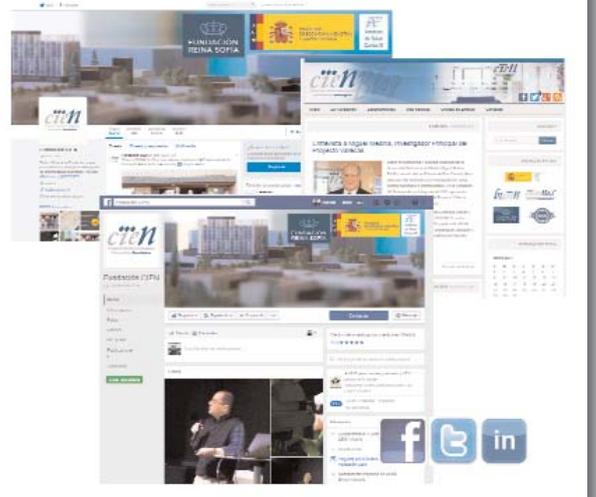
- **Inventors: José Ramón Naranjo Orovio**, Britt Mellström, **Alberto Rábano Gutiérrez del Arroyo**
Title: Methods for the prognosis and diagnosis of neurodegenerative diseases
Registration N°: EP13382108.2
PCT/EP2014/055928
Application date: 25/03/2013
Type: National/European



Social dissemination

In 2016 the CIEN Foundation has kept on leading outreach activities in the field of neurodegenerative diseases. Disseminating the scientific advances through different activities has allowed to bring closer to society the most relevant information, encourage citizen participation and raise awareness around neurodegenerative diseases. The recognition by the scientific community of the work of the CIEN Foundation is a motivation to keep on organizing activities such as the Tree of Memories, the Vallecas Project Volunteer's Day or the celebration for the first time of a tribute to the brain tissue donors. The media and social networks also add to the visibility of the Foundation's activities.





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7.1. Social outreach

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.

For this reason, 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.

Family Associations of Alzheimer, Parkinson and Huntington patients and other meetings

During 2016, CIEN Foundation organized and participated in a series of meetings with associations of relatives of Alzheimer's, Parkinson's and Huntington's patients, developing joint actions to disseminate advances in the research field. This was the case of the Meeting of Alzheimer Associations organized by CIEN Foundation on January 20, 2016. Different associations working in the field of research and treatment of Alzheimer's disease participated in the event. Also in attendance were the director of the National Alzheimer Reference Center (CREA, for its acronym in Spanish), M^a Isabel González Ingelmo; the new president of the National Confederation of Associations of Relatives of Alzheimer (CEAFA, for its acronym in Spanish), Rosa María Cantabrana Alutiz; the director of the Neuroalianza network, Josune Méndez; the counselor of the Alzheimer Spain Foundation, Adolfo Toledano, and representatives of other regional family associations such as Córdoba, Valencia, León and Soria.

Jesús Ávila de Grado, scientific director of the CIEN Foundation and CIBERNED; M^a Ángeles Pérez, manager of both entities; Miguel Medina, deputy scientific director of CIBERNED; and José Luis Nogueira,

secretary of the Queen Sofia Foundation, hosted the event. During the meeting, the entities reviewed their history and work in the area of Alzheimer's, in search of identifying common spaces of action and objectives for the different institutions.

World Parkinson's Day, was the date chosen to carry out the Social Forum, organized on April 11, 2016 by CIBERNED, CIEN Foundation and the Extremadura Regional Parkinson Association. The Day, which took place at the headquarters of the aforementioned Association in Mérida, was addressed to patients, relatives, doctors and researchers and was attended by the Minister of Health and Social Policies, Mr. José María Vergeles and the former President of Extremadura, Mr. Juan Carlos Rodríguez Ibarra. The Forum began with the presentation of the epidemiological study on the prevalence of Parkinson's disease in Extremadura, by Drs José Manuel Fuentes (University of Extremadura) and Ignacio Casado (Head of the Neurology Section of the San Pedro de Alcántara Hospital of Cáceres). Afterwards, it was held a roundtable moderated by Ms. M^a Ángeles Pérez, manager of the CIEN Foundation and CIBERNED, as attended by the researcher José Manuel Fuentes, the President of the Spanish Confederation of People with Organic and Physical Disabilities, Jesús Gumiel, as well as by a Parkinson's patient, a family caregiver, a professional caregiver, a doctor and a neurology specialist. Lastly, the specialist Justo García de Yébenes delivered a lecture on the origins and treatment of Parkinson's disease.

Within the framework of the IV International Conference on Research and Innovation in Neurodegenerative Diseases held in Alicante (see section 5 of International Cooperation Activities in this report), a meeting with associations of patients with Alzheimer's in the Valencian Community was organized. The event took place on September 20, at the Museum of Contemporary Art of Alicante-(MACA) and was promoted by the Queen Sofia Foundation, the CIEN





Foundation, CIBERNED and the Valencia federation of Associations of People with Alzheimer (FEVAFA, for its acronym in Spanish) . This meeting brought together experts and researchers such as Dr. Javier Sáez Valero, principal investigator of CIBERNED in the Neurosciences Institute of Alicante-Miguel Hernández University; Dr. Jordi Alom, Head of Neurology of the Hospital of Elche and specialist in Alzheimer's; the president of FEVAFA, Mr. Emili Marmaneu; Dr. Esther

López, psychologist-gerontologist from AFA Alicante; the neuropsychologist from AFA Elche Ms. Carmen Alonso; and Ms. María Isabel González Ingelmo, director of the CRE of Care for People with Alzheimer's disease and other Dementias in Salamanca (IMSERSO). An appropriate space for discussion and debate was created through the "Cuéntame" radio show to disseminate results from recent psychosocial research, as well as deepening of the ethical and



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economic aspects related to psychosocial care and research in the context of dementias. The meeting ended up with the emotional performance of the Choir "Voices of Memory" from AFA Valencia.

Another 2016 event worth mentioning is the Huntington Relatives Meeting, which took place on December 17 in Madrid. These meetings are held regularly between researchers and relatives of people affected by Huntington's disease, with the aim of updating research results, as well as possible new therapies or clinical trials. The program of the meeting was structured in seven presentations. In one of them, Dr. Alberto Rábano, neuropathologist and director of the Tissue Bank of the CIEN Foundation, explained the evolution of the Tissue Bank, since its creation in 2007, to the present day. Among other speakers, Dr. López Sendón, neurologist at the Ramón y Cajal Hospital, delivered a lecture on "Latest novelties in the treatment of Huntington's disease"; while Dr. María Santos, from the Severo Ochoa Center for Molecular Biology in Madrid, summarized the "Huntington European Congress"; and Dr. Montojo, neurologist at the Jiménez Díaz Foundation in Madrid, spoke about the "Metabolic study". Finally, the session was closed by Mrs. Asunción Martínez, President of the Huntington Association.

Educational talks

CIEN Foundation researchers are committed to raising awareness of the importance, on the one hand, of preventing Alzheimer's disease through the transmission of guidelines for active healthy aging, in order to improve the quality of life of these people as they age; and on the other hand, of the importance of the donation of tissues for research through programming annual informative talks in associations and centers for the elderly at different points of the Spanish geography. As an example of the former, it is noteworthy the lecture by Marina Ávila, neuropsychologist of the CIEN Foundation, at the Day Cen-

ter of the ASMI Foundation, in Zafra, coinciding with its X anniversary in the month of May. The researcher spoke about Alzheimer's disease, its symptoms, explained how it is possible to help prevent it, and provided an overview on the latest advances in research. With regards to the second topic mentioned above, it can be highlighted the conference in the old City of Leon entitled "Towards a brain bank in Spain", organized by Alzheimer Leon delivered by the director of the CIEN Foundation Tissue Bank, Alberto Rábano, in September. The scientist stressed once again the importance of brain tissue donation for research and emphasized that it is an irreplaceable tool in the study of neurodegenerative diseases. In addition, he warned of the need to overcome the limitations imposed by the administrative distribution marked by the autonomous communities, and advocated creating a large national network.

Other Outreach Activities

During 2016 the CIEN Foundation has continued to develop other dissemination actions among which we highlight the following.

► Closing conference of the artistic project "FromBubble"

Several experts in dementia research and treatment participated on January 21, 2016, at the Queen Sofia Foundation Alzheimer Center, in the closing round table of the artistic project "From Bubble", whose central exhibition has been set up in Madrid's CentroCentro since October of the previous year. As part of it, a series of debate panels on scientific and social health were held, ending up in the celebration of the round table "The metamorphosis of the self". Focused on reflecting on the evolution of Alzheimer's disease and how it transforms the patient's body and brain, it was attended by José Luis Nogueira, secretary of the Queen Sofia Foundation; Javier DeFelipe, principal investigator of CIBERNED and CSIC; Pablo





Martínez-Lage, from the CITA-Alzheimer Foundation; Miguel Medina, deputy scientific director of CIBERNED; Rosa Brescané, member of the Board of Directors of CEAFA; M^a Isabel González Ingelmo, director of Salamanca's CRE-Alzheimer-IMSERSO; and Luis Agüera, president of the Spanish Psychogeriatric Society. The panelists agreed on the need to "take Alzheimer's patients out on the street" to help make the disease visible. A "shared" disease, which generates a great burden on the family of those affected, and who needs a supporting network in which the empathy of society is a key element. Miguel Medina, member of the scientific advisory committee of the CIEN Foundation, said "Alzheimer's is eminently a problem of society", which should be addressed "with a certain naturalness" eliminating the stigma and allowing not forgetting that the patients "before patients, they are people". "Placing Alzheimer's in broad daylight in the heart of Madrid, and uniting in the same project such diverse professional profiles is already a resounding success," he said. For Medina, it is important "for society to know that it is possible to participate in science without being a scientist", and to encourage its involvement in fundamental studies for the advancement in knowledge of such complex diseases as Alzheimer's. In this sense, Javier DeFelipe declared "the human brain is one of the great challenges of modern science", and in the specific field of neurodegeneration, the collaboration of all professional fields and society is needed to be able to know "why our brain is losing its ability to create memory", and to delay and even slow down the effects of aging. In this closing ceremony also participated M^a Ángeles Pérez, manager of the CIEN Foundation; M^a Soledad Frías, general director of the Area of Equity, Social Rights and Employment from the Madrid City Council; César Antón, general director of IMSERSO; M^a Paz Cotarelo, director of the From Bubble project; and Daniel Bagnon, artist and project author.

► "Donor Card" Award Ceremony

On March 30, the CIEN Foundation, in collaboration with the Queen Sofia Foundation, held a meeting in the Auditorium of the Queen Sofia Alzheimer Center with brain tissue donors and associations of patients of neurological diseases and their relatives, an act of recognition of people who give their brain to scientific research, given its key role in the study of neurological diseases, especially those of degenerative type.

During the event, attended by H.M. Queen Sofia, a symbolic "Donor Card" Award was presented, in which the oldest male donor, José Ramón González Sánchez, 82 years old, was recognized; the oldest female donor (88 years old), M^a del Carmen Álvarez; the youngest donor (22 years old), Marta Pérez Campos; and posthumously José Luis Ortega García, who belonged to the Association of Relatives of Alzheimer of Soria and whose recognition was collected by a family member.

Her Majesty was accompanied by the secretary of the Queen Sofia Foundation, José Luis Nogueira; the manager of the CIEN Foundation, M^a Angeles Pérez; its scientific director, Jesús Ávila; and the head of the Tissue Bank, Alberto Rábano; in addition to the researchers Miguel Calero and Alberto Lleó.

► Vallecas Project Volunteer's Day

CIEN Foundation and Queen Sofia Foundation are aware of the role of the volunteer, crucial to carry out our research projects. Therefore, from CIEN Foundation we feel very grateful for the great generosity of each and every one of the 1,213 people who attended our call and, above all, the fidelity with which year after year keep coming to the corresponding visits of the Vallecas Project. Hence, since 2013, every year we pay them tribute through the already established "Vallecas Project Volunteer's Day". The last act of tribute, celebrated on April 2 at the Monumental Theater of Madrid, was attended by H.M. Queen Sofia and featured



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the performance of the RTVE Choir, as well as a magic show and a video tribute.

► “Searching Dory” Solidarity Pass

Concurring with the week in which World Alzheimer's Day is celebrated, the Queen Sofia Foundation wanted to continue supporting the research on this terrible disease affecting one million people in our country. Thanks to the collaboration of the Capitol cinema, a charity pass of the Disney-Pixar movie Searching Dory was screened on September 24. On this occasion, the sequel to the popular animated film Finding Nemo stars Dory, with memory problems, whose friends Nemo and Marlin will help to remember their past. The cost of the entrance was entirely used to fund the "Vallecas Project for the Early Detection of Alzheimer's Disease" that the CIEN Foundation carries out in the Queen Sofia Foundation Alzheimer Center.

► Christmas Tree of Memories

After the success of the previous campaign, the CIEN Foundation wanted to go a step further with its traditional "Tree of Memory", placed in the latest editions at the Villa de Vallecas food market. In addition to this Vallecan Tree of Memories, unveiled in December, with the support of the Queen Sofia Foundation, the Villa de Vallecas District Board, the Region of Madrid Directorate General for the Elderly and the Villa de Vallecas Market, a new "Tree of Memories" was also unveiled in parallel at CentroCentro Cibeles in Madrid. 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 "Tree of Memories" planted on





December 2016 was intended to be special, on the occasion of the tenth anniversary of the transfer of the CIEN Foundation to the Queen Sofia Foundation Alzheimer Center, which will be celebrated in 2017. Therefore, it was the first time that has been installed in the center of the capital, in such an emblematic place as CentroCentro Cibeles, 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 #arbolde lamemoria. 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.

7.2. Awards and Honours

Awards of the Spanish Society of Neurology (SEN)

H.M. Queen Sofia was distinguished for Her commitment to Alzheimer's with a distinction that rewards Her support for patients with neurological diseases,



especially those affected by Alzheimer's disease, through various initiatives of the Queen Sofia Foundation.

The event was held in May at the headquarters of the Royal National Academy of Medicine, where the Spanish Society of Neurology held an institutional ceremony in which were presented its Annual Awards in recognition of the scientific and social activity of organizations and people committed with Neurology.

H.M. received this honorable mention for the initiatives promoted by the Queen Sofia Foundation, created in 1977 and which has established promoting Alzheimer's research as one of its priorities, and supports the Queen Sofia Foundation Alzheimer Center in the Madrid district of Vallecas, started in 2007 and where various research projects are promoted through the CIEN Foundation, such as the Vallecas Project or the PICA V, and care is provided to people affected by the disease, as well as their families.

"Mano Amiga" Awards

On October 14, the traditional "Mano Amiga" (Friendly Hand) Awards Ceremony by Alzheimer Leon, was held. In this edition, Alzheimer Leon wanted to emphasize the importance of research, an area to which the association directs a large part of its efforts at present.

Therefore, in the course of the gala the CIEN Foundation (Center for Research in Neurological Diseases - Health Institute Carlos III of Madrid) received about 12,000 euros raised through the sponsors of Alzheimer Leon who have collaborated in the Mano Amiga Awards through their campaign "Invest in research and together we will erase Alzheimer's".

The funds are being allocated to the Vallecas Project, a study launched in 2011 by the CIEN Founda-

tion and the Queen Sofia Foundation, which analyzes the activity of the human brain before Alzheimer's disease manifests itself. To this end, a cohort of 1,213 cognitively healthy volunteers aged between 70 and 85 is being studied. The main objective is to identify markers for the early diagnosis of the disease.

In addition, for Her effort and personal dedication over decades to the fight against Alzheimer's, the Anonymous Prize with name went to H.M. Queen Sofia. This support has been translated into the founding of the Queen Sofia Foundation Alzheimer Center, a social-health project in which Alzheimer's disease is addressed from three different aspects: research, training and healthcare service for patients. The Award wants to reward the constant defense that H.M. Queen Sofia makes of Alzheimer's disease research, Her presence in all the situations in which it is required, as well as Her support and closeness beyond her institutional agenda.

7.3. Presence in media

Due to the growing importance of digital media in the generation of news impact (IpN), there is a tendency to evaluate the IpN qualitatively and not only quantitatively. Thus, for example, only during the actions corresponding to the IV CIEN – International Conference on Research and Innovation in Neurodegenerative Diseases (Alicante, 21-23 September 2016), over 200 impacts were generated in the press (agencies and national media), 150 in online media (including the digital version of traditional media) plus a notorious impact in social networks, especially Twitter.

Extrapolating these metrics, and considering actions that were carried out in 2016 such as the Volunteer's Day and the Tree of Memories at CentroCentro Cibeles and the Vallecas market (December 13, 2016 to January 7, 2017), with the support of Madrid





City Council, the number of impacts reached 1,600 for the media as a whole in 2016, an increase of 46.39% when compared to 2015. The growing impact on social networks and the digital ecosystem of CIEN Foundation/CIBERNED should also be noted, which includes their profiles on social networks, web pages and blogs.

The communication actions referred, not only to the Conference, but also to the activity of the CIEN Foundation. In addition, the constant flow of press releases and publications in social networks reflects the updated information on the Foundation and the Vallecas Project, its most relevant project.

7.4. Presence in social networks

The CIEN Foundation has experienced significant progress, both in its presence in social networks, already fully consolidated, and in its recognition at national and international level as an organization.

The impulse strategy carried out by the CIEN Foundation has paid off in concrete and measurable cases, such as the excellent results obtained by the Foundation's Tissue Bank last year, driven by the digital section.

Since the beginning of 2016, the entire community has the support and advice of numerous experts who can address their doubts and queries in real time through social networks.

The acquired presence, as well as the experienced increase in traffic, has been caused partially by different campaigns and events published and/or spread out through social networks, which have a great interaction of users, many of whom are professionals who see CIEN Foundation as a reference within the sector.

The interaction of the audience has also increased thanks to publications related to the campaigns pro-



www.emo.es

La Reina Sofía preside este miércoles en Alicante un congreso de Enfermedades Neurodegenerativas



La reina Sofía, en un momento, antes de su discurso y con el congreso. / EFE

Se trata de un centenar de expertos internacionales en la ciudad hasta el próximo viernes, con intervenciones de referencia en su país.

Se tratarán los últimos avances científicos en la investigación y tratamiento de Alzheimer, Parkinson, Huntington y otras enfermedades.

La reina Sofía preside este miércoles en Alicante el IV Congreso de Enfermedades Neurodegenerativas, que reúne a más de un centenar de expertos internacionales en la ciudad hasta el próximo viernes. Los ponentes contarán con la presencia de investigadores de referencia mundial como Bengt Winblad, del Instituto Karolinska, Escocia; Anthony D. Roses, del IGC, Leiden, o el Iñaki Menaibarrena, del IGCN de Navarra (España).

El Congreso se celebrará en el sede de la Oficina de Promoción Industrial de la Unión Europea (EIPRO) por sus siglas en inglés), cuyo edificio fue diseñado y se le encargó, en el año 2004, por el arquitecto español, según ha informado la Fundación Centro de Investigación en Enfermedades Neurodegenerativas (CIEN) en un comunicado.

La Fundación Basas Sola, la Fundación CIEN y el Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas (CIBERNED) organizan este tipo de congresos sobre las principales patologías de la investigación y tratamiento de Alzheimer, Parkinson, Huntington y otras enfermedades.



La reina Sofía abre en Alicante el Congreso sobre Enfermedades Neurodegenerativas



La reina Sofía ha presidido en Alicante la inauguración de la cuarta edición del Congreso Internacional sobre Enfermedades Neurodegenerativas.

La reina Sofía estuvo acompañada por el presidente de la Generalitat, Xosha Roa, el delegado del Gobierno en la Comunidad Valenciana, Juan Carlos Rodríguez Urdampal, el delegado del Gobierno en el Principado de Asturias, Julián García, y el delegado del Gobierno en Aragón, Juan Carlos Rodríguez Urdampal. El congreso, que se celebrará hasta el viernes en el Palacio de la Reina Sofía, contará con la presencia de más de un centenar de expertos internacionales en la investigación y tratamiento de Alzheimer, Parkinson, Huntington y otras enfermedades.

El congreso cuenta con la presencia de expertos internacionales en el campo de la investigación y tratamiento de Alzheimer, Parkinson, Huntington y otras enfermedades.

El congreso cuenta con la presencia de expertos internacionales en el campo de la investigación y tratamiento de Alzheimer, Parkinson, Huntington y otras enfermedades.



Este miércoles, los asistentes al IV Congreso Internacional de Enfermedades Neurodegenerativas volvían a escuchar las mismas palabras de boca del director científico del Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas, Jesús Avila.

El responsable de CIBERNED anunciaba que, por segundo año consecutivo, una universidad estadounidense ha propuesto a la reina Sofía (77 años) para el Premio Nobel de la Paz.



La reina Sofía, en una imagen de archivo. / Olycom

Es una persona merecedora del Nobel no sólo por su papel contra el Alzheimer, sino porque se dedica a otras muchas actividades y con



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moted by the CIEN Foundation or those in which it participates as well as to the events covered by its social networks, which have enjoyed great interaction among users, such as the hashtag #ÁrbolDeLa-Memoria, generating great traffic of publications on Twitter.

Several publications and campaigns about Alzheimer's disease have been organized that acquired great virtual impact, such as #ProyectoVallecas, from which we can highlight the promising advances obtained, which have already resulted in several publications in prestigious scientific journals.

It is noteworthy that during the year 2016 the presence of the CIEN Foundation in social networks has been consolidated, achieving a significant increase in followers in their accounts; especially in the Facebook account, which has grown more than 15% over the previous year.

On the other hand, the Service Level Agreements (SLAs) of 2016 have taken a leap forward in quality with respect to the 2015 data – as well as the Customer Service - thanks to the Chrysalis Care model, which ensures a Time Service Factor (TSF) below 5 minutes in 90% of the procedures.

The important traffic generated by the #HazteDonante campaign, promoted in the social networks of the Foundation with the aim of encouraging the donation of brain tissue, is also noteworthy. Users have shown great capacity for empathy by disseminating and commenting on related publications. One of these campaigns and events that generated more traffic than usual was the IV CIIIEN, which coincided with World Alzheimer's Day and was broadcasted live by Streaming and whose publication in social networks had great engagement (interaction between the community).

Facebook:

The 2016 ended with 4,550 followers, who have been increasing progressively and whose positive trend continues constant. This figure represents a 15% increase over the previous year.

Twitter:

By the end of 2016, the profile counted on 12,248 followers with whom it has constant interaction, receiving numerous comments, retweets and likes. The number of followers have experienced an increase of almost 4% compared with the previous year.

Google+:

The CIEN Foundation actively engages in sharing its publications both in its profile as well as in groups related to health, prevention and neurodegenerative diseases.



Annual Report 2016



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