

cién

Fundación Centro Investigación
Enfermedades **Neurológicas**



Annual
report
2015

CIEN FOUNDATION
Research Center for
Neurological Diseases Foundation

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“Brain frills” (“Florituras cerebrales”)

Artistic rendering that combines the idea of the existence of multiple neurotransmitters (coloured brains) with the action of these neurotransmitters through the brain cells.

Javier de Felipe

Annual report
2015



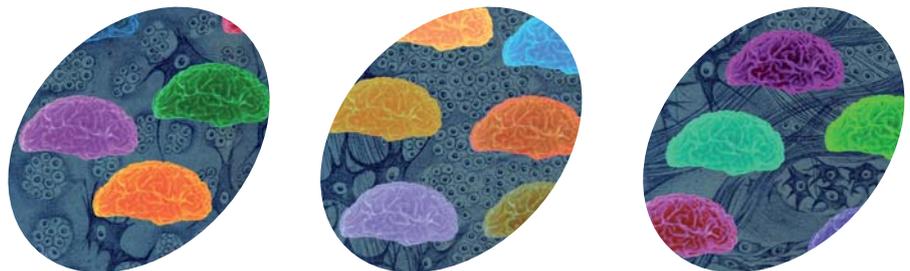
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Profile and presentation

The mission of CIEN Foundation, attached to the Ministry of Economy and Competitiveness through the Carlos III Institute of Health, is to promote and coordinate research in neurological diseases, mainly Alzheimer's and other dementias.

The work carried out since its establishment has positioned itself as a reference entity in this field. And thanks to the continued support of the Queen Sofia Foundation, CIEN Foundation has emerged as an example of "public-private" partnership in the research field, applying a translational model for the benefit of society.





1.1. Who we are



A Foundation from the public sector

The Research Center for Neurological Diseases (CIEN, for its acronym in Spanish) Foundation was established by resolution of 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 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

CIEN Foundation is one of the best examples of public-private collaboration in scientific research in Spain. 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 Neurodegenerative 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.

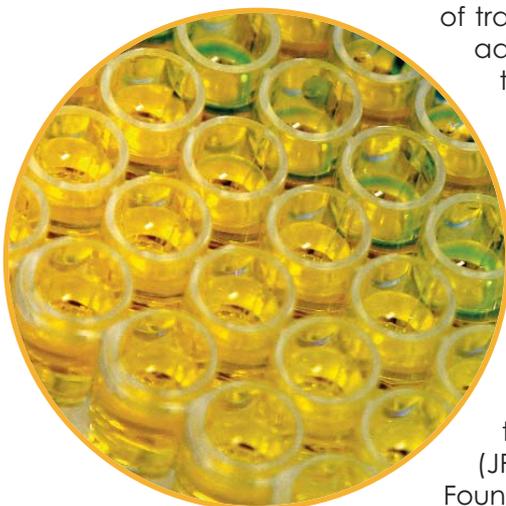
1. A live-in residence for 156 Alzheimer's patients.
2. A day-care outpatient center for 40 Alzheimer's patients.
3. An Alzheimer's research center: the so-called Alzheimer's Project Research Unit (UIPA), managed by the CIEN Foundation.
4. A training center for healthcare staff, relatives and volunteers.

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, management of UIPA, devoted to research, was assigned to CIEN Foundation, while the Ministry of Family and Social Affairs of the Community of Madrid is responsible for healthcare and training activities.



Focused on research in neurodegenerative diseases

Among the tasks assigned to the CIEN Foundation include: implement a model of translational research for conveying effectively and efficiently scientific advances in basic research into clinical practice; promote continuous training of professionals involved with neurological diseases research by conducting seminars, lectures and doctoral theses; disseminate the calls made by funding agencies, both nationally and internationally, promoting participation; and foster the implementation of coordinated research projects in neurological diseases.



In addition, CIEN Foundation manages other centers related to neurodegenerative diseases research: the UIPA and Center for Networked Biomedical Research in Neurodegenerative Diseases (CIBERNED), and has collaboration agreements with the Carlos III Institute of Health for the implementation of the strategic agenda of the European Union Joint Programming in Neurodegenerative Diseases (JPND), particularly Alzheimer's disease, and the Madri+D Knowledge Foundation to regulate the participation of the Foundation in the M + VISION program.



1.2. The CIEN Foundation in 2015

Key figures

- ▶ The CIEN Foundation overall budget for 2015 was reduced 18.6% compared with the previous year, up to a little over 2.5 million €.
- ▶ Almost 34% of the CIEN Foundation budget comes from the General State Administration budget through the ISCIII.
- ▶ It is noteworthy the continued financial commitment of the Queen Sofia Foundation which in 2015 contributed more than 400,000 €, in addition to the assignment of the facilities that house CIEN Foundation and the available equipment.

Scientific activity

- ▶ Overall scientific production: 46 impacts. Similar level to that of 2014.
- ▶ Publications in scientific journals: 45. Similar level to that of 2014.
- ▶ The average impact factor of publications within the first and second quartile is 4.718. Increases 8% versus 2014.
- ▶ Clinical neurology and Neurosciences remain the main subject categories for publication according to the distribution of publications.



1. PROFILE AND PRESENTATION

Highlighted events

- 
- ▶ During 2015 the second, third, fourth and fifth visits of the 1,213 volunteers involved in Vallecas project have progressed concurrently, surpassing the halfway point of this five years study.
 - ▶ CIEN Foundation researchers have produced 46 scientific publications in 2015. Among them, an article in the journal "Frontiers in Aging Neuroscience" describing the objectives and the methodology used in the Vallecas project.'
 - ▶ In 2015 the process of recruitment of participants in the project: "Detection of proteins in tears as biomarkers of Alzheimer's disease" has ended. In the study we participated together with the Association of Alzheimer's and other dementias patients relatives from Soria, the Leon Alzheimer's Association, and the Center for Molecular Biology Severo Ochoa. In total 100 samples have been collected to be analyzed at the Center for Molecular Biology Severo Ochoa throughout 2016.
 - ▶ The international activity of CIEN Foundation has continued to strengthen during 2015. Thus, to the the management of the development of the Research Strategic Agenda of the European Union Joint Programme in Neurodegenerative diseases, particularly Alzheimer's disease (JPND) in collaboration with ISCIII, and its participation in the Network of Centers of Excellence in Neurodegeneration (COEN), we must add the involvement of our scientists in the projects DEMTEST, on dementia, and REGISTRY, on Huntington's disease.
 - ▶ In September 2015, Malaga hosted the third edition of the International Conference on Research and Innovation in Neurodegenerative Diseases (CIIEN). Among the speakers at the Congress include some international researchers who are world leaders in its field of research.
 - ▶ At December 31, 2015, the CIEN Foundation Tissue Bank (BT-CIEN, for its acronym in Spanish) had more than 600 registered donors. Meanwhile, the Neuropathology lab processed 125 cases in 2015, of which 83 were cases of donation extracted and processed in the UIPA and 42 were consultation cases.
 - ▶ In 2015, the Neuroimaging Department has carried out 5,547 MRI studies on 963 subjects. Over 43,864 sequences have been performed since the inception of the department.



1.3. Letter from the Manager of the CIEN Foundation



One more year is a pleasure for me to address you to review the activities undertaken by the Center for Research in Neurological Diseases (CIEN, for its acronym in Spanish) Foundation during the year just ended.

2015 could be defined as a consolidation period of actions initiated in prior years and of future projection, always aligned with the principal axes that have marked our progress in recent years: commitment to a model of translational research and internationalization of our project. Without the constant support provided by the Queen Sofia Foundation for a decade now and without the commitment of pe-

María Ángeles Pérez Muñoz
Manager of the CIEN Foundation

ople within CIEN Foundation, this would not be possible.

At CIEN Foundation we conceive research as a applied model that allows us to translate progress in a benefit to society. Research should be a shaft generating innovation. In this regard, this year CIEN Foundation has collaborated as co-owner in three patent applications, both national and international.

Among the activities launched in previous years highlights the Vallecas project, one of the most ambitious studies being developed in Spain to advance the early diagnosis of Alzheimer's disease. In 2015, some of the 1,213 volunteers who selflessly participate in the project underwent the fifth follow-up visit. Currently, the third, fourth and fifth follow-up visits are being carried out simultaneously.

The Vallecas Project has also begun to bear fruit. Our researchers have published in the journal *Frontiers in Aging Neuroscience* an article describing the objectives and the methodology used in the study. This article is included among the 46 scientific publications produced in 2015, among which also highlights the publication in the journal *Alzheimers & Dementia*, which has led to the first high impact publication based on data from clinical-pathological correlation from Vallecas Alzheimer Center Research Program (PICAV, from its acronym in Spanish). During 2016 it is planned to publish new work in which the first findings of the project will be presented Vallecas.

At the end of the year has concluded the recruitment of participants in the new multicenter research project led by CIEN Foundation, in collaboration with Alzheimer Leon and Alzheimer Soria associations: detection of TAU protein in tears as a possible biomarker of Alzheimer's disease. During 2016, professionals from the Center for Molecular Biology Severo Ochoa will analyze the 100 samples that have been collected.

1. PROFILE AND PRESENTATION

Meanwhile, the CIEN Foundation Tissue Bank (BT-CIEN, for its acronym in Spanish) has reached a record high in the number of yearly donations (76) and at year-end has registered 600 brain donations since its inception in 2010. In addition, an area of sample management has been set up to manage, process and track tissue samples requested by the different research groups, both nationally and internationally.

At the institutional level, this has also been a fruitful year. In September, the third edition of the International Conference on Research and Innovation in Neurodegenerative Diseases (CIIEN), a scientific meeting that brings together the efforts of the Queen Sofia Foundation, CIEN Foundation and CLBERNED, was held and it has established itself as an international scientific congress of reference in this field.

The work developed at CIEN Foundation has once again been recognized by different institutions outside the research field. More specifically, INESE has granted the Vallecas project one of its Insurance Solidarity Awards and the Fuerteventura Association of Hotel and Tourism choose CIEN Foundation as the beneficiary of the Fuerteventura Grant. In particular, it allocated 24,000 euros to fund research in Alzheimer's disease.

From a social perspective, activity has also been intense. In February we celebrate the third edition of 'Vallecas Project Volunteer's Day' and coinciding with the Christmas holiday season, we set up for the fifth consecutive year the 'Tree of Memories' in the Municipal Market of Villa de Vallecas, with the support of the Villa de Vallecas District Board, the Directorate General of the Elderly of the Madrid Region, and traders from the market itself.

I cannot conclude without making special mention of the actions in the area of Human Resources. The ongoing training of our professionals and the recruit-

ment and retention of talent are crucial factors for the future development of the CIEN Foundation. In this regard, in 2015 we have adhered to the program of "Grants to promote young employment and implementation of the Youth Guarantee in R+D+i" within the framework of the State Plan for Scientific and Technical Research and Innovation 2013-2016, which has resulted in the execution of four contracts. We have also renewed the agreement with the Madrid M + VISION project, with the collaboration of the Massachusetts Institute of Technology (MIT). The goal is to attract international renowned researchers within the COFUND program from the EU Seventh Framework Programme.

The invaluable collaboration of our trustees and benefactors and the work of our professionals are two solid pillars that support the future of CIEN Foundation. Our ultimate goal, to keep fighting what many people describe as the new epidemic of the XXI century: Alzheimer's disease.

¹ Zea-Sevilla et al. *Alzheimers Dement.* 2015 Nov;11(11):1358-66





1.4. Letter from the Scientific Director of CIEN Foundation



During 2015, the Alzheimer Project Research Unit located in the Queen Sofia Alzheimer Center has been developing the proposed aims. This development is leading to the consolidation of CIEN Foundation, whose existence is due to the financial support of the Carlos III Institute of Health and the Queen Sofia Foundation, and in 2017 will let us reach our first 10 years of existence. Thus, I would like to begin this letter by thanking both institutions. This year 2015 we have had the honor to receive several visits of H.M. Queen Sofia to the CIEN Foundation. We have also been visited by the ISCIII Director General and I would like to echo the kind words of the Director General of the Institute, who said during his visit that if

Jesús Ávila de Grado
Scientific Director of CIEN Foundation

the CIEN Foundation did not exist, it would have to be created in order to have a national reference in the area of neurodegeneration that is comparable to what exists in neighboring countries.

Our main objective is the development of Vallecas Project, a study that has advanced to publish this year not only what the project is about but also the first results that indicate several risk factors that can accelerate the transition from a cognitively healthy state to a mild cognitive impairment, a decline that may be at the beginning of disease progression. These data will be essential to carry out in the future, on a consolidated CIEN Foundation, clinical trials with the at-risk population, which can be classified by the presence of the risk factors identified.

During 2015 we published 46 scientific articles, several of them in collaboration with CIBERNED groups, institution with which we share several joint interests in the common goal of preventing and treating neurodegenerative diseases; and with which we carry out scientific meetings and our Annual Congress, developed this year 2015 in Malaga with the support of the Queen Sofia Foundation and during which, in addition to its high scientific level, we had the pleasant news to know that HM Queen Sofia was one of the nominees to Peace Nobel Prize this year.

I would not like to conclude without thanking all the members of the CIEN Foundation, including the scientific and technical, administrative, managerial staff as well as the Scientific Advisory Committee. Their hard work and efforts, which is what allows the improvement and gradual development of the Foundation, of which we hope to meet many more years.

Thank you all.

1. PROFILE AND PRESENTATION





1.5. Organizational chart

CIEN Foundation 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.

Board members at the end of 2015 are:

CIEN FOUNDATION BOARD OF TRUSTEES

Position	Title	Name
Honorary Chair	Minister of Economy and Competitiveness	Mr. Luis de Guindos Jurado
Chair	State Secretary of Research, Development and Innovation	Ms. Carmen Vela Olmo
Vice-Chair	Director of the Carlos III Institute of Health	Mr. Jesús Fernández Crespo
Ex-officio Members	General Secretary of Health and Consumer Affairs, Ministry of Health, Social Services and Equality	Mr. José Javier Castrodeza Sanz
Ex-officio Members	General Director de Scientific and Technical Research, Ministry of Economy and Competitiveness	Ms. Marina Pilar Villegas Gracia
Ex-officio Members	Director of the Technical Secretary, Executive Committee for Economic Affairs, President of the Government's Economics Office	Ms. Cristina Ysasi-Ysasmendi
Ex-officio Members	Deputy Director General of Evaluation and Promotion of Research, Carlos III Institute of Health	Ms. Belén Bornstein Sánchez
Ex-officio Members	Director General of Public Health, Quality and innovation, Ministry of Health, Social Services and Equality	Ms. Elena Andradas Aragonés
Ex-officio Members	President of the Higher Council for Scientific Research	Mr. Emilio Lora Tamayo
Member And Secretary	Deputy General Director of Cooperative Research Networks and centers, Carlos III Institute of Health	Ms. Margarita Blázquez Herraiz
Elected Members Andalusia	General Director of Research, Technology and Business	Mr. Manuel García León
Elected Members Valencia	Director General for Research, Innovation, Technology and Quality, Public Health Department	Mr. Óscar Zurriaga Lloréns
Elected Members Canary Islands	Director General of Welfare Programs, Canary Islands Health Service	Mr. Bernardo E. Macías Gutiérrez
Elected Members Castilla La Mancha	Secretary General of the Health Service of Castilla-La Mancha (SESCAM)	Mr. Fernando Sanz García
Legal Advisor	State Attorney	Mr. José Luis Beotas López
Invited guests	Scientific Director, CIEN Foundation	Mr. Jesús Ávila de Grado
Invited guests	Managing Director, CIEN Foundation	Ms. María Ángeles Pérez Muñoz
Invited guests	Queen Sofia Foundation	Mr. Jose Luis Nogueira Guastavino
Invited guests	Queen Sofia Foundatio Advisor to the Office of the Secretary of State for Research	Mr. Agustín Larrañaga Elorriaga
Invited guests	Assistant to the Secretary	Ms. M ^a Dolores Donoso Mencía



1. PROFILE AND PRESENTATION

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

- On April 6, 2015 the termination of Mr. Antonio Luis Andreu Pérez is registered and Mr Jesús Fernández Crespo is appointed as Vice President and Trustee of the Foundation by virtue of his position as Director of the Carlos III Institute of Health.
- On January 20, 2015 are registered the termination of Ms. Maria Mercedes Vinuesa Sebastian and the appointment of Mr. José Javier Castrodeza Sanz as Trustee of the Foundation pursuant to his position as Director General of Public Quality and Innovation of the Ministry of Health, Social Services and Equality.
- On October 9, 2015 are registered the termination of Ms. Maria Antonia Pérez Pérez and the appointment of Mr. Bernardo Emilio Macias Gutierrez as Trustee of the Foundation in accordance with his position as Director General of Welfare Programs of the Canary Islands Health Service .
- On October 30, 2015 the termination of Ms Pilar Viedma Gil de Vergara is registered and Mr. Oscar Ernesto Zurriaga Lloréns is appointed as Trustee of the Foundation pursuant to his position as Director General for Research, Innovation, Technology and Quality Public Health Department of Valencia.
- On 30 November 2015 are registered the termination of Mr. José Javier Castrodeza Sanz and the appointment of Ms. Elena Andradas Aragones as Trustee of the Foundation in accordance to her position as Director General of Public Health Quality and Innovation of the Ministry of Health, Social Services and Equality. In addition. Termination of Mr. Ruben Fausto Moreno Palanques and appointment of Mr. José Javier Castrodeza Sanz as Trustee of the Foundation as Secretary General for Health and Consumer Affairs, Ministry of Health, Social Services and Equality, are registered.

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. The proposed Committee consists of: Miguel Medina Padilla, who will act as coordinator, Javier de Felipe Oroquieta, José Ramón Naranjo Orovio, Fernando Rodriguez Artalejo and Joaquín Arenas Barbero.

Scientific Advisory Committee

In order to improve scientific quality, optimize available resources and exploit the peculiarities of the Queen Sofia Foundation and the Alzheimer Center, the creation of a CIEN Foundation Scientific Advisory Committee was approved in late 2013.

From its inception, several joint working meetings between UIPA researchers, members of the CIEN Foundation Scientific Advisory Committee and representatives of the Queen Sofia Foundation have taken place. In the last one, on February 19, 2015, H.M. Queen Sofia met with the CIEN Foundation Scientific Advisory Committee. Upon arrival at the Center, the Queen was received by the Director General of the Carlos III





Institute of Health, Antonio Andreu; the Scientific Director of CIEN Foundation and Network Center for Biomedical Research in Neurodegenerative Diseases (CIBERNED), Jesus Avila; and the Manager of CIEN Foundation and CIBERNED, Maria Angeles Perez.

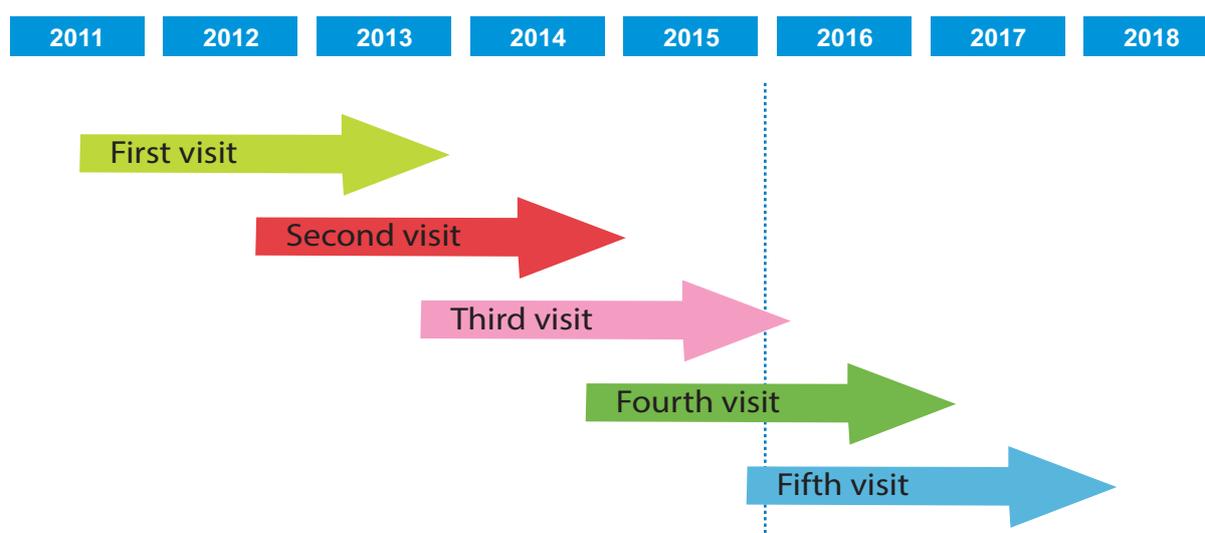
Therafter, the Queen held a briefing with members of the CIEN Foundation Scientific Advisory Committee, including Miguel Medina Padilla, Deputy Scientific Director of CIBERNED; Jose Ramon Naranjo, a researcher at the National Center for Biotechnology of the CSIC (CNB) and CIBERNED; Javier de Felipe, CIBERNED principal investigator and Professor at the Higher Centre for Scientific Research (CSIC); and Fernando Rodriguez Artalejo, Professor of Preventive Medicine and Public Health at the Autonomous University of Madrid.

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. Once the recruitment of volunteers and the constitution of the cohort study of Vallecas project was completed in late 2013, second, third, fourth, and fifth visits from volunteers have been occurring simultaneously during the year 2015, so that

the half-way point of this 5-year longitudinal study has been surpassed, as shown in the following figure.

During this year validation of historical data collected to date by the different areas has been completed and a single integrated and anonymized, newly created database has been established. This database is intended to ensure the reliability and security of data while in turn allowing a more effective analysis. The first evaluation of data from the first two



1. PROFILE AND PRESENTATION

visits have been submitted to the CIEN Foundation Scientific Advisory Committee and members of the Queen Sofia Foundation. In addition to presenting our preliminary results in different conferences and scientific meetings during 2015 the first description of the Vallecas project has been published in an international scientific journal (see Section 6 of this report). The project is generating great interest among the scientific community and we look forward to presenting our results in national and international conferences and publishing scientific papers of the first longitudinal analysis throughout 2016.

As the project progresses it is producing a number of increasingly richer and more relevant information about the earliest stages of cognitive impairment in subjects that progress to that state, as well as the most suitable biomarkers (clinical, biochemical and neuroimaging) to characterize and identify the population at increased risk of developing it.

In the coming months we will initiate the necessary contacts so that information obtained from assessments of the volunteers, their biological samples and neuroimaging studies undertaken could integrate with other national and international cohorts, which significantly will increase the potential of each one of them and the Vallecas project itself.

In addition to the Vallecas project, the Alzheimer project will continue to be an essential project for the Queen Sofia Foundation Alzheimer Center and CIEN Foundation and a growing source of information (clinical, molecular, neuroradiological and neuropathological) on mild and severe dementia stages. This longitudinal study, initiated in 2007, aims to monitor residents at the Queen Sofia Foundation Alzheimer Centre and users of the Day Center.

In the coming months and years the information gathered since the beginning of the project will provide important clues on how the two main pathologies

that lead to dementia in our environment, the Alzheimer's and cerebrovascular disease, interact and result in defined progression pathways. A better understanding of the various forms of expression of these diseases, when presented alone or, more commonly, in combination, will allow to approach in depth their role in the origin of dementia and to identify patient groups who require special care or that can benefit from specific therapies.

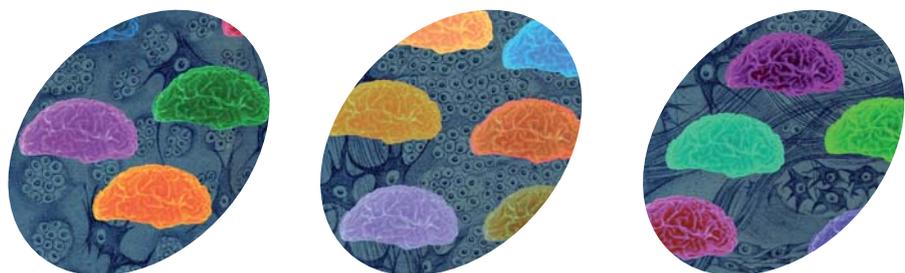
The research model implemented in the Alzheimer Center can be equally applied to other residences and other Day centers around the Region of Madrid. In fact, the Alzheimer Project model in other social health environments is being put into in Day Centers from the Associations of Relatives of Alzheimer patients (AFA) in Soria, León, and other towns, in order to incorporated subjects diagnosed with mild cognitive impairment and mild dementia in future Foundation projects.

Moreover, a new study (the Madrid+CIEN project) has been designed in collaboration with the Region of Madrid General Directorate for the Elder and the European University, aimed at establishing a cohort of hundred-year-old subjects in our Region. The project aims at establishing the cognitive profile of centenarians who have no dementia, studying cognitive profile progression over a period of three years and establishing a cohort of centenarians in which would be possible to set up studies with non-pharmacological therapies.



Mänagement *re*port

During 2015, CIEN Foundation has continued to implement a management model marked by resource optimization and rationalization of expenditure to fit a budgetary reality marked by a funding crisis, although CIEN Foundation is committed with maintaining investment in research, development and innovation as a guarantee of future and putting results to the service of society. CIEN Foundation promotes the education of their researchers as basic support for quality research as well as strategic and differential value.





2.1. General management

The income budget managed by CIEN Foundation during the year 2015 slightly surpasses the 2.5 million Euros, arising mainly from the ISCIII annual contribution, which amounted in 2015 to 825,000 €. It is remarkable, once again, the effort and commitment of the Queen Sofia Foundation with the research work carried out by CIEN Foundation, materialized on an income above 400,000 € in 2015, in addition to the transfer of use of the building and equipment.

During 2015 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).

The International Network of Centers of Excellence in Research on Neurodegenerative Diseases (COEN) has approved funding for five "Pathfinder" projects for an amount of around three million euros. The Foundation has committed 550,000 € to finance projects selected in this call, which will be carried out by CIBERNED groups.

- 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. 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

The CIEN Foundation is a statewide under the Ministry of Economy and Competitiveness.

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

The Carlos III Institute of Health, exercising their functions of planning, development and coordination of biomedical and health research and innovation resolves to grant the CIEN Foundation with a nominative allocation for current expenditure for the year 2015 of 675,000 € and a nominative allocation for capital expenditures of 150,000 €. The allocation corresponding to fiscal year 2014, experienced a significant budget reduction compared to previous years, due to different factors such as the termination of several cooperation agreements between CIEN Foundation and other institutions, which were distant from the aims of the Foundation. Also, by resolution of ISCIII a nominative allocation of 50,000 € for 2014 was granted to the CIEN Foundation.





The breakdown of total revenues in 2015 and 2014 were as follows:

The management entrustment for the following two projects has terminated during 2014: "Strengthening the health system and prevention in the fight against infectious diseases in the Amhara-Ethiopia region" (Project Amhara-Eth) and "Reference center for control of endemic diseases of Equatorial Guinea" (CRCE, for its acronym in Spanish). This fact is reflected in a decrease in the revenue amount for 2015.

The item "Cash grants and subsidies" corresponds to the balance arising from the audit of the II call for research projects in Alzheimer's disease and related diseases and the subprogram INNPACTO (2012 call).

In addition, the Foundation has received additional income from the provision of services as a result of various activities:

With regards to expenditure, a proportion similar to the year 2014 expenditure has maintained during 2015. The significant reduction in the item "Monetary aid and others" is the result of the termination of the entrustment management agreement of the two projects listed above (Amhara-Eth and CRCE).

All other items of expenditure experience less noticeable decreases as a result of general efforts to reduce costs, in line with the budgetary reality marked by the financial crisis. The departure of staff increases due to the payment of part of the bonus for December 2012.

2.3. Management of Human Resources

The Department of Human Resources at CIEN Foundation manages the scientific and technical staff that cooperates in conducting the various research projects, both those granted by public as private organizations. CIEN Foundation encourages personal

CIEN Foundation revenues during 2015

	2015	2014
ISCIII anual grant	825.000,00 €	50.000,00 €
ISCIII grants remaining from previous years	89.068,99 €	1.028.109,01 €
Management entrustments	0,00 €	733.278,65 €
ISCIII capital subsidies charge to income	65.365,39 €	69.059,16 €
Reimbursement of grants and subsidies	45.074,96 €	828,61 €
Public project grants	423.582,70 €	417.818,22 €
Donations and legacies assigned to projects	377.567,78 €	311.844,42 €
Others donations and legacies	637.018,49 €	441.132,26 €
Sales and other income from commercial activity	110.379,36 €	104.587,59 €
Financial income	1.219,24 €	6.728,54 €
	2.574.276,91 €	3.163.386,46 €



2. MANAGEMENT REPORT

Revenues from provision of services during 2015

	2015	2014
Energy production	12.982,68 €	8.028,32 €
Income from performing MRIs and collaborative research projects	91.748,90 €	95.093,62 €
TOTAL	104.731,58 €	103.121,94 €

and collective commitment to the institutional mission as well as the sense of belonging to the organization. It promotes habits and procedures adjusted to the needs and expectations of our researchers who provide inestimable added value and in which the personal satisfaction and talent retention are critical. CIEN Foundation encourages the education of their researchers as basic support for quality research and is committed to maintaining investment in research, development and innovation, as a guarantee of future and placing results to the service of society.

CIEN Foundation researchers, in addition to carrying out the assigned projects, collaborate with other institutions in educational and social outreach activities related to the latest advances and new techniques for the prevention of Alzheimer's disease and other neurodegenerative disorders. The close collaboration with Alzheimer associations from different Regions help us develop a research of recognized prestige and sensitive to society. CIEN Foundation, thanks to the work of its professionals, has become a national and international reference in the investigation of neurological diseases.

CIEN Foundation breakdown expenditure 2015

	2015	%	2014	%
Monetary aid and others	341.349,65 €	13,34%	871.813,84 €	27,71%
Variation in stock of merchandise	-19.290,78 €	-0,75%		
Supplies	173.885,09 €	6,79%	203.325,46 €	6,46%
Personnel costs	850.264,09 €	33,22%	804.343,96 €	25,56%
Other operating expenses	705.055,86 €	27,54%	742.897,00 €	23,61%
Depreciation and amortization	508.305,00 €	19,86%	508.804,38 €	16,17%
Impairment and gains on disposal fixed assets	0,00 €	0,00%	15.175,15 €	0,48%
Exchange differences	84,51 €		92,53 €	
TOTAL EXPENDITURE	2.559.653,42 €		3.146.452,32 €	





CIEN Foundation is aware of working in an increasingly globalized and dynamic environment, more competitive and influenced both by new technologies as well as the new demands of society. Therefore, the true differentiator and success generator in research lies in the quality and contribution of the professionals that make up your organization. From this perspective, the development of the research carried out in our Foundation is subject to their core competencies, such as personal effectiveness, leadership and management skills. Therefore, from CIEN Foundation, we care about the constant development of all our professionals, always taking into account equal opportunities.

Human resources devoted to carrying out the activities of the Foundation

The CIEN Foundation, in accordance with its policy attracting and retaining talent, has continued to focus its selective processes to recruit highly qualified staff, whose levels of technical and behavioral competencies are appropriate to the published job profiles.

All positions offered by the CIEN Foundation are defined with a specific profile, required qualifications, position requirements and functions to be performed. In addition, there have been procured by an open competition process, based on criteria of capacity, merit and publicity, having been published on CIEN Foundation, ISCIII and CIBERNED websites, honoring the principle of free competition and objectively evaluating the merits of the applicants. This procedure is in accordance with section 6.2 of ISO 9001:2008.

During 2015, CIEN Foundation has counted on a total of 58 employees, 33 of which have been hired from competitive grants, 14 are fellows, 3 in-training laboratory and anatomy technicians, 2 volunteers who have worked selflessly in the activities of the

CIEN Foundation, 1 resident Intern in training and 5 have developed their activity thanks to various cooperation agreements signed.

Are also part of the CIEN Foundation staff, the research and technical support personnel funded through CIBERNED and research collaboration agreements signed by the CIEN Foundation.

CIEN Foundation, following its commitment to young researchers and collaboration with public and private institutions participated in the program "Promoting Youth Employment and Implementation of the Youth Guarantee in R+D+i within the framework of the State Plan for Scientific and Technical Research and Innovation 2013-2016" with four contracts awarded in 2015 and one in 2016. It has also signed an agreement with the Community Madrid in collaboration with the Massachusetts Institute of Technology (MIT) within the M+VISION Project to attract international renowned researchers within the CO-FUND program from the EU Seventh framework Programme, under the FP7-PEOPLE-2011-COFUND call".

The departments comprising the CIEN Foundation in which our professionals, medical, research and management staff carry out their work with a high degree of commitment are the following:

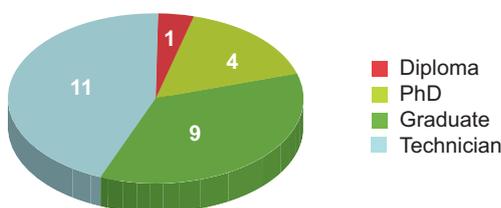
- **Department of Management and Administration**
- **Department of Neuroimaging**
- **Department of Neuropathology**
- **Department of Cell Biology Laboratory and Neuropathology**
- **Multidisciplinary Support Unit (UMA for its acronym in Spanish)**

Human resources devoted to carrying out the activities of the Foundation during 2015 are reflected in the following table:



2. MANAGEMENT REPORT

Research personnel by category



List of CIEN Foundation staff in 2015:

Research personnel by area of expertise



2.3.1 Training Program

Continuous training and updating knowledge and professional skills are configured as a training system that tries to go with workers in their capacity for personal development and career advancement. It constitutes a fundamental support for the competitive and innovative capacity of organizations based on quality human resources.

The main objective of CIEN Foundation with regards to training is to provide suitable means for the development of professional skills in order to effectively manage the challenges that each position implies.

Training is an integral part of our culture as an organization and we are aware of the need to continuously improve the knowledge and skills of our professionals.

Among the courses conducted by our staff are the following:

- SPSS application and statistical analysis
- Specialized Care in Occupational Therapy
- Administrative functions in healthcare centers
- Leadership, teamwork organization and problem solving
- Emergency Studies in Computed Tomography: skull
- Technicians and nosocomial infection

In 2015 CIEN Foundation has offered or participated in the following training activities:

Courses and events

- "V Course on Neurodegenerative Dementias". From March 9th to 13th, 2015. UIPA (Alzheimer Project Research Unit, CIEN Foundation- Queen Sofia Foundation) and UNED (Basic Psychology I Department). Madrid, Spain.
- Course on "Prevention of Occupational Hazards in MRI rooms for medical use" April 21st to 22nd, 2015. National Institute for Safety and Occupational Health, CIEN Foundation. Madrid, Spain.
- "International Day of Radiology" November 8th, 2015. CIEN Foundation, Queen Sofia Foundation and Spanish Association of Radiology Graduates (AETR). Madrid. Spain.
- Course on "Specialized Care in Occupational Therapy". Belen Frades Payo. October-December, 2015. Organised by Comisiones Obreras.

Internships

- Neuropathology internship. IES Moratalaz. Laura Sáiz Auz. From September 2014 until March 2015. Madrid, Spain.





- Neuropathology internship. Autonomous University of Madrid. Valentina González Álvarez. June-December 2015.
- PhD program. Autonomous University of Madrid. Neuropathology. M^o Dolores Arrabal Ortiz. July 2014 – June 2017. Madrid, Spain.
- Psychology end-of-Master internship. Rey Juan Carlos University. Virginia Chaves Morillo. January – March 2015. Madrid, Spain.
- Psychology end-of-Master internship. Autonomous University of Madrid. Sandra Martín Sesma. October 2015 – January 2016. Madrid, Spain.
- Psychology end-of-Master internship. University of Santiago de Compostela. Carlos M. Nieto Doval and Clara Suárez Varela. September 2014 – May 2015. Madrid, Spain.
- Neuroimaging internship. Santa Gema School. Marta Molero Carton. January – February 2015. Madrid, Spain.
- Law internship. Carlos III University. Administration-Neuropathology. Lorena Hernández de Cáceres. February – May 2015. Madrid, Spain.
- Neuropathology Residence Internship. La Paz University Hospital. Lara Sanz Irene. January – December 2015. Madrid, Spain

Postgrads studies

- End of Master studies. Alcala de Henares University. UMA. Isabel Faro Burgos. June – September 2015.
- End of degree studies. Complutense University of Madrid. Neuropatología. Rebeca Pérez Rodríguez. February – April 2015.
- End of Master studies. Apolipoprotein E4: Neuropsychological characterization and relationship with cognitive impairment. Master in Psychology Research conducted by the National University of Distance Education (UNED). Marina Ávila Villanueva. September 2015.
- PhD in Neurosciences, Complutense University of Madrid (UCM). Doctor of Psychology Degree to Miguel Angel Fernandez Blazquez with the thesis: "Study of the variables associated with

the appearance of the attentional blink". September 2015.

- End of Master studies on Physical Anthropology (Human Evolution and Biodiversity): "Dermatoglyphic Profile of Alzheimer's disease". Isabel Lighthouse Burgos. Co-directed by Meritxell Valenti and Esperanza Gutierrez Redomero. September 2015. Alcala de Henares University.

Fellowships

- MAPFRE- Queen Sofía Foundation 2015-2016. Participation in research project on neurodegenerative diseases, for a period of 6 months extended for additional 6 months. UMA. Ana Rebollo Vazquez. April 2015 - April 2016.
- Madrid-MIT +VISION Scholarship in Translational Biomedical Imaging. Neuroimaging. Christopher Long. November 2014 - November 2015.
- European Scholarship. Psychology internship. Ilaria Giovanelli, Italian student. October - December 2015.

Teaching

- Module "Professional profile of the Neuropsychologist". Master of Clinical Neuropsychology. January 2015. Higher Institute of Psychological Studies (ISEP).
- Module "Neuropsychological assessment: attention, gnosis, praxis and executive functions." Master of Clinical Neuropsychology. Taught by Miguel A. Fernandez. (UMA). February 2015. Institute for Psychological Studies (ISEP).
- Module "Neuropsychological examination, screening tests. Beyond the Mini Mental and workshop on neuropsychological examination". Course on being up-to-date in the early diagnosis of cognitive impairment. Taught by Miguel A. Fernandez (UMA). April 2015. Sanitas.
- Course "Neuropsychological assessment of brain damage". Taught by Miguel A. Fernandez. (UMA). September 2015. School of Health Sciences and Social Care, Government of Extremadura.



2. MANAGEMENT REPORT





- Module "Adapted Physical Education as an educational tool in childhood (motor behavior, neurological bases of movement)". Master course on specific needs of educational support. Taught by Miguel A. Fernandez. (UMA). November 2015. University of Vigo.

2.3.2 Prevention of Occupational Hazards

Those activities resulting from the preventive management carried out during 2015, which contributed to the successful implementation and enforcement of the plan of prevention of occupational risks established in the organization, are listed below.

In collaboration with the External Prevention Service, an annual program of preventive activities including activities such as conducting safety and monitoring visits, planning of medical examinations or adjustment of positions for particularly sensitive workers has been established.

In June the annual emergency drill with complete evacuation of the center, in which all staff members and volunteers and contributors were involved was carried out.

In relation to health surveillance, there have been 15 specific medical examinations.

The following table lists the different types of medical examinations followed by employees depending on the risks inherent to their activities, under Article 22 of the Law on Occupational Health and Safety.

Health screenings have included a work history with a detailed description of the job, the time spent on it, the risks identified in the analysis of working conditions and prevention measures, anamnesis data, clinical examination, biological control and complementary studies directed and chosen according to the risks inherent to the work performed.

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

Since its inception CIEN Foundation develops research projects focused in particular on Alzheimer's disease and related conditions. In Spain this disease affects about half a million people and is expected that, with increasing life expectancy, by 2050 this figure will double, since age is a major risk factor for dementia. It affects 10% of the population over age 65 and nearly half of those over 85.

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, pro-

Type of medical examinations	Nº of employees
ME Data Display	11
ME Biological agents – Data display	1
ME Biological agents – Data display – Strained positions- Chemicals	3



2. MANAGEMENT REPORT

moting 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 2015 are the following:

- Vallecas Project: Multidisciplinary study for early detection of Alzheimer's disease. 2015 budget: 302.320,12€.
- Alzheimer Project: 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: Budget for 2015: 914,068.99€.
- Research projects awarded under competitive calls active during 2015:
 - PI12/03018: Profile of Alzheimer's pathology associated with age (85+CIEN Study). 3-year





project funded by the Carlos III Institute of Health and led by Dr. Alberto Rábano. Budget for 2015 adds up to 4,840,00 € (project total budget: 19,965.00€).

- PT-2012-0769-010000: Design and construction of a system for the diagnosis of Alzheimer's disease based on laser raman spectroscopy (INNFACTO program). 3-year project funded by the Ministry of Economy and Competitiveness, Directorate General for Innovation and Competitiveness, led by Dr. Alberto Rábano. Budget for 2015 adds up to 17.295,00 € (project total budget: 93,320.00€).
- 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.

2.4.2 Fellowships and grants

During 2015 the CIEN Foundation has awarded the following fellowships and grants:

- MAPFRE-Queen Sofia Foundation Fellowship 2013-2015. Stay of six months, renewed for a similar period (maximum 12 months) in the Research Program in Dementia at the Alzheimer's Disease Center, University of Texas, San Antonio, supervised by Prof. George Perry, and the Case Western Reserve University, Cleveland, Ohio. Gorka Guereñu Lopetegui stay ended in January 2015.
- 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.

- PEJ-2014-C-19788. Resolution of 23 October, 2015 of the Secretary of State for Research, Development and Innovation of the Ministry of Economy and Competitiveness granting subsidies 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. The contracts signed to this effect shall have a minimum duration of two years.

2.5. Quality Policy

Quality Objectives are established annually in order to achieve continuous improvement in processes and obtaining higher levels of user satisfaction, both external and internal.

The Quality Management System is based on processes. To do so, the basic processes of the Foundation are continuously analyzed, which is a tool that allows constant improvement to meet user requirements, applicable laws and regulations, as well as optimize the resources of the Foundation.

The tools used to carry out the monitoring of the Quality Management System are:

- 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.

The quality policy of CIEN Foundation seeks to ensure and optimize processes related to: the orientation to the external and internal user, leadership, staff participation, a process-based approach, and continuous improvement.



2. MANAGEMENT REPORT

2.6. Personal Data Protection Law

CIEN Foundation has files containing personal data (including information systems, support and equipment used to treat them), of which is responsible and should be protected according to the provisions of current legislation, Organic Law 15/1999 of 13th December on the Protection of Personal Data [LOPD, for its acronym in Spanish]. These files are contained in the Security Document, as well as those involved in the treatment thereof and the premises in which they are located, Valderrebollo, 5; 28031-Madrid.

As the only responsible for the files, CIEN Foundation is committed to fulfilling its obligation of secrecy of

personal data and its duty to guard it, and to take the necessary measures to prevent alteration, loss, or unauthorized access, taking into consideration the current state of technology, ensuring compliance with the LOPD.

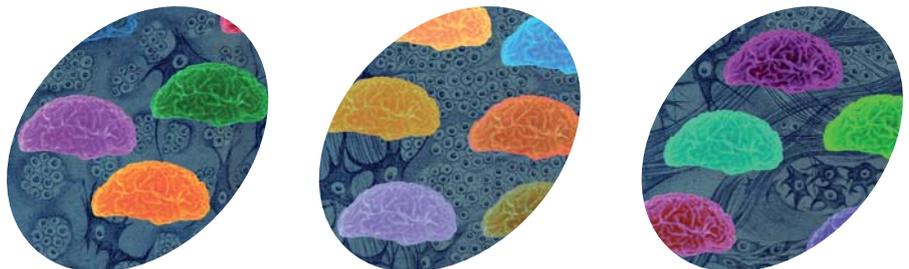


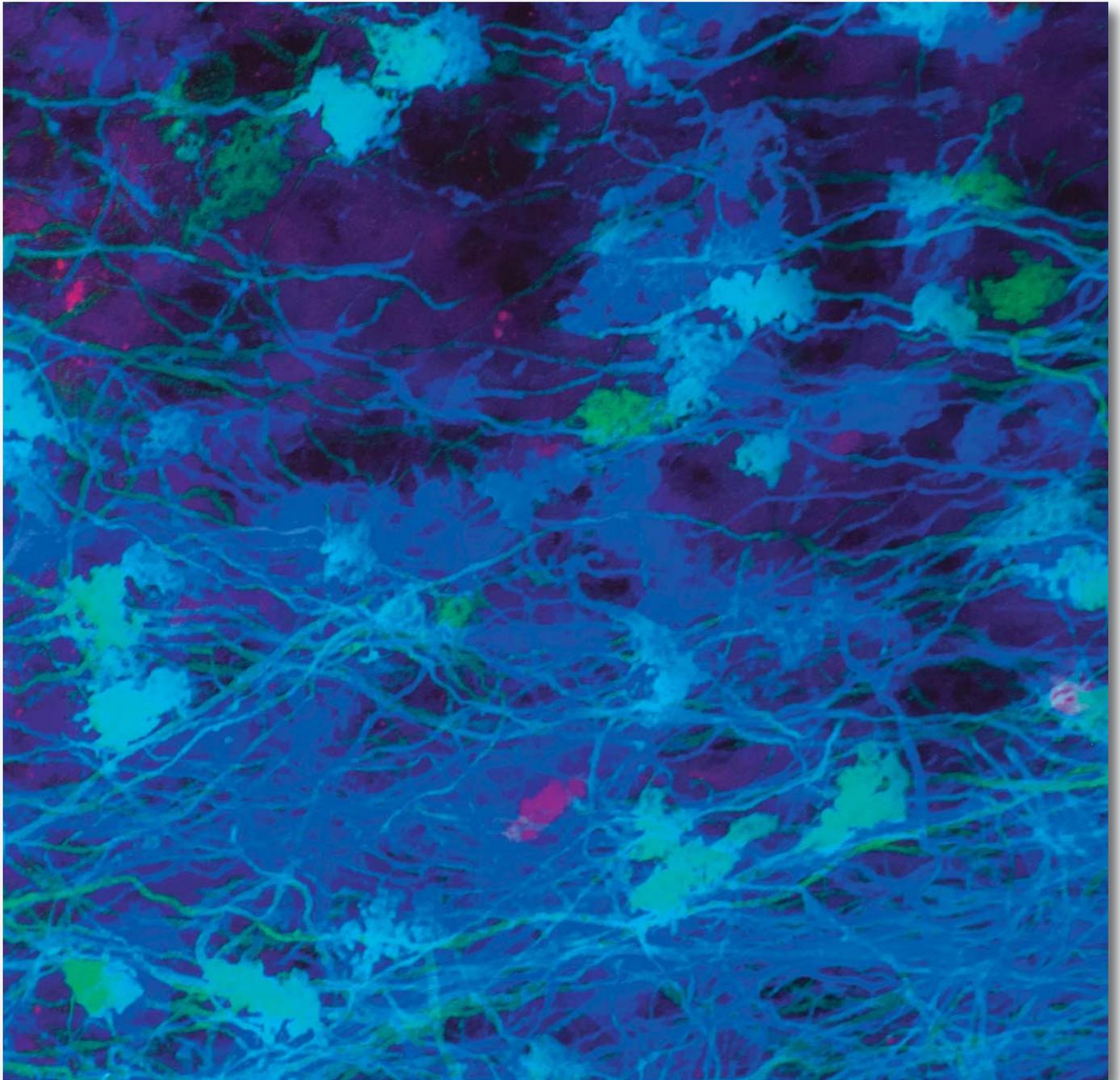
Department of Management and Administration of the CIEN Foundation - CIBERNED



Scientific activity

The UIPA consists of four departmental areas: Multidisciplinary Support Unit, Neuroimaging, Neuropathology and Laboratory. During 2015, it has continued working primarily on the Vallecas project, in addition to other research projects such as Alzheimer's Project, the 'Detection of proteins in tears as biomarkers of Alzheimer's disease' project, the '85+CIEN' Study como biomarcadores de la enfermedad de Alzheimer', el estudio '85+CIEN' or the REGISTRY international project on Huntington's disease. Moreover, the BT-CIEN has continued to increase the number of registered donors, which now exceeds 600 people.





3. SCIENTIFIC ACTIVITY

3.1. Overview

Since January 18, 2006, by virtue of an agreement signed with the Queen Sofia Foundation, the CIEN Foundation manages the Alzheimer's Project Research Unit (UIPA). The UIPA was promoted by Queen Sofia Foundation within the framework of a larger project, namely the Alzheimer Complex, located in Vallecas and consisting of a Residence for patients with Alzheimer's and related diseases, a day-care outpatient Hospital and a Teaching Unit, in addition to the Research Unit itself. The UIPA began operating in April 2007, while the healthcare activities started at full capacity during the second half of 2007.

Since then, the UIPA has set up four departments with different functions. Among others, they aim at processing and managing biological samples, studying such tissues or conducting neuroimaging research projects in the field of neurodegenerative diseases with emphasis on Alzheimer's disease and related dementias. Genetic and molecular knowledge gained from these studies have different applications: illustrate researchers into the pathogenic mechanisms of the disease, can be implemented in the diagnosis field and hopefully may lead to the development of better treatments.

However these advances, far from promising a simple solution to the problem of neurodegenerative dementias, 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.

The main feature of neurodegenerative diseases is its complexity, 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.

Result of the parallel development of both biological and clinical aspects has given rise to concepts such as translational research in medicine. This is at the core of the scientific activity at the CIEN Foundation: moving progress made in basic research to the clinical setting. This requires establishing communication links to help focus and capitalize on efforts.

3.2. Departmental Structure

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

- Multidisciplinary Support Unit (UMA)
- Department of Neuroimaging
- Department of Neuropathology
- Department of Laboratory

From the clinical aspect, Multidisciplinary Support Unit (UMA, for its acronym in Spanish) staff maintain daily contact with patients attending the Queen Sofia Foundation Alzheimer Center (CAFRS, for its acronym in Spanish) and with those people responsible for healthcare tasks of these patients as well as with the cohort of volunteers from the "Vallecas Project" (study to which we devote a full section in this report, please see Section 4). One of the UMA research lines involves conducting a clinical, syndromic, and etiologic diagnosis of patients staying at the CAFRS either in live-in regime (Life Units) or in day care (Day Center). In addition, the set of clinical data obtained will be very useful for investigations of the rest of the UIPA scientific areas.

From the basic research side, UIPA's original project contemplated the creation of departments of Laboratory; Neuropathology; and Neuroimaging. These three disciplines bring together the most promising areas in research on the biological processes involved in dementia.





UMA members are in continuous contact with these professionals, preparing and contrasting hypotheses, and carrying out research projects. Finally, UMA staff plays a mediating role between basic researchers and patients relatives and caregivers. This role is critical for patients, their relatives and caregivers getting to know UIPA's research aims, authorizing and collaborating with the various research lines.

3.2.1. Multidisciplinary Support Unit

Dementia patients care requires an accurate and early diagnosis, an assessment of the cognitive areas affected and the severity of the impairment, along with the implementation and monitoring of treatment. It is imperative that various medical disciplines become involved, due to the need of following up further evolution, the particular treatment, the observation of complications, the application of countermeasures and the associated practice of healthcare resources.

The Multidisciplinary Support Unit (UMA) was established in 2007 with a translational vocation to deepen the clinical-evolutionary knowledge of dementia. It stands as a link between basic science and clinical fields and social sciences related to health, to advance knowledge about neurodegenerative dementias and their application. It stands as a link between basic science and clinical and social

science fields related to health, to advance knowledge on neurodegenerative dementias and its application. The Unit consists of a team of specialists in Neurology, Psychiatry, Psychology and Sociology, along with the participation of geriatricians, occupational therapists, physiotherapists and social workers from the Center's healthcare area. Evaluations performed in the UMA constitute the clinical and sociological database, and in addition to its intrinsic interest for research, it gives support to the biological samples and neuroimaging data obtained systematically at the Center.

Progress in the knowledge of neurodegenerative diseases, particularly Alzheimer's disease is among UMA's priorities, from a primarily clinical perspective. The main purpose of the UMA is to advance knowledge of the degenerative diseases that cause dementia to ultimately get a better treatment for those who, directly or indirectly, suffer from these disorders.

Department activities

In addition to the large dedication of UMA professionals to the Valleca 'Project, they systematically perform a clinical, syndromic, and etiologic diagnosis of patients who are in the CAFRS, either in live-in regime (Life Units) or day care (day center). To achieve this diagnosis, UMA staff together with the people responsible for healthcare tasks keep daily

PERIODIC MULTIDISCIPLINARY ASSESSMENTS DURING 2015

Admissions in Day Centre and Residence	53
Informed Consents	35
Baseline Assessments	34
Clinical Evaluations	490
Brain MRI Studies	40
Blood testing	249



3. SCIENTIFIC ACTIVITY

close contact with the patients coming to CAFRS. Another role of UMA is the periodic monitoring of the patients progress, from a multidisciplinary perspective, with standardized contributions of Neurology, Psychiatry, Neuropsychology, Health Sociology, Occupational Therapy, Physiotherapy and geriatrics.

Reviews are conducted every six months, based on a rigorous protocol that enables continuous and sustained monitoring of each patient through checks of their quality of life, neurological status and their mental, affective and functional behavior. The objective of this process is to establish and collect variables that allow for a subsequent correlation and analysis with respect to other analytical, genetic, histopathological and neuroimaging variables.

In 2015 there were 53 admissions at Day Center and Residence, 35 of whom signed consent to participate in regular multidisciplinary evaluations. Along with the 34 baseline assessments, a total of 490 clinical evaluations (every six months), 40 brain MRI studies (annually) and 249 blood tests were performed.

Research projects

CIEF Foundation supports the use of new technologies in prevention, diagnosis, prognosis, treatment and monitoring of neurodegenerative diseases. With these and other goals, during 2014, the following research projects have conducted:

Detection of proteins in the tear as biomarkers of Alzheimer's disease

Currently, many researchers believe that both the development of amyloid plaques, and the formation of neurofibrillary tangles (NFT) are relatively late events in the course of the disease, which may or may not reflect the fundamental biochemical-molecular dysfunctions that give rise to the disease. This assumption, increasingly accepted, suggests that

the disease has an important systemic component that manifests with peripheral alterations years before symptoms appear. Considering that future potential therapies have to be implemented in very early stages of the disease where clinical diagnosis accuracy decreases, and currently accepted biomarkers (tau, tau and p-A τ 42) require CSF collection, many research groups are focusing their interest in the search for biomarkers of disease in accessible tissues and fluids such as blood or saliva.

The eye is a structure that is highly innervated by the sympathetic and parasympathetic nervous system. In particular by the parasympathetic nervous system, via the neurotransmitter acetylcholine, controls numerous processes such as tear secretion, pupil diameter or intraocular pressure (Pintor, 2009).

The parasympathetic nerve terminals, coming from the ciliary ganglion, stimulate the main lacrimal gland through the M1 and M3 muscarinic receptors, and as a consequence acetylcholine favors the production of the aqueous component of the tear secretion as well as proteins that are part of this (Dartt, 2009).

Therefore, it is hypothesized that AD biomarkers, such as Tau protein, which has been modified the activity of muscarinic acetylcholine receptors in laboratory animals (Gómez-Ramos et al., 2009 Martínez-Eagle et al. 2014), may also be present in human tears and the same could happen with other AD-related protein markers such as 14.3.3 (Sluchanko NN, 2011, HY Qureshi, 2013), β -amyloid 40 and 42 (Van Setten, 1996) or some proinflammatory cytokines (Benito MJ, 2014, VanDerMeid KR, 2011), among others.

The objectives of the project are:

- Recruitment, characterization and classification of the participants in the project through a comprehensive neurological and





neuropsychological evaluation to know the clinical and cognitive profile of the participants.

- After signing informed consent, sampling of tears (Schirmer technique) in participants (individuals with no cognitive impairment, patients with mild cognitive impairment and patients diagnosed with mild Alzheimer disease - Reisberg stages GDS 3 and 4).
- Determination in the laboratory of the biomarkers.
- Comparison of the results from the three study groups.
- And developing a database to harbor all associated patient information / controls and samples.

All this in order to find biomarkers related to AD that allow us to make the diagnosis of the disease and to elucidate its evolution and prognosis.

Recruitments of participants begun in 2014 and finished during 2015. It involves the Association of Relatives of Alzheimer's patients and other dementias at Soria, Leon Alzheimer's Association, CIEN Foundation and Center of Molecular Biology Severo Ochoa. About 100 samples have been collected in total, which will be analyzed at the Center for Molecular Biology Severo Ochoa throughout 2016.

Among the activities in the area of Neuropsychiatry of UMA are included the following:

IDEAL Scale

Participation in "Validation of the IDEAL Scale in Spanish population: a multicenter study in patients with dementia." The study attempts to validate in Spain a scale that values multiple dimensions of dementia. The aim is to better detect the different needs of care for patients with dementia. It is known that different patients with dementia have different needs, but there are currently no adequate screening me-

thods that meet all these needs. Information from 20 patients attending the Alzheimer Day Centre Foundation Reina Sofia Center (CAFRS) with their informed consent available has been gathered for this study. Clinical information was obtained both through interviews with family members as well as with the application of different existing validated scales that assess behavioral and psychological symptoms of dementia (BPSD), caregiver burden, functionality and overall cognition.

Personality in dementia

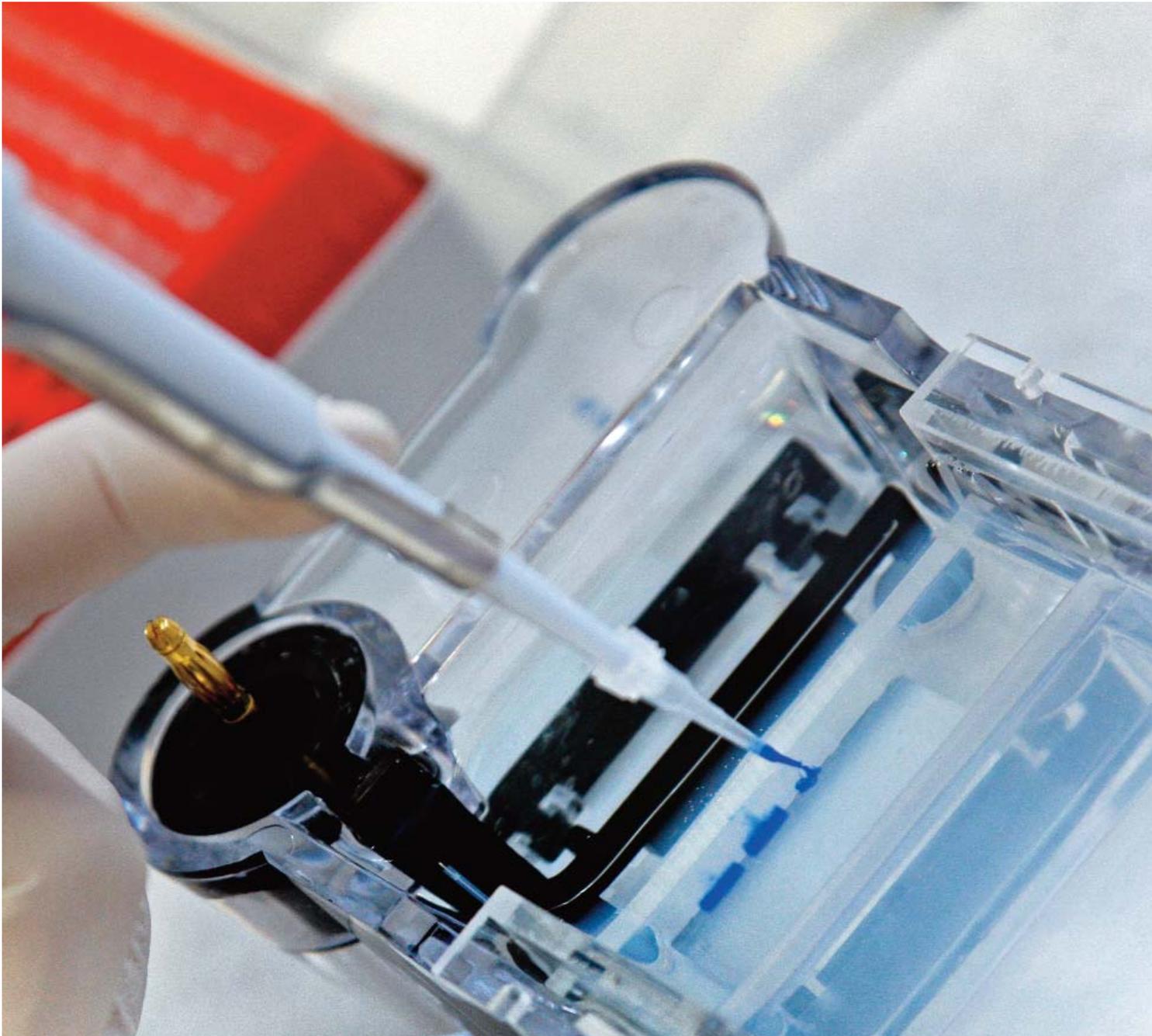
This research line attempts to relate the previous personality of the patient with the development of different BPSD or other cognitive symptoms in dementia. For years, during the initial evaluation of patients it was included the performance by the reference family of the NEO-FFI inventory. This year the Hetero-anamnesis Questionnaire of Personality (PAH, in its original Dutch version) has been included after its translation to Spanish. The goals of this research are the validation of this scale in Spain, its comparison with the results obtained in the inventory NEO-FFI and its correlation with clinical data of the patients under study.

Longitudinal study of CAFRS patients

It consists of gathering information every other year from all patients at Day Care Centre and the Residence who have provided consent to perform the evaluation tests. There is a longer yearly assessment held in the first half of the year, and a shorter assessment in the second half. In patients from Residence information is gathered through the reports of the coordinators of the CAFRS Life Units. In the semester information is collected on the following tests: Neuropsychiatry Inventory (NPI), Cornell Scale for Depression in Dementia, Cohen-Mansfield Agitation Scale in Dementia (CMAI), Apathy Inventory (IA), and NH APADEM Apathy Scale. In the second se-



3. SCIENTIFIC ACTIVITY





mester information is collected on NPI, IA and APA-DEM-NH. Information from Day Center patients is gathered through telephone interviews with relatives of reference. In the first semester information is collected on NPI, Cornell Scale for Depression in Dementia, CMAI and IA; In the second semester information is collected on NPI and IA.

This systematic data collection since the patient becomes part of the study until either is transferred to another Day Center or the patient dies, along with systematic information collected at neurological, neuropsychological and functional level allow the creation of a clinical database that can be exploited by themselves or in combination with neuroimaging and/or neuropathology data.

Project REGISTRY

REGISTRY is an international multicenter observational study conducted by the European Group on Huntington's disease (EHDN, for its acronym in Spanish) with the following objectives:

- Obtain data from the natural history of the disease in a large spectrum of people affected by Huntington's Disease (HD).
- Develop new measurement instruments to monitor or predict the onset and progression of the disease as well as improve existing tools.
- Determine how the environmental and genetic factors influence both the onset of symptoms and progression of the disease and determine the family variability of these factors.
- Accelerate the identification and inclusion of participants in clinical trials.
- Planning future observational or interventional research studies aimed at better control symptoms and delay the disease onset or slow the progression of Huntington's disease.

The strength of the REGISTRY study lies in its collaborative nature. We can all participate: subjects with genetic mutation and symptoms, subjects with the genetic mutation without symptoms, subjects descended from a family with a history but they ignore whether they have the mutation, subjects descended from a family with a history but have a negative genetic study, subjects who are not descended from a family with affected people... Starting from the information gathered, a large database of biological and clinical data (blood and urine) will be created to enable:

- Better understand the natural progression of Huntington's disease and the factors involved, besides the Huntington gene, at its onset, presentation and progression.
- Identifying disease modifiers at the genetic, biological and environmental level.
- Identify more accurate and reliable HD biomarkers.
- Review the drugs used in the management of symptoms of HD.
- Assessing co-morbidities with HD.
- Study the less frequent types of Huntington disease (as juvenile EH).
- For many people it is a chance to participate in future clinical trials and intervention studies.

REGISTRY is being carried out in 173 centers from 20 European countries and has already registered more than 12,000 subjects. Among these centers is the CIEN Foundation, where 33 participants were registered during 2014.

Since the second half of 2015, REGISTRY is gradually transitioning to ENROLL-HD, a prospective registry study of a global cohort with HD (Europe, USA, Canada, Argentina, Chile and others).



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Team

The UMA team is composed of the following professionals with multidisciplinary expertise:

Area of Neurology

- Teodoro del Ser Quijano (Dr. Medicine, Neurology). Coordinator of Neurology. Collaborator.
- María Ascensión Zea Sevilla (Dr. Medicine, Neurology).
- Meritxell Valentí Soler (Grad. Medicine, Neurology).
- Javier Olazarán Rodríguez (Dr. Medicine, Neurology) (until April 2015).

Area of Psychiatry

- Jorge López Álvarez (Grad. Medicine, Psychiatry) (until June 2015).

Area of Neuropsychology

- Miguel Ángel Fernández Blázquez (Dr. Psychology, Neuropsychology) Coordinator of Neuropsychology Neuropsicología.
- Marina Ávila Villanueva (Grad. Psychology, Neuropsychology).
- Belén Frades Payo (Grad. Psychology, Neuropsychology).
- Ana Rebollo Vázquez (Grad. Psychology, Neuropsychology) (Since April 2015).
- María García Otero (Grad. Psychology, Neuropsychology) (since December 2015).

UMA Administration

- Francisca Martínez Lois (Administrative Assistant).



3. SCIENTIFIC ACTIVITY

Collaborators

The following CAFRS staff also collaborated during 2015:

- Irene Rodríguez Pérez (Occupational therapist).
- Almudena Pérez (Occupational therapist).
- Inmaculada Barrero Rodríguez (Occupational therapist, Day Center).
- Cynthia Pérez Muñano (Technician in training and Occupational therapist).
- Emma Osa Ruiz (Physiotherapist).
- Álvaro Sanabria Luque (Physiotherapist, Residence).
- Carolina Mendoza Rebolledo (Grad. Psychology, Neuropsychology).
- Gema Melcón Borrego (Social worker).
- Lidia Espada Raboso (Social worker).
- Belén González Lahera (Grad. Medicine, Geriatrics).
- Rubén Díaz Campos (Physiotherapist, Day Center) (until September 2015).
- Irene Gamarro García (Physiotherapist, Day Center) (since September de 2015).



UMA's team





3.2.2. 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 2015 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.
- **"Clozapine in early outbreaks of schizophrenia as potential preventive treatment from brain**

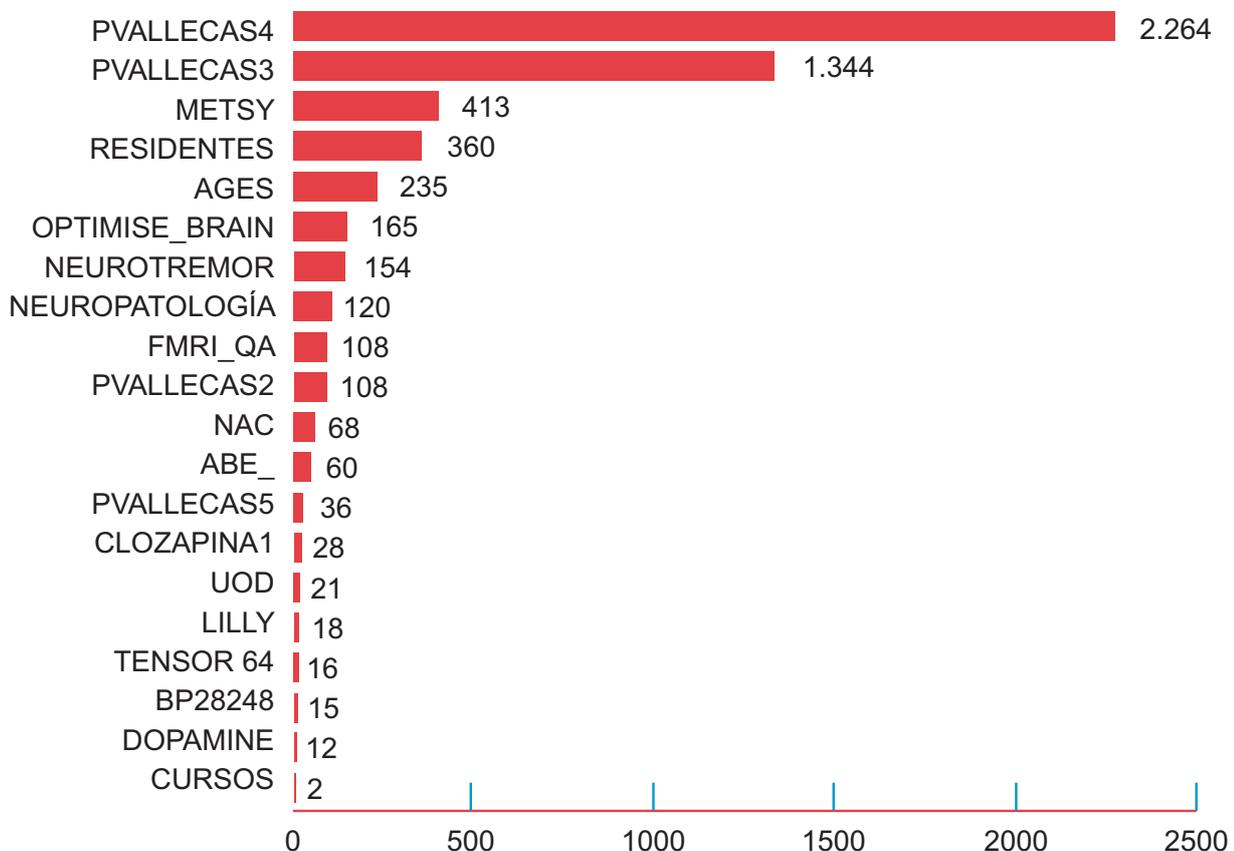


3. SCIENTIFIC ACTIVITY

and clinical impairment". Reference protocol: CLOZAPINE-1, N° EudraCT: 2006-00200-34. PI: Dr. Francisco Javier Sanz Fuentenebro. 2010-2013. 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 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 Maranon Hospital. PI: Celso Arango.

Number of studies by project 2015





- **"BP28248"** A Phase III, multicenter, randomized, double-blind, parallel group, placebo-controlled trial to investigate the safety and efficacy of RO4602522 added to background therapy with acetylcholinesterase inhibitors, donepezil or rivastigmine in patients with moderate Alzheimer's Disease". Protocol N° BP 28248, Promoter F. Hoffmann-La Roche Ltd.

During 2015 the acquisition of MR images from a total of 963 subjects has been completed. Overall, 5,744 MRI studies have been performed distributed among the different research projects.

A total of 43,864 MRI sequences have been conducted since the creation of the department, distributed by year and type of sequence.

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 and FSL.

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).
- Dr. Christopher Long (PhD, Engineering, Specialist in Biomechanical Imaging, Madrid-Massachusetts Institute of Technology Vision Program).
- Eva Dueñas Moreno (BSc, Biology). Since December 2015.
- María Molina Matas (BSc, Physics). Since December 2015.

Radiodiagnostics

- Mabel Torres Llacsá (MD, Radiodiagnostics).

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).



3. SCIENTIFIC ACTIVITY

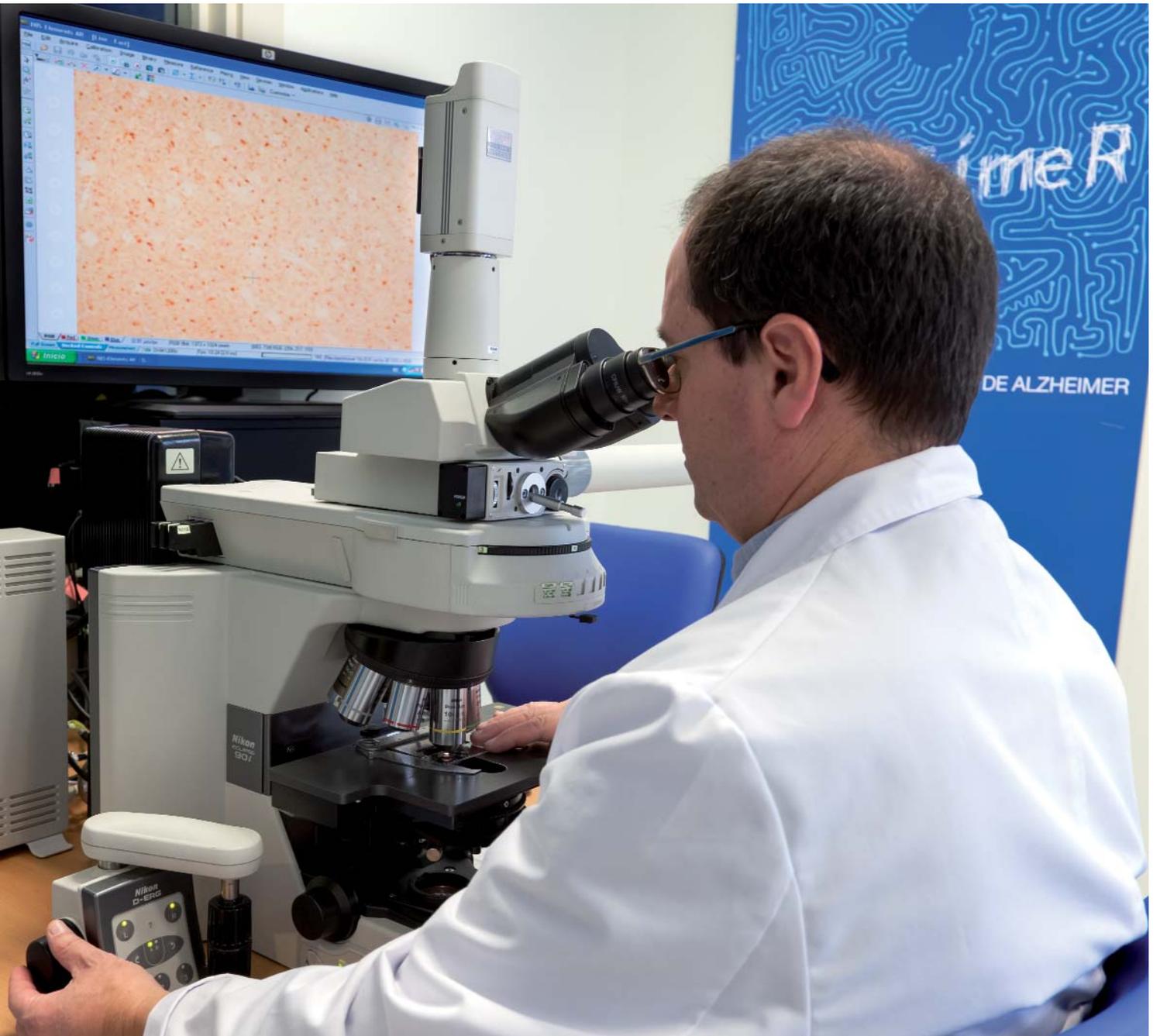
Other Collaborators

- Roberto García Álvarez (PhD, Physics).
- Emily R. Lindemer (PhD Student, Laboratory for Computational Neuroimaging Harvard-MIT Division of Health Sciences & Technology).



Neuroimaging team





3. SCIENTIFIC ACTIVITY

3.2.3. Department of Neuropathology

Neuropathology is a specialty in continuous progress with capacity for contrasting clinical judgment and performance of any diagnostic test with the final diagnosis ("gold standard"). However, research-wise their work goes beyond that and provides essential information about the molecular components of the characteristic lesions, the pathogenic mechanisms of the disease, and potential biomarkers, especially in the field of neurodegenerative diseases.

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.).

Also, the definition of diagnostic criteria from large series of brains has allowed to address 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 diagnosis 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 pre-

served. This need can be met by the brain banks, and CIEN Foundation has one of the major brain banks in the country, the Tissue Bank CIEN (BT-CIEN).

Neuropathology also provides significant support to the 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 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 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 cerebral small vessel vascular disease.
- Distinctive features of Alzheimer-type pathology in nonagenarians and centenarians.
- Characterization and pathogenic study of dementia-associated hippocampal sclerosis.
- Advance age-associated brain pathology in other animal species. Search for natural models of Alzheimer in primates and other mammalian groups.





Among the funded research projects in this area the following can be highlighted:

- Age-associated Alzheimer's pathology profile (The 85+CIEN Study). Project funded by FIS, 2013-2015.

The segment of population over 85 years is the one with the highest relative growth in recent decades and will increase even more in the next, especially in Spain, which will become the country with the oldest population in the European Union. Several controversies have focused in recent years the study of dementia and healthy cognitive profile in these population group. Overall, clinical and pathological studies suggest that Alzheimer's disease shows specific clinical, neuropathological and genetic beyond age 85, with greater involvement of vascular pathology and similar phenomena are observed in other neurodegenerative disorders (synucleinopathies, tauopathies). This project aims to address this set of issues in a large series of post-mortem brains from donations to four biobanks from three Spanish Regions. More than 500 brains with associated basic clinical information, and in a proportion of cases (75 estimated cases) with detailed cognitive data from their last year of life, will be studied. Clinical, neuropathological, neuropsychological gathered will be analyzed according to the main diagnostic groups, associated pathologies, observed stages in the different diseases and age groups at death and at disease onset. Clinical-pathological correlation of findings in relation to dementia in the subgroup of cases with cognitive tracking information will be analyzed. Results will provide a neuropathological and clinical-pathological profile of cognitive disorders observed in tissue donors, particularly in cases of the oldest-old.

The Department also participates in the project below, funded by BBVA Foundation:

- Complete genome analysis of 'splice' variants in Huntington's disease. Principal Investigator: José Javier Lucas Lozano (Centro de Biología Molecular "Severo Ochoa", CSIC).

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.

- Neuropathological autopsies of donors brain tissue, from both the Region of Madrid, as neighboring Regions.
- Management of a biobank of neurological samples. Transfer of samples to researchers according to the BT-CIEN standard operating protocols.
- Diagnostic consultations of neuropathological cases. Among the external consultations those made in support of other neurological samples biobanks (Murcia, Salamanca and Cordoba) can be highlighted.
- Performing neurohistological and immunohistochemical techniques in neurological samples of human and experimental origin.
- Evaluation of new antibodies in human brain tissue.
- Collaboration in research projects from other institutions

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.



3. SCIENTIFIC ACTIVITY

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).

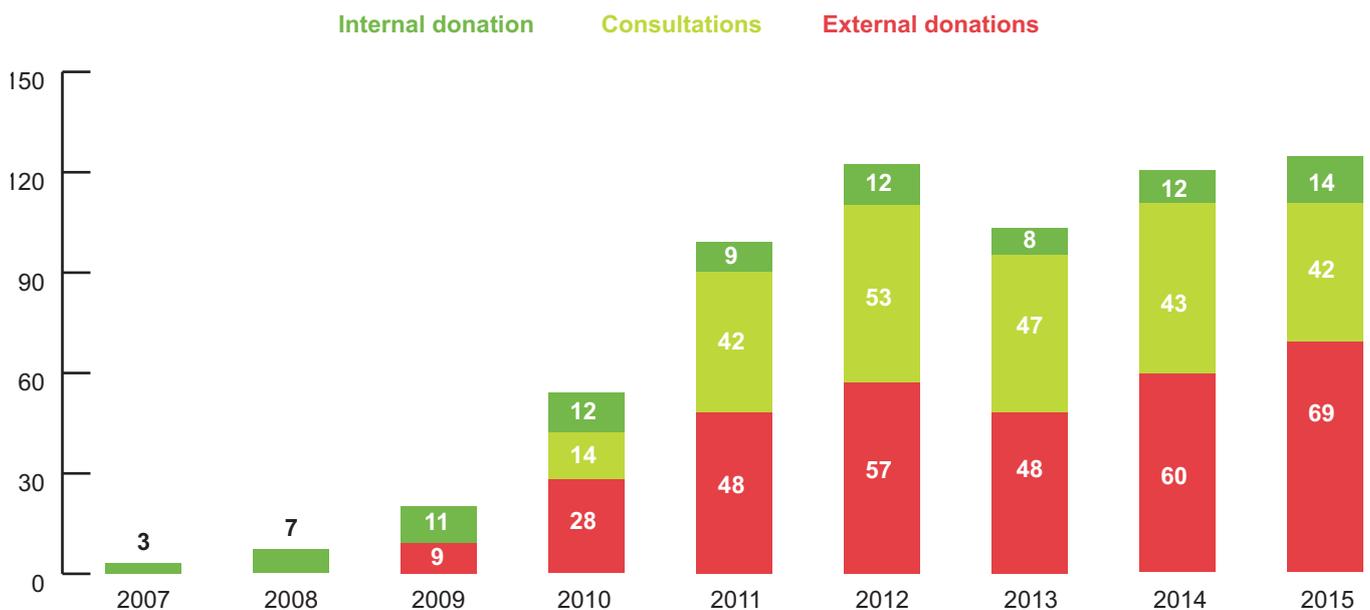
One of the missions of BT-CIEN is to promote the creation of new neurological samples biobanks whenever they are demanded by donors and researchers. The Region of Murcia Brain Bank (BCRM), the Neurological Tissue Bank from the Insti-

tute of Neuroscience of Castilla y León (BTN-CyL) and the of Queen Sofia University Hospital Biobank from Cordoba are active examples of this commitment.

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

In January 2014 the Biobanks National Network Platform (PRNBB, for its acronym in Spanish), promoted and funded by the Carlos III Institute of Health (2014-2017) was constituted, with participation of the main biobanks in the country, both hospital and non-hospital, including BT-CIEN. PRNBB mission is to create a stable organizational structure that allows the coor-

Distribution of donation cases by origin in 2015





minated activity of participating biobanks in the collection, management and transfer of biological samples of human origin. Moreover, the BT-CIEN has renewed its ISO 9001/2008 quality certification.

The BT-CIEN registry had over 600 registered donors by December 31, 2015.

125 cases were processed in the Neuropathology laboratory during 2015, with the following distribution depending on the origin:

- 69 donations from the External Program.
- 14 donations from the Internal Program.
- 42 consultation cases.

Hence, the number of donation cases extracted and processed entirely at the UIPA during 2015 went up to 83. It is thus observed a stabilization of the number of studied cases at the BT-CIEN around 120, and donations extracted in the BT-CIEN in the range of 60-75 per year, with an upward trend.

In 2015 the average post-mortem interval obtained is six hours, slightly longer than the average of previous years, mainly due to the higher rate of external donations coming from different Regions.

The research centers that have received samples from BT-CIEN during 2015 have been:

- Karolinska Institute, Stockholm, Sweden.
- National Center of Microbiology, ISCIII, Madrid.
- Center for Molecular Biology "Severo Ochoa", CSIC, Madrid.
- Center of Biomedical Technology, Technical University, Madrid.
- Faculty of Medicine, University of Castilla-La Mancha, Ciudad Real.
- Institute of Neurobiology Ramón y Cajal, CSIC, Madrid.

- Institute of Research in Health Sciences Germans Trias i Pujol, Badalona.
- CEU San Pablo University, Madrid.
- Institute of Neuroscience, Autonomous University of Barcelona.
- Príncipe Felipe Research Center, Valencia.

By the end of 2015, the accumulated number of the BT-CIEN donations was 405, of which about 50% are cases of Alzheimer-type pathology.

Team

During 2015, the Department of Neuropathology staff was composed of the following professionals:

- Dr. Alberto Rábano (Grad. Medicine, Pathology), Head of Department and BT-CIEN.
- Elena Gómez Blázquez (Pathology Technician).
- Izaskun Rodal González (Pathology Technician).
- Mario Lozano Enguita (Pathology Technician). Since December 2015.

Collaborators (autopsies):

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



3. SCIENTIFIC ACTIVITY



Neuropathology team





3.2.4. Department of Laboratory

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.

Neuritic plaques contain extracellular deposits of β -amyloid peptide surrounded by dystrophic neurites, activated microglia and reactive astrocytes. These peptides derive from the β -amyloid precursor protein (APP) through the sequential processing by different proteolytic complexes called β and γ -secretases.

Neurofibrillary tangles (NFT) are intraneuronal bodies composed of paired and helically wound filaments (paired helical filaments, PHF) of a hyperphosphorylated form of the microtubule-associated protein, tau. The NFT appear in many of the dystrophic neurons around amyloid plaques. 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.

Department activities

The Department of Laboratory is focused on the study of biomarkers and susceptibility genes for Alzheimer's disease. This study has the following primary objectives: to gain further insight into the molecular basis of the disease and to develop predictive algorithms that combine information on genetic, biochemical and neuroimaging markers with diagnostic, prognostic or responsive to disease-modifying therapies markers.

For this purpose, the Department's research is connected with the activities of the Multidisciplinary Support 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 Alzheimer project and the Vallecas project.

Because of its location in the CAFRS, the UIPA is best placed for obtaining biological samples from patients with minimal discomfort for them and their families.

The Alzheimer Project

The Alzheimer Project 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. Patients are recruited into the monitoring program after signing an Informed Consent by a family member or guardian. 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.



3. SCIENTIFIC ACTIVITY

The CAFRS takes care of 156 patients in residence, and 40 patients in the Day Centre.

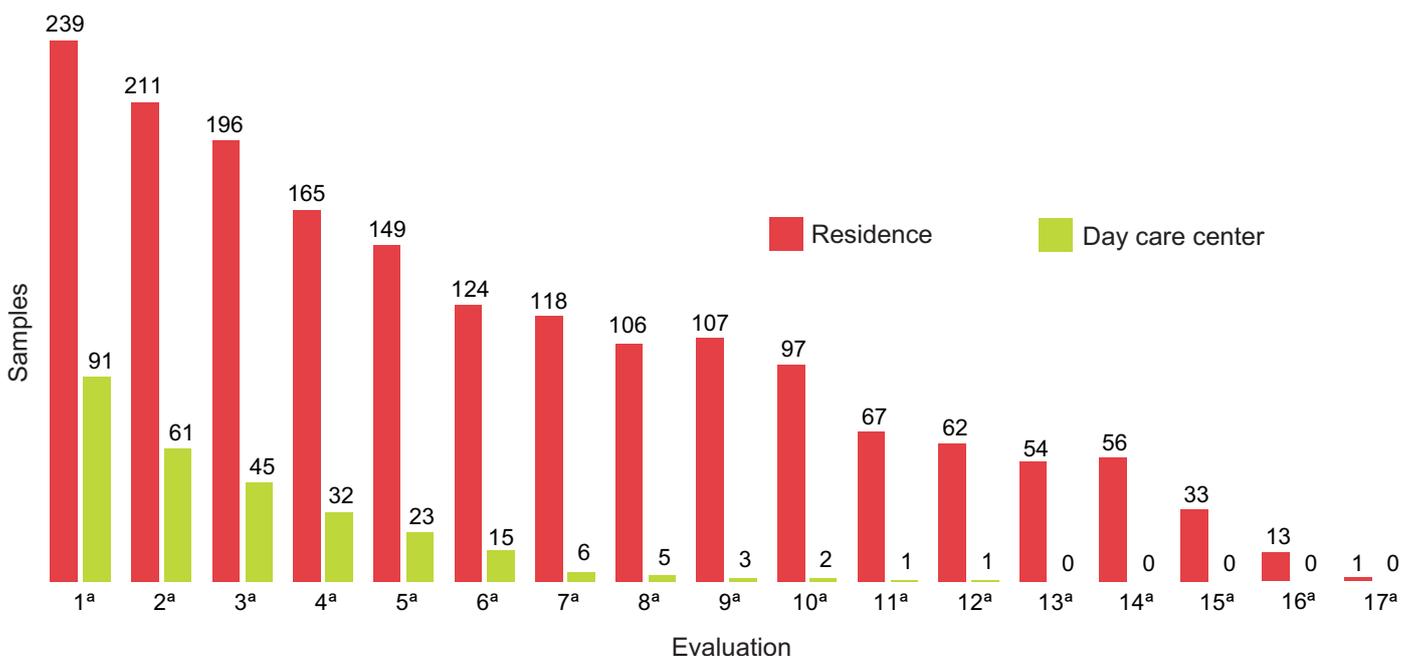
The Alzheimer project monitoring program includes obtaining a blood sample biannually coinciding with the one routinely performed at the Center for conventional analytics. Thus, performing a venipuncture in the patient for research purposes only is avoided. After extraction, each blood sample is processed 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-

ocols 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 2,084 (13.7% patients corresponding to the Day Centre), which have resulted in a total of 29,176 aliquots.

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

Samples obtained up to December 31, 2015 according to the number of semiannual evaluations





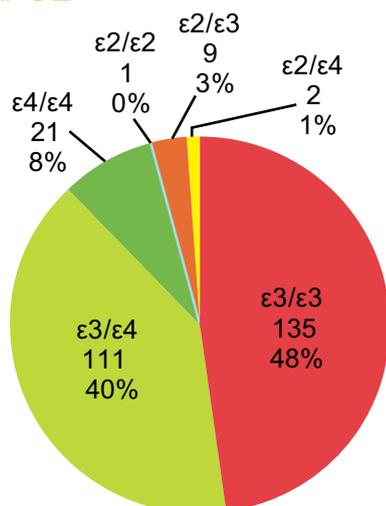
The Vallecas Project

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 an 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.

Distribution of APOE genotypes in the CAFRS patients cohort

Genotypes APOE



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 2015 we have studied 22 volunteers to complete the second follow-up study, 245 volunteers on the third visit, 445 on the fourth visit, and 5 from the third 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 department of laboratory, the Vallecas Project activity in figures is shown in the attached table.

Primary aliquots in duplicate are collected for the following fractions:

- 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



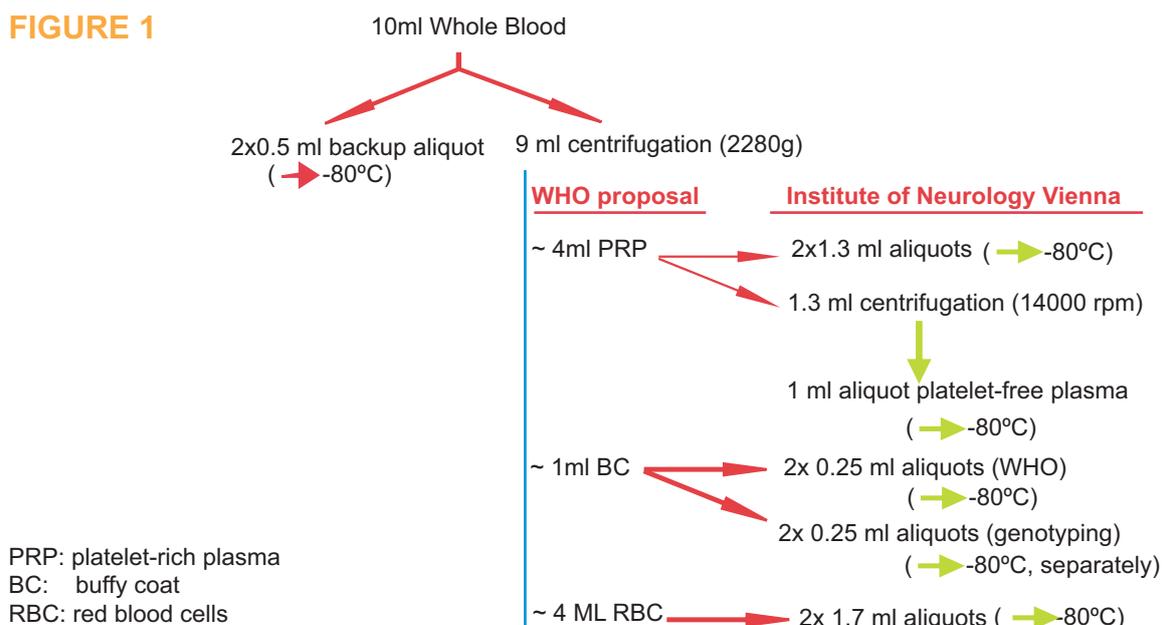
3. SCIENTIFIC ACTIVITY

The Vallecas Project activity in figures

Evaluation	1°	2°	3°	4°	5°	TOTAL
Samples	1.169	829	577	15	0	2.633
2015 samples	0	22	245	441	5	757
Total	1.169	851	822	456	5	3.390
Aliquots	16.366	11.914	11.508	6.384	70	47.460

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

FIGURE 1





comparison of the frequency of APOE allele $\epsilon 4$ carriers between CAFRS patients and 'Vallecas Project' volunteers confirms the risk to suffer from Alzheimer's disease with an OR = 4.2 ($p < 0.01$). Also, in order to define different subpopulations of genetic risk, other possible genetic susceptibility genes have also been analyzed in a subset of participants (see below).

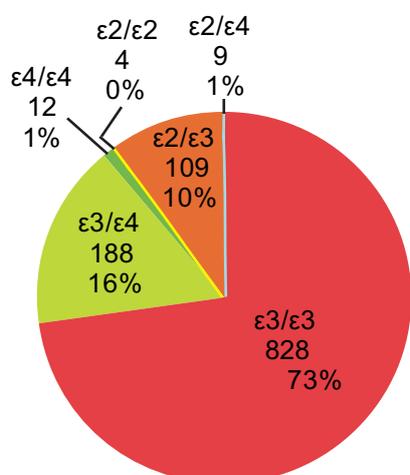
It is also important to emphasize that the samples obtained from Vallecas Project volunteers aged between 70 and 85 years that include a comprehensive assessment of cognitive, sociological and neuroimaging state are optimal for its use as a control population in various projects related to neurodegenerative 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. In this sense, we are currently working on three different research projects based on the joint use of biochemical markers and genetic data to define endophenotypes. Specifically, funding has been obtained for the following research lines:

- Vascular dysfunction associated with Alzheimer's disease (FIS project).
- Diagnosis of rapidly progressive dementia based on biomarkers (EU Joint Programme – Neurodegenerative Disease Research).
- Development of diagnostic tools for Alzheimer's disease (R&D&i grant, INNPACTO program).
- Epigenetic mechanisms involved in the etiology and progression of rapidly progressive neurodegenerative dementias (CIBERNED cooperative project).

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

Genotypes APOE



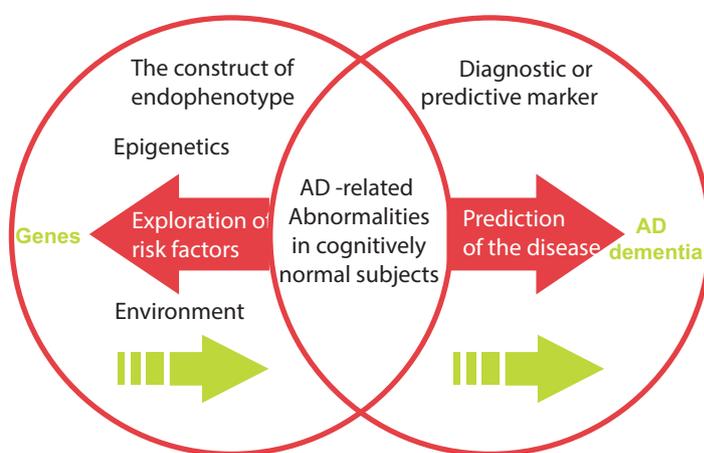
Also during this year, CIEN Foundation has joined the Dementia Genetics Spanish Consortium (DEGESCO), in which several Spanish groups bring together genetic data for achieve greater power in genetic studies on dementia and especially Alzheimer's disease. As a result of this collaboration, an interesting study on the association of the MAPT H1 haplotype gene APOE allele non-carriers $\epsilon 4$ has been published.

Besides the study on the APOE gene, using samples from the Vallecas Project (controls) and the Alzheimer Project (AD cases), it have been conducted genetic association studies of key AD-associated genes including SORL1, LDLR, BIN1, CLU, ABCA7, CR1, PICALM, BACE1 and PRNP. These association studies, in addition to serving to reproduce in a Spanish population studies conducted in other populations, enable us to determine the most important genetic factors in the development of cognitive dysfunction in our Vallecas Project cohort and define endophenotypes based on genetic variations and specific, measurable features of patients and controls based



3. SCIENTIFIC ACTIVITY

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



on clinical, neuroimaging, biochemical or pathological outcomes (see Figure below).

Designing and building of a Raman laser spectroscopy-based system for diagnosing (INNFACTO Program)

This project represents a technological development plan and implementation of an innovative diagnosis system for Alzheimer's disease. It is led by Biocross SL and supported by a consortium of researchers from various scientific institutions such as the CSIC and CIEN Foundation.

The project's starting point previous is the work of a research team consisting of researchers from CSIC (Institute of Structure of the Matter and Cajal Institute), CIEN Foundation, the Carlos III Institute of Health and 12 de Octubre Hospital in Madrid. These

studies demonstrated the potential usefulness of blood analysis using spectroscopic techniques (which are not normally used in the in vitro diagnostics) to distinguish samples from AD patients and control samples (cognitively healthy). According to this previous study, it has been determined that approximately 9% proteins in control population have beta structure versus 14% in AD patients. This change reflected in the spectroscopic properties of samples allowed to classify the samples from cases and controls with an accuracy approaching 90%.

The project is organized into two main integrated and complementary lines, whose main goals are:

- Validate Raman laser spectroscopy-based technology to detect Alzheimer's disease (AD) in blood samples.





3. SCIENTIFIC ACTIVITY

- Develop a new "ultra-compact" Raman-laser technology equipment, specifically designed for marketing in vitro diagnostics (clinical analysis laboratories, hospitals, etc.).

The combination of a new system (with unique features by leveraging the know-how of previous developments in the field of the aerospace industry) along with the validation of Raman-laser spectroscopy-based diagnostic markers represents an opportunity to enter a solution in the market for innovative diagnostics and clearly differentiated from the competition.

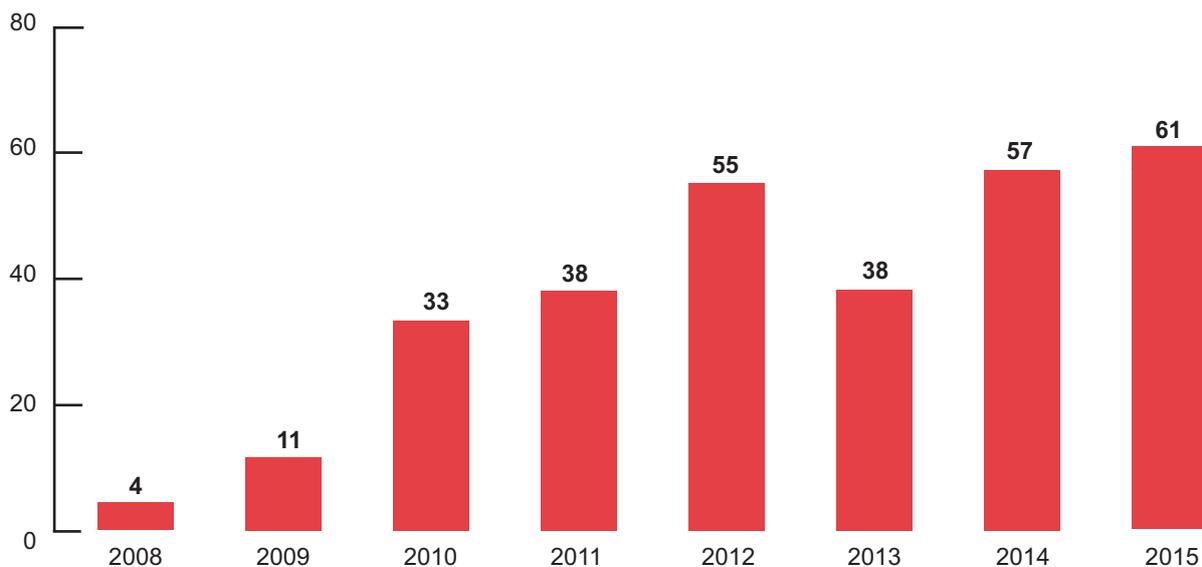
This project builds on the Biocross's and CIEN Foundation's experience in developing biomarkers for the diagnosis of Alzheimer's disease. This innovative project will create a multidisciplinary platform where companies and research centers join together, allo-

wing the development of a diagnostic system for a socially very relevant disease like Alzheimer's.

In connection with the study of biomarkers and the collaborative context with Biocross as well as various Spanish hospitals, this year we have published an important metabolomic study in plasma of people with Alzheimer's disease, mild cognitive impairment, or with no cognitive dysfunction. The obtained results show the possibility of classifying cases and controls through a blood sample with high accuracy, even at early stages of the disease. These results are now in the process of validation in a larger multicenter and international cohort.

Within the framework of CIBERNED cooperative project SIGNAL led by Dr. Alberto Lleó, this year we have also published a paper in which we have been able to identify new AD markers, and to suggest that in-

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





Inflammation in the central nervous system increases with normal aging, and signs of inflammation can be detected in preclinical stages of Alzheimer's disease long before the first symptoms appear.

Contribution to the 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 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 160 CSF samples from donor's brain.

Team

During 2015, the team of the Laboratory Department was composed of the following personnel:

- Miguel Calero Lara (PhD, Chemistry), Head of Department.
- Olga Calero Rueda (PhD, Biology).
- Ana Belén Pastor López (Laboratory Technician).
- Alicia Jalvo Sánchez (Laboratory Technician). Since november 2014.
- Juana San Emeterio Mardomingo (Laboratory Technician). April-November 2015.
- Andrés Rodríguez Martín (Laboratory Technician, CIEN Foundation-Biocross).



3. SCIENTIFIC ACTIVITY

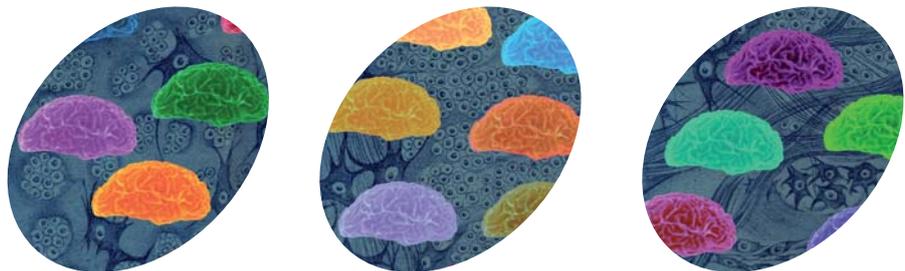


Lab team



The Vallecas Project

During 2015, the 'Vallecas Project' has brought numerous new features, surpassing the half way point of the study. The second, third, fourth or fifth visit, as appropriate for each specific case, of the 1,213 volunteers enrolled in this project have been carried out, focusing on the early diagnosis of Alzheimer's Disease. In addition, the work performed by our researchers has already begun to translate into scientific publications, which is expected to continue during 2016.





4. 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. As a result 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 impact on his/her family and social environment with regards to 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 which 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 safely predict 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 eventually determine 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.

A total of 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, a total of 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 2015, we are at the end of the third visit for the entire cohort and about the middle of the fourth visit (see figure in section 1.3 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. 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:

- Vascular risk factors: blood pressure, diabetes mellitus, smoking, heart disease, stroke.

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%)





- 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 assessment protocol was designed in order to comprehensively assess neuropsychological functioning of study participants. Starting from the application of different measuring instruments (screening and cognitive assessment tests, scales and questionnaires) information is collected from both the global neuropsychological functioning and the specific cognitive processes, especially in information processing speed, attention, episodic memory, procedural learning, language, visuoconstruction and executive functions. Furthermore, neuropsychologi-

cal assessment is completed by a self-reported subjective memory complaints, a scale to assess the performance of instrumental activities of daily living and other scales to assess anxiety and depression symptoms.

Mini Mental State Examination (MMSE)

This is a test of global cognitive assessment. It consists of 20 items that gather a rough information on the level of orientation, attachment, attention, calculation, recall, language and viso-constructive praxis of the subject. The score for this test is made over a maximum of 30 points to the extent that all items are answered correctly. Cognitive impairment diagnosis is performed based on a score of 24 points as the cutoff.

Memory Complaints Scale (UIPA)

This scale is based on a self-reported test comprising 11 items to assess memory complaints from study participants.

Functional Activities Questionnaire (FAQ)

It is a classic questionnaire to assess autonomously performing of instrumental activities of daily living. The questionnaire should be answered by a reliable informant. It consists of 11 items with 4 response options to assess the degree of dependence or independence of the subject in different daily tasks (managing finances, shopping, doing housework, preparing meals, pay attention and discuss news, remembering dates, managing medication or going out alone on the street). The diagnosis of Alzheimer disease occurs from a score of 6 as the cutoff point.

Rey complex figure test

Is a classic neuropsychological evaluation task consisting in performing a copy of a complex pattern

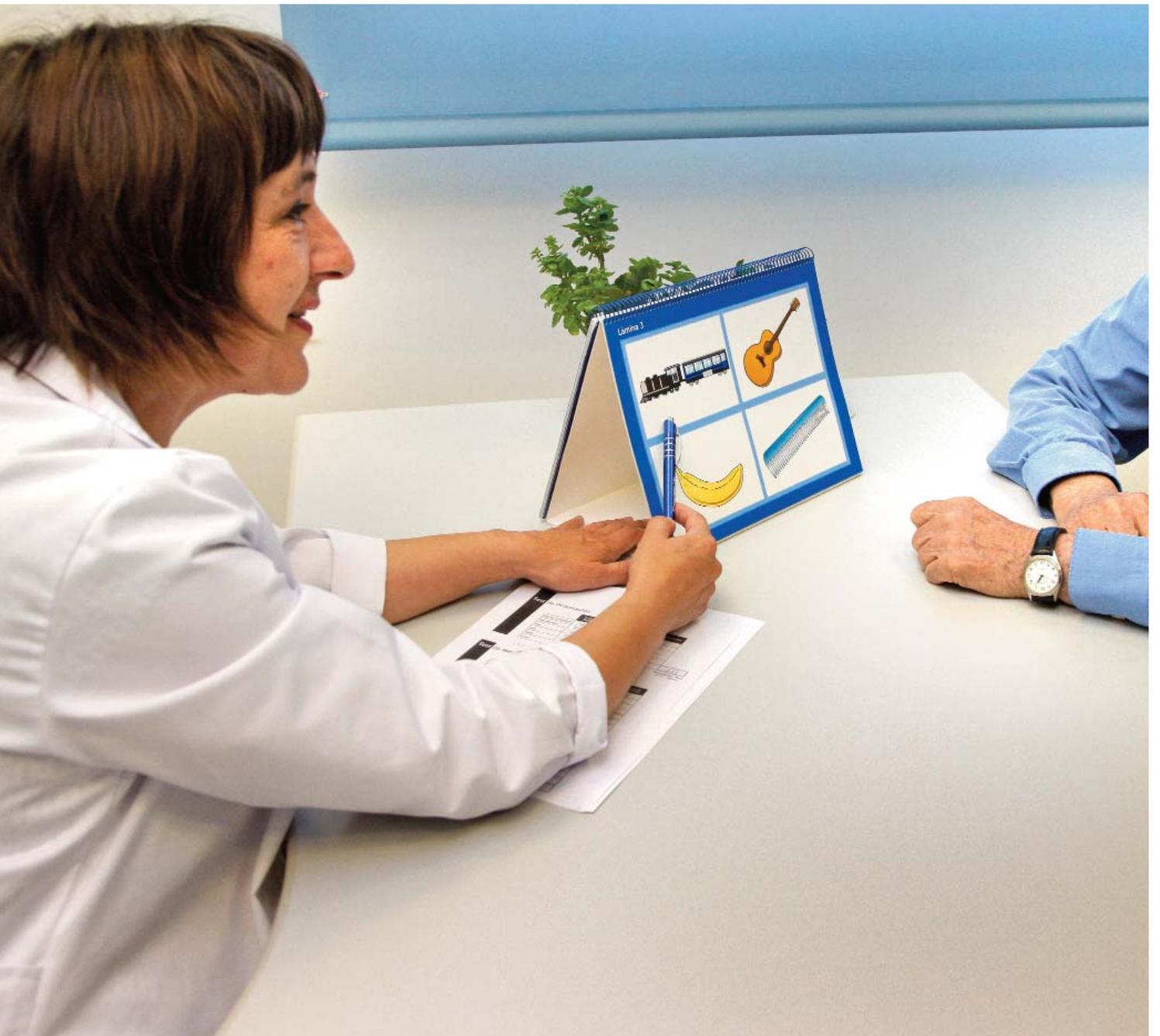


4. VALLECAS PROJECT

(the time it takes for copying is recorded) and subsequent immediate recall (within 3 minutes), after performing a distraction task, delayed (after 30 minutes) and a recognition task. This test allows to evaluate a large number of cognitive processes related

to planning, visuoconstruction, impulsiveness, episodic memory, incidental learning, etc. It has also been adapted and rated in the Spanish population over 60 years of age.





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Free And Cued Selective Reminding Test (FCSRT)

It is based on the assessment of learning ability and verbal episodic memory. The test consists of the consecutive presentation of 4 sheets with 4 words written each (a total of 16 words) that the subject must learn.

To facilitate this task, the examiner provides a key for each of the words that will be helpful later to recall more items. After a simple 20 seconds task interference people are asked to remember as many words as possible spontaneously. After 90 seconds, clues to help the memory of those words that did not recalled by himself/herself will be provided. Then the words he/she could not recall with the help of the clue are reminded of and another interference task is proposed. This procedure is performed three times, so that there are three free recall tests and three facilitated recall through the clues. After 30 minutes the delayed free and with clues recall condition is carried out. The indexes that are considered in this test are the total free recall, the total learning, free delayed recall and the overall delayed recall. The test has Spanish ratings.

Semantic lexical evocation

The task consist in providing the highest number of words beginning with a certain letter (P, M, and R) or belonging to a specific category (animals, fruits/vegetables, and cookware) for one minute. Furthermore, in the case of phonological evocation the contribution of people names or words that share the same lexical root is not allowed. The number of responses that the subject provides in periods of 15 seconds is recorded, as well as the total number of correct responses, intrusions and perseverations in the minute-long test. This task allows the systematic assessment of both the language proficiency as the semantic system of the subject. More-

over, it must be highlighted that this task has been validated and rated on Spanish population over 60 years.

Clock drawing test

It is an easily applicable screening test to evaluate both the visoconstructive ability as the semantic component associated with the knowledge of the hour. The subject is asked to draw the face of a clock, with all numbers in the correct place and with the hands pointing to 11 and 10. The score of the drawing is based on criteria related to the quality of the clock face, the presence and sequence of numbers, as well as the presence and location of the hands. The maximum score corresponds to 10, considering 6 as a cutoff for the diagnosis of cognitive impairment.

Reading test of intelligence (TELEI)

This test provides a measure of the level of pre-morbid intelligence of the patient through a reading task contained 60 words in the dictionary of the Royal Spanish Academy. An important feature of this test is that the items have a low frequency of use in our country, those who should carry written accent do not carry it and foreign words are also included between them.

The subject's task is to read the words in the right way, for what is allowed to rectify if deemed appropriate. The test raw score is the number of words read correctly.

Wechsler Adult Intelligence Scale (WAIS)

This is part of the WAIS scale for assessing intelligence. Natural numbers from 1 to 9, each of them associated with a different symbol, are presented on





a test sheet. Below appear random numbers from 1 to 9 without any associated symbol.

The task of the subject is to write the symbols for each number as quickly as possible for one minute. To avoid interference of possible memory alterations on test performance, the model with numbers and symbols for each of them remain in the top of the sheet. This test provides a measure of information processing speed and procedural learning ability to the extent of it will become less necessary for the subject to look at the model because unconscious learning.

Global Depression Scale (GDS-15)

Is a self-reported scale to evaluate depressive symptoms. It consists of 15 questions related to the state of mind to which the subject must respond dichotomously (yes/no). The cutoff point beyond which the likelihood of major depressive disorder increases is 5.

State-Trait Anxiety Inventory (STAI)

This self-reported test evaluates anxiogenic symptoms related to both a specific time and intensity variable period (anxiety state) as well as a more stable personality pattern tending to perceive situations as threatening (anxiety trait). Thus, there are two scales of this test, each consisting of 20 items with 4 response options (scored by a Likert type scale of 0-3). The total score is the sum of the individual scores for each item. Spain has recently adapted this test in nonclinical populations. After the second visit the neuropsychological examination protocol suffered a slight transformation in order to optimize collection of cognitive information. For this purpose, a series of assessment tests that allow to obtain more information on attention, language, praxis and executive functions from all selected study subjects.

Forward and reverse digits (subtest Wechsler Adult Intelligence Scale, WAIS)

This test allows to evaluate the hearing attentional amplitude and the individual's central executive of the working memory. The subject's task consists in repeating the growing sequences of numbers that the evaluator presents at one digit per second. The test is divided into two separate subtests, so that repetition of the first digit is applied in the same order of presentation (Direct digits) and then in reverse order (Inverse digits). The task ends when the subject is not able to repeat two sequences of the same length of digits. In both subtests, the number of correct repetitions and the maximum amplitude of digits that the subject is able to repeat are counted.

Boston Naming Test (15 items version)

It is a reduced version of the classic subtest included in the Boston test for the diagnosis of aphasia. The Boston Naming Test is used in clinical consultations to assess the ability of naming visual stimuli by visual confrontation. The subject's task is to name each of the 15 drawings that are presented, for which he/she is given a maximum of 20 seconds per image. If the subject does not give the correct answer spontaneously, the examiner provides a semantic or phonological clue if the above is not enough. Total score is the sum of correct spontaneous responses and the number of drawings called using the semantic hint. The correct answers after the phonological key are considered as an indicator of the kind of difficulty to name drawings.

Symbolic gesture (Revised Barcelona Test)

This test explores performing of a series of symbolic gestures of communication. They are simple, intransitive gestures made with a single upper limb. The pri-



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mary endpoint of the test is the body position in relation to space and the body.

Imitation of bilateral postures (Revised Barcelona Test)

This test consists in the imitation by the subject of a number of postures that the examiner performed with both hands. This test evaluates the integrity of ideomotor praxis.

Rule Change (Behavioral Assessment of the Dysexecutive Syndrome BADS subtest)

This test involves the presentation of a sequence of 21 cards from the French card deck. The subject must respond "yes" or "no" as fast as he/she can and as accurately as possible according to a rule that is in plain view. In the first part of the test rule is to respond "yes" when the card is red and "no" when is black. The second part introduces a variation of the first rule that the subject must respond "yes" when the card is the same color as above and "no" when it is a different color. The number of errors made by the subject in the second part of the test is registered and the score based on such errors is recorded. This test assesses the ability to fulfill one simple rule and the subject flexibility to adapt to a new different rule.

Test of the five points: This is a test that measures the subject's cognitive flexibility regarding the ability to design novel visual shapes

A DIN A4 sheet of paper with 40 identical matrices of 5 dots arranged in eight rows and five columns is provided. The subject's task is to produce for 3 minutes as many figures as possible by connecting the dots within each matrix and the following rules: i) the figures may not be repeated; ii) only straight lines in any direction (horizontal, vertical or diagonal) can be used to connect the dots; and iii) it is not necessary to join the 5 points of the matrix.

4.3.6. Neuropsychiatric Examination

Psychiatric symptoms are part of the evolution of dementia. The concept of "behavioral and psychological symptoms of dementia" (BPSD) refers to all those psychiatric manifestations and behaviors that may occur in the context of cognitive impairment or dementia.

According to various studies, these BPSD could not only manifest themselves in the phase of already established dementia, but may also appear in prodromal stages or even in preclinical stages prior to cognitive decline.

Specifically, in recent years the interest in both depressive symptoms and apathy in the absence of depression has increased, in order to establish their relationship with the development of dementia. The Vallecas Project includes a specific exploration of both major psychiatric disorders as the most common BPSD to collect more information regarding the factors related to the onset of Alzheimer's disease.

4.3.7. 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 determine, by PCR and sequencing techniques, genetic markers associated with the various polymorphisms of the following genes: APOE, CR1, BIN1, CLU, PICALM, ABCA7, SORL1, PRNP, GRM8, BACE1.

Furthermore, the blood samples collected and derivatives are used to determine a number of biochemical markers among which the following are of special interest:

- Vascular damage markers, cytokines and chemokines involved in human lipid metabolism and proinflammatory.
- The following molecules: 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 y MMP-3.

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	851
Third visit	822
Fourth visit	456
Fifth visit	5
Total	3.390

4.3.8. 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



4. VALLECAS PROJECT

determine the volume reduction of the amygdala, hippocampus, entorhinal cortex, etc.

- Diffusion Study (b: 800)**
 White matter, partly due to Wallerian degeneration and partly to reduced connectivity by decreased cortical activity, presents ultrastructural changes that can be detected with diffusion techniques (DTI).
- Brain Perfusion Study**
 Cerebral perfusion related to cortical activity may be assessed -without needing to inject contrast-through MR sequences (Arterial Spin Labelling, ASL) and therefore hypofunctioning areas will present decreased perfusion.

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 (Supercom-

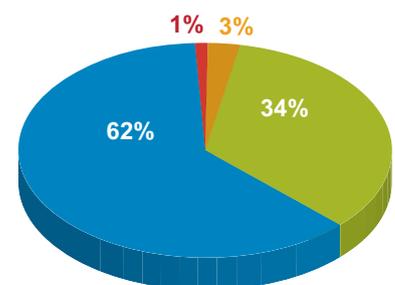
puting and Visualization Center of Madrid), a center from the UPM (Technical University of Madrid) has also been established.

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 have been used to present a paper at the last meeting of the 'Society for Neuroscience (Neuroscience 2015 "MRI in the healthy elderly predicts subsequent development of mild cognitive impairment", Chicago, 17 to

Vallecas Project activities during 2015

Number of second visit assessments	24
Number of third visit assessments	258
Number of fourth visit assessments	469
Number of fifth visit assessments	6

- Second visit
- Third visit
- Fourth visit
- Fifth visit



NEUROIMAGING ACQUISITIONS	
Second visit	18
Third visit	224
Fourth visit	377
Fifth visit	6
Total	625





21 October 2015).

4.3.9. 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 2015, we have combined the second, third, fourth and fifth visits from volunteers, already surpassing study's half point.

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

In order to ensure the reliability of the data collected so far in the context of the Vallecas Project, throughout 2015 we have continued with the validation process of all information registered by the various departments. The first analysis of data from

the first two visits have been designed to assess three different but complementary aspects. First, we studied the possible correlation between the information obtained from medical records (gender, age, medication, past illnesses, ApoE genotype, etc.) of the volunteers with the appearance or not of mild cognitive impairment (MCI). Secondly, we have also examined the possible association between cognitive complaints expressed by the volunteers on the first visit and its role as an early marker of progression to MCI a year later. Finally, we have carried out a comparative study of magnetic resonance imaging of the volunteers who have transitioned from a cognitively healthy status to show signs of MCI in the second visit of 'Vallecas Project'. The purpose of this study was to try to identify changes in brain structure that can be determined by neuroimaging techniques. Some of these results have been submitted and are pending publication in scientific journals. In addition to continuing with ongoing studies, new

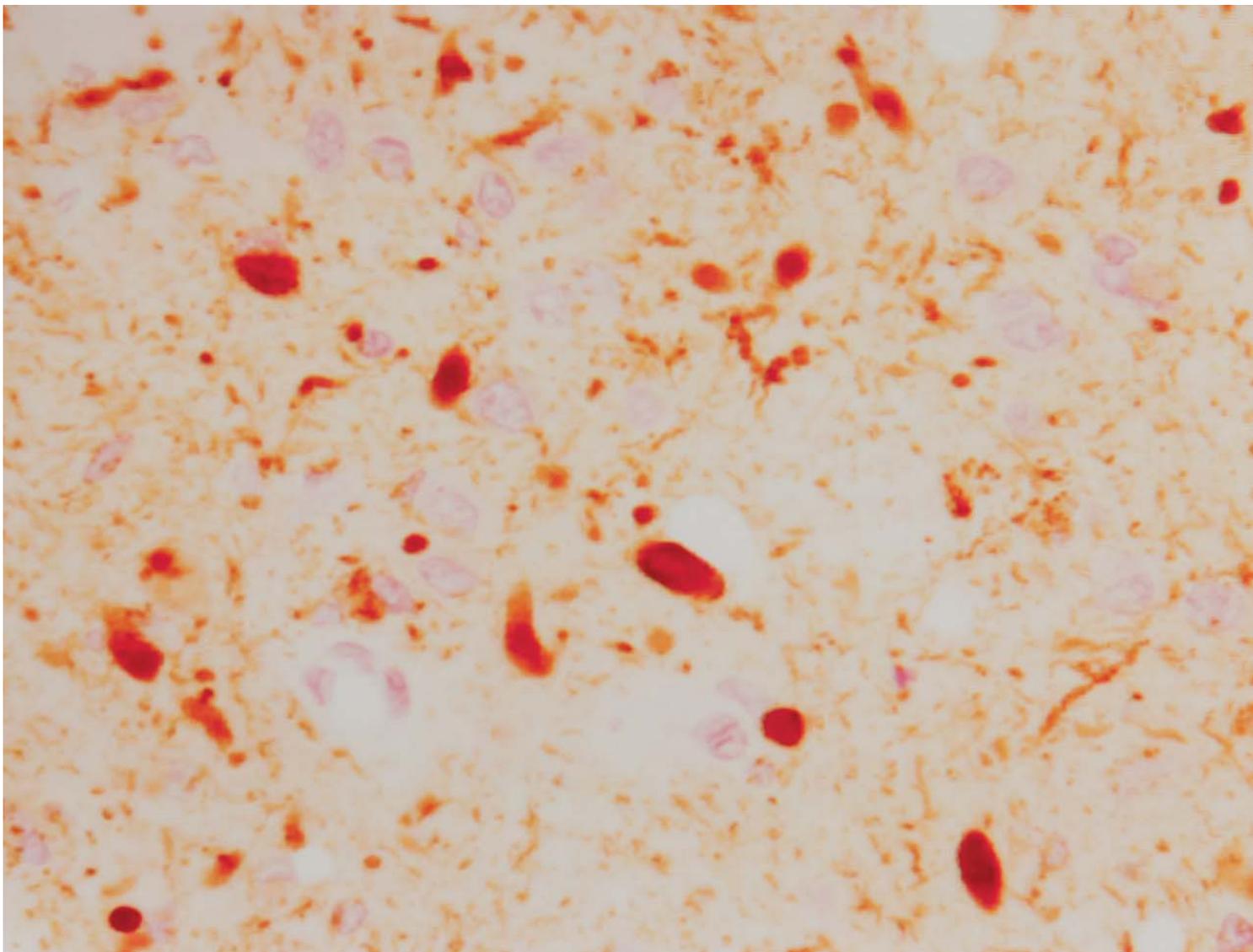
VALLECAS PROJECT CLINICAL EVALUATIONS (OCTOBER 2011-DECEMBER 2015)	
First visit	1.175
Excluded at baseline	47
Second visit	966
Third visit	836
Fourth visit	484
Fifth visit	6
Drop outs	395
Do not comply with inclusion criteria	30
Deceased	17
Diagnosis of neurological disease	31
Volunteer withdrawal	317



4. VALLECAS PROJECT

lines of research will open around the 'Vallecas Project' during 2016. Among other studies, we will examine the effect of drugs on neuropsychological performance of the elderly; the role of bilingualism and cognitive reserve as protection mechanisms against possible cognitive impairment; or finding

new neuropsychological markers in combination with neuroimaging techniques to discriminate individuals at risk of developing cognitive impairment.

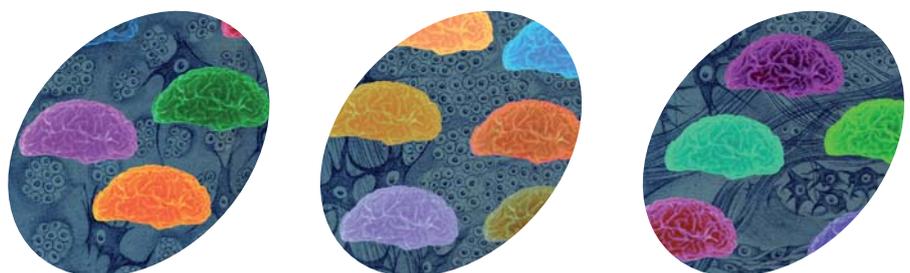


International *re*lations

In recent years, CIEN Foundation has fostered its relations with international organizations to further promote research excellence in the field of neurological diseases, and especially Alzheimer's disease.

Its participation in the Joint EU Programme in Neurodegenerative Diseases Research and its integration into the Network of Centers of Excellence in Neurodegeneration are two clear examples.

International scientific collaboration is essential for further





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. This comes to show that age-related neurodegenerative disorders are one of the leading medical and social challenges facing our society.

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

International scientific collaboration increases more and more, not only because of the availability of in-

ternational funding and the drive of modern communication technologies, but also because science itself has become a truly international collaborative activity. In particular, the scope and scale of the problem of neurodegenerative diseases in today's society require a global response to confront this great challenge and thus has been recognized by various international institutions such as the European Union (EU), the Organization for Economic Cooperation and Development (OECD), the World Health Organization (WHO), etc.), and the industrialized countries that constitute the G8. This global concern has led to the creation of the World Dementia Council (WDC) with the aim of collectively spur action against dementia worldwide in the areas of research, clinical care and social awareness.

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

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





Supporting research in Alzheimer's disease and related disorders has been and is one of the working priorities of the Queen Sofia Foundation since 2002, the year that promoted the construction of the Queen Sofia Foundation Alzheimer Center (CAFRS, for its acronym in Spanish), and from which it has continued to support the work of the institutions related to this dementia, both financially as well as with the invaluable drive and personal interest of Queen Sofia. In this context, in recent years CIEN Foundation together with the Network Center for Biomedical Research in Neurodegenerative Diseases (CIBERNED, for its acronym in Spanish) has given a boost to its relations with international organizations in the area of research in neurodegenerative diseases such as the EU Joint Programme for Research in Neurodegenerative Diseases (JPND) and the Network of Centers of Excellence in Neurodegeneration (COEN), among other initiatives. These and other internationalization activities carried out during 2015 by CIEN Foundation are detailed below.

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, Drs. Jesús Avila.

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

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

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

In this regard, during 2011 took place the first call for European research projects JPND. Under the theme "Optimization of biomarkers and harmonization of their use in the clinic", four transnational projects were awarded for the period 2012-2015, one of which has the participation of CIEN Foundation:

DEMTEST: Biomarker based diagnosis of rapid progressive dementias-optimisation of diagnostic protocols.



5. INTERNATIONAL RELATIONS

Total Funding: 2,2 M€ (approx.)
Start Date: May, 2012
Duration: 3 years
Coordinator: Inga Zerr, University Medical Center Göttingen, Germany
CIEN Foundation participation: Miguel Calero

Project partners:

- Inga Zerr, University Medical Center Göttingen, Germany
- Carsten Korth, Heinrich Heine University Medical School, Düsseldorf, Germany
- Hans Kretzschmar, Ludwig-Maximilians-University, Munich, Germany
- Jean-Louis Laplanche, Hopital Lariboisiere AP-HP, France
- Olivier Andreoletti, UMR-INRA-EVNT, France
- Theodoros Sklaviadis, Aristotle University of Thessaloniki, Greece
- Stefano Ruggieri & Maurizio Pocchiari & Anna Ladogana, University "Sapienza", Rome, Italy
- Pawel Liberski, Medical University of Lodz, Poland
- Catarina Resende Oliveira, University of Coimbra, Portugal
- Eva Mitrová, Slovak Medical University Bratislava, Slovakia
- Gorazd Bernard Stokin, University Psychiatric Hospital, Ljubljana, Slovenia
- Miguel Calero, Carlos III National Health Institute, Spain
- Pascual Sanchez-Juan, IFIMAV and CIBERNED, University Hospital, Spain
- Anna-Lena Hammarin, Swedish Institute of Communicable Disease Control, Sweden
- Adriano Aguzzi & Herbert Budka, University Hospital Zürich, Switzerland
- John Collinge, University College London, United Kingdom
- Robert G. Will, Western General Hospital, United Kingdom

DEMTEST has established a large European and global collaboration between national surveillance units and dementia research centres, facilitating co-

operation between neurologists, neuropathologists and neuroscientists.

Our goals are:

- To harmonize the protocols involved in patient documentation, biomaterial sampling/ storage, biomarker testing/assay analysis and data sharing.
- To standardise a more precise diagnosis in patients with rapidly progressive dementia by analysis of the biochemical markers in the cerebrospinal fluid and blood.
- To improve CSF based diagnosis in dementia by application of new methodologies.

In DEMTEST we work on standardisation of tests that are currently available and harmonise their use between centers worldwide. We define standards for biochemically based diagnosis in most relevant rapid progressive dementia such as CJD and rapidly progressive Alzheimer's disease. We will improve innovative methods for amplification assays for mis-folded proteins and introduce their use into clinical routine. As an add-on value, we will define criteria for early differential diagnosis between rapidly progressive neurodegenerative or potentially reversible dementia.

The DEMTEST collaboration allowed us to perform a genome wide association study (GWAS) in prion diseases. Because of that, we published in 2012 an association between MTMR7 gene and susceptibility to new variant Creutzfeldt-Jakob disease (CJD); this study was followed by an attempt of sequencing our top candidate genes where we found a risk variant in PLCXD3 gene. In 2014, we finalized the second part of our analysis; we performed a GWAS and replicated the results with samples from sporadic CJD patients from all partner countries. We have suc-





cessfully replicated an intronic SNP in GRM8 gene associated to sporadic CJD risk. In collaboration with our JPND partners (ISCIII Miguel Calero), we sequenced the exons of that gene in a large sample of Spanish cases. In parallel, we correlated genomic data with CSF markers in a sample of German patients from the group of Dr Zerr. Results of these analyses were published during 2015.

The other main results from this project were fruit of direct collaborations with the coordinator of the consortium, Dr. Inga Zerr. We carried out studies evaluating new biomarkers for rapidly progressive dementia (desmoplakin) and analysis of clinical data to generate new diagnostic algorithms for other prion disorders like fatal familial insomnia.

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

An important hurdle for the advancement of research on neurodegenerative diseases is the relative lack of common rules and mechanisms for validation of potentially relevant results in preclinical and clinical studies as well as in population-based studies. One approach to addressing these challenges on a large scale is through a more effective use of large research centers and institutes, where there is already the necessary critical mass of resources and expertise. Increased collaboration between national centers of excellence must also provide the opportunity to accelerate progress in understanding the basic mechanisms of the disease.

To this end, on June 10, 2010, the Canadian Institutes of Health Research (CIHR), the German Centre for Neurodegenerative Diseases (DZNE, Germany) and the Medical Research Council (MRC, UK) launched a funding initiative to establish a collaborative approach to research in neurodegenerative diseases, called "Centers of Excellence in Neurodegeneration (COEN)". These founding members were later joined

by other European institutions and thus, in December 2011 the COEN membership application by CIBERNED-CIEN Foundation was approved, recognizing the scientific excellence in both basic and clinical science of the institution which became part of the COEN Oversight Group. In 2012, 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, Slovakia
- CIBERNED-CIEN Foundation, Spain
- Agence Nationale de la Recherche (ANR), France

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

Since 2012, CIBERNED and CIEN Foundation are part of the Oversight Group to be actively involved in the



5. INTERNATIONAL RELATIONS





design of COEN future scientific strategy. Dr. Miguel Medina, CIBERNED Deputy Scientific Director and member of the Scientific Advisory Committee of the CIEN Foundation, represents both institutions in the COEN Oversight Group.

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

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

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

During 21st to 23rd September 2015, it was held in Malaga the Third International Congress on Research and Innovation in Neurodegenerative Diseases (CIIEN), promoted by the Queen Sofia Foundation in collaboration with CIEN Foundation and CIBER-

NED. 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 is 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 third edition of CIIEN was once again chaired by Her Majesty Queen Sofia and the scientific program consisted of three plenary sessions and five scientific sessions. Among the invited speakers at the conference can be highlighted some international researchers who are leaders in their field of research such as Zaven Khachaturian, President of the US 2020 Alzheimer's disease Prevention Campaign; Martin Rossor, Clinical neurologist from the British National Health System, an expert in prevention of dementia, especially Alzheimer's disease; or David Rubinsztein, Deputy Director of the Medical Research Council in Cambridge, a scientist pioneer in proposing autophagy positive feedback (a process that plays a role in the elimination of toxic proteins abnormally accumulated in the brain of patients) as



5. INTERNATIONAL RELATIONS

a potential therapy in neurodegenerative diseases. Rui Costa, a scientist from the Champalimaud Foundation (Portugal) and Angel Cedazo-Minguez, from the Karolinska Institute (Sweden), completed the international presence, focused on the study of the connectivity between different brain areas and the effects of its dysfunction, the first, and pathological mechanisms associated with known risk factors, the second.

The remaining scientific sessions addressed various aspects of frontier research in neurodegenerative di-

seases. In addition, less common neurodegenerative diseases such as Charcot-Marie-Tooth were also discussed during the congress, as were topics such as neuroimaging techniques, research in glial cells, neuronal plasticity in Huntington's disease or neuronal signaling in Parkinson's disease. Moreover, in line with the interest to boost the training of CIBERNED young researchers, the Young Researcher (basic and clinical research) Prizes were awarded during the Congress to Marta Fernández-Nogales and Juan Fortea, respectively, who made presented the studies which have been granted such recognition.





Ultimately, this event establishes in its third edition as a meeting point for the world's leading experts in neurodegenerative diseases, enabling sharing of knowledge, working methods, new advances and discoveries in a field in which international cooperation between different institutions is becoming increasingly important to obtain optimum results in research.

5.5. Other activities of international cooperation Champalimaud Foundation

On February 28, 2015 H.M. Queen Sofia visited the Champalimaud Foundation in Lisbon, a Portuguese institution devoted to advanced biomedical research. Joined by José Luis Nogueira, Secretary of the Queen Sofia Foundation and María Ángeles Pérez, Manager of CIEN Foundation and CIBERNED, the visit aimed at looking for new avenues of research in neurodegeneration.

Received on arrival by Leonor Beleza, Chair of Champalimaud Foundation, Queen Sofia was joined during Her visit to the Foundation facilities (internationally renowned for its work in oncology and neuroscience) by the Scientific Director and Nobel Laureate Zvi Fuks, Professors Carlo Greco, Rui Costa and Carlos Cordon-Cardo, and the Managing Director of the Foundation, Joao Silveira.

During the day a series of scientific meetings, mainly on neuroscience, were held where research projects were reviewed and in which the participating entities (Queen Sofia Foundation, CIEN Foundation, CIBERNED, and Champalimaud Foundation) focused on identifying joint collaboration and research lines to foster the knowledge of both countries in a field still as unknown as neuroscience.

At these meetings, also attended the Scientific Director of CIEN Foundation and CIBERNED, Dr. Jesús

Ávila de Grado, and CIBERNED Deputy Scientific Director, Dr. Miguel Medina Padilla. Dr. Avila intervened by reviewing the scientific activity that the institution carries out as part of the Alzheimer Project of the Queen Sofia Foundation, which focuses mainly on knowledge of neurodegenerative diseases (with particular emphasis on Alzheimer's disease), confluent with the priorities and knowledge of the Champalimaud Foundation.

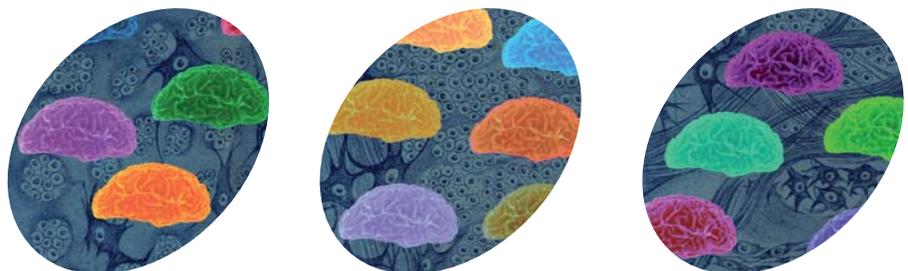


5. INTERNATIONAL RELATIONS



Scientific productivity

In 2015, researchers from CIEN Foundation have maintained the trend followed in previous years in terms of scientific productivity with 46 publications, although the average impact factor of the original articles within first or second quartile has increased by 8%. More than 78% of the articles have been published in journals classified in these categories.





6. SCIENTIFIC PRODUCTIVITY

6.1. Bibliometric analysis

A significant and steady growth in the scientific productivity of CIEN Foundation has been confirmed in recent years, largely due to the strong commitment maintained by the Foundation to research and the generation of scientific knowledge in improving diagnosis and treatment of neurodegenerative diseases.

During 2015, the CIEN Foundation researchers have produced a total of 46 publications, of which 45 have been published in scientific journals of national and international recognition (38 original articles, three reviews, three proceedings, and one editorial) and a clinical guideline.

The analysis of these publications has allowed studying, through a series of quantitative indicators, both the CIEN Foundation scientific activity as the production, topic, 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 4.367 in 2014 to 4.718 in the year 2015.

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 fac-

tor of the journals in which it has been published) and degree of collaboration at national and international levels.

Among 2015 milestones we can highlight that the CIEN Foundation researchers have published 46 scientific papers, of which 40 (86.7%) have been in journals under the coverage of the Science Citation Index Expanded, accessible through the Web of Science portal (WoS, Thomson Reuters) and 36 (78.3%) have been published in journals ranked within the first and second quartile in their category. Considering the type of document, 84.4% of the publications in scientific journals (38) correspond to original articles.

Moreover, according to their scientific subject category 77.8% of the publications within the first and second quartiles, have focused on the following categories: Clinical Neurology, Neurosciences, Multidisciplinary Sciences, and Anatomy and Morphology.

As scientific dissemination activities in meetings and national and international events during the year 2015 there have been a total of 23 participations at scientific conferences, nine of which correspond to lectures and oral presentations, and fourteen correspond to written communications in the form of posters. These communications have been presen-

2015 Indicators

Total number of publications.....	46
Total number of publications in the ISI citation index within the first and second quartile.....	36
Cumulative impact factor of publications within the first and second quartile.....	170,384
Average impact factor of the publications of the first and second quartile.....	4,733
Number of collaborative publications of all kinds (CIBERNED, other national groups, international groups) within the first and second quartile.....	32
Number of international collaborative publications within the first and second quartile.....	11
Number of national collaborative publications within the first and second quartile	21
Number of collaborative publications with other CIBERS and networks within the first and second quartile.....	4





ted at national (16) and international scientific conferences (7).

Other noteworthy scientific activities include 20 scientific presentations at training courses, a PhD in Neurosciences, an end-of-Master in Psychological Research internship and the co-direction of end-of-Master in Physical Anthropology internship.

6.2. Publications

References of scientific publications from CIEN Foundation professionals are listed below according to type of publication: 45 publications in scientific journals (38 original articles, three reviews, three proceedings and one editorial) and a clinical guide.

6.2.1. Journal articles

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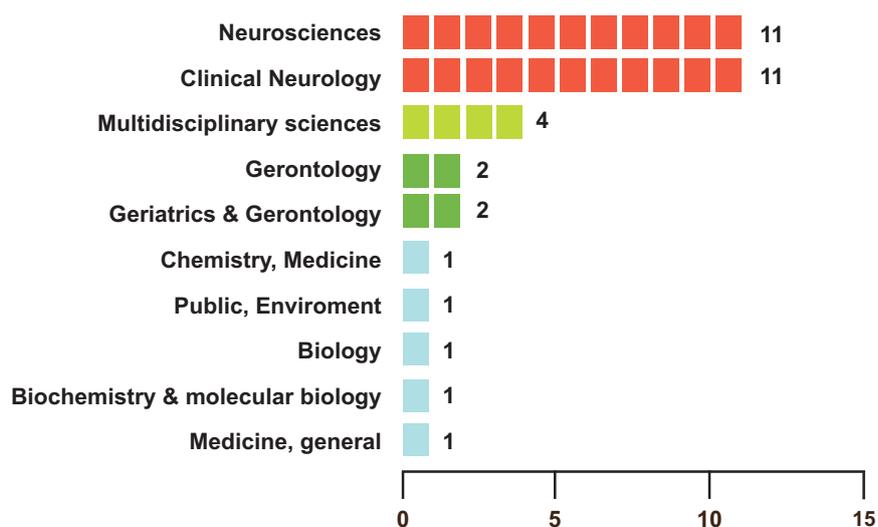
6. SCIENTIFIC PRODUCTIVITY





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Number of publications by subject category in 2015



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6. SCIENTIFIC PRODUCTIVITY

Institucionalizadas. Madrid: Escuela Nacional de Sanidad, Instituto de Salud Carlos III – Ministerio de Economía y Competitividad; 2015. N.I.P.O. en línea: 725-15-027-X.

6.3. Funded projects

During 2015 the CIEN Foundation researchers have participated in 8 scientific research projects obtained through various national and international com-

petitive calls and funded by different institutions. Funded research projects are cited below:

- **Code FCIEN-005/11**

Principal Investigator: Dr. Miguel Medina
Title: Proyecto Vallecas – Early detection of alzheimer's disease

Funding agency: Queen Sofia Foundation

Duration: 2011-2016

Total budget: 1,800.000 €

2015 budget: 302,320.12 €





- **Code: PI12/03018**

Principal Investigator: Dr. Alberto Rábano
 Title: Profile of the age-associated Alzheimer pathology (85+CIEN Study)
 Funding agency: Carlos III Institute of Health
 Duration: 2013-2015
 Total budget: 19,965 €
 2015 budget: 4,840.00€

- **Code: PT13/0010/0045**

Principal Investigator: Alberto Rábano
 Title: Biobanks Platform
 Funding agency: Carlos III Institute of Health
 Duration: 2014-2016
 2015 budget: 44,178.26€

- **Code: Proyecto IPT-2012-0769-010000 (INNPACTO)**

Principal Investigator: Dr. Alberto Rábano
 Title: Design and manufacture of a system for the diagnosis of Alzheimer's disease based on laser Raman spectroscopy
 Funding agency: Ministry of Economy and Competitiveness
 Duration: 2012-2015
 Total budget: 720,218 €; CIEN Foundation 93,320€
 2015 budget: 17.295,00€

- **Code: Universidad Ulhm**

Principal Investigator: Dr. Pablo Martínez Martín y Dra. María Ascensión Zea Sevilla.
 Title: The multi-site prospective neural history cohort study entitled "Registry".
 Funding agency:
 Duration: 2013-2015
 Budget: 6.930 €

- **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 €
 2015 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 €
 2015 budget: 22,500 €

6.4. Patents

During 2015 three patent applications remain ongoing, 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



6. SCIENTIFIC PRODUCTIVITY

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.

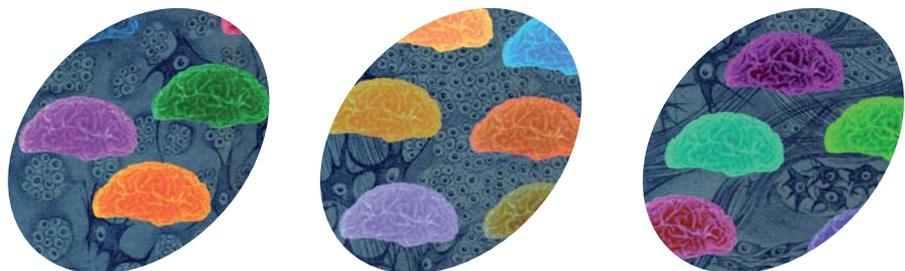
- **Inventors:** José Ramón Naranjo Orovio, Britt Mellström, **Alberto Rábano Gutiérrez del Arroyo.**
Title: Methods for the prognosis and diagnosis of neurodegenerative diseases
Registration N°: EP13382108.2
PCT/EP2014/055928
Application date: 25/03/2013
Type: National/European



Social dissemination

CIEN Foundation in 2015 has continued to promote various activities to bring to society the latest advances in research on neurological diseases, complemented with specific actions to encourage citizen participation allowing to raise funds for Alzheimer's disease research.

Thus, to the more traditional activities, such as the 'tree of memories' or the Vallecas Project Volunteer's Day, we must add numerous meetings with patient associations, conferences, exhibitions or concerts. This work has been recognized in the year with different awards.





7. SOCIAL DISSEMINATION

7.1. Outreach activities

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

For this reason, the responsables of the CIEN Foundation departments have organized, as every year, various activities that allow the dissemination of the research work carried out by its professionals. This allows them to bring the scientific field to society in a kinder way, while translating results and relevant information on the various neurological diseases under study.

During 2015, CIEN Foundation continued to develop activities to disseminate the research carried out by its professionals, which has been so successful in previous editions. It is the case of the World Parkinson's Day. On April 10, 2015, María Ángeles Pérez, Manager of the CIEN Foundation and CIBERNED, participated in the main event, organized by the Catalan Association for Parkinson (ACAP, for its acronym in Spanish). During the event, held in CaixaForum, Barcelona, the Clinic Hospital neurologist and member of CIBERNED Steering Committee Eduardo Tolosa spoke about the role of the patient and Associations in Parkinson's research, and three round tables were held devoted to complex treatments in fluctuating Parkinson's disease: apomorphine, duodopa, and deep brain stimulation. A conference reviewing new treatments and technologies that will shape the future of research and treatment of the disease, which affects between 120,000 and 150,000 people in Spain, also took place.

It is also the case of several meetings organized by Institutions throughout Spain in which participated Alberto Rábano, Head for Neuropathology and director of the CIEN Foundation Tissue Bank. An example is the 'Meeting of Huntington's disease families', held at the San Carlos Hospital in Madrid, on 3 November 2015. Or the "NeuroMeeting: Experts Dialo-

gue on Neurodegenerative Diseases", organized by the Spanish Alliance for Neurodegenerative Diseases (Neuroalianza) on 25 June 2015 at the Ministry of Health, Social Services and Equality, and aimed at all those involved in improving the quality of life of people affected by neurodegenerative diseases: responsables and workers in patient associations, social health professionals, those affected and their relatives, representatives of the administration, etc. At the meeting, public institutions, health authorities, experts, associations and affected individuals analyzed, on the one hand, the social initiatives that exist to protect and improve the quality of life of people affected by neurodegenerative diseases and, secondly, advances and current research for an integrated approach to these pathologies. The aim of this meeting was to establish a meeting point and generate debate around reality, the current situation and approach to neurodegenerative diseases in our country, thanks to the participation of the main authorities involved in these pathologies.

The conclusions drawn from the conference will serve Neuroalianza to continue with its mission to represent and defend the interests of the people it stands in for. The meeting has a discussion or dialogue format and there were representatives of the institutional and health, social and scientific sectors.

In addition, in May 2015, Dr. Rábano participated in Salamanca at the Third Meeting of the State Group on Dementias, of which we the Foundation is a member since its inception in 2014. The meeting addressed, among other issues, conclusions and proposals to advance the definition of an national policy on Alzheimer, while the external technical evaluation report of this disease in Spain was analyzed. This group was created with the mission to develop a of National Cooperation Network on Dementias that allows for offering Spanish society with a response to the social reality of these disorders and the vision to place Spain as an international re-





ference in the social, health, legal and research approach in dementia through a shared national strategy. The group seeks to promote the exchange of knowledge, experiences and best practices among professionals. For this, the IMSERSO, which oversees the State Reference Center of Care for People with Alzheimer's disease and other Dementias (Alzheimer CRE, for its acronym in Spanish) of Salamanca, has created the Collaborative Environment. The aim of this initiative is to incorporate and classify documents, to be accessible to all participants in this group. CRE Alzheimer will be responsible for incorporating documents that each group member or

ganization deemed relevant and will manage and control the uploading of documentation.

Among the outreach activities undertaken during the year it also stands out the development of a series of videos of general interest, so that everyone knows and is involved in the investigations on the brain that are underway in Spain. This initiative is the result of the collaboration of CIEN Foundation and the Spanish Brain Council. In the video devoted to CIEN Foundation, in-house researchers from the four major areas of work, such as Ascension Zea, a neurologist at the UMA; Alberto Rábano, Head of the Tis-



7. SOCIAL DISSEMINATION

sue Bank; Miguel Calero, Head of Laboratory; Alba Sierra, neuroscientist from the area of neuroimaging; and Marina Avila, a neuropsychologist at the UMA, give a clear and concise overview of the work they carry out in this indisputable reference center.

In addition, a series of activities with the dual aim of promoting citizen participation and raise funds for research into Alzheimer's disease have been scheduled during 2015. Among these outreach activities raised with this duality, these can be highlighted: two street markets from the "Edición Recuerda" (Remember Edition) and the fifth edition of "The Christmas Tree of Memories".

"Edición Recuerda" street markets

As part of the "Edición Recuerda" project launched by the Queen Sofia Foundation, CIEN Foundation and Villa de Vallecas District Council joined forces again to set up two "Edición Recuerda" street markets. The first one took place on April 17 and 18 in the District of Villa de Vallecas. Those interested could buy vintage products re-manufactured by the participating Spanish companies. Products with memory designed to support and help those who no longer have it.

On May 9 and 10, again with the intention to remember and work with those who cannot do it any longer, CIEN Foundation and the Queen Sofia Foundation organized another joint selling of re-manufactured vintage products, this time in the popular Engines Market, located in the Railway Museum, which opens in Paseo de las Delicias, Madrid, the second weekend of each month.

Christmas tree of memories

Due to the success of the previous campaign, CIEN Foundation has once again set up its traditional "Tree of Memories", placed in previous years in the Queen

Sofia Foundation Alzheimer Center, at the Villa de Vallecas food market, in an awareness campaign that, for the second consecutive year, allows for not only bringing the reality of Alzheimer to society in general, but also strengthening the role of the Villa de Vallecas District in this task.

From December 2, 2015 to January 5, 2016, everyone who visited the market could leave a written special memory about Christmas in previous years, which were then hanged like Christmas tree ornaments. During the campaign, market traders placed in their shops a small display for the sale of solidarity bracelets. In addition, a space was enabled on the market for the sale of surplus from the Queen Sofia Foundation "Edición Recuerda".

The funds obtained from the sale of these products have been allocated to research projects on Alzheimer undertaken by CIEN Foundation as the managing body of the Queen Sofia Foundation Alzheimer Project Research Unit, especially the Vallecas Project.

Other Outreach Activities

During 2015 the CIEN Foundation has continued to develop other dissemination actions among which we highlight the following.

- On the occasion of the American film "Still Alice" release on January 16, 2015, Grupo Senda and Golem organized few days earlier in Madrid its premiere and subsequent debate, which was attended by María Ángeles Pérez, Manager of the CIEN Foundation; María Ascension Zea, a neurologist from the UMA; Rosa Brescané, president of the Federation of Associations of Relatives of Alzheimer patients (FAFAL, for its acronym in Spanish); and José Luis Nogueira, Secretary of the Queen Sofia Foundation. "Still Alice" has enjoyed box office and reviews success. Julianne Moore, who plays the leading





role, provides a universal vision of how families behave in illness and in facing old age. According to the actress, what most attracted her about the film was "the idea of giving people the space to be who they are and not judge them by what is happening with their disease. That was something that really touched me".

- In March 2015, CIEN Foundation was visited by secondary school students from the Program on Educational Enrichment for Gifted Students (PEAC, from its acronym in Spanish) of the Ministry of Education, Youth and Sports of the Region of Madrid (CAM, from its acronym in Spanish). This Program provides students with opportunities to deepen in different areas of



7. SOCIAL DISSEMINATION

knowledge through experimentation, research and development, implemented through various methodological strategies. During the visit, CIEN Foundation researchers taught a series of lectures and highlt educational workshops in different areas: pathology, neuropsychology and neuroimaging.

- Since October 2015, we could enjoy the exhibition "FromBubble", created by Daniel Bagnon to raise awareness throughout society of what Alzheimer's disease means in the personal, family and social environment, through the interaction of contemporary art with other scientific and social disciplines. Queen Sofia inaugurated the exhibition on October 30, accompanied by the mayor of Madrid, Manuela Carmena; the Director of the art project, Maria Paz Cotorelo; and the CIEN Foundation Manager and member of the Art and Science Project, María Ángeles Pérez, who along with the creative artist of this art proposal, Daniel Bagnon, visited the exhibit.
- The exhibition was open to the public until January 24, 2016 on the third floor of Culture and Citizenship Cibeles CentroCentro, a City of Madrid cultural space located at Cibeles Palace, which also hosted numerous conferences such as by Dr. Miguel Medina, or Javier de Felipe members of the CIEN Foundation Scientific Advisory Committee, as well as other activities related to Alzheimer's disease. Noteworthy among other project artworks, was the main piece 'Brain', a sculpture located in the central room of the exhibition. With FromBubble, Daniel Bagnon drew a parallel between the Alzheimer's damaged brain and a bubble element that represents the complexity of the disease. In this way, he sought to show not only the reality of the patient but also that people who go with them through this struggle. In addition, to convey the message of this artistic proposal to a much wider audience, FromBubble took to the streets of Madrid. 3,000 bubbles were placed in cultural and historical points of the city, creating a route of over seven

kilometers. Manuela Carmena, was responsible for placing the first of these bubbles in Plaza de Cibeles, in an urban action participated by 100 volunteers.

These points highlight the 'Performance multidisciplinary conference' about Alzheimer's disease from the scientific and social perspective of art, delivered at the Plaza de Callao in Madrid by members of the Committee of Art and Science, including Dr. Miguel Medina.

7.2. Awards and Honours

Candidacy of Her Majesty Queen Sofia to the Nobel Peace Prize

For his personal commitment for years with Alzheimer's research, Her Majesty Queen Sofia has been one of the candidates for the Nobel Peace Prize 2015, after being selected from the initial 273 nominations presented by national and international organizations.

Queen Sofia nomination, proposed by a university in the southern United States, is due to its continuing thrust to Alzheimer's disease research, a task to which we at CIEN Foundation, as management office of the Alzheimer Project from Her Foundation, wanted to show our greatest support.

The Vallecas Project received the INESE Award at the XV edition of the Insurance Solidarity Awards

The Vallecas Project, being conducted by CIEN Foundation with the support of the Queen Sofia Foundation, was one of 25 selected out of 243 proposals that applied to the fifteenth edition of the Insurance Solidarity Awards 2015, under the topic "The heart drive us" were awarded on 24 November in Madrid.

Proposed by the Queen Sofia Foundation, the project has been chosen to be supported by one of the





25 insurance companies participating in the Awards, that provide a prize of 4,500 € to the sponsored project.

INESE, organizer of the Awards, was the organization that supported the 'Vallecas Project', a study launched in 2011 by CIEN Foundation and the Queen Sofia Foundation, to find common patterns in the progression of Alzheimer's disease that advance the identification of early markers for early diagnosis of the disease. The 'Vallecas Project' is studying the evolution of more than 1,200 cognitively healthy people between 70 and 85 years of age.

The Insurance Solidarity Awards 2015 show the support of the insurance industry towards organizations working to improve the quality of life of people from various fields. Thus, 25 NGOs, Foundations and Associations have received financial contributions by 25 insurance and service companies to develop projects concerning children, disability, social exclusion, women, and cooperation in the framework of its Corporate Social Responsibility.

AEHTF Solidarity dinner

In its fourth edition, held on April 25, 2015, the Fuerteventura Association of Entrepreneurs of Hotels and Tourism (AEHTF, from its acronym in Spanish) elected the Association of Relatives of Alzheimer's and other dementias of Lanzarote and Fuerteventura (AFALF, from its acronym in Spanish) and CIEN Foundation as equal beneficiaries of the money raised (8,000 €). The money intended for CIEN Foundation has been allocated to the Fuerteventura Grant, which finances one of the research lines being carried out to eradicate Alzheimer's pathology.

Vallecas Project Volunteer's Day

CIEN Foundation is aware of the role of the volunteer, fundamental 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 come 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" and activities organized for the residents of CAFRS, many of them also volunteers in the Alzheimer Project of the Queen Sofia Foundation.

The event, chaired by H.M. Queen Sofia, was held on 20 February 2015 at the La Latina Theater in Madrid. With Irma Soriano as master of ceremonies, the tribute included two actions: the performance of the unique in Spain choir "Voices of Memory", composed by Alzheimer's patients from the Association of Relatives of Alzheimer of Valencia (FSMA, for its acronym in Spanish); and the play "Who said love?" by the Forja Theater Company.

Christmas concert "Music of Recycling"

Queen Sofia attended on December 18 a Christmas concert held at the Queen Sofia Foundation Alzheimer Center, home of CIEN Foundation, played by a group of children and several teachers of the project "Music of Recycling" by the Oberon Trio.

The project, promoted by Ecoembes and supported by the Queen Sofia Foundation, educates musically and in values 80 children and young people from the Villapaz (Pozuelo de Alarcón) Shelter and Nunez de Arenas (Vallecas) public school, who are learning to build their own instruments with and play music from recycled materials.

The concert was aimed at Alzheimer patients residing in the Queen Sofia Foundation Alzheimer Center under the management of the Madrid Region. There are 156 people living with Alzheimer's in the



7. SOCIAL DISSEMINATION

Center and 40 more patients are cared for through the Day Center.

María Ángeles Pérez, Manager of CIEN Foundation, said that "supporting charity projects is a wonderful way to welcome Christmas in the Queen Sofia Foundation Alzheimer Center".

José Luis Nogueira, Secretary of the Queen Sofia Foundation, expressed his gratitude to Ecoembes "to include the Queen Sofia Foundation at the wonderful initiative" which means the "Music of Recycling project", to CIEN Foundation and the Madrid Region for making possible the Alzheimer project of the Queen Sofia Foundation, and the protagonists, who are the children who take part of the project and their teachers, for bringing joy and memories to residents of the Queen Sofia Foundation Alzheimer Center.

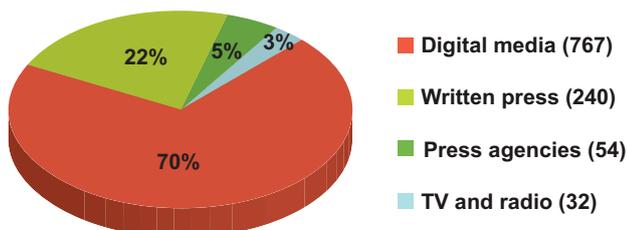
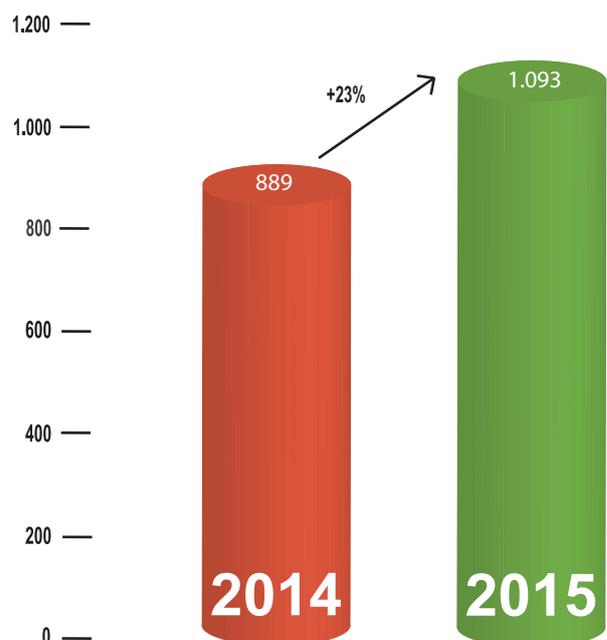
Oscar Martin, CEO of Ecoembes, expressed his gratitude to the Queen Sofia as "the breath that continues to motivate us to keep this initiative alive every day"; to the Queen Sofia Foundation for their support since the beginning of the project and CIEN Foundation and the Madrid Region "for the opportunity to give this concert, aimed at Alzheimer's patients, and for the commendable work done on behalf of our elders". "We want to spread the joy of Christmas," he said, "share and celebrate the magic that comes from the union of music and recycling".

Her Majesty was also joined during the concert by the Minister of Social Policy and Family of the Madrid Region, Carlos Izquierdo Torres; Director General of Care for Dependent and the Elder, Carlos Gonzalez Pereira; Director General of the Family and Children, Alberto San Juan; Director of the Healthcare Area of the Queen Sofia Foundation Alzheimer Center, Laura Fernández Pérez; and the CIEN Foundation Manager, María Ángeles Pérez; as well as Javier Urrea and Maria Franco, "Music of Recycling" Support Committee members

7.3. Presence in media

During 2015 there we produced 46 web contents, 26 press releases and we managed up to 28 interviews in the media, which resulted in the generation of of 1,093 impacts in the media, distributed as follows.

Evolution of the impacts in 2015





Málaga hoy



Carmen Ibañez inaugura el Congreso acompañado de la reina Sofía, el alcalde de Málaga y el consejero de Salud, ayer.

La reina Sofía es propuesta para recibir el Nobel de la Paz

La iniciativa parte de una universidad del sur de FFJJ. Entre los candidatos se encuentra el Papa

M. Ubach / **EL PAÍS**
La reina Sofía es una de las candidatas al Nobel de la Paz y a la presidencia de una prestigiosa universidad del sur de España. Sofía, de 86 años, es una de las candidatas más populares. La iniciativa parte de una universidad del sur de España, concretamente de la Universidad de Sevilla, que ha lanzado una campaña para que la reina Sofía sea propuesta para recibir el premio Nobel de la Paz y la presidencia de la Universidad de Sevilla. El proyecto ha sido impulsado por un grupo de investigadores de la Universidad de Sevilla, que han lanzado una campaña para que la reina Sofía sea propuesta para recibir el premio Nobel de la Paz y la presidencia de la Universidad de Sevilla.



José Ibañez muestra la reina Sofía entre los doctores investigadores, ayer.

LA PROVINCIA

La patronal turística entrega en Madrid 24.000 euros para el estudio del alzhéimer

El dinero procede de la recaudación de la cena solidaria destinada a esta enfermedad

A. C.

FUERTO DEL ROSARIO

El presidente de la Asociación de Empresarios de Hostelería y Turismo de Fuerteventura (Aehft), Antonio Hormiga, y el consejero insular de Bienestar Social y Juventud, Víctor Alonso, hicieron entrega de 24.000 euros a la Fundación Centro de Investigación en Enfermedades Neurológicas (Fundación CIEN), en un acto celebrado ayer en el Centro Alzhéimer Fundación Reina Sofía (Carf) de Madrid. La delegación majorera fue re-

cibida por Margarita Blazquez, subdirectora del Instituto de Salud Carlos III, entidad mediante la cual la Fundación CIEN es dependiente del Ministerio de Economía y Competitividad, así como de otros responsables del citado organismo.

Durante el acto se hizo entrega formal del cincuenta por ciento del dinero recaudado, una vez descontados gastos, con la celebración de la IV Cena Solidaria de la patronal majorera, que tuvo lugar el pasado 25 de abril bajo el lema "Mirando por ti". Un evento que contó con la participación de más de quinién-

comentan su estructura el Papa Francisco.

Concretado con el título Mundial del Alzheimer, se celebra por el III Congreso Internacional del Alzheimer, que se celebra en Málaga y que reúne a más de 150 expertos en enfermedades neurodegenerativas para analizar los últimos avances en la investigación de Alzheimer, Parkinson y Huntington. El evento está organizado por la Fundación Reina Sofía, la Fundación Centro de Investigación en Enfermedades Neurológicas (CIEN) y el Congreso Internacional de Neurología y Neurociencias (CIN) en colaboración con el Ayuntamiento de Málaga.

Más de 150 expertos analizarán los avances en el Alzheimer, Parkinson y Huntington

El primer día se celebró un simposio sobre el Alzheimer, en el que se analizaron los últimos avances en la investigación de esta enfermedad. El evento estuvo organizado por la Fundación Reina Sofía, la Fundación Centro de Investigación en Enfermedades Neurológicas (CIEN) y el Congreso Internacional de Neurología y Neurociencias (CIN) en colaboración con el Ayuntamiento de Málaga.

Además, entre los asistentes se celebró una cena solidaria para recaudar fondos para la investigación de esta enfermedad. El evento estuvo organizado por la Fundación Reina Sofía, la Fundación Centro de Investigación en Enfermedades Neurológicas (CIEN) y el Congreso Internacional de Neurología y Neurociencias (CIN) en colaboración con el Ayuntamiento de Málaga.

LA RAZÓN

DOÑA SOFÍA, CANDIDATA AL PREMIO NOBEL DE LA PAZ

La Reina Sofía ha sido propuesta como candidata al Premio Nobel de la Paz por una universidad estadounidense de la que no se ha revelado el nombre. Así lo anunció el director de la Fundación Centro de Investigación en Enfermedades Neurológicas (CIEN), José Ibañez, quien actuará a raíz de su selección: la implicación de Doña Sofía con la enfermedad de Alzheimer. Su labor es reconocida en el ámbito de la investigación, tanto por el trabajo que realiza como por su participación en los congresos. El importante anuncio lo efectuó ayer José Ibañez ante un congreso internacional sobre enfermedades neurodegenerativas en Málaga, presidido por la reina Sofía. En la imagen, junto a la secretaria de la Junta de Investigación, Doña María de Irujo, y la presidenta de la Fundación, Carmen Vela.



EM

entremayores

Fundación Reina Sofía, Fundación Cien y Cibermed homenajean a los voluntarios del Proyecto Vallecas

El acto incluyó la actuación del coro "Las Voces de la Memoria" que, por otro lado, es el único de España formado por enfermos pertenecientes a la Asociación de Familiares de Enfermos de Alzheimer de Valencia (Afav)

Redacción/EM

La Fundación Reina Sofía, la Fundación Centro de Investigación de Enfermedades Neurológicas (Fundación CIEN) y el Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED) homenajearon, a finales del mes pasado y por tercer año consecutivo, el Día del Voluntario Vallecas, un homenaje a los sujetos de estudio del Proyecto Vallecas, una investigación longitudinal a cinco años, cuya finalidad es analizar las posibles interacciones tempranas de la



Una de las actuaciones del coro "Las Voces de la Memoria". FUNDACIÓN CIEN

Desde 2011, se han realizado más de 2.300 estudios de resonancia magnética y se han analizado más de 2.500 muestras de sangre

(36.232 personas). Actualmente, el proyecto de estudio en su tercer año de seguimiento, y realiza de forma anual resonancias y extracciones sanguíneas a las 1.913 personas que se incluyen en el mismo, mediante la realización de pruebas (tele-



Víctor Alonso (l) y Antonio Hormiga (c), durante la entrega del dinero, ayer en Madrid. JIB/IMP

tos comensales, y que logró 18.000 euros íntegros para combatir el alzhéimer, siendo beneficiarias, a partes iguales, la Fundación CIEN y la Asociación de Familiares de Alzhéimer y otras demencias de Lanzarote y Fuerteventura.

La gerente de la citada Fundación, María Angeles Pérez, agradeció la donación recibida, y explicó, que "se dirigirá a financiar, a través de la Beca Fuerteventura, los servicios de un investigador que colaborará con la Unidad de Investi-

gación del Proyecto Alzhéimer, un estudio longitudinal a cinco años que persigue identificar perfiles de riesgo en enfermedad de alzhéimer y, además, aportar información valiosa sobre el inicio de esta patología.



7. SOCIAL DISSEMINATION

With regards to year 2014, we observed an overall positive trend, having increased by 23% the number of hits in the media, thanks to an increase of 109% in print and 13% on digital media.

7.4. Presence in social networks

CIEN Foundation has an established presence in social networks where it is recognized as a reliable source of information on research in dementia. In addition, its efforts to promote healthy aging and the results being obtained in the Vallecas project and the Alzheimer project are particularly appreciated.

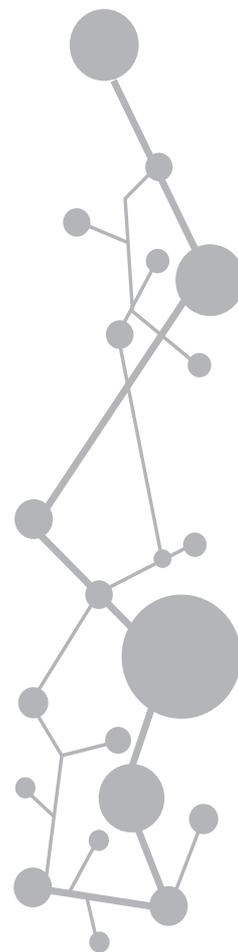
The digital presence of CIEN Foundation has established itself due to the great interest and follow-up of blog posts about researchers' activities and the great interaction through social networks with both professionals in the field and the general public.

Moreover, online public participation in events held in CIEN Foundation and broadcasted through live streaming, such as the International Conference on Research and Innovation in Neurodegenerative Diseases and the International Day of Radiology is also achieved through the web and social networks. Hundreds of people from different countries had the chance of virtually attend both events. Highlighting the impact obtained with the broadcast for the first time the International Day of Radiology: the #IdorSPAIN conversation got more than 1.5 million impacts, a record of visibility for the benefit of Medical Radiology in Spain, where the CIEN Foundation had a key role in hosting this event. In addition, coverage was also given in real time on Twitter to other conferences and events.

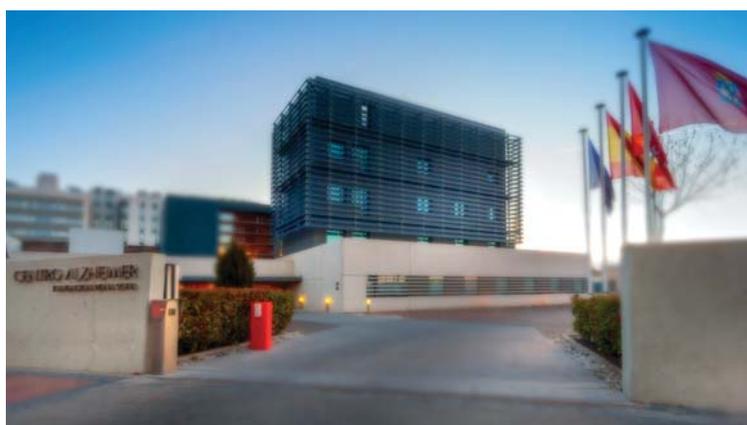
In 2015 the CIEN Foundation website was adapted to a responsive design, optimizing its functionality on mobile devices and thus promoting its search engine positioning. The site was visited by 100,000 users who viewed 128,400 pages.

- **Facebook:**
The year 2015 closed with a total de 3,956 fans following our page, with a high number of shared publications, likes and comments.
- **Twitter:**
By the end of 2015 the profile counted on 11,800 followers with which has constant interaction, receiving numerous comments, retweets and publications bookmarked.
- **LinkedIn:**
A profile aimed at a professional audience, in which contents of interests in dementias is published in various groups, promoting scientific outreach and public debate
- **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. Year 2015 ended with a total of 123,329 visits.





Annual report 2015



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