



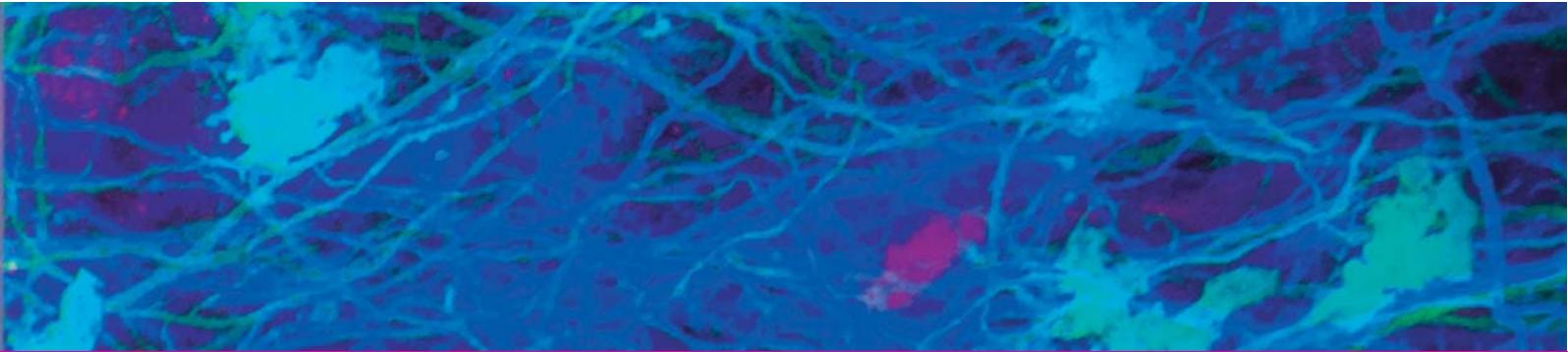
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Fundación Centro Investigación
Enfermedades **Neurológicas**

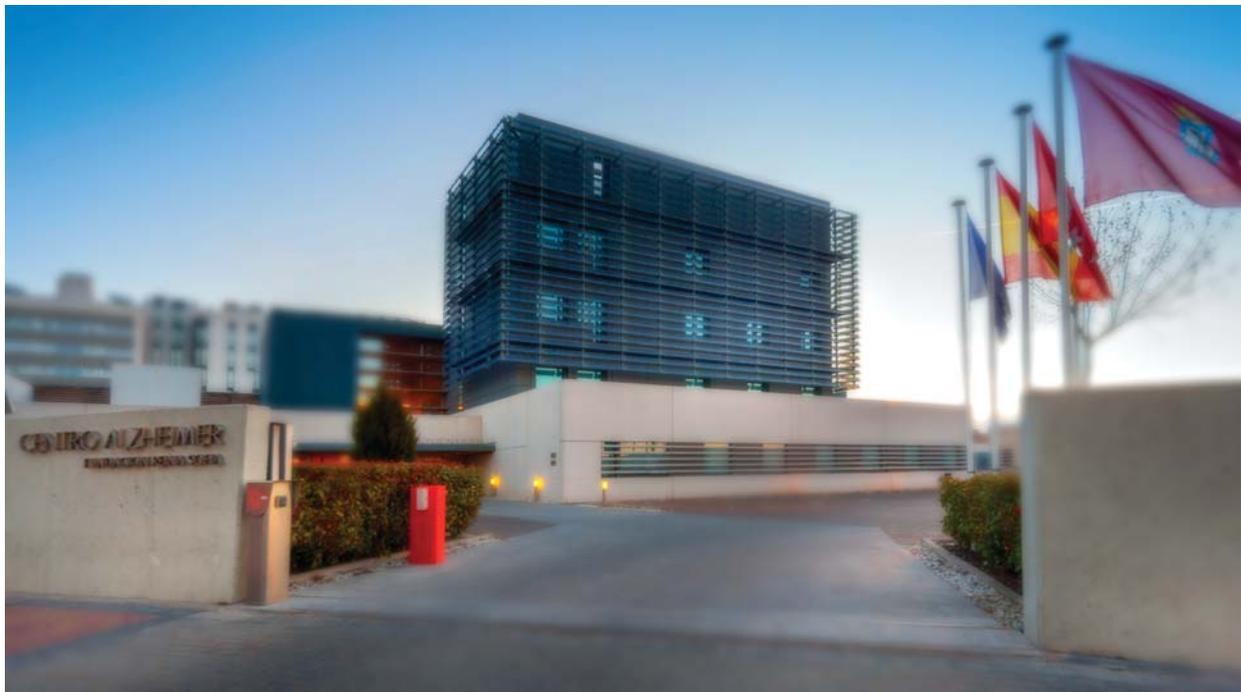
Annual Report 2014

CIEN Foundation
Research Center for
Neurological Diseases Foundation

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Annual Report 2014

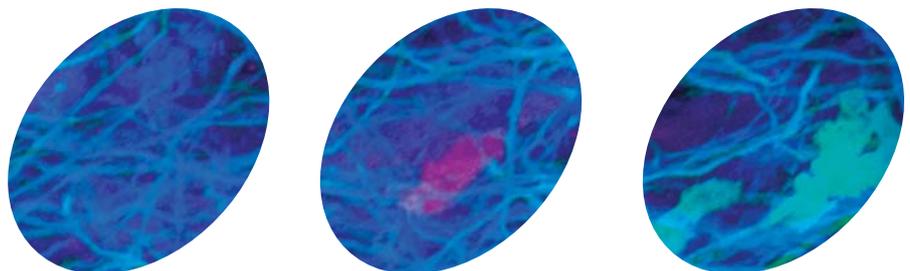


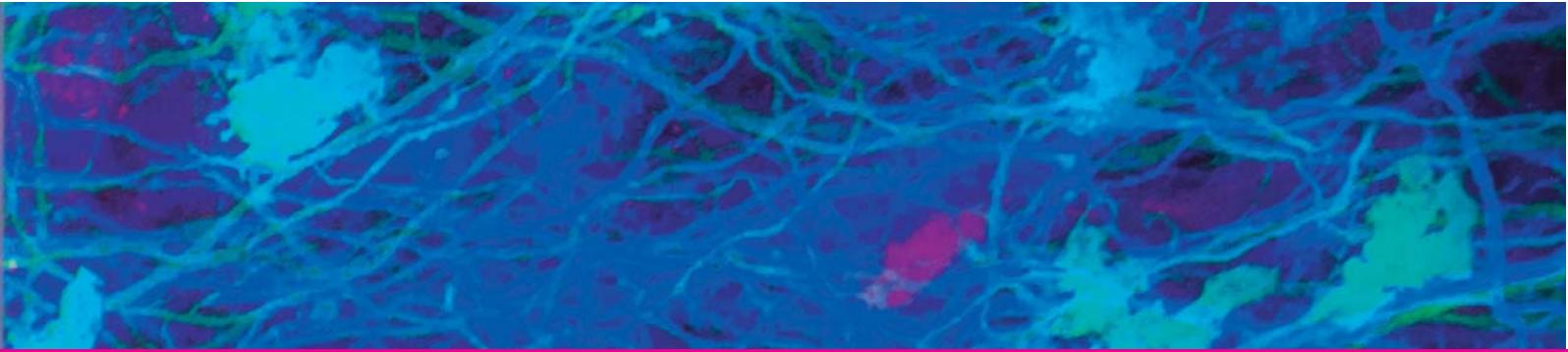
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Profile and presentation

CIEN is a public sector Foundation that promotes and coordinates research on neurological diseases, mainly Alzheimer's and other dementias. Its model is based on two criteria: at the research level applies a translational model that benefits all of society; regarding management it is an example of "public-private" partnership thanks to continuous support from the Queen Sofia Foundation.





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. We are a non-profit Foundation from the public sector with State-wide scope and competence under the Ministry of Economy and Competitiveness through the Carlos III Institute of Health.

Our founding goal is to support, promote and coordinate research on neurological diseases. For it, we special focus our efforts in neurodegenerative disorders and the coordination of renowned Spanish research groups.



Collaboration with the Queen Sofia Foundation

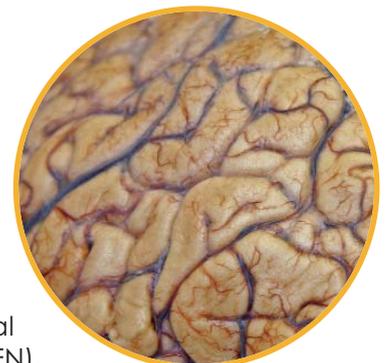
CIEN Foundation headquarters are located at the Queen Sofia Foundation Alzheimer Center pursuant to an agreement signed by the two institutions on January 18, 2006. Under the agreement, the Queen Sofia Foundation donated the complex built in Vallecas for implementing the Alzheimer Project.

This is a clear successful example of public-private partnership, already since its inception CIEN Foundation manages and coordinates the Alzheimer Project Research Unit (UIPA, for its acronym in Spanish) established by the Queen Sofia Foundation and located in the Alzheimer Center that bears his name. The Alzheimer Project comprehensively addresses the impact that this disease has on both sufferers and their family environment.

A Center of Reference in Spain on Alzheimer's disease Research

In 2011 after being proposed by ISCIII, UIPA and CIBERNED (two centers managed by Foundation CIEN) were designated Centers of Excellence in Research on Neurodegenerative Diseases by the European Union.

UIPA and CIBERNED are the only two institutions in Spain that are participating in the 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 have allowed both institutions integrate into the international network of Centres of Excellence in Research on Neurodegeneration (COEN).



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An innovative, integrated vision of the fight against AD

The CIEN Foundation and the Queen Sofia Foundation share a common goal: of approaching Alzheimer's disease from a holistic perspective, in which research is one of the mainstays. Thus, the main backbones of the Alzheimer Project converge in the Queen Sofia Foundation Alzheimer Center:



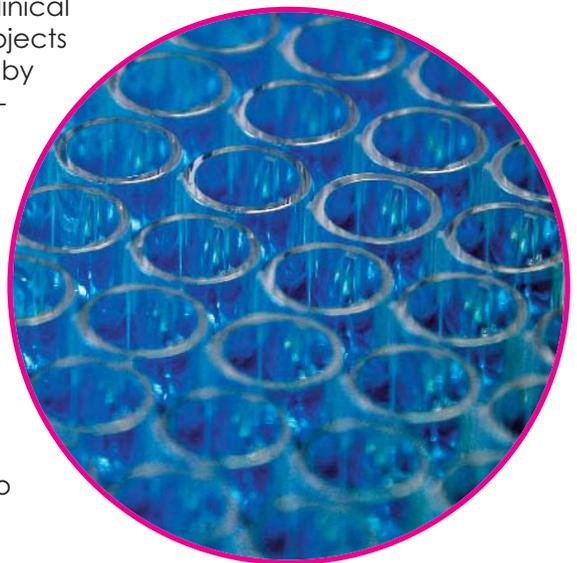
1. A live-in residence for 156 Alzheimer's patients.
2. A day-care outpatient center for 40 Alzheimer's patients.
3. An Alzheimer's research center: the so-called Alzheimer's Project Research Unit (UIPA), managed by the CIEN Foundation.
2. A training center for healthcare staff, relatives and volunteers.

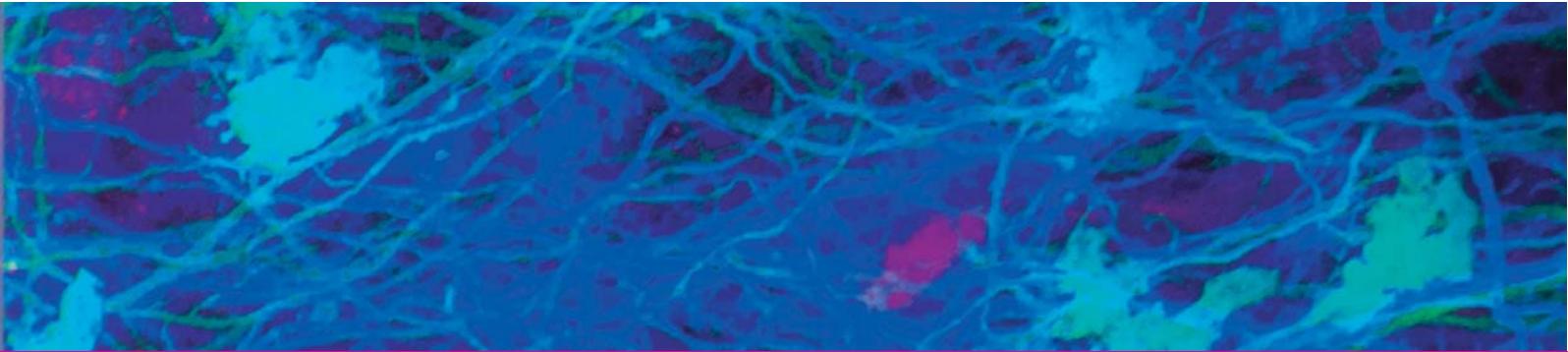
When the Queen Sofia Foundation built the Alzheimer Center in the Madrid neighborhood of Vallecas, instructed UIPA management to CIEN Foundation, while the healthcare and training activities were assigned to the Region of Madrid Council of Family and Social Affairs. This model has sought throughout summoning the will and interests of all parties involved: Government (Central, Regional and Local) and Civil Society.

Focused on neurodegenerative diseases research

Translating scientific advances achieved in basic research to clinical practice, promoting the execution of coordinated research projects in neurological diseases, promoting participation in calls made by national and international funding agencies, and supporting training through specific activities such as seminars, lectures or PhD programs are some of the tasks assigned to the CIEN Foundation.

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 2014

Key figures



- ▶ The CIEN Foundation overall budget for 2014 was reduced 17.2% compared with the previous year, up to a little over € 3 million.
- ▶ 15.28% 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 2011 contributed more than € 2.1 million, enforceable in the following four years.

Scientific activity



- ▶ Overall scientific production: 47 impacts
Decreases 44.7% versus 2013
- ▶ Publications in scientific journals: 46
A 24.6% decrease versus 2013
- ▶ The average impact factor of publications within the first and second quartile is 4.99.
Increases 10,2% versus 2013
- ▶ Clinical neurology y Neurosciences remain the main subject categories for publication.

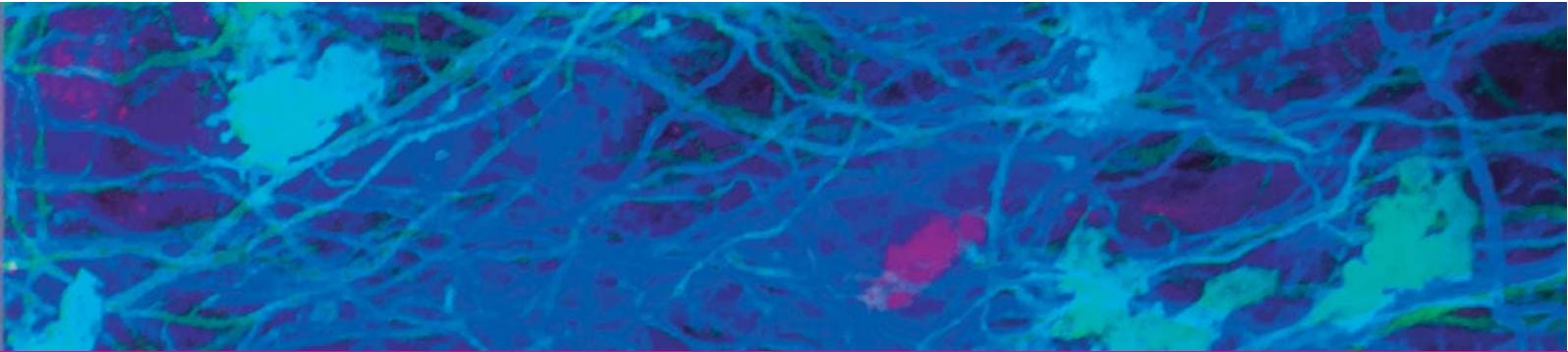


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Highlighted events

- ▶ The process of recruiting volunteers for the Vallecas Project has been completed. A total of 1,213 subjects are included in this five-year study.
- ▶ The project's half-way point has been surpassed during 2014, synchronizing the second, third and even fourth visit to some of the volunteers. During 2015 it is planned to confirm and publish some preliminary results from the data gathered so far in the study.
- ▶ CIEN Foundation has continued throughout 2014 managing various projects, including: the establishment of the Strategic Agenda of the European Union Joint Programming in Neurodegenerative Diseases (JPND), particularly Alzheimer's disease, in collaboration with the ISCIII.
- ▶ The Network of Centers of Excellence in Neudegeneration (COEN) has approved in 2014 funding for five new Pathfinder research projects, three of which will have Spanish participation. These five projects will have a budget of € 3 million, of which 550,000 € will be provided by CIEN Foundation.
- ▶ CIEN Foundation has signed a collaboration agreement with the Windesheim University of Applied Sciences under the RAAK International Programme for the development of the research project "New friends, old emotions".
- ▶ In late 2013 and during 2014 CIEN Foundation has completed various collaboration agreements with other institutions. Thus, projects such as "Strengthening the health system and prevention in the fight against infectious diseases prevalent in the region of Amhara-Ethiopia" and "Project Reference Centre for the Control of Endemic Diseases in Equatorial Guinea " have been completed.
- ▶ In January 2014 the National Network of Biobanks Platform, promoted and financed by the Carlos III Institute of Health, and to which the CIEN Foundation Tissue Bank (BT-CIEN, for its acronym in Spanish) belongs, was established.
- ▶ Only during 2014, 106 new donors to the BT-CIEN were enrolled, ending the year with more than 600 people enrolled.
- ▶ In addition, the BT-CIEN renewed in 2014 its Certification of Quality according to ISO 9001/2008 standards.
- ▶ During 2014, the Department of Neuroimaging has carried out more than 5,744 MRI studies to 687 subjects. Over 38,000 sequences have been performed since the creation of the department.





1.3 Letter from the Managing Director of the CIEN Foundation



María Ángeles Pérez Muñoz
Managing Director of the CIEN Foundation

Dear trustees, benefactors, contributors and friends of the CIEN Foundation, For five years now, I take this opportunity to take stock of the activities undertaken by the by the Centre for Research in Neurological Diseases (CIEN) Foundation, responsible for the management and coordination of the Alzheimer Project Research Unit (UIPA) and the Center for Networked Biomedical Research on Neurodegenerative Diseases (CIBERNED).

During these years CIEN Foundation has grown exponentially supported on two main factors: the continued support received from the Queen Sofia Foundation from our birth, whose contributions are essential to the development of new research activities, and the personal and professional qualities of the people within it.

It is the case of Professor Jesús Avila, who in his first year in charge of the scientific management of CIEN Foundation has contributed its extensive experience in the field of neuroscience. His experience will serve as a pillar on which sustain our progress in the research of neurological diseases. It is the perfect setting for continuing to develop the main management and activity lines initiated in previous years: CIEN Foundation internationalization and commitment to a model of translational research closer to society.

Regarding internationalization activities undertaken during 2014, I would like to highlight the appointment of Alberto Rábano, director of the CIEN Foundation Tissue Bank (BT-CIEN), as a member of the Legal and Social Aspects Ethics (ELSA) Committee of the Human Brain Project, a research project funded by the European Union seeking to reproduce the human brain features using the latest technologies available. In addition, for the third consecutive year, our researchers are involved in different European translational research projects convened by the Joint Programme in Neurodegenerative Diseases (JPND), and continue to work in the Registry project, an observational study of the European of Huntington's Di-

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sease Network (EHDN). These facts strengthen our commitment to internationalization initiated in previous years and endorsed by the recognition of the CIEN Foundation and CIBERNED as the only centers in Spain included in the International Network of Centers of Excellence in Research on Neurodegenerative Diseases (COEN).

2014 has seen the consolidation of the International Conference on Research and Innovation in Neurodegenerative Diseases (CIIRN), that brings together the efforts of the Queen Sofia Foundation, CIEN Foundation and CIBERNED in this field. This scientific meeting, chaired by Her Majesty Queen Sofia, has established itself as the best example in the field of research in neurodegenerative diseases in Spain and, after the success in its first two editions, is enjoying great international prestige.

Several milestones in terms of research can be highlighted during the year 2014: First, the "Vallecas Project", one of the most ambitious initiatives launched in Spain to advance our knowledge of Alzheimer's disease, continues to meet the deadlines. During 2014, our professionals have begun to carry out the fourth assessment visit to some of the 1,213 volunteers enrolled in this five-year study.

Concerning this project, the second edition of "Vallecas Project Volunteer's Day" was held on February 21. This year, in addition to the events organized for that day, we wanted to strengthen our commitment to the volunteers. In collaboration with Queen Sofia Foundation and the Spanish Railway Foundation, we launched two free cultural activities for "Vallecas Project" volunteers: guided tours of the Fernán Nuñez Palace, home of the Spanish Railways Foundation, and the Railroad Museum, both located in Madrid. In the field of research this year also deserves special mention the BT-CIEN activities. Our tissue bank participates in the National Biobank Network Platform, created in 2014 and funded by the Carlos III Institute of Health (ISCIII), and its director, Alberto Rá-

bano, is a member of the platform Steering Committee. In addition, BT-CIEN is involved in the "Genome wide analysis of splice variants in Huntington's disease" project, funded by the BBVA Foundation.

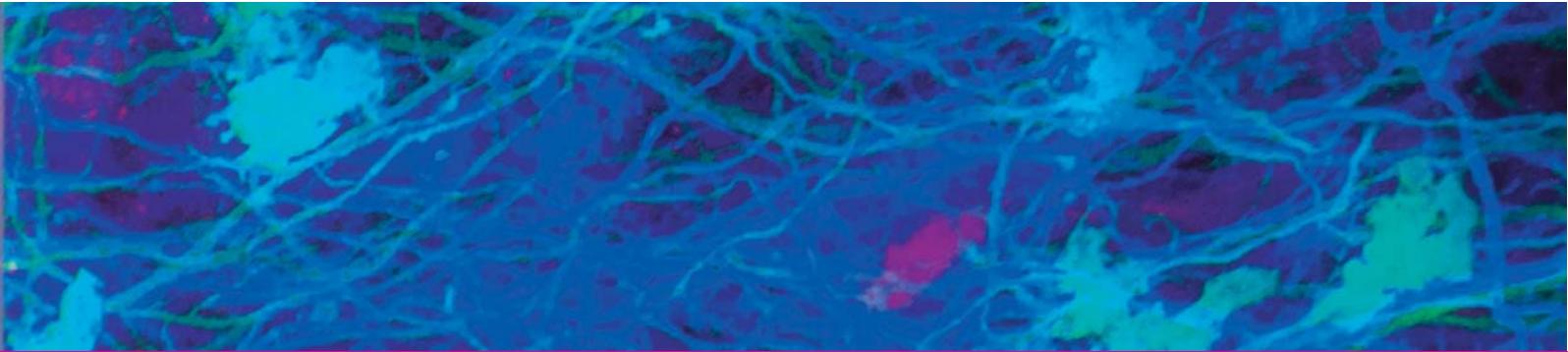
In this sense, it is also noteworthy the launch of a multi-center study for the detection of the tau protein in teardrops as a potential biomarker of Alzheimer's disease in collaboration with the Alzheimer patient associations from León and Soria. This collaboration with patient associations is a clear demonstration of our commitment to society with a translational research model that allows us to bring the research conducted in the laboratory closer to clinical practice.

As in previous years, we wanted to be closer to citizens and encourage their commitment to research with the "Christmas Tree of Memories", an initiative launched four years ago in the Queen Sofia Foundation Alzheimer Center and that we have expanded this year. With the support of the Villa de Vallecas District Board, General Directorate for the Elder of the Community of Madrid and the Villa de Vallecas municipal marketplace, we were able to install a second tree in that market. The response from retail traders and residents of the district has been magnificent.

I do not want to finish without mentioning the recognition received by two of our scientists in 2014. Dr. Jesús Avila, CIEN Foundation scientific director has received the "Alzheimer León Mano Amiga" international award and the director of BT-CIEN, the Dr. Alberto Rábano, has been recognized by the newspaper La Razón with the 'To your health' award to the investigator of the year.

These awards, which recognize the work of these great professionals, reinforces our commitment to fight one of the main challenges of the XXI century: Alzheimer's disease.





1.4 Letter from the Scientific Director of CIEN Foundation



Jesús Ávila de Grado
Scientific Director of CIEN Foundation

Before briefly summarizing the activity carried out in the Alzheimer Project Research Unit during 2014, I would like to devote my first lines to thank the continuous support given us by both the Queen Sofia Foundation and the Carlos III Institute of Health and CIBERNED in the work that from CIEN Foundation is being performed in the Queen Sofia Foundation Alzheimer Center. Without their collaboration and researchers and professionals in the Foundation's activity during this year it would not have been possible.

CIEN Foundation efforts during 2014 in the scientific and research side have focused on consolidating the goals set in previous years. In this sense, there are two fundamental aspects: the Vallecas project, the main research project of the Foundation in terms of budget and human resources devoted to, and the consolidation of the CIEN Foundation internationalization process initiated in previous years, that allows us to collaborate with some of the leading research centers in neurodegeneration in Europe.

In 2014, the Vallecas project, in which Dr. Pablo Martínez-Martin has had an important contribution, has reached his half-way point. It has completed the recruitment of volunteers and already has carried out the second, third and even fourth visit to the vast majority of the 1,213 subjects who participate in this project. In fact, the excellent work by all departments that make up the CIEN Foundation (Multidisciplinary Support Unit, consisting of neurologists, psychiatrists and neuropsychologists, Neuroimaging area, which performs the analysis of structural and functional MRI, the Laboratory department, which conducts genetic and biochemical studies, and the Neuropathology area, which integrates the Tissue Bank) has resulted in several publications, some of them with a high impact factor such as BA Strange et al. *Nat Rev Neurosci.* 2014 Oct; 15 (10): 655-69.

Furthermore, several projects are underway in the department of Neuropathology focusing on diffe-

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rent approaches: joint implementation of neuropathological criteria for Alzheimer's disease and vascular pathology; detecting proteins in teardrops as disease biomarkers; the search for protective factors that can facilitate the maintenance of cognitive ability over age 85 (85 + CIEN study), which also have begun to lead to publications (see Alzheimer & Dementia, Mar 21, 2015).

In total, 47 publications have been produced in 2014, with an average impact factor of 4.99 in the first and second quartiles, representing a 10.2% increase over the prior year.

With regards to internationalization, several significant milestones can be highlighted. The recognition of CIEN Foundation and CIBERNED as the only Spanish Centers of Excellence in Neurodegeneration by the COEN International Network, which has allowed the collaboration and participation of Spanish research groups from CIEN Foundation as CIBERNED in the "Pathfinder" call for projects.

I wish to highlight the collaboration agreement signed with the Champalimaud Foundation (Portugal) for seeking common interests and synergies in the field of translational research in the area of neurodegenerative diseases.

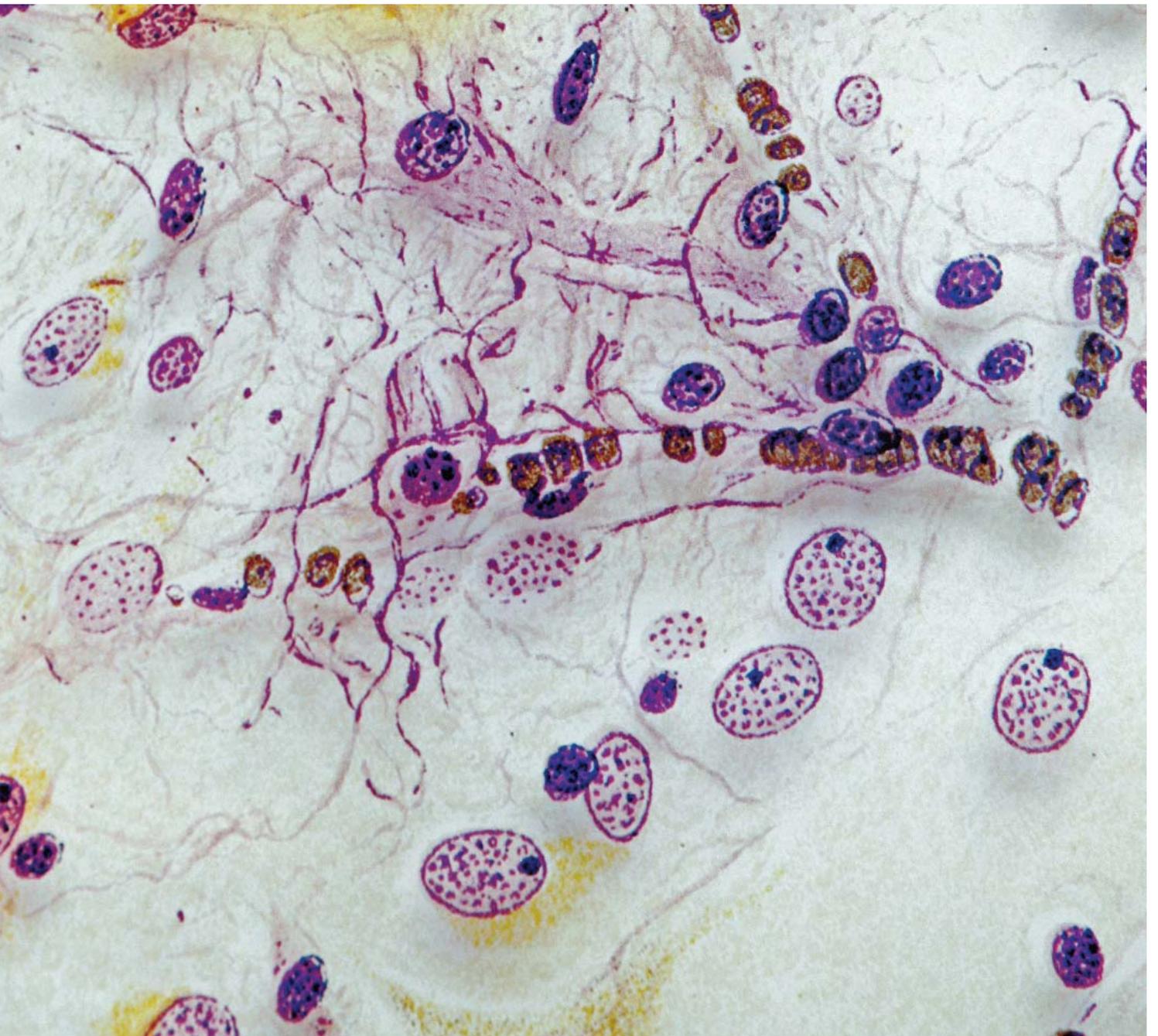
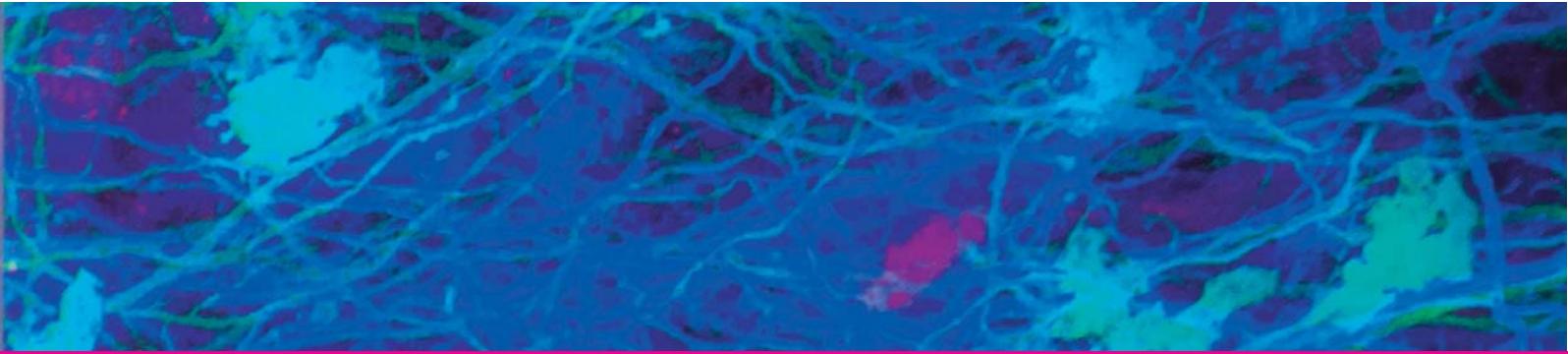
I cannot conclude without mentioning the successful convening of the Second International Congress on Research and Innovation in Neurodegenerative Diseases (CIIEN) that took place in Barcelona on September 2014 and which, as every year, was chaired by Her Majesty Queen Sofia and had the assistance of some leading international researchers that are references in their field.

We are thus in a process of consolidation and expansion of the project originally launched by HM Queen Sofia, the Alzheimer Project, which has been supported by the Carlos III Institute of Health and other public and private institutions, and that for

another a year has presented very satisfactory results.

We hope that with the support of those institutions and our effort we can keep improving our research work aimed at preventing neurodegenerative problems in our country.





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1.5 Organizational chart

CIEN Foundation Board of Trustees:

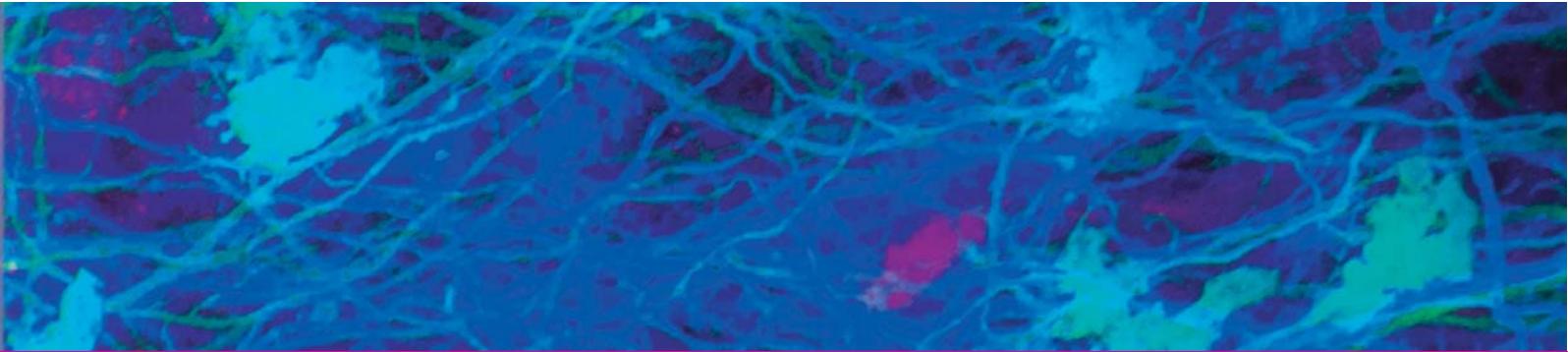
The Board of Trustees is responsible for the government and representation of the CIEN Foundation as well as for the fulfillment of the Foundation objectives, administration and management of its capital assets. Board members represent all sectors involved in neurological diseases research: public institutions related to the field of health, research, social and industrial policy, technology, business and education.

Board members at the end of 2014 are:

CIEN FOUNDATION BOARD OF TRUSTEES		
Board members at the end of 2014 are:		
Position	Title	Name
Honorary Chair	Minister of Economy and Competitiveness	Mr. Luis de Guindos Jurado
Chair	State Secretary of Research, Development and Innovation	Ms. D ^a Carmen Vela Olmo
Vice-Chair	Director of the Carlos III Instituto de Salud	Mr. Antonio Luis Andreu Pérez
Ex-officio Members	General Secretary of Health and Consumer Affairs, Ministry of Health, Social Services and Equality	Ms. Pilar Farjas Abadía
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	Mr. Jesús Fernández Crespo
Ex-officio Members	Director General of Public Health, Quality and Innovation, Ministry of Health, Social Services and	Ms. M ^a Mercedes Vinuesa Sebastián
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	Ms. María Sol Calzado García *
Elected Members Valencia	General Director of Health Planning, Evaluation and Research	Ms. Pilar Viedama Gil de Vergara
Elected Members Canary Islands	General Director of Welfare Programs	Ms. Soledad Rodríguez Izquierdo *
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
Scientific Director	CIEN Foundation	Mr. Jesús Ávila de Grado
Managing Director	CIEN Foundation	Ms. María Angeles Pérez Muñoz

*Pendientes de aceptar su cargo D^a. María Sol Calzado García y D^a. Soledad Rodríguez Izquierdo.





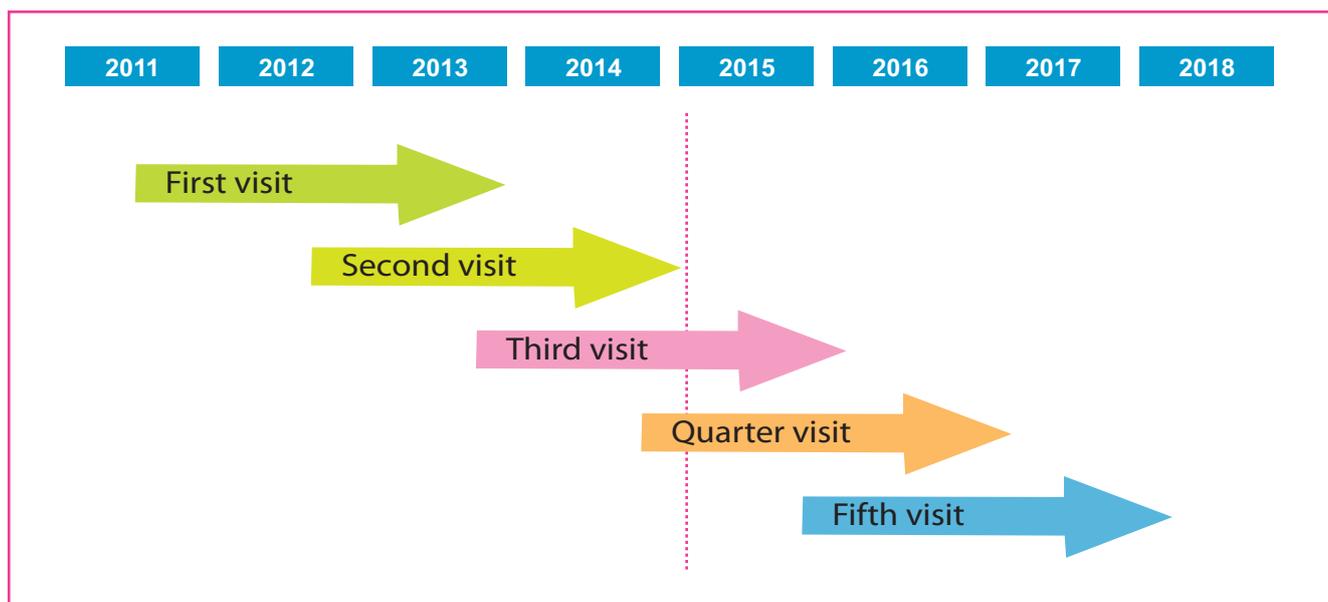
External Scientific Advisory Committee

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 Rodríguez Artalejo and Joaquín Arenas Barbero.

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 and fourth visits from volunteers have been occurring simultaneously during the year 2014, so that the half-way point of this 5-year of this longitudinal study has been passed, as shown in the following figure.

During this year we have also carried out the validation of the data collected so far by the different areas and established a newly created, integrated and anonymized single database, with the aim of ensuring the reliability and security of data and at the same time allow a more effective data analysis. The first analysis (still preliminary) of data from the first two visits has been submitted to the CIEN Foundation Scientific Advisory Committee and members of the Queen Sofia Foundation. We hope to present at international conferences and publish the first scientific papers throughout 2015.



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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 incorporate subjects diagnosed with mild cognitive impairment and mild dementia in future Foundation projects.

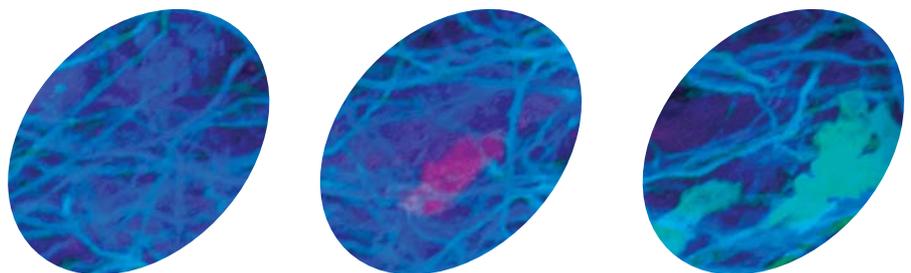
The research model developed at the Alzheimer Center can be equally applied to other residences and other Day Care Centers around the Madrid Region.

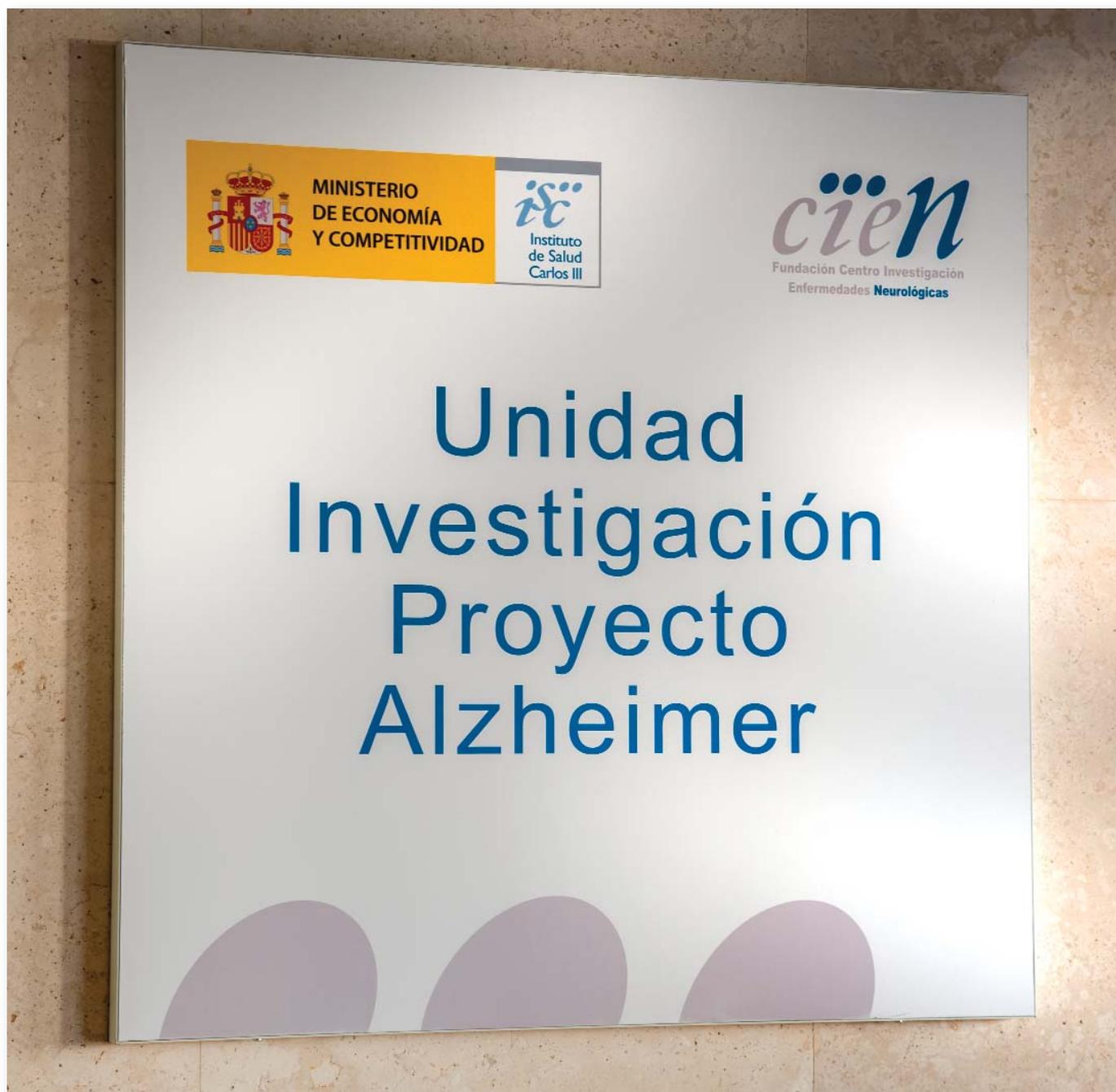
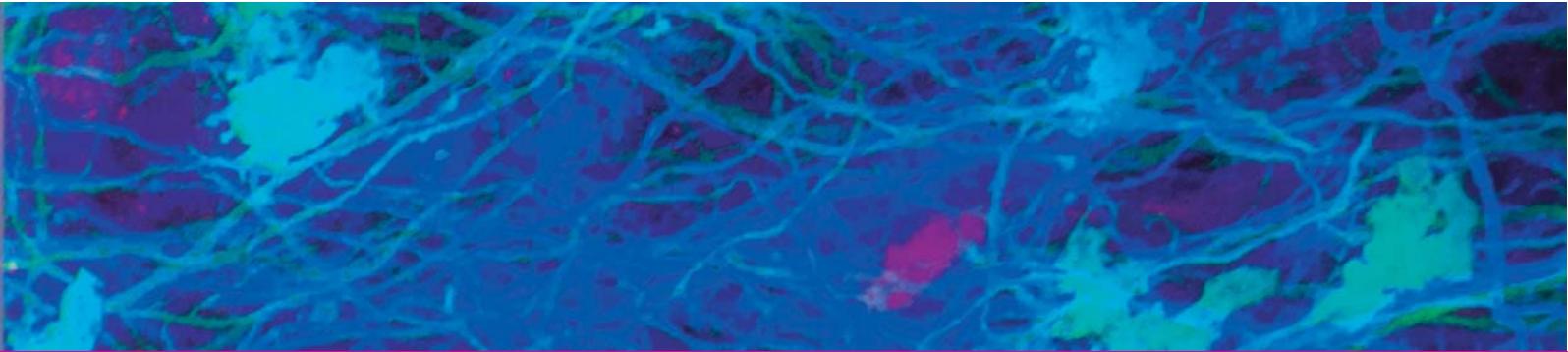
Moreover, a new study (the Madrid+CIEN project) has been designed in collaboration with the Region of Madrid General Directorate for the Elder and the European University, aimed at establishing a cohort of centenarians subjects in our Region. The project aims at establishing the cognitive profile of 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

CIEN Foundation management model is built around three axes: optimization of resources and rationalization of expenditure, multidisciplinary and continued training of professionals as a differential and strategic value, and a commitment to internationalization.





2.1. General management

The budget managed by CIEN Foundation during the year 2014 has seen a significant reduction from previous years, slightly surpassing the three million euros.

This reduction in the budget was due to various factors related to the completion of several agreements between CIEN Foundation and other institutions.

In the first place the termination of the agreement with the Carlos III Institute of Health concerning cooperation in the management of the European Projects Office (OPE, for its acronym in Spanish) and projects associated with that Office. On January 3, 2011 the Carlos III Institute of Health (ISCIII) and CIEN Foundation formalized an agreement for managing the so-called European Project Office project, establishing as its object the collaboration in the maintenance and management of the OPE. Addenda for the years 2012 and 2013 were signed on November 29, 2011 and December 20, 2012, respectively. This agreement ended on December 31, 2013.

The collaboration for managing the "Prevention for combating infectious diseases prevalent in the region of Amhara-Ethiopia" project (Project Amhara-Eth) has also been completed. This cooperation agreement signed with the Carlos III Institute of Health in December 2011, was intended to regulate the collaboration between ISCIII and CIEN Foundation for the financial management of the technical activities envisaged in the "Project for Strengthening Health System Prevention and the fight against infectious diseases prevalent in the region of Amhara-Ethiopia" (Project Amhara-Eth). On April 2, 2012 was renewed for the activities to be carried out until May 2013. A month before the end of this renewal, on April 3, 2013, an extension of the period of performance for nine months was requested. The project ended on December 23, 2013.

Moreover, in 2014 it has also ended the Project Reference Center for the Control of Endemic Diseases

in Equatorial Guinea (CRCE, for its acronym in Spanish), signed in January 2011, extended to a second phase to develop from 2012 until May 2013 and later renewed until February 14, 2014 pursuant to the May 14, 2013 resolution of the Director of the Spanish Agency for International Cooperation for Development (AECID, for its acronym in Spanish). On November 14, 2011 a Resolution of Management Assignment of the Director of the AECID was issued by which the ISCIII was entrusted to carry out the activities covered by the aid in kind.

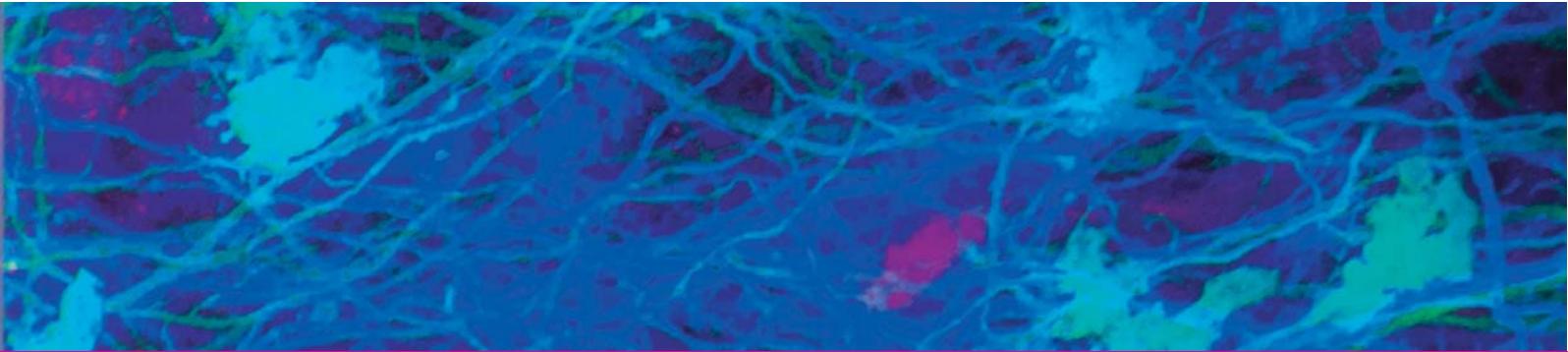
During 2014 CIEN Foundation continues to manage the following activities:

- 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 call is resolved with the approval of five projects, three of them with Spanish participation. 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.

- Agreement between the CIEN Foundation and the Windesheim University of Applied Sciences under the RAAK International Programme for the

collaboration in developing the research project "New friends, old emotions".

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 2014 of 50,000 euros.

The breakdown of total revenues in 2014 and 2013 were as follows:

CIEN FOUNDACIÓN CIEN REVENUES DURING 2014

DESCRIPTION	2014	2013
Grants, donations and legacies charged to surplus for the year	2.521.736,66 €	3.069.526,43 €
Reimbursement of grants and subsidies	828,61 €	30.883,32 €
Sales and other income from commercial activity	103.121,94 €	178.977,61 €
Other income	1.465,65 €	9.190,85 €
Grants, donations and legacies transferred to capital surplus for the year	529.505,06 €	524.966,77 €
Financial income	6.728,54 €	11.013,59 €
TOTAL	3.163.386,46 €	3.824.558,57 €



2. MANAGEMENT REPORT

REVENUES FROM PROVISION OF SERVICES DURING 2014

	2014	2013
Energy production	8.028,32 €	8.166,66 €
Income from performing MRIs and collaborative research projects 2014	95.093,62 €	170.810,95 €
TOTAL	103.121,94 €	178.977,61 €

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

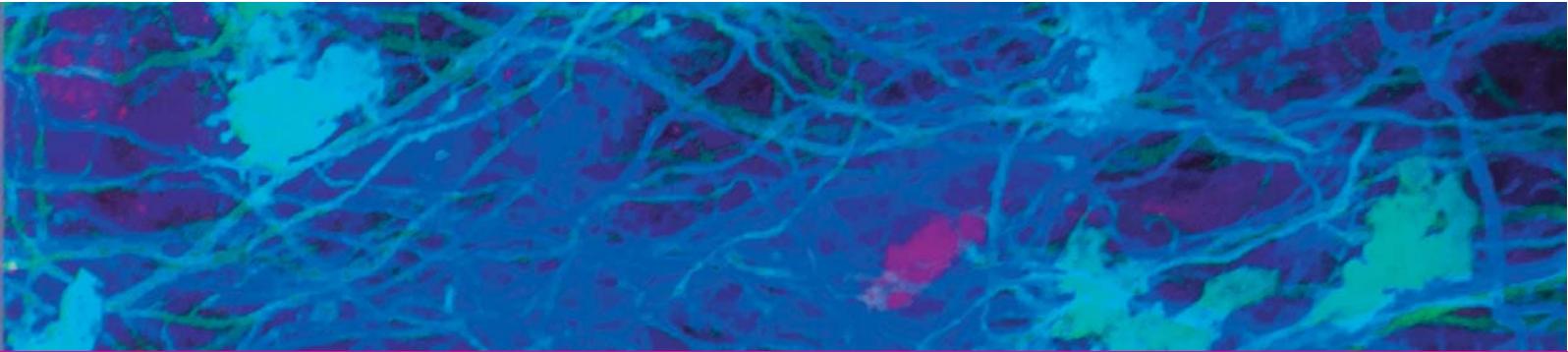
Significantly, there is a decline in revenues from commercial activity developed by the Foundation, primarily through the Department of Neuroimaging, due to the deep restructuring experienced by this department during 2014.

The distribution of expenses in the exercise keeps the proportions of previous years, focusing efforts in maintaining the standard scientific activity. In 2014 25.56% has been allocated to personnel costs, decreasing significantly compared to 2013 because of the end of the management agreements with OPE (and projects that depended thereof) whereas 30.07% were allocated at operating expenses and supplies.

CIEN FOUNDATION EXPENDITURE DURING 2014

	2014	%	2013	%
Monetary aid and others	871.813,84 €	27,71%	240.094,34 €	6,29%
Supplies	203.325,46 €	6,46%	391.619,64 €	10,26%
Staff costs	804.343,96 €	25,56%	1.564.373,15 €	40,99%
Other operating expenses	742.897,00 €	23,61%	1.097.724,90 €	28,76%
Depreciation and amortization	508.804,38 €	16,17%	521.519,31 €	13,66%
Impairment and gains on disposal fixed assets	15.175,15 €	0,48%	1.240,74 €	0,03%
Exchange differences	92,53 €		-	
TOTAL EXPENDITURE	3.146.452,32 €		3.816.572,08 €	





The increase in the item "Monetary aid" reflects the amounts paid to scholars, researchers and other beneficiary institutions to promote research activities corresponding to the calls for International Cooperation Scholarships of the National School of Health, Mapfre Scholarships and the agreement with CIBERNED to manage the CoEN call for projects.

2.3. Management of Human Resources

The strategic and differential value of CIEN Foundation are the people who make up the institution. On this premise, CIEN Foundation is firmly committed to

maintaining investment in research. We view research as an applied model that allows us to translate progress in a benefit to society. In implementing this model the continuous training of our professionals and the retention of talent, two pillars that sustain the future development of CIEN Foundation, it is essential.

Our researchers conduct agile, flexible, dynamic research, adapted to current needs. These features allow us to develop a prestigious, reference research both in Spain and internationally, thanks to the excellent results obtained. And above all, sensitive to



List of CIEN Foundation staff in 2014

Head of Management

- 1 Managing Director
- 1 UIPA Scientific Director

Medical and Research staff by department

- 1 Neuropathologist
- 2 Psychiatrists
- 3 Neurologists
- 3 Psychologists (research projects)
- 1 HEAd of Neuroimaging (Universidad Politécnica de Madrid Agreement)
- 1 Biologist (CIBERNED)
- 1 Biologist (12 de octubre Hospital)
- 1 PhD Engineer Multimodal Neuroimaging, (Madrid M+VISION program)
- 1 University Diploma in Nursing
- 2 APA Technicians
- 3 Neuroimaging Technicians
- 3 Laboratory technicians (private company collaboration agreement)
- 1 Laboratory technician in training (collaboration agreement IES)
- 11 Fellows (collaboration agreement)
- 1 Resident Medical Intern (MIR)
- 5 Department Administrative Assistants

Management and Administration

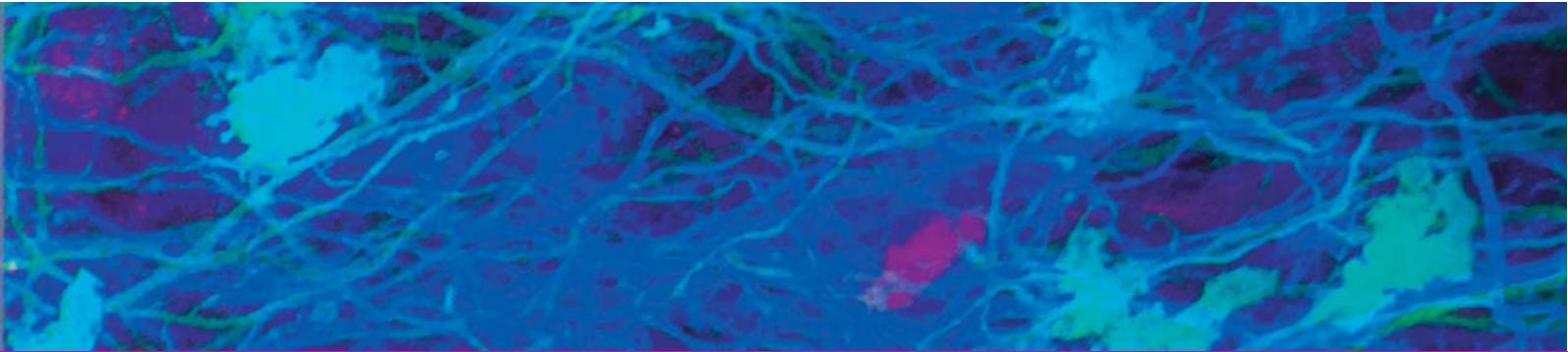
- 1 Managing Director Assistants
- 1 Administrative Officer
- 2 Graduates (CIBERNED)
- 2 Administrative assistants (CIBERNED)

Other staff

- 3 Volunteers

Total staff employed by CIEN Foundation: 29, from which 18 are hired under grants, and 11 under research projects.
Note: out of the total staff employed, 17 are full-time staff, and 12 are part-time.





society, accessible to citizens, and close. A fundamental aspect in a translational research model.

CIEN Foundation is aware that acting in a highly competitive environment such as research requires adding value to society through technical and financial capabilities. All of it framed on values of professionalism, accountability, efficiency and effectiveness in development work, commitment to society, research and scientific progress, and quality management.

Leadership, responsibility, effort and passion for what we do are some attributes that share everyone who is part of CIEN Foundation.

Human resources devoted to carrying out the activities of the Foundation

The CIEN Foundation, in accordance with the policy adopted in previous years, has continued to focus its selective processes to get highly qualified personnel, whose levels of technical and behavioral competencies are appropriate to the published job profiles.

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

The CIEN Foundation, following the guidelines from the Ministry of Economy and Competitiveness, has adjusted the number of calls and hired personnel. All positions offered are defined with a specific profile, required qualifications, requirements and functions to be performed.

During 2014, the CIEN Foundation has counted on a total of 47 professionals, including 29 hired from competitive grants, 11 fellows, 3 volunteers who have collaborated selflessly with the CIEN Foundation, 1 in-training Resident Medical Intern and 5 professionals who developed their activity under signed collaboration agreements.

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.

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)**
- **Diagnostic Guidance Unit (UOD for its acronym in Spanish)**

Human resources devoted to carrying out the activities of the Foundation during 2014 are reflected in the graphs on the following page.

2.3.1 Training Program

Retraining and continuing professional development are two main pillars to achieve the objectives of efficiency and professional training. Training is not only relevant to achieve the required levels of competitiveness and quality, but is also a tool for motivation and creating values, personal and professional growth, and transmission and preservation of



2. MANAGEMENT REPORT

Staff distribution by category in 2014



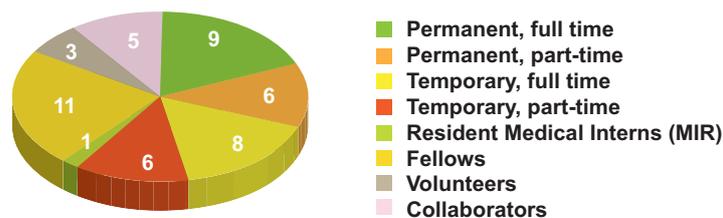
knowledge. All of these are hallmarks of the most advanced and efficient organizations and directly affect the best performance of the members of our organization.

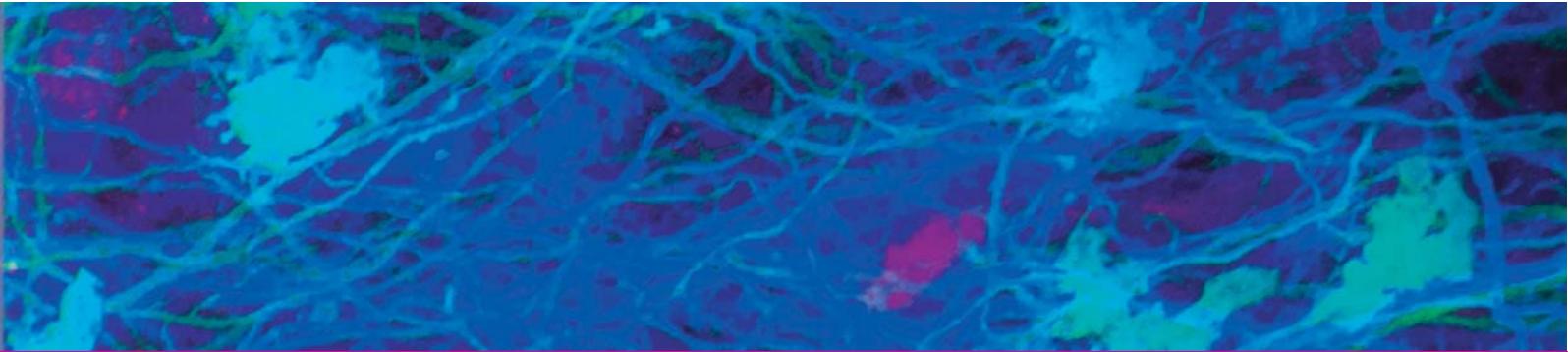
In this regard, the CIEN Foundation develops its Training Program as a key piece that meets the requirements of competitiveness, efficiency and quality and at the same time, satisfy the expectations of professional and personal development of its employees. It comes to encourage and promote all those training activities that enhance professional development for their full integration into the organization, with the commitment to establish an motivating environment and working system.

The following courses, meetings and workshops have been carried out during 2014:

- Course on “Research in patients with cognitive disorder: Neuropsychological Assessment and Intervention”. February 14 – March 8, 2014. CIEN Foundation and León Alzheimer Association. León, Spain.
- “IV Course on Neurodegenerative Dementias”. February 24-28, 2014. UIPA (Alzheimer Project Research Unit, CIEN Foundation- Queen Sofía Foundation) and UNED (Basic Psychology I Department). Madrid, Spain.
- Course on “Prevention of Occupational Hazards in MRI rooms for medical use” May and October, 2014. Institute for Safety and Health at Work, CIEN Foundation. Madrid, Spain.

CIEN Foundation Staff in 2014





- "IV theoretical and practical course on neuroimaging techniques with MRI" June 6-8, 2014. CIEN Foundation, Ministry of Economy and Competitiveness, DIM Foundation and Ruber International. Madrid, Spain.
- "International Day of Radiology" November 12, 2014. CIEN Foundation, Queen Sofia Foundation and Spanish Association of Radiology Technicians (AETR). Madrid. Spain.
- Training Course on Neuropathology. IES Moratalaz. January 2014 – June 2014.
- Training Course on Psychology. Rey Juan Carlos University. February 2013 – June 2013.
- Training Course on Neuropsychology. Autonomous University of Madrid. October 2014 – January 2015.
- 6 months MAPFRE scholarships for abroad stays, renewable for a similar period (maximum 12 months). January 2014 – January 2015.
- Training Course on Law. Carlos III University. February– May 2014.

2.3.2 Prevention of Occupational Hazards

The activities related to occupational safety and health carried out by the CIEN Foundation in 2014 can be summarized as those listed below:

- In collaboration with the External Prevention Service, in early 2014 the Risk Assessment of facilities and all job positions has been revised, in order to assess the current and real situation of the Foundation for the year. New information sheets have been developed regarding the specific risks of the job and the measures to be taken in each case, as well as a new planning of preventive activity.
- As for activities related to emergency situations, classroom specific training in fire prevention and emergency has been provided prior to the annual fire drill, held in May. All staff received information about "Basic rules of action in case of emergencies", "Basic Instructions of action for Intervention Teams", "Basic rules of Fire Prevention and basic performance standards

for Evacuation Teams" Furthermore, the workers responsible for the coordination and performance in an emergency were formally designated.

In addition to this emergency campaign, a second campaign was conducted specifically to address musculoskeletal injuries. Each employee received the "Guide for the Care of the back".

- As for health monitoring, there have been 23 specific medical examinations.

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

The research projects, fellowships and grants managed by the CIEN Foundation aim to support and promote research and study on Alzheimer's and related diseases, enhance researcher's mobility facilitating that some part of their training can be carried out in renowned research centers, and promote clinical research as well as research into health outcomes and translational research.

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.

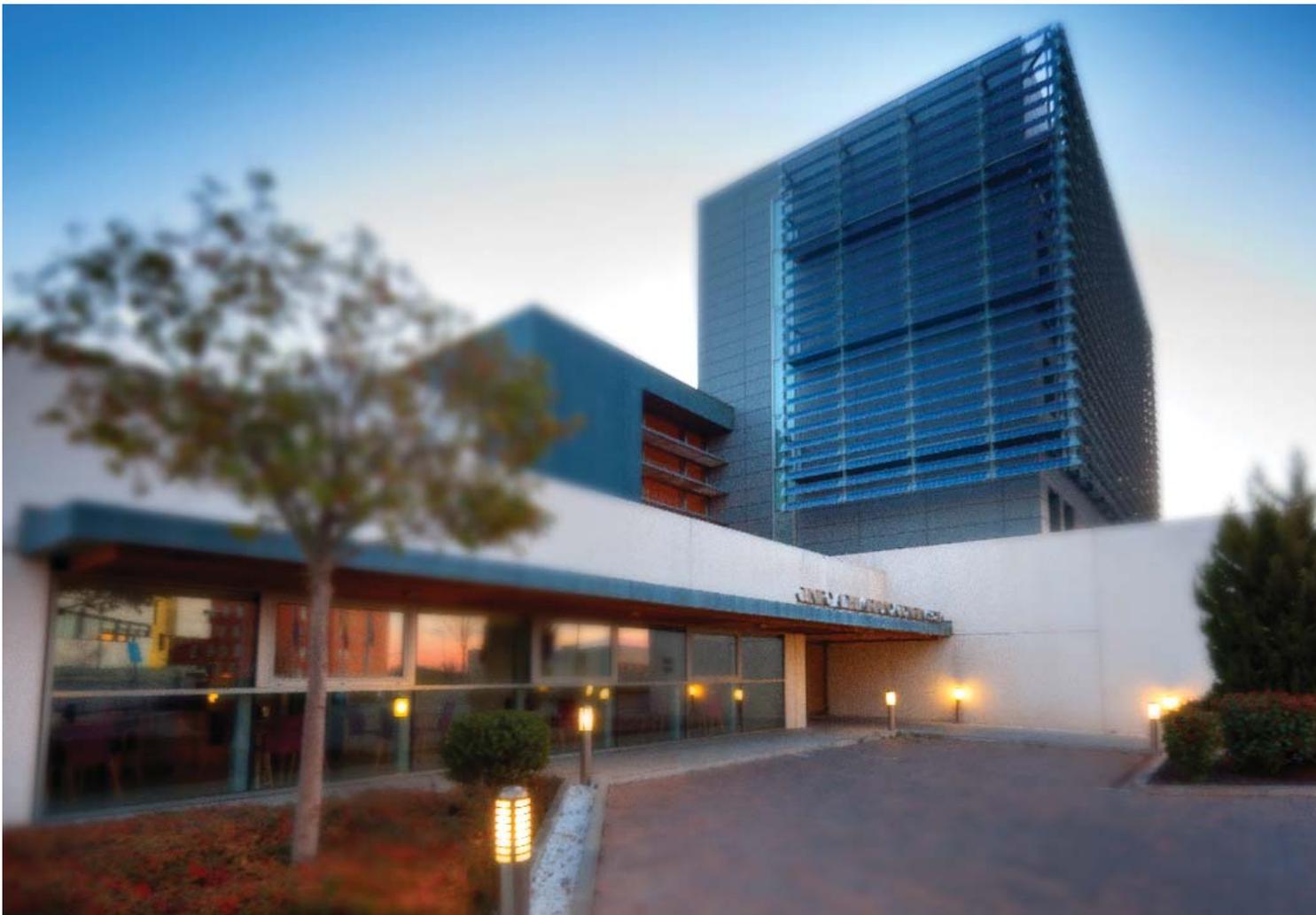


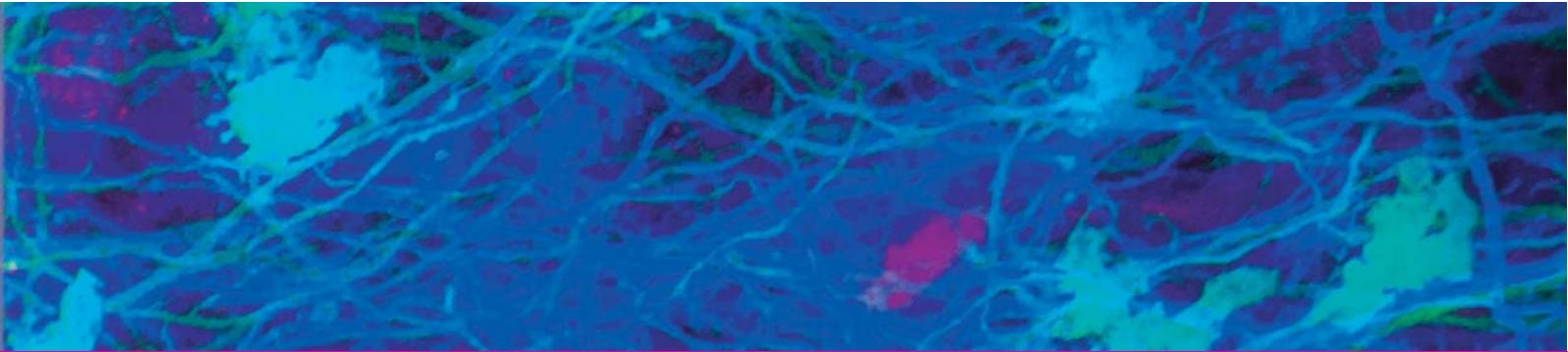
2. MANAGEMENT REPORT

The CIEN Foundation recognizes the importance of research and collaboration among all levels of society, in its effort to improve the living conditions of the current society and its continued interest in deepening the understanding of diseases causing dementia. It is also aware of the deep distress caused both in the individual and its environment as well as society in general, and for that reason promotes collaboration with various entities having similar concerns.

With this objective it has worked during 2014 in a number of actions financed through its own funds along with other donations and grants received, and whose main projects are:

- Vallecas Project: Multidisciplinary study for early detection of Alzheimer's disease. 2014 budget: 329,039.60€.
- Research projects awarded under competitive calls active during 2014:





- 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 2014 adds up to 7,2865.00€ (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 2014 adds up to 41,062.50€ (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 46,500.00€ for 2014. 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 2014 the CIEN Foundation has awarded the following fellowships and grants:

- MAPFRE-Queen Sofia Foundation Fellowship. Stay of six months, renewable for a similar period (maximum 12 months). Research Program in Dementia at the Alzheimer's Disease Center, the University of Texas, San Antonio, supervised by Prof. George Perry, and the Case Western Reserve University. Cleveland, Ohio.
- MAPFRE-Queen Sofia Foundation Fellowship stay extension Implementation of the fellowship extension granted in 2012: Stay for six months from January to July 2014.. Research Program, Department of Pathology and Psychiatry, Alzheimer's Disease Center at NYU School of

Medicine, New York, supervised by Prof. B. Frangione.

2.5. Quality Policy

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

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.

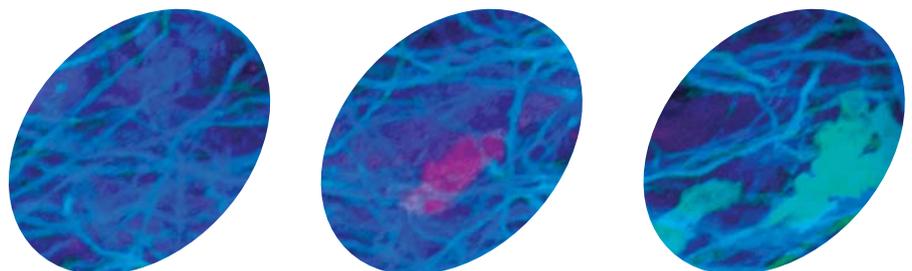


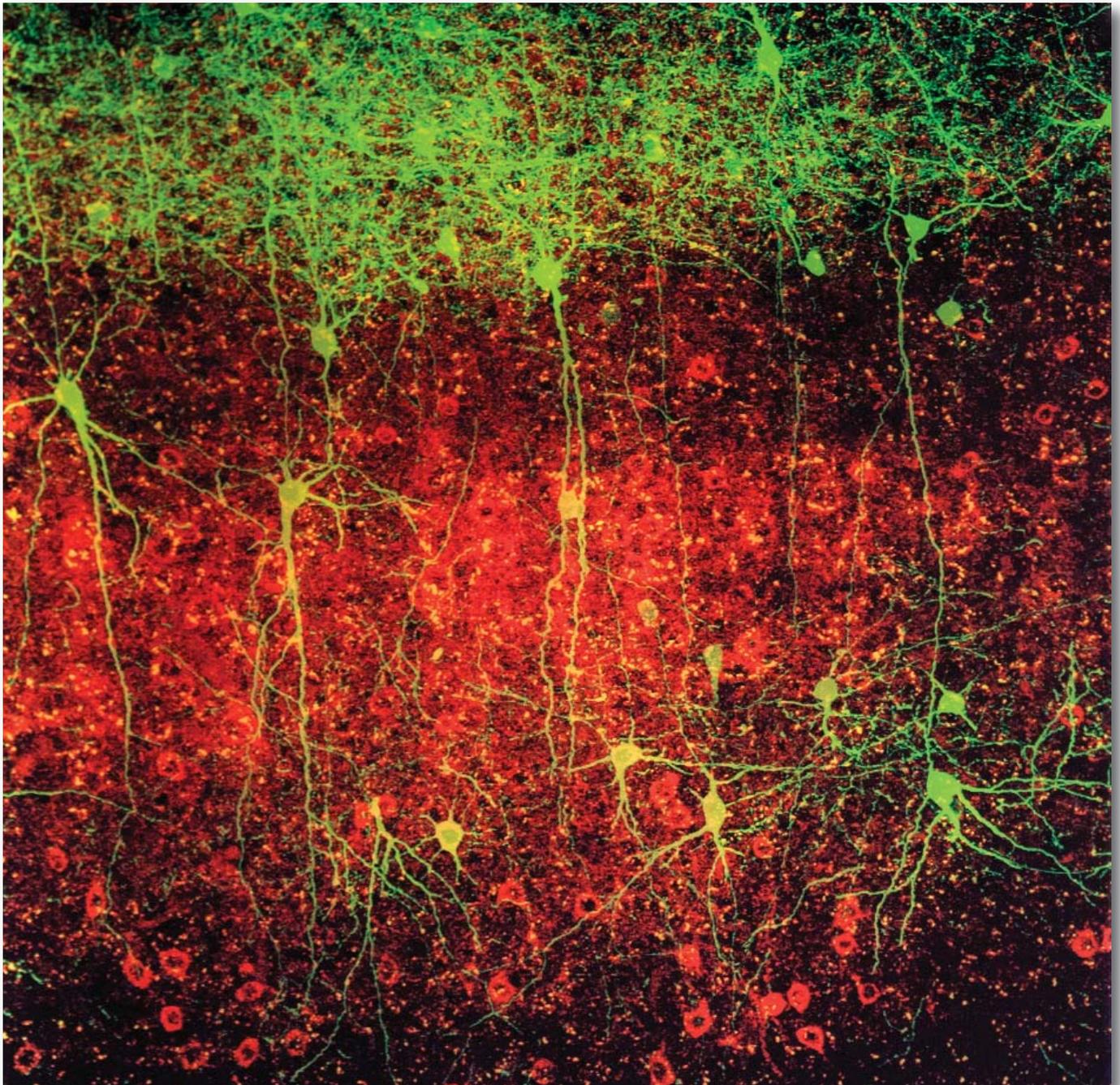
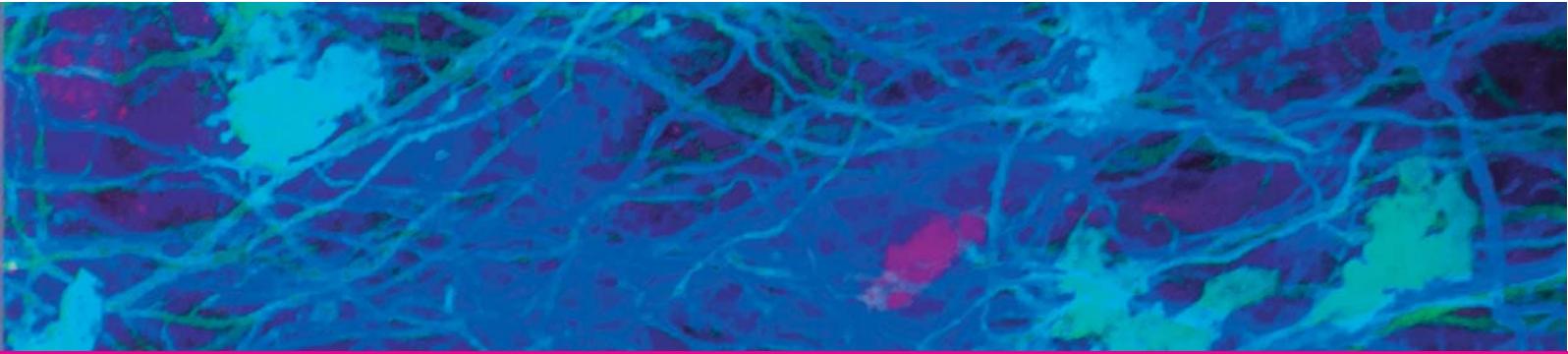
CIEN Foundation - CIBERNED Administration Team



Scientific activity

The UIPA consists of four departmental areas: Multidisciplinary Support Unit, Neuroimaging, Neuropathology and Laboratory, and Diagnostic Guidance Unit. Among the new research projects launched this year it can highlight the study 'Detection of proteins in tears as biomarkers of AD' and the participation of BT-CIEN in the National Biobank Network Platform promoted and funded by the ISCIII.





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, genetic and molecular 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

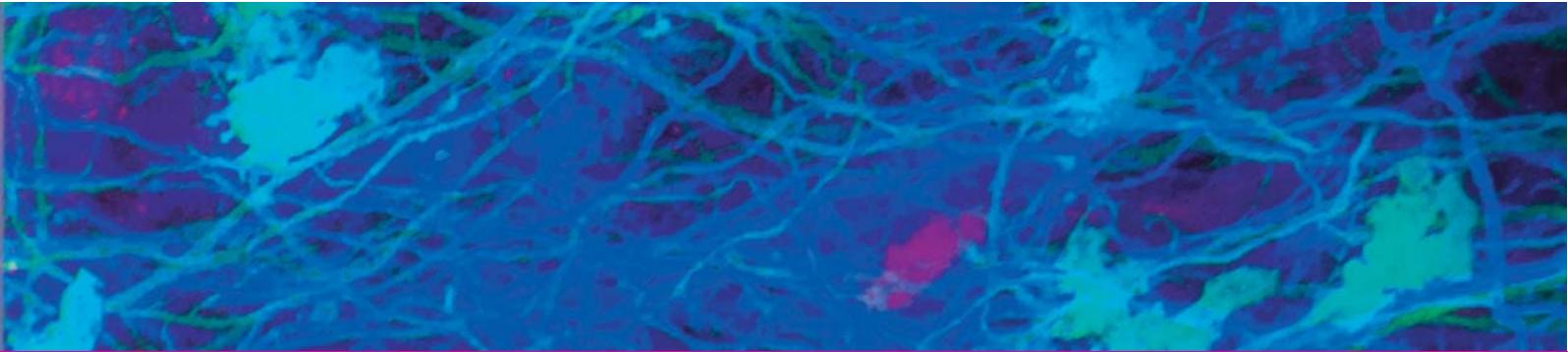
The scientific activity of UIPA is structured around four complementary research areas:

- 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 work of these patients. As described below, one of the UMA research lines involves conducting a clinical, syndromic, and etiologic 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 Biochemistry, Molecular and Cell Biology; Pathology;





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 developing 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 knowing UIPA's research purpose, authorizing and collaborating with the research groups.

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 so-

ciological 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

Among the various activities carried out within the UMA, unit personnel 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 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.

Finally, UMA staff plays a mediating role between basic researchers, patients relatives and caregivers. This role is critical for patients, their relatives and ca-



3. SCIENTIFIC ACTIVITY

regivers knowing UIPA's research purpose, authorizing and collaborating with the internal and external research lines.

In 2014 there were 45 admissions at Day Center and Residence, 30 of whom signed consent to participate in regular multidisciplinary evaluations. Along with the 30 baseline assessments, a total of 268 clinical evaluations (every six months), 42 brain MRI studies (annually) and 352 blood tests were performed.

Research projects

CIEN 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:

New friends, old emotions (Nieuwe vrienden, oude emoties)

CIEN Foundation collaborates with the University of Windesheim Flevoland and other centers such as: Zuyd University of Applied Sciences, La Salle, Zorggroep Almere, Flevoland Woonzorg and Dignis Lentis, in the embodiment of a guide for the use of robot animals in care for elderly people with dementia,

designed for healthcare professionals and caregivers

Currently, there are technical instructions on the use of robots but there are no guidelines on its use in therapy for people with dementia. In this project, therapists and researchers from the CIEN Foundation and the Queen Sofia Foundation Alzheimer Center contribute their knowledge and experience acquired over the years within the "Robototherapy in dementia" clinical trial.

Project REGISTRY

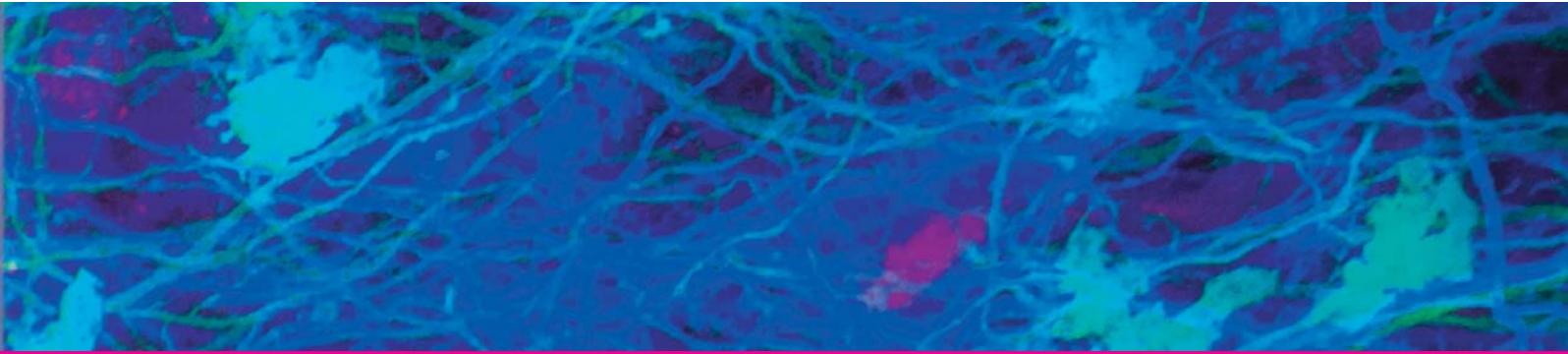
REGISTRY is an international multicenter observational study conducted by the European Group on Huntington's disease (EHDN, for its acronym in Spanish) with the following objectives:

- 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

PERIODIC MULTIDISCIPLINARY ASSESSMENTS DURING 2014

Admissions in Day Centre and Residence	45
Informed Consents	30
Baseline Assessments	30
Clinical Evaluations	268
Brain MRI Studies	42
Blood testing	352





3. SCIENTIFIC ACTIVITY

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 been carried out 173 centers of 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.

During the second half of 2015, REGISTRY will make way for ENROLL-HD, a prospective registry study of a HD global cohort (Europe, USA, Canada, Argentina, Chile and others).

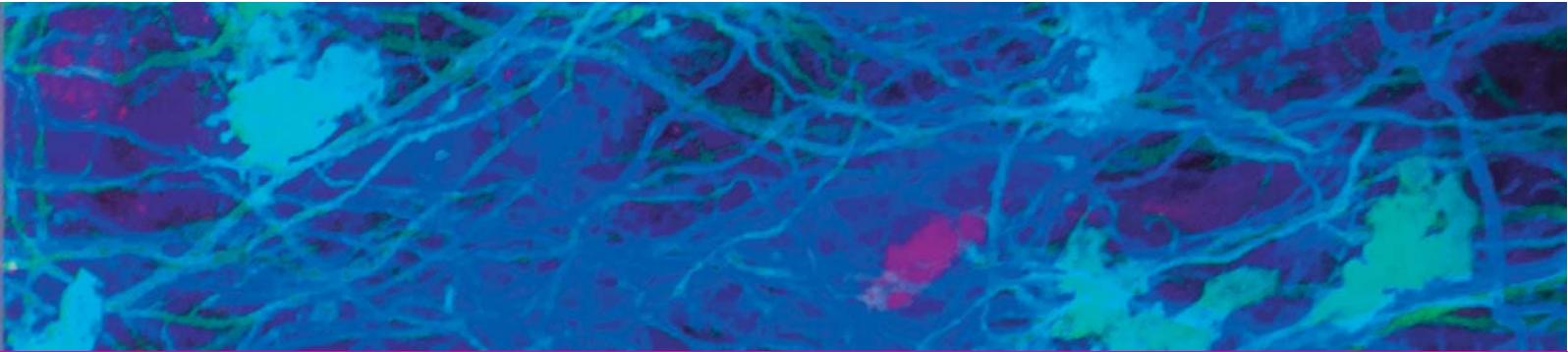
Study to evaluate the contribution of vascular pathology to the clinical-pathological correlation in advanced dementia

Alzheimer's disease is the most prevalent form of dementia in our environment. However, both neuroimaging and postmortem analysis of brain tissue have shown that quite often the Alzheimer's pathology is associated with concomitant vascular injury. Thus, it is now beginning to think that cognitive decline in patients with dementia may be a direct consequence of both types of pathology. This hypothesis is particularly interesting to the extent that if we were able to identify specific cognitive profiles for Alzheimer's disease and vascular disease, both diagnosis and intervention with these patients would improve.

However, unlike what happens with the neuropathological criteria for Alzheimer's disease, there are no consensus criteria for vascular pathology. The joint application of a classification system that combines both types of lesions would allow to quantify cognitive deficit underlying each type of pathology. With that idea, a study to jointly apply neuropathological criteria for Alzheimer's disease and vascular pathology was launched in 2013.

The combination of both approaches in 70 brains donated from CAFRS to BT-CIEN has allowed to classify a cohort of residents in our center with advanced dementia (64.1% exclusively with Alzheimer's





disease, 6.3% with vascular dementia and 29.6% with mixed dementia). Furthermore, we have studied the relationship between diagnosis and a series of cognitive and motor tests.

Specifically, significant differences were observed in cognitive evaluation tests in so far as the vascular group showed superior cognitive performance to the other two conditions. Also, the fact that no difference was appreciated between groups of AD and mixed dementia suggests that once the Alzheimer disease has spread through the vascular damage cortex has little added effect on the cognitive status of the patient. Therefore, these results support the combined use of Alzheimer and vascular pathology scales to characterize the cognitive profile of patients with advanced dementia.

The work was submitted to the prestigious scientific journal *Alzheimer's & Dementia*, being accepted later in the year for publication in 2015: Zea-Sevilla MA, Fernández-Blázquez MA, Calero M, Bermejo-Velasco P, Rábano A. "Combined Alzheimer's disease and cerebrovascular staging explains advanced dementia cognition". *Alzheimers Dement*. 2015 Mar 21. pii: S1552-5260(15)00059-X. doi: 0.1016/j.jalz.2015.01.004, [Epub ahead of print].

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-Abeta42) 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.

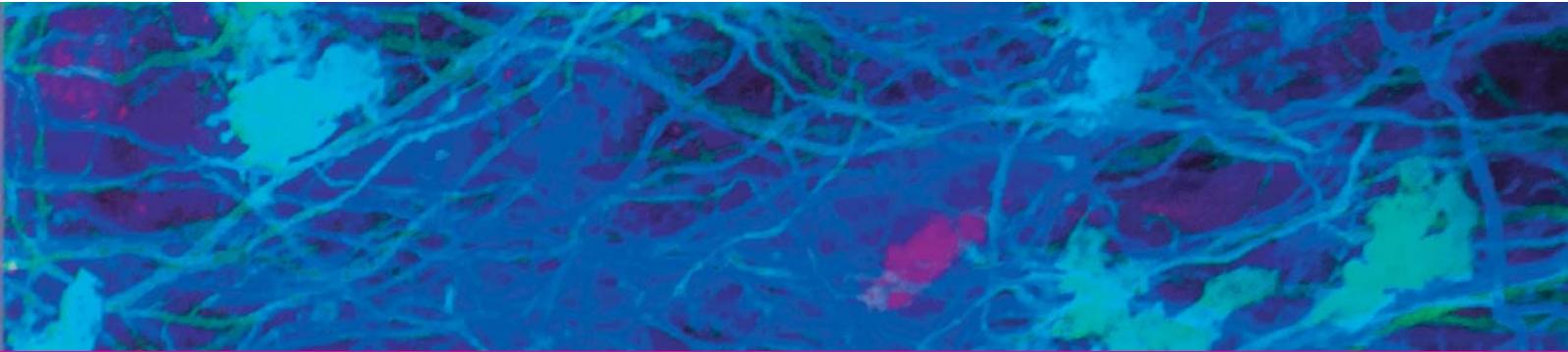
The objectives of the project are:

- 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



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(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.

The project started in 2014 and will continue in 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. In late 2014, 60 samples of tears had been already collected, a figure that will continue to increase during 2015.

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 methods 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

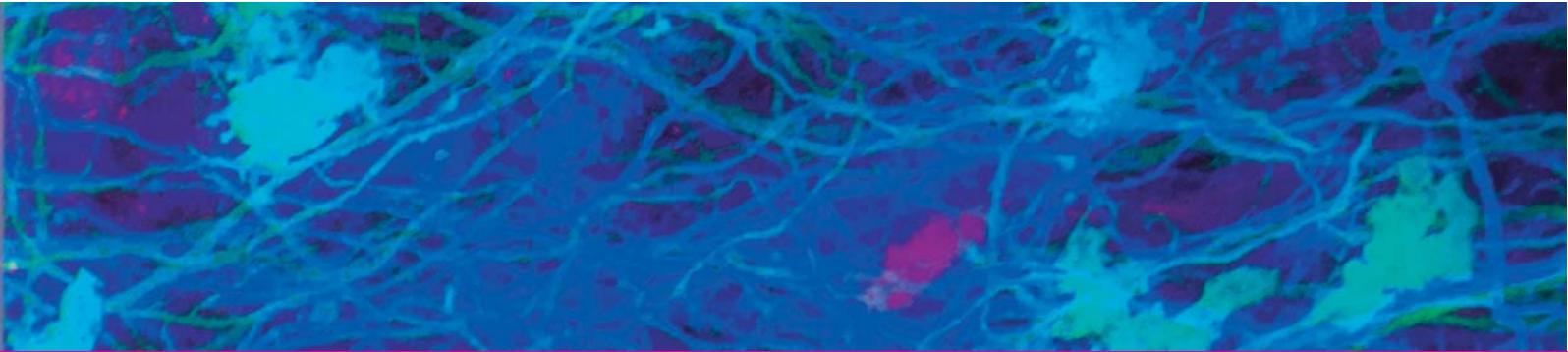


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members as well as with the application of different existing validated scales that assess behavioral and psychological symptoms of dementia (BPSD), caregiver burden, functionality and overall cognition.

- Study "Personalized music treatment of agitation states in dementia". A pilot project to assess the efficacy, safety and tolerability of using a single type of music therapy, personalized music, has been conducted in 32 patients from both the Day Center and the Residence at the Queen Sofia Foundation Alzheimer Center (CAFRS). The aim is to explore the usefulness of a form of non-pharmacological treatment (NPT) that is inexpensive, easy to apply and does not require a qualified professional application. Currently the project is in the phase of analysis of results.
 - Apathy: The study of apathy in dementia is one of the main and oldest research lines in the area of psychiatry at the UMA. The following review article has been published this year. "Apathy in dementia. From neurobiology to the clinic". Lopez-Alvarez J and Agüera-Ortiz L., *Informaciones psiquiátricas* 2014 (216): 15-34. ISBN: 0210-7279, and we have continued the development of an article on apathy in patients with moderate and/or severe dementia and different neuroimaging (volumetric study, FLAIR and diffusion tensor), and have conducted advisory work for data analysis of study "Rotherapy in Dementia
 - 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.
- Drugs in the Vallecas Project: There is growing scientific evidence of the deleterious effects of polypharmacy and specific drugs on cognition in the elderly. There is conflicting evidence about an alleged "dementing" effect of drugs with anticholinergic action, from articles with more "soft" scenarios, where these drugs would relate to worst cross- performance in cognitive tests, but without leading to longitudinal deterioration or dementia up to articles with "harder" hypothesis, in which a real risk that these drugs increase over time the likelihood of cognitive impairment and dementia is found. First, an update of the state of the art was carried out, that resulted in indexed review article in 2014: Lopez-Alvarez A, Zea-Sevilla MA, Agüera-Ortiz L, Fernández-Blázquez MA, Valenti-Soler, M, Martinez -Martin P. "Effect of drugs on cognitive impairment anticholinergic in the elderly. *Journal of Psychiatry and Mental Health*". January-March 2015; 8 (1): 35-43. PubMed PMID: 25087132. Epub 2014/08/05. Extensive information on the medication received by all participants in the first visit of Vallecas project has been collected and a correlation between the consumption of certain drugs and no-recollection of medication was found (still unpublished). The next goal is the search for correlations between polypharmacy and/or consumption of specific drugs, such as anticholinergics and neuropsychological variables.
 - Longitudinal study of CAFRS patients: It consists gathering information biannually from all patients both at Day 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 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 semester information is collected on NPI, IA and APADEM-NH. Information from Day Center patients is gathered through telephone interviews with relatives of reference. In the first semester information is collected on Neuropsychiatry Inventory (NPI), Cornell Scale for Depression in Dementia, Cohen-Mansfield Agitation Scale in Dementia (CMAI) and the Apathy Inventory (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.

Team

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

Area of Neurology

- Pablo Martínez-Martín
(Dr. Medicine, Neurology)
UIPA Scientific Director (until March 2014)
- Javier Olazarán Rodríguez
(Dr. Medicine, Neurology)
UMA Coordinator
- Meritxell Valentí Soler
(Grad. Medicine, Neurology)
- María Ascensión Zea Sevilla
(Dr. Medicine, Neurology)

Area of Psychiatry

- Luis Agüera Ortiz
(Dr. Medicine, Psychiatry)
- Jorge López Álvarez
(Grad. Medicine, Psychiatry)

Area of Neuropsychology

- Miguel Ángel Fernández Blázquez
(Grad. Psychology, Neuropsychology)
Neuropsychology Coordinator
- Belén Frades Payo
(Grad. Psychology, Neuropsychology)
- Marina Ávila Villanueva
(Grad. Psychology, Neuropsychology)

UMA Administration

- Francisca Martínez Lois
(Administrative Assistant)



3. SCIENTIFIC ACTIVITY

Collaborators

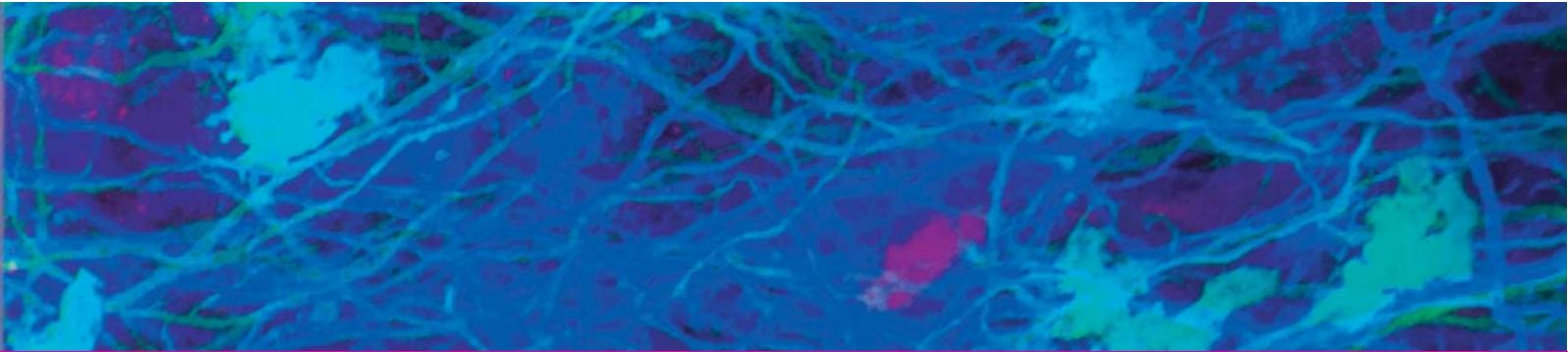
The following CAFRS staff also collaborated during 2014:

- Irene Rodríguez Pérez (Occupational therapist)
- Almudena Pérez (Occupational therapist)
- Laura Carrasco Chillón (Occupational therapist)
- Cynthia Pérez Muñano (Technician in training and Occupational therapist)
- Emma Osa Ruiz (Physiotherapist)
- Silvia Felipe Ruiz (Physiotherapist).
- Ester Huélamo Sáez (Physiotherapist)
- Carolina Mendoza Rebolledo (Grad. Psychology, Neuropsychology)
- Gema Melcón Borrego (Social worker)
- Lidia Espada Raboso (Social worker).
- Belén González Lahera (Grad. Medicine, Geriatrics)



UMA Team





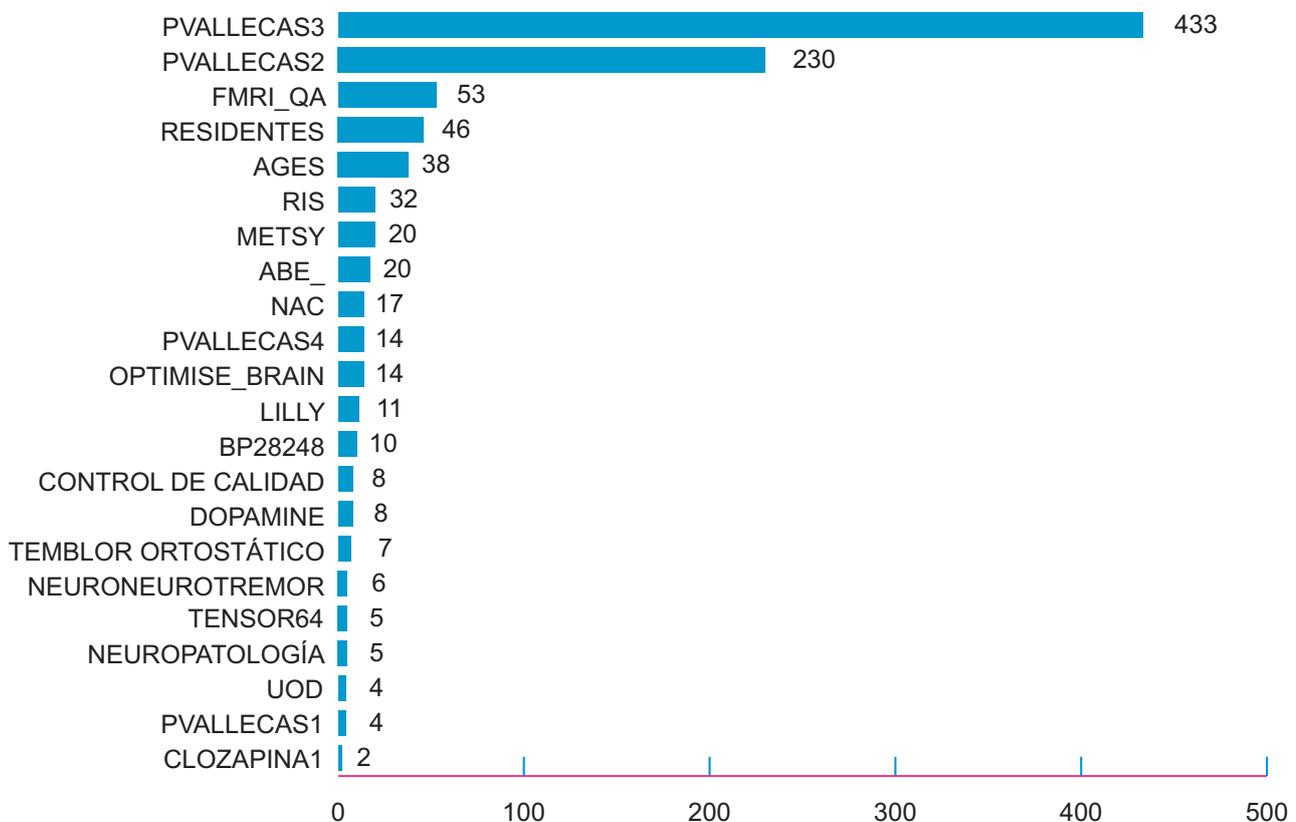
3.2.2 .Department of Neuroimaging

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 diag-

nosis 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 mi-

Number of visitors according to origin in 2014



3. SCIENTIFIC ACTIVITY

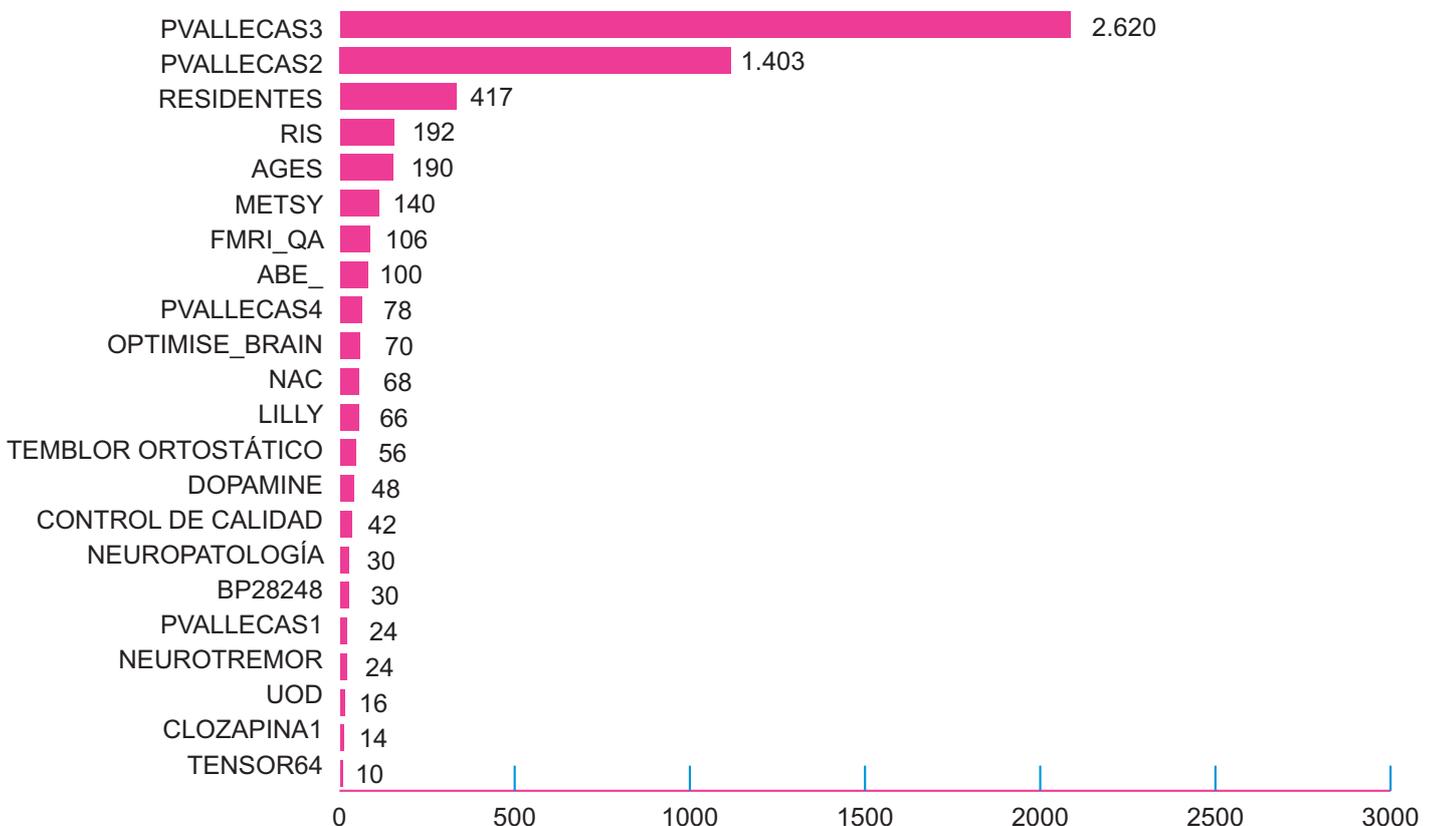
crostructural changes dependent on age who have been described in post-mortem studies of brain tissue.

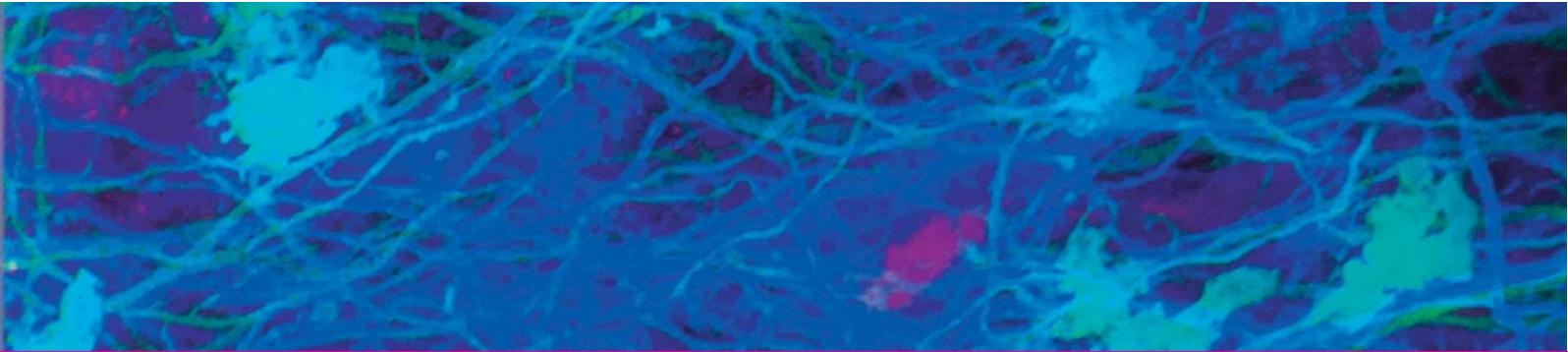
For this reason, the Department of Neuroimaging has a state-of-the-art 3 Tesla (T) MRI equipment as well as a collaboration agreement for research with the supplier: General Electric.

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

Number of studies according to origin in 2014





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 2014 the Department of Neuroimaging has participated in MRI studies in the following clinical trials:

- "Lilly" (Multicentric, European) • "Eli Lilly H8A-MC-LZAN". Effect of passive immunization on the evolution of Alzheimer's disease: LY2062430 against placebo.
- "Optimise" PI: R. Kahn. University Medical Center Utrech. 2011-2013. CIBERSAM.
- "Clozapine in early outbreaks of schizophrenia as potential preventive treatment from brain 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 Marañon Hospital. PI: Celso Arango.
- "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 2014 the acquisition of MR images from a total of 687 subjects has been completed. Overall, 5,744 MRI studies have been performed since the establishment of the department among the different research projects.

A total of 38,378 MRI sequences have been conducted since the creation of the department, distributed by year and type of sequence as shown in the chart below.

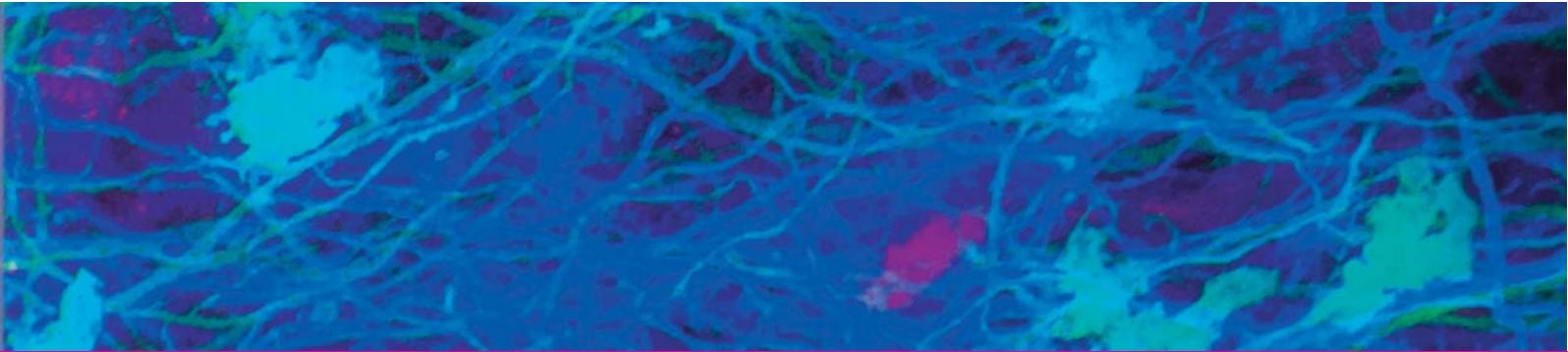
Provision of services

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.



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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

- Christopher J.Long (PhD, Engineering, Specialist in Biomechanical Imaging, Madrid-Massachusetts Institute of Technology Vision Program)
- Alba Sierra-Marcos (Grad. Medicine, Neurology)

Radiodiagnostics

- Mabel Torres Llacsá (Grad. Medicine, Radiodiagnostics)



3. SCIENTIFIC ACTIVITY

Image Acquisition

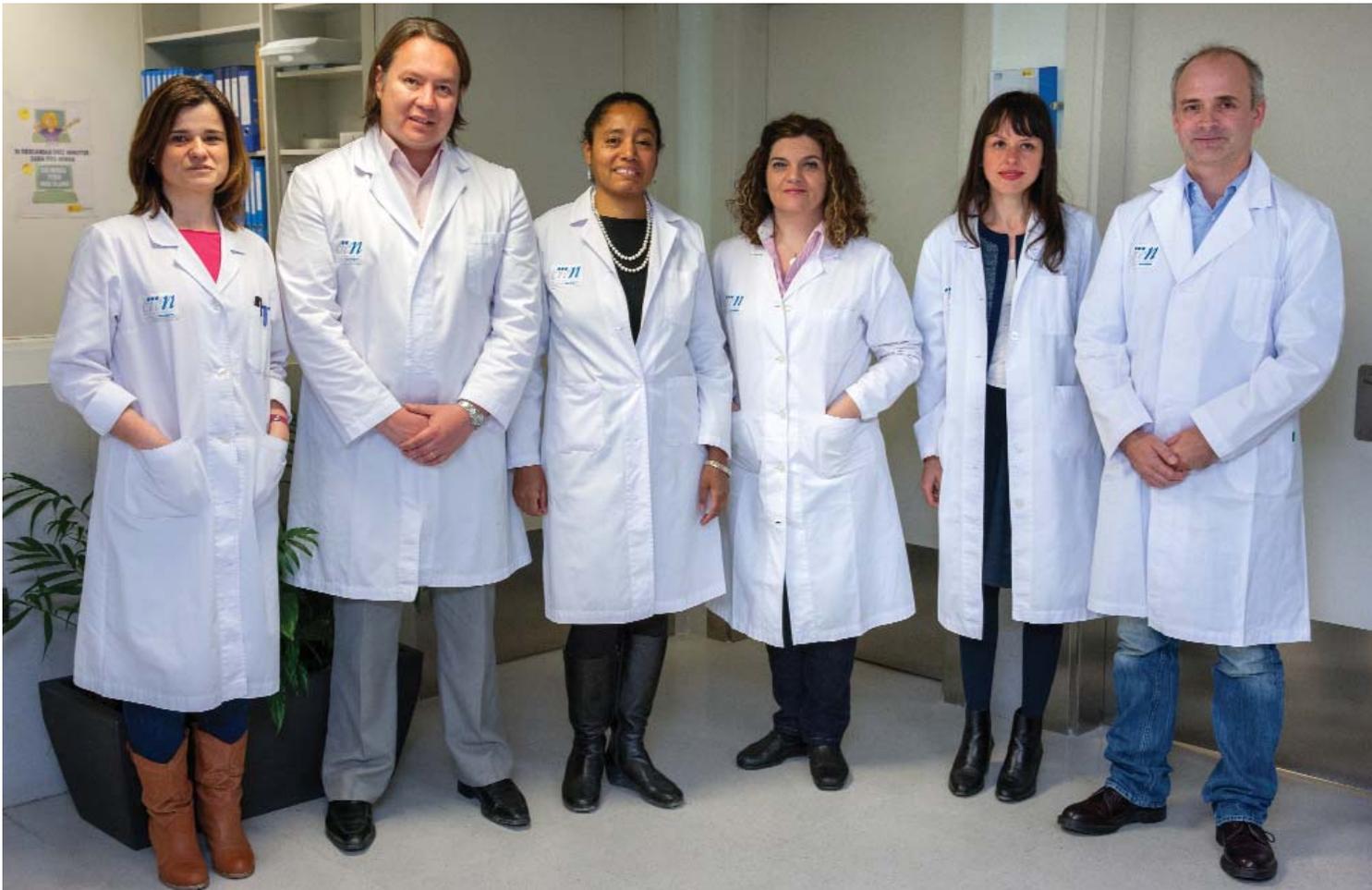
- Eva Alfayate Sáez
(Technical Coordinator Técnico in Radiodiagnostics)
- Felipe García Fernández
(Advanced Technician in Diagnostic Imaging)
- Carmen Rojas Obregón
(Technician in Radiodiagnostics)

Administration

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

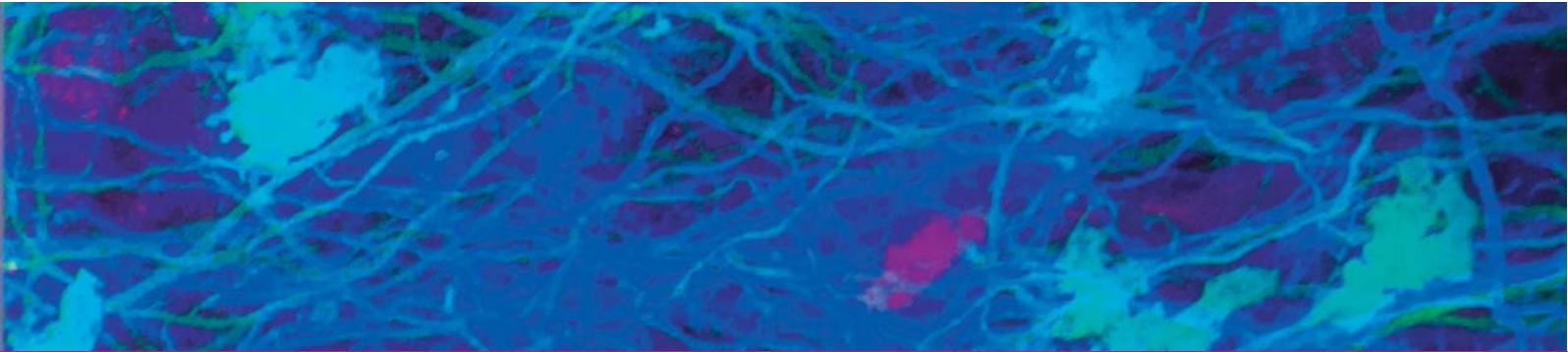
Collaborators

- Roberto García Álvarez
(PhD, Physics)



Neuroimaging Team





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, specially 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.

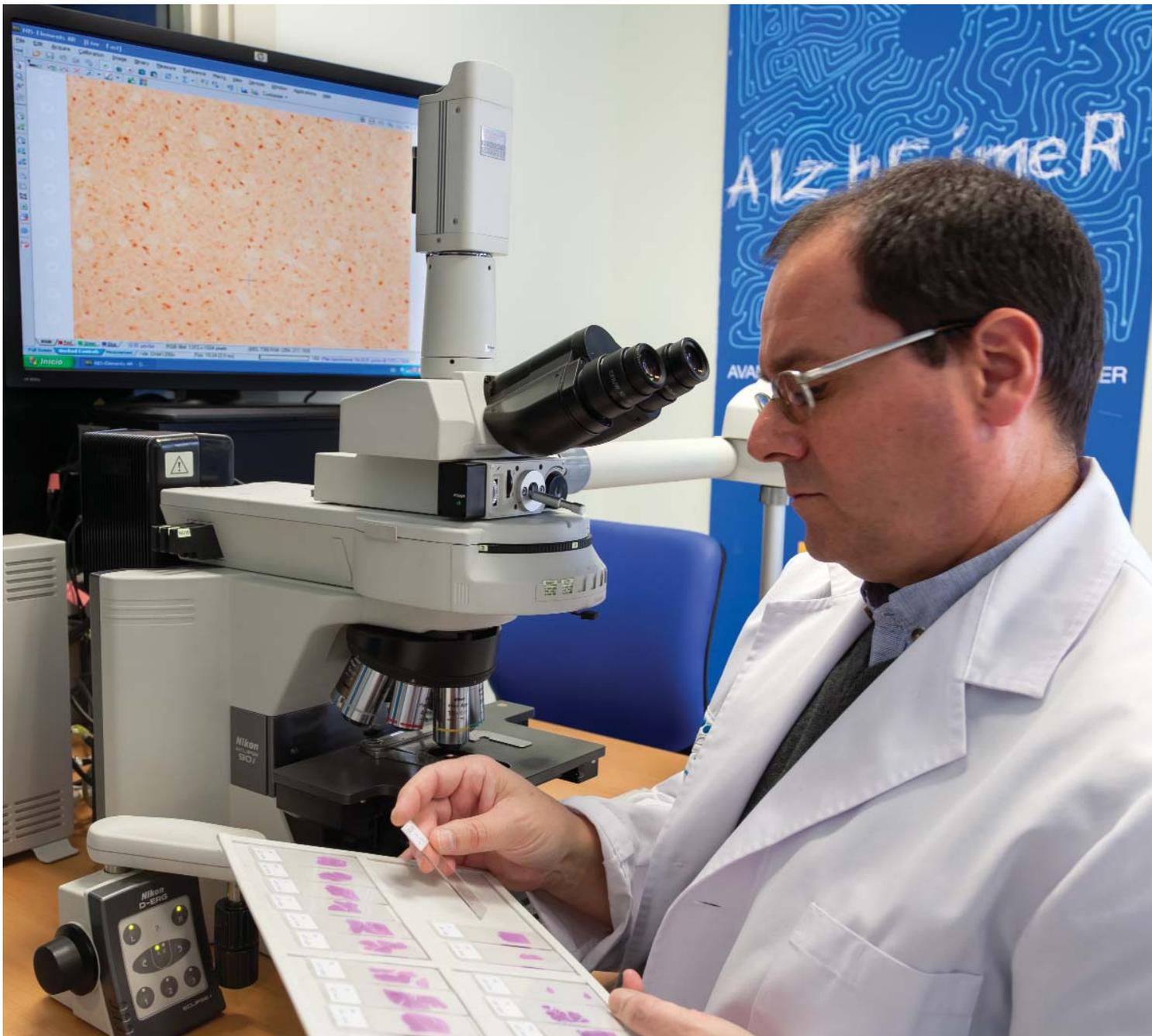
Among the active lines of research in the Department are the following:

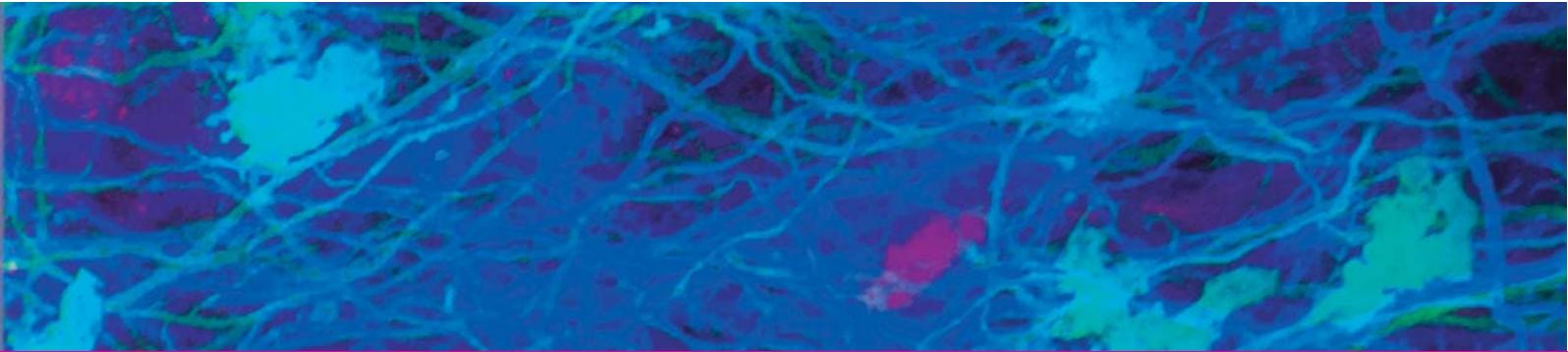
- Neuropathological and molecular study of tauopathies, including Alzheimer's disease. Pathogenic significance and spread of associated cellular lesions.
- Clinicopathological profiles in advanced dementia. Characterization of cerebral small vessel vascular disease.
- Distinctive features of Alzheimer-type 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:



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Age-associated Alzheimer's pathology profile (The 85+CIEN Study)

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.

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.

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, that 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 Re-



3. SCIENTIFIC ACTIVITY

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

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

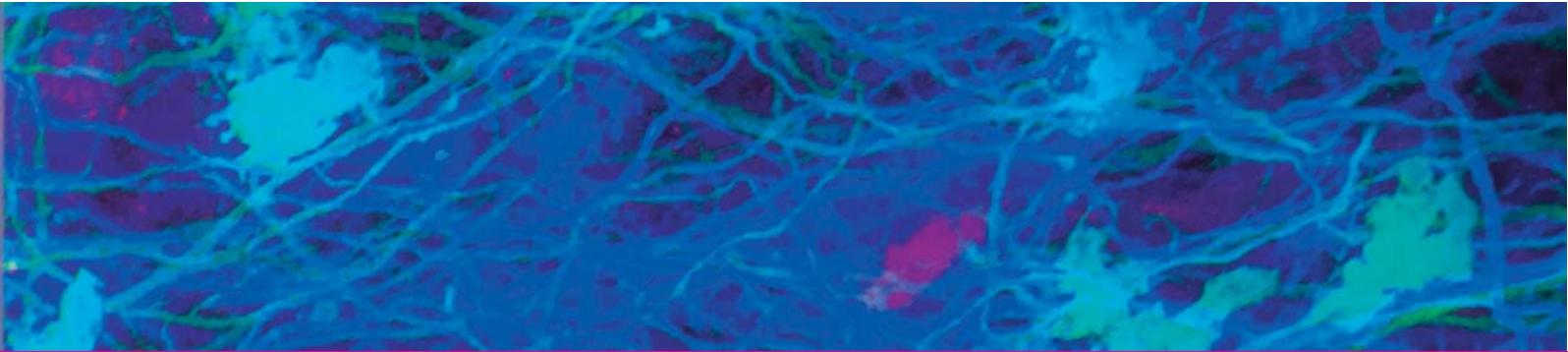
In January 2014 the Biobanks National Network Platform (PRNBB, for its acronym in Spanish), promoted and funded by the Carlos III Institute of Health (2014-2017) was constituted, with participation of the main biobanks in the country, both hospital and non-hospital, including BT-CIEN. PRNBB mission is to create a stable organizational structure that allows the coordinated activity of participating biobanks in the collection, management and transfer of biological samples of human origin. Moreover, the BT-CIEN has renewed its ISO 9001/2008 quality certification.

The BT-CIEN registry had over 600 registered donors by December 31, 2014. 106 new donors were enrolled during 2014.

115 cases were processed in the Neuropathology laboratory during 2014, with the following distribution depending on the origin:

- 60 donations from the External Program
- 12 donations from the Internal Program
- 43 consultation cases





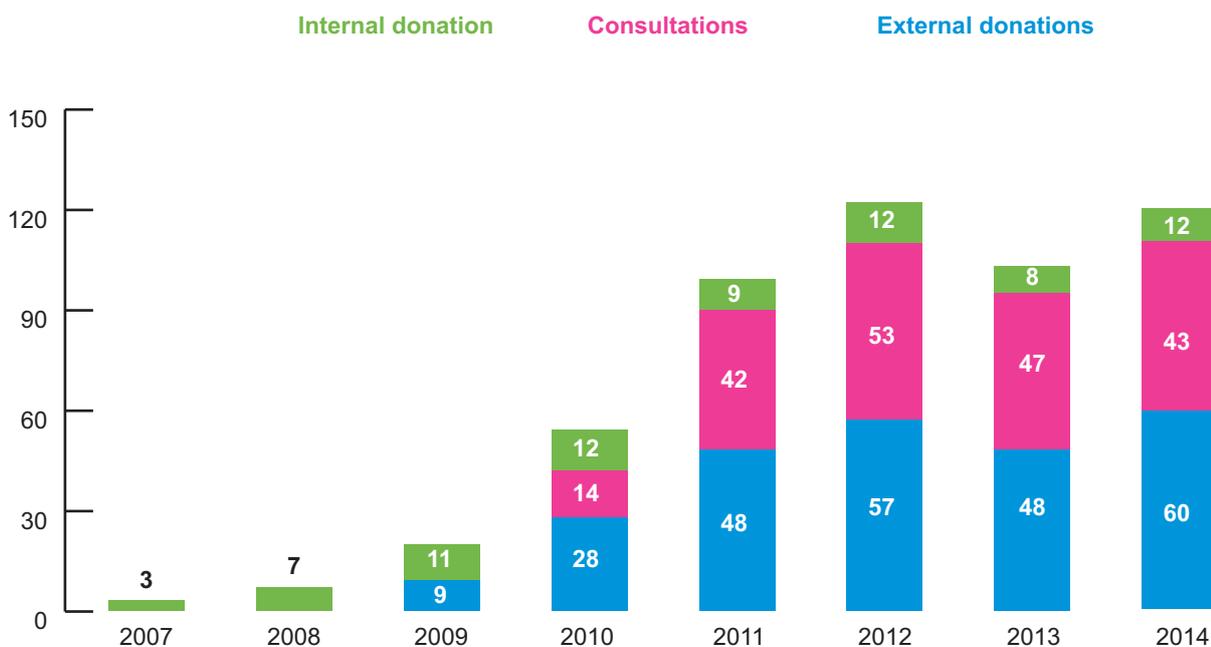
Hence, the number of donation cases extracted and processed entirely at the UIPA during 2014 went up to 72. It is thus observed a stabilization of the number of studied cases at the BT-CIEN in the range of 100-120 annually, and donations extracted in the BT-CIEN in the range of 50-75 per year.

In 2013 the average post-mortem interval obtained is 5.9 hours, slightly longer than the average of previous years, mainly due to the higher of external donations coming from different Regions.

The Research Centers that have received samples from BT-CIEN during 2013 have been:

- Center for Biomedical Research, CSIC, Madrid.
- National Center of Microbiology, ISCIII, Madrid.
- National Hospital of Paraplegics, Toledo, SESCAM (2 research groups).
- School of Medicine, Complutense University, Madrid.
- University of Vigo.
- Institute for Health Research I+12, Madrid.
- Grenoble Institut des Neurosciences, Grenoble.
- Center for Molecular Biology "Severo Ochoa", CSIC, Madrid.
- Center of Biomedical Technology, Technical University, Madrid.

Distribution of donation cases by origin in 2014



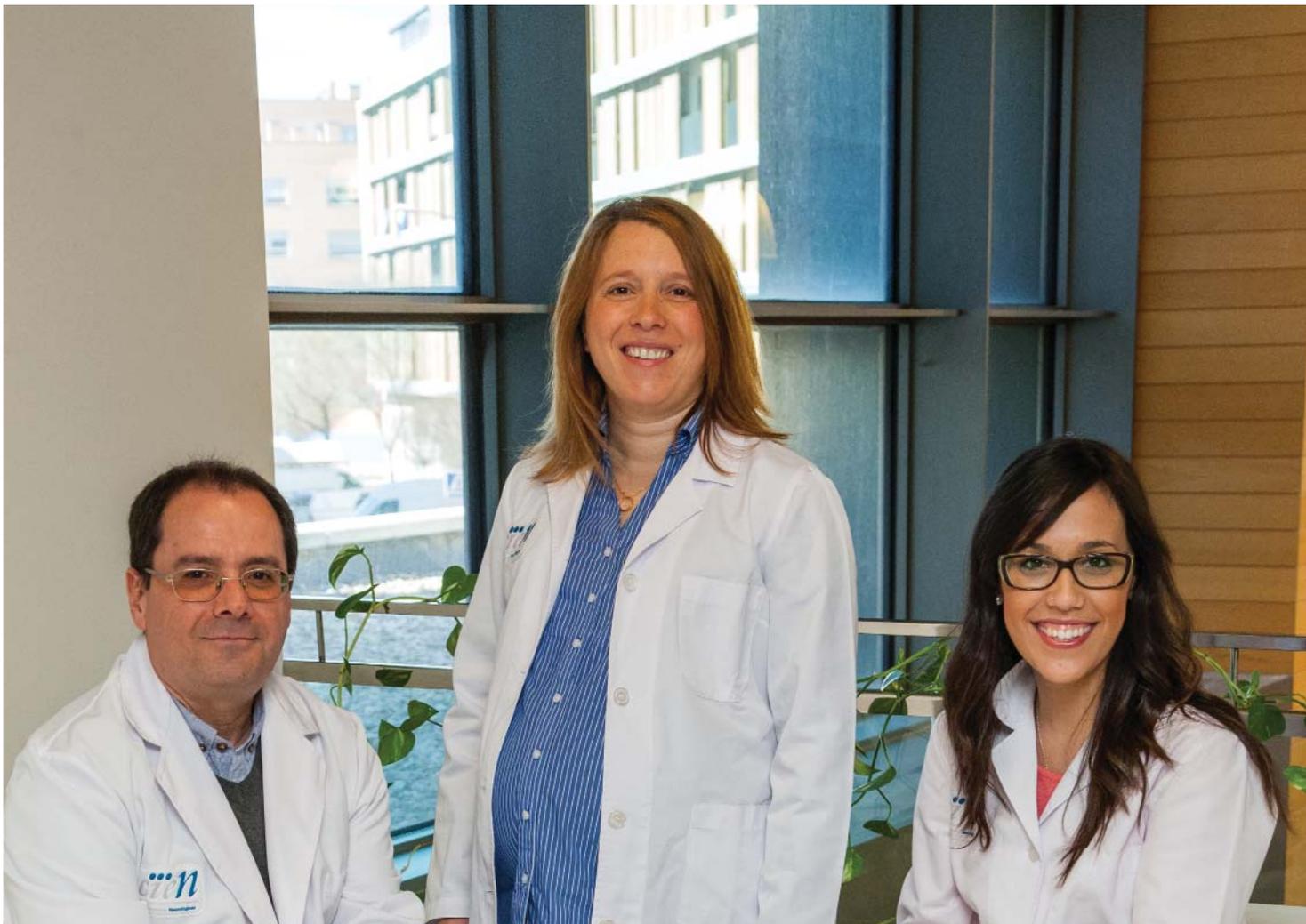
3. SCIENTIFIC ACTIVITY

By the end of 2014, the accumulated number of the BT-CIEN donations was 328, of which about 50% are cases of Alzheimer-type pathology.

Team

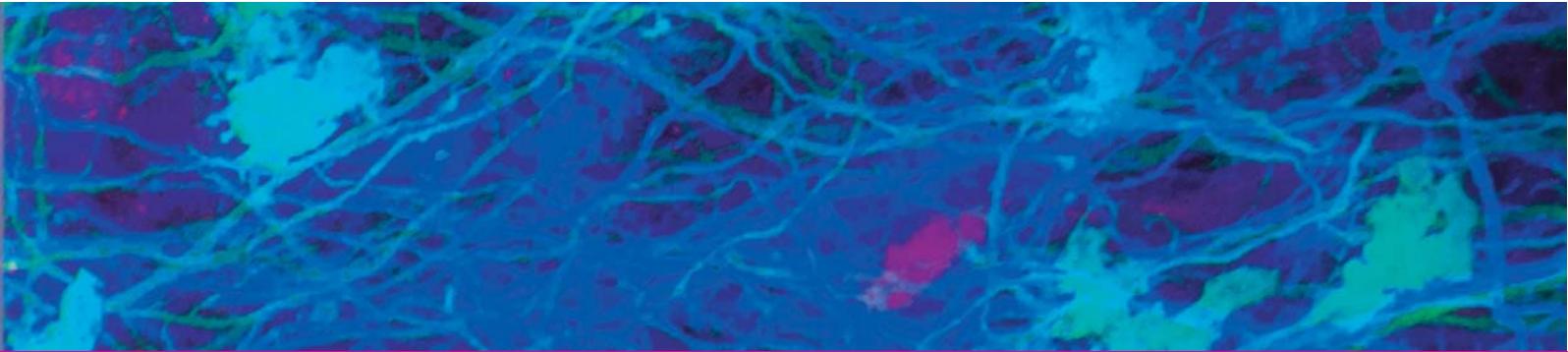
During 2014, the Department of Neuropathology staff was composed of the following professionals:

- Dr. Alberto Rábano (Grad. Medicine, Pathology), Head of Department and BT-CIEN
- Luis Javier Martín Lentijo (Pathology Technician)
- Elena Gómez Blázquez (Pathology Technician)
- Izaskun Rodal González (Pathology Technician)



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 (PA) 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 (IC) by a family member or guardian. The PA 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 protocols of the biobank. The total number of samples incorporated to the BT-CIEN so far, corresponding to the Alzheimer project monitoring program, adds up

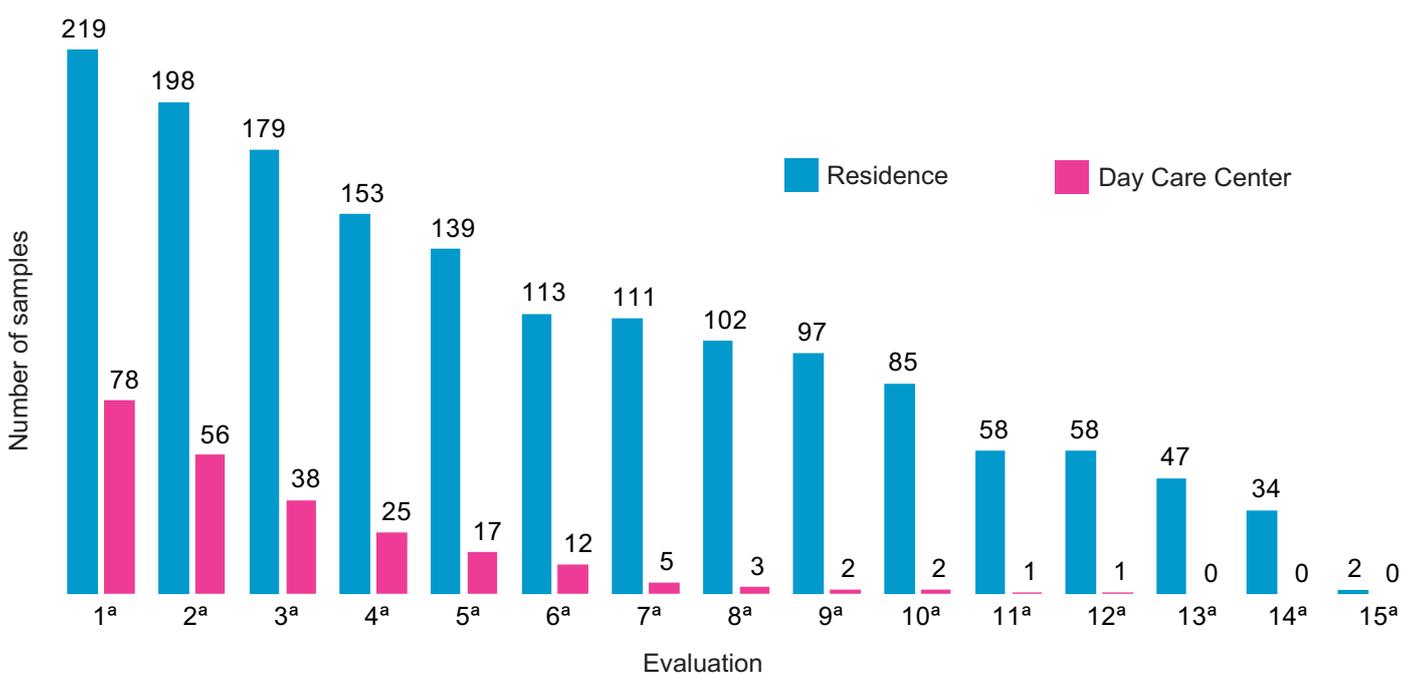
to 1,595 (13.1% patients corresponding to the Day Centre), which have resulted in a total of 25,690 aliquots.

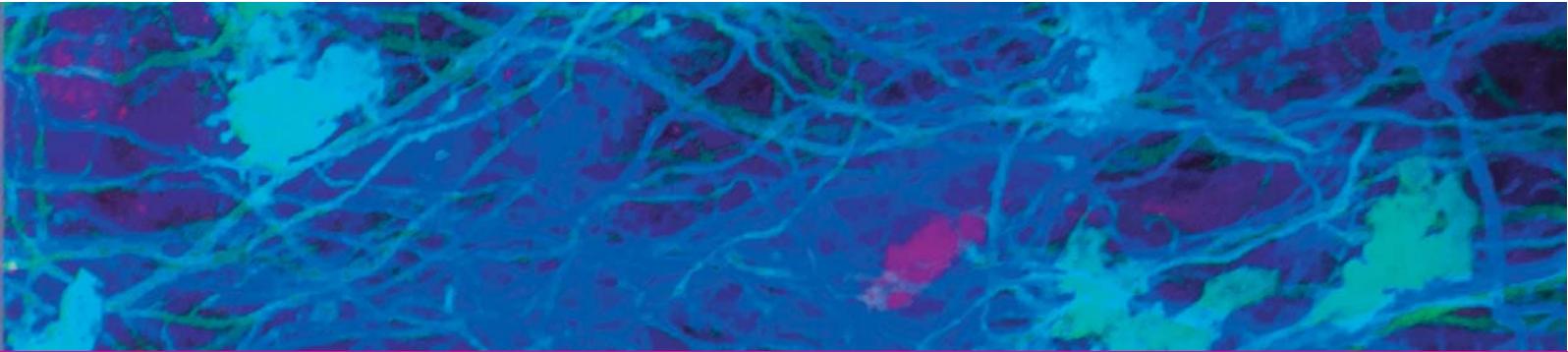
EConsistent with other studies, the analysis of the APOE gene polymorphism in CAFRS patients revealed a high presence of allele $\epsilon 4$, that in this population appears to be more prevalent in men. Also, the phenomenon of advancement of the age of onset of Alzheimer's disease associated with the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

The Vallecas Project

It is currently known that the pathological processes that determine Alzheimer begin many years before

Samples obtained up to Dec 31, 2014 according to the number of biannual evaluation



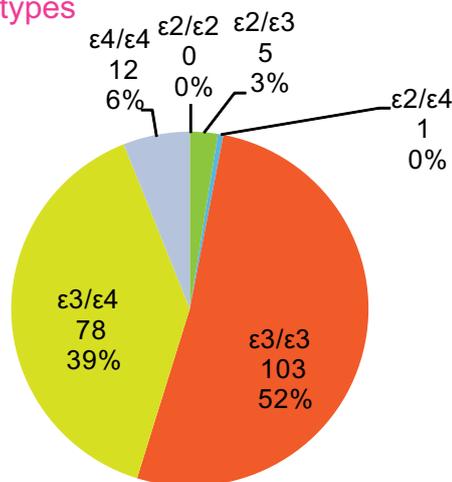


the disease leads to the first noticeable symptoms in patients. Years before that future drug treatments preventing or slowing down disease progression could be applied to the "population at risk" who has developed these subclinical lesions, or has an higher risk of developing it than the rest of the 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.

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, for its acronym in Spanish), Neuroimaging, and Laboratory. During 2014 we have studied 161 volunteers to complete the first follow-up study, 527 volunteers on the second visit and 15 from the third visit.

Distribution of APOE genotypes in the CAFRS patients cohort

APOE Genotypes



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 1). Additionally, one blood tube (BD-CPT citrate Vacutainer) for the isolation of mononuclear leukocytes, together with another tube lacking anticoagulant to obtain serum are processed.

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

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

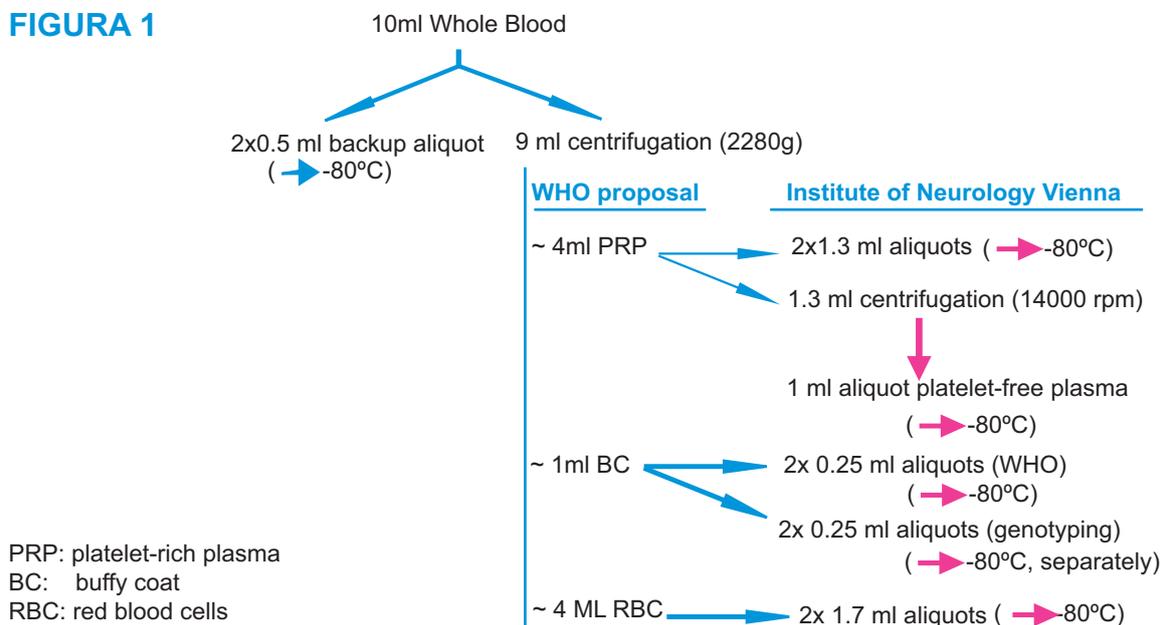
Finally, in this context, it is important to emphasize that the samples obtained from Vallecas Project volunteers aged between 70 and 85 years that include a comprehensive assessment of cognitive, sociological and neuroimaging state are optimal for its use as a control population in various projects 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.



3. SCIENTIFIC ACTIVITY

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

FIGURA 1



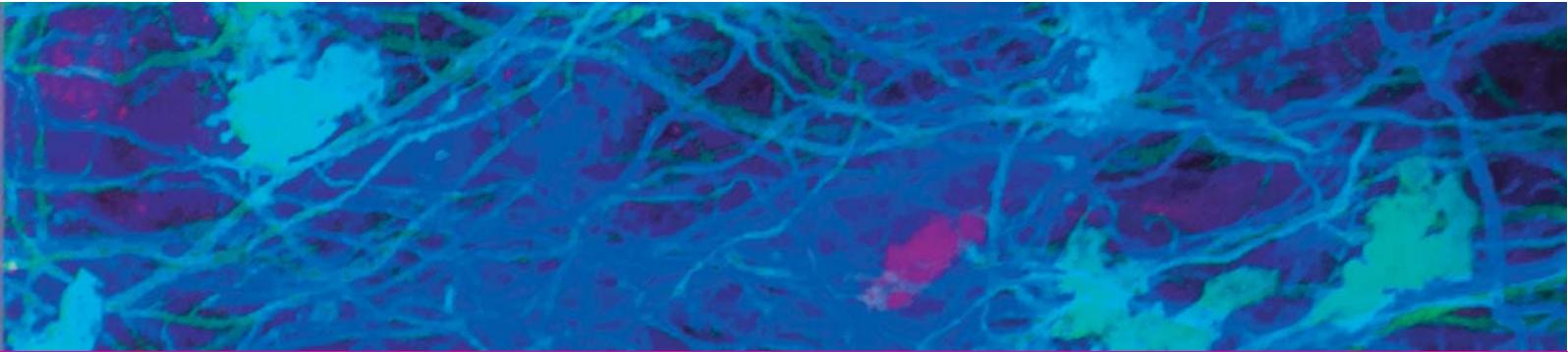
In this sense, we are currently working on three different research projects based on the joint use of biochemical markers and genetic data to define endophenotypes. Specifically, funding has been obtained for the following research lines:

- 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 granr, Innpackto program)

The Vallecas Project activity in figures:

EVALUATION	1°	2°	3°	4°	TOTAL
Extractions(n)	1.212	829	577	15	2.633
Aliquots (n)	16.968	11.606	8.078	210	36.862





Also during this year, CIEN Foundation has joined the consortium of Genetics in Dementia (DEGESCO), in which several Spanish groups pool genetic data for greater power in genetic studies of dementia and especially Alzheimer's disease.

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, PI-CALM, 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 on clinical, neuroimaging, biochemical or pathological outcomes (See figures 2 and 3 in the following page).

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

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

APOE genotype	2/2	2/3	2/4	3/3	3/4	4/4	Total
Normal	3	104	9	750	161	6	1.033
AD-type cognitive dysfunction	1	8	1	78	31	5	124
Total	4	112	10	828	192	11	1.157

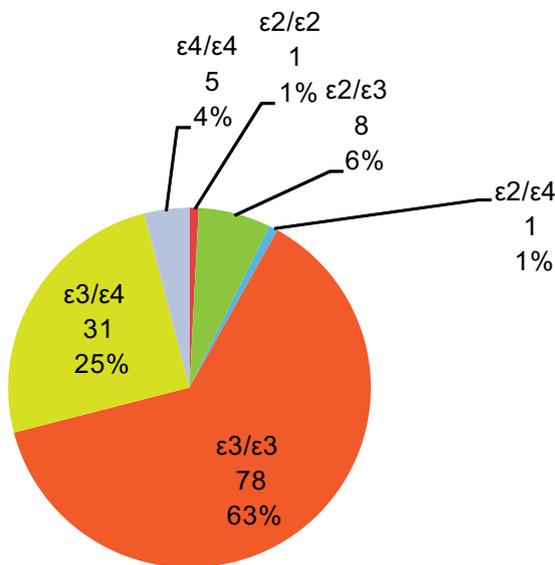


3. SCIENTIFIC ACTIVITY

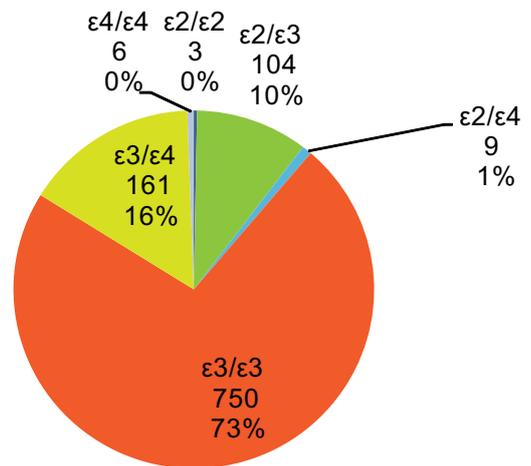
The combination of a new system (with unique features by leveraging the know-how of previous developments in the field of the aerospace industry) along with the validation of Raman-laser spectroscopy-based diagnostic markers represents an opportunity to enter a solution in the market for innovative diagnostics 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, allowing the development of a diagnostic system for a socially very relevant disease like Alzheimer's.

Distribution of APOE alleles in Vallecas Project volunteers according to the the presence of AD-type cognitive dysfunction (amnestic or multidomain MCI, or dementia)



AD-type cognitive dysfunction



Normal



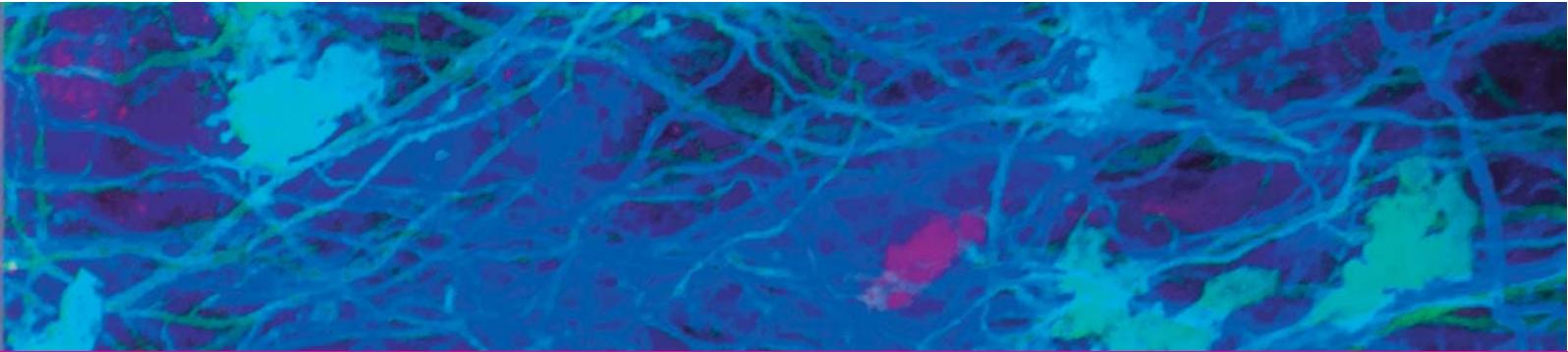


Illustration of the concept of endophenotypes for defining at-risk homogenous populations based on certain genetic variants and biomarkers in Alzheimer's disease. Modified from During et al. 2011

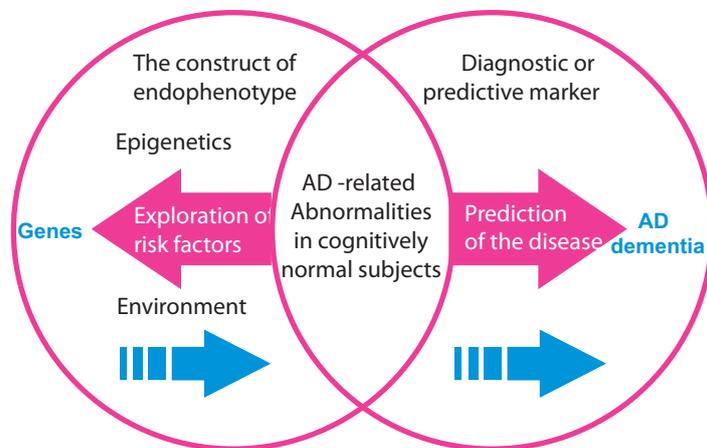


FIGURA 2 Crosstabulation

Count	DIAGNOSIS_1		Total
	CONTROL	AD	
ABCA7_rs3764650 TT	559	146	705
TG	151	35	186
GG	8	5	13
Total	718	186	904

ABCA7

Chi-Square tests

	Value	df	asymptotic significance (2-sided)
Pearson Chi-Square	2,904 ^a	2	,234
Likelihood ratio	2,541	2	,281
Linear by linear association	,062	1	,804
Number of valid cases	904		

^a0 0 squares (0.0%) have expected count less than 5. The minimum expected count is 2,67.

Crosstabulation

Count	DIAGNOSIS_1		Total
	CONTROL	AD	
PICALM_rs3851179 GG	356	94	450
AG	268	76	344
AA	65	17	82
Total	689	187	876

PICALM

Chi-Square tests

	Value	df	asymptotic significance (2-sided)
Pearson Chi-Square	,189 ^a	2	,910
Likelihood ratio	,188	2	,910
Linear by linear association	,038	1	,845
Number of valid cases	876		

^a0 0 squares (0.0%) have expected count less than 5. The minimum expected count is 17,50.



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FIGURA 3 Crosstabulation

Count

	DIAGNOSIS_1		Total
	CONTROL	AD	
BIN1_rs744373 TT	430	92	522
CT	225	81	308
CC	68	14	72
Total	713	187	900

Chi-Square tests

BIN1

	Value	gl	asymptotic significance (2-sided)
Pearson Chi-Square	9,256 ^a	2	,010
Likelihood ratio	9,032	2	,011
Linear by linear association	3,951	1	,047
Number of valid cases	900		

^a0 c0 squares (0.0%) have expected count less than 5. The minimum expected count is 14,96.

Crosstabulation

Count

	DIAGNOSIS_1		Total
	CONTROL	AD	
CLU_rs11136000 GG	243	81	324
TC	334	89	423
AA	107	18	125
Total	684	188	872

Chi-Square tests

CLU

	Value	gl	asymptotic significance (2-sided)
Pearson Chi-Square	6,124 ^a	2	,047
Likelihood ratio	6,418	2	,040
Linear by linear association	5,910	1	,015
Number of valid cases	872		

^a0 c0 squares (0.0%) have expected count less than 5. The minimum expected count is 26,95.

Crosstabulation

Count

	DIAGNOSIS_1		Total
	CONTROL	AD	
CR1_rs3818361 CC	476	112	588
TC	205	63	268
TT	26	12	38
Total	707	187	894

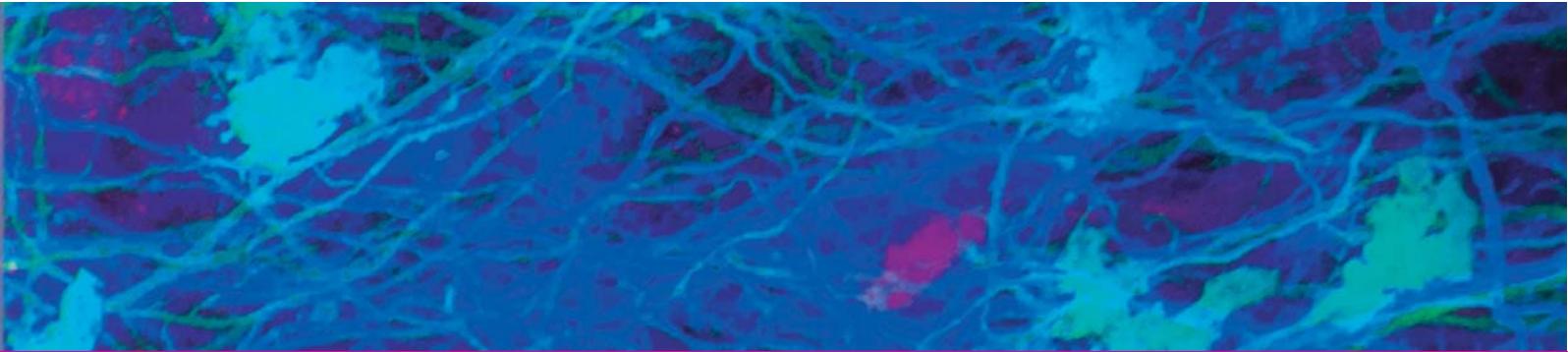
Chi-Square tests

CR1

	Value	df	asymptotic significance (2-sided)
Pearson Chi-Square	4,941 ^a	2	,085
Likelihood ratio	4,683	2	,096
Linear by linear association	4,752	1	,029
Number of valid cases	894		

^a0 0 squares (0.0%) have expected count less than 5. The minimum expected count is 7,95.





Contribution to BT CIEN

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

In the context of research focused on the study of biomarkers and genetic susceptibility factors, the UIPA Laboratory department is responsible for collecting, processing and storing biological samples 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 2014, 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
- Andrés Rodríguez Martín
(Laboratory Technician, CIEN Foundation-
Biocross)

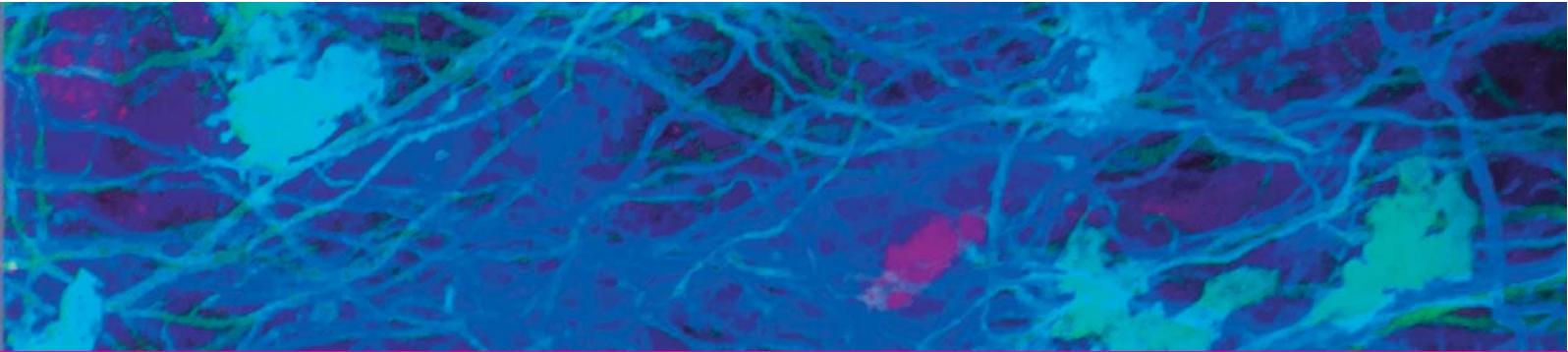


3. SCIENTIFIC ACTIVITY



Laboratory Team





3.2.5. Diagnostic Guidance Unit

Dementia involves by definition the impairment of cognitive functions and thereby the loss of independence and functionality in performing basic activities of daily living. The progressive aging of the population in recent decades seems to indicate an increase of dementia worldwide. In this sense, the World Health Organization (WHO) is warning of the potential consequences of increasing population diagnosed with dementia and suggesting the need for governments to take measures to reduce the social and health impact of this devastating disease. Alzheimer's disease (AD) is the leading cause of dementia in our midst. It is estimated that alone or in combination with cerebrovascular disease represents over 75% of the etiology of dementia, and at present its prevalence is estimated at around 7.3% of the population over 65 (Antón Jiménez M. 2010, Jellinger K.A. et al. 2010).

Diagnosis of cognitive impairment is a complex process that requires a series of steps such as confirmation of their presence, characterization, study of the potential causes, establishment of its intensity and final diagnosis as well as a well-coordinated multidisciplinary action.

Usually, when suspicion of possible cognitive impairment arises, a screening including appropriate recollection of clinical history data and a general physical and neurological examination is applied, which serve to confirm the actual existence of a cognitive deficit. If determined that the patient has a general cognitive deficit intervenes then specialized personnel (usually neurologists and neuropsychologists) that study the patient in depth to determine the cause of the impairment, its magnitude and features.

A series of complementary tests (neuroimaging, blood test, etc.) are essential to identify the causal

pathology and especially to rule out treatable causes. Finally, with all available information and applying internationally accepted clinical criteria, a presumptive diagnosis is issued, which carries the corresponding monitoring, treatment and prognosis.

In our setting, the activity of the health professionals involved in these tasks (from GPs and geriatricians to molecular biologists and geneticists) and available technology allows for high quality diagnostic. It should be emphasized that, so far, no complementary test exists to make a diagnosis of cognitive impairment or dementia. This diagnosis only can come from the well-informed, expert clinical action. Therefore, the fundamental core of the process is clinical and begins with the classic medical act (history and examination), ideally with support from the neuropsychologist.

Why a Diagnostic Guidance Unit?

When a person begins to appreciate problems with their cognitive abilities such as memory loss, difficulty retaining new information, or to use the appropriate words, or to perform common mathematical operations, etc., fear and uncertainty about the possibility of developing dementia in general and Alzheimer disease, in particular, appear.

The saturation of healthcare services is well known. The social situation concerning an aging population and limited economic resources makes it likely that increased assistance will be required and fewer resources to face it will exist. The rational solution to this situation is closely linked to advances in research and therefore internationally significant efforts are being conducted in this regard. Also in Spain increased resources are allocated for research in dementia and neurodegenerative pathology.

The establishment of the Diagnostic Guidance Unit within the Research Unit of the Queen Sofia Foun-



3. SCIENTIFIC ACTIVITY

dation Alzheimer Center (UIPA, for its acronym in Spanish), which is managed by the CIEN Foundation of the Carlos III Institute of Health and that has been funded by the Mutua Madrileña Foundation, bring the following benefits to users:

- Quick attention by specialists (neurologist, neuropsychologist, psychiatrist) with specific expertise in cognitive impairment and dementia.
- Evaluation of people aged 60 or older (members of the Mutua, spouses or parents of first grade) with or without first-degree relatives with Alzheimer's, who suspect having cognitive failures or think they might be having cognitive impairment.
- Checking the cognitive status and functional impact.
- Performing an extensive battery of clinical and neuropsychological tests to detect, qualify and quantify the deficit, if any.
- Performing if needed (as appropriate) a very high quality cranial MRI study to rule out or characterize the underlying brain pathology.
- Preparation of a report summarizing the outcome of all tests carried out, as baseline both in case of impairment as well as if it has been discarded. Such information will be, in any case, of great value for further studies needed in the patient healthcare system, saving a lot of time, or for comparison with future assessments.
- Effectively contribute to research in this disorder, if the subject consents to it, with the inclusion of the results of their tests on the database of the Research Unit of the Queen Sofia Foundation Alzheimer Center.

Composition of the Diagnostic Guidance Unit.

The following resources are available to carry out this activity has:

- 1 neurologist and 1 neuropsychologist.
- A proportion of subjects studied (undetermined in principle) might require consultation with a

psychiatrist, so that this professional consultation should be accessible.

- Department of Neuroimaging by Magnetic Resonance (3T-MRI).
- A nurse.
- An administrative assistant responsible of appointments, reports, etc.
- Appropriate offices for consultations.
- IT equipment, test supplies, etc.

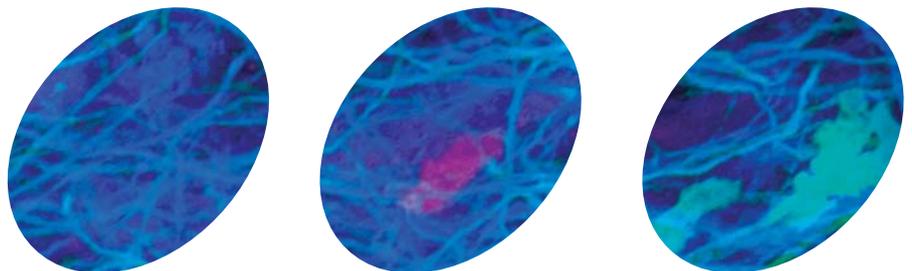
Protocol of Action

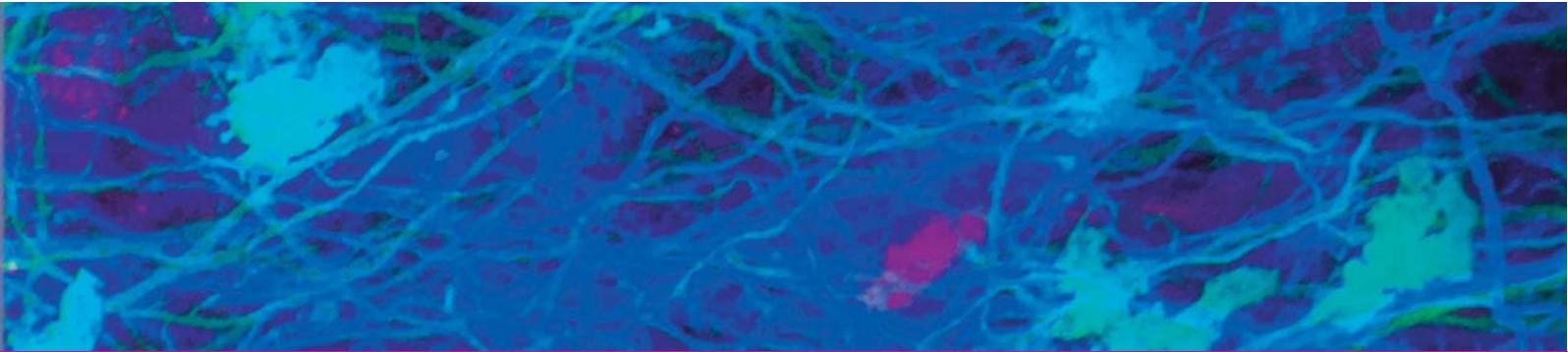
- **Neurology consultation** (in all cases). Thorough interview with the assessment applicant and relatives, stating the reason for consultation. Completing the detailed clinical history, including family history (with special attention to ancestors with dementia), past medical-surgical personal history and current medication. Performing a neurological examination. Administration of cognitive screening tests.
- **Neuropsychology consultation** (in cases where detailed cognitive assessment is required). Sociodemographic data collection and application of various types of tests and assessments selected based on the specific characteristics for each case. In general, a comprehensive neuropsychological study that includes measures cognitive, neuropsychiatric, behavioral and functional type is performed.
- **Psychiatry consultation** (as appropriate).
- **Neuroimaging studies** - 3Teslas brain MRI (as appropriate).
- **Preparation of a detailed clinical report** (in all cases).
A total of 203 had been attended by year end.



The *e* Vallecas Project

The half way point for this five-year study devoted to advancing early diagnosis of Alzheimer's disease has been passed during 2014. We have already begun to integrate and analyze the data collected in the second, third and even in some cases the fourth visit, from the 1,213 volunteers enrolled in the Vallecas project. It is planned the publication of preliminary results during 2015.





4. THE VALLECAS PROJECT

4.1. Introduction

Alzheimer's disease (AD) is the leading cause of dementia in our country. according to the National Center of Epidemiology, at present at 7.3% of the population over 65 years suffers from this disease, constituting over 75% of the etiology of dementias, alone or in combination with cerebrovascular pathology. The outlook for the coming years is an increase of dementia worldwide, due to the progressive aging of the population. It is expected that by 2050 a third of the population in our country will be over 65 years and close to a million Spaniards will suffer from dementia.

By definition, the degree of functionality of the person deteriorates because of dementia. The rate of disability in Spain stands at ninety dementia cases per thousand inhabitants, according to the Survey of Disability, Personal Autonomy and Dependency Situations developed by the National Institute of Statistics, ranking fifth in frequency of diagnoses. By analyzing the profile of the person by range of age affected of dementia, there are no direct consequences on the working life of the patient but it does on the caregiver. 54.5% of caregivers work with people with this disease and thus greatly reduce their productivity.

While the impact of dementia is directly produced on the patient, it also has a great impact on his/her social environment to which affects in important aspects: affective, emotional, organizational, roles change as well as economic aspects. In this respect, dementia is problem for everyone and should be approached as a true family disease and, ultimately, a disease of society.

The transit of a cognitively normal individual subject with AD-type dementia is a continuum in which some intermediate states can be recognized. These stages do not meet the consensus criteria for the diagnosis of dementia because some issues are still not fully determined. These are cases where there is

a dimly distinguishable mild cognitive disorder. If we had the ideal therapy to largely stop or slow disease progression pre-dementia in these intermediate stages, we could drastically reduce the prevalence of clinically overt AD.

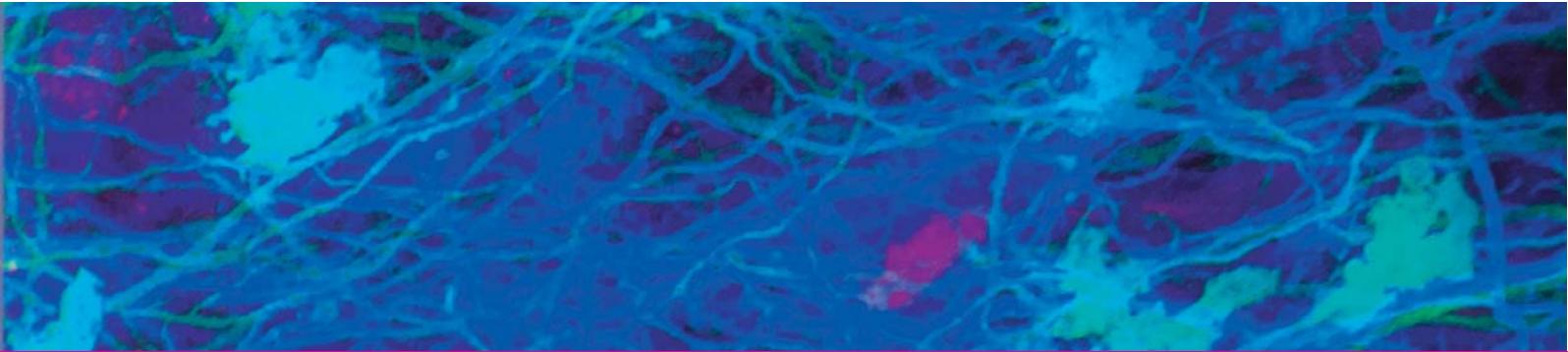
Nowadays, there is no known method to determine which individuals in those pre-dementia states will end up being demented patients (not all convert to severe cognitive impairment), or to accurately identify individuals at high risk of dementia and AD in the general population. With the help of sophisticated, expensive and invasive techniques, it can be fairly reliably predicted which patients selected from the population (eg, familial EA) will progress to dementia. However, these advances are not yet useful for everyday practice or for population screening, as they are only useful in research. Furthermore, the absence of an effective, high performance detection system, it is not possible to verify the effectiveness of future therapies to stop or slow the progression of AD in the general population and in the preclinical stages of most interest.

The main objective of the population-based study "Vallecas Project" for Early Detection of Alzheimer's Disease, is elucidate, through progression tracking, the best combination of clinical parameters and tests (imaging and laboratory) that allow deciphering what medium- and long-term (3 to 5 years after the baseline observation) features 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, began the final implementation of the Vallecas Project, which started its activity gradually in October 2011.

The Vallecas Project, which is being carried out in the Queen Sofia Foundation Alzheimer Center Research Unit by researchers from the CIEN Foundation (Carlos III Institute of Health) 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).

During the process of selection of the sample population, the project aims to recruit 1,200 individuals aged 70-85 years, of both genders, with no symptoms of dementia at the time of the baseline evaluation. Once included in the study a 5 year follow up is intended through annual assessments that will allow to identify participants who develop symptoms of dementia during that period in order to establish a combination of assessment components that could indicate a special risk of dementia.

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.



4. THE VALLECAS PROJECT

- Visual and hearing abilities that allow conducting the study tests.

Within the exclusion criteria of the study were, among others, the existence of suspected or diagnosed dementia, inability to conduct brain imaging studies, alcohol abuse, mental retardation, pre-

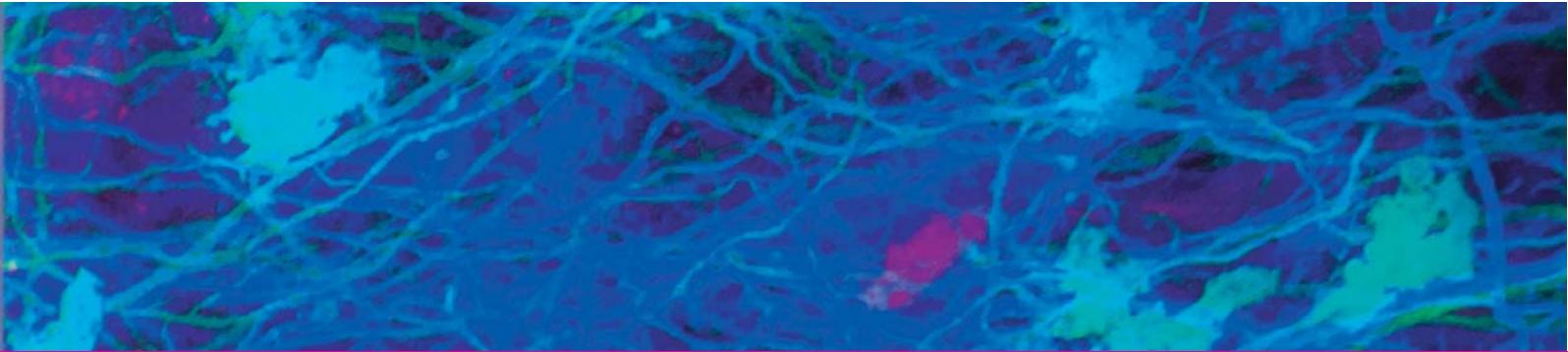
sence of a history of certain diseases (for instance, schizophrenia, stroke, severe head trauma, CNS infections, uncorrected vitamin deficiencies, etc.

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

THE VALLECAS PROJECT IN FIGURES

Recruited sample	1.213
Excluded at baseline	47 (3,87%)
Age	
Sample mean	74,46 años
Age 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%)





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.

Annually, volunteers also fill out a "social" questionnaire that collected data on:

- Quality of life and subjective well-being: mobility, self-care, daily activities, pain/discomfort, anxiety/depression, perceived health status.
- Lifestyle: nutrition, sleeping habits, social relations and leisure, physical exercise, values/beliefs/expectations.

4.3.3. Clinical evaluation

During the evaluation, researchers collected through a semi-structured interview annual data regarding:

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

failure, renal failure, Obstructive Sleep Apnea Syndrome (OSA)...

- Family history with special attention to the history of dementia or movement disorders, developmental delay or psychiatric disorders.
- Regular drug treatment during the last 5 years.

4.3.4. General examination

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

- **Gait disturbance**
- **Handwriting**
- **Instrumental activities of daily living**

4.3.5. Neuropsychological Examination

The 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, neuropsychological 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.

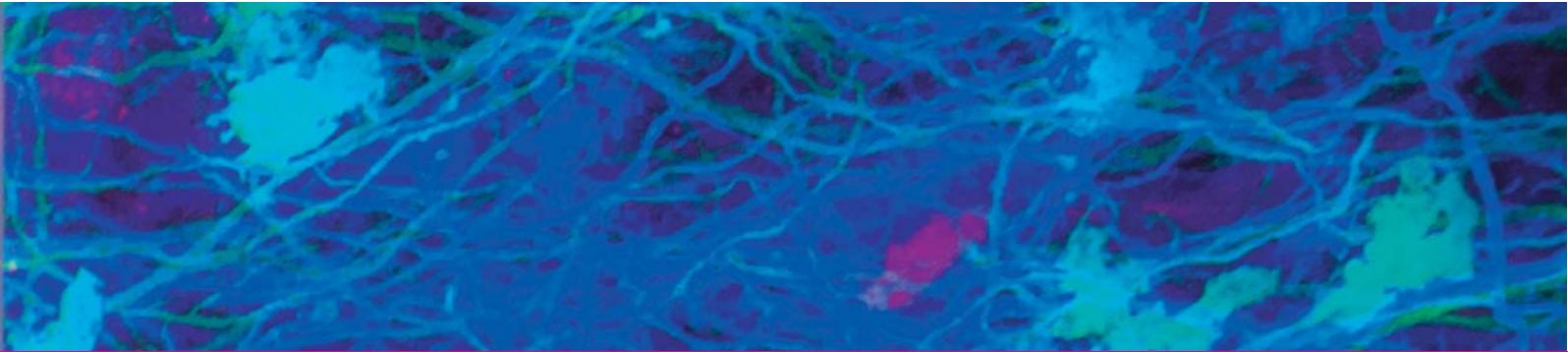


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Mini Mental State Examination (MMSE)

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 inde-

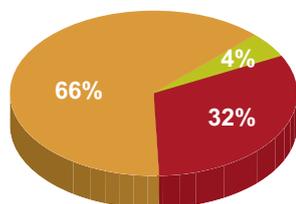
pendence of the subject in different daily tasks (managing finances, shopping, doing housework, preparing meals, pay attention and discuss news, remembering dates, managing medication or going out alone on the street). The diagnosis of Alzheimer disease occurs from a score of 6 as the cutoff point.

Rey Complex Figure Test

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

Vallecas Project activities during 2014

Number of second visit assessments	257
Number of third visit assessments	525
Number of fourth visit assessments	14



- Second visit
- Third visit
- Fourth visit

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



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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. Moreover, 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.

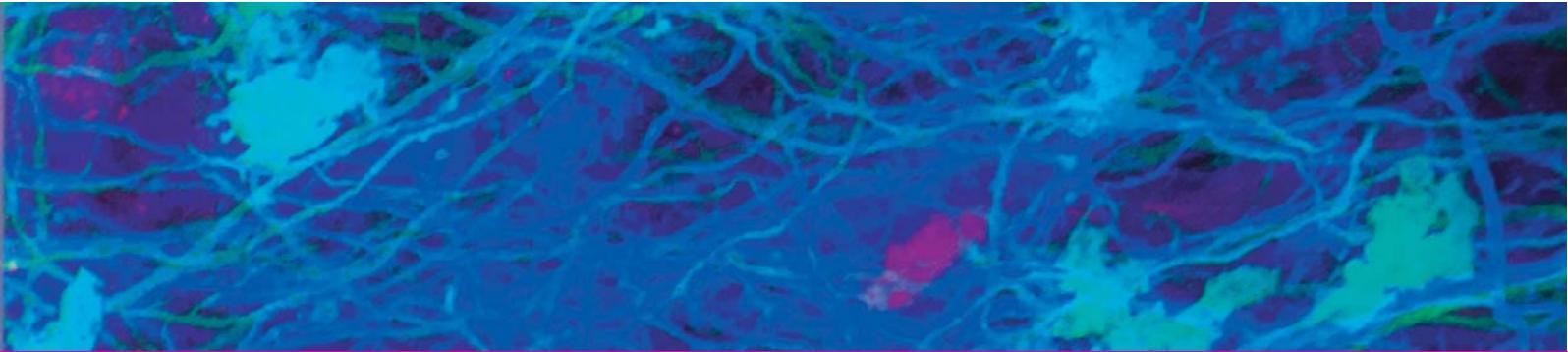
Global Depression Scale (GDS-15)

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, lan-



4. THE VALLECAS PROJECT

guage, 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, intran-

sitive gestures made with a single upper limb. The primary 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 arbitrary postures that the examiner performed with both hands. This test evaluates the integrity of ideomotor praxis.

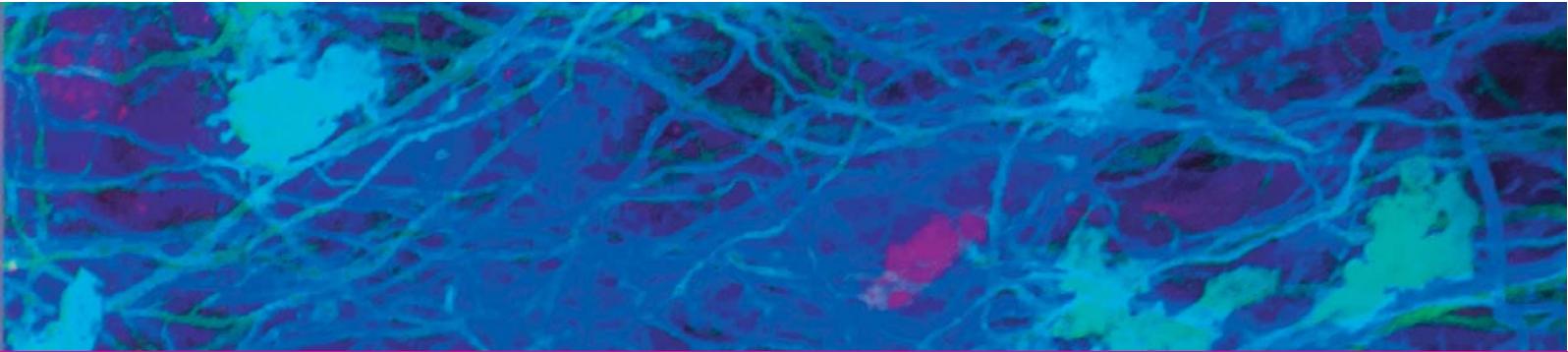
Rule Change (Behavioral Assessment of the Dysexecutive Syndrome BADS subtest)

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

It is known since the first descriptions of dementia that psychiatric symptoms are an intrinsic part of its evolution. The concept of "behavioral and psychological symptoms of dementia" (BPSD) now includes those of cognitive or functional manifestations of dementia syndromes.

Several published works in recent years have concluded that these BPSD could not only manifest themselves in a phase of dementia, with well established cognitive impairment, but it could either be risk factors for developing dementia or "heralds" of the same, that is, events that precede the cognitive impairment.

Thus, both depression and apathetic clinical symptoms in the absence of depression, are studied in recent years in order to establish its relationship with the development of each type of dementia. In the Vallecas project, an exploration of both major psychiatric disorders and the most common BPSD is performed in order to provide more information on factors related to the onset of the dementia phase during 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, MMP-3.
- Aβ40/42 peptides

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 of the following page.



4. THE VALLECAS PROJECT

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.

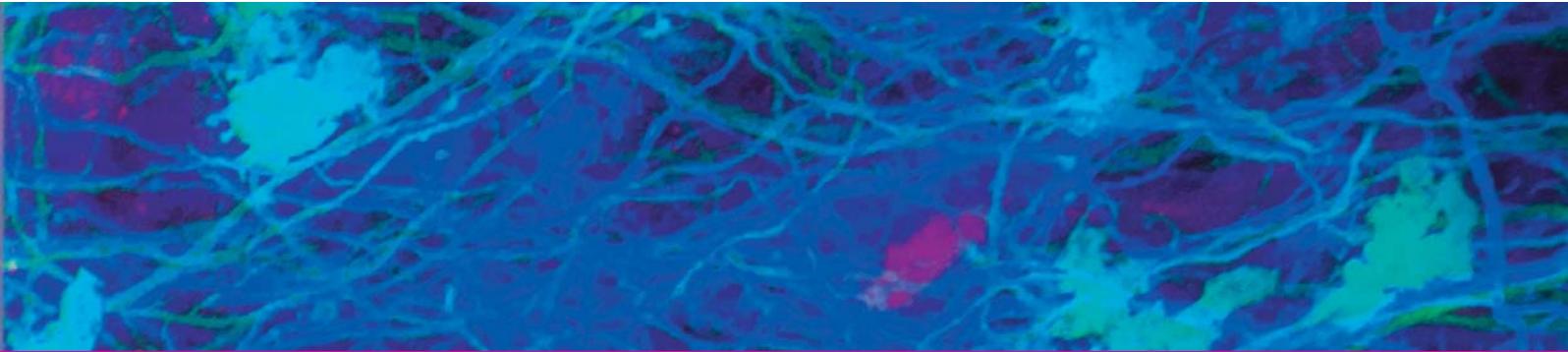
However, conventional MRI techniques are unable to detect and quantify age-dependent microstructural changes who have been described in post-mortem studies of brain tissue. Accordingly, the project aims to conduct a series of studies based on various MRI modern techniques that can provide volumetric 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

EXTRACTIONS

Firts visit	1.212
Second visit	829
Third visit	577
Fourth visit	15
TOTAL	2.633
AVAILABLE SAMPLES	
Whole blood	100%
Platelet-rich plasma	100%
Platelet-poor plasma	100%
Serum	99%
Buffy coat	100%
Erythrocytes	100%
Mononuclear leukocytes	99%
DNA	100%
APOE	98%





choice in research. The discriminatory power of volumetry in degenerative pathologies such as Alzheimer's disease (volumetric reduction in amygdala, hippocampus, entorhinal cortex, etc..) decreases if age-dependent morphological changes are not well established in control samples, so that it is critical to have large, well quantified samples.

- Structural Study (3D volumetry, T2 and FLAIR)**
 Determining the progressive loss of brain volume during aging, especially in white matter provides volumetric quantitative indexes of the morphological aging-associated changes. In this sense, the VBM (Voxel-Based Morphometry) techniques, based on creating statistical comparisons of gray and white matter patterns constitute the method of choice, and allows us to determine the volume reduction of the amygdala, hippocampus, entorhinal cortex, etc.
- Diffusion Study (b: 800)**
 White matter, partly due to Wallerian degeneration and partly to reduced connectivity by decreased cortical activity, presents ultrastructural changes that can be detected with diffusion techniques (DTI).
- Brain Perfusion Study**
 Cerebral perfusion related to cortical activity may be assessed -without needing to inject

contrast-through MR sequences (Arterial Spin Labelling, ASL) and therefore hypofunctioning areas will present decreased perfusion.

4.3.9. 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. In 2014, we have combined the second, third and fourth visits from volunteers, surpassing study's half point.

During this year we have also carried out the validation of the data collected so far during in the project by the different departments and enter them in a single, newly created, integrated and anonymized database, in order to ensure the reliability and security of data and allow for more effective analysis thereof.

The first analysis (still preliminary) of data from the first two visits have been designed to analyze three different but complementary aspects: first, we have studied the possible correlation between the information obtained from the medical history (gender, age, medication, previous illnesses, ApoE genotype,

NEUROIMAGING ACQUISITIONS

Baseline visit	4
Second visit	230
Third visit	433
Fourth visit	14
Total	681



4. THE VALLECAS PROJECT

etc.) of the volunteers with the presence or absence of mild cognitive impairment (MCI). Secondly, we have studied the possible association between subjective memory and cognitive complaints at the baseline visit and the emergence of MCI after a year of follow-up. Finally, we have started the comparative study of brain magnetic resonance images obtained from volunteers who have passed during the first year of study from a cognitively healthy stage to show signs of MCI in order to try to identify parameters that have changed in the brain and can be determined by neuroimaging techniques. Some preliminary results were presented to the CIEN Foundation Scientific Advisory Committee and to members of the Queen Sofia Foundation and we hope that throughout 2015 we would be able to confirm and publish some of these results.

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

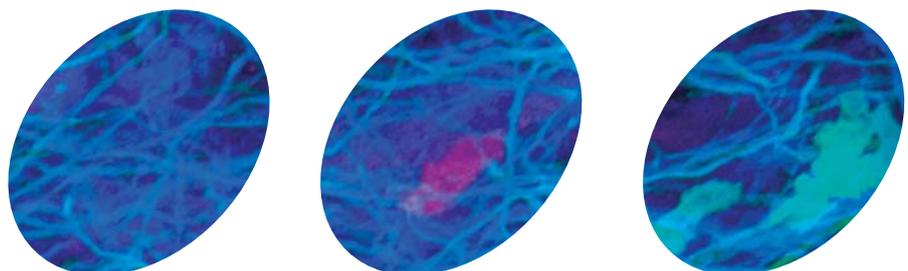
VALLECAS PROJECT CLINICAL EVALUATIONS (OCTOBER 2011-DECEMBER 2014)

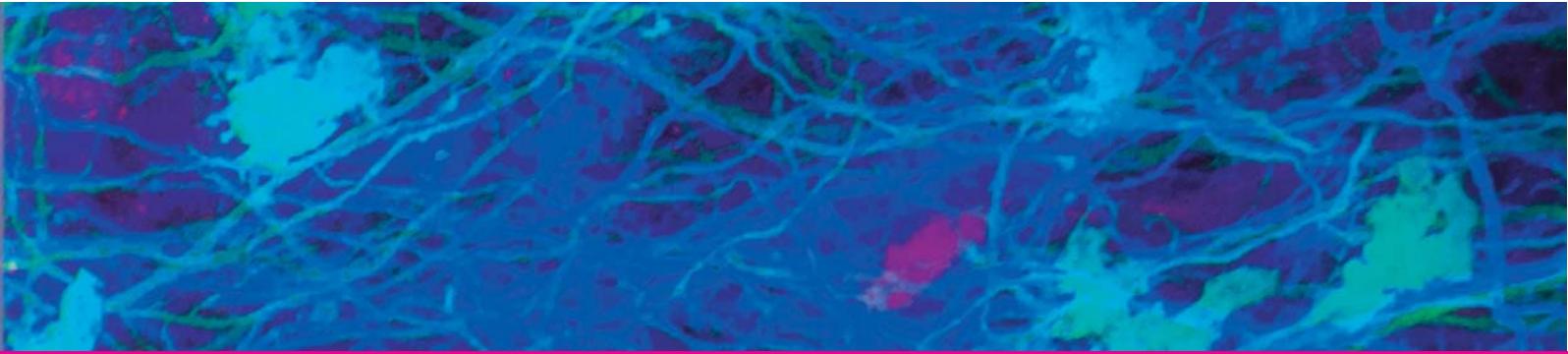
First visit	1.175
Excluded at baseline	47
Second visit	970
Third visit	582
Fourth visit	14
Drop outs	233
Do not comply with inclusion criteria	30
Deceased	11
Diagnosis of neurological disease	24
Volunteer withdrawal	168



International cooperation activities

The year 2014 has been especially fruitful with regards to the international presence of CIEN Foundation. To the consolidation of projects launched in previous years such as the active participation, together with CIBERNED in the JPND European program and the COEN network, or the Registry project and the 'New friends, old emotions' study, starting this year is added the collaboration with the Portuguese Champalimaud Foundation, the participation in the first French-Spanish AVIESAN-ALINNSA symposium and the holding of the 9th International Conference on Neural and Brain Diseases in our facilities.





5. INTERNATIONAL RELATIONS

5.1. Introduction

Neurodegenerative diseases (ND) 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 causing impairment of approximately 7 million people in Europe. This figure is expected to double every 20 years, due to the progressive aging of the population. Currently, healthcare and treatment of patients with some form of dementia in Europe, represents a cost around € 130 billion per year, according to estimations of the European Commission Joint Programme in Neurodegenerative Diseases. This highlights that age-associated neurodegenerative diseases constitute one of the main medical and social challenges facing our society.

International scientific collaboration increases more and more, not only because of the availability of international funding and the drive of modern communication technologies, but also because science itself has become a truly international collaborative activity. In particular, the scope and scale of the problem of neurodegenerative diseases in today's society require a global response to confront this great challenge and thus has been recognized by various international institutions such as the European Union (EU), the Organization for Economic Cooperation and Development (OECD), the World Health Organization (WHO), etc.), and the industrialized countries that constitute the G8. 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.

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

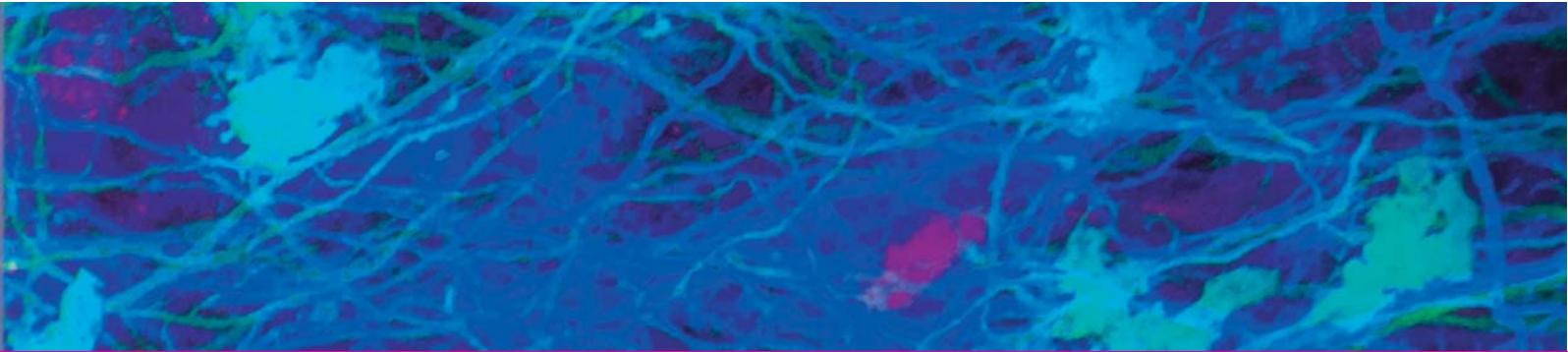
number of people at risk. This budgetary effort should be accompanied by sound policies and legislative initiatives to encourage public-private partnerships. History has shown that collaboration between academic researchers, government agencies and pharmaceutical and biotechnology companies is an essential ingredient in promoting this type of ambitious initiatives, especially when resources are limited.

Support for research in Alzheimer's disease and related diseases has been (and continues to be) one of the main priorities of the Queen Sofia Foundation since 2002, when it prompted the building of the Queen Sofia Foundation Alzheimer Center (CAFRS, for its acronym in Spanish), and from which it has continued to support the activities of the institutions related to this dementia, both financially and with the invaluable drive and personal interest of Queen Sofia. In this context, in recent years CIEN Foundation together with Center for Networked Biomedical research in neurodegenerative Diseases (CIBERNED) has given a boost to its relations with international organizations in the area of research in neurodegenerative diseases such as the EU Joint Programme for Research in Neurodegenerative Diseases (JPND) and the Network of Centres of Excellence in Neurodegeneration (COEN), among other initiatives.. These and other internationalization activities conducted by CIEN Foundation during 214 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. CIEN Foundation Scientific Director, Dr. Jesús Avila, has a significant participation in the JPND Scientific Advisory Committee.

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

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

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

In this regard, during 2011 took place the first call for European research projects JPND. Under the topic "Optimization of biomarkers and harmonization of

their use in the clinic", a total of four transnational projects were awarded for the period 2012-2014, one of which has participation of CIEN Foundation.

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

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 Kretschmar, 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



5. INTERNATIONAL RELATIONS

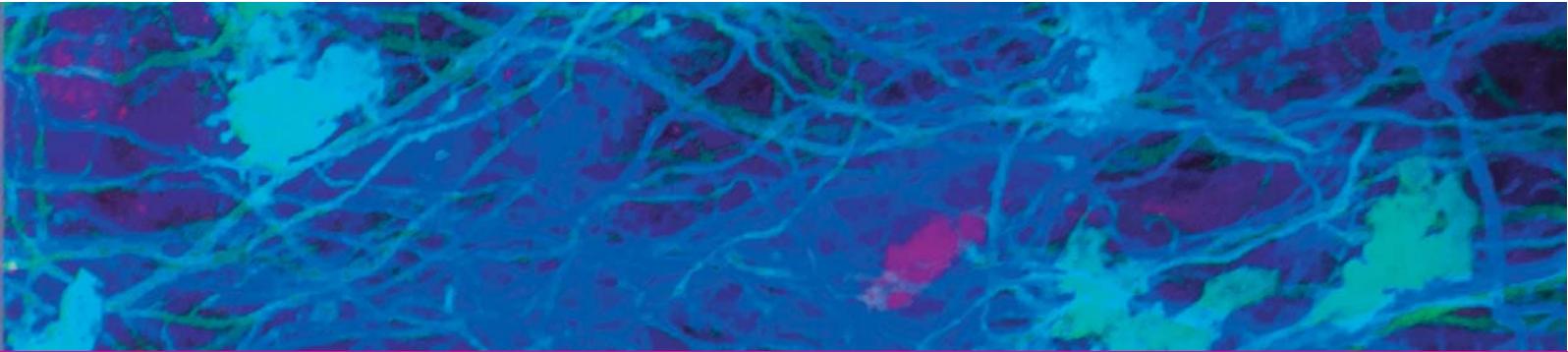
- Adriano Aguzzi & Herbert Budka, University Hospital Zürich, Switzerland
- John Collinge, University College London, United Kingdom
- Robert G. Will, Western General Hospital, United Kingdom

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

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

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

To this end, on June 10, 2010, the Canadian Institutes of Health Research (CIHR), the German Centre for Neurodegenerative Diseases (DZNE, Germany) and the Medical Research Council (MRC, UK) launched an 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, recogni-

zing the scientific excellence in both basic and clinical science of the institution which became part of the COEN Oversight Group.

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

There are very advanced discussions for the incorporation into the initiative of Australia and France during 2015. 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 actively participate in the design of COEN future scientific strategy. Both institutions are represented in the COEN Oversight Group by Dr. Miguel Medina, CIBERNED Deputy Scientific Director and member of the Scientific Advisory Committee of the CIEN Foundation.

The first phase of the COEN initiative began in late 2010 and has been aimed at the development of common resources and methodological approaches that underpin future studies. Some of the key is-



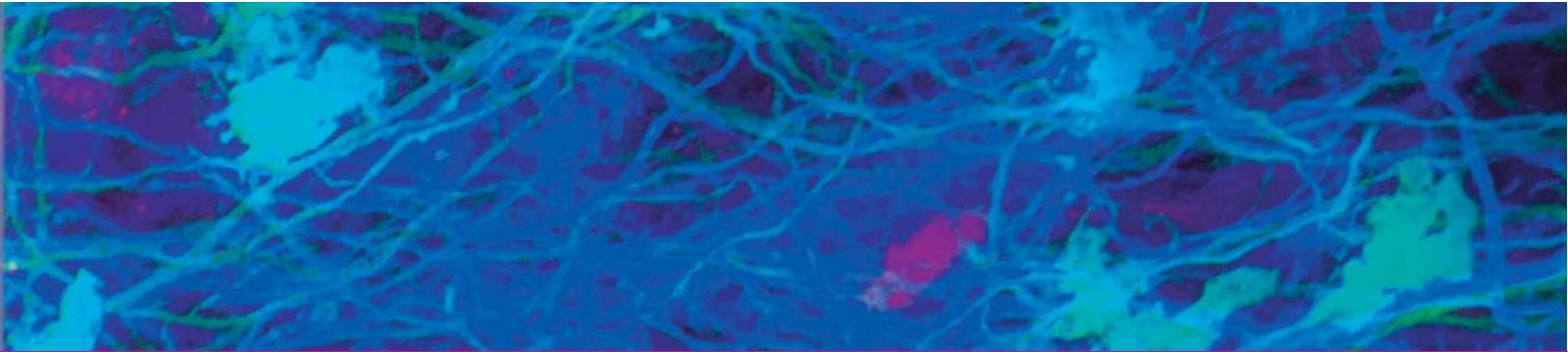
5. INTERNATIONAL RELATIONS

sues addressed are: the development and validation of cell and animal models of disease; development of new measures to define subgroups of patients for clinical studies; identification of new biomarkers to support translational research; the development and harmonization of the battery of cognitive tests for the diagnosis and monitoring of disease progression; and the establishment of common platforms for improved data analysis and exchange.

As described in the 2013 Annual Report, 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 euros (of which Spain has provided 600,000 euros) in this call to establish an innovative and progressive research program to address the major challenges in this field. The call is 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 for 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 it is expected to further collaboration between Centers of Excellence, the projects would also serve to provide a platform for future collaboration with industry. A second call for Pathfinder projects is foreseen for the first half of 2015.

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

During 22nd and 23th of September, 2014 took place in Barcelona the second International Congress in Research and Innovation on Neurodegenerative Diseases (CIIEN), promoted by the Queen Sofia Foundation in collaboration with CIEN Foundation. The main objective of CIIEN is having a forum in which to share progress and information of interest on neurodegenerative diseases among the scientific community.

CIIEN consolidates the merger of the two major scientific conferences neurodegenerative diseases in general and Alzheimer's disease in particular, organized in Spain: the X International Symposium Advances in Alzheimer's Disease, promoted annually by the Queen Sofia Foundation and CIEN Foundation, and the 8th CIBERNED Scientific Forum, that brings together every year more than 500 scientists constituting the CIBER on 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 Carlos III Institute of Health. This new structure seeks greater effectiveness and efficiency in research, promoting the interaction of the different research groups.

This second edition of CIIEN was chaired by Her Majesty Queen Sofia and the scientific program consisted of an opening session and eight scientific sessions covering various aspects of cutting edge research in neurodegenerative diseases, such as stem cells, biomarkers, preclinical changes, aging, immunity, genetics, mechanisms of neurodegeneration and neuroprotection. Among the speakers at the conference can be highlighted some international researchers who are leaders in their field of research such as Michael Heneka (University of Bonn), Vincenzo Bonifati (Erasmus University, Rotterdam), Ammar Al-Chalabi (King's College Institute of Psychiatry, London), Anders Fjell (University of Oslo), and Leslie M. Thompson (University of California, Irvine).

Thus, this event establishes in its second 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 and between different institutions is becoming increasingly important to obtain optimum results in research.

5.5. Other activities of international cooperation

5.5.1. Champalimaud Foundation

On June 26, 2014, Ms. Leonor Beleza, Chair of the Champalimaud Foundation, Portuguese institution devoted to advanced biomedical research visited CIEN Foundation and CAFRS facilities. Hosted by H.M. Queen Sofia and accompanied by M^a Ange-



5. INTERNATIONAL RELATIONS

les Pérez, managing director of CIEN Foundation, José Ramón Menéndez Aquino, Madrid Director General of the Elder (institution managing the health-care side of the Queen Sofia Foundation Alzheimer Center, and Jesús Avila de Grado, Scientific Director of CIEN Foundation, Ms. Beleza was briefed on the research projects being developed at CIEN Foundation and the Queen Sofia Foundation Alzheimer Project Research Unit.

Among those projects presented by the CIEN Foundation researchers are: the Vallecas Project, a longitudinal study that is examining more than 1,200 volunteers for the identification of early biomarkers of AD, and the Alzheimer Project of the Queen Sofia Foundation, in collaboration with the medical center run by the Region of Madrid. Furthermore, H.M. The Queen and the Chair of the Champalimaud Foundation visited the CIEN Foundation Laboratory area where biological samples from various research projects are analyzed; the Neurology and Neuropsychology department, where the volunteers of the Vallecas project are evaluated; the Neuroimaging department, where the acquisition and analysis of brain magnetic resonance imaging it carried out; and the Tissue Bank, with brain tissue and other samples of neurological interest.

Queen Sofia and Leonor Beleza also visited the CAFRS residential area, divided into nine modules, called as "live units". Finally, both shared a coffee with CIEN Foundation staff and members of the Scientific Advisory Committee.

As a conclusion of this visit, the three Foundations Queen Sofia, Champalimaud and CIEN, decided to deepen contacts for finding common interests and synergies in the field of translational research in neurodegenerative diseases. The first result was the assistance of Ms. Beleza as a guest to the second edition of CIIEN, held in Barcelona in September (see section 5.4), where a visit to the headquarters of

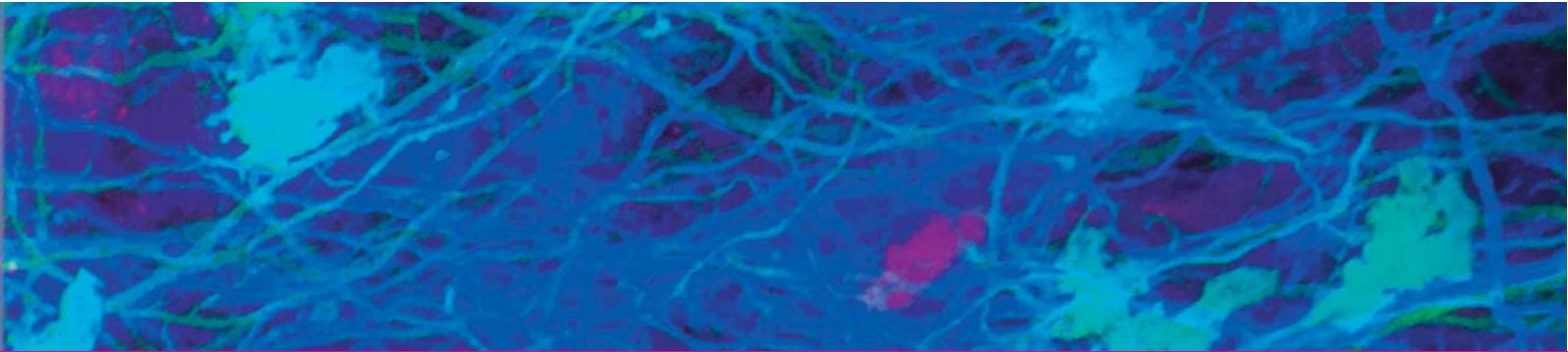
the Champalimaud Foundation in Lisbon by early 2015 was also agreed.

5.5.2. Bilateral UK-Spain Meeting

On March 18 took place in the Ernest Lluch Hall of the Institute of Health Carlos III a bilateral conference United Kingdom-Spain, organized by the British Embassy in Madrid and in collaboration with the Carlos III Institute of Health and the Sanitas Foundation, entitled "Dementia: A Global Challenge". The aim of the conference was to bring together scientists, health professionals, policy advisers, companies and associations of health care services, to debate the challenge posed by dementia, an issue of national importance both for the UK and Spain.

During the meeting was held a round table on the importance of research in dementia policies, with the participation of Robin Buckle, Director of Science





Programs at the Medical Research Council UK (MRC); Jesus Avila, Scientific Director of CIBERNED; Agustin Ruiz, Research Director and CSO of the ACE Foundation; Steve Parr, Director of Business Development in Ixico; Pablo Martinez-Lage, Head of Neurology at the CITA Foundation and member of CIBERNED group led by Dr. Adolfo Lopez de Munain; Martin Orrell, Professor at University College London; and Antonio Paez, Head of the Department of Clinical Operations at Grifols Institute.

Among those attending were also Antonio Andreu, Director General of the Carlos III Institute of Health; Simon Manley, British Ambassador in Spain; Mercedes Vinuesa, Director General of Public Health; Lorraine Jackson, Director of Policy Assistance for Dementia of the UK Department of Health; and Joaquín Casariego, Director of Development and International Relations, Faculty of Medicine at the University Francisco de Vitoria.

The conference constituted a meeting point for contrasting experiences and establish an excellent forum for discussion to reduce the personal, social and economic impacts posed by dementia.

5.5.3. I AVIESAN-ALINNSA Symposium

On February 6 took place in the Gustavo Pittaluaga Aula Magna of the National Health School of the Carlos III Institute of Health, the First Symposium between the French Alliance for Life Sciences and Health (AVIESAN) and the Spanish Alliance for Research and Innovation in Health (ALINNSA). The aim of the initiative was to foster cooperation of existing agents, through the coordination, joint programming, internationalization and promotion of public-private partnerships.

The conference was inaugurated by the Secretary of State for Research and Innovation of the Ministry of Economy and Competitiveness, Ms. Carmen

Vela, and the Ambassador of France Mr. Jerome Bonnafont. In addition, André Syrota, President of AVIESAN, and Antonio Andreu, President of ALINNSA presented the alliance between the two initiatives.

During the event, a joint working group (ALINNSA-AVIESAN Joint Meeting : Opportunities for future cooperation) was established, where experts from both countries shared, in several subgroups, knowledge on thematic priorities from a multidisciplinary perspective, identifying actions and opportunities for joint future collaboration.

In the working subgroup on Developmental Neurobiology and Neurodegenerative Diseases, Miguel Medina, CIBERNED Deputy Scientific Director, presented the structure and scientific objectives of CIBERNED and CIEN Foundation, as well as some opportunities for potential future scientific collaborations. In this group also participated Miguel Calero, member of the CIBERNED group led by Jesus de Pedro.

5.5.4. 9th International Conference for Neurons and Brain Diseases

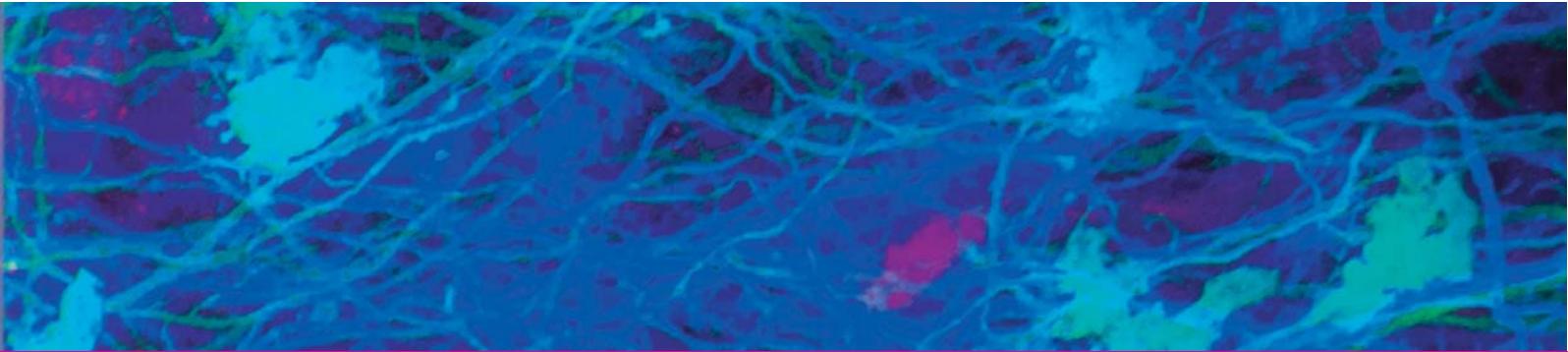
The Queen Sofia Foundation Alzheimer Centre and CIEN Foundation were host on July 14-16, 2014 to the ninth International Conference for Neurons and Brain Diseases organized by the Association the Study of Neurons and Disease (AND), an international group of neuroscientists with a particular interest in the biological causes of neurodegenerative diseases.

The seemingly unstoppable growth in life expectancy in the developed world carries with it an inevitable increase in the incidence of neurodegenerative diseases for which age is the greatest risk factor. It is now widely accepted that finding ways to alleviate and ultimately prevent these diseases is one of the major challenges facing society.



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Over the course of two and a half days of scientific sessions, the delegates heard a total of 37 talks by scientists from Europe, North America, China, Japan and Korea, covering a wide range of research into animal models of human diseases such as Alzheimer's, Parkinson's, Huntington's, multiple sclerosis, and epilepsy, as well as others on the biology of memory, and on the progression of human neurodegenerative diseases.

A focus of the meeting was on synaptic plasticity and its role in brain disorders. Ever since the end of the 19th century when Ramón y Cajal, the great Spanish neuroanatomist, first proposed that nerve cells made connections with each other at specialized junctions called synapses, it has been assumed that memories are stored in the brain as changes in the strengths of synaptic connections. This presumed property of synapses to change their strength – either upwards or downwards – is called synaptic plasticity.

It was not until the 1970's that the ability of synapses to undergo persistent changes in strength was definitively identified, in an area of the brain called the hippocampus. This structure is an early target for cell degeneration in Alzheimer's disease, which helps to explain why memory loss is one of the first symptoms of the disease. Indeed, one factor in Alzheimer's disease may be over-activation of a particular kind of synaptic plasticity that leads first to a reduction in synaptic strength, and ultimately, to the loss of synapses.

In some circumstances, following injury or inflammation, synaptic plasticity can lead to the development of permanent changes in the neural pathways which carry pain signals to the spinal cord and brain, leading to the development of chronic pain. As for neurodegenerative diseases, an understanding of the biology of this distressing condition provides the best hope for developing strategies to treat the condition.

Professors Min Zhuo (University of Toronto) and Bong-Kian Kaang (Seoul National University), the founders of AND, have expressed their thanks to the local hosts Professor José Ramón Naranjo (CIBERNED-CNB-CSIC, Madrid) and M^a Angeles Pérez, CIEN Foundation managing director, and Aina Frontera from CIEN Foundation for providing an ideal environment for a highly successful meeting.

5.5.5. International Research Projects

A couple of international scientific projects with the active participation of CIEN Foundation researchers are also worth mentioning: REGISTRY, an international multicenter observational study project coordinated by the European Group on Huntington's disease (more details in Section 3.2.1 of this Report) and the project "New friends, old emotions" which aims at making a guide for the use of animals in robot care for elderly people with dementia, designed for healthcare professionals and caregivers (more details in Section 3.2.1 of this Report).

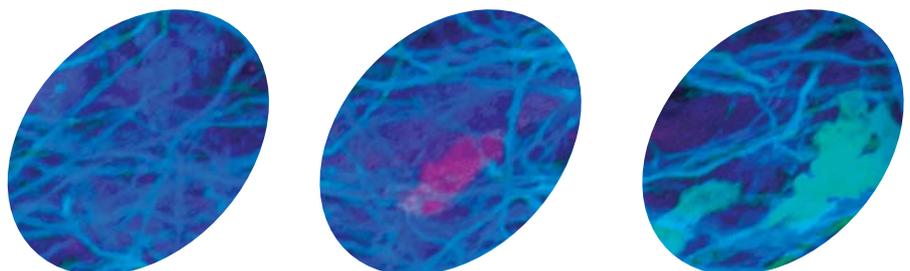


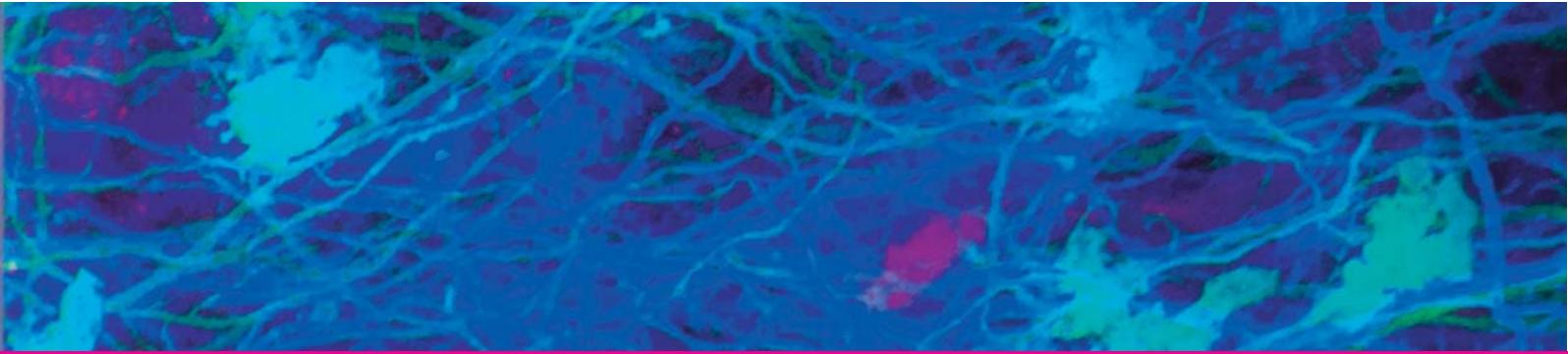
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Scientific productivity

CIEN Foundation researchers have produced 47 scientific publications in 2014. Of these, almost 92% were in journals included in the Science Citation Index Expanded and over 78% have been published in journals ranked within the first and second quartiles. Moreover, they have fulfilled their activity of scientific dissemination with 27 participations in various conferences.





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 2014, researchers CIEN Foundation have produced a total of 47 publications, of which 46 have been published in scientific journals of national and international recognition (39 original articles, 4 reviews, 1 editorial, 1 proceeding, and 1 letter) 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, 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 4.53 in 2013 to 4.99 in this year 2014.

The following table shows output indicators of production (number of publications), quality (publications in journals ranked within the first and second quartile of their subject category), impact (determined by the accumulated and average impact factor of the journals in which it has been published)

and degree of collaboration at national and international levels.

Among 2014 milestones we can highlight that the CIEN Foundation researchers have published 47 scientific papers, of which 43 (91.5%) have been in journals under the coverage of the Science Citation Index Expanded, accessible through the Web of Science portal (WoS, Thomson Reuters) and 38 (79.2%) have been published in journals ranked within the first and second quartile in their category. Considering the type of document, 83% of the publications in scientific journals (39) correspond to original articles.

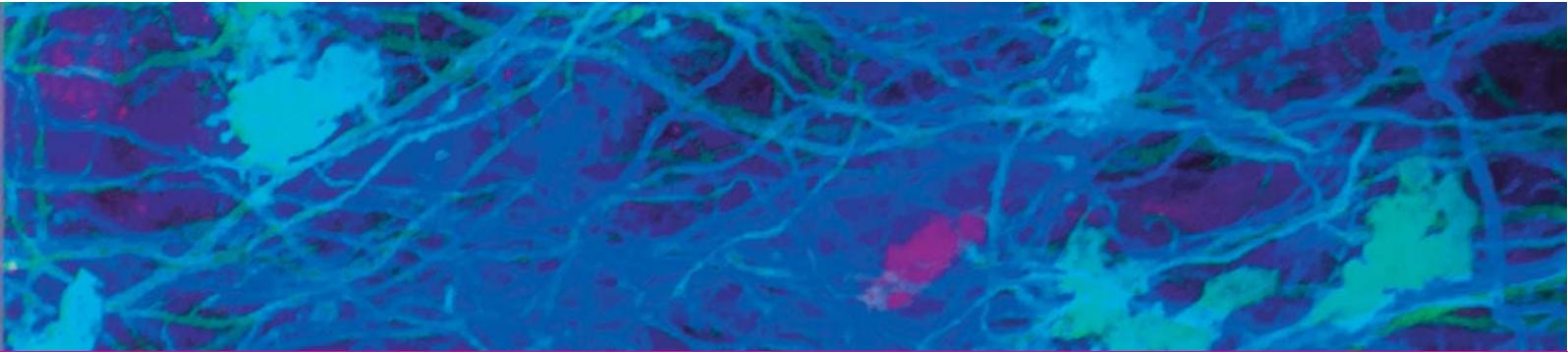
Moreover, according to their scientific subject category, 68% of the publications within the first and second quartiles, have focused on the following categories: Clinical Neurology, Neurosciences, Multidisciplinary Sciences, and Anatomy and Morphology.

As scientific dissemination activities in meetings and national and international events during the year 2014 there have been a total of 27 participations at scientific conferences, 18 of which correspond to lectures and oral presentations, and 9 correspond to written communications in the form of posters. These communications have been presented at national (21) and international scientific conferences (6).

Indicador 2014

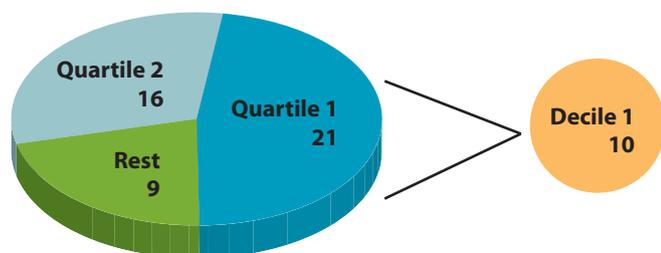
Total number of publications.....	47
Total number of publications in the ISI citation index within the first and second quartile.....	37
Cumulative impact factor of publications within the first and second quartile.....	187,91
Average impact factor of the publications of the first and second quartile.....	4,99
Number of collaborative publications of all kinds (CIBERNED, other national groups, international groups) within the first and second quartile.....	37
Number of international collaborative publications within the first and second quartile.....	6
Número de publicaciones colaborativas nacionales (no FCIEN) en primer y segundo cuartil.....	10
Número de publicaciones colaborativas con otros CIBERs y redes en primer y segundo cuartil.....	1





Other noteworthy scientific activities include 34 scientific presentations at training courses.

Publications according to the ISI citation index in 2014



6.2. Publications

The 47 scientific papers cited below were published by CIEN Foundation professionals according to the following typology: 46 peer-reviewed scientific journals (39 original articles, 4 reviews, 1 editorial, 1 proceeding and 1 letter) and 1 clinical guideline.

6.2.1. Journal articles

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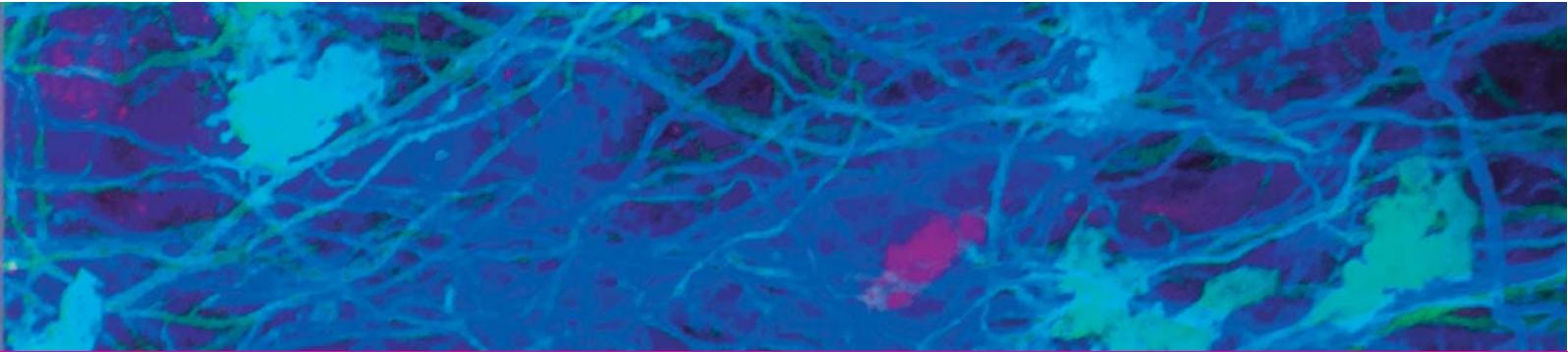


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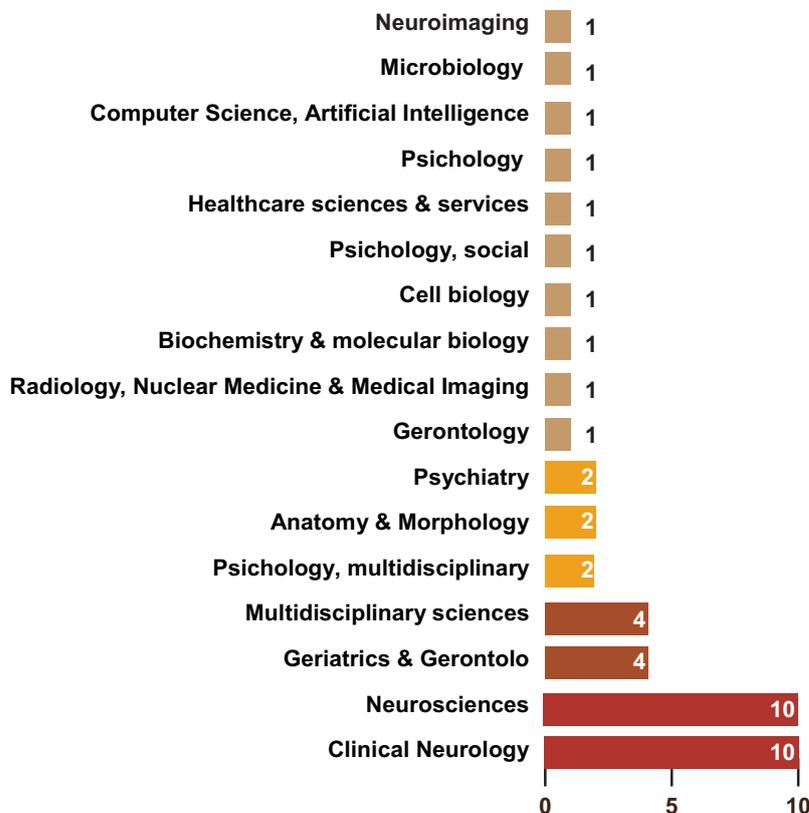
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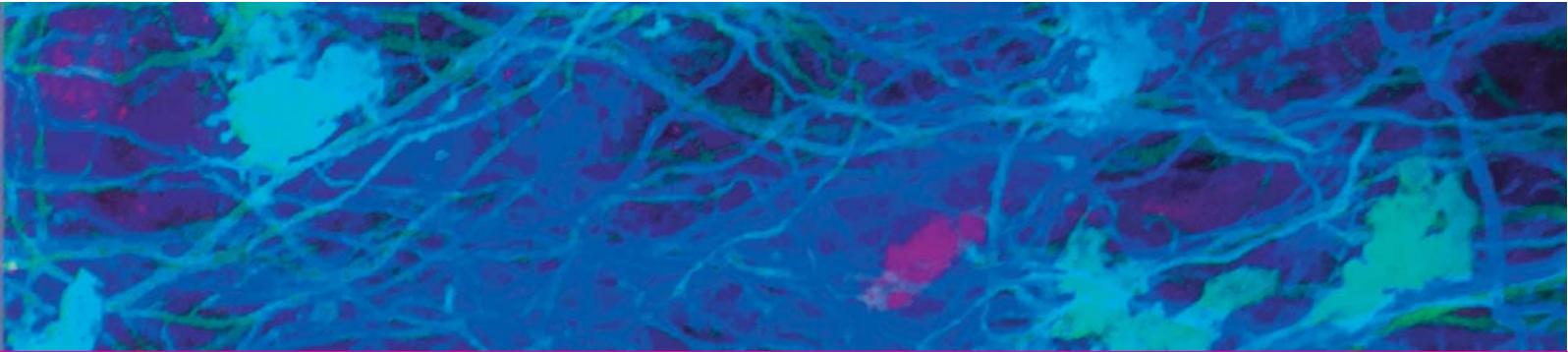


6. SCIENTIFIC PRODUCTIVITY

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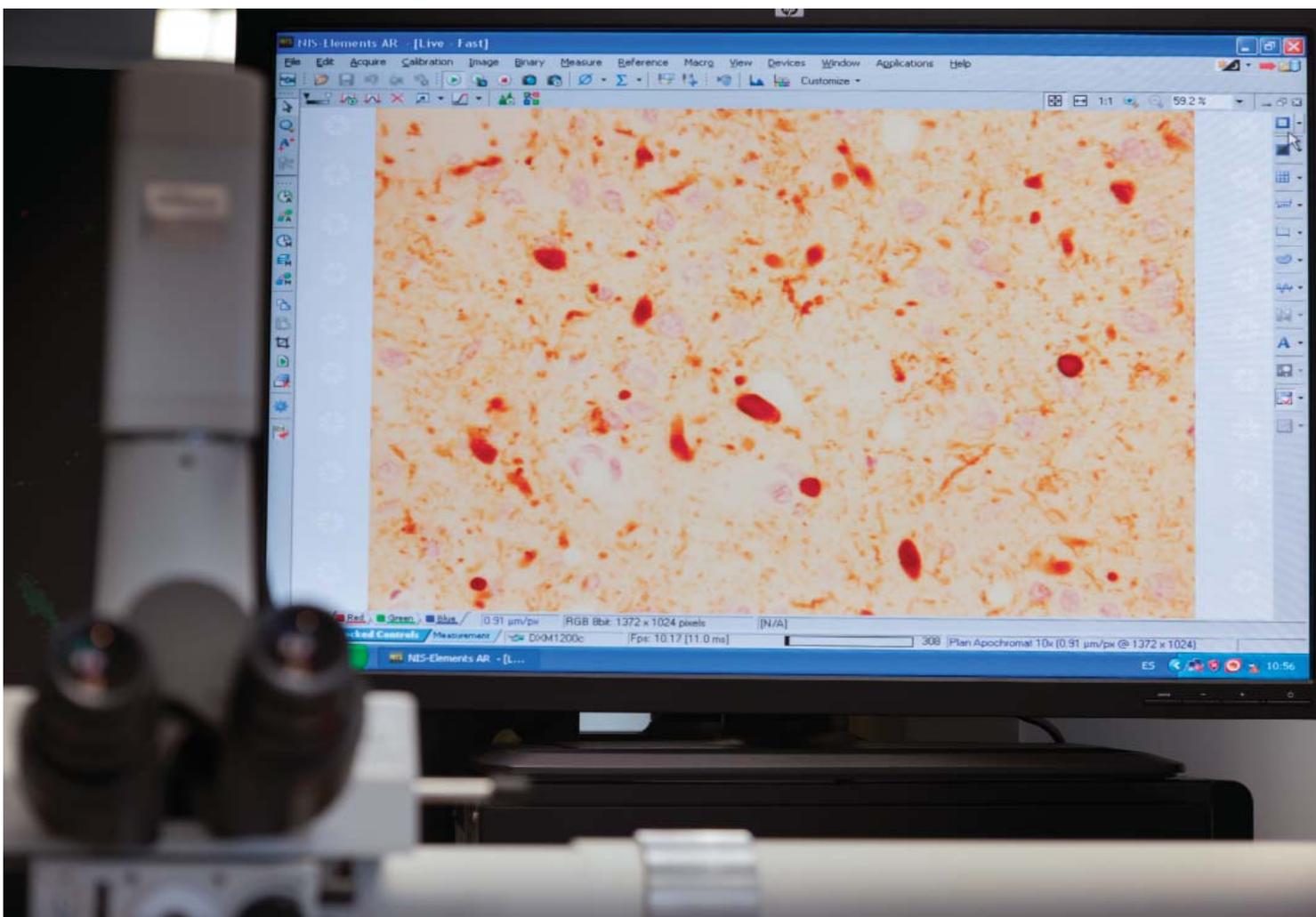
6. SCIENTIFIC PRODUCTIVITY

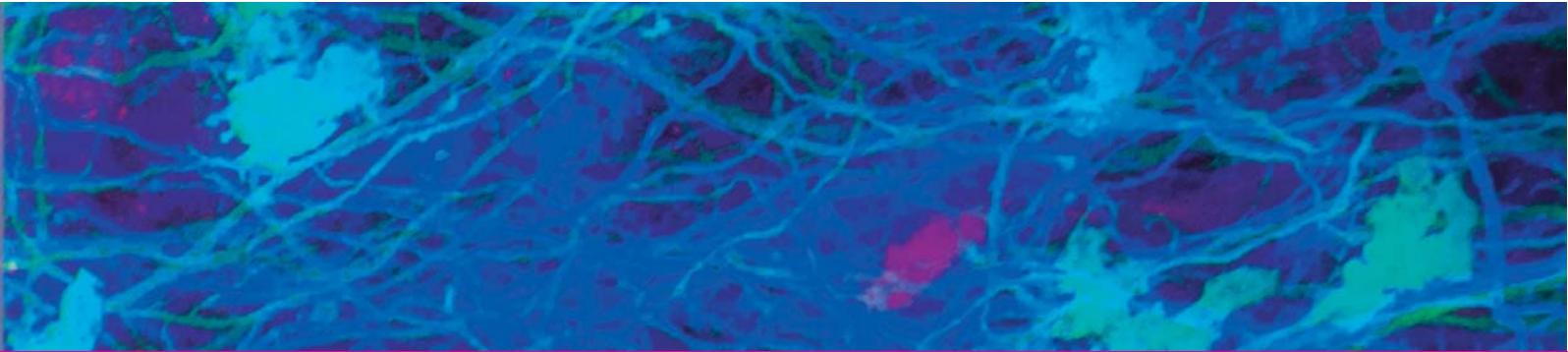
6.3. Proyectos financiados

During 2014 the CIEN Foundation researchers have participated in 8 scientific research projects obtained through various national and international competitive calls and funded by different institutions.

Funded research projects are cited below:

- **Code FCIE-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 €
2014 budget: 329.039,60 €





- **Code: 500009**
Principal Investigator : Dr. Marcel Heerink
Title: Nieuwe vrienden, oude emoties
Funding agency: SIA-Raak Project 2011-3-30 int
New Friends, Old emotions
Duration: 2012-2014
Total budget: Fundación CIEN: 18.180 €
2014 budget: 18.180 €
- **Código: 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 €
2014 budget: 7.865 €
- **Código: PT13/0010/0045**
Principal Investigator: Alberto Rábano
Title: Biobanks Platform
Funding agency: Carlos III Institute of Health
Duration: 2013-2014
Total budget: 46.500 €
- **Código: Proyecto IPT-2012-0769-010000**
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 €; Fundación CIEN 93.320 €
2014 budget: 41.062,50 €
- **Código: METC 11-4-057**
Principal Investigator: Dr. Pablo Martínez Martín
Title: Assessing and diagnosing anxiety in patients with Parkinson's Disease
Funding agency: Michael J. Fox Foundation
Duration: 2011-2014
Total budget FCEN: 72.905,96 €
- **Código: Proyecto ARDOUIN**
Principal Investigator: Dr. Pablo Martínez Martín and Pr. Franck Durif (International)
Title: Behavioral Assessment in Parkinson's Disease. Validation of a scale.
Funding agency: Université Clermont-Ferrand (France)
Duration: 2010-2014
Budget: 9.555 €
- **Código: Universidad Ulm**
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

6.4. Patents

Four patents currently co-owned by CIEN Foundation have remained active during 2014 in national and international phases.

- **Inventors:** Pablo Martínez Martín, Pedro Carmona Hernández, Adolfo Toledano Gasca, Miguel Calero Lara, Félix Bermejo Pareja
Title: Infrared analysis of fractions obtained from peripheral blood to indicate cognitive development.
Registration N°: 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

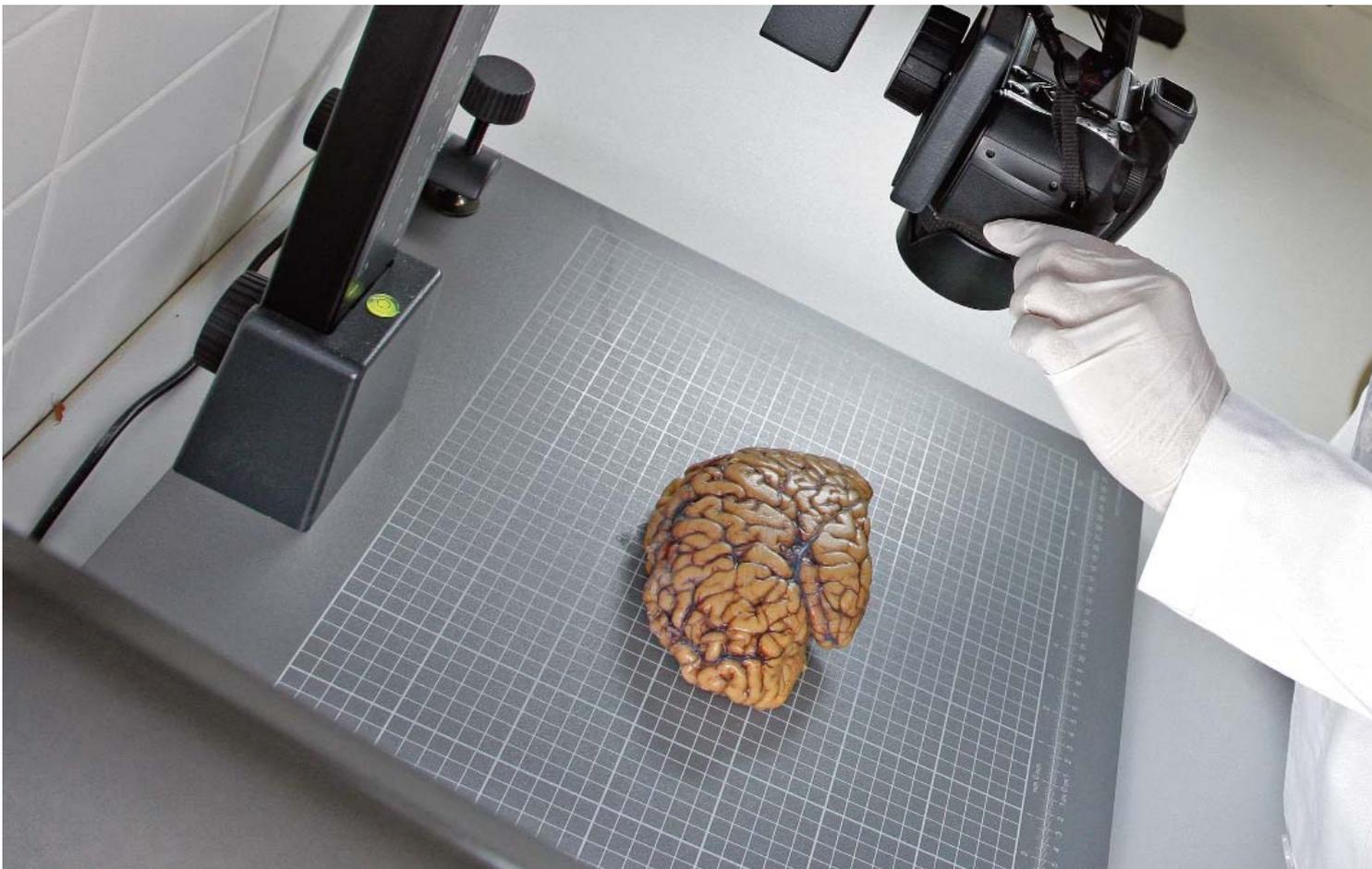


6. SCIENTIFIC PRODUCTIVITY

PCT/EP/2013/067304
Application date: 20/08/2012
Type: National/European
Licensing agreement with Biocross

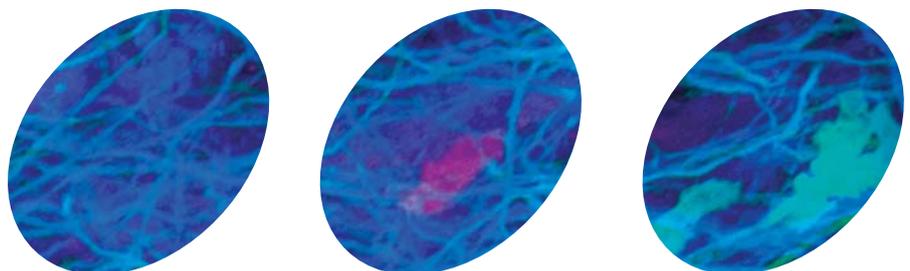
- Inventors: José Ramón Naranjo Orovio, Britt Mellström, Diego Villar Lozano, Mara Dierssen Sotos, Alberto Rábano Gutiérrez del Arroyo.
Title: Compounds for the treatment of neurodegenerative diseases
Registration N°: PCT/ES2012070020
Application date: 13/01/2011
Type: European

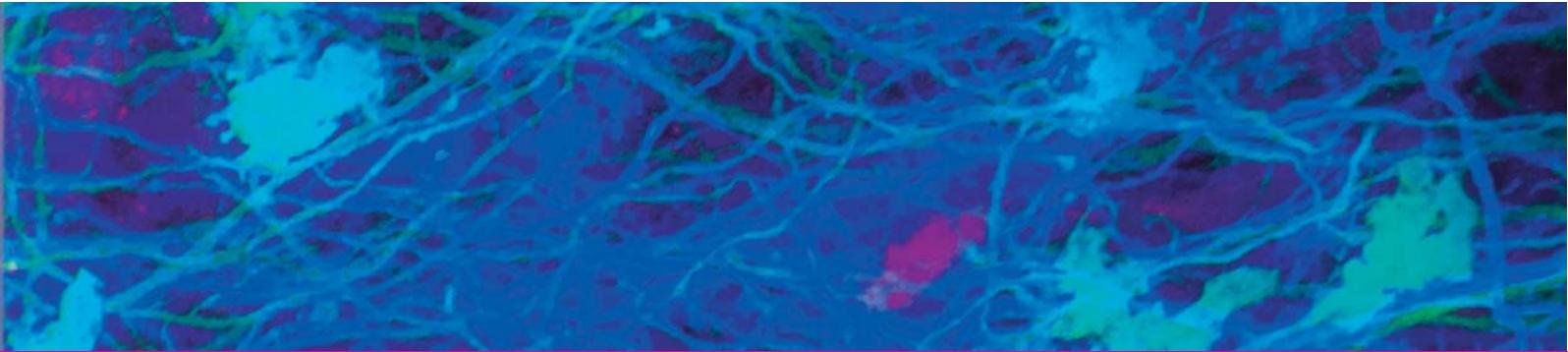
- Inventors: José Ramón Naranjo Orovio, Britt Mellström, Alberto Rábano Gutiérrez del Arroyo.
Title: Methods for the prognosis and diagnosis of neurodegenerative diseases
Registration N°: EP13382108.2
PCT/EP2014/055928
Application date: 25/03/2013
Type: National/European



Social dissemination

The second International Congress on Research and Innovation in Neurodegenerative Diseases (CIEN) was held in 2014, inaugurated by HM Queen Sofia and whose objective is to share progress and information of interest on neurodegenerative diseases among the scientific community. Likewise, continuing the important CIEN Foundation outreach activities, a new edition of the now traditional "Christmas tree of memories" and the "Vallecas Project Volunteer's Day" also took place.





GACETA MEDICA

Nuevos enfoques terapéuticos en la enfermedad de Alzheimer

Aumentar el número de chaperonas neurales mejora la capacidad de memoria

Medical article layout with text, images of laboratory equipment, and a photo of a group of people. Includes sub-headers like 'Necesidad de investigación' and 'LA RAZON'.



7. SOCIAL OUTREACH ACTIVITIES

7.1. II International Conference in Research and Innovation on Neurodegenerativas (CIIEN)

On the occasion of the World Alzheimer's Day celebrate on September 21, took place in Barcelona the Second International Conference for Research and Innovation on Neurodegenerative Diseases (CIIEN).

The event, promoted by the Queen Sofia Foundation in collaboration with the CIEN Foundation has as its main objective to provide a scientific forum where to share progress and relevant information about neurodegenerative disease among the scientific community.

CIIEN, created in 2013, was born to unify the two major scientific conferences on neurodegenerative diseases in general, and Alzheimer's disease in particular, organized in Spain: the International Symposium on Advances in Alzheimer's disease, which was annually promoted by the Queen Sofia Foundation and CIEN Foundation, and the CIBERNED Scientific Forum, which annually brought together the more than 54 research groups that constitute CIBERNED.

The consolidation of both events is a first step in creating a new operating structure in the two main institutions involved in research on neurological and neurodegenerative diseases in Spain: CIEN Foundation and CIBERNED, both under the Ministry of Economy and Competitiveness through the Carlos III Institute of Health.

This new structure seeks greater effectiveness and efficiency in research, promoting the interaction of the different research groups.

Chaired by Her Majesty the Queen, with the presence of the State Secretary for Social Services and Equality, Susana Camarero, and the Director of the Carlos III Institute of Health, Antonio Andreu, the Conference was organized around two plenary sessions and eight scientific sessions in which three main

topics were addressed: identification of biomarkers for these disorders. cell therapies and neuroprotective mechanisms.

2014 Alzheimer Social Forum

As part of the complementary activities related to the International Alzheimer's Day, at the end of the Conference it was held a Social Forum in the form of journalistic debate intended to reflect the "full" reality of the disease from different viewpoints.

This initiative seeks to promote common grounds for reflection and move toward a more comprehensive understanding of the disease and the reality that it entails.

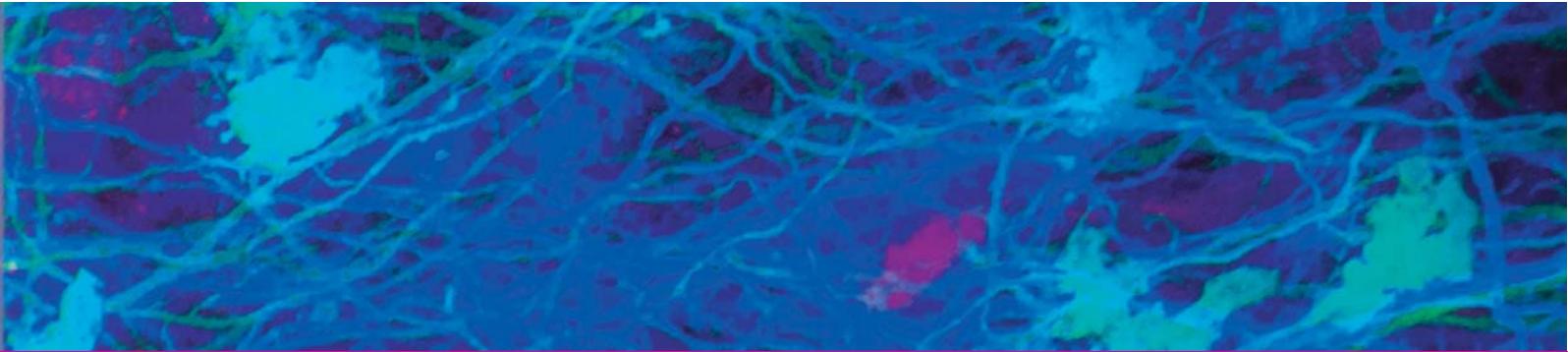
The debate, moderated by Emilio Benito, Health and Science specialized journalist from the newspaper El País, was broadcast by streaming and featured a diverse group of participants composed of: Alberto Lleó, researcher; Manel Martí, suffering from Alzheimer's; M^a Carmen Pardina Sierra, a relative of Alzheimer's patient; Carmen Ponce, non-relative caregiver; Merce Agusti Pareda, PCP; and Inmaculada Fernández Verde, representative of association of patient's relatives.

Following the discussion, with the aim of giving also visibility to Huntington's and Parkinson's diseases, two lectures were delivered on both conditions:

- "Lessons learned from Huntington's" by Saul Martinez Horta, coordinator of the European Group for Huntington's disease.
- A lecture on Parkinson's by Eduardo Tolosa, director of the Parkinson's and Movement Disorders Unit of Barcelona Clinic Hospital and Principal Investigator (PI) of CIBERNED.

As part of the Forum, in order to enrich the debate and encourage participation by patients, relatives





or patients' associations, the campaign "You have a role in the fight against Alzheimer's" was designed. The hashtag #PapelAlzheimer helped to promote social participation in social networks, served to draw together the efforts of all participant associations of Alzheimer's patients and to achieve higher visibility for the Social Forum.

7.2. Dissemination activities

One of the objectives of the CIEN Foundation is to convey to society in an accessible manner the progress made in the research on neurological diseases.

For this reason, the heads of the CIEN Foundation departments have organized various activities to inform on the research work of its professionals. This allows them to bring science closer to society in a friendly manner while moving data and information of interest about the various neurological diseases under study. Among these outreach activities undertaken in 2014 are included the second edition of the "Vallecas Project 'Volunteer's Day'" and the third edition of "The Christmas Tree of Memories".

Furthermore, the coordinators of the CIEN Foundation different research areas have also participated

in various seminars and meetings, with the aim of contributing to dissemination of science in society.

'Vallecas project Volunteer's Day'

The "Vallecas Project Volunteer's Day" is the tribute that since 2013, the CIEN Foundation and the Queen Sofia Foundation, render to the volunteers participating in this project managed by the CIEN Foundation.

Over 1,000 people attended its second edition, held on February 21 at the Apolo Theater in Madrid and presented by journalist Irma Soriano. During the event a video tribute to the Vallecas Project volunteers was shown, followed by the contest "Do you remember? ", devised by the project managers, and the theater play "Paralela-mente" was also staged.

'Christmas Tree of Memories'

In 2014, CIEN Foundation has moved its traditional "Christmas Tree of Memories", placed each year in the Queen Foundation Alzheimer Center Sofia, to the Villa de Vallecas marketplace, as part of an awareness campaign which allows not only bring Alzheimer's reality to society in general, but also highlight the role of the Villa de Vallecas district in this work.

Thus, the tree was installed in the market of Villa de Vallecas between 10th and 31st December. To complement this action, posters and stickers with the slogan "Villa de Vallecas with Alzheimer's research" were distributed to retailers, which helped to raise greater awareness of the disease and the research activities of the Foundation. Furthermore, solidarity bracelets with the same slogan were also designed and distributed among retailers. Market customers could buy them for the symbolic price of 1 euro and thus collaborating with research in Alzheimer's disease.



7. SOCIAL OUTREACH ACTIVITIES

Other Outreach Activities

During 2014 the CIEN Foundation has continued to develop other actions to disseminate the research work of its professionals which have resulted so successful in previous editions. This is the case of the informative lectures organized by patients associations throughout Spain. In these lectures, Dr. Alberto Rábano, head of the CIEN Foundation Tissue Bank, promotes the work done in tissue banks as the BT-CIEN and encourages the donation of brain tissue, essential for researchers to continue advancing in their research projects by having samples that accurately reflect the consequences of neurodegenerative diseases such as Alzheimer's or Parkinson's, among others.

In addition, CIEN Foundation collaborated with other foundations and institutions bid to offer during 2014 a series of activities in the form of cultural visits or educational lectures, mainly targeting volunteers involved in the Vallecas Project:

- As part of the "Edición Recuerda" project launched by the Queen Sofia Foundation, the Spanish Railways Foundation provided free guided tours to visit the Fernán Núñez Palace, headquarters of the Foundation and the Railway Museum in Madrid.
- In collaboration with the Directorate General for the Elder, several guided tours of the Banco Santander Foundation Art Gallery, located in the facilities of the Banco Santander Financial City in Boadilla del Monte (Madrid) were also made. There, the volunteers could enjoy the temporary exhibition "Everybody is nobody for somebody", assigned by the collector Grazyna Kulczyk, one of the most important art collectors in Poland and Central and Eastern Europe, with more than 100 works from Polish and international contemporary artists since the end of the 40s until today.

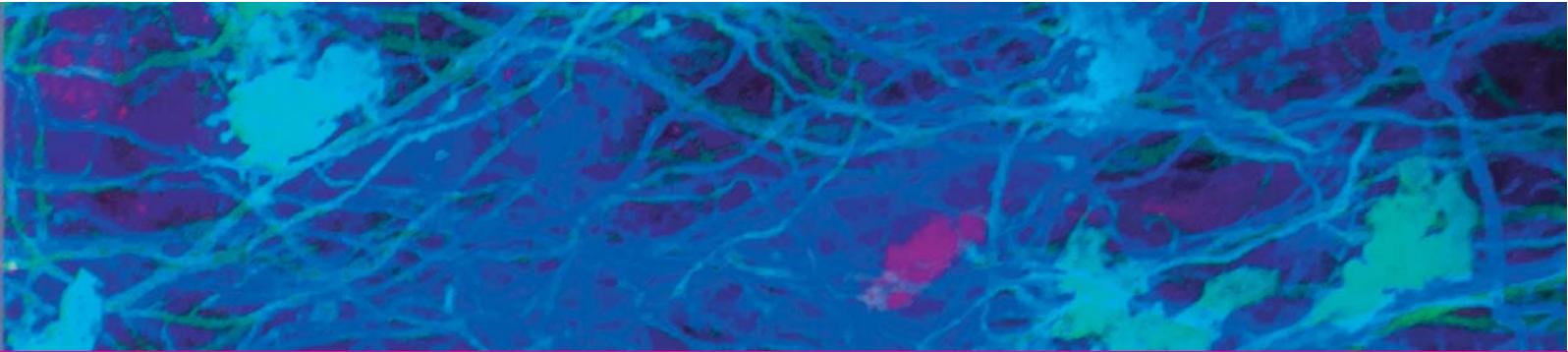
- In June 2014, CIEN Foundation hosted a lecture about food and cooking for the elderly, within the activities of the Directorate General for the Elder in collaboration with the Madrid Institute for Research and Rural, Agriculture and Food Development (IMIDRA. for its acronym in Spanish).

7.3. Joint meetings with the Queen Sofia Foundation

Throughout 2014 there have been several joint workshops between UIPA researchers, members of the CIEN Foundation Scientific Advisory Committee and representatives of the Queen Sofia Foundation::

- **On January 29, 2014**, Her Majesty the Queen, accompanied by the State Secretary for Research, Development and Innovation and Chair of the CIEN Foundation Board, Carmen Vela, and Madrid's Director General for the Elder, José Ramón Menéndez Aquino, held a business meeting with management and researchers responsible for the various Research Center in Neurological Diseases Foundation (CIEN Foundation) projects together with members of its Scientific Advisory Committee, coordinated by Dr. Jesús Avila . During the meeting the status of implementation of ongoing projects, most notably the Vallecas project (one of the most ambitious studies in our country on Alzheimer's disease), was exposed as well as the main priorities to successfully deal with such projects and future challenges.
- **On June 24, 2014**, H.M. Queen Sofia hosted Leonor Belezza, Chair of the Champalimaud Foundation, Portuguese institution devoted to advanced biomedical research. Leonor Belezza, at the hands of H.M., was briefed on the research projects being developed at CIEN Foundation. The visit is detailed in paragraph 5 of this report.





- **On October 29, 2014**, Her Majesty The Queen attended a meeting with representatives of CIEN Foundation. He was welcomed by M^ª Angeles Pérez, Managing Director of CIEN Foundation, Jesús Avila de Grado, Scientific Director of CIEN Foundation and the Center for Networked Biomedical Research on Neurodegenerative Diseases (CIBERNED) and Miguel Medina, Principal Investigator of the Vallecas Project and Deputy Scientific Director of CIBERNED and CIEN Foundation.

At the meeting, Queen Sofia was also accompanied by José Ramón Naranjo, Javier de Felipe and Fernando Rodríguez Artalejo, members of the CIEN Foundation Scientific Advisory Committee and several Foundation researchers and staff.

M^ª Angeles Pérez, Managing Director of CIEN Foundation, opened the session with a brief presentation of the research projects being carried out in CIEN Foundation with the support of the Queen Sofia Foundation.

Next, Jesús Avila, Scientific Director of CIBERNED and CIEN Foundation, presented Queen Sofia with a publication on the Second International Conference on Research and Innovation in Neurodegenerative Diseases (CIIEN), held in September under the Chairmanship of Queen Sofia, and also with the support of the Foundation that bears his name.

Miguel Medina, Principal Investigator of the Vallecas Project and Deputy Scientific Director of CIBERNED and CIEN Foundation, presented an update to Her Majesty on the status of this five-year longitudinal study that is examining a cohort of 1,213 subjects between 70 and 85 years of age intended to advance in the early diagnosis of Alzheimer's disease (see section 4 of this report). Queen Sofia showed great interest in the preliminary hypotheses drawn from the first round of assessments, which is now completed, and also by the high participation of women in the study.



7. SOCIAL OUTREACH ACTIVITIES

Finally, Bryan Strange, coordinator of the CIEN Foundation Neuroimaging Department, explained to Her Majesty the specifics of their study on the structure of the hippocampus and its role in memory and spatial orientation, research conducted with the recent Nobel Prize in Medicine Edvard I. Moser. This work suggests, based on recent genetic and anatomical studies, that the hippocampus is organized in gradients where there are multiple functional domains.

Queen Sofia also visited the facilities and various research areas of the CIEN Foundation, which is responsible for the research side of the Queen Sofia Foundation Alzheimer Project, a social health project launched by the Queen Sofia Foundation in 2002 that resulted in a social health complex, the Queen Sofia Foundation Alzheimer Center (CAFRS), which deals with Alzheimer's viewed from three perspectives: research, education and healthcare service to patients.

7.4. Awards

"A tu salud" Award to the Investigator of the Year

In June 2014, during the third edition of "A tu salud" Awards, granted by the newspaper La Razón to recognize research activities in various fields, Dr. Alberto Rábano received the Researcher of the Year Award in the Science category for his push of a brain bank that helps to a deeper understanding of neurodegenerative processes such as Alzheimer's.

The Department of Neuropathology of the Alzheimer Project Research Unit (UIPA) has as one of its key goals conducting brain post-mortem studies in order to establish a definitive neuropathological diagnosis and long-term preserve brain tissue and other neurological samples for use in research.

"Mano Amiga" International Award

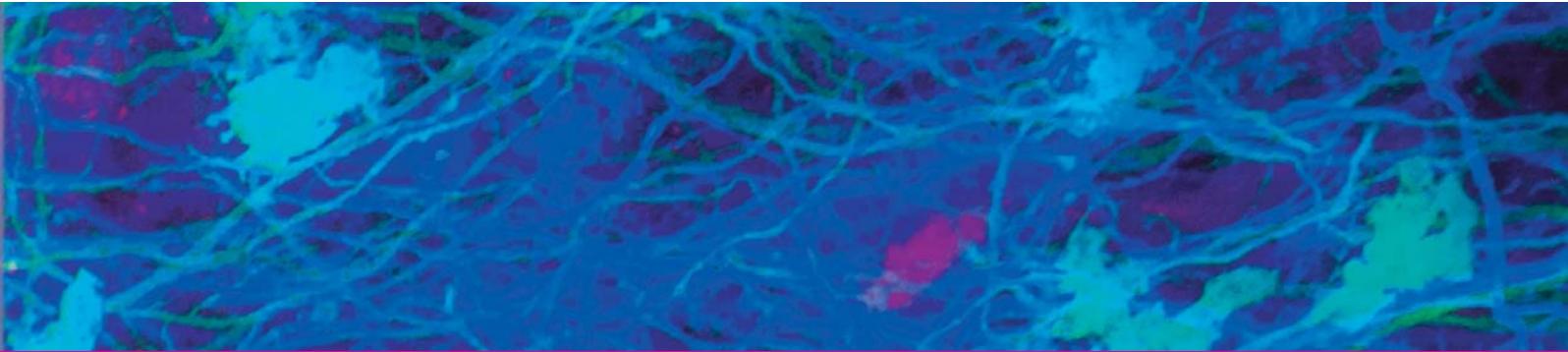
On November 6, 2014 took place the fourth edition of the Alzheimer León's "Mano Amiga" International Awards.

The meeting brought together over 700 people in the City Auditorium at León to recognize the work of professionals, institutions and anonymous people who work in support of those affected by this disease and their relatives.

In this edition, the "Mano Amiga" Award in the individual category, which recognizes the work of professionals in this field, went to the Spanish biologist and scientist Jesús Avila de Grado, Scientific Director of CIBERNED and CIEN Foundation and Research Professor at CSIC's Center of Molecular Biology Severo Ochoa for his contribution to the knowledge of neurodegenerative disorders, particularly Alzheimer's disease. His research on the role of microtubule proteins in neurodegenerative processes were particularly acknowledged.

Among many other awards Dr. Jesús Avila has received the Royal Academy of Mathematics, Physics and Natural Sciences Prize and the Santiago Ramón y Cajal National Research Award in 2004. He has been a pioneer in Spain in the study of neurodegenerative processes and has performed outstanding research on the potential role of tau protein in the development of pathologies like Alzheimer's disease. The Alzheimer León's "Mano Amiga" International Awards also recognized the government of France in the Institutional category, and caregiver Manuel Diez, who has cared for his Alzheimer's suffering wife for nearly 30 years, in the Anonymous category.





Perfiles



II CONGRESO INTERNACIONAL SOBRE INVESTIGACIÓN E INNOVACIÓN EN ENFERMEDADES NEURODEGENERATIVAS (CIEN)

Necesidad de investigación

Las enfermedades neurodegenerativas enfrentan un problema común: el limitado, aunque extenso, conocimiento del cerebro y la tardanza en el diagnóstico. Esto las convierte en patologías sin cura ni tratamiento efectivo.

tes de la fibra

C...erivadas por provocar la progresiva muerte de neuronas en diferentes regiones del sistema nervioso, con el consiguiente deterioro funcional de las partes afectadas, los síntomas más frecuentes y conocidos son las enfermedades de Alzheimer y de Parkinson, aunque existen otras patologías, como la enfermedad de Huntington o la Esclerosis Lateral Amiotrófica (ELA), que cada vez cuentan con más apoyo en la investigación y tratamiento y que, de forma paralela, surtirán en incidencia.

En estas enfermedades, de enorme impacto en las vidas de enfermos, familiares y en el conjunto de la sociedad, han crecido el II Congreso In-

ternacional sobre Investigación e Innovación en Enfermedades Neurodegenerativas, que la Fundación Reina Sofía, la Fundación Centro de Investigación sobre Enfermedades Neurológicas (Fundación CIEN) y el Centro de Investigación Biomédica en Red en Enfermedades Neurodegenerativas (CIBERned), han col-

LA RAZÓN

Congreso Internacional sobre Enfermedades Neurodegenerativas La Reina Sofía vuelve a Cataluña

Doña Sofía presidió ayer su primer acto oficial en Cataluña tras la proclamación de Don Felipe, cumpliendo con dos de los propósitos marcados por el nuevo monarca: mantener la presencia de la Corona en la comunidad y aprovechar la experiencia de sus padres para ampliar el contacto con la sociedad. La Reina Sofía presidió en el hotel Barceló Santis la inauguración del Congreso Internacional sobre Enfermedades Neurodegenerativas, una iniciativa en la que participa la Fundación Reina Sofía. En la imagen, entre la delegada del Gobierno, María de los Llanos, y la secretaria de Estado de Igualdad, Susana Camarero.



ABC

AGENDA 63



La Reina Doña Sofía saluda al personal del Centro de Alzheimer de Vallecas

FAMILIA REAL La Reina Doña Sofía visita la Fundación CIEN

En su primera aparición pública desde que Don Felipe fue proclamado Rey, la Reina Doña Sofía visitó ayer el Centro de Alzheimer de Vallecas de la Fundación CEIN (Centro de Investigación de Enfermedades Neurológicas). La Reina estuvo acompañada durante su recorrido por el centro por la presidenta de la Fundación portuguesa Champalimaud, Leonor Beleza. Doña Sofía y la presidenta de la Fundación Champalimaud, institución dedicada a la investigación biomédica avanzada, fueron recibidas a la entrada del centro por la directora gerente de la Fundación

CIEN, María Ángeles Pérez; el director general del Mayor de la Comunidad de Madrid, José Ramón Menéndez Aquino; y el director científico de esta institución, Jesús Ávila de Grado.

La Reina presidió una reunión informativa en la que investigadores y responsables de la Fundación CEIN han presentado las líneas generales de los proyectos actualmente en marcha en relación con el alzhéimer, entre ellos el denominado Proyecto Vallecas, programa piloto en el que colabora la Fundación Reina Sofía, que impulsó en 2002 la construcción del Centro de Alzheimer en el distrito madrileño de Vallecas y que dedica una de sus principales líneas de actuación a fomentar la investigación de esta enfermedad.

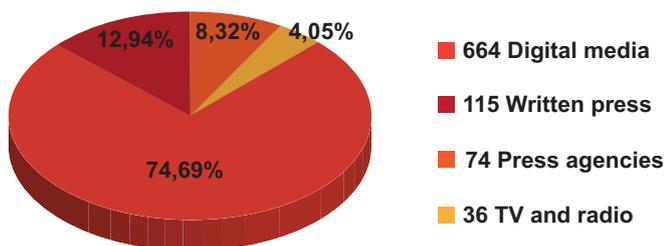


7. SOCIAL OUTREACH ACTIVITIES

7.5. Presence in media

Throughout 2014, we have continued to promote the presence of CIEN Foundation researchers in the media. To do this, 35 press releases on various aspects of the activities being performed in the Foundation were distributed, also 45 web contents were produced and a total of 47 interviews were managed in specialized and general media.

This information generated a total of 889 impacts in media, distributed as follows:



Moreover, in 2014, the fluency in the internal communication between the different departments of the Foundation and the areas of communication and social networks has also been favored, resulting in higher production of content and an increase of almost 31% over the previous year.

7.6. 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 are particularly appreciated.

The work performed both from social networks and the CIEN Foundation blog, which reports on the activities of its professionals, has enabled to spark the interest of the community, both scientific and general public.

This interest has resulted in high levels of participation in the various initiatives that have been developed in the offline world and that has transferred to the online world. For example, the streaming broadcast from the CIEN Foundation website of the second edition of CIIEN, or the Social Forum, in which questions submitted through Facebook were answered in real time or the Twitter live coverage of the lectures.

Thus, almost 100,000 users visited the CIEN Foundation website during 2014 and viewed 128,400 pages. The analysis by individual social networks would be as follows:

- **Facebook:** <https://www.facebook.com/FundacionCIEN>: Year 2014 closed with a total of 3,083 fans with a high number of shared publications, likes and comments.
- **Twitter @Fund_CIEN:** By the end of 2014 the profile counted on 10,130 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 2014 ended with a total of 66,172 visits.





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