cïeN

**Fundación Centro Investigación
Enfermedades Neurológicas**

Annual Report

2012

Annual Report

2012

MINISTERIO
DE ECONOMÍA
Y COMPETITIVIDAD

Instituto
de Salud
Carlos III

cïeN
Fundación Centro Investigación
Enfermedades **Neurológicas**

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Profile
and pres*e*ntation

The CIEN Foundation is a public foundation devoted to promoting and coordinating research in neurological diseases, mainly Alzheimer's and other dementias. Its collaboration with the Queen Sofia Foundation places it as successful example in implementing a "public-private" management model in the field of scientific research.
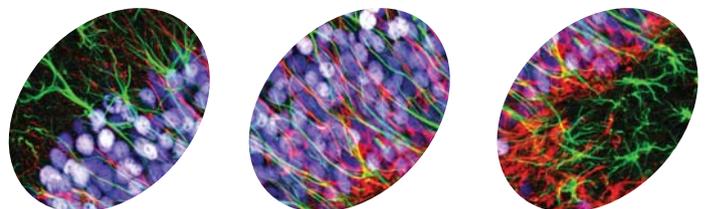
1.1. Who we are

A Foundation from the public sector

The Research Center for Neurological Diseases (CIEN) Foundation was established by resolution of the Council of Ministers on December 27, 2002 as a non-profit Foundation from the public sector with State-wide scope and competence. It is currently depending on the Ministry of Economy and Competitiveness through the Carlos III Institute of Health.

Its founding purpose is to support, promote and coordinate research into neurological diseases, with special emphasis on neurodegenerative diseases, joining and coordinating efforts of Spanish leading research groups.

Colaboration with the Queen Sofia Foundation

Since its creation, the CIEN Foundation manages and coordinates the Alzheimer's Disease research Unit (UIPA), set up by the Queen Sofia Foundation and located in the Alzheimer Center bearing its name.This collaboration represents a clear example of establishing a "public-private" management model.

Since April 2007, the CIEN Foundation headquarters are located in the Queen Sofia Foundation Alzheimer Center, by virtue of the agreement signed between the two institutions on January 18, 2006. Under this agreement, the Queen Sofia Foundation donated the complex built in Vallecas to develop the Alzheimer Project, a social health approach that comprehensively addresses the impact that this disease causes both to patients and their relatives.

A Center of Reference in Alzheimer's Disease Research in Spain

In 2011 UIPA and CIBERNED, both managed by the CIEN Foundation, were designated as Centers of Excellence in neurodegenerative disease research by the European Union. They are the only two Spanish

institutions with this qualification participating in the Joint Programme for Neurodegenerative Diseases (JPND). This means being integrated into the International Network of Centers of Excellence in Neurodegenerative Disease Research (CoEN). The excellent infrastructure to provide both institutions, their technical and technological capabilities and research critical mass provided by CIBERNED, have allowed both institutions to become part of the International Network of Centers of Excellence in Research on Neurodegeneration (COEN).

An innovative, integrated vision of the fight against AD

The CIEN Foundation and the Queen Sofia Foundation share the pioneering objective of approaching Alzheimer's disease from a holistic perspective, in which research is one of the mainstays.

The main exponent of this integrative model is Queen Sofia Foundation Alzheimer Center, where the main Alzheimer Project backbones converge.

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

When the Queen Sofia Foundation built the Alzheimer Center in Madrid's Vallecas neighborhood, entrusted UIPA management to the CIEN Foundation, while welfare and education activities were assigned to the Region of Madrid Council of Family and Social Affairs. This model has constantly tried to bring wills together and combine the interests of all parties involved: Government (Central, Regional and Local) and the Civil Society.
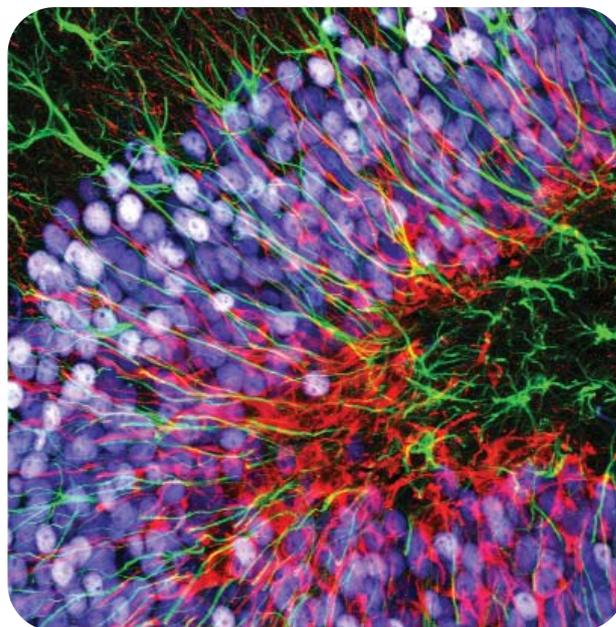
Experts in global management of research in neurodegenerative diseases

Translating scientific advances achieved in basic research to clinical practice, promote the execution of coordinated research projects in neurological diseases, promote participation in calls made by funding agencies, both nationally and internationally, and increasing training through specific activities as seminars, lectures or doctoral theses are some of the tasks of the Foundation CIEN.

In addition, the CIEN Foundation complement these tasks with the management of UIPA and the Center for Networked Biomedical Research in Neurodegenerative Diseases (CIBERNED), representing of the Carlos III Institute of Health (ISCIII) European Projects Office, leading the reference Center for Endemic Diseases Control in Equatorial Guinea project, and coordinating the International Cooperation Scholarships for graduate studies of the National School of Health-ISCIII. This report will only cover UIPA management though.

1.2 The CIEN Foundation in 2012

Key figures

► The CIEN Foundation overall budget for 2012 was 3,327,316€

► 24,8% of the CIEN Foundation budget comes from the General State Budget through the ISCIII

► It is noteworthy the continued commitment of the Queen Sofia Foundation on the budget, contributing in 2011 over 2.1 million euros for the next four years

Scientific activity

► Overall scientific production: 74 publications 27.6% increase versus 2011

► Publications in scientific journals: 57 29.5% increase versus 2011

► Book Publications: 17 21.4% increase versus 2011

► Participation in scientific meetings conferences: 104 Similar to 2011

► Participation in courses: 80 Similar to 2011

1. PROFILE AND PRESENTATION

Highlighted events

► In late 2011, the first round of European research projects from the Joint Programme in Neurodegenerative Diseases (JPND) was launched, awarding four translational research projects for 2012-2014. One of them has the participation of researchers from the CIEN Foundation

► In December 2012 two new JPND calls for projects were launched, one of which focuses on the study of risk factors in neurodegenerative diseases - it is open to the participation of CIBERNED and CIEN Foundation research groups

► In that same month a call for "Pathfinder" research projects also launched by the International Network of Centers of Excellence in Neurodegeneration (COEN), from which CIEN and CIBERNED Foundation are part of

► The "Vallecas Project" has already recruited and conducted an initial assessment to 1,000 volunteers, representing approximately 85% of people planned to participate in this five years study

► Only in 2012 190 new donors to the CIEN Foundation Tissue Bank were registered, which ended the year with a total of 450 people registered

► The BT-CIEN obtained accreditation of quality according to ISO 9001-2008

► During 2012, the Department of Neuroimaging has performed over 9,100 MRI scans on about 1,500 subjects

► In 2012, CIEN Foundation has collaborated with ISCIII in managing the Ahmara-Ethiopia project, devoted to " Strengthening the Health and Prevention System in the fight against infectious diseases prevalent in that region

► Collaboration has been renewed for the management of the Carlos III Institute of Health European Projects Office and the Reference Center for Control of Endemic diseases in Equatorial Guinea project

► Management of the 'International Cooperation Grants for postgraduate studies at the National School of Health - Carlos III Institute of Health has been renewed

1.3 Letter from the Managing Director of the CIEN Foundation

Dear benefactors, contributors and friends of the CIEN Foundation.

As Managing Director of the Research Center for Neurological Disease Foundation (CIEN Foundation), an institution in charge of managing and coordinating the Alzheimer's Project Research Unit (UIPA) promoted by the Queen Sophia Foundation, I am addressing you to assess our activity over the year 2012.

I would like to begin this letter by reaffirming our strong commitment to the research activity being developed at the Queen Sofia Foundation Alzheimer Center. The year 2012 has been characterized

by a hardening of the economic crisis, which has resulted in a reduction of the investment effort from the State. Faced with this budgetary adjustment, the CIEN Foundation has boosted a public-private collaboration approach to research, an area where we have always believed and nurtured as a way to develop our work of excellence.

The resources allocated in 2012 by the State General Administration Budget, received as grants from the Ministry of Economy and Competitiveness, remain at similar levels than in 2011. By contrast, the contributions made by our private benefactors, primarily by the Queen Sofia Foundation, have increased by 19.26%. This unprecedented success reinforces the reference position that CIEN Foundation has in Alzheimer's disease research, allowing us to continue developing ongoing projects and launching new initiatives with which to convey to society the work our researchers perform.

In this sense, it can be highlighted the creation of the Unit Diagnostic Guidance that position CIEN Foundation and Queen Sofia Foundation Alzheimer Center at the forefront of research in neurodegenerative diseases. In the year just ended, besides promoting private fundraising, we have strengthened our policy of optimizing available resources implemented in previous years to ensure excellence in research of neurodegenerative diseases in general and Disease Alzheimer's in particular. Thus, we have deepened the existing partnership between CIEN Foundation and CIBERNED in order to generate synergies that result in greater efficiency in the management of equipment and resources available.

Every year, for almost a decade now, the Queen Sofia Foundation, in collaboration with the CIEN Foundation, organizes in the Alzheimer Center an International Symposium named after it: Advances in Alzheimer's Disease. In parallel, CIBERNED has held its own Annual Scientific Forum where the latest scientific advances in the field of neurodegenera-

tive diseases research are presented. From 2013 onwards, both meetings will be unified into a single international scientific conference that will bring together some of the most renowned national and international experts in the field of basic and clinical research. It will become, therefore, the largest and most relevant scientific meeting held on this type of pathology in Spain.

At the institutional level, and in order to strengthen one of the main CIEN Foundation research projects, known as the "Vallecas Project", an agreement with various sectors of the Public Administration in Madrid has been signed to promote volunteer recruitment and participation in this pioneering study, whose main goal is the search for biomarkers that facilitate early diagnosis of Alzheimer's Disease. In this regard, I want to express my appreciation for the commitment shown by the Region of Madrid Department of Family and Social Affairs, the Madrid City Hall, through the Municipal District Board, and the Carlos III University of Seniors. Once we presented the project to them, its positive response to collaborate in promoting the study was immediate. Thanks to her involvement we have had a great response.

Noteworthy is the work by the CIEN Foundation as far as projection and social dimension is concerned. In 2012, the Association of Relatives of Alzheimer's and other dementias patients of León granted us the "Mano Amiga" (Helping Hand) Award, an award which we are proud of, as it acknowledges the work done by the professionals of the Foundation to advance the understanding of these diseases and reinforces our commitment to collaboration with associations of patients and families. Much of this effort is channeled through the Tissue Bank - CIEN Foundation (BT-CIEN), to promote the donation of brain tissue for research.

In addition, during 2012 we have continued to foster our relationships with the media, with the dual purpose of contributing to disseminate scientific knowledge and raise public awareness about the importance of research. It is only with the effort of researchers such as ours that we can advance our understanding of neurodegenerative diseases to bring new diagnostic and therapeutic approaches that contribute not only to innovation, but also to improved healthcare and quality of life of patients.

As we have been doing so far, in successive years we will keep our commitment to society and the continuous training of our researchers, who has given such good results so far. Only by promoting excellence of our staff we can make progress in the fight against Alzheimer's disease and reinforce our reference position in the field of neurodegenerative diseases.

María Ángeles Pérez Muñoz
Managing Director of the CIEN Foundation

1.4 Letter from the Scientific Director of the UIPA, managed by the CIEN Foundation

Dear benefactors, collaborators and friends of the CIEN Foundation.

As Scientific Director of the Alzheimer's Project Research Unit (UIPA), managed by the CIEN Foundation and promoted by the Queen Sophia Foundation, I am addressing you, once again, to evaluate our activity during 2012. A year in which the economic crisis has continued affecting the Spanish economy.

However, thanks to the support and confidence you show us year after year our patrons and other private entities actively collaborating with the CIEN Foundation, we have continued in UIPA to carry out our research efforts, both through ongoing projects started in previous years as launching new projecys based on three objectives: to advance our understanding of neurodegenerative diseases, allowing us to address in a comprehensive way diseases such as Alzheimer's disease (AD) and other dementias, to develop new therapeutic applications for patients and to improve the quality of life of patients and, by extension, of their families.

In this sense, it becomes yet more meaningful the effort that the CIEN Foundation has made in recent years, and will continue to make, to promote training and projection of our researchers, not only in Spain, but also in the international arena. This was recognized by the European Commission when selected CIEN Foundation and CIBERNED as the only centers in Spain designated as Centers of Excellence in the European research framework on these conditions: the EU Joint Programme in Neurodegenerative Diseases (JPND). In 2012, this projection has resulted in 44 ongoing research projects, as scientific production continues the upward trend seen in recent years: 57 articles published in scientific journals and 17 book chapters besides participation, in one way or another, in 104 scientific meetings and 80 courses.

As far as specific research projects are concerned, in 2012 we have reinforced a major ongoing study, involving personnel from all CIEN Foundation departments: the "Vallecas Project". What initially was planned as a pilot study, supported by the Queen Sofia Foundation and AFAL Contigo, designed to search for clinical, biological and neuroimaging data that could help determine the risk of developing AD, has become during 2012 one of the more ambitious studies currently being developed in Spain to advance the preclinical diagnosis of this disease. Being more specific, we have finished the first year of the five proposed in the study, exceeding the expectations originally set. By December 31, 2012 we had 1,000 volunteers already rated, representing 85% of the overall target number set at 1,200 volunteers. I want to specifically thank the collaboration of the

people who have already registered in the project, a fact that confirms the high degree of awareness of Spanish society to advance our understanding of AD, a disease that, due to the progressive aging of the Western societies, will become the main epidemic of the XXI century.

This social commitment became also evident at the Open Doors Day that the CIEN Foundation Tissue Bank (BT-CIEN) organized in 2012. During this exercise, the BT-CIEN reinforced its activities of extraction and preservation of brain tissue and other biological samples for its use in research. Donors enrolled in the bank, about 450 people, were able to see firsthand how it works, the activities they perform, and the importance of their donation, in an activity put forward from a didactic and pedagogical perspective.

I cannot end without highlighting two projects that I consider essential for the future development of UIPA and CIEN Foundation. For its pioneering nature, I would like to highlight a project started in 2011: "Robot therapy in dementia," in which a multidisciplinary team of researchers aims to compare the social interaction, behavioral disturbances, apathy and the quality of life of patients with dementia following therapy with robots, versus others who do not participate in this type of non-pharmacological therapies. This project has opened, in parallel, a specific interest in the technologies applied to the care and treatment of people with dementia in some Unit's investigators.

Second, but not least, I want to make special mention of the support of the Queen Sofia Foundation for creating within the Alzheimer Center that bears his name the Diagnostic Guidance Unit, coordinated by CIEN Foundation staff. This initiative aims, apart from obtaining information of scientific interest, to provide quality service to society in uncertain or problematic clinical cases, reinforcing the work of clinicians in charge of care of these patients.

These are some of the most significant events that marked the year 2012, but will find more detailed information on each of the four departments that make up the UIPA (Neuroimaging, Neuropathology, Multidisciplinary Unit Support - UMA-and Laboratory) in the present report.

Finally, I would like to conclude by thanking, especially this year, all the support of our benefactors and private entities that trust us and allow us to provide our researchers with the tools to develop their work. Also to each and every one of the professionals of the CIEN Foundation, without whom we could not meet our goals: deepen the understanding of neurodegenerative diseases and translating these advances into alternatives diagnosis, new therapies, improved quality healthcare increased quality of life of patients suffering from any neurological disorder.

Dr. Pablo Martínez Martín
Scientific Director of the UIPA
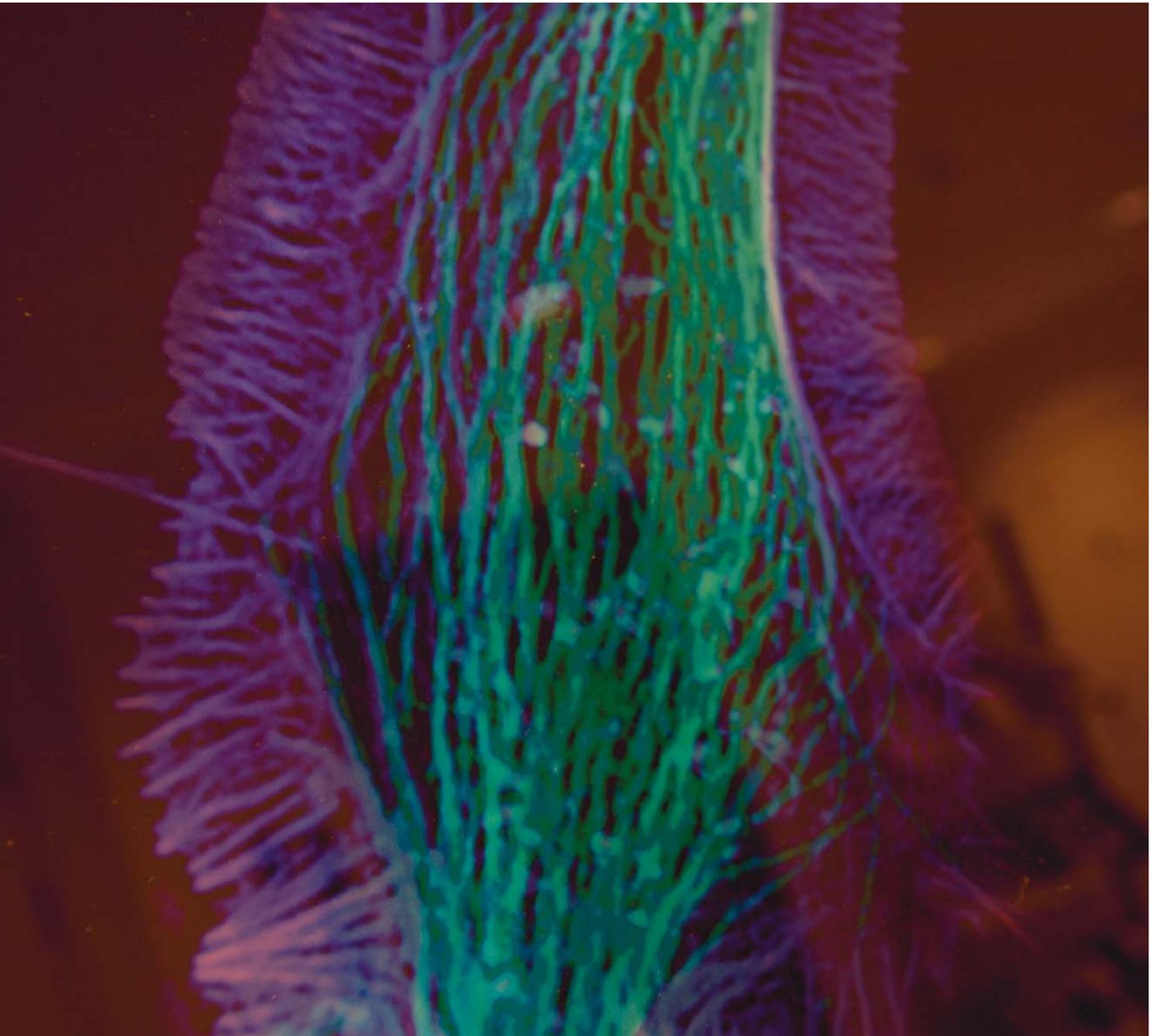
1.5 Organizational Chart

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.

It is chartered as a collegiate body composed of the following members:

CIEN FOUNDATION BOARD OF TRUSTEES		
The members of the CIEN Foundation Board of Trustees on December 31, 2012 are the following:		
Position	**Title**	**Name**
Honorary Chair	MINISTRY OF ECONOMY AND COMPETITIVENESS	Excmo. Sr. D. Luis de Guindos Jurado
Chair	MINISTRY OF ECONOMY AND COMPETITIVENESS	Excma. Sra. Dª Carmen Vela Olmo
Vice Chair	CARLOS III INSTITUTE OF HEALTH	Dr. D. Joaquín Arenas Barbero
Ex officio member	MINISTRY OF HEALTH, SOCIAL SERVICES AND EQUALITY	Sra. Dª Pilar Farjas Abadía
Ex officio member	MINISTRY OF ECONOMY AND COMPETITIVENESS	Sr. D. Juan María Vázquez Rojas
Ex officio member	PRESIDENCY OF THE GOVERNMENT	Sra. Dª María Fernández Pérez
Ex officio member	CARLOS III INSTITUTE OF HEALTH	Sr. D. Antonio Luis Andreu Périz
Ex officio member	CARLOS III INSTITUTE OF HEALTH	Sra. Dª Margarita Blázquez Herranz
Ex officio member	MINISTRY OF HEALTH, SOCIAL SERVICES AND EQUALITY	Sra. Dª Mª Mercedes Vinuesa Sebastián
Ex officio member	NATIONAL SCIENTIFIC RESEARCH COUNCIL	Sr. D. Emilio Lora-Tamayo D'Océn
Elected member, Regions	DEPT OF ECONOMY, INNOVATION, SCIENCE AND EMPLOYMENT	Sra. Dª Eva Mª Vázquez Sánchez
Elected member, Regions	REGION OF VALENCIA DEPARTMENT OF HEALTH	Sra. Dª Pilar Viedama Gil de Vergara
Elected member, Regions	CANARY ISLANDS HEALTH SERVICE	Sra. Dª Hilda Sánchez Janáriz
Elected member, Regions	CASTILLA-LA MANCHA HEALTH SERVICES	Sr. D. Juan Fernández Martín
Secretary	CARLOS III INSTITUTE OF HEALTH	Sr. D. Javier Arias Díaz
Legal Advisor	STATE GENERAL LEGAL OFFICE	Sr. D. José Luis Aranda Estévez
Secretary Support	CARLOS III INSTITUTE OF HEALTH	Sr. D. José Luis Chavarría del Valle
Secretary Support	CARLOS III INSTITUTE OF HEALTH	Sr. D. Javier García del Pozo
CIEN Foundation	CIEN FOUNDATION	Sra. Dª Mª Ángeles Pérez Muñoz

Changes during 2012:
In February 2012, D. Jerónimo Jose Navas Palacios was replaced by D. Joaquín Arenas Barbero.

ISCIII Ethics Committee for Research and Animal Welfare:

Since June 2010 the research activity of the CIEN Foundation, both for clinical projects and for the Tissue Bank activity, is supervised by the ISCIII Ethics Committee Research for and Animal Welfare.

The Carlos III Institute of Health Ethics Committee for Research and Animal Welfare is a collegiate body as described in Article 12 of the July 3, 1412007 Law about Biomedical Research and in Articles 22, 23 and 24 of the October 10, 1201/2005 Royal Decree about the protection of the animals used for experimental and other scientific purposes.

Regarding the competences described in the 14/2007 Law on Biomedical Research, the Committee provides service to the Carlos III Institute of Health Centers and Units, Foundations promoted by the Institute itself, and joint or associated centers recognized by the Carlos III Institute of Health.

1.6 Vision

During 2013 and subsequent years, the CIEN Foundation will continue boosting its research activity that has positioned it as a reference in Spain for research on Alzheimer's and other dementias.

Moreover, it will continue to promote the internationalization of its activities in the mid-term. This commitment will be based on three main pillars that until now have provided excellent results: the participation of Foundation staff in both international research projects and scientific conferences and meetings to present progress in this field; the implementation of own initiatives or mandates of the Carlos III Institute of Health outside our borders; and the involvement of CIEN Foundation together with CIBERNED in the Joint Programme in Neurodegenerative Disease launched by the European Union, as well as the synergies that can be derived from joining the COEN network.

In Spain, the launch of the Diagnostic Guidance Unit (UOD), sponsored by the Queen Sofia Foundation, will enable CIEN Foundation to offer the new services with high added value for society. People who wish so can access to prompt attention by a multidisciplinary team consisting of neurologists, psychiatrists and neuropsychologists specialized in cognitive impairment and dementia, within the framework of agreements signed for this purpose. In addition, on a case-by-case basis, a complete health check could be performed thanks to the latest technological resources available at the Alzheimer Project Research Unit, including: brain MRI without contrast, and a series of clinical and neuropsychological tests to define the possible cognitive deficit, if any.
After the study, subjects will receive a complete report with all tests results, which they may bring back to their primary physician, thus saving time and costs for the NHS.

The future development of the UOD is compounded by the consolidation of new research projects launched in the UIPA. The "Vallecas Project", the main ongoing study at the CIEN Foundation in terms of size and amount of resources devoted to, will complete the volunteer recruitment stage during 2013 to reach the originally intended sample size: 1,200 people aged 70 to 85 years of age who are not suffering from dementia at the time of inclusion in the study.

According to the protocol, the 1,000 volunteers who already had entered the project by December 31, 2012 will enter in the second year of the project (first follow-up after baseline) during 2013. The CIEN Foundation expects to start communicating results of specific aspects related to the main aim of the project by the end of 2014 or beginning of 2015, as well as preliminary results on the study's goal. It focuses on the search for a combination of markers (socio-demographic, clinical, and biological) that allow for probabilistic preclinical diagnosis of Alzheimer's disease with high reliability.

As far as management goes, the mid-term evolution of CIEN Foundation shall be governed by the same criteria applied since its inception: sustainable management, opting for a model of public-private partnership, the continuing education of professionals, which ensures an outstanding research model, and the dissemination of information and awareness provided by the Foundation to translate to society the importance of research in advancing our understanding of neurodegenerative diseases in general and Alzheimer's disease in particular.

Management report

The main lines of action of the CIEN Foundation in terms of management are sustained on three pillars: resource optimization and streamlining of expenses, continuous multidisciplinary training of its professionals, and a commitment to internationalization.
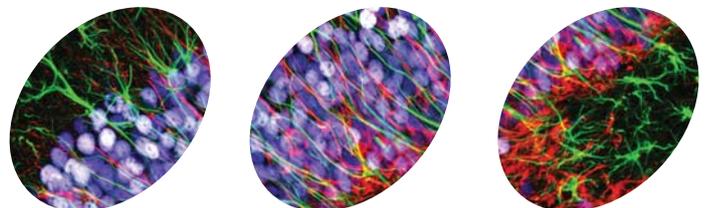
2. Management report

2.1. General management

In 2012, CIEN Foundation has managed a budget of over € 3 million. In a complex macroeconomic environment, resource optimization and streamlining of expenses have remained as the main lines of action in management in order to guarantee continuity of ongoing research projects and ensure long-term permanence of the researchers.

This commitment to the CIEN Foundation research team, extended to the people who perform their duties in management and administrative tasks, also translates into a commitment to continuous and multidisciplinary training, tailored to the needs of each departmental area. Thus, the courses offered by the CIEN Foundation in 2012 not only had a specialized profile, but they have also included workshops aimed at strengthening the internationalization of CIEN Foundation and ongoing projects, and to promote alternative funding of these research projects.

This consolidation of the internationalization process initiated by the Foundation in previous years has resulted in the allocation of the management of a new project: "Strengthening Health System and prevention in the fight against infectious diseases prevalent in Amhara, Ethiopia". This new assignment is added to management commissions already being carried out by the CIEN Foundation.

Furthermore, the incorporation of CIEN Foundation, and CIBERNED, to the EU Joint Programme for Research in Neurodegenerative Diseases (JPND) and the International Network of Centers of Excellence in Neurodegenerative Disease (COEN), has begun to bear fruit. One of the four projects awarded under the first JPND call open in late 2011 has the participation of CIEN Foundation researchers Specifically, Miguel Calero, Head of the Laboratory Department, is one of the researchers who is part of the working group of the project "Biomarker based diagnosis of rapid progressive dementias - Optimisation of diagnostic protocols", coordinated

by Inga Zerr, from the University Medical Center of Göttingen, Germany.

2.2 Management of financial and economic resources

As statewide Foundation under the Ministry of Economy and Competitiveness, almost 25% of its total budget comes from a government grant awarded through the Institute of Health Carlos III. Thus, the CIEN Foundation budget for 2012 allocated in the General State Administration Budget, amounted to 825,280€, divided into 655,490€ as current expenditure and 169,340€ capital expenditure, remaining at similar levels to those of previous years.

During 2012 the CIEN Foundation has maintained and renovated the cooperation agreements with ISCIII for managing the following initiatives:

- The Carlos III Institute of Health European Project Office, with a budget for 2012 of 380,000€. At the same time, the Foundation provides administrative support in managing competitive projects that depend on this office.

- The project as Center of Reference for the Control of Endemic Diseases in Equatorial Guinea, with a budget for 2012 of 402,688€ under agreement.

- The National School of Health-ISCIII International Cooperation Fellowships for postgraduate studies, which during 2012 had a budget of 143,360€.

By virtue of the CIEN Foundation management performance in previous projects, during 2012 it has been entrusted the Amhara-Ethiopia Project, with a budget of 83,988.96€.

The combined budget of the outlined activities accounts for over 60% of the amount received by way of grants, donations and legacies.

As far as costs are concerned, the main items refer to activities aimed at maintaining regular scientific activities. For this reason, personnel costs account for 40.3% and operating and provisioning expenses total 42.7% overall versus total expenditure.

2.3 Management of Human Resources

One of the aims of the CIEN Foundation is to generate valuable knowledge for society and contribute, in an effective way, to their development and welfare through the results and progress derived from our research and projects. However, the true distinguishing feature and success builder is provided by the professionals that make up our organization.

We are well aware that the CIEN Foundation staff constitutes our most important resource. So, through the selection process for our job offers, we intend to bring together a highly qualified team, whose levels of technical and ethical competences meet the qualitative parameters that the CIEN Foundation has set since its origins. Moreover, we guarantee our professionals solid job prospects and long-term commitment.

CIEN Foundation revenues since 2006

	2006	2007	2008	2009	2010	2011	2012
Grants, donations and endowments	719.754,00	1.659.612,00	1.698.242,00	2.123.270,00	2.521.998,28	2.006.682,76	3.014.795,08
Service provisions	1.904,00	0,00	70.017,00	98.997,00	187.989,48	227.997,55	281.006,80
Financial revenues	35.396,00	65.217,00	88.734,00	31.638,00	17.754,01	38.625,53	31.514,15
	762.153,00	1.746.130,00	2.317.659,00	2.253.905,00	3.228.845,77	3.956.222,90	3.327.316,03

Revenue distribution in 2012

0,9%

8,5%

90,6%

■ Grants, donations and endowments

■ Service provisions

■ Financial revenues
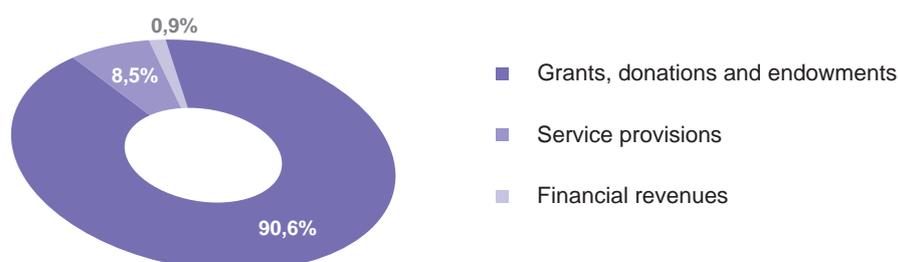
In this sense, the successful development of research projects depends on key elements such as personal effectiveness, leadership and management skills. From the Department of Human Resources we work on integrated talent management, focusing efforts on offering qualified support to the most valuable professionals.

We consider vital working in creating a value proposition for the For us it is essential to create value for our employees and do so from a culture that rewards performance and worry about the constant development of all its professionals.

In summary, the Human Resources philosophy of CIEN Foundation is based on four concepts:

• Talent management, understood as an essential strategy to promote the leadership of our researchers. To this end, we support and encourage their professional and personal growth through the elaboration of Personal Development Plans.

• Equality and reconciliation plans, implementing policies that promote access to employment, training and promotion, as well as the reconciliation of personal, family and professional life, equal wages and improved working and occupational health conditions of Foundation employees, regardless of gender.

CIEN Foundation Expenditure since 2006

	2006	2007	2008	2009	2010	2011	2012
Monetary aid	0,00	0,00	460.666,00	420.333,00	703.265,00	897.702,48	97.651,00
Supplies	1.513,00	48.791,00	48.941,00	72.429,00	287.807,78	197.266,07	416.244,86
Staff costs	122.707,00	269.513,00	450.060,00	477.593,00	624.457,01	1.224.706,74	1.457.394,91
Operating expenses	94.705,00	290.227,00	465.492,00	632.877,00	679.152,50	1.046.318,84	1.129.164,47
Depreciation	17.754,00	893.951,00	911.046,00	932.921,00	934.163,48	909.576,49	512.609,31
	236.679,00	1.502.482,00	2.336.205,00	2.536.153,00	3.228.845,77	4.275.570,62	3.613.064,55

Distribution of expenses in 2012

- 2,7%
- 11,52%
- 14,19%
- 31,25%
- 40,34%

■ Monetary aid

■ Supplies

■ Staff costs

■ Operating expenses

■ Depreciation
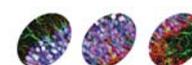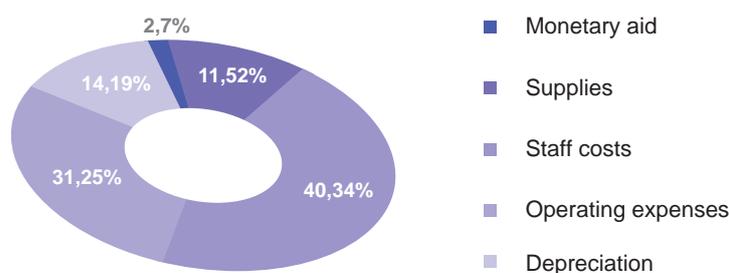
- Diversity management, ruling out any discriminatory practice in hiring candidates.
- Occupational health and safety, improving health and safety conditions in which CIEN Foundation professionals carry out their activities, and demonstrating our commitment to the prevention of occupational hazards.

CIEN Foundation Staff

During 2012, the CIEN Foundation has counted on a total of 75 professionals, including 33 hired from competitive grants, 4 fellows, 4 volunteers who have collaborated selflessly with the CIEN Foundation , 1 in-training Resident Medical Intern and 33 professionals who developed activity thanks to signed collaboration agreements.

All positions offered by the CIEN Foundation have been procured through an open competition process having been published on the CIEN Foundation, ISCIII and CIBERNED websites, abiding by the principle of free competition and objective assessment of the applicants' merits.

Are allso 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 Laboratory
- Multidisciplinary Support Unit (UMA for its acronym in Spanish)
- Diagnostic Guidance Unit (UOD for its acronym in Spanish)

2.3.1 Training Program 2012

Considering that the primary objective of health research is to deepen our understanding of the different disease mechanisms and public health issues as well as to develop strategies for prediction, prevention, treatment and rehabilitation, continuous training it is needed in order to influence the development of CIEN Foundation professionals, in all ranks, levels and specialties.

The training provided is aimed at updating knowledge, improving skills and attitudes, provide solutions to the problems of our employees and increase their skills and maintaining their professional qualifications.

Training is delivered by renowned professionals specialists in each of the topics covered.
The following training activities carried out during 2012 can be highlighted:

- Neuroimaging Master courses, training courses and seminars: 31 nationals and 2 internationals.
- Presentations at conferences and symposia for Neuroimaging: 14 internationals and 7 nationals.
- CIEN Foundation Tissue Bank Open Doors Day.
- 5 training seminars on various topics.
- III Queen Sofia Foundation Alzheimer Center Multidisciplinary Training Course on neurodegenerative dementias
- European funding of research projects Day.
- Alzheimer's disease pharmacological treatment
- Actualización de criterios diagnósticos clínicos y neuropatológicos de la Enfermedad de Alzheimer.
- Cholesterol and Alzheimer. Epidemiologic Data and genetic link
- 2 Continuous Education Courses on Laboratory.
- 1 Resident Medical Intern

2. Management report

MANAGEMENT

- 1 Managing Director
- 1 UIPA Scientific Director
- 1 Managing Director secretary
- 1 Administrative Officer
- 6 Administrative Assistants
- 2 Graduates (CIBERNED)
- 3 Administrative Assistants (CIBERNED)

MEDICAL AND RESEARCH PERSONNEL

- 1 Neuropathologist
- 2 Psychiatrists
- 4 Neurologists
- 1 Sociologists
- 5 Psychologists
- 1 PhD in Mathematics
- 11 Engineers (collaboration agreements)
- 3 Neuropsychologists (Research projects)
- 2 Neuroradiologists (DIM Foundation collaboration agreement)
- 3 Physicists (collaboration agreements)
- 1 Biologist (CIBERNED)
- 1 D.U.E.
- 4 Technicians APA
- 3 Neuroimaging Technicians
- 2 Laboratory Technicians (1 industry collaboration agreements)
- 2 Laboratory Technicians in training (Teaching agreement I.E.S)
- 2 Fellows (collaboration agreement)
- 1 MIR

OTHER STAFF

- 4 Volunteers

Total staff hired by the CIEN Foundation from Grants and Projects: 33; from grants:22 and from Projects: 1

• Note: full time personnel: 16, part-time personnel: 17

2.3.2 Prevention of occupational hazards

During 2012, the Foundation has made HUNDRED, in coordination with the Department of Prevention, various preventive activities in order to ensure the protection of occupational health and safety and to comply with the Law 31/1995 on Prevention of Occupational Hazards .

An annual schedule of activities has been established, which include preventive activities to be carried out by the external Prevention Service provider and the completion estimated dates. These include review of job risk assessments, planning of preventive activities and implementation of emergency measures by conducting a full evacuation drill of the CIEN Foundation facilities.

As in previous years, specific courses on prevention of occupational hazards have been specifically aimed at the different positions within the Foundation: lab staff, research staff, administrative officers, health and management staff.

As for health monitoring, within the management period under review, there have been the following prevention activities: annual program of preventive activities to be carried out by the Department of Health Surveillance of the external Prevention Service provider and estimated dates of completion, review of protocols by post for conducting medical examinations and completion of 32 specific medical examinations.

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

Staff distribution by contract type in 2012

- Permanent, full time
- Permanent, part-time
- Temporary, full time
- Temporary, part-time
- Resident Medical Interns (MIR)
- Fellows
- Volunteers
- Collaborators
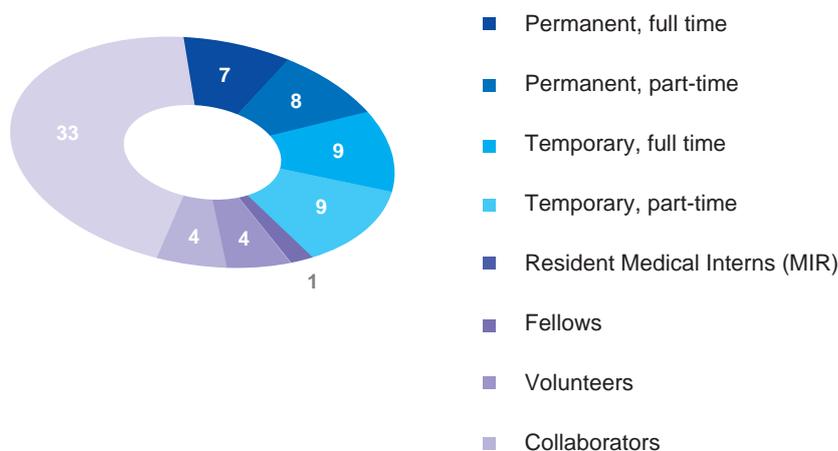
according to the risks inherent to the work performed.

Additionally, we provide newly hired personnel with information about occupational hazards resulting from the job, preventive measures to be adopted, rules of conduct in case of emergency and first aid.

Finally, we emphasize that the CIEN Foundation has met the objectives for workplace accidents in 2012, not having registered any absence from work by occupational accident.

## 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

Despite the advances that have taken place in recent years in the areas of diagnosis, therapy and prevention, and the great attention and efforts rendered to improve health care quality, Alzheimer's disease remains a major challenge for research.

In its pursuit of excellence CIEN Foundation has been conducting research projects focused on Alzheimer's disease and related conditions. These projects aim to characterize the pathology, advancing early diagnosis, studying clinical and psychosocial aspects of the disease and new drug targets.

Staff distribution by category in 2012

- Managing Director
- Scientific Director
- Administrative
- Bachelor
- PhD
- Engineers
- Technical Engineers
- Graduates
- Advanced Technicians
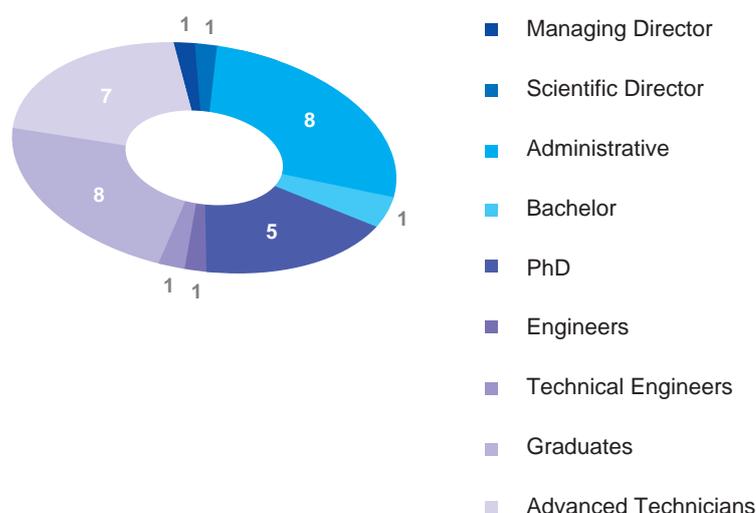
The CIEN Foundation recognizes the importance of research and collaboration among all levels of society, in its effort to improve the living conditions of the current society and its continued interest in deepening the understanding of diseases causing dementia.

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. Thus, in 2010 the CIEN Foundation, in collaboration with the Queen Sofia Foundation, launched an ambitious research project called "Vallecas Project". This is a pioneering project in Spain aimed at the early detection of Alzheimer's disease. This project will provide a set of clinical, biochemical and neuroimaging data that will allow assessing whether any of the parameters analyzed could be a reliable marker of the development of Alzheimer's disease, essential information for the development of future therapies. This study is carried out on volunteers aware of the problems of the disease with an altruistic spirit of full collaboration with the research
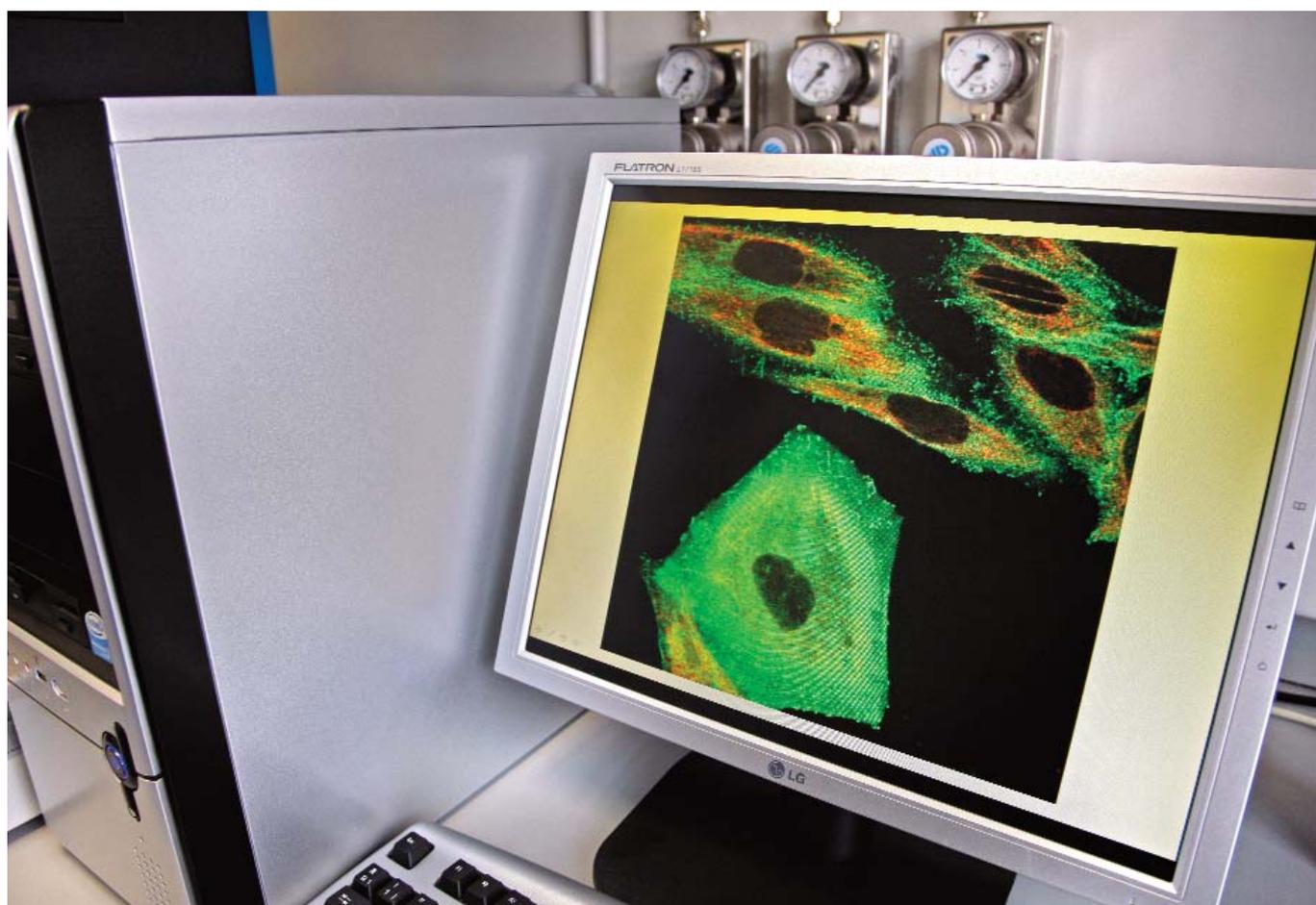
2. Management report

2.4.2 Fellowships and grants

During 2012 the CIEN Foundation, in collaboration with government agencies, the Queen Sofia Foundation, the MAPFRE Foundation, the Mutua Madrileña Foundation, IMSERSO, and the National School of Health, has awarded the following fellowships and grants:

- The Queen Sofia Foundation and the MAPFRE Foundation have offered a six months fellowship in the renowned Alzheimer's Disease Center at the University of New York, which provides a great opportunity for interaction with the multidisciplinary team led by Professor B. Frangione.

- The Queen Sofia Foundation and the MAPFRE Foundation have offered two fellowships to hire a neurology specialist and a neuropsychologist for CIEN Foundation. These fellowships, apart from being an excellent career opportunity for young neurologists and neuropsychologists, also

offers a special setting for research on Alzheimer's disease and related pathologies

- The IMSERSO has funded the recruitment of a Computer Engineer and Computer Technical Engineer in IT management through the project "Comparative pilot study of social robots-assisted therapy vs Therapy in Dementia patients".

- The ISCIII National School of Health has entrusted the CIEN Foundation the management of fellowships for postgraduate studies specializing in "International Public Health" and "Health Promotion".

2.5. Quality Policy

The CIEN Foundation operates under a ISO 9001:2008 Quality Management System, certified by TÜV Rheinland, in order to ensure and optimize purchasing and recruitment processes.

The certification of the various departments of the Foundation have been renewed during 2012. Moreover, the ISO 9001:2008 quality system has been implemented in the Tissue Bank of CIEN Foundation, which has been certified as of May 20, 2012.

Quality Objectives are annually set at CIEN Foundation in order to achieve continuous improvement in purchasing and staff recruitment processes as well as to achieve higher levels of customer satisfaction, both external and internal.

Implementation of the Quality Management System in CIEN Foundation ensures optimal performance of materials and services purchasing, staff recruiting, their management thereof and proper associated documentation archiving.

2. Management report


CIEN Foundation - CIBERNED Administration Team

Scientific activity

The UIPA is composed of four departmental areas:
Multidisciplinary Support Unit, Neuroimaging, Neuropathology,
and Laboratory. Among the active projects during 2012, the "Vallecas Project"
and the "Robot therapy in dementia" are particularly noteworthy, both with a
common nexus: applying a translational research model.
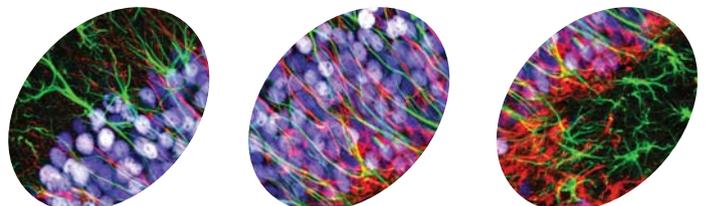
3. SCIENTIFIC ACTIVITY

3.1. Overview

The CIEN Foundation manages the Alzheimer's Project Research Unit (UIPA) since January 18, 2006, by virtue of an agreement signed with the Queen Sofia Foundation. 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.

In an era of increasing genetic and molecular knowledge related to neurodegenerative diseases such as nowadays, this knowledge not only enlighten us on the pathogenic mechanisms, but begin to be applied in the diagnosis and, hopefully, will result in 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. If the biological landscape is complex, not less is the clinical and individual picture. In the advent of dementia not only biological mechanisms are involved but also psychological and social ones, as legal and ethical issues play an increasing role, for instance the right to health information and involvement in medical decisions.

In recent years, the parallel development of biological and clinical aspects has highlighted the need to establish communication links to help focus and capitalize on efforts. Thus, the concept of translational research in medicine, central to the CIEN Foundation scientific activity was born.

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 Neuropathology

From the clinical aspect, Multidisciplinary Support Unit (AMU) staff maintain daily contact with patients attending the Queen Sofia Foundation Alzheimer Center (CAFRS) 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 kno-

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

3.3 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. Throughout the course of the disease, specific treatment, monitoring of complications, implementation of countermeasures and proper implementation of healthcare resources involves various medical disciplines.

The Multidisciplinary Support Unit (UMA) was established in 2007 with a translational vocation to deepen the clinical-evolutionary knowledge of dementia. It stands as a link between basic science and clinical fields and social sciences related to health, to advance knowledge about neurodegenerative dementias and their application. It stands as a link between basic science and clinical and social science fields related to health, to advance knowledge on neurodegenerative dementias and its application. The Unit consists of a team of specialists in Neurology, Psychiatry, Psychology and Sociology, along with the participation of geriatricians, occupational therapists, physiotherapists and social workers from the Center's healthcare area. Evaluations performed in the UMA constitute the clinical and sociological database, and in addition to its intrinsic interest for research, it gives support to the biological samples and neuroimaging data obtained systematically at the Center.

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

3.3.1 Department activities

A UMA systematic activity consists in performing 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 this end, UMA staff keep daily contact with patients who come to CAFRS and with those people responsible for healthcare tasks with these patients.

Another activity related to CAFRS patients is the periodic monitoring their progress, from a multidisciplinary perspective, with standardized contributions of Neurology, Psychiatry, Neuropsychology, Health Sociology, Occupational Therapy, Physiotherapy and geriatric of patients staying in the CAFRS. The objective of this activity is to establish and collect variables that allows for a subsequent correlation and analysis with respect to other analytical, genetic, histopathological and neuroimaging variables. Reviews are conducted every six months, based on a rigorous protocol and subject to an appropriate timeline, allowing continuous and sustained monitoring of each patient through checks of their quality of life, neurological status and their mental, affective and functional behavior.

Finally, UMA staff plays a mediating role between basic researchers, patients relatives and caregivers. This role is critical for patients, their relatives and caregivers knowing UIPA's research purpose, authorizing and collaborating with the internal and external research lines.

3.3.2. "Robot therapy in dementia" Project

In the absence of curative therapy for neurodegenerative disease causative of dementia, palliative

3. SCIENTIFIC ACTIVITY

medication and non-pharmacological therapy are the only ways that can improve symptoms and slow its progression. Non-pharmacological therapy focuses on enhancing the mental, physical and emotional activities of the patient. These actions seek to maintain the functional capacity of the individual, while ensuring their levels of quality of life and autonomy.

For about 20 years, there have been studies of therapy using animals to assess their impact on social behavior in agitation and aggressiveness in patients with dementia (Filan et al, 2006). The results obtained in the above studies have shown:

- better social behavior in patients during the animal's presence (Churchill et al, 1999; Richerson, 2003)
- decreased behavioral problems (verbal aggressiveness and agitation) without involving the need for changes in drug treatment
- a slight decrease in diastolic blood pressure levels and heart rate
- the response to therapy with animals is independent of the severity of dementia (Kanamori et al, 2001).

However, it is not always possible to use animal therapy for reasons such as: health and safety issues (possible source of allergies, infections, bites and scratches), maintenance costs and the attention they require.

Therapeutic use of social robots (Wada, 2008) as reasonable substitutes for animal therapy in people with dementia started in 2000. These robots:

- simulate an interaction with the patient (Tamura, 2004) because their sensors can respond to environmental changes (movements, sounds ...)
- allow monitoring of patients
- allow to perform cognitive therapy (Lauriks et al, 2007; Anerdi et al, 2008)
- do not involve adverse effects (such as drug therapy)

- do not involve the responsibility and the need to have adequate facilities for an animal
- do not require specially trained staff (unlike the other therapies such as music therapy, pet therapy, etc..)

After conducting a pilot test of acceptability of robot therapy with users of our Center, we designed a clinical trial to determine whether the changes in the outcome of this therapy were only due to the introduction of the robot in therapy or it was the robot action that produced the changes. Once proven, we moved into the second phase of the study, the comparison of therapy with the use of animal-like robots versus the use of humanoid appearance robots.

A controlled, double-blind (in terms of evaluators and statistical analyst), randomized by blocks of severity of dementia, 3-arm parallel-group, clinical trial was carried out to compare robot-assisted therapy versus standard therapy in patients diagnosed with dementia seen in Queen Sofia Foundation Alzheimer Center.

The aim of the project was the comparison of an innovative therapy with social robots versus standard therapy in relation to::

1. Quality of life
2. Behavior changes
3. Apathy of the participants.

Therapy performed with the use of animal-like robots (PARO: baby seal) and the use of human aspect robot (NAO) it is also compared.

People with dementia who participated in this study were divided into three treatment groups: standard, with animal-like robot and a human aspect robot. Study experimental sessions were conducted two days a week for three months under the same conditions (personnel, facilities and equipment) and with the same objectives. Assessment was performed before and after treatment by specialists blind to the tool used. The results of these assessments were analyzed by a statistician also blind to the experimental conditions.

The study results will be submitted during this year in national and international events and published in scientific literature. The table below shows the status of clinical evaluations conducted up to the date of preparation of this Report:

Year	Baseline and final evaluations	Drop-outs
2011	121	24
2012	121	20
2013	146 (estimated)	10

3.3.3. Diagnostic Guidance Unit

In the second half of 2012 was launched the Diagnostic Guidance Unit (UOD), sponsored by the Queen Sofia Foundation. This Unit has the following objectives:

1. Quick attention by specialists (neurologist, psychiatrist, neuropsychologist) with specific expertise in cognitive impairment and dementia.
2. Performing an extensive battery of clinical and neuropsychological tests to detect, qualify and quantify the deficit, if any.
3. Immediate performing, if appropriate, of a cranial magnetic resonance study of the highest quality to rule out or characterize underlying brain pathology.
4. Preparation of a report on the results of all tests carried out, a great value for further studies needed in the patient healthcare system, having saved so much time and establishing a

sound basis for future assessments.

5. Subject follow up if deemed suitable for more accurate clinical judgments or if the subject wish so. In this situation, data obtained will be included in the database of the Queen Sofia Foundation Alzheimer Center Research Unit and will be used for research after user permission.

Unit's staff also serves as essential reinforcement for the Vallecas Project which, given its magnitude requires strong support from human resources (eg, clinical aspects require more than three hours per participant in the study), and facilitates other activities of the Research Unit.

3.3.4 Team

The UMA team is composed of 12 professionals with a multidisciplinary expertise, led by Dr. Pablo Martínez.

Area of Neurology
- Pablo Martínez-Martín (Dr. Medicine, Neurology). UIPA Scientific Director
- Javier Olazarán Rodríguez (Dr. Medicine, Neurology). UMA Coordinador
- José Luis Dobato Ayuso (Dr. Medicine, Neurology)
- Meritxell Valentí Soler (Grad. Medicine, especialidad 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 Sociology
- Beatriz León Salas (Grad. Sociology, Demography and Sociology of Health)

Area of Neuropsychology
- Belén Frades Payo (Grad. Psychology, Neuropsychology). Neuropsychology Coordinator

- Miguel Ángel Fernández Blázquez (Grad. Psychology, Neuropsychology)
- Marina Ávila Villanueva (Grad. Psychology, Neuropsychology)

UMA Administration
- Pablo Sánchez Cordeiro (Administrative)

Collaborators

The following CAFRS staff also collaborated during 2012:
- Ilrene 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)
- Vanesa Herrero Cano (Physiotherapist)
- Ester Huélamo Sáez (Physiotherapist)
- Carolina Mendoza Rebolledo (Grad. Psychology, Neuropsychology)
- Gema Melcón Borrego (Social worker)
- Raquel Díaz Rodríguez (Social worker)
- Belén González Lahera (Grad. Medicine, Geriatrics)

UMA Team

3.4. Department de Neuroimaging

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

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

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

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

3.4.1. 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.

Technical advisory services also include collaborations with industry, especially with General Electric to develop new 3T MRI sequences, and the Massachusetts Institute of Technology (MIT), for the development of software and hardware in 3T and 7T. This activity complements the internal seminars and external courses, both nationals and internationals, on specific neuroimaging techniques.

During 2012 the Department of Neuroimaging has participated in MRI studies in the following clinical trials:

- "Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel group study on the efficacy and safety of Bapineuzumab (AAB-001, ELN115727) in subjects with of mild to moderate Alzheimer's disease carrying the apolipoprotein" with reference protocol Wyeth 3133K1-3000-3001- WW and protocol extension 33133K1-3302& 3133K1-3003. Wyeth (Multicentric, European).
- "Eli lilly H8A-MC-LZAN". Effect of passive immunization on the evolution of Alzheimer's disease: LY2062430 against placebo. Lilly (Multicentric, European).

- "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.

In 2012 the acquisition of MR images from a total of 1,532 subjects has been completed. Overall 9,146 MRI studies were performed between the different research projects.

9,146 MRI studies have been made since the creation of the Department, divided by year and type of study.

3.4.2 Provision of services

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

For Functional MRI studies the Unit has audio/video system compatible with 3T MRI and a propietary olfactometer, capable of displaying up to 9 aromas. It also works with 5 different stimuli presentation programs, although the system is compatible with other stimulation programs. Finally, there is the possibility of estimating brain activation in real time (3-4 sec. resolution).
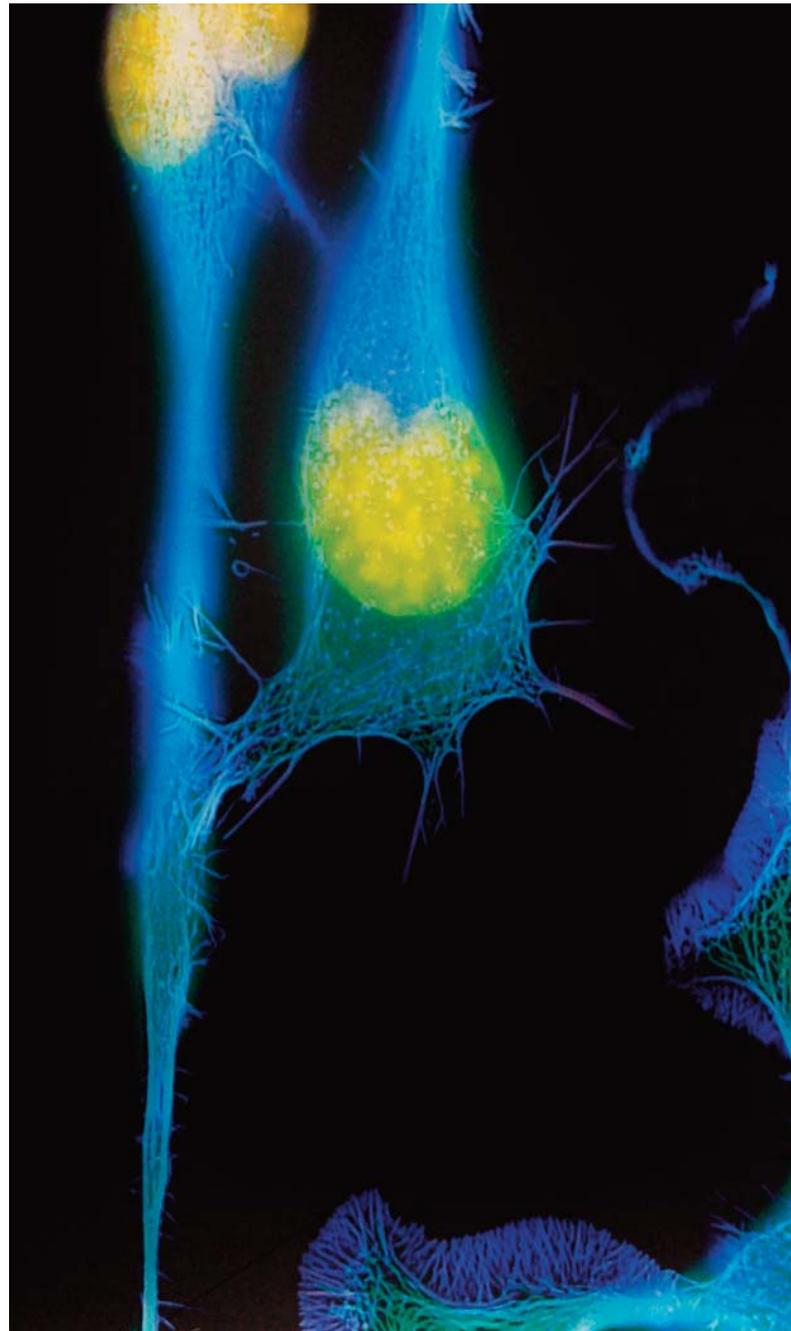
A variety of software packages is used, depending on the post-processing type required in the clinical and research study. Some of them have been developed ad-hoc. Listed below are the most relevant software packages used in the laboratory:

- LONI pipeline processing environment
- Free-Surfer
- BrainVoyager
- SPM
- 3DSlicer
- ITK-SNAP

- FSL
- LCMODEL
- DTI Studio
- MRIcro
- SPSS (Statistical Package for the Social Sciences)
- Developed in our own laboratory:
  - MCTWP (Multi-Clinical Trial Web-PACS)
  - Iron quantification
  - AMIL (Automated Medical Image Lab)
  - Normalization of Spectroscopy in Neurodegenerative diseases
  - Automatic Detection and Quantification of White Matter damage

- Quantification of Magnetization Transfer
• Stimulus/paradigms presentation software:
- Superlab Pro (Cedrus)
- Superlab 4. (Cedrus)
- Presentation (Neurobehavioral Systems)
- Paradigm Manager (GE)
- Ad-hoc software

Volumetry

Acquisition of isotropic 3D studies with 1x1x1mm to 0.5x0.5x0.5mm resolution with T1 and T2 sequences.

Global brain volumetry: automatic segmentation and quantification of gray, white matter, and cerebrospinal fluid is performed using the "AMIL" software developed in the laboratory. Once done, a report with the results obtained is generated in PDF format. After all the volumetric quantifications of the current study is carried out, the laboratory performs group statistics introducing as confounding variables: gender, age and intracranial volume of each subject. In addition, in case there are other type of socio-demographic variables, or psycho-cognitive test results, statistical estimates are made relating volumetry with such study variables.

Maps of fractional anisotropy and mean diffusivity

Acquisition of Diffusion Tensor images (DTI) with Eco-Planar (EPI) sequences with Parallel Image (PI) with b value of up to 10,000 mm2/sec. Gradient directions from 6 to 50. Spatial resolution from 3x3x3mm to 1x1x1mm.

Tractography

Obtaining of 3D reconstructions from the major white matter tracts (Commisures, Corticospinal tract, Optic radiations, Arcuate Fascicle, Inferior Fronto-Occipital Fascicle).

Regional blood flow maps

Perfusion sequence acquisition with the Arterial Spin Labeling (ASL) technique with whole brain coverage and resolution from 4x4x4mm to 2x2x2mm in 3D mode.

Mapping brain activity

Acquisition of BOLD sequences with whole brain coverage and spatial resolution from 4x4x4mm to 1x1x1mm. Activation of primary areas (olfactory, visual, auditory, somatosensory) and maps of cognitive processes (language, attention, memory, executive functions, emotions, etc..)

Hydrogen spectroscopy

Single voxel spectrum acquisition with PRESS and STEAM sequences with 2x2x2cm up to 0.7x0.7x0.7cm volume. Multiple voxel sequences (CSI) with up to 0.5x0.5x0.5cm voxel. Quantification of metabolites with the LC- Model software.

T2 maps

Obtaining of T2 maps with the Multi Echo technique for calculating iron deposits in basal ganglia, midbrain, hippocampus. Iron quantification images

Studies on experimental animals

High-resolution structural studies with dedicated coils suitable for mice and rats. T1, PD, T2, T2* sequences. Possibility of volumetry. Hydrogen Spectroscopy, Diffusion Tensor.

Imaging on brain preparations

Imaging studies on preparations. Treatment with agar. T1, PD, T2 sequences with 3D capability. Possibility of comparative study in Pathology.

Services from the Imaging Laboratory

- Volumetry
  Generation of population templates with DARTEL.
  Normalization.
  Basic Segmentation (Vol. SG. SB y LCR).
  ATLAS-based advanced segmentation
  VBM.
  Statistics. GLM. Including co-variables.
  Statistics. Factorial Analysis.
  Generation of Result Images.
  Bias Correction
- DTI
  Generation of Anisotropy Maps
  Generation of Diffusion Maps
  Generation of population templates with DARTEL.
  Normalization.
  ROIS-based quantification over template
  VBM.
  Statistics. GLM. including co-variables.
  Statistics. Factorial analysis
  Generation of Result Images.
  Adaptive Distortion Correction.
  Multimodal Fusion
- Voxel Spectroscopy
  Quantification with LCMODEL.
  SAGE quantification
  Partial Volume Correction.
  Iron correction.
  GLM Statistics with SPSS
- Iron
  Quantification by ROIS
  ATLAS-based quantification by segmentation
  Multimodal Fusion
- Perfusion
  Quantification by ROIS (after normalization).
  ATLAS-based quantification by segmentation
  Multimodal Fusion
- PET
  Quantification by ROIS (after normalization).

ATLAS-based quantification by segmentation
Multimodal Fusion
- White Matter damage
  Quantification by ROIS (after normalization).
  Global quantification
- fMRI/ASL (with SPM, BrainVoyager or FSL)
  First level statistics (4 Runs).
  Second level statistics (2 Runs).
  Third level statistics (1 Run).
  GLM statistics (1 Run).
  Factorial statistics (1 Run).
  Resting State (1 Run).
  Resting State . GLM (1 Run).
  Resting State. Factorial (1 Run).
- fMRI/BOLD (with SPM, BrainVoyager or FSL).
  First level statistics (4 Runs).
  Second level statistics (2 Runs).
  Third level statistics (1 Run).
  GLM statistics (1 Run).
  Factorial statistics (1 Run).
  Resting State (1 Run).
  Resting State. GLM (1 Run).
  Resting State. Factorial (1 Run).

3.4.3. Team

The Department of Neuroimaging team, led by Dr. Juan Alvarez-Linera (MD, Radiodiagnostics Specialist), has a highly multidisciplinary nature and consists of the following personnel::

Scientifc Clinic Section
◉ Ana Ramos González (Grad. Medicine, Radiodiagnostics)

Acquisition Section
◉ Eva Alfayate Sáez (Radiodiagnostics Technician))
◉ Felipe García Fernández (Advanced Technician in Imaging for Diagnostics)
◉ Carmen Rojas Obregón (Radiodiagnostics Technician)

Laboratory of Analysis Medical Imaging

- Juan A. Hernández Tamames, Head of laboratory (Grad. Physics, Dr. Bioengineering)
- Norberto Malpica de la Vega (Dr. Telecommunications Engineer)
- Susana Borromeo López (Dr. Industrial Engineer)
- Alicia Quirós Carretero (Dr. Mathematics and Statistics)
- Pablo García-Polo Garcia (Telecommunications Advanced Technical Engineer)
- Gonzalo Pajares Giménez (Telecommunications Advanced Technical Engineer)
- Emanuele Schiavi (Dr. Applied Mathematics)
- Javier González Zabaleta (IT Engineer)
- Ana Beatriz Solana Sánchez (Telecommunications Advanced Technical Engineer)
- Elena Molina Molina (Telecommunications Engineer)
- Guillermo Luna García (Industrial Engineer)
- Daniel García Frank (IT Engineer)
- José Ángel Pineda (Telecommunications Engineer)
- Ángel Torrado (Telecommunications Engineer)
- Eva Manzanero Sáenz (Telecommunications Engineer)
- Adrián Martín Fernández (Computer Engineer, Grad. Mathematics)

Functional Imaging Section

- Marcos Ríos Lago (Dr. Psychology)
- José Antonio Periañez Morales (Dr. Psychology)
- Genny Lubrini (Grad. Psychology)
- Luis Carretie Aranguena (Dr. Psychology)
- Óscar Morales (Grad. Psychology)

Imaging and Cognition Section

- Roberto Colom Marañón (Dr. Psychology)
- Miguel Burgaleta Díaz (Dr. Psychology)
- Kenia Martínez Rodríguez (Grad. Psychology)
- Francisco Javier Román (Grad. Psychology)

Difussion Section

- Julián Benito (Dr. Medicine, Neurology)

Administration

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

Other collaborators

- Roberto García Álvarez (Dr. Physics)
- Javier Gálvez Cervantes (Radiodiagnostics Technician)

3. SCIENTIFIC ACTIVITY

Neuroimaging Team

3.5. 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, their work goes beyond that and provides absolutely essential information about components contained in the characteristic lesions, the pathogenesis of the disease, potential markers, etc.

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..).
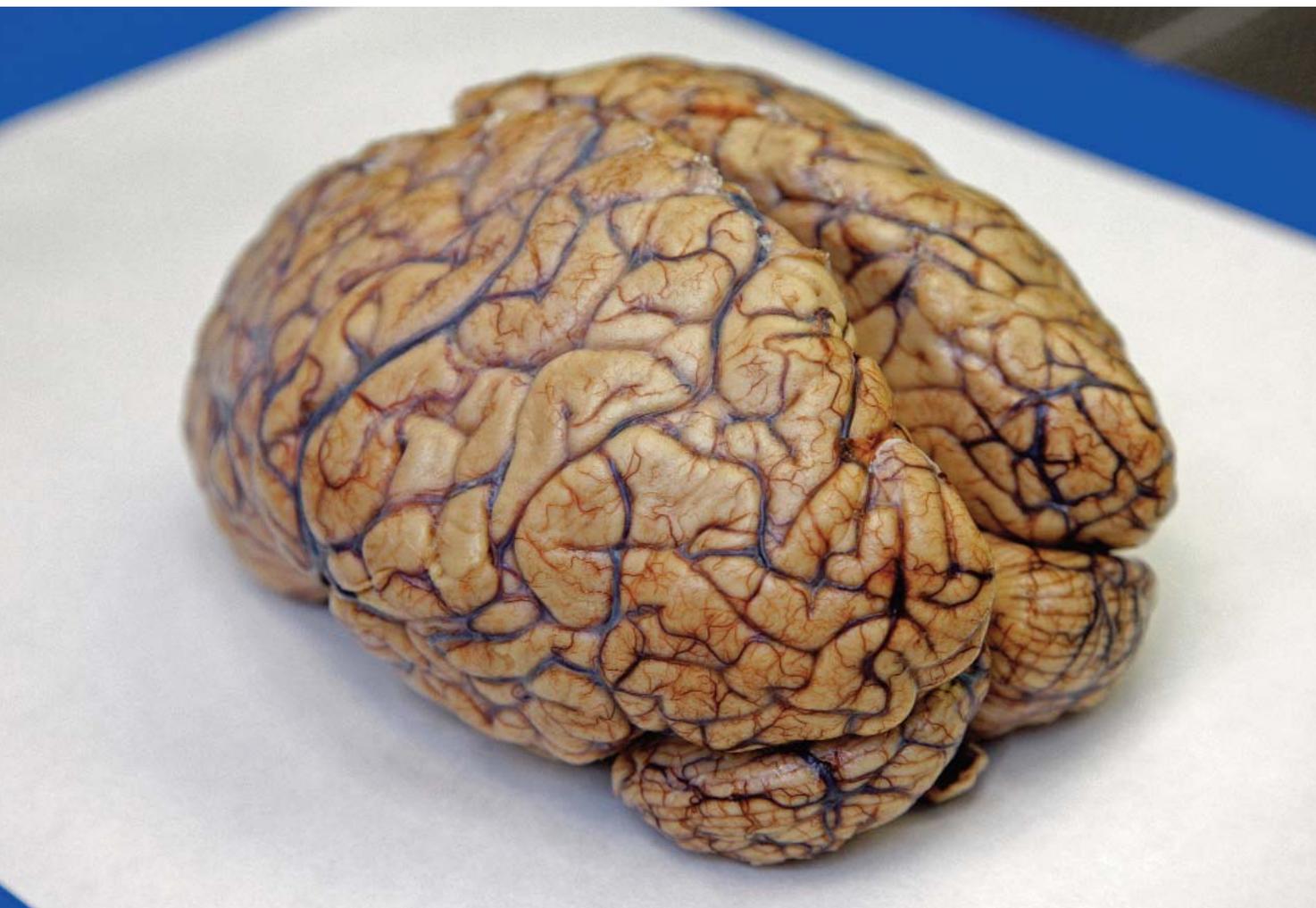
Also, the definition of diagnostic criteria from large series of brains has allowed to address the problem of combined and mixed pathology, specifically regarding Alzheimer's disease.

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 preserved. 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 models of disease natural.

3.5.1 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:

- Characterization and pathogenic study of dementia-associated hippocampal sclerosis.
- Neuropathological and molecular study of tauopathy in Alzheimer's disease and other tauopathies affecting the limbic brain regions.
- Differential features of Alzheimer-type pathology in nonagenarians and centenarians.
- Neuropathology of language in degenerative dementias

3.5.2. 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.
- Perfoming 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

3.5.3. 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 Neuros-

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

Like other biobanks of the country, the BT-CIEN is currently engaged in the process of authorization and official register in accordance with the recent Royal Decree 1716/2011 on biobanking. Adapting to this new regulatory framework and the progressive extension of the brain bank activity throughout the na-

3. SCIENTIFIC ACTIVITY

tional territory as a network are the major challenges for the BT-CIEN in the foreseeable future.

In 2012, the BT-CIEN quality obtained accreditation according to the ISO-9001-2008 quality standards. The BT-CIEN registry had a total of 450 registered donors by December 31, 2012. 190 new donors were enrolled during 2012.

122 cases were processed in the Neuropathology laboratory during 2012, with the following distribution:

- 57 donations from the External Program.
- 12 donations from the Internal Program.
- 53 consultation cases.

Thus, 69 donation cases extracted and processed entirely at the UIPA. Overall, the number of cases studied in 2012 represented an 23% overall increase when compared to 2011 (19% of external donations, 33% of internal donations and 26% of external consultations).

Figure 4 shows the gradual increase in the different types of study over the years.

The achieved postmortem interval is 5.49 +/- 2.21 hours.

The Research Centers that have received samples from BT-CIEN during 2012 have been:of

- Faculty of Medicine, University of Valencia.
- Evotec AG, Hamburg, Germany.
- Department of Microbiology, Oslo University Hospital, Norway.
- European Neuroscience Institute, Göttingen, Germany.
- Center for Molecular Biology, CSIC, Madrid.
- Cajal Institute, CSIC, Madrid.
- Center for Biomedical Research, CSIC, Madrid.
- Bellvitge Institute of Biomedical Research, Barcelona.
- Institute of Biomedical Research, Barcelona.
- National Center of Microbiology, ISCIII, Madrid.

Distribution of cases by pathology during 2012

* **Graph** 4

Legend:
- Internal donations
- Consultations
- External donations

Year	Internal donations	Consultations	External donations
2007	3		
2008	7		
2009	9	11	
2010	28	14	12
2011	48	42	9
2012	57	53	12

Distribution of cases by pathology during 2012

* **Graph** 5

Pathology	Cases
Alzheimer's disease	115
Motor neuron disease	20
Frontotemporal dementia	11
Parkinson/ Lewy body dementia	15
Tauopathies	7
Ataxias/AMS	8
Vascular	6
Huntington	3
Control	8
Others	17
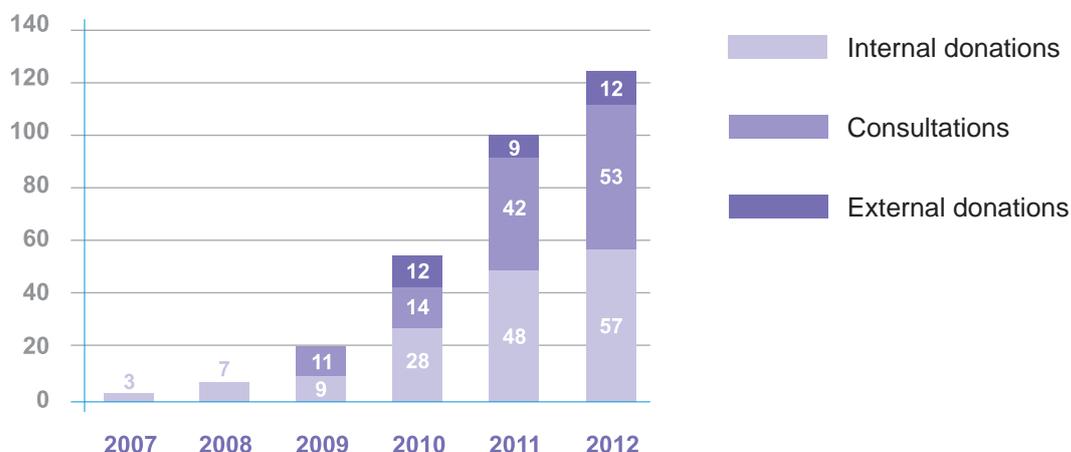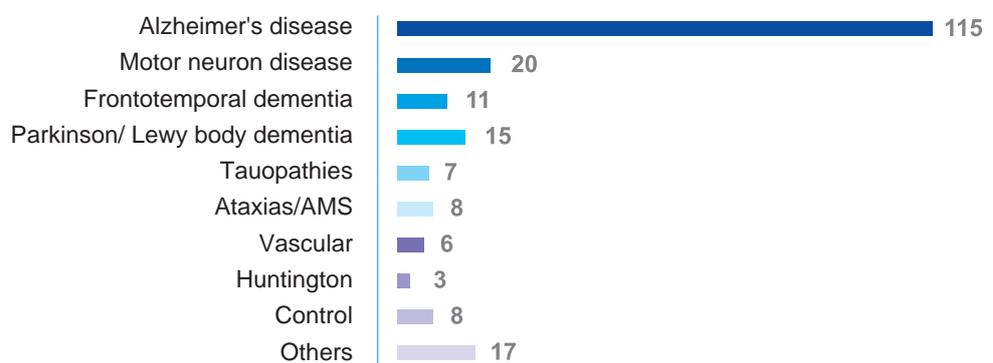
By the end of 2012, the BT-CIEN filed cases break-down by pathology showed a predominance of Alzheimer's disease cases, as shown in Figure 5. Especially significant is the small number of Parkinson's disease cases, despite being one of the most prevalent neurodegenerative diseases in the population.

3.5.4. Team

During 2012, 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)
- ◉ Ana Belén Rebolledo (Pathology Technician)

3. SCIENTIFIC ACTIVITY

Neuropathology Team

3.6 Department of Laboratory

At present, there are no standardized diagnostic tests that may be applied in routine clinical practice to reliably diagnose Alzheimer's disease. Diagnosis is based on clinical criteria that allow diagnostic approximation of "probability", after ruling out other causes. The accurate diagnosis of the disease can only be achieved through post-mortem neuropathological studies.

Numerous research groups have worked in recent years on finding pre-mortem biomarkers capable of accurately diagnosing the disease. Many molecules have been proposed as potential markers of pathology, however, so far, none of them meet the criteria established by the American Psychiatric Association (DSM-III-R) or National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA).

3.6.1 Department activities

The Department of Laboratory is focused on the study of biomarkers and susceptibility genes for Alzheimer's disease and other neurodegenerative disorders. One of the primary objectives is directed to the development of 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.

These objectives are specified in 3 main lines of research on:

- Characterization of peripheral vascular dysfunction associated with late-onset Alzheimer's disease (AD) and how it is modified with disease progression and its interaction with age (FIS grant).
- To analyze, at the level of biomarkers and genetic risk factors, the various presentations of AD (e.g. rapid progression vs. slow progression) in order to define homogeneous groups (endophenotypes) of patients that allow us to study and diagnose with greater accuracy thisheterogeneous and polygenic disease (Joint Programme in Neurodegenerative Diseases - JPND - grant).

3. SCIENTIFIC ACTIVITY

- To study various common and differential susceptibility factors in different neurodegenerative diseases such as AD and prion diseases. The Department of Laboratory also contributes to BT-CIEN with processing of various samples, and collaborates in various external projects focused on Alzheimer's disease and other neurodegenerative diseases.

the context of research focused on the study of bio-markers and genetic susceptibility factors, the UIPA Department of Laboratory is responsible for the collection, processing and storage of biological samples for various research projects or to be deposited in the BT-CIEN, whose ultimate aim is their use in different research areas on neurodegenerative disease. Currently, the Department contributes to the BT-CIEN with various biological samples:

- Several blood samples and other blood fractions are obtained every six months, coinciding with the periods in which the neuropsychological assessment and neuroimaging are performed, are collected from most patients in the Queen Sofia Foundation Alzheimer Center (CAFRS) residence and Day Care Center.
- A set sampling schedule is followed for all other individuals within the execution of each project or collaboration. These include: healthy volunteers from the Project Vallecas (n=896+94), VIBRA-CSIC project (n=50), Innpacto project-Biocross, CIEN Foundation - Marqués de Valdecilla Foundation Project.
- CSF samples (n=173) from brain donors are also being collected in collaboration with the Department of Neuropathology.

Samples analyzed during 2012

Residence   Day Care Center
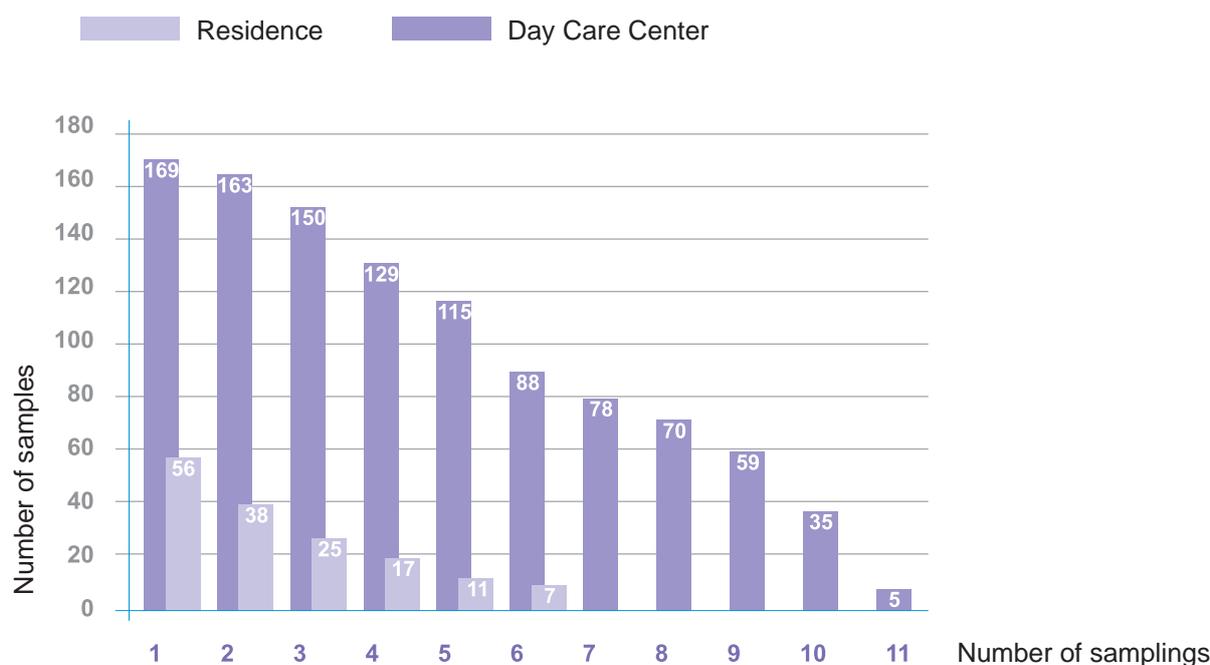
At the end of 2012, virtually 100% of individuals/patients with blood samples also possess genetic material processed and stored properly, which is routinely used for genotyping of the APOE gene, a clear risk factor and modulator Alzheimer's disease. Also during this year various aliquots of biological material have been tranferred to different research groups upon request to BT-CIEN: DNA (n=67), CSF (n=51), peripheral blood mononuclear cells (PBMCs) (n=66), serum (n=29), buffy coat (n=15), erythrocytes (n=7), platelet-poor plasma (n=5).

Among the new initiatives launched in 2012 can be emphasized the establishment of a European consortium led by Dr. Inga Zerr (Germany) in order to study collaboratively the clinicopathological variability of various neurodegenerative entities, especially AD and Creutzfeldt-Jakob disease. In this context, from the Departments and Neuropathology and Laboratory we will study typical and atypical Alzheimer from the genetic and neuropathological standpoint.

This project proposal has been presented to the 2nd JPND call for projects by Dr. Alberto Rábano as the CIEN Foundation sub-project coordinator.

On the other hand, the last Health Research Fund (FIS) call for projects has granted a coordinated project between the UIPA Departments of Neuropathology and Laboratory jointly with the Carlos III Institute of Health and the October 12 Hospital in order to address the study "Age-associated profile of the pathology of Alzheimer (85+CIEN study)" (coordinator: Dr. Alberto Rábano).

This sub-project, directly associated with the Department of Laboratory and ISCIII, will specifically address the "vascular dysfunction associated with aging in Alzheimer's disease."

3.6.2. Team

During 2012, the team of the Laboratory Department was composed of the following personnel::

- Miguel Calero Lara (Dr. Chemistry), Head of Department
- Olga Calero Rueda (Dr. Biology)
- Ana Belén Pastor López (Laboratory Technician)
- Andrés Rodríguez Martín (Laboratory Technician, Fundación CIEN-Biocross)

3. SCIENTIFIC ACTIVITY

Laboratory Team

Th*e* Vallecas project

The Vallecas Project is a research study aimed at finding biomarkers
for the early diagnosis of Alzheimer's disease. Various institutions collaborate
in this project, funded by the Queen Sofia Foundation, including AFAL Contigo,
the Region of Madrid Department of Family and Social Affairs, Madrid City
Council, through the Municipal District Boards, and Carlos III University for Seniors.
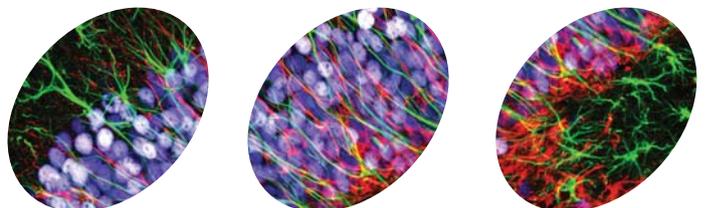
4. THE VALLECAS PROJECT

4.1. Overview

Alzheimer's Disease (AD) is the leading cause of dementia in our country. It is estimated that, alone or in combination with cerebrovascular disorders, accounts for over 75% of the etiology of dementia, the prevalence of which stands at present at 7.3% of the population over 65 years, according to the National Center of Epidemiology.

But the progressive aging of the population seems to indicate an increase of dementia worldwide in the coming years. For example, in Spain it is estimated that by 2050 one in three Spanish will be over 65 years and about a million subjects will be affected by dementia.

Dementia by definition involves deterioration in the degree of functionality of the individual. According to the Survey of Disability, Personal Autonomy and Dependency Situations, the disability rate due to dementia in Spain stands at 90/1000 inhabitants and ranks fifth in the frequency of diagnoses. And while dementia by the affected age group has no direct impact on the working life of the patient, it does on the caregiver. 54.5% of this group is affected by this disorder, significantly diminishing their productivity.

The transition from cognitively normal individual to dementia by EA is a continuum in which some intermediate stages are recognized, not yet well characterized in some ways, in which there is hardly noticeable or mild cognitive impairment, so that fails to meet the consensus criteria for the diagnosis of dementia. Those pre-dementia intermediate stages can last for years, and having the appropriate therapy to stop the disease in that stage or substantially delay it once detected, would drastically reduce the prevalence of clinically overt AD.

At present there is no method to identify which of these pre-dementia states will end up being really dementia (not all convert to severe cognitive impairment), or to accurately identify individuals at high risk of dementia and AD in the general population. In selected population (e.g. familial AD), it can be fairly reliably predicted with sophisticated, expensive and invasive methods who will progress to dementia, but such developments are only useful in research, not for daily practice or for population screening. On the other hand, the verification of the efficiency of future therapies to stop or slow the progression of AD in the general population and most interestingly in pre-clinical phases is currently not possible, as there is no effective, high performance detection method.

The "Vallecas Project" for Early Detection of Alzheimer's Disease, is a population-based study whose main objective is to elucidate by evolutionary tracking the best combination of clinical parameters and tests (laboratory and imaging) that allow mid- and long-term (3 to 5 years after the baseline observation) deciphering what characteristics differentiate people 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 could have each individual to develop the disease in the future.

4.2 Background: Pilot project

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

1. To verify the feasibility of the working procedure, the cooperation of the target population and the adequacy of screening protocols to the study objectives.
2. 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.

3. To get experience in the implementation of the different elements of the protocol and to estimate the burden of the evaluator and the evaluated.
4. 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 partipated 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 (social awareness campaign in the media, visits to centers for seniors, contact pensioner's organizations, etc..) was established. 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.

During the second half of 2012 was launched the Queen Sofia Foundation-sponsored Diagnostic Gui-

dance Unit (UOD), the incorporates the Support Multidisciplinary Unit aforementioned. This Unit has the following objectives:

1. Quick attention by specialists (neurologist, psychiatrist, neuropsychologist) with specific expertise in cognitive impairment and dementia.
2. Performing an extensive battery of clinical and neuropsychological tests to detect, qualify and quantify the deficit, if any.
3. Immediate performing, if appropriate, of a cranial magnetic resonance study of the highest quality to characterize or rule out any underlying brain pathology.
4. Preparation of a report on the results of all tests carried out, a great value for further studies needed in the patient care system, saving much time and establishing a sound basis for future assessments.
5. Subject follow up if deemed suitable for more accurate clinical judgments or if the subject wish so. In this situation, data obtained will be integrated into the Queen Sofia Foundation Alzheimer Center Research Unit database to be used for research purposes, after user permission.

Staff working in this Unit also serves as essential reinforcement for carrying out the Vallecas Project which, given its magnitude requires strong support from human resources (e.g. clinical aspects require

Volunteers

- Participants
- Future participants
- Recruited volunteers
- Pending of response

4 / **2%**
78 / **44%**
80 / **45%**
15 / **9%**
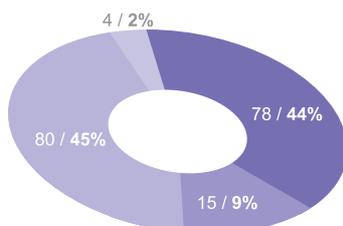
Excluded volunteers

- Do not meet criteria
- Lack of transport
- Not found
- Do not know the study
- Main carers

3%
10%
11%
52%
24%
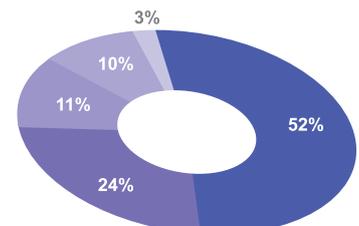
over three hours per participant in the study), and facilitates other activities of the Research Unit.

The Vallecas Project, 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 70-85 years of age individuals, of both genders, not showing symptoms of dementia at the time of initial evaluation. Once included in the study a 5 year follow up is intended through annual assessments that 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.

the Vallecas Project is the main research project conducted by the CIEN Foundation, both in terms of resources spent as well as its social impact. During 2012, the project has reached its cruising speed, having carried out the initial assessment of nearly 1,000 volunteers, of which over a hundred have already made the second annual visit.

4.3.1. Initial evaluation

Before entering the study, volunteers interested in participating in it are subject to an initial assessment to determine if they meet the criteria for inclusion and/or an exclusion criterion exists. There are four inclusion criteria to be met in order for an individual to enter in the study:

- Informed consent.
- Be aged between 70 and 85 years old.
- Availability and ability to travel to the Alzheimer Centre for visits.
- Visual and hearing abilities that allow performing of the study tests.

Among the exclusion criteria of the study are, among others, the existence of suspected or diagnosed dementia, inability to perform brain imaging studies, alcohol abuse or mental retardation, among others. The presence of a history of certain diseases such as schizophrenia, stroke, severe head trauma, CNS infections, uncorrected vitamin deficiencies, etc. is also checked for.

The table shows some overall details of the approximately 1,000 patients evaluated to date.

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.

A "social" questionnaire is also performed in which data are collected with regards to:

- 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

Through semi-structured interview data are collected on:

- 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, os-

THE VALLECAS PROJECT IN FIGURES	
Sample recruited up to date	984
Excluded	34 (3,3%)
Age	
Sample Mean	74,54 años
Age group 69-74	540 (54,9%)
Age group 75-79	309 (31,4 %)
Age group >80	135 (13,72%)
Gender	
Females	628 (63,8%)
Males	356 (36,2%)
Educational level	
Sample Mean	10,25 años
Illiteracy	4 (0,4%)
Read-Write	52 (5,4%)
Minimum studies (numeracy skills)	135 (14,1%)
Primary Education	303 (31,6%)
Senior High School / Professional Training	236 (24,7%)
University Education	226 (23,6%)

teotendinous reflexes, midline release reflexes, etc. The following parameters are analyzed in a very 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, visoconstruction 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

Mini Mental State Examination (MMSE)

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

Memory Complaints Scale (UIPA)

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

Functional Activities Questionnaire (FAQ)

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

The 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, visoconstruction, impulsiviness, episodic memory, incidental learning, etc. It has also been adapted and rated in the Spanish population over 60 years of age.

Free And Cued Selective Reminding Test (FCSRT)

It is based on the assessment of learning ability and verbal episodic memory. The test consists of the consecutive presentation of 4 sheets with 4 words written each (a total of 16 words) that the subject must learn. To facilitate this task, the examiner provides a key for each of the words that will be helpful later to recall more items. After a simple 20 seconds task interference people are asked to remember as many words as possible spontaneously.

After 90 seconds, clues to help the memory of those words that did not recalled by himself/herself will be provided. Then the words he/she could not recall with the help of the clue are reminded of and another interference task is proposed. This procedure is performed three times, so that there are three free recall tests and three facilitated recall through the clues. After 30 minutes the delayed free and with clues recall condition is carried out.

The indexes that are considered in this test are the total free recall, the total learning, free delayed recall and the overall delayed recall. The test has Spanish ratings.

Semantic Lexical Evocation

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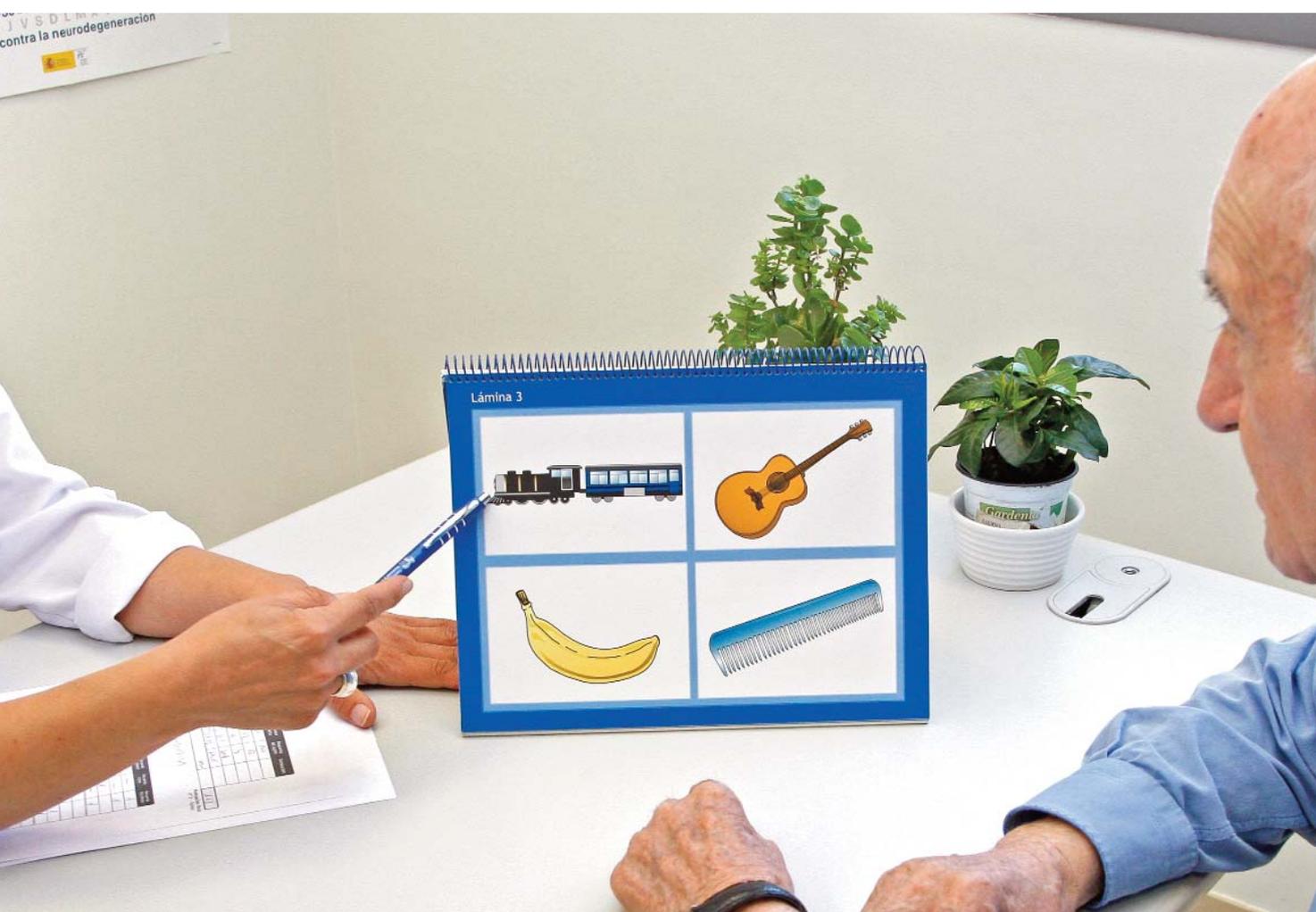
or belonging to a specific category (animals, fruits/vegetables, and cookware) for one minute. Furthermore, in the case of phonological evocation the contribution of people names or words that share the same lexical root is not allowed. The number of responses that the subject provides in periods of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

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 dee-

med appropriate. The test raw score is the number of words read correctly.

The 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.

4.3.6. Neuropsychiatric examination

The depressive symptoms may be a risk factor for the disease, act as an early manifestation or appear during its course. Therefore, it is interesting to know the history of depression and the presence of depression in the cohort study, to assess its possible contribution to the risk of subsequent development of dementia. This could suggest a prominent role of vascular risk factors and their relationship to the involvement of fronto-subcortical circuits in depressed patients who develop AD, who have received little attention so far.

One factor related to depression, but of a different nature, would be apathy. The link between apathy and dementia has been even less explored than that of depression, but may also act as an early manifestation.

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

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:

CLINICAL EXAMINATIONS	
First visit	984
Excluded	34
Second visit	164
Drop outs	20
Decease	1
Diagnosis of possible dementia	3
Diagnosis of Parkinson's disease	1
Change of residence abroad	1
Voluntary	14

- APOE
- CR1
- CLU
- PICALM
- SORL1
- PRNP
- CTS3

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

- Aβ40/42 peptides
- Pro-inflammatory cytokines
- GSK-3β
- CREB
- Homocysteine

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

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

4.3.8. Neuroimaging studies

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

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

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

EXTRACTIONS	
First visit	984
Second visit	141
TOTAL	1125
Available samples	
Whole Blood	100%
Platelet-rich plasma	100%
Platelet-poor plasma	100%
Serum	99.8%
Buffy Coat	100%
Erythrocytes	100%
Mononuclear leukocytes	99.2%
DNA	100%
ApoE measurements	984 (97.5%)

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.

Functional Resting State Study

Resting State Functional MRI (fMRI) shows the decrease connectivity in the early stages of the disease and can be very helpful.

The table below shows the status of MR image acquisition studies up to February 2013.

Despite the fact that the use of multiple MRI techniques significantly lengthens the scan, which may be an issue in older subjects and/or cognitive impairment, the use of a 3T magnet makes possible to acquire the data in half the time that in a 1.5T magnet, which in most cases allows obtaining all the data in a single scan.

Finding markers predictive of dementia (especially AD), would allow a preventive approach (presymptomatic), pharmacological (not yet available) or non-pharmacological (education, psychologic) that result in a reduction of the social, economic and healthcare impact of dementia.

| NEUROIMAGING ACQUISITIONS	
Pilot Project	92
Vallecas Project	893
Vallecas Project (first review visit)	94
TOTAL Vallecas Project	987

International relations

The CIEN Foundation is the only institution in Spain, along with CIBERNED, which actively participates in the Joint Programme for Research in Neurodegenerative Diseases (JPND) launched by the European Union, and in the International Network of Centers of Excellence in Neurodegeneration (COEN).
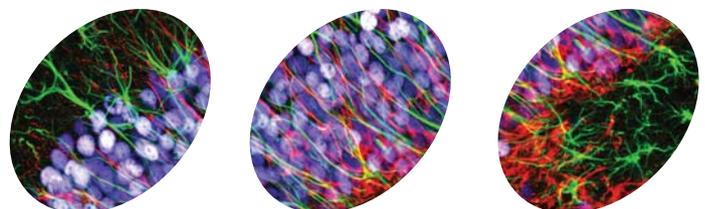
5. INTERNATIONAL RELATIONS

5.1. Overview

The pursuit and promotion of quality and excellence necessarily go through strengthening and increasing the quality of technical and scientific research developed by research groups, centers and institutions in our country. In addition, it should be supplemented by fostering cutting-edge knowledge generation, advancing the development of emerging technologies and facilitating the availability and access to an advanced network of infrastructures and scientific and technical equipment in order to progress in the forefront of scientific and technological knowledge.

In this sense, in the last two years CIBERNED has given major boost to its relations with international organizations in the area of research in neurodegenerative diseases, such as the EU Joint Research in Neurodegenerative Diseases (JPND, for short in English) and the Network of Centres of Excellence in Neurodegeneration (COEN).

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, a figure which is expected to double every 20 years, due to the progressive aging of the population. Currently, care and treatment of patients with some form of dementia in Europe, represents a cost around € 130 billion per year, showing that neurodegenerative diseases associated with aging, constitute a major medical and social challenge facing our society.

5.2. European Union Joint Programme on Neurodegenerative Diseases 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.

5.2.1. JPND Research Strategy

This Research Strategy 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.

Scientific priorities

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. A number of thematic priorities for future research have been identified:

- The origins of neurodegenerative diseases (ND): Further knowledge is needed regarding the causes of specific ND, the factors that determine people's risk and resilience, and the triggering events leading to illness.
- Disease mechanisms and models: A better understanding of the underlying disease mechanisms is required to underpin the development of new diagnostic and therapeutic approaches, as well as to identify appropriate time-windows for intervention.
- Disease definitions and diagnosis: Standard clinical assessments fail to capture the

presumed complexity of common ND, necessitating refinement and updating of the current diagnostic criteria.

- Treatment and prevention: Progress in the identification of new therapeutic targets and drug development against them will be further strengthened through the promotion of a two way connection between studies in cell and animal models and patients
- Healthcare and social care: At present there is inefficient co-ordination between health and social care systems in individual countries, necessitating an evaluation of the equity of access to, and the effectiveness and cost-effectiveness of, pathways to diagnosis, treatment, care and support for ND across Europe.

Support activities

A number of activities will be needed to ensure the advancement of scientific priorities described above:

- Knowing our research capability: National and European-level ND research activity has been mapped to identify both research gaps and those opportunities that can be addressed through improved co-ordination and investment.
- Supportive infrastructure and platforms: In seeking to create an enabling environment for ND research, there is a need to encourage integration and harmonisation of data and

materials, and promote an open-access approach to their use.

- Working in partnership with industry: Many different commercial organisations engage with ND research, ranging from the pharmaceutical, diagnostic and biotechnology sectors to assisted living and healthcare providers, including the care home industry.

- Working with regulatory organisations: The promotion of effective translation of research through to patient benefit requires engagement and co-operation with the key European and national regulatory agencies to ensure that regulation is easily understood by researchers and proportionate to risk.

- International partnership beyond Europe: It is recognised that the unmet clinical need and societal impact of ND is a global issue, and that opportunities may emerge to link to worldwide research efforts in this area.

- Capacity building: Certain areas of research lack capacity and need to be strengthened. Accordingly, networks should be established across and between disciplines and researchers

- Education and training: The advice provided to patients with ND across the range of different health and social care professionals should be based upon a good understanding of the disorder, the patient needs characteristic of these conditions, and the available evidence-based options for treatment.

- Connection to policy makers: JPND will provide a framework through which to highlight important issues for national policy consideration, which should promote compatibility between the policy approaches of different countries.

- Communication and outreach: For effective translation into policy and practice, the research agenda must connect and engage with a wide range of sectors.

5.2.2. Launch of the Research Strategy

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

In this regard, during 2011 took place the first call for European research projects JPND. Under the theme "Optimization of biomarkers and harmonization of their use in the clinic", a total of four transnational projects were awarded for the period 2012-2014, one of which has participation of CIEN Foundation research group:

DEMTEST: Biomarker based diagnosis of rapid progressive dementias - Optimisation of diagnostic protocols.
Coordinator: Inga Zerr, University Medical Center Göttingen, Germany
CIEN Foundation research group: M. Calero

In December 2012 the second call for JPND collaborative research projects was launched targeting two identified thematic areas of particular interest within this Research Strategy:

Topic 1

Identification of genetic, epigenetic and environmental risk and protective factors for Neurodegenerative Diseases.

This call for proposals aims to attract international teams of researchers to explore the different processes involved in normal aging versus those that occur during neurodegenerative processes and to determine the potential role of genetic and environmental factors. Factors such as family history, sex, stress levels, nutrition and others can affect the risk of an individual, and provide protection, or even resistance against neurodegenerative diseases.

However, it is likely that a combination of factors are involved, so that a critical step is to establish the relationship between genetic, epigenetic, environmental and social factors, and their relative importance in order to identify those that may be changed or modified.

Modern research techniques have allowed researchers to create models of risk and protective factors. The purpose of this call is to attract researchers to use these techniques and apply them to neurodegenerative diseases.

The ultimate goal is to use the knowledge generated to develop strategies that can delay or even prevent these diseases.

Topic 2

Evaluation of health care policies, strategies and interventions for Neurodegenerative Diseases

It is widely accepted that better integration and co-ordination of approaches to health and social care in Europe would help reduce costs and improve the quality of care for patients with neurodegenerative diseases and their caregivers. To address this problem, the first step must be an assessment of the strengths and weaknesses of formal care (e.g., hospitals) and informal (family and home). Establishing what works best will create a firm foundation to support new initiatives to address inequality and inefficiency and build an equitable, fair and efficient health care and social system for neurodegenerative diseases.

This call seeks to build research teams to evaluate and compare policies, strategies and interventions related to the care of neurodegenerative diseases, in terms of quality, access and cost-effectiveness.

Examples of the areas to be evaluated include care pathways, psychosocial interventions, end of life strategies, and educational programs that benefit not only people with neurodegenerative diseases, but also to their caregivers and families. The call will also seek proposals for improving the various indicators currently used to assess the impact of health care and social care interventions on quality of life of patients and caregivers - for example, the inclusion of the perspective of patients and of caregivers. This call for proposals is being financed with a total of 29 million euros to be distributed between the two areas: 19 million for topic 1 and 10 millions for topic 2. Funding decisions will be taken during the first half of 2013.

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, recognizing 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, Canada).
- 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, España.

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. This first phase of the initiative COEN was launched in November 2010 and will run for three years.

The aim of the first call for proposals, launched in February 2011, is the establishment of common resources and methodological approaches that underpin future studies. Some of the key issues 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. This will be managed as a coordinated flow of funds while maintaining the internal funding for development of the national components of the joint research activities.

Phase II of the Initiative has been launched during 2012 with the aim of catalyzing collaborative research between centers with a critical mass of resources and expertise in order to promote a radical change in research on neurodegeneration. The countries participating in COEN are contributing a

total amount of 5.5 million euros (of which Spain contributes 600,000€) in this call to establish a program of innovative and forward thinking research to address major challenges in this field. The call is intended to encourage the community to think outside the preestablished frameworks and stimulate new approaches and creative solutions to the challenges of research in neurodegeneration.

Teams are expected to combine their research strengths 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 in neurodegeneration. The projects will address issues that are not easily funded through the standard grant mechanisms by COEN partners, and are expected to, in addition to the collaboration between Centers of Excellence, also serve to provide a platform for future collaboration with industry.

To maximize the potential for innovation, scientific topics of these projects Pathfinder are open. They may include studies aimed at improving our understanding of neurodegenerative mechanisms, or creating technological advances to support new diagnostic or therapeutic approaches. Research concerning related areas, such as inflammation and sensory neuroscience, or vascular and mental health, as well as reaching out to experts in fields such as physics and computer science will be stimulated. The call was opened last November 2012 and funding decisions will be announced during the first half of 2013.

5. INTERNATIONAL RELATIONS
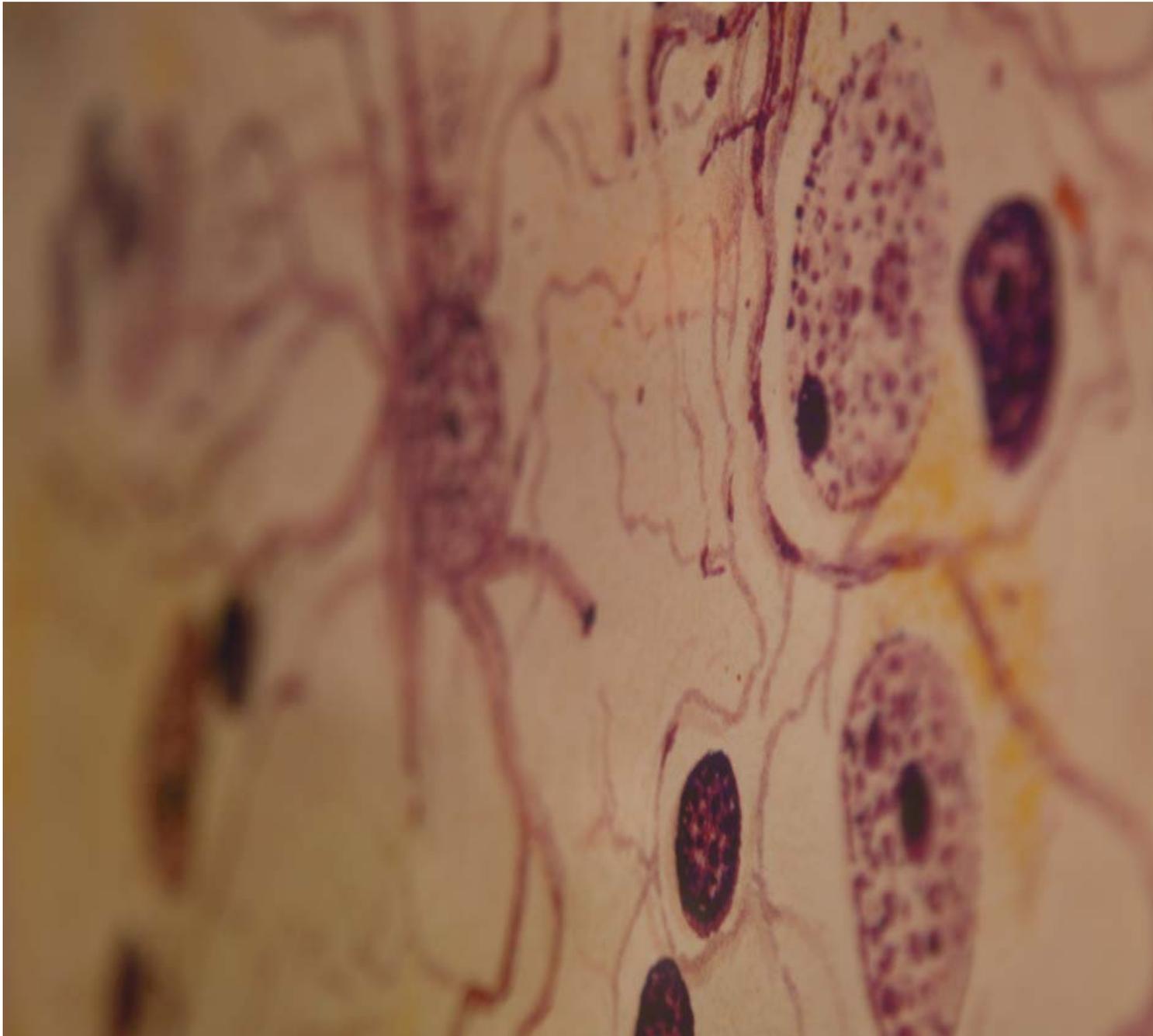
Scientific productivity

During 2012 the CIEN Foundation researchers have produced 74 scientific publications, including articles, books and book chapters, representing an 27.6% increase over the previous year. The continuing increase of this ratio in recent years is completed with similar increments in the organization and / or participation in conferences and scientific meetings.
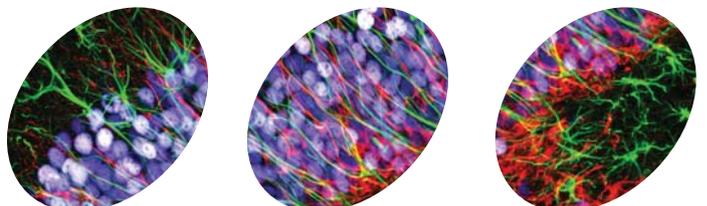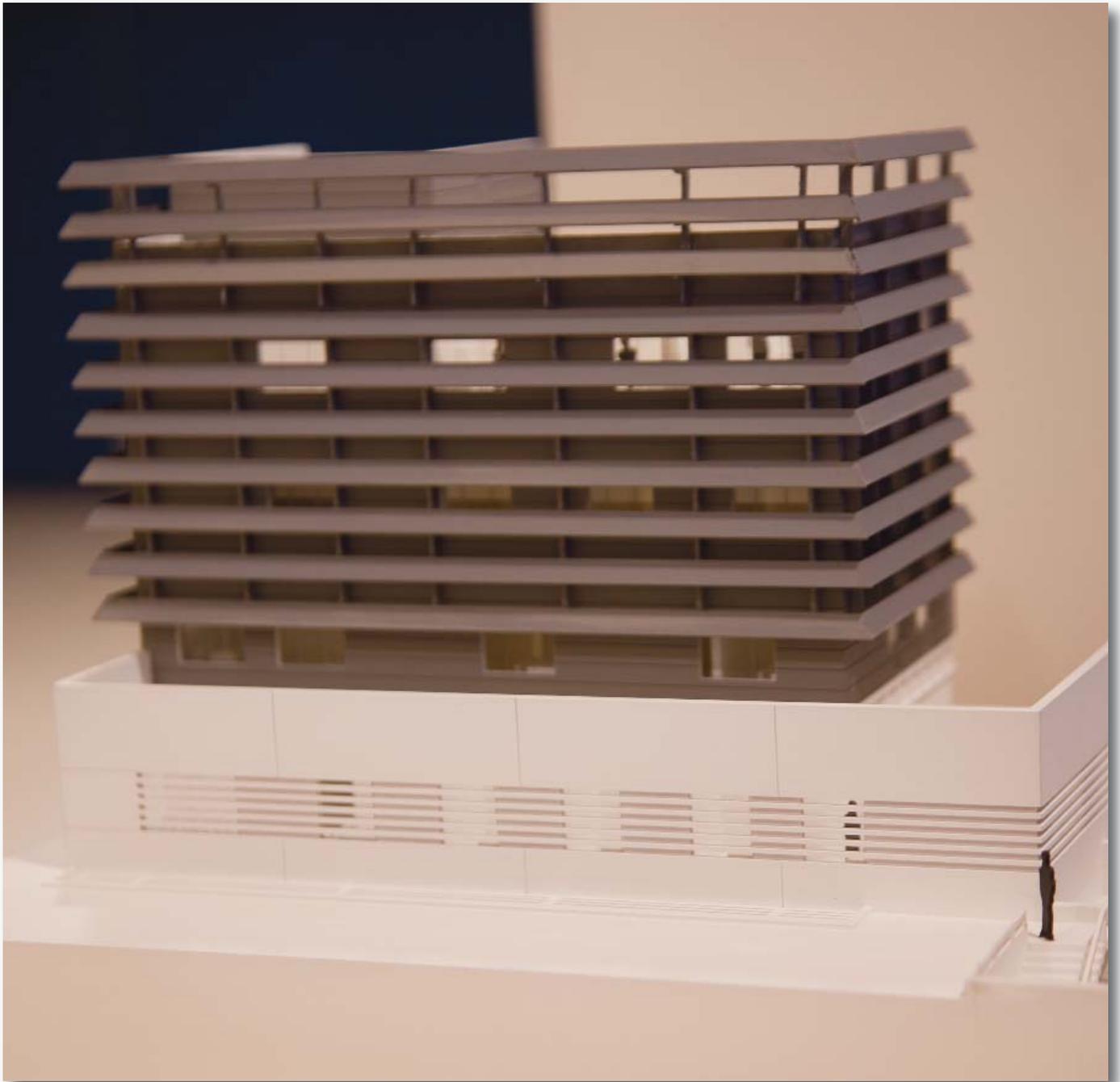
6. SCIENTIFIC PRODUCTIVITY

6.1. Bibliometric analysis

The bibliometric analysis shows the existence of a significant and sustained improvement in the main indicators of scientific productivity in recent years. For example, in 2012, researchers at the CIEN Foundation have produced a total of 74 scientific publications, representing an 27.6% increase over the previous year, of which 57 are scientific journal articles and 17 specialized books and book chapters. The analysis of these publications enables the study of a series of quantitative indicators of the CIEN Foundation scientific activity as well as the monitoring of production, topics, degree of collaboration and impact of scientific publications of the Foundation.

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:

As shown in the table, CIEN Foundation researchers have published 57 scientific articles during 2012, of which 42 (73.7%) have been in journals included within the coverage of the Science Citation Index Expanded, accessible via the internet portal Web of Science (WoS, Thomson Reuters), 33 of which (78.6%) have been published in journals ranked in the first and second quartile of their respective categories. Following the types of documents recognized by this database, the vast majority (92.9%) of these publications are original articles (53 out of 57).

Depending on the scientific category, Clinical Neurology, Gerontology and Neuroscience constitute the major specialties in which the 33 publications by CIEN Foundation researchers have been published.

Communications to scientific congresses are the next type of document in order of frequency. During 2012, there has been a total of 104 participations at scientific meetings. The full distribution of these contributions, depending on type, has been: lectures and oral communications (56), written communica-
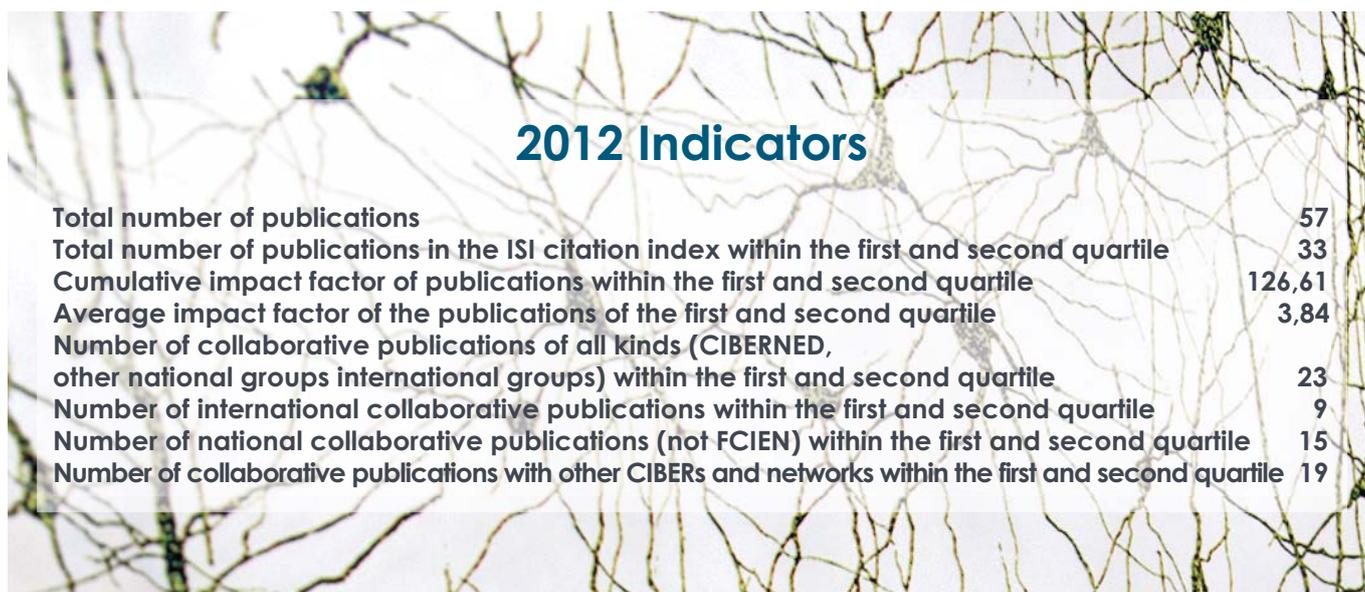
2012 Indicators

Total number of publications	**57**
Total number of publications in the ISI citation index within the first and second quartile	**33**
Cumulative impact factor of publications within the first and second quartile	**126,61**
Average impact factor of the publications of the first and second quartile	**3,84**
Number of collaborative publications of all kinds (CIBERNED, other national groups international groups) within the first and second quartile	**23**
Number of international collaborative publications within the first and second quartile	**9**
Number of national collaborative publications (not FCIEN) within the first and second quartile	**15**
Number of collaborative publications with other CIBERs and networks within the first and second quartile	**19**

tion as a poster (48), in national (54) or international (50) scientific conferences.

Other noteworthy scientific activities are the 80 scientific presentations at various training courses, 24 participations as reviewer and 7 participations in scientific journals editorial boards. The activity carried out in 2012 confirms the continuing and positive developments registered by these indicators over the past years at the CIEN Foundation.

6.2. Publications

The following are 74 scientific publications which are referenced above:

6.2.1. International Publications

◉ Armero C, Cabras S, Castellanos M, Perra S, Quiros A, Oruezabal M et al. Bayesian analysis of a disability model for lung cancer survival. Stat Methods Med Res. 2012; [Epub ahead of print].
◉ Barbey AK, Colom R, Grafman J. Distributed neural system for emotional intelligence revealed by lesion mapping. Soc Cogn Affect Neurosci. 2012; [Epub ahead of print].
◉ Barbey AK, Colom R, Grafman J. Dorsolateral prefrontal contributions to human intelligence. Neuropsychologia. 2012; [Epub ahead of print].
◉ Barbey AK, Colom R, Solomon J, Krueger F, Forbes C, Grafman J. An integrative architecture for general intelligence and executive function revealed by lesion mapping. Brain. 2012; 135(Pt 4): 1154-64.

Evolution of scientific production 2009 - 2012

	2009	2010	2011	2012
Publications in scientific journals	17	97	44	57
Publications in books and book chapters	16	5	14	17
Research projects	37	35	43	44
Participation in scientific meetings	39	53	108	104
Participations in courses	26	51	85	79
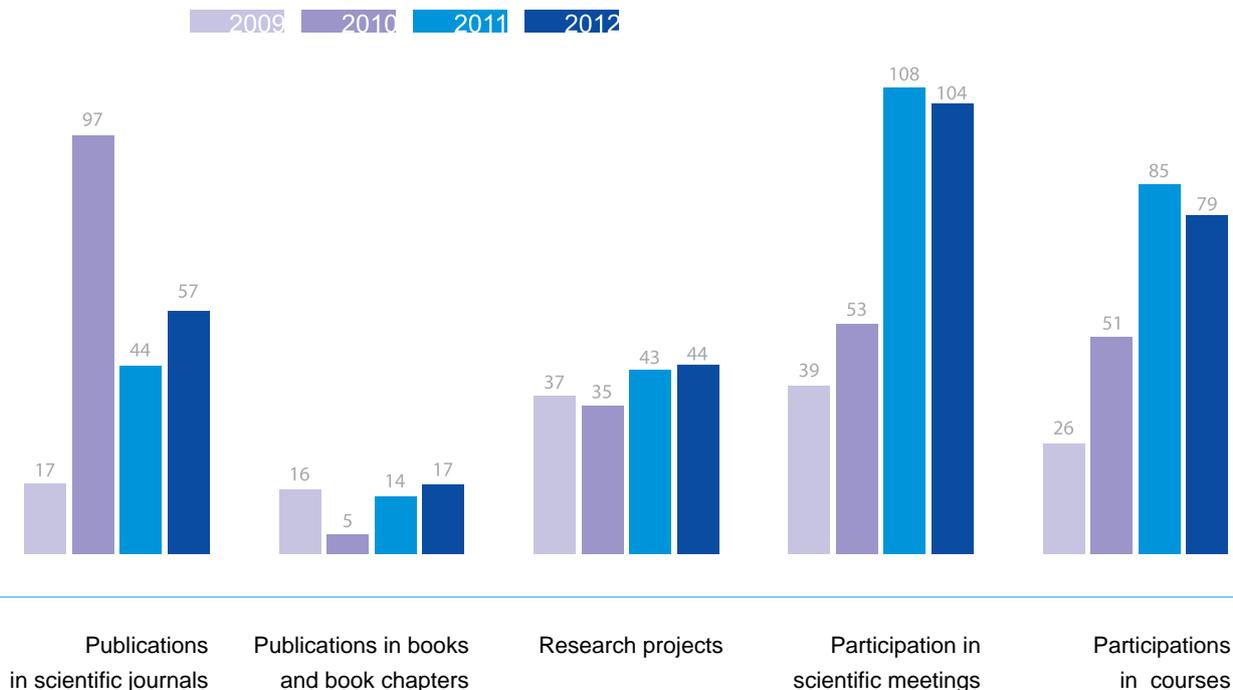
6. SCIENTIFIC PRODUCTIVITY

◉ Baron M, Gomez-Tortosa E, Bochdanovits Z, Gobernado I, Rabano A, Munoz DG et al. Extended kindred with recessive late-onset Alzheimer disease maps to locus 8p22-p21.2: a genome-wide linkage analysis. Alzheimer Dis Assoc Disord. 2012 ; 26(1): 91-5.

◉ Borchani H, Bielza C, Martínez-Martín P, Larranaga P. Markov blanket-based approach for learning multi-dimensional Bayesian network classifiers: an application to predict the European Quality of Life-5 Dimensions (EQ-5D) from the 39-item Parkinson's Disease Questionnaire (PDQ-39). J Biomed Inform. 2012; 45(6): 1175-84.

◉ Bruner E, de la Cuetara JM, Colom R, Martin-Loeches M. Gender-based differences in the shape of the human corpus callosum are associated with allometric variations. J Anat.2012; 220(4): 417-21.

◉ Burgaleta M, Head K, Alvarez-Linera J, Martinez K, Escorial S, Haier R, Colom R. Sex Differences in Brain Volume Related to Specific Skills, not to General Intelligence. Intelligence. 2012; 40: 60-68.

◉ Calero O, Bullido MJ, Clarimon J, Frank-Garcia A, Martinez-Martin P, Lleo A et al. A common BACE1 polymorphism is a risk factor for sporadic Creutzfeldt-Jakob disease. PLoS One. 2012; 7(8): e43926

◉ Calero O, Bullido MJ, Clarimon J, Hortigüela R, Frank-Garcia A, Martinez-Martin P et al. Genetic variability of the gene cluster CALHM 1-3 in sporadic Creutzfeldt-Jakob disease. Prion. 2012; 6(4): 407-12.

◉ Calero M, Rostagno A, Ghiso J. Search for amyloid-binding proteins by affinity chromatography. Methods Mol Biol. 2012; 849: 213-23.

◉ Calero M, Gasset M. Featuring amyloids with Fourier transform infrared and circular dichroism spectroscopies. Methods Mol Biol. 2012; 849: 53-68.

◉ Carmona P, Molina M, Calero M, Bermejo-Pareja F, Martinez-Martin P, Alvarez I et al. Infrared spectroscopic analysis of mononuclear leukocytes in peripheral blood from Alzheimer's disease patients. Anal Bioanal Chem. 2012; 402(6): 2015-21.

◉ Carretie L, Rios M, Perianez JA, Kessel D, Alvarez-Linera J. The role of low and high spatial frequencies in exogenous attention to biologically salient stimuli. PLoS One. 2012; 7(5): e37082.

◉ Colom R, Quiroga MA, Solana AB, Burgaleta M, Roman FJ, Privado J, Escorial S, Martinez K, Alvarez-Linera J, Alfayate E, Garcia F, Lepage C, Hernandez Tamames JA, & Karama S. Structural Changes after Videogame Practice Related to a Brain Network Associated with Intelligence. Intelligence. 2012; 40(5):

◉ Colom R, Solomon J & Barbey AK. A method for mapping the neural architecture of the human mind. JOVE: Visualized Journal of Experiments. 2012; [Epub ahead of print].

◉ Crosiers D, Pickut B, Theuns J, Deyn PP, Van Broeckhoven C, Martinez-Martin P et al. Non motor symptoms in a Flanders-Belgian population of 215 Parkinson's disease patients as assessed by the Non-Motor Symptoms Questionnaire. Am J Neurodegener Dis. 2012; 1(2): 160-7.

◉ Cruz-Orduna I, Bellon JM, Torrero P, Aparicio E, Sanz A, Mula N et al. Detecting MCI and dementia in primary care: efficiency of the MMS, the FAQ and the IQCODE. Fam Pract. 2012; 29(4): 401-6.

◉ Cunillera T, Fuentemilla L, Perianez J, Marco-Pallarès J, Krämer UM, Càmara E et al. Brain oscillatory activity associated with task switching

Communications to scientific meetings 2012

Lectures | Posters

|	National	International
Posters	28	20
Lectures	26	30
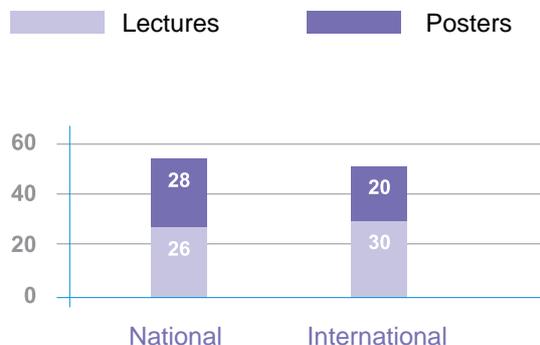
and feedback processing. Cogn Affect Behav Neurosci. 2012; 12(1): 16-33.

◉ de Pedro Cuesta J, Ruiz Tovar M, Ward H, Calero M, Smith A, Verduras CA et al. Sensitivity to biases of case-control studies on medical procedures, particularly surgery and blood transfusion, and risk of Creutzfeldt-Jakob disease. Neuroepidemiology. 2012; 39(1): 1-18.

◉ Ebisch SJ, Perrucci MG, Mercuri P, Romanelli R, Mantini D, Romani GL et al. Common and unique neuro-functional basis of induction, visualization, and spatial relationships as cognitive components of fluid intelligence. Neuroimage. 2012 ; 62(1): 331-42.

◉ Fernandez-Mayoralas G, Giraldez-Garcia C,

Forjaz MJ, Rojo-Perez F, Martinez-Martin P, Prieto-Flores ME et al. Design, measures and sample characteristics of the CadeViMa-Spain survey on quality of life in community-dwelling older adults. Int Psychogeriatr. 2012; 24(3): 425-38.

◉ Forjaz MJ, Ayala A, Rodriguez-Blazquez C, Prieto-Flores ME, Fernandez-Mayoralas G, Rojo-Perez F et al. Rasch analysis of the International Wellbeing Index in older adults. Int Psychogeriatr. 2012; 24(2): 324-32.

◉ Lastres-Becker I, Ulusoy A, Innamorato NG, Sahin G, Rabano A, Kirik D et al. a-Synuclein expression and Nrf2 deficiency cooperate to aggravate protein aggregation, neuronal death and inflammation in early-stage Parkinson's

Distribution of publications by scientific category during 2012

Category	Count
Surgery	1
Statistics & Probability	1
Radiology, Nuclear Medicine & Medical Imaging	1
Psychology, Multidisciplinary	1
Psychology, Experimental	1
Psychology, Clinical	1
Psychology	1
Pharmacology & Pharmacy	1
Pathology	1
Neuroimaging	1
Medicine, General & Internal	1
Geriatrics & Gerontology	1
Applications	1
Computer Science, Interdisciplinary	1
Chemistry, Analytical	1
Behavioral Sciences	1
Biochemistry & Molecular Biology	2
Biology	2
Anatomy & Morphology	2
Public, Environmental & Occupational Health	3
Neurosciences	3
Gerontology	3
Clinical Neurology	12

disease. Hum Mol Genet. 2012; 21(14): 3173-92.

◉ Leentjens AF, Dujardin K, Marsh L, Martinez-Martin P, Richard IH, Starkstein SE . Anxiety and motor fluctuations in Parkinson's disease: a crosssectional observational study. Parkinsonism Relat Disord. 2012; 18(10): 1084-8.

◉ Martinez K, Solana AB, Burgaleta M, Hernandez-Tamames JA, Alvarez-Linera J, Roman FJ et al. Changes in resting-state functionally connected parietofrontal networks after videogame practice. Hum Brain Mapp. 2012; [Epub ahead of print].

◉ Martin F, Agüero C, Canas JM, Abella G, Benitez R, Rivero S, Martinez-Martin P, Valenti M. Robotherapy with Alzheimer patients [Workshop]. Proceedings of XIII Workshop on Physical Agents, WAF-2012, Santiago de Compostela, 3rd-4th september 2012: 99-104.

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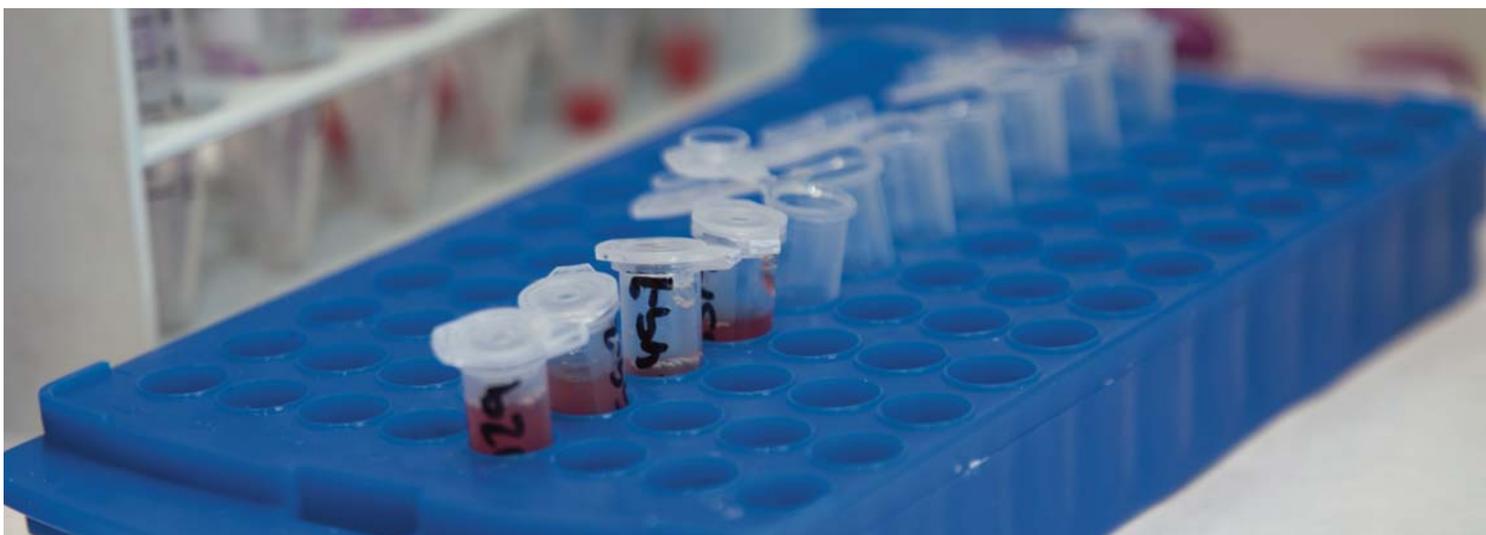
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Publications in books and book chapters during 2012

■ Books
■ Book chapters

4

13
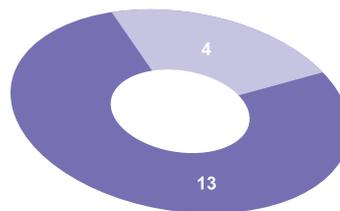
6. SCIENTIFIC PRODUCTIVITY

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Distribution of scientific articles by type during 2012

- Originals
- Reviews
- Letters
- Proceedings

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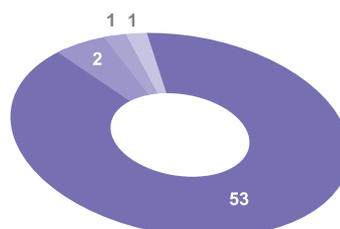
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6.3. Funded Projects

A total of 8 research projects have been active at CIEN Foundation during 2012, 6 of which have been granted to our researchers in various national and international competitive grant calls funded by different institutions. The research projects funded are highlighted below:

Code: FIS PI10/02567
Principal Investigator: Dr. Pablo Martínez Martín
Title: Roboterapia en demencia
Funding institution: Fondo de Investigación Sanitaria – Instituto de Salud Carlos III
Duration: 2011-2013
Total budget FCIEN: 33.112,86€,
2012 budget: 1.310,43€

Code: FCIEN-005/11
Principal Investigator: Dr. Pablo Martínez Martín
Title: Vallecas Project - Alzheimer's disease early detection
Funding institution: Queen Sofia Foundation – CIEN Foundation
Duration: 2011-2016
Total budget: 1.800.000€.
Budget 2012: 412.295,45€

6. SCIENTIFIC PRODUCTIVITY

Code: IMSERSO 231/2011
Principal Investigator: Dr. Pablo Martínez Martín
Title: Robot therapy in dementia
Funding institution: Ministry of Health,
Social Policy and Equality - IMSERSO
Duration: 2012
Budget: 33.000€

Code: BCR-ALZ-2011
Principal Investigator: Dr. Javier Olazarán
Title: Identification of blood biomarkers fo
r multiparametric diagnosis of Alzheimer's disease
Funding institution: Biocross
Duration: 2011-2013
Budget: 20.000€ (depending on the number o
f patients. In 2012: 5.000,00€)

Code: IPT-2012-0769-010000
Principal Investigator: Dr. Alberto Rábano
Title: Design and construction of a system for th
e diagnosis of Alzheimer's disease based
on laser raman spectroscopy
Funding institution: Ministry of Economy
and Competitiveness
Duration: 2012- 2015
Budget: 720.218,00; CIEN Foundation: 93.320€

Code: METC 11-4-057
Principal Investigator: Dr. Pablo Martínez Martín
Title: Assessing and diagnosing
anxiety in patients with Parkinson's Disease
Funding institution: Michael J. Fox Foundation
Duration: 2011-2014
Budget 2012: 7.443,54€

Code: 500009
Principal Investigator: Dr. Marcel Heerink
Title: Nieuwe vrienden, oude emoties
Funding institution: SIA-Raak Project 2011-3-30 int
New Friends, Old Emotions
Duration: 2012-2014
Total budget: 7.200,00€, FCIEN budget
Budget 2012: 1.500,00€

Code: DENDRIA
Principal Investigator: Dr. Alberto Rábano
Title: Innovative solutions to accelerate
the identification and development of drugs
for diseases of the nervous system
Funding institution: Ministry of Science
and Innovation
Duration: 2010-2013
Budget CIEN Foundation: 80.000€

So*c*ial dissemination

One of the commitments of the CIEN Foundation is transferring recent research progress on Alzheimer's and other dementias to the scientific community and society. The annual symposium organized by the Foundation in collaboration with the Queen Sofia Foundation is the greatest exponent of this responsibility. From the point of view of communication, the year 2012 closed with nearly 1,000 impacts in press, radio and television, and a consolidation of their online channels.
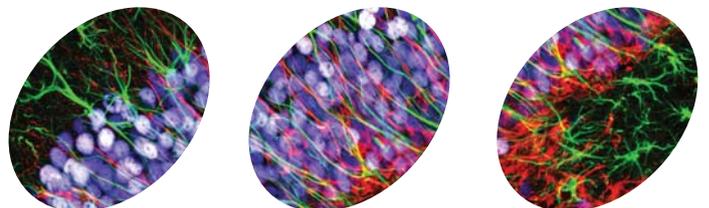
7.1.   International Symposium: Advances in Alzheimer's disease

On September 21, 2012, on the occasion of the celebration of World Alzheimer's Day, Her Majesty Queen Sofia presided over the eighth edition of the "International Symposium: Advances in Alzheimer's Disease", a scientific meeting sponsored annually by the Queen Sofia Foundation and CIEN Foundation, in collaboration with the National Alzheimer's Association (AFALcontigo), and the Spanish Confederation of Associations of Families of patients with Alzheimer's and other dementias (CEAFA). This eighth edition counted on, among other authorities, with the presence of Ms. Carmen Vela, Secretary of State for Research, Development and Innovation, and D. Salvador Victoria, at that time Minister of Social Affairs of the Region of Madrid.

Overall, the symposium had 11 briefings by national and international researchers. Preclinical diagnosis, predictive factors, potential therapeutic targets and improving the quality of care were the focus of the most active areas of research presented at this scientific meeting.

This scientific meeting, held the occasion of the World Alzheimer's Day, has become a meeting point for researchers and institutions, with the aim of providing updated knowledge, promoting research excellence and fostering R&D on neurodegenerative diseases such as Alzheimer's disease (AD).

7.2. Dissemination activities

One of the objectives of the CIEN Foundation is to transfer to society recent progress in research on neurological diseases in general and Alzheimer's disease in particular. For this reason, members of the different Foundation departmental areas are actively engaged in activities performed by patient organizations, with institutions involved in the field of education and knowledge as well as with agencies and private entities closely related to the elderly,

since one of the main risk factors for Alzheimer's disease is age.

Thus, in 2012, and under the agreement that CIEN Foundation has signed with the City of Madrid and the Region of Madrid Ministry of Social Services to promote "Vallecas Project", Foundation professionals have conducted a series of informative talks about this study in different centers, aimed at recruiting volunteers to participate in the project.

Moreover, for the seconved consecutive year CIEN Foundation and the Queen Sofia Foundation launched the 'Christmas Tree of Memories', an initiative to encourage citizen participation and to bring society closer to the area of research.

In this second edition, which has had the collaboration of El Corte Inglés, the tree was decorated with Christmas motifs developed by some of the patients residing Queen Sofia Foundation Alzheimer Center or the people attending the day care center. Both groups participate in activities designed by the occupational therapist and the Center's sociocultural cheerleader, based on making up simple hand-

crafts, adapted to the capacities that still retain by using materials such as wool, felt or cardboard. Artistic expression is strengthened and the development of personal capabilities encouraged through these activities.

Citizens who wished could come to the Alzheimer Center, where the tree was set up, in order to write their favorite memory associated with Christmas, or to post a message on Twitter using the hashtag #arbolrecuerdos.

Regarding collaboration with stakeholders, the BT-CIEN focused in 2012 the CIEN Foundation outreach activities with patient associations. Thus, Dr. Alberto Rábano, presented the Tissue Bank at meetings of patient family associations meetings at Valdemoro (Madrid), Torrejón de Ardoz (Madrid) and Parla (Madrid). Moreover, the head of BT-CIEN also participated in the 'XII AFALcontigo Days' and meetings organized by Euro-Huntington in Badajoz and Salamanca. In academia, Dr. Rábano has lectured during the "Brain Week", organized by the Complutense University of Madrid and the University of Cádiz Medical Schools.

7.3. Outreach activities

In July 2012, the Tissue Bank CIEN Foundation (BT-CIEN) organized the I Open Doors Day. The aim of this initiative was twofold: to show registered donors, family members of deceased donors, and representatives of neurodegenerative disease patients associations, how a brain bank works, what is done and what it is obtained from donated tissue, how it is processed and what progress can be achieved with the information contained in these samples. The second stated goal was to raise public awareness of the importance of brain tissue donation for research as a way to facilitate the sustainability of research projects that help advance the understanding of neurodegenerative diseases.

The conference, which attracted great interest given the large influx of people, was completed with various specialized presentations that showed external researchers with particular cases analyzed using cerebral tissue coming from the brain tissue bank.

7.4. Prizes and awards

During 2012, the Association of Relatives of Alzheimer's and other Dementias of León, granted in its second edition the award "Helping Hand" within the institutional category to the CIEN Foundation for its research effort in Alzheimer's disease and excellent management of CIBERNED. In the first edition of these awards, the Queen Sofia Foundation, trustee of the Foundation CIEN, was recognized with this award in the same category for the initiative "International Alzheimer 2011: Year of the Alzheimer's Research".

On the individual level, some of the CIEN Foundation investigators have also received several awards for their work during 2012. Thus, UIPA scientific director, Dr. Pablo Martinez, was awarded the "Gonzalo Rodríguez Lafora" clinical research Prize that annually grants the Madrid Association of Neurology for his work titled "The impact of symptoms on non-engine health-related quality of life of patients with Parkinson's disease ". In addition, an oral communication by María Ascensión Zea at the LXIV Spanish Society of Neurology Annual Meeting, titled "Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). New

familial genetic mutation" was nominated as congress stellar communication.

7.5. Presence in media

During 2012, the CIEN Foundation has stably mainatined its presence in media and ended the year with a total of 982 impacts in press, online, radio and television. The goal achieved is even more valuable considering the overall context of the media in Spain last year, characterized by the disappearance or reduction of the frequency of headers, reductions in staff or reduced space or time devoted to health and research information.

Therefore, CIEN Foundation has further consolidated during 2012 its leading position on research in neurological diseases in Spain, but specially, as the main source of reference for the media on any topic related to Alzheimer's disease.

By type of media, press coverage both in print and online has totaled 850 impacts, while audiovisual media, radio and television, have grabbed the 132 remaining impacts accumulated over the year.

Appearances in media during 2012

Category	Value
Press & Internet	850
Radio	44
Television	88
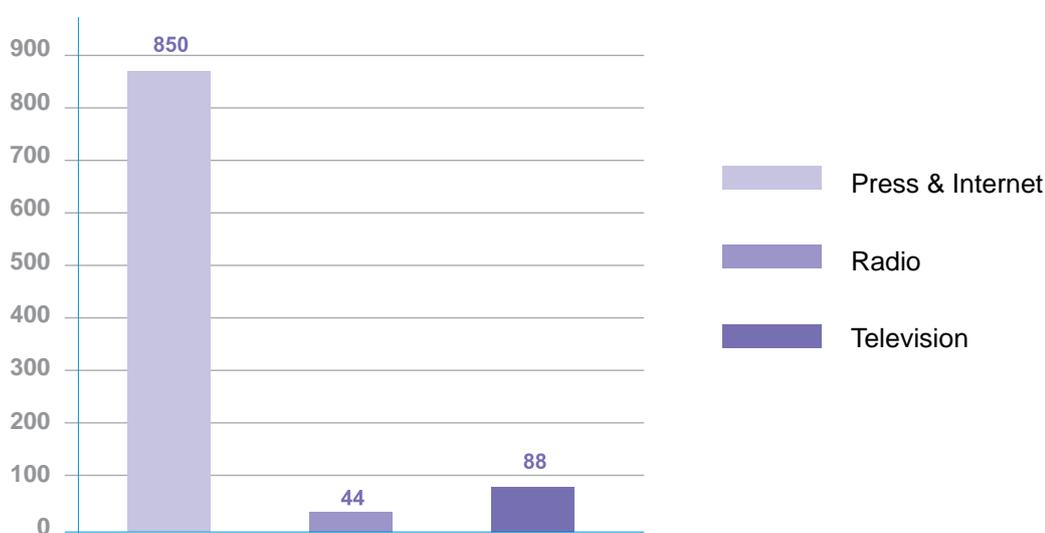
7.6. Presence in social networks

In September 2011 the CIEN Foundation decided to achieve greater visibility for their research in Alzheimer's and other dementias through social networks. To do that profiles on Facebook, Twitter, LinkedIn and Google+ were created.

The year 2012 marked the consolidation of these networks, which have been confirmed as a channel of communication between the Foundation and people interested in knowing about advances in research on dementias in general and on Alzheimer's disease in particular, as well as a channel to interact with specialists such as doctors, nurses, therapists ...

- **Facebook:**
  https://www.facebook.com/FundacionCIEN: The first four months of activity in 2011 were closed with 300 people following - "Like" - the activity of the Foundation. After a year of work, in December 2012 the account had surpassed 1,675 fans, reaching 754,632 friends of friends and a weekly reach of 3,102 people.

- **Twitter:**
  @Fund_CIEN, had 1,717 followers in December 2011 who interacted with about 549 monthly retweets. A year later we managed to reach 4,950 followers, doing 2,708 tweets and increasing to 6,085 mentions and 2,354 monthly retweets.

- **LinkedIn:**
  The Foundation continues to publish information of interest in various groups. The profile is aimed at a professional audience

- **Google+:**
  The CIEN Foundation shares the information generated by its activity and the different articles published in his blog with an audience more interested in technological advances

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