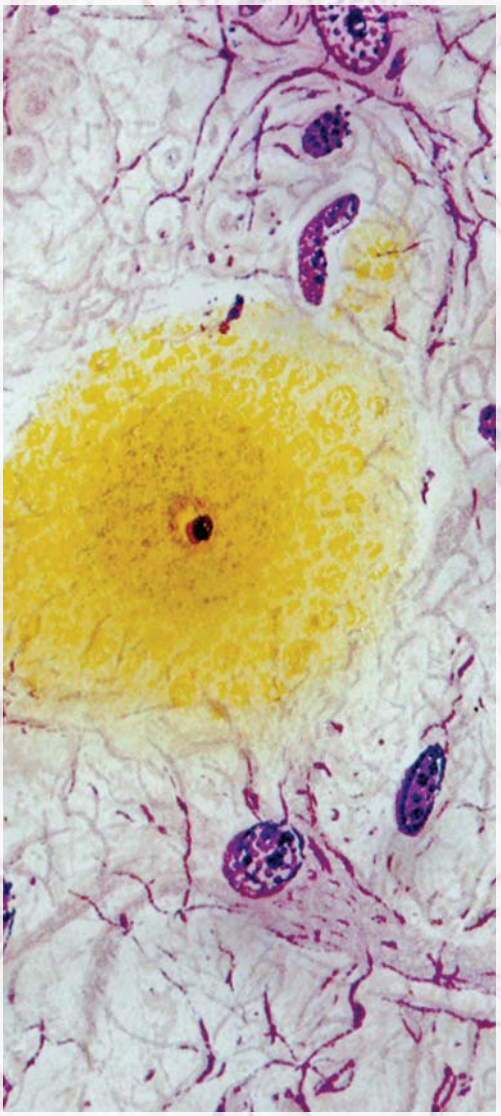
Fundación Centro Investigación
Enfermedades **Neurológicas**



Annual Report 2013

CIEN Foundation
Research Center for
Neurological Diseases Foundation

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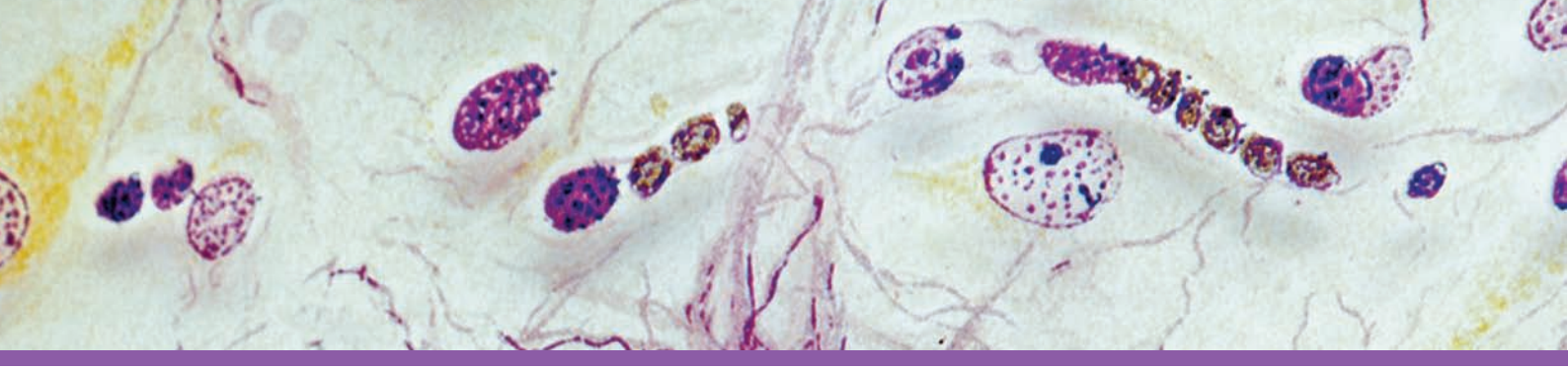

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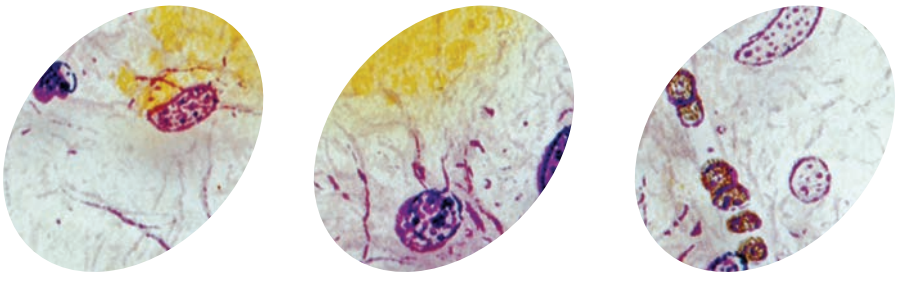
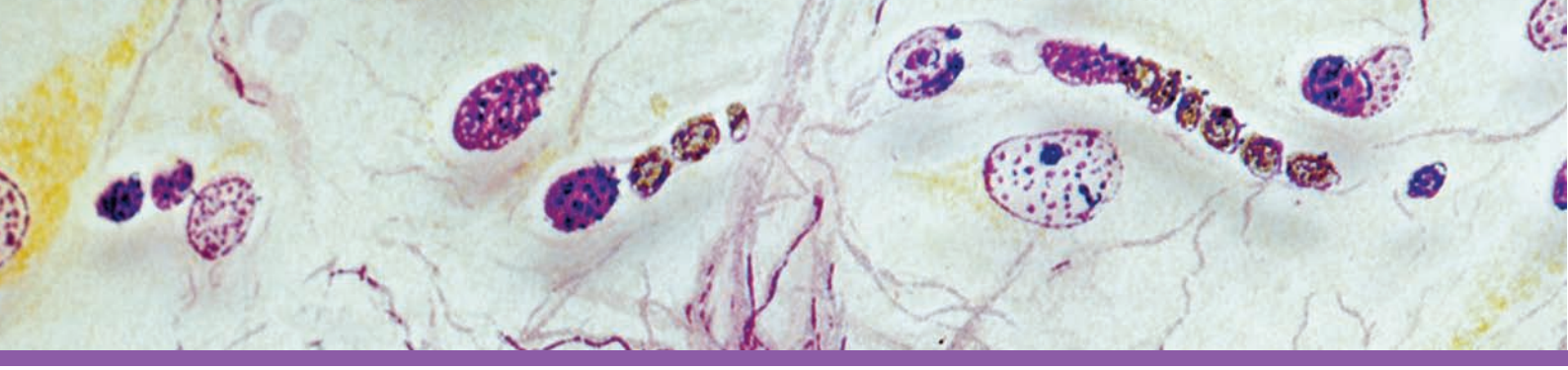
Profile and presentation

CIEN Foundation is a public sector devoted to promote and coordinate research in neurological diseases, mainly Alzheimer's and other dementias. Its collaboration with the Queen Sofia Foundation places it as a case of successful implementation of a model of "public-private" in the management research field.





1.1. Who we are

An example of public-private research collaboration with the Queen Sofia Foundation

CIEN Foundation is one of the best examples of public-private collaboration in scientific research in Spain. Since its inception, manages and coordinates the Alzheimer Research Unit Project (UIPA, for its acronym in Spanish) established by the Queen Sofia Foundation and located in the Alzheimer Center that bears his name.

Since April 2007, CIEN Foundation headquarters are located at the Queen Sofia Foundation Alzheimer Center. This space, located in the Madrid neighborhood of Vallecas, was conceived as a pioneer research center in Spain wherein comprehensively address the impact Alzheimer's has on both sufferers and to their families. It provided an complementary answer to the healthcare project of the Alzheimer Project of the Queen Sofia Foundation.

A Center of Reference in Alzheimer's Disease Research

The only two Spanish institutions participating in the Joint Programme for Neurodegenerative Diseases (JPND for its acronym in English) research that is being developed in the European Union are UIPA/CIEN Foundation and CIBERNED. Its excellent infrastructures, modern methodologies and cutting edge technologies at their disposal as well as the available critical mass of researchers were the criteria most valued by the representatives of this organization when they were proposed by the Carlos III Institute of Health. In addition, both CIEN Foundation as CIBERNED are integrated into the international network of Centres of Excellence in Research on Neurodegeneration (COEN).

A Foundation from the public sector

The Research Center for Neurological Diseases (CIEN, for its acronym in Spanish) Foundation was established by resolution of the Council of Ministers on December 27, 2002. By definition it is 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. Some of its founding purposes include supporting, promoting and coordinating research on neurological diseases, with special emphasis on neurodegenerative diseases. Its objectives also stress its unifying role and coordinator of prominent Spanish research groups in this field.

1. PROFILE AND PRESENTATION

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 assigned to the CIEN Foundation.

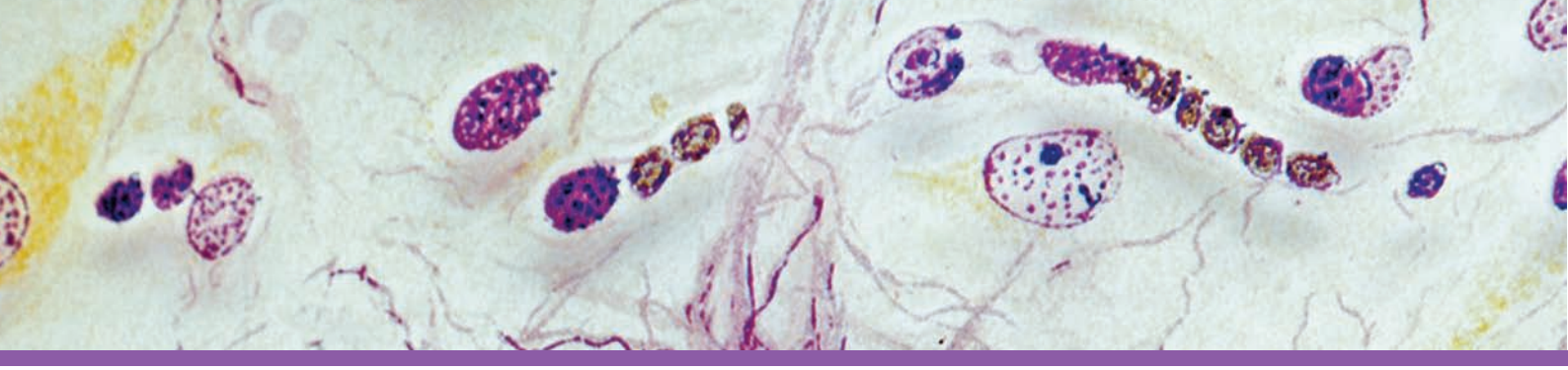
Among the tasks assigned to the CIEN Foundation the following can be highlighted: To implement a model of translational research for effectively and efficiently conveying scientific advances in basic research to clinical practice; promote continuous training of professionals involved in the neurological diseases research by conducting seminars, lectures and dissertations; disclose the calls made by national and international funding agencies, encouraging participation; and promote the development of coordinated research projects in neurological diseases.

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.

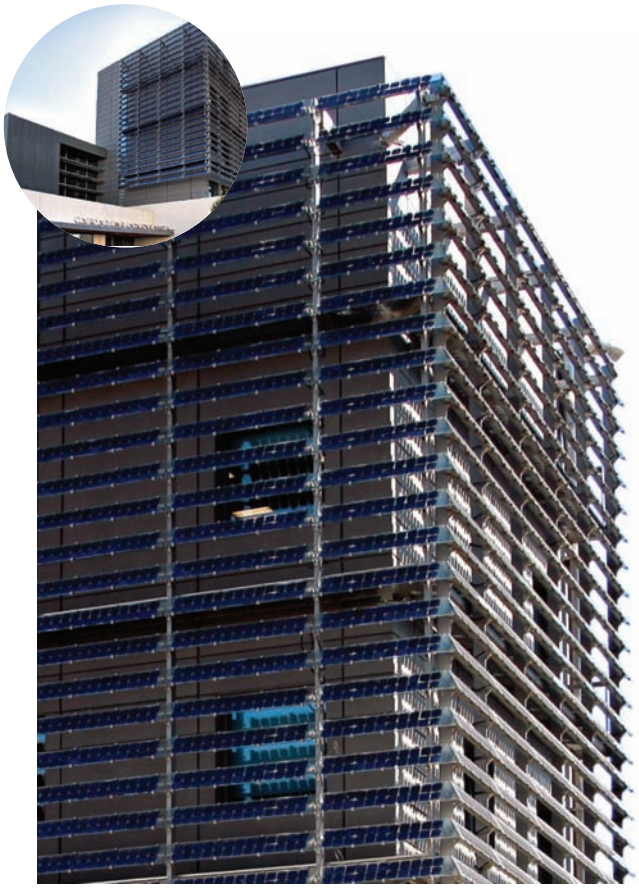
The management model implemented by the Queen Sofia Foundation Alzheimer's Center has tried to summon the will and interests of all parties involved: Administration (Central, Regional and Local) and Civil Society. For this reason, management of UIPA reserach activities were assigned to CIEN Foundation, while healthcare and training activities are responsibility of the Ministry of Family and Social Affairs of the Madrid Region.

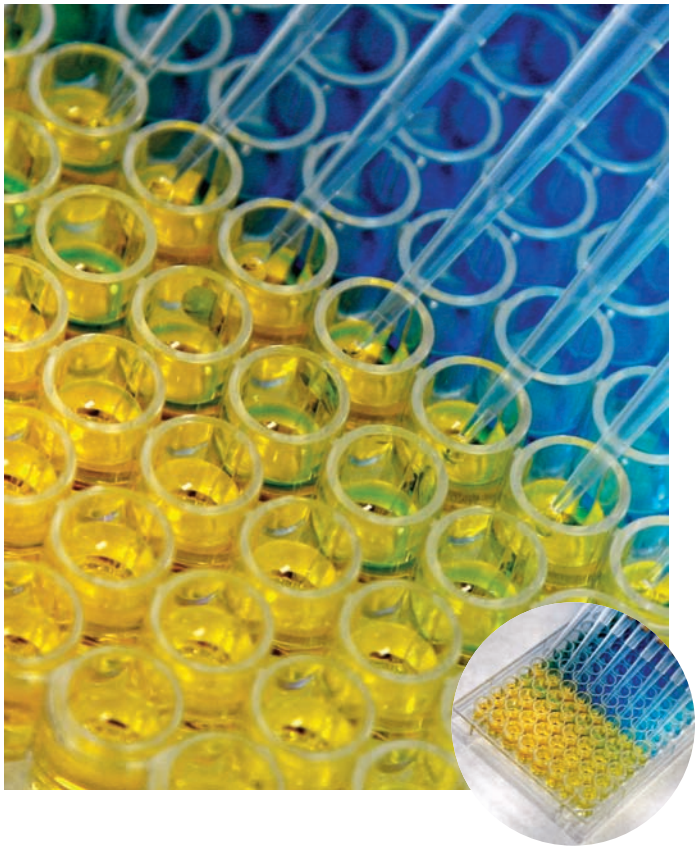


1.2. The CIEN Foundation in 2013

Key figures

- The CIEN Foundation overall budget for 2013 was 4,319,116.44€, a 29,8% increase compared with the previous year.
- 17.25% of the CIEN Foundation budget comes from the General State Administration budget through the ISCIII
- In 2013 the Queen Sofia Foundation has contributed with 646,011.89€ as part of overall commitment of contributing 2.1 million euros in the period 2011-2014.



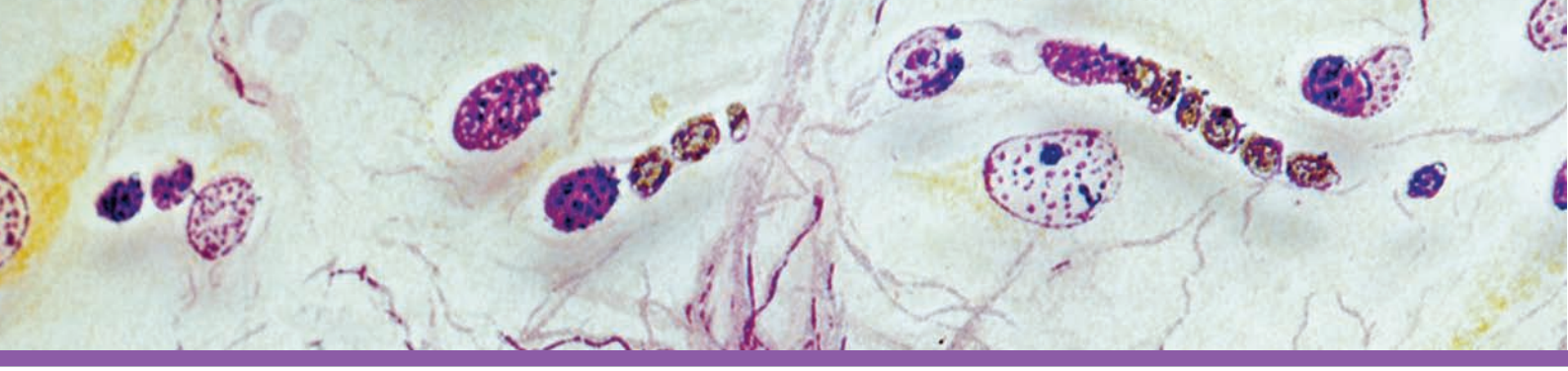


Scientific activity

- Overall scientific production: 85 impacts
  14.9% increase versus 2012
- Publications in scientific journals: 81
  42.1% increase versus 2012
- Publications in books and clinical guides: 4
  76.5% decrease versus 2012
- Participation in scientific meetings conferences: 82
  21.1% decrease versus 20121
- Participation in courses: 46
  42.55 decrease versus 2012

Highlighted events

- **For second consecutive year, CIEN Foundation researchers are engaged in some of the translational research projects summoned by the European Joint Programme in Neurodegenerative Diseases (JPND).**
- **The process of recruiting volunteers for the "Project Vallecas" ended during 2013. A total of 1,213 people participate in this five-year study. About 62% of registered volunteers had already made it through the second evaluation at year-end.**
- **CIEN Foundation established February 22 as the Vallecas Project Volunteer Day in recognition of their altruistic cooperation in research.**
- **The CIEN Foundation Tissue Bank (BT-CIEN for its acronym in Spanish) has received official accreditation from the Council of Health of the Madrid Region as a biobank. The BT-CIEN is integrated into the National Biobank Network and has the certification of quality management under ISO 9001-2008.**
- **75 new brain donors have been registered in the CIEN Foundation Tissue Bank during 2013, which ended the year with a total of 625 people registered.**
- **During 2013, the Department of Neuroimaging has performed a total of 7,839 MRI scans on 1,329 subjects.**



1.3. Letter from the Managing Director of the CIEN Foundation

María Ángeles Pérez Muñoz
Managing Director of the CIEN Foundation

Dear trustees, benefactors, contributors and friends of the CIEN Foundation.

As every year I am addressing you to review the activities undertaken by the Research Centre in Neurological Diseases (CIEN), responsible for the management and coordination of the Research Unit of the Alzheimer Project (UIPA) and the Centre for Foundation Biomedical Research in Neurodegenerative Diseases (CIBERNED).

If one were to define the year 2013 in one word, no doubt that would be consolidation, both at the institutional level and as regards to research activities of the Center. Consolidation of an internationalization project launched two years ago when CIEN Foundation and CIBERNED were designated as the only research centers in Spain included in the International Network of Centres of Excellence on Neurodegenerative Disease Research (COEN). And confirmation of an integrative management model that in practice has led us to unify the research activity of UIPA and CIBERNED under the umbrella of the CIEN Foundation. A model on which we will continue to deepen in future years in order to optimize more effectively and efficiently the available resources and to encourage and enhance communication between the research groups of both institutions.

In 2013 this process of internationalization has achieved two new milestones. First, I would like to highlight the agreement that CIEN Foundation has signed with the University Hospital of Ulm (Germany) to participate in the Project Registry, an observational study coordinated by the European Network of Huntington's Disease (EHDN, for its acronym in English) aimed at further advancing the knowledge of this neurodegenerative disease.

Second, deserves particular mention the collaboration that CIEN Foundation have established with the

Scientific Advisor to the UK Foreign Office to held the first UK-Spain bilateral conference, a scientific meeting in which professionals from both countries has gathered to put together the various policies and ongoing projects to globally address a challenge that affects all developed societies alike: dementia.

Finally, as the greatest exponent of the two aspects of consolidation mentioned above, internationalization and effective integration of UIPA and CIBERNED, I would like to highlight the celebration of the First International Conference on Research and Innovation in Neurodegenerative Diseases (CIIIEN for its acronym in Spanish). This scientific meeting, chaired by Her Majesty The Queen, is born thanks to a joint agreement between the CIEN Foundation, the Queen Sofia Foundation and CIBERNED and it is aimed at unifying the two major symposia that used to be annually held in Spain in the field of research on neurodegenerative diseases: the International Symposium Advances in Alzheimer's Disease, sponsored by the Queen Sofia Foundation and the CIEN Foundation, and the CIBERNED Scientific Forum.

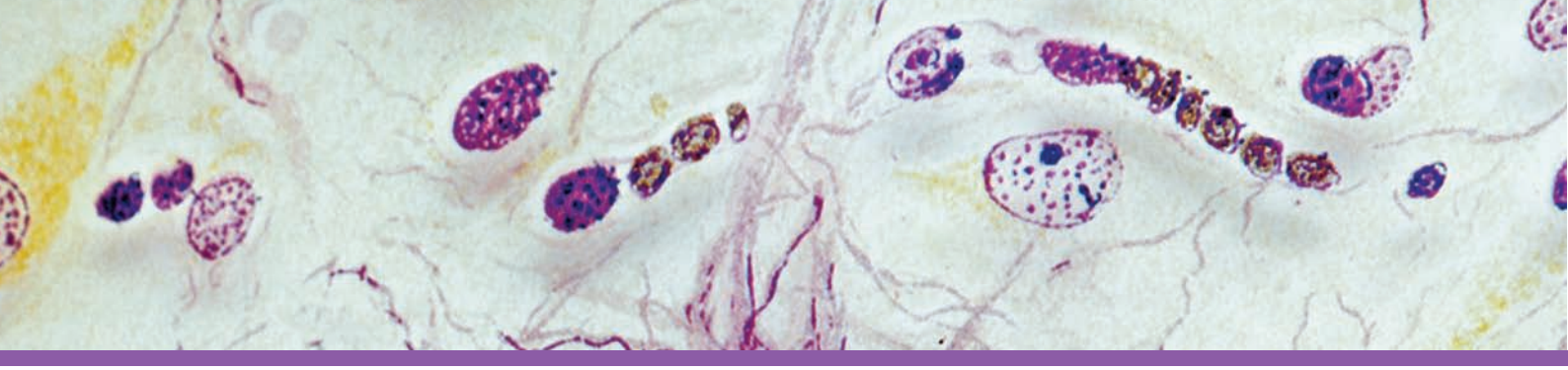
The success in the number of attendants to this first edition of CIIIEN and the conclusions drawn from it have confirmed the wisdom of this decision.

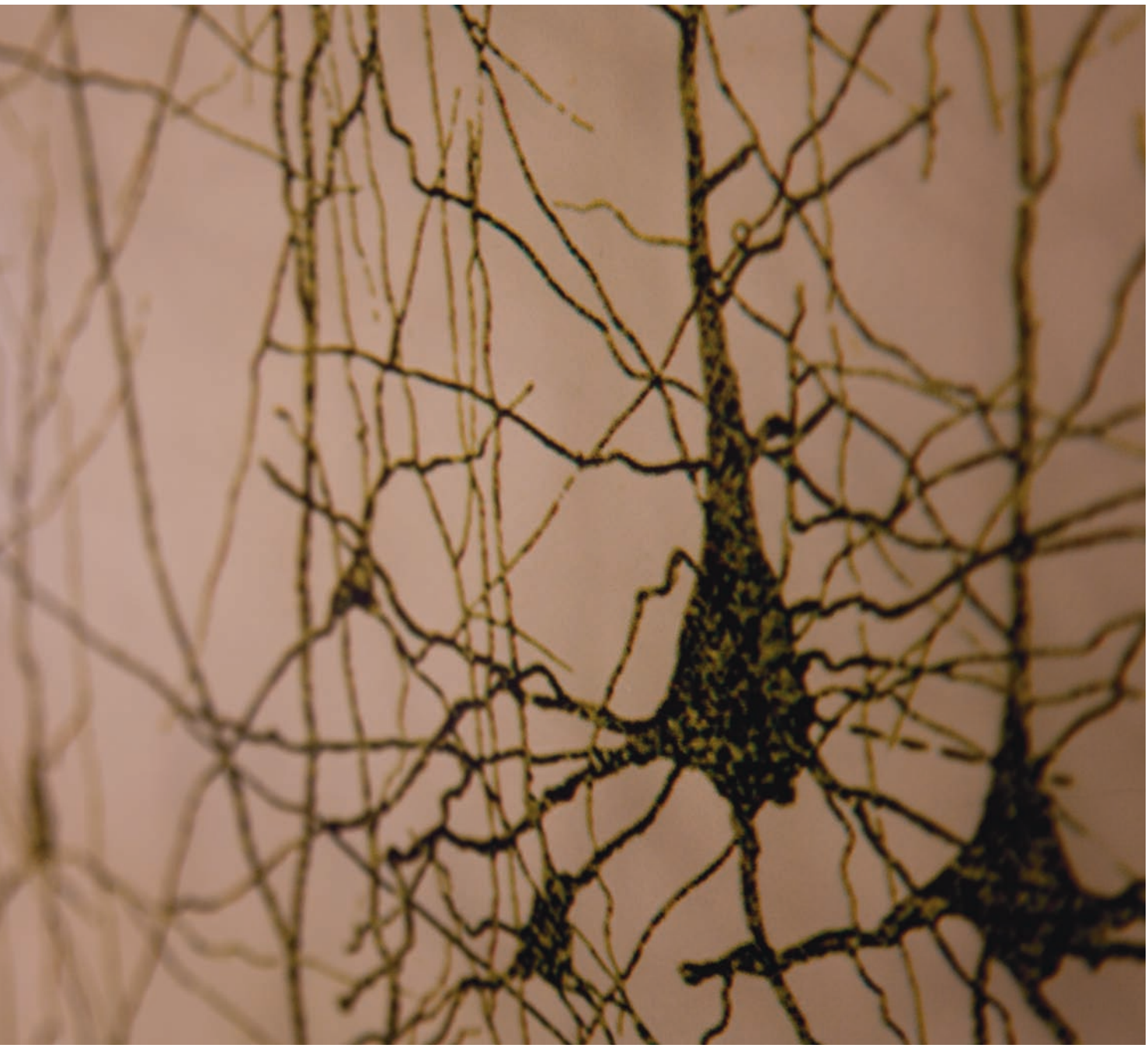
As it could not be otherwise, 2013 has also been particularly significant in the research field. In the year just ended the process of recruiting volunteers for the "Vallecas Project" has been completed. This longitudinal observational study is one of the most ambitious initiatives launched in Spain to advance our understanding of Alzheimer's disease. A total of 1,213 people participate in this five-year project, which already has made the first and even the second annual assessment by CIEN Foundation professionals. The first partial results of this study are expected during 2014.

I want to take this opportunity to deeply thank those 1,213 volunteers for their willingness to participate in a project in which we have placed significant resources, both financial and human, to obtain results that allow us trying to understand why this diseases generates and how it progresses. A gratitude that I was pleased to personally convey to some of them with the occasion of the Vallecas Project Volunteer Day held on February 22, 2014.

In the CIEN Foundation we have decided to established that Day in recognition of their invaluable help in supporting scientific research. Initiatives such as this allow us to bring society the fundamental role that researchers such as those from the CIEN Foundation and CIBERNED make, without which it would not be possible to continue carrying out the projects that have placed this institution at the forefront of scientific research in Spanish neuroscience. In order to continue to promote citizen engagement and awareness with research, we have launched "The Christmas Tree of Memories ", which in 2013 has completed its third edition. A project that has brought us great joy and allows people to get close to scientific research in a more friendly way.

Bringing research closer to society and translating all the progress made in the laboratory into clinical practice is one of the major goals behind the origin of the CIEN Foundation. With the volunteers invaluable assistance, we are getting and will continue working in the future to fight a major plague of XXI century: Alzheimer's disease.





1.4. Organizational chart

CIEN Foundation Board of Trustees:

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

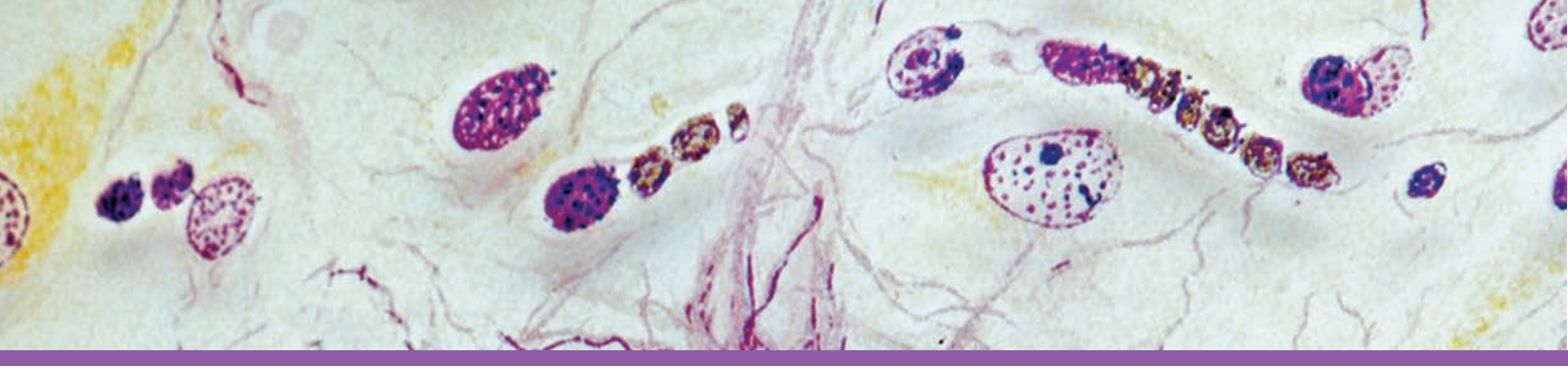
Board members in 2013 are:

CIEN FOUNDATION BOARD OF TRUSTEES		
The members of the CIEN Foundation Board of Trustees on December 31, 2013 are the following:		
Position	**Title**	**Name**
Honorary Chair	Ministry of Economy and Competitiveness	Excmo. Sr. D. Luis de Guindos Jurado
Chair	State Secretary for Research, Development and Innovation	Excma. Sra. Dª Carmen Vela Olmo
Vice Chair	Director of the Carlos III Institute of Health	Dr. D. Antonio Luis Andreu Périz*
Ex officio member	Ministry of Health, Social Services and Equality	Sra. Dª Pilar Farjas Abadía
Ex officio member	General Manager of Scientific and Technical Research	Sr. D. Juan María Vázquez Rojas
Ex officio member	Presidency of the Government Economic Bureau	Sra. Dª María Fernández Pérez
Ex officio member	Carlos III Institute of Health	Sr. D. Lisardo Boscá Gomar
Ex officio member	Carlos III Institute of Health	Sra. Dª Margarita Blázquez Herranz
Ex officio member	General Manager of Public Health, Quality and Innovation	Sra. Dª Mª Mercedes Vinuesa Sebastián
Ex officio member	National Scientific Research Council	Sr. D. Emilio Lora-Tamayo D'Ocón
Elected member, Andalucía	General Manager for Research, Technology and Business	Sra. Dª María Sol Calzado García *
Elected member, Valencia	General Manager of Planning, Evaluation and Health Research	Sra. Dª Pilar Viedama Gil de Vergara
Elected member, Canarias	General Manager of Welfare Programs	Sra. Dª Hilda Sánchez Janáriz *
Elected member, Castilla La Mancha	Secretary General of the Health Service of Castilla-La Mancha (SESCAM)	Pending acceptance
Secretary	Carlos III Institute of Health	Sr. D. Javier Arias Díaz *
Legal Advisor	State General Legal Office	Sr. D. Jose María Ayala de la Torre *
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
Managing Director	CIEN Foundation	Sra. Dª Mª Ángeles Pérez Muñoz

Changes in the board of trustees during the year 2013:

Following the restructuring of government ministries and the implementation of its basic organizational structure made by the Administration in 2012, the Carlos III Institute of Health, from which depends the CIEN Foundation, was organically attached to the Ministry of Economy and Competitiveness.

*** In April 2013 Joaquín Arenas D. Barbero is replaced by Antonio Luis Andreu Périz**
*** In September 2013 Mr Javier Arias Díaz was replaced by Ms. Margarita Blázquez Herranz**
*** In September 2013 Mr José María Ayala de la Torre was replaced by José Luis Beotas**
*** Pending acceptance: Ms. María Sol Calzado García and Ms. Hilda Sánchez Janariz**

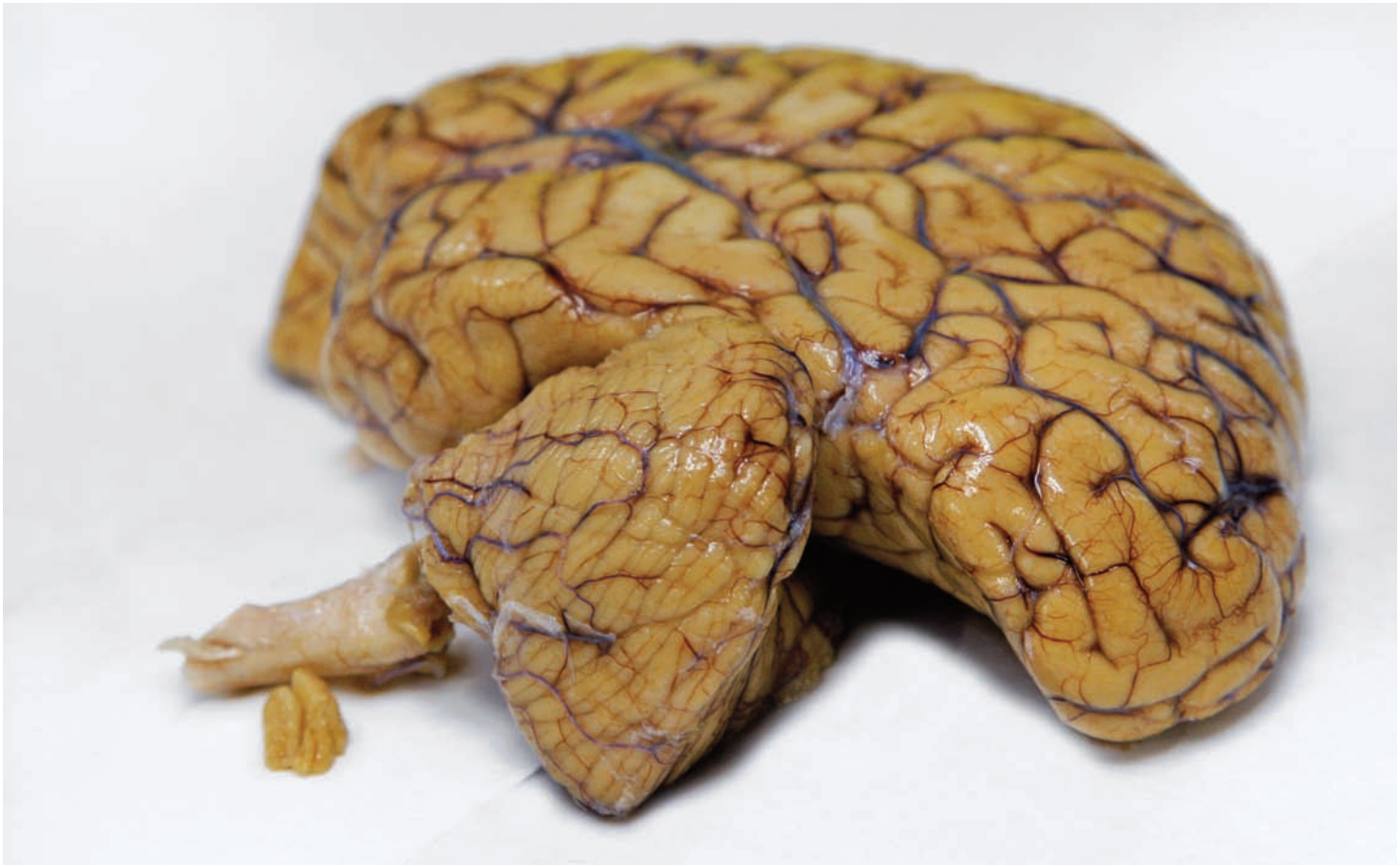


ISCIII Ethics Committee for Research and Animal Welfare:

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.



1.5. Vision

The recruitment of volunteers engaged in the Vallecas Project was completed in late 2013, thus concluding the establishment of the study cohort. In fact, much of the subjects have already attended the first annual follow-up evaluation. From now on the project will provide increasingly richer and more relevant information about the earliest stages of cognitive decline in subjects that develop and the most suitable biomarkers (clinical, biochemical and neuroimaging) to characterize and to identify the population at higher risk of developing it. It is also likely that in the near future the information obtained from assessments of volunteers, their biological samples and neuroimaging studies performed are integrated with other national and international cohorts, significantly increasing the potential of each one of them.

The Alzheimer Project was initiated in 2007 as a longitudinal study based on the residents of the Queen Sofia Foundation Alzheimer Center and the patients of the Day Care Center and has no specific date of completion. It is thus a structural project of the Queen Sofia Foundation Alzheimer Center and the CIEN Foundation and a growing source of information (clinical, molecular, neuroradiological and neuropathological) on dementia in their moderate and advanced stages.

In the coming months and years the information collected since the start of the project will provide important clues about how the two main pathologies causing dementia, Alzheimer's disease and cerebrovascular disease, interact with each other and result in defined progression pathways. A better understanding of the different forms of expression of these diseases, when they occur in isolation or, more often, in combination, will allow to address in depth its role in the onset of dementia and to identify groups of patients requiring care or that may benefit from specific therapies.

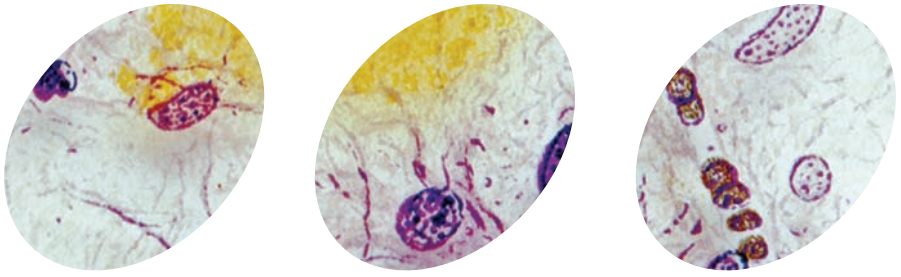
The research model developed at the Alzheimer Center can be equally applied to other residences and other Day Care Centers around the Madrid Region. On this basis we have designed a project called Madrid+CIEN, in collaboration with the Directorate General of the Elderly of the Madrid Region and the European University of Madrid, aimed at creating a cohort of centenarian subjects in our Region.

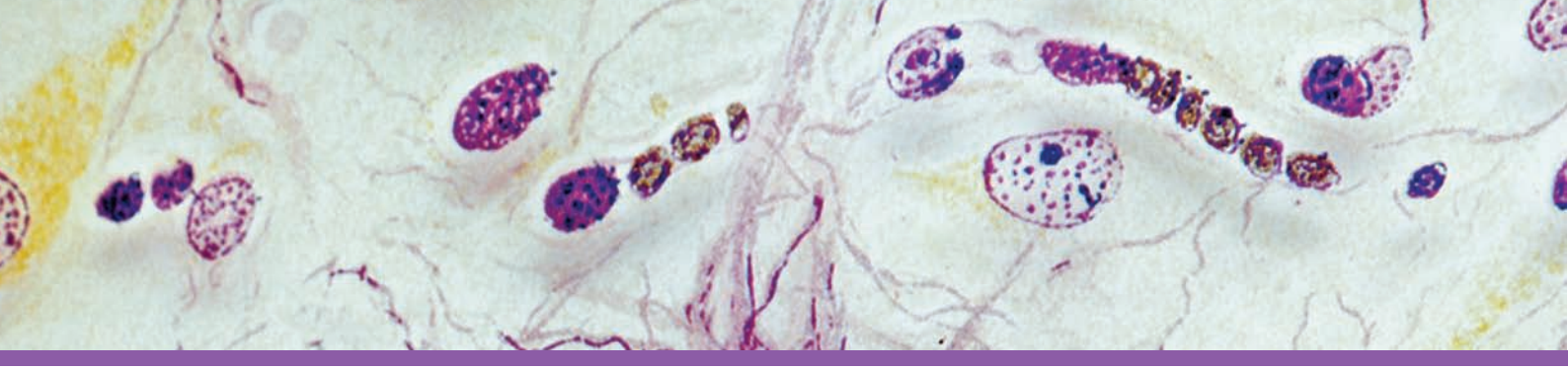
The main objectives of this study are to establish the cognitive profile of centenarians who do not suffer of dementia; study the evolution of this profile over a period of three years; include the subjects from our brain tissue donation program that voluntarily wish to do so; and have a group of centenarians in which it would possible to establish non-pharmacological treatment studies.

Replication of the Alzheimer Project model in other health environments is being implemented to Day Care Centers from Associations of Relatives of Alzheimer's Patients (AFA for its acronym in Spanish) of León, Soria, and other cities, in order to count on future projects Foundation with subjects diagnosed with mild cognitive impairment and mild dementia.

Management report

CIEN Foundation management model is based on three main lines of action: the optimization of resources and streamlining of expenditure, multidisciplinary and continuous training of its professionals, and a commitment to internationalization.






CENTRO ALZHEIMER FUNDACION REINA SOFIA

2.1. General management

In 2013, the CIEN Foundation has managed a budget of over € 4 million. The optimization of resources and streamlining of expenditure have remained as the main lines of action in management in order to guarantee the continuity of ongoing research projects and to ensure the long-term permanence of researchers.

This commitment with CIEN Foundation human 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.

The budget increase in 2013 over the previous year was due primarily to two factors: the increase in projects managed by the Office for European Projects and approved grants in the framework of the COEN initiative.

The remaining activity has followed a stable implementation, with adjustments in expenditure items, mainly in administrative units. Thus, the ratio of euros spent on research versus spent on management has reached 3.30 points, up from 2.90 for the year 2012 This reflects the significant effort made to optimize resources as well as support to the current lines of research.

2.2. Management of financial and economic resources

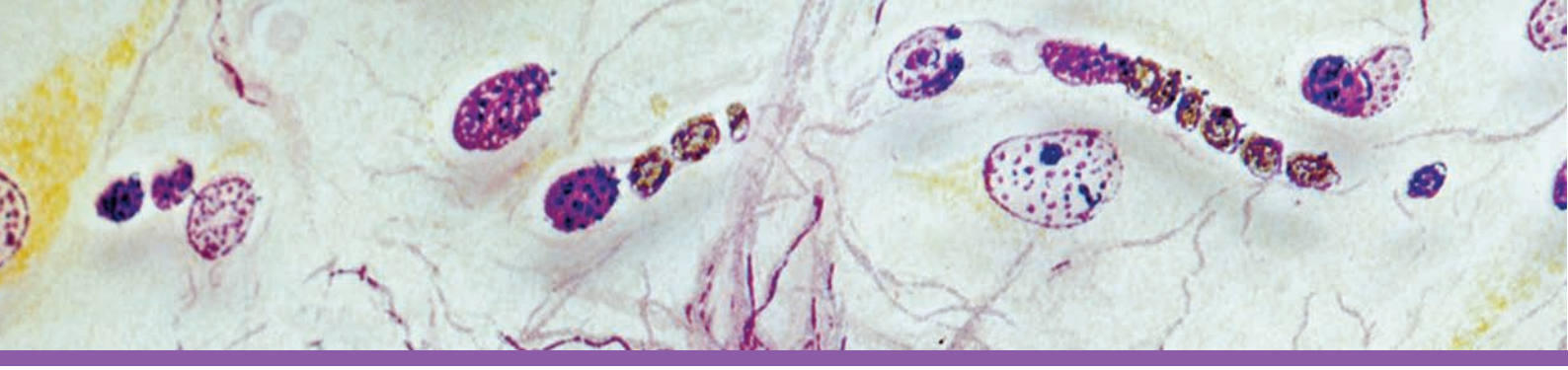
The CIEN Foundation is a statewide under the Ministry of Economy and Competitiveness. Around 18% of its annual budget comes from the official annual grant from the Carlos III Institute of Health. This item, recorded in the General State Administration Budget for 2013, amounts to a total of 825,280€, distributed as 655,490€ intended to finance current expenditure and 169,340€ for capital expenditures. These amounts are remain in the same level as in fiscal years 2011 and 2012.

The distribution of expenditure in the exercise keeps the ratios of previous years, focusing efforts in maintaining the regular scientific activity. In 2013, 36.3% has been allocated to expenditure on personnel and 34.6% to operating expenses and provisioning.

During 2013 is observed a significant increase in the amount allocated to monetary aid derived basically from the approval of grants under the COEN initiative, funded with € 550,000. This item includes the National School of Health fellowships and the Queen Sofia-Mapfre scholarship.

During 2013 the CIEN Foundation has continued to manage the following initiatives:

- The Carlos III Institute of Health European Project Office, with a budget for 2012 of 380,000€. The term of the collaboration agreement has ended on Dec. 31, 2013, extending its effects to all dependent competitive projects from this office in which handling the CIEN Foundation collaborated:
  - HEALTH-NCP-NET - Coordination Action for Reinforcing the Health National Contact Points Network.
  - FIT FOR HEALTH - Promoting sustainable participation of high-technology, research-intensive SMEs operating in the Health Sector in FP7
  - EUROCIENCIA
  - JPI´S TO CO-WORK - JPI's: a process of mutual learning: TOwards a COmmon adoption of framework
  - COMMHERE - Communication of European Health Research
  - EU-LAC HEALTH - Defining a Roadmap for Cooperative Health research between the EU and Latin o America-Caribbean countries: a Policy Oriented Approach
  - HDHL-CSA - A Healthy Diet for a Healthy Life
- JPI AMR - Coordination Action for the early implementation of the Joint Programming Initiative on Antimicrobial Resistance



- The project as Center of Reference for the Control of Endemic Diseases in Equatorial Guinea, with an initial budget for 2013 of 414,157€, under agreement to which later was added the amount of 141,044.06€ in order to conclude implementation activities authorized after the corresponding extension up to 14 February 2014.
- The Amhara-Ethiopia Project; collaboration agreement for on budget management activities of technical nature provided in the project on "Strengthening of the Health System for preventing and combating infectious diseases prevalent in the Amhara Region of Ethiopia".
- 2013 International Cooperation Scholarships call for postgraduate studies at the National School of Health - Carlos III Institute of Health (Diploma in International Public Health and Diploma in Health Promotion). On April 23, 2013 the Carlos III Institute of Health and the CIEN Foundation signed an agreement by which the Foundation commits to manage the call proceedings and the resolution of scholarships, with a budget of € 128,000. During the year 2013 the number of grants fell from 28 to 25, and the allocated budget decreased by 10%.

2.3. Management of Human Resources

As a research center, our culture is made up of values that promote a creative, flexible, involvement and teamwork environment. In the CIEN Foundation, research teams are composed of young researchers led by highly skilled professionals looking for maximum visibility of its research, which is made accessible to the citizens and society, in addition to being a national and international reference due to the results of excellence obtained.

The CIEN Foundation focuses its human resources policy efforts on the excellence in management and the competence of its professionals, giving researchers a solid project for continuous learning and a unique professional experience, all within the framework of an expansion and internationalization process. The values that define the Foundation are:

- Innovation.
- Multidisciplinary teamwork.
- Professionalism based on efficiency, competition and rigor.
- Retention of talent.
- Knowledge Management.

CIEN Foundation revenues since 2011

	2013	2012	2011
Grants, donations and bequests charged to surplus for the year	3.577.933,53	2.487.041,42	2.567.436,35
Reimbursement of grants and subsidies	30.883,32	0,00	0,00
Sales and other commercial operating revenues	178.977,61	281.006,80	227.997,55
Other revenues	9.190,85	7.740,84	0,00
Grants, donations and capital bequests transferred to surplus for the year	511.113,54	512.609,31	909.576,49
Financial revenues	11.013,59	31.514,15	38.625,53
TOTAL	**4.319.112,44**	**3.319.912,52**	**3.743.635,92**

True to the corporate values of the CIEN Foundation, in which people are the pivot on which to articulate its development, during 2013 we have continued to deploy a model of management which collects the policies and principles of human resource management, defines processes and development of systems, creates the levers to drive these processes, and seeks the precision and continuous improvement of this model with outcome measurement tools.

The research groups and the technical support office effectively and efficiently manage research with criteria and innovative and quality instruments, offering a professional service and personal attention oriented towards user satisfaction, through collaboration and promoting the objective of the CIEN Foundation or promoting research, innovation and the transfer of results to society.

Human resources devoted to carrying out the activities of the Foundation

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

The CIEN Foundation, following the guidelines from the Ministry of Economy and Competitiveness, has adjusted the number of calls and hired personnel.

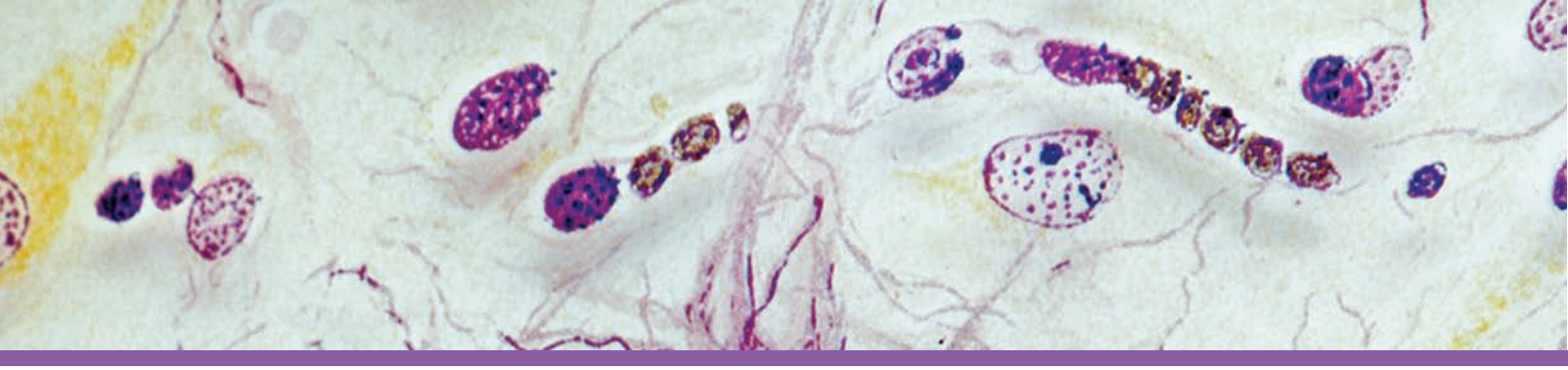
All positions offered are defined with a specific profile, required qualifications, requirements and functions to be performed.

During 2013, the CIEN Foundation has counted on a total of 66 professionals, including 29 hired from competitive grants, 3 fellows, 3 volunteers who have collaborated selflessly with the CIEN Foundation , 1 in-training Resident Medical Intern and 30 professionals who developed activity thanks to signed collaboration agreements.

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

CIEN Foundation Expenditure since 2011

	2013	2012	2011
Monetary aid and other	744.261,34	97.651,00	897.702,48
Supplies	391.619,64	416.244,86	197.266,07
Staff costs	1.564.373,15	1.457.394,91	1.224.706,74
Other operating expenses	1.097.724.90	1.129.164,47	1.046.318,84
Depreciation and amortization	507.666,08	512.609.31	909.576,49
Impairment and gains on disposal fixed assets	1.240,74	0,00	0,00
TOTAL	**4.306.885,80**	**3.588.512,3**	**4.275.570,60**



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

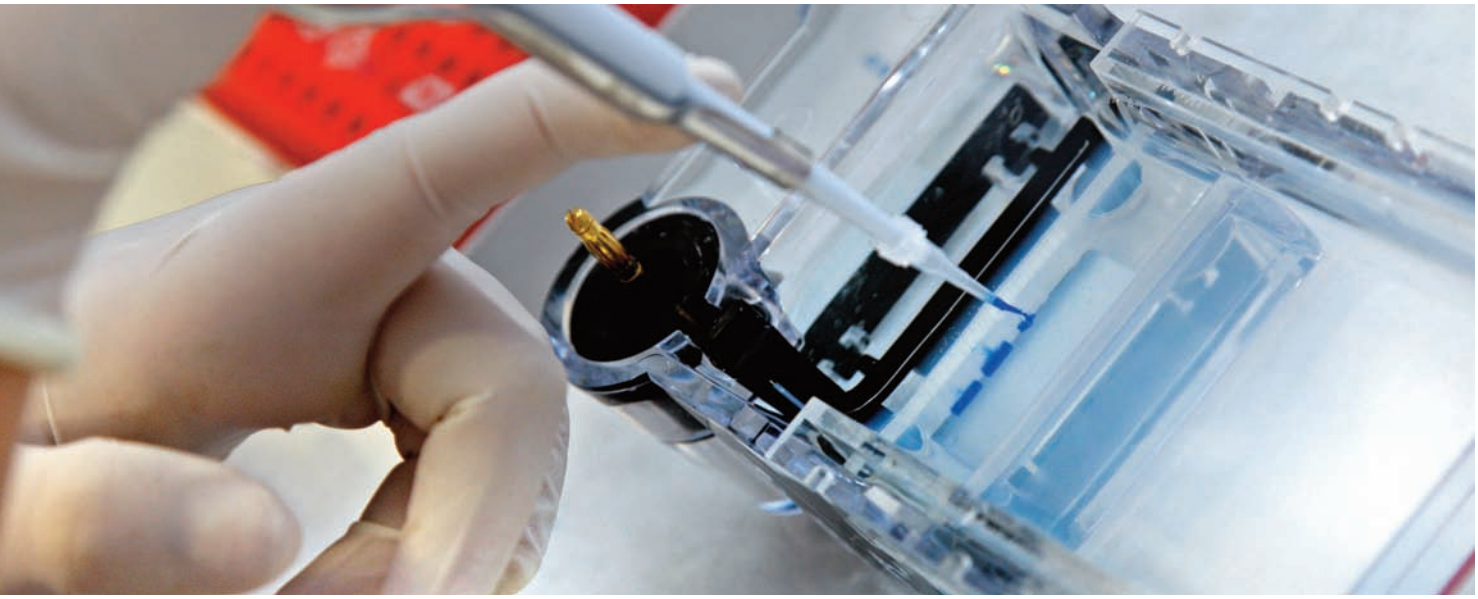
Retraining and continuing professional development are two main pillars to achieve the objectives of efficiency and professional training. Training is not only relevant to achieve the required levels of competitiveness and quality, but is also a tool for motivation and creating values, personal and professional growth, and transmission and preservation of knowledge. All of these are hallmarks of the most advanced and efficient organizations and directly affect the best performance of the members of our organization.

In this regard, the CIEN Foundation develops Training Program as a key piece that meets the requirements of competitiveness, efficiency and quality and at the same time, satisfy the aspirations of professional and personal development of its employees.

It comes to encourage and promote all those training activities that enhance professional development for their full integration into the organization, with the commitment to establish an motivating environment and working system.

The following courses, meetings and workshops have been carried out during 2012:

- "International Day of Radiology. MRI in the study of Alzheimer's disease" November 8, 2013. CIEN



List of CIEN Foundation staff in 2013

Head of Management

1	Managing Director
1	UIPA Scientific Director

Medical and Research staff by department

1	Neuropathologist
2	Psychiatrists
5	Neurologists
1	Psychologists
5	Dr. in Mathematics
11	Engineers (collaboration agreements)
3	Neuropsychologists (research projects)
2	Neuroradiologists (DIM Foundation collaboration agreement)
3	Physiscists (collaboration agreements)
1	Biologist (CIBERNED)
1	University Diploma in Nursing
2	APA technicians
3	Neuroimaging technicians
3	Laboratory technicians (private company collaboration agreement)
1	Laboratory technician in training (collaboration agreement IES)
2	Fellows (collaboration agreement)
1	Resident Medical Intern (MIR)
5	Administrative assistants

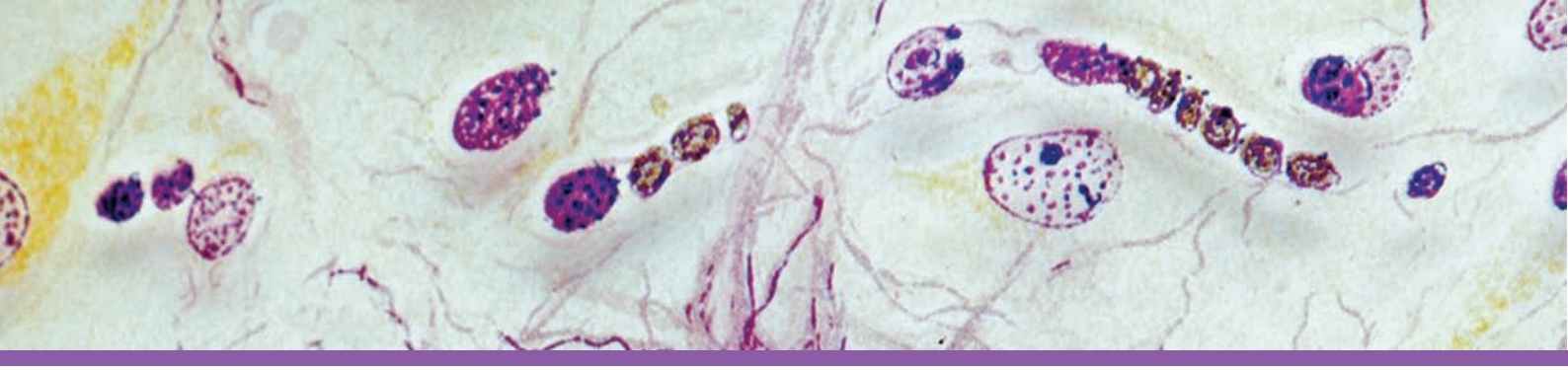
Management and Administration

1	Managing Director Secretary assistants
1	Administrative official
2	Graduates (CIBERNED)
2	Administrative assistants (CIBERNED)

Other staff

3	Volunteers

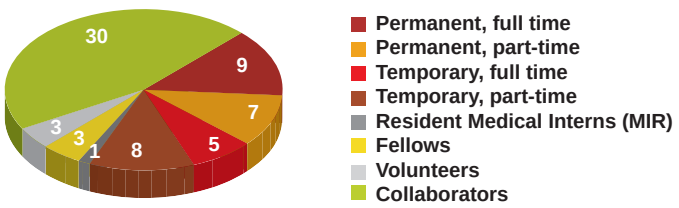
Total staff employed by CIEN Foundation: 29; under grants: 18; Projects: 11
Note: full-time staff: 14. Part-Time: 15



Foundation, Queen Sofía Foundation and Spanish Association of Radiology Technicians (AETR). Madrid. Spain.

- Course on "Prevention of Occupational Hazards in MRI rooms for medical use" 23-24 Ocober, 2013. Institute for Safety and Health at Work, CIEN Foundation. Madrid, Spain.
- "8th theoretical and practical course on Functional Magnetic Resonance spectroscopy and cerebral for technical Functional Magnetic Resonance and cerebral spectroscopy for technicians" 26-28 September, 2013. CIEN Foundation, Ministry of Economy and Competitiveness, DIM Foundation and Ruber International. Madrid, Spain.
- Seminar "On the importance of fast and accurate EM modeling in Next-Generation High-Field MRI Technology" September 6, 2013. Jorge Fernández Villena. Post-Doctoral Associate at Massachusetts Institute of Technology (MIT), USA. CIEN Foundation. Queen Sofía Foundation. Madrid, Spain.
- Workshop on quantification and postprocessing in neuroimaging with magnetic resonance, May 27-30, 2013, CIEN Foundation, Ministry of Economy and Competitiveness, DIM Foundation and King Juan Carlos University. Madrid, Spain
- "Neuroimaging y Brain Banks" within the enrichment for highly gifted students Program. CAM. April 20, 2013. CIEN Foundation. Madrid, Spain.
- Seminar "Statistics in Neuroimaging" April 11 and 16, 2013. Medical Imaging Analysis Laboratory, Rey Juan Carlos University. CIEN Foundation. Queen Sofía Foundation. Madrid. Spain.
- Course on "Prevention of Occupational Hazards in MRI rooms for medical use" April 10-11, 2013. Institute for Safety and Health in the Workplace, CIEN Foundation. Madrid, Spain.
- "3rd theoretical and practical course on neuroimaging techniques with MRI" January 25, 2013. CIEN Foundation, Ministry of Economy and Competitiveness, DIM Foundation and Ruber International. Madrid, Spain.
- Training Course on Neuropathology. IES Moratalaz. January 2013 – June 2013.
- Training Course on Neuropsychology. Autonomous University of Madrid. October 2013 – January 2014.
- Training Course on Psychology. Rey Juan Carlos University. February 2013 – June 2013.
- MIR. Yale University. November 2012 - August 2013.
- 6 months fellowshios for international stays.

CIEN Foundation Staff in 2013



2.3.2. Prevention of occupational hazards

In order to ensure protection of health and safety in the workplace and to comply with the Law on Prevention of Occupational Hazards, in 2013, the CIEN Foundation has carried out several preventive activities. These included performing an emergency drill with full evacuation of the CIEN Foundation facilities, the completion of a course of fire prevention and the delivery to the entire staff of the FREMAP's "Basic Guide for fire prevention".

As for health monitoring, there have been 23 specific medical examinations. Health screenings have included a work history with a detailed description of the job, the time spent on it, the risks identified in the analysis of working conditions and prevention measures, anamnesis data, clinical examination, biological control and complementary studies directed and chosen according to the risks inherent to the work performed.

As for the accident rate data, the CIEN Foundation has not recorded any accident, so it has fulfilled the goal of workplace accidents.

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.

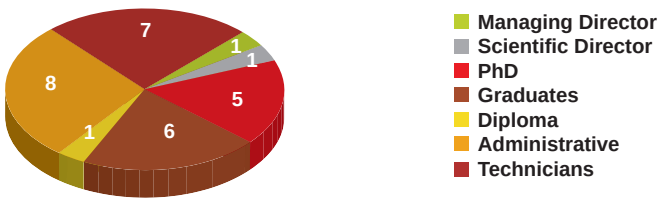
2.4.1. Research projects

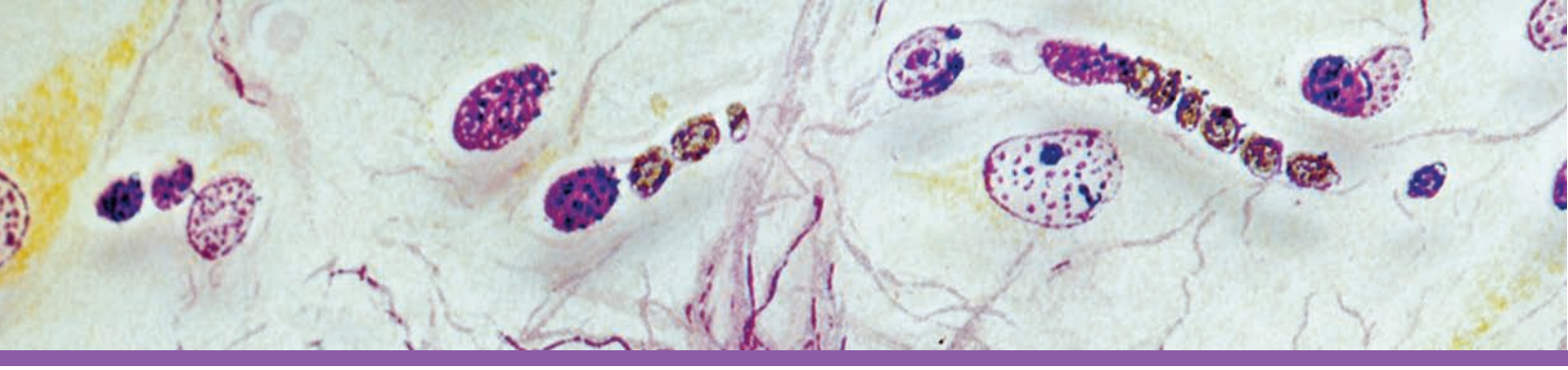
In its pursuit of excellence CIEN Foundation has been conducting research projects focused on Alzheimer's disease and related conditions. These projects aim to characterize the pathology, advancing early diagnosis, studying clinical and psychosocial aspects of the disease and new drug targets. The CIEN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

It is also aware of the deep distress caused both in the individual and its environment as well as society in general, and for that reason promotes collaboration with various entities having similar concerns.

With this objective it has worked during 2013 in a number of actions financed through its own funds along with other donations and grants received, and whose main projects are:

Staff distribution by category in 2013





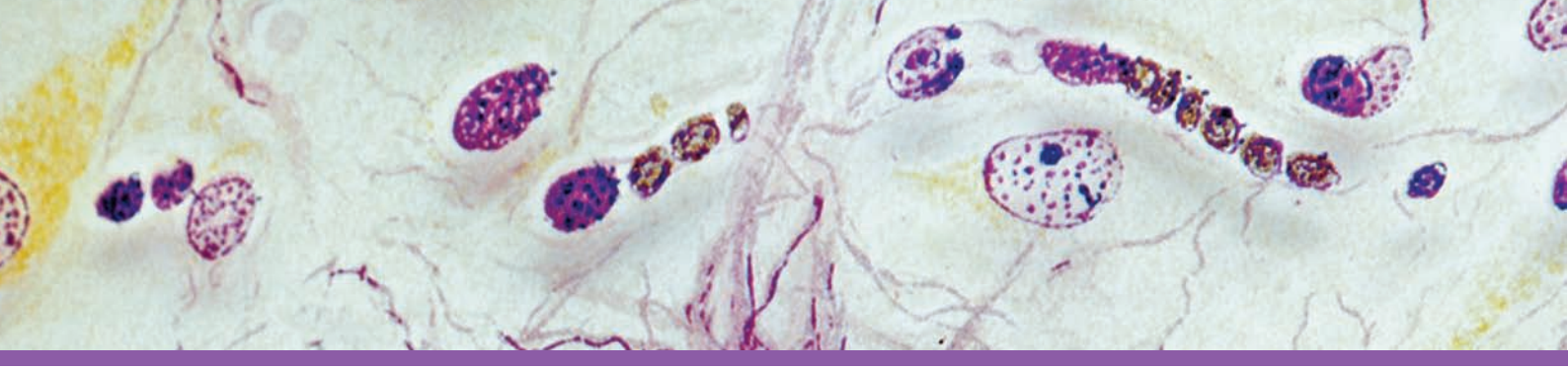
- Vallecas Project: Multidisciplinary study for early detection of Alzheimer's disease. 2013 budget: 377,814.93€.
- Diagnostic Guidance Unit: Consultation Unit for individuals with memory loss complaints or other incipient cognitive impairment or suspection of onset of early dementia. 2013 budget: 100,000€.
- Research projects awarded under competitive calls active during2013:
  - PI10/02567: Robot-theraphy in dementia. 3 years project funded by the Carlos III Institute de Health coordinated by Dr. Pablo Martínez-Martín. Budget for 2013 amounts to 2.762,43€ (project total budget: 33,112.86€).
  - PI12/03018: Profile of Alzheimer's pathology associated with age (85+CIEN Study). 3-year project funded by the Carlos III Institute of Health and led by Dr. Alberto Rábano. Budget for 2013 adds up to 7,260.00€ (project total budget: 19,965.00€).
  - PT-2012-0769-010000: Design and construction of a system for the diagnosis of Alzheimer's disease based on laser raman spectroscopy (INNPACTO program). 3-year project funded by the Ministry of Economy and Competitiveness, Directorate General for Innovation and Competitiveness, led by Dr. Alberto Rábano. Budget for 2013 adds up to 34,962.50€ (project total budget: 93,320.00 €).
  - PT13/0010/0045: Biobank Platform. Principal Investigator: Dr. Alberto Rábano. Project funded by the Carlos III Institute of Health with an annual budget of 46,500.00€ for five years.

2.4.2. Fellowships and grants

During 2013 the CIEN Foundation has awarded the following fellowships and grants:

- 2013-2014 MAPFRE-Queen Sofia Foundation Fellowship. Stay of six months, renewable for a similar period (maximum 12 months). Research Program in Dementia / Alzheimer's Disease Center at the University of Texas, San Antonio. USA (Prof. George Perry).
- 2012-2013 MAPFRE-Queen Sofia Foundation Fellowship stay extension Implementation of the

2. MANAGEMENT REPORT



fellowship extension granted in 2012: Stay for six months, renewable for a similar period (maximum 12 months). Research Program, Department of Pathology and Psychiatry, Alzheimer's Disease Center at NYU School of Medicine, New York (Prof. B. Frangione).
- 2013 National School of Health Scholarships: Granting 25 scholarships for graduate studies in public health that should be granted to 25 trainees from the following countries: Angola, Argentina, Belize, Bolivia, Brazil, Cape Verde, Colombia, Costa Rica, Cuba, Chile, Ecuador, Philippines, Guatemala, Equatorial Guinea, Guinea Bissau, Honduras, Mexico, Mozambique, Nicaragua, Panama, Paraguay, Peru, Dominican Republic, El Salvador, Uruguay and Venezuela

2.5. Quality Policy

During 2013 CIEN Foundation has successfully passed the certification monitoring of the Quality Management System according to ISO 9001:2008, certified by TÜV Rheinland, in the areas of management and the CIEN Foundation Tissue Bank.

Quality Objectives are established annually in order to achieve continuous improvement in processes and obtaining higher levels of user satisfaction, both external and internal. The quality policy of CIEN Foundation seeks to ensure and optimize processes related to:

- The orientation to the external and internal user.
- Leadership.
- Staff participation.
- The process-based approach.
- Continuous improvement.

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

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

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

2.6. Personal Data Protection Law

CIEN Foundation has files containing personal data (including information systems, support and equipment used to treat them), of which is responsible and should be protected according to the provisions of current legislation, Organic Law 15/1999 of 13th December on the Protection of Personal Data [Data Protection Act].

These files are contained in the Security Document, as well as those involved in the treatment thereof and the premises in which they are located, Valderrebollo, 5; 28031-Madrid.

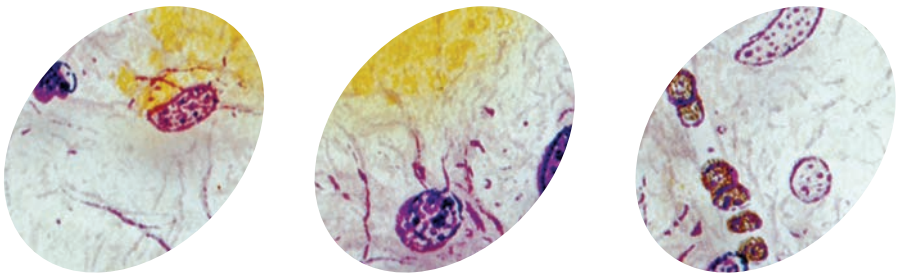
As being solely responsible for the files, CIEN Foundation is committed to fulfilling its obligation of secrecy of personal data and its duty to guard it, and to take the necessary measures to prevent alteration, loss, or unauthorized access, taking into consideration the current state of technology, ensuring compliance with the Data Protection Act.

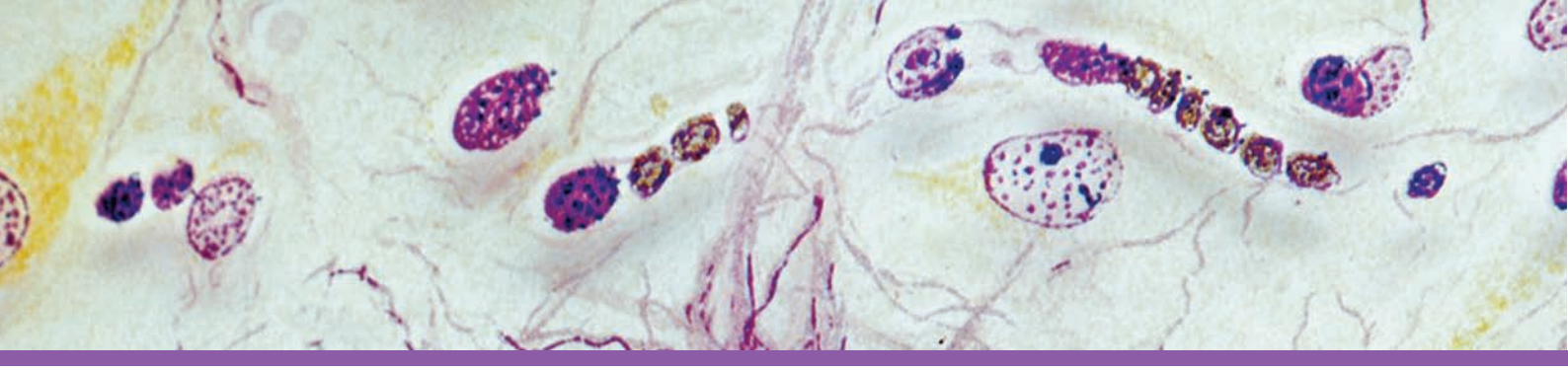
2. MANAGEMENT REPORT

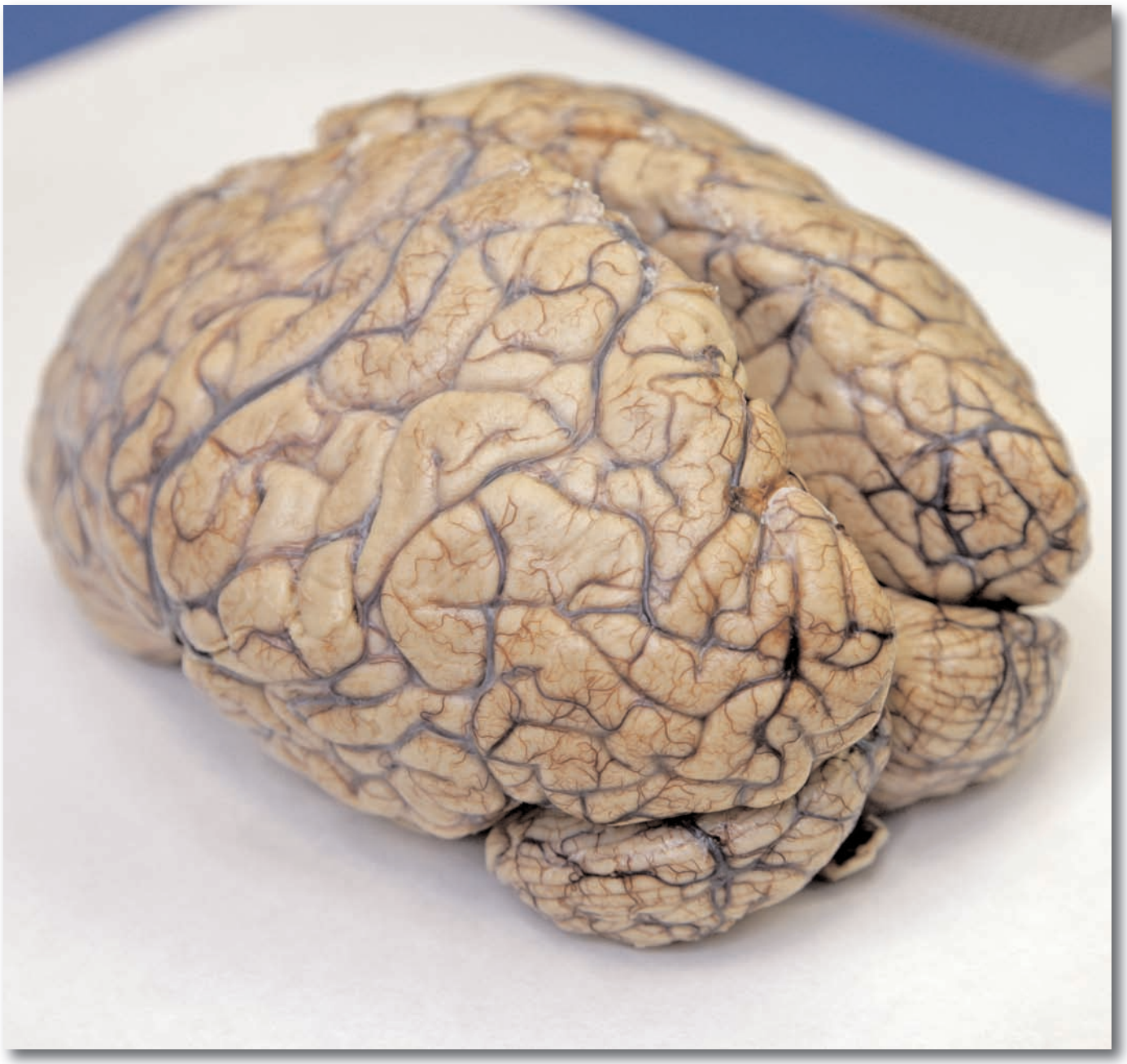
CIEN Foundation - CIBERNED Administration Team

Scientific activity

The UIPA consists of four departmental areas: multidisciplinary support unit, neuroimaging, neuropathology, and laboratory, as well as a diagnostic guidance unit. Among the active projects during 2013 the following are noteworthy: the Vallecas Project, the "robot therapy in dementia" project, the registry project and the madrid+cien project. they all have a common link: applying a model of translational research.







3.1. Overview

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

Since then, the UIPA has set up four departments with different functions. Among others, they aim at processing and managing biological samples, studying such tissues or conducting neuroimaging research projects in the field of neurodegenerative diseases with emphasis on Alzheimer's disease and related dementias.

Genetic and molecular knowledge gained from these studies have different applications: illustrate researchers into the pathogenic mechanisms of the disease, can be implemented in the diagnosis field and hopefully may lead to the development of better treatments.

However, genetic and molecular advances, far from promising a simple solution to the problem of neurodegenerative dementias, anticipate an increasingly complex picture, in which the remedies will be achieved through small goals, and only by the complementary and synergistic work of many research groups.

The main feature of neurodegenerative diseases is its complexity, since they affect both the biological aspect as well as the clinical and personal level. Thus, the psychological and social aspects involved in dementia need to be taken into account and be aware that ethical and legal issues such as the right to information and participation in medical decisions are increasingly gaining prominence every day.

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

3.2. Departmental Structure

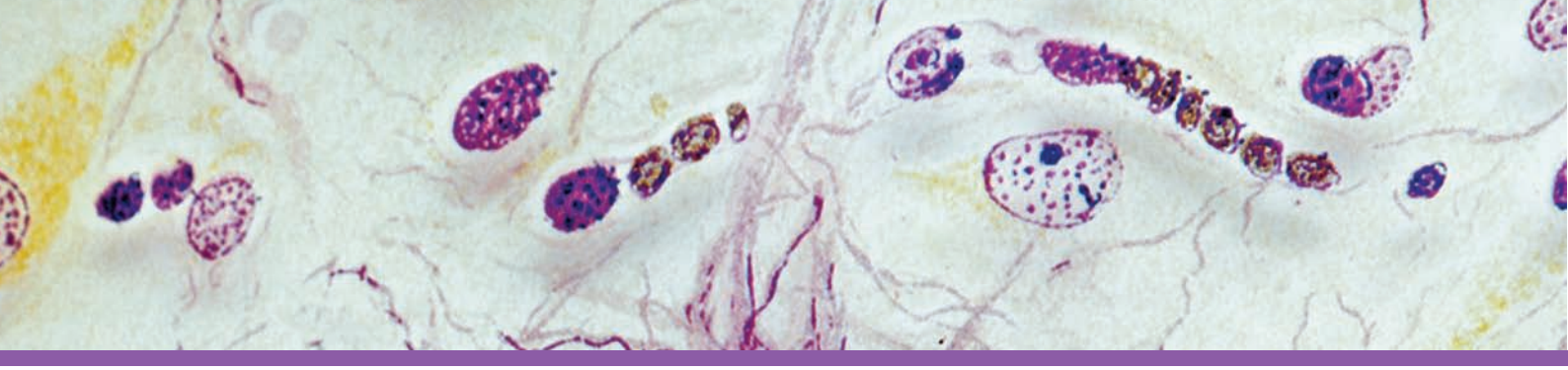
The scientific activity of UIPA is structured around four complementary research areas:

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

From the clinical aspect, Multidisciplinary Support Unit (UMA, for its acronym in Spanish) staff maintain daily contact with patients attending the Queen Sofia Foundation Alzheimer Center (CAFRS, for its acronym in Spanish) and with those people responsible for healthcare work of these patients. As described below, one of the UMA research lines involves conducting a clinical, syndromic and etiologic of patients staying at the CAFRS either in live-in regime (Life Units) or in day care (Day Center).

In addition, the set of clinical data obtained will be very useful for investigations of the rest of the UIPA scientific areas.

From the basic research side, UIPA's original project contemplated the creation of departments of Biochemistry, Molecular and Cell Biology; Pathology; and Neuroimaging. These three disciplines bring to-



gether the most promising areas in research on the biological processes involved in dementia.

UMA members are in continuous contact with these professionals, preparing and contrasting hypotheses, and developing research projects. Finally, UMA staff plays a mediating role between basic researchers and patients relatives and caregivers. This role is critical for patients, their relatives and caregivers knowing UIPA's research purpose, authorizing and collaborating with the research groups.

3.3. 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. It is imperative that various medical disciplines become involved, due to the need of following up further evolution, the particular treatment, the observation of complications, the application of countermeasures and the associated practice of healthcare resources.

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

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

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

3.3.1. Department activities

Among the various activities carried out within the UMA, unit personnel systematically perform a clinical, syndromic and etiologic diagnosis of patients who are in the CAFRS, either in live-in regime (Life Units) or day care (day center). To achieve this diagnosis, UMA staff together with the people responsible for healthcare tasks keep daily close contact with the patients coming to CAFRS.

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

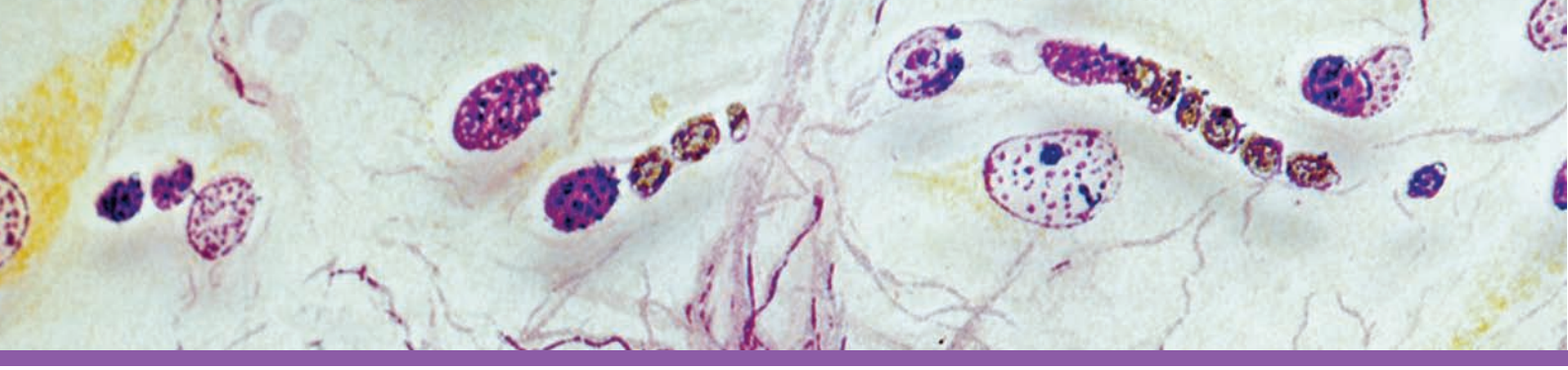
Reviews are conducted every six months, based on a rigorous protocol that enables continuous and sustained monitoring of each patient through checks of their quality of life, neurological status and their mental, affective and functional behavior. The objective of this process is to establish and collect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

Finally, UMA staff plays a mediating role between basic researchers, patients relatives and caregivers.

This role is critical for patients, their relatives and caregivers knowing UIPA's research purpose, authorizing and collaborating with the internal and external research lines.

During 2013 there were 32 admissions in the Day Center and Residence 20 of whom signed consent to participate in regular multidisciplinary evaluations.

PERIODIC MULTIDISCIPLINARY ASSESSMENTS IN 2013	
Admissions in Day Centre and Residence	32
Informed consents	20
Baseline Assessments	20
Clinical Evaluations	267
Brain Magnetic Resonance studies	56
Blood testing	267



Along with the 20 baseline assessments, a total of 267 clinical evaluations (every six months), 56 brain MRI studies (annually) and 265 blood tests were performed.

3.3.2. Diagnostic Guidance Unit

Dementia involves by definition the impairment of cognitive functions and thereby the loss of independence and functionality in performing basic activities of daily living. The progressive aging of the population in recent decades seems to indicate an increase of dementia worldwide. In this sense, the World Health Organization (WHO) is warning of the potential consequences of increasing population diagnosed with dementia and suggesting the need for governments to take measures to reduce the social and health impact of this devastating disease.

Alzheimer's disease (AD) is the leading cause of dementia in our midst. It is estimated that alone or in combination with cerebrovascular disease represents over 75% of the etiology of dementia, and at present its prevalence is estimated at around 7.3% of the population over 65 (Antón Jiménez M. 2010, Jellinger K.A. et al. 2010).

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

Usually, when suspicion of possible cognitive impairment arises, a screening including appropriate recollection of clinical history data and a general physical and neurological examination is applied, which serve to confirm the actual existence of a cognitive deficit. If determined that the patient has a general cognitive deficit intervenes then specialized personnel (usually neurologists and neurops-

ychologists) that study the patient in depth to determine the cause of the impairment, its magnitude and features.

A series of complementary tests (neuroimaging, blood test, etc.) are essential to identify the causal pathology and especially to rule out treatable causes. Finally, with all available information and applying internationally accepted clinical criteria, a presumptive diagnosis is issued, which carries the corresponding monitoring, treatment and prognosis.

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

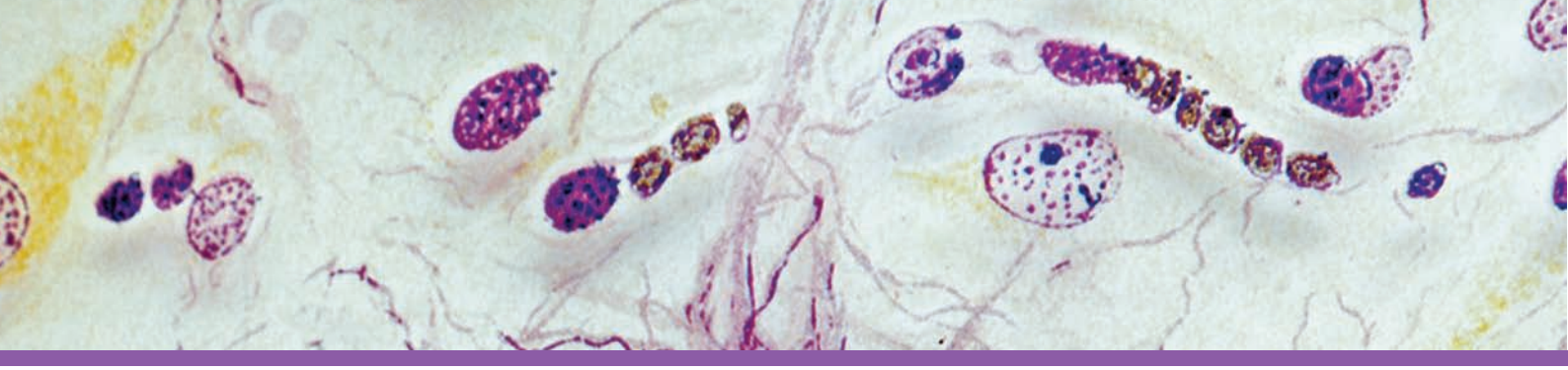
Why a Diagnostic Guidance Unit?

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

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

The establishment of the Diagnostic Guidance Unit within the Research Unit of the Queen Sofia Foundation Alzheimer Center (UIPA, for its acronym in Spanish), which is managed by the CIEN Foundation of the Carlos III Institute of Health and that has been funded by the Mutua Madrileña Foundation, bring the following benefits to users:

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



Research Unit of the Queen Sofia Foundation Alzheimer Center.

Composition of the Diagnostic Guidance Unit

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

- 1 neurologist and 1 neuropsychologist.
- A proportion of subjects studied (undetermined in principle) might require consultation with a psychiatrist, so that this professional consultation should be accessible.
- Department of Neuroimaging by Magnetic Resonance (3T-MRI).
- A nurse.
- Un administrativo para control de citas, informes, etc.
- Appropiate offices for consultations.
- IT equipment, test supplies, etc.

Protocol of Action

- **Neurology consultation**
  (in all cases).
  Thorough interview with the assessment applicant and relatives, stating the reason for consultation. Completing the detailed clinical history, including family history (with special attention to ancestors with dementia), past medical-surgical personal history and current medication. Performing a neurological examination.
- **Neuropsychology consultation**
  (in all cases).
  Collection of sociodemographic data.
  - Battery of cognitive tests and scales: Mini-Mental State Examination, Orientation Test (WMS-III), Clock Drawing Test, Visual Memory Subtest (7 minutes test), Digit Span (WMS-III), Brief Attention Test (BTA, for its acronym in Spanish), Phonological and Semantic Verbal Fluency (FAS and SET, for its acronyms in Spanish), Verbal Learning Test Spain-Complutense (TAVEC, for its acronym in Spanish), Logical Memory I - text A (WMS-III), Logical Memory I - text B (WMS-III), Trail Making Test (TMT), Go No-Go Task, Copying Figures in Perspective (PIEN-B), Imitation of Bilateral Postures (PIEN-B), Similarities-Abstraction (PIEN-B), Boston Naming Test-15, cambio de reglas BADS, Logical Memory II (WMS-III), Rey Complex Figure Test, Word Pairs (WMS-III), Word Pairs II and recognition (WMS-III), Series of Letters and Digits (WMS-III).
  - Test battery and behavioral scales: Anxiety and Depression Scale of Goldberg, Geriatric Depression Scale of Yesavage, Frontal Assessmente Batery (FAB), FAQ.
  - Functional evaluation: Hughes Clinical Dementia Rating Scale (CDR).
  - Diagnostic criteria: DSM IV, SEN and NINCDS-ADRDA standardized clinical criteria for dementia and cognitive impairment.
- **Psychiatry consultation**
  (as appropriate).
- **Neuroimaging studies**
  3T brain MRI (as appropriate).
- **Preparation of a detailed clinical report**
  (in all cases).
  Between June and September 2013, 423 applications for evaluation were received. A total of 160 had been attended by year end. All cases were treated by a neurologist and a neuropsychologist and all were provided with the appropriate clinical report. The CIEN Foundation supports the use of new technologies in the prevention, diagnosis, prognosis, treatment and monitoring of neurodegenerative diseases. To this end, several research projects have been carried out during 2013.

3.3.3. Project "Robot therapy in dementia"

The project for **Robot therapy in dementia** began in 2009 and during this time has compared two innovative non-pharmacological therapies: the use of animals and the use of robots.

In recent decades there have been studies of therapy using animals to evaluate its impact on social behavior, agitation and aggression in patients with dementia.

The obtained results have shown improved social behavior in patients during the presence of the animal, a decrease in verbal aggression and agitation as well as an increase in the frequency of physical and eye contact and smiles. However, it is not always possible to provide animal therapy due to several obstacles in their use.

In recent years, several projects have been initiated based on the therapeutic use of social robots (as reasonable substitutes for animals) in the therapy of persons suffering from dementia. Most elderly people like the robots and their presence leads to increased communication, decreased sense of loneliness and mood enhancement.

Thanks to the collaboration of patients and their relatives in the residence and the day center the third phase of the clinical trial has been carried out, aimed at comparing two innovative therapies (with social robots and animal therapy) versus the standard therapy, in relation to:

- Behavioral changes
- Apathy of the participants
- Quality of life

The social robot used in this phase of the study was a baby seal robot. On the other hand, a specifically trained dog was used for testing the animal therapy, who has been provided altruistically by two animal-assisted therapy associations: **Hydra Association** and **Bocalán Foundation**.

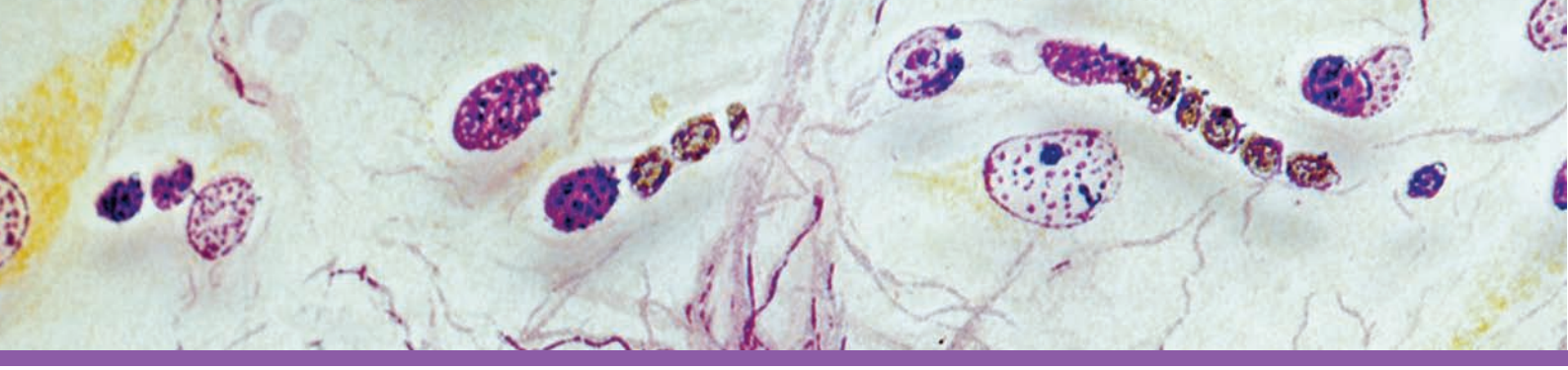
Both groups participated in the training sessions with occupational therapists and physiotherapists for the use of trained and oversaw each animal therapy session.
The results of this study will be presented in the coming months.

3.3.4. Project REGISTRY

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

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

The strength of the REGISTRY study lies in its collaborative nature. We can all participate: subjects with genetic mutation and symptoms, subjects with the genetic mutation without symptoms, subjects descended from a family with a history but they ignore whether they have the mutation, subjects descended from a family with a history but have a negative genetic study, subjects who are not descended from a family with affected people... Starting from



the information gathered, a large database of biological and clinical data (blood and urine) will be created to enable:

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

REGISTRY is been carried out 173 centers of 20 European countries and has already registered more than 12,000 subjects. Among these centers is the CIEN Foundation, where 33 participants were registered during 2013.

In 2014, REGISTRY will make way for ENROLL-HD, a prospective registry study of a HD global cohort (Europe, USA, Canada, Argentina, Chile and others).

3.3.5. Project MADRID+CIEN: Pilot longitudinal study on a cohort of centenarians in the Region of Madrid

In developed countries, the progressive increase in life expectancy and low birth rates are causing an accelerated growth rate in elderly people. This growth is particularly fast in the segment of the very old ("oldest old" in English literature; nonagenarians and centenarians).

The increase in life expectancy has as its counterpart an increase in age-associated disorders. Among them dementia, especially Alzheimer's disease (AD), which is a particularly serious disorder to the extent that not only causes progressive and irreversible deterioration of mental faculties and brings about severe behavior disorders, but also is the leading cause of dependence in our country due to the direct and indirect economic costs involved.

While there is a certain agreement between the prevalence rates of dementia in older people aged 65-85 years, notable discrepancies exist between existing data from 90 onwards. Likewise, it is equally difficult to define the criteria for cognitive and neuropathological normality beyond 90 years of age. Longitudinal studies conducted so far with very old people are very scarce and have not allowed even to define the morphological substrate of the preservation of cognitive level in the very elderly.

Therefore, prospective longitudinal studies are needed to identify those cognitive and functional aspects that function as protective or risk factors associated with dementia in this population group, and in this regard has been designed MADRID + CIEN project.

The main objective of this project is to create a cohort of centenarians subjects without cognitive impairment in order to configure their social, cultural, educational, nutritional, functional, clinical and neuropsychological profile.

From the data obtained will be possible to: a) determine the prevalence of cognitive impairment in this population and get the conversion rate to dementia during the study period; b) validate a protocol for neuropsychological assessment and obtain normative data for this population group; c) study the frequency and behavior of certain genetic polymorphisms in non-demented centenarians; d) know the pattern of Alzheimer's pathology in the population ≥100 years and its correlation with cognitive sta-

tus and other antemortem neurological and molecular variables.

The project will be implemented within the area of the Region of Madrid, in Dependent Residential Homes dependent on the Council of Social Affairs of the Madrid Region.

The proposed study follows a descriptive, observational, longitudinal and prospective design. Clinical and neuropsychological assessments of the participants, as well as telephone follow-ups, will be held annually during the three years of study. The genetic study will be made from sampling of peripheral blood or mucosa of the oral cavity on the first visit. A post-mortem neuropathological study can also be performed in those cases in which participants have voluntarily donated his brain to the Tissue Bank CIEN. This project will be launched in 2014 and will have the support of the Directorate General of the Elderly (Council of Social Affairs of the Madrid Region).

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

Alzheimer's disease is the most prevalent form of dementia in our environment. However, both neuroimaging and postmortem analysis of brain tissue have shown that quite often the Alzheimer's pathology is associated with concomitant vascular injury.

Thus, it is now beginning to think that cognitive decline in patients with dementia may be a direct consequence of both types of pathology. This hypothesis is particularly interesting to the extent that if we were able to identify specific cognitive profiles for Alzheimer's disease and vascular disease, both diagnosis and intervention with these patients would improve.

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

With that idea, a study to jointly apply neuropathological criteria for Alzheimer's disease and vascular pathology was launched in 2013.

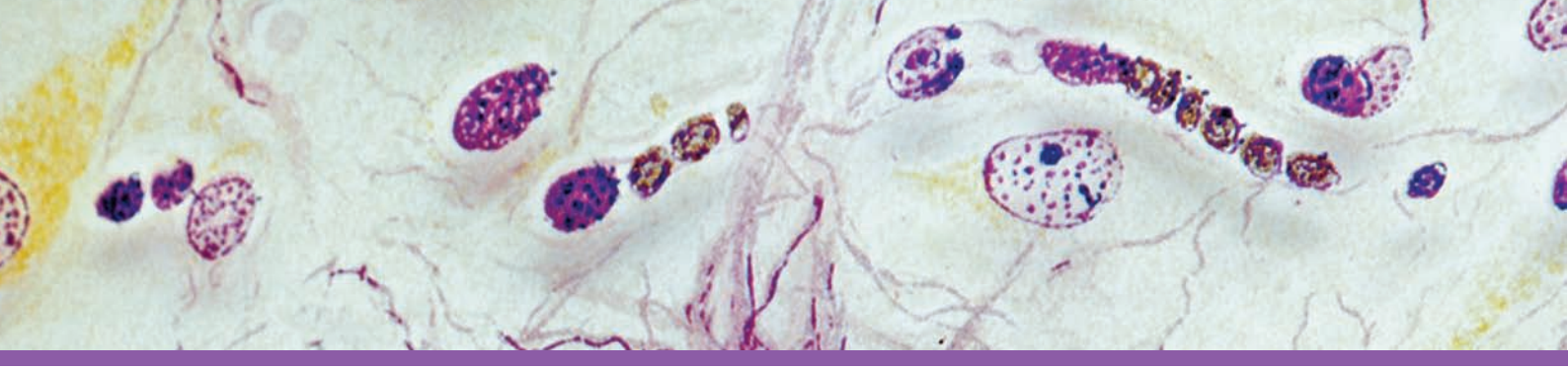
The combination of both approaches has allowed to classify a cohort of residents in our center with advanced dementia (58% exclusively with Alzheimer's disease, 12% with vascular dementia and 28% with mixed dementia). Furthermore, we have studied the relationship between diagnosis and a series of cognitive and motor tests.

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

3.3.7. Pilot study of assisted cognitive therapy with electronic tablets and robots to patients with dementia

At present, the use of mobile devices such as smartphones and electronic tablets is found increasingly diversified in many areas of daily life. One such areas is education and cognitive stimulation.

That is why, together with the Department of Telematic Systems and Computing at the King Juan Car-



los University, the CIEN Foundation and the Queen Sofia Foundation Alzheimer Center are designing applications for electronic tablets so that these applications can provide support to patients, therapists, and geriatricians in the treatment and monitoring of people with dementia

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

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

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

3.3.9. Analysis of oral health, chewing ability and oral quality of life in patients with neurodegenerative disorder. Alzheimer's disease

Oral health can be defined as the absence of chronic orofacial pain, oral and throat cancer, oral sores, birth defects such as cleft lip or cleft palate, periodontal disease (gum disease), tooth decay and tooth loss, as well as other diseases and disorders that affect the mouth and oral cavity (Mathers et al., 2003).

The most common oral diseases are dental caries and periodontal diseases. But severe periodontal disease, which can lead to tooth loss, affects to 5-20% of middle-aged adults; the incidence varies by geographic region (Mathers et al., 2003).

This state of health and disease is measured through a series of indices among which we highlight the following:

- DMFT: Describe the prevalence of caries.
- CPI: Describe the periodontal status.
- ADOH: Measures oral hygiene.
- Leake: Examines chewing ability.
- OHIP: Shows the quality of life related to oral health.

The relationship between neurological disease and oral health status is well established.

Examples of these are: cognitive and/or motor deficits can disable the individual to have a proper daily hygiene by either forgetfulness or motor inability to operate tools of daily hygiene; and many drugs used can alter the state of oral health by causing xerostomia (dry mouth) that induces increased proliferation of bacterial plaque and in turn can lead to tooth decay, periodontal disease and gingival hyperplasia.

But the disease signs and symptoms themselves can also contribute to a great extent to diminish the oral health status such as the difficulty in swallowing (dysphagia) that appears on conditions such as Alzheimer's disease and/or Parkinson's.

However, there is a great void in the literature concerning oral health in patients with neurological disorders, and very few articles deal with the subject. That is why this study, 'Analysis of oral health, chewing ability and oral quality of life in patients with neurodegenerative diseases: Alzheimer's disease and Parkinson's disease', aims to clarify some relationships between neurodegenerative diseases such as Alzheimer's and Parkinson's and the oral health

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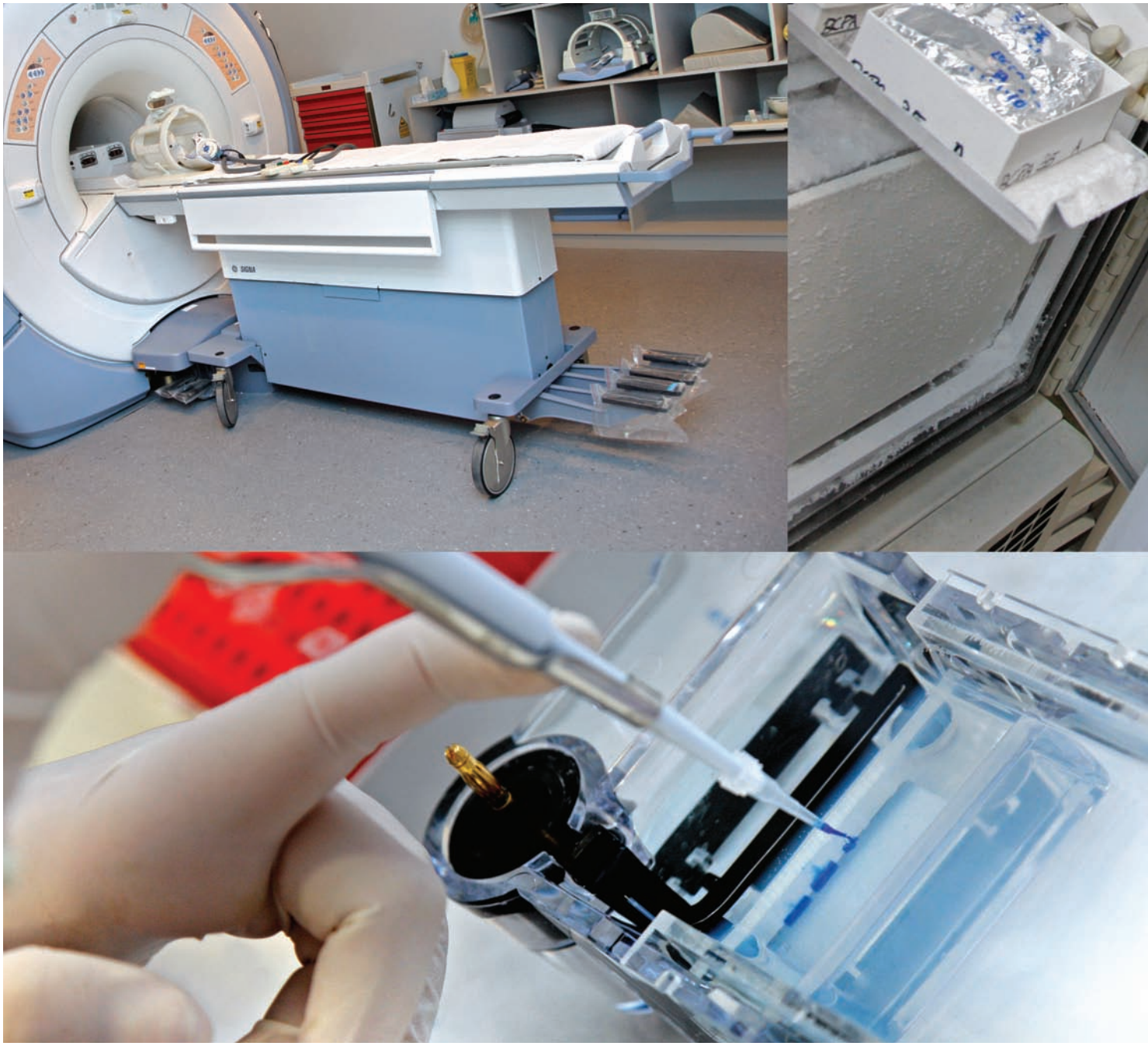
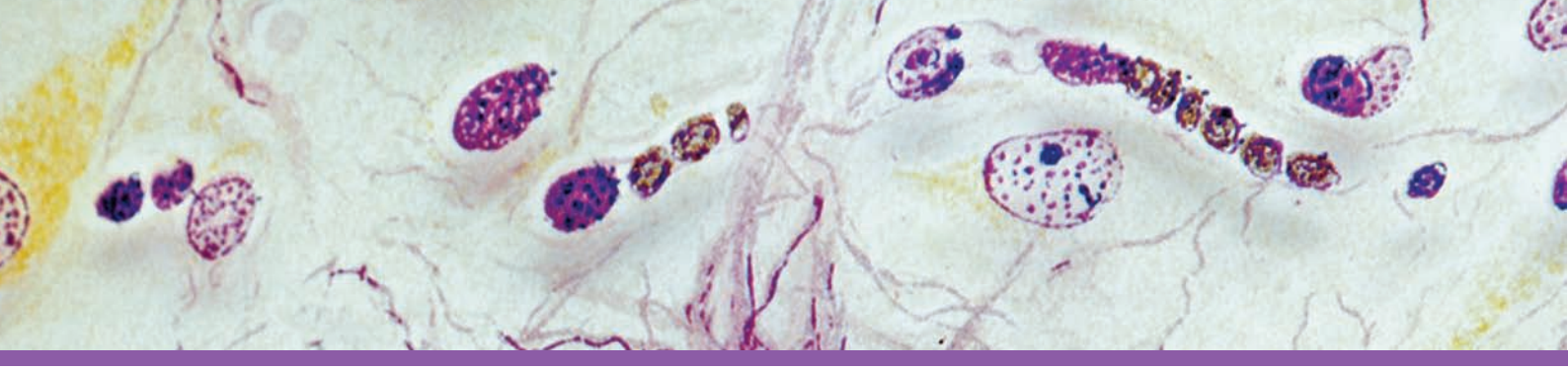




status of patients, including the state of oral health through different internationally used dental indices.

Results of the study will be presented throughout the year in national and international fora and published in scientific literature.

3.3.10. 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)
- 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)

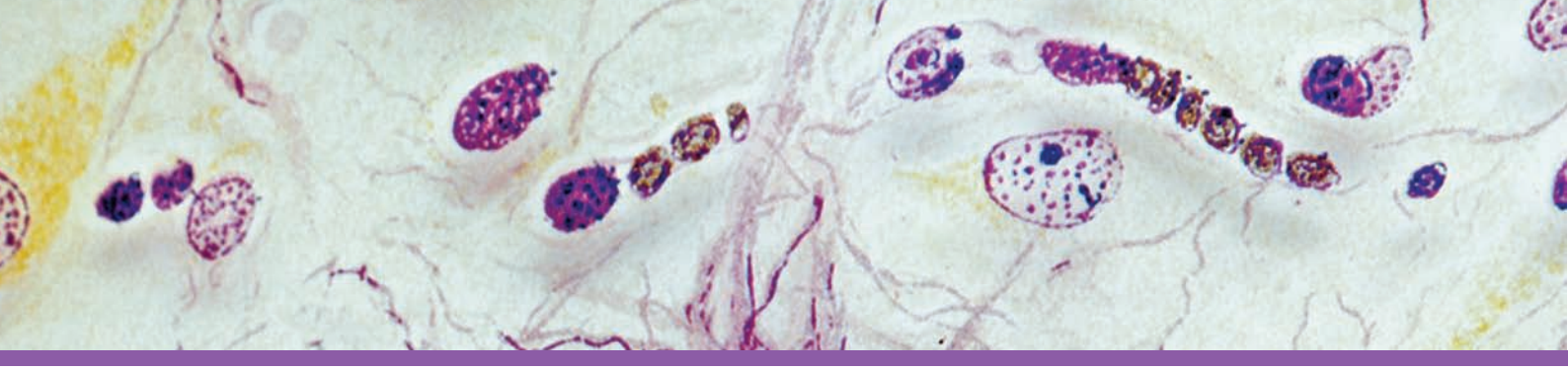
Collaborators

The following CAFRS staff also collaborated during 2013:

- Irene Rodríguez Pérez (Occupational therapist)
- Almudena Pérez (Occupational therapist)
- Laura Carrasco Chillón (Occupational therapist)
- Cynthia Pérez Muñano (Technician in training and Occupational therapist)
- Emma Osa Ruiz (Physiotherapist)
- Vanesa Herrero Cano (Physiotherapist). Until April 2013
- Silvia Felipe Ruiz (Physiotherapist). Since April 2013
- Ester Huélamo Sáez (Physiotherapist)
- Carolina Mendoza Rebolledo (Grad. Psychology, Neuropsychology)
- Gema Melcón Borrego (Social worker)
- Raquel Díaz Rodríguez (Social worker). Until April 2013
- Lidia Espada Raboso (Social worker). Since April 2013
- Belén González Lahera (Grad. Medicine, Geriatrics)

3. SCIENTIFIC ACTIVITY

UMA Team



3.4. Department of Neuroimaging

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

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

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

The main objectives Department of Neuroimaging are:

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

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 2013 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, Nº 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 2013 the acquisition of MR images from a total of 1,329 subjects has been completed. Overall, 9,146 MRI studies have been performed since the establishment of the department among the different research projects.

Since the establishment of the department 7,839 MRI studies have been performed, distributed by year and type of study as shown in the Figure below.

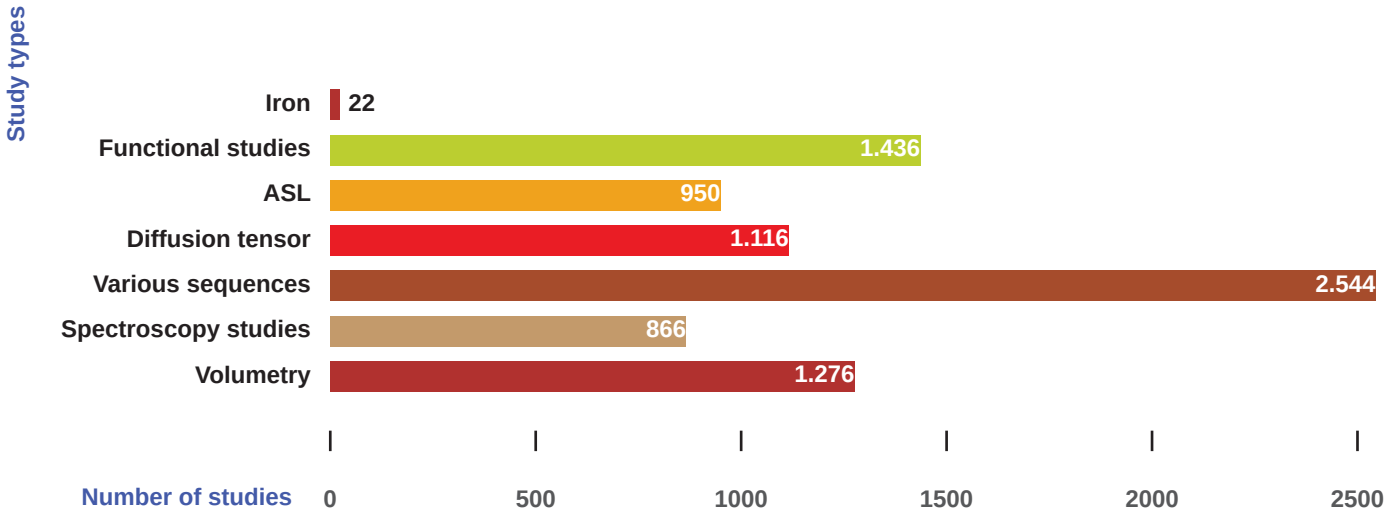
3.4.2. Provision of services

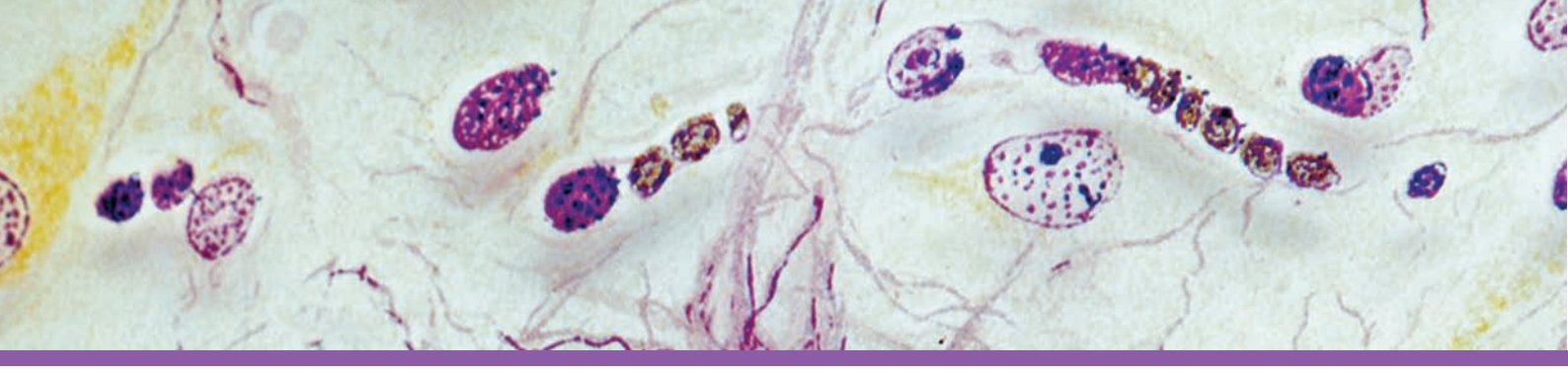
The Department of Neuroimaging has a 3T MR scanner (GEHC, HDxt) system equipped with dual gradient system of up to 50mt/m, 3 antennas for brain studies (transmitter/receiver quadrature antenna, receiving 8 channels antenna and 16 channels receiving antenna) and small antennas for rats and mice. Data 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 de-

Classification of studies performed in 2013



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veloped 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

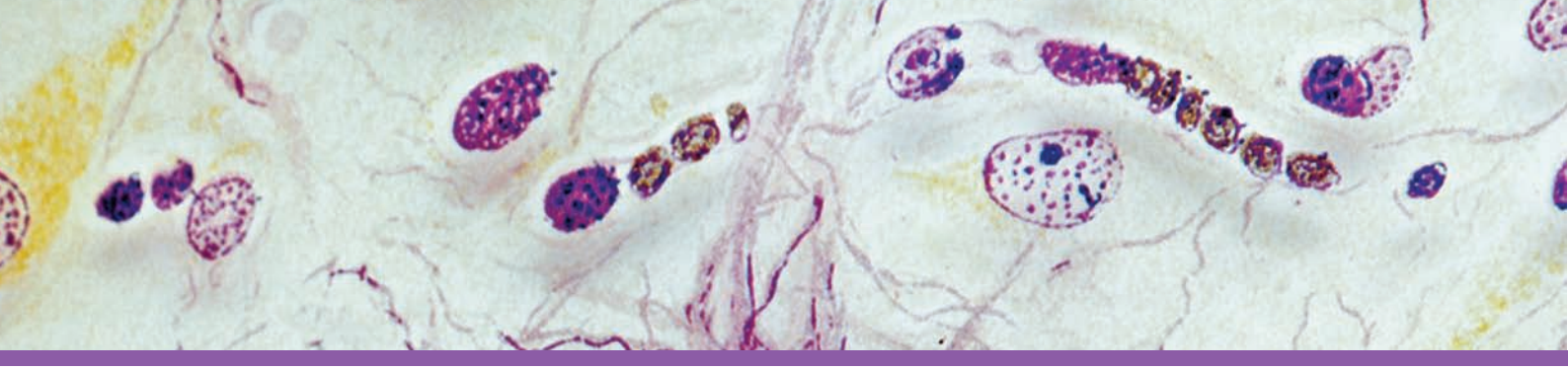
Perfusion sequence acquisition with the Arterial Spin Labeling (ASL) technique with whole brain coverage and resolution from 4x4x4mm to 2x2x2mm in 3D mode.

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, mid-brain, 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.

Image 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).

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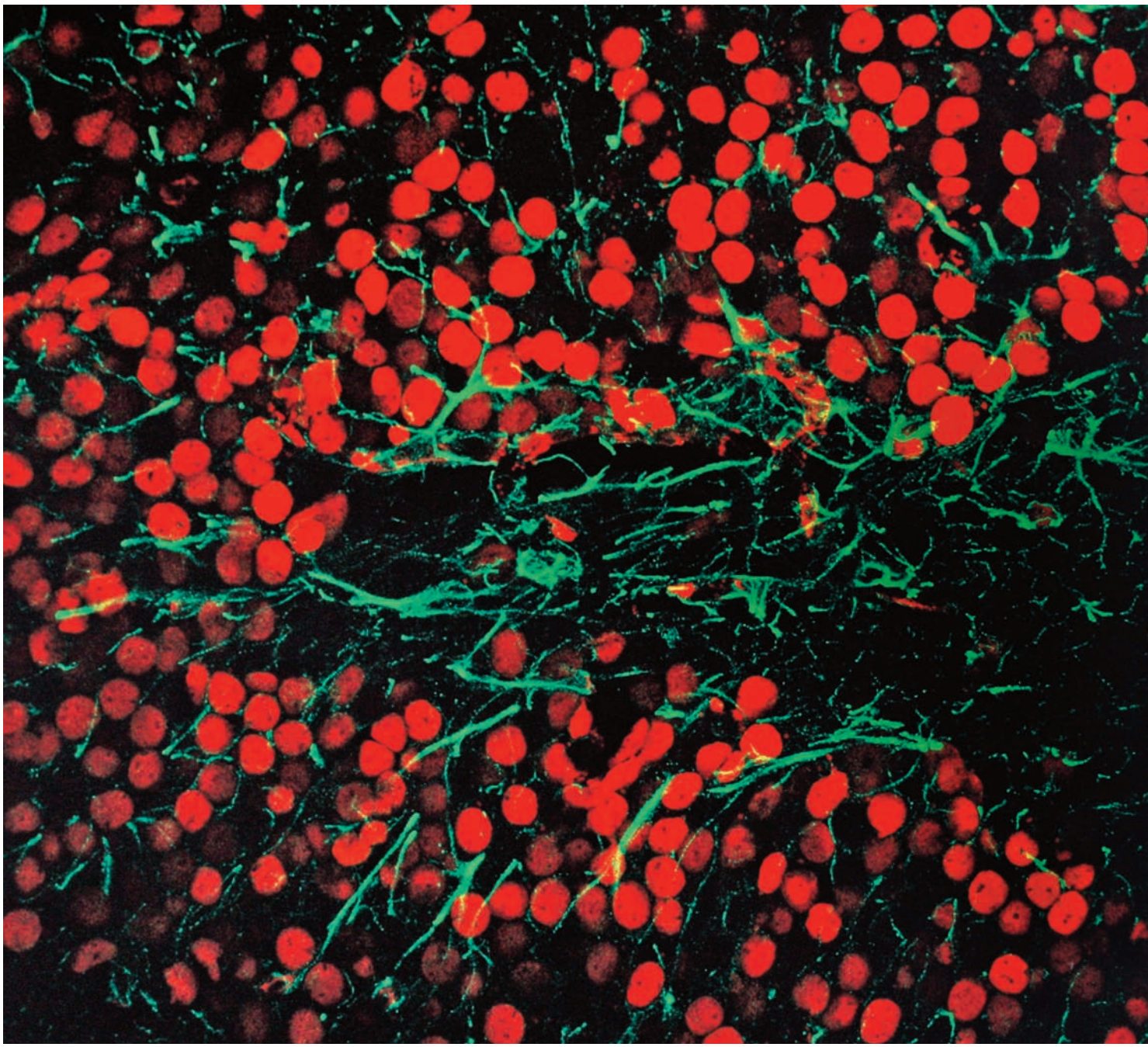
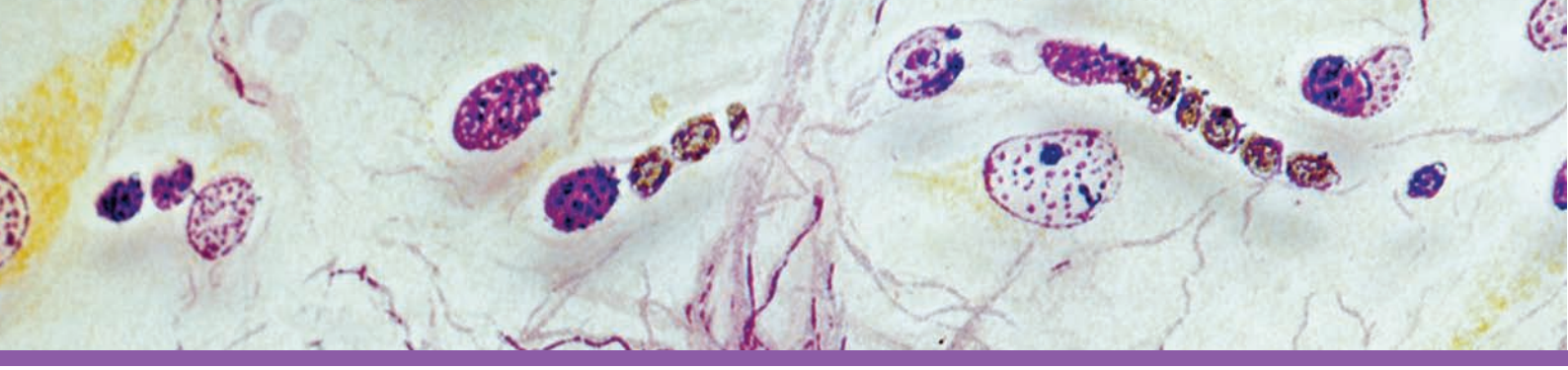




3.4.3. Team

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 García (Telecommunications Advanced Technical Engineer)
- Virginia Mato Abad (Dr. Computer Engineer)
- Gonzalo Pajares Giménez (Telecommunications Advanced Technical Engineer)
- Ana Beatriz Solana Sánchez (Telecommunications Advanced Technical Engineer)
- Daniel García Frank (IT Engineer)
- José Ángel Pineda (Telecommunications Engineer)
- Ángel Torrado (Telecommunications Engineer)
- Eva Manzanero Sáenz (Telecommunications Engineer)

Functional Imaging Section

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

Imaging and Cognition Section

- Roberto Colom Marañón (Dr. Psychology)

Difussion Section

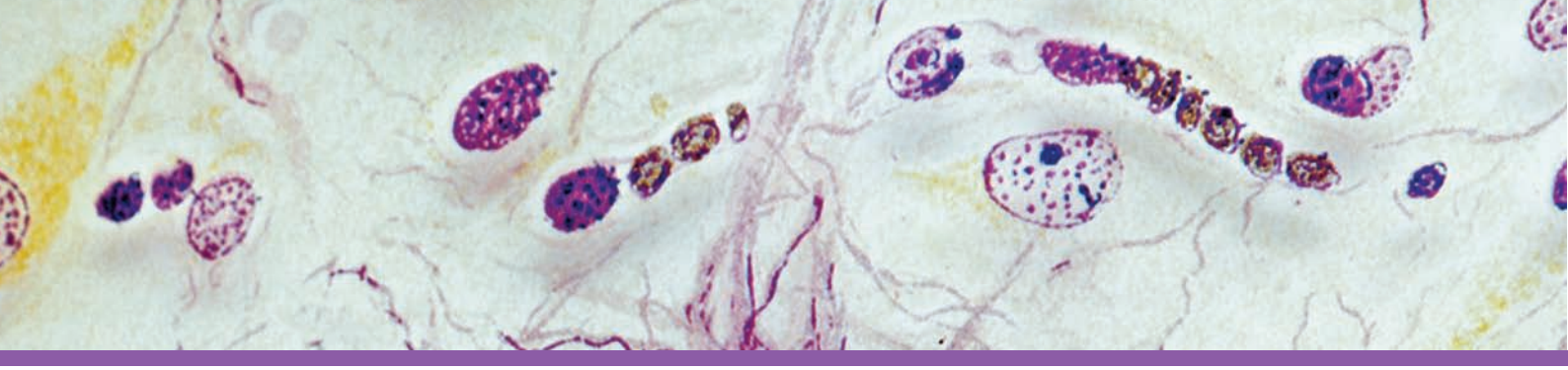
- Julián Benito (Dr. Medicine, Neurology)

Administration

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

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, research-wise their work goes beyond that and provides essential information about the molecular components of the characteristic lesions, the pathogenic mechanisms of the disease, and potential biomarkers, specially in the field of neurodegenerative diseases.

The neuropathology of dementia landscape has dramatically changed in recent years. The incorporation to the neuropathological diagnosis of new antibodies for immunostaining and new molecular techniques has helped establishing the boundaries and internal heterogeneity of entities such as dementia with Lewy bodies and frontotemporal dementia, and has also led to the discovery of new entities in this area (DFT-TDP. DFT-FUS, etc.).

Also, the definition of diagnostic criteria from large series of brains has allowed to address the problem of combined and mixed pathology, specifically regarding Alzheimer's disease. The evolution of the diagnostic criteria (eg, new diagnostic classification criteria for Alzheimer patients, National Institute of Aging, 2012) and molecular techniques are turning the histological diagnosis in a critical element in the process of classifying dementia, definite or quasi-definite in some cases, but partial or probabilistic in many others.

As demonstrated by the clinicopathological sessions, the final classification of a case requires integration of all clinical, neuroradiological, neuropathological and molecular, when available.

A need for research in dementia is the provision of brain tissue perfectly diagnosed, classified and 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 natural models of disease.

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:

- Neuropathological and molecular study of tauopathy in Alzheimer's disease and other tauopathies affecting the limbic brain regions (i.e. argyrophilic grain disease).
- Distinctive features of Alzheimer-type pathology in nonagenarians and centenarians.
- Characterization and pathogenic study of dementia-associated hippocampal sclerosis.
- Neuropathology of language in degenerative dementias.
- Advance age-associated brain pathology in other animal species

3.5.2. Provision of services

The range of activities undertaken by the department derives from the ability of its members to co-

llect, process, evaluate and diagnose brain tissue sample from human or animal origin.

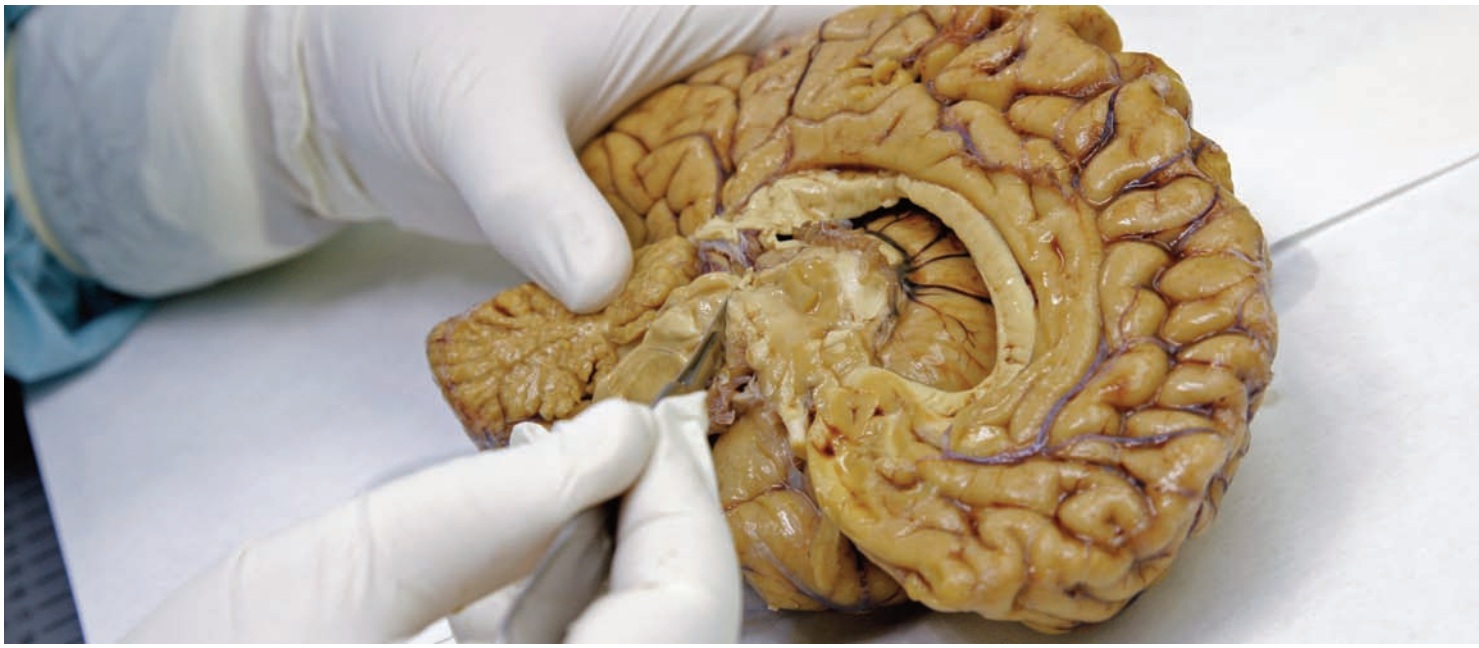
- Neuropathological autopsies of donors brain tissue, from both the Region of Madrid, as neighboring Regions.
- Management of a biobank of neurological samples. Transfer of samples to researchers according to the BT-CIEN standard operating protocols.
- Diagnostic consultations of neuropathological cases. 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

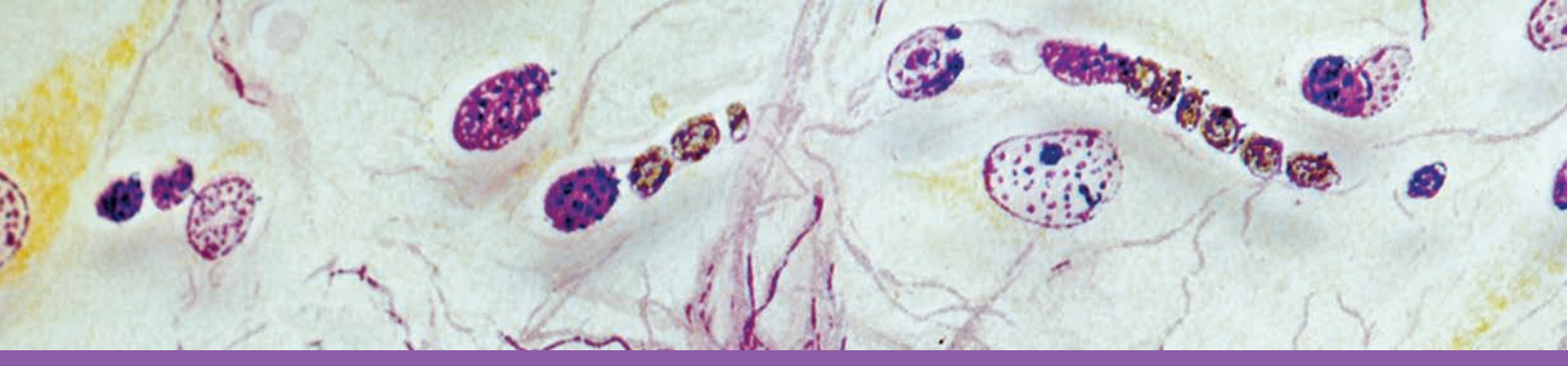
3.5.3. CIEN Foundation Tissue Bank (BT-CIEN)

Since its opening in May 2010, the CIEN Foundation Tissue Bank (BT-CIEN) has traveled a path of growth and consolidation in the field of Spanish Neuroscience, supporting national and international research groups and maintaining close contact with neurological disease patients and relatives associations.

The number of registered donors in the BT-CIEN registry has continued to grow every year, as has the tissue donations made at our Center within our Internal Donation Program, 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.

Throughout 2013, the BT-CIEN has renewed its ISO 9001 certification and has been accredited by the Council of Health of the Region of Madrid as biobank, according to the requirements established in the Royal Decree 1716/2011 which regulates the operation of such research structures. Consequently, the BT-CIEN has been included in the National Register of Biobanks. Adapting to this new regulatory framework and the progressive extension of the brain bank activity throughout the national territory as a network are the major challenges for the BT-CIEN in the foreseeable future.

The BT-CIEN registry had over 600 registered donors by December 31, 2013. 75 new donors were enrolled during 2013. 103 cases were processed in the Neuropathology laboratory during 2013, with the following wing distribution depending on the origin:

- 48 donations from the External Program.
- 8 donations from the Internal Program
- 47 consultation cases

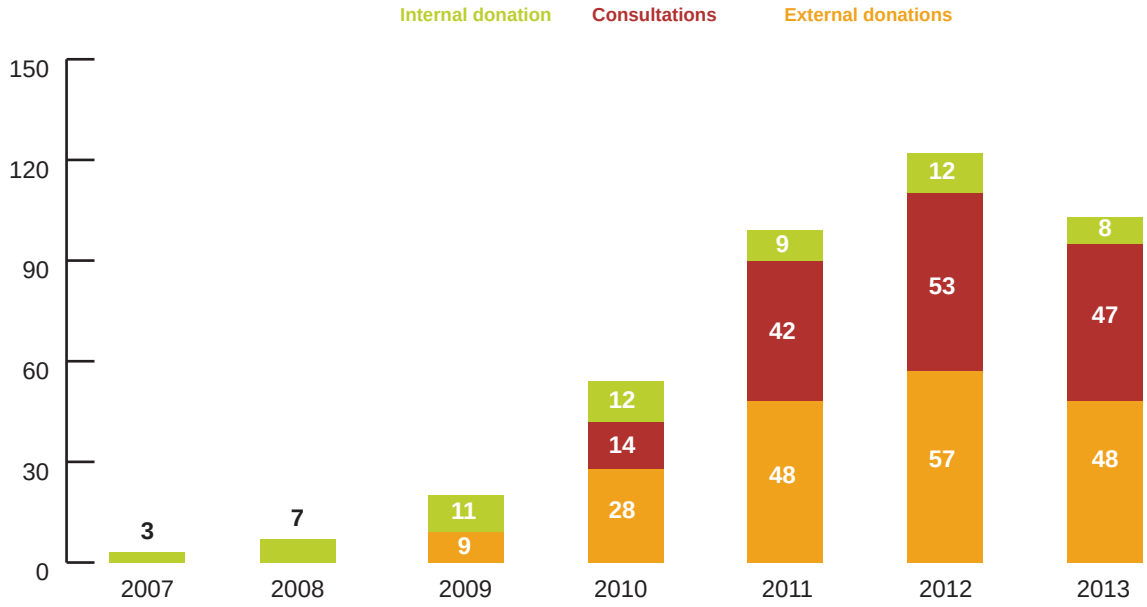
Hence, the number of donation cases extracted and processed entirely at the UIPA during 2013 went up to 56. It is thus observed a stabilization of the number of studied cases at the BT-CIEN in the range of 100-120 annually, and donations drawn in the BT-CIEN in the range of 50-70 per year.

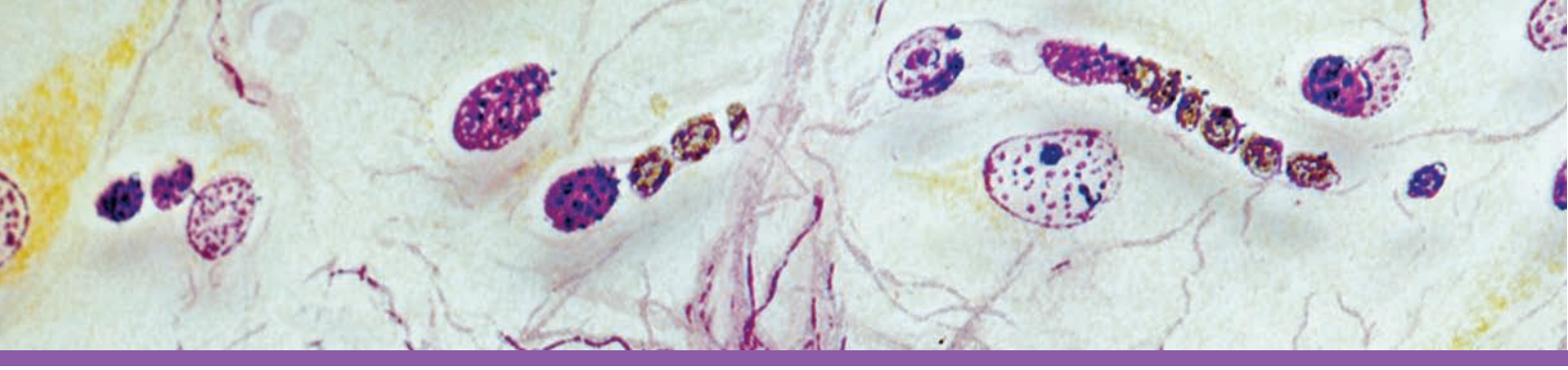
The graph below shows the evolution of the various types of studies during the last few years (orange: external donations; red: consultations cases; green: internal donations).

In 2013 the average post-mortem interval obtained is 5.6 hours, in line with the average of previous years. The Research Centers that have received samples from BT-CIEN during 2013 have been:

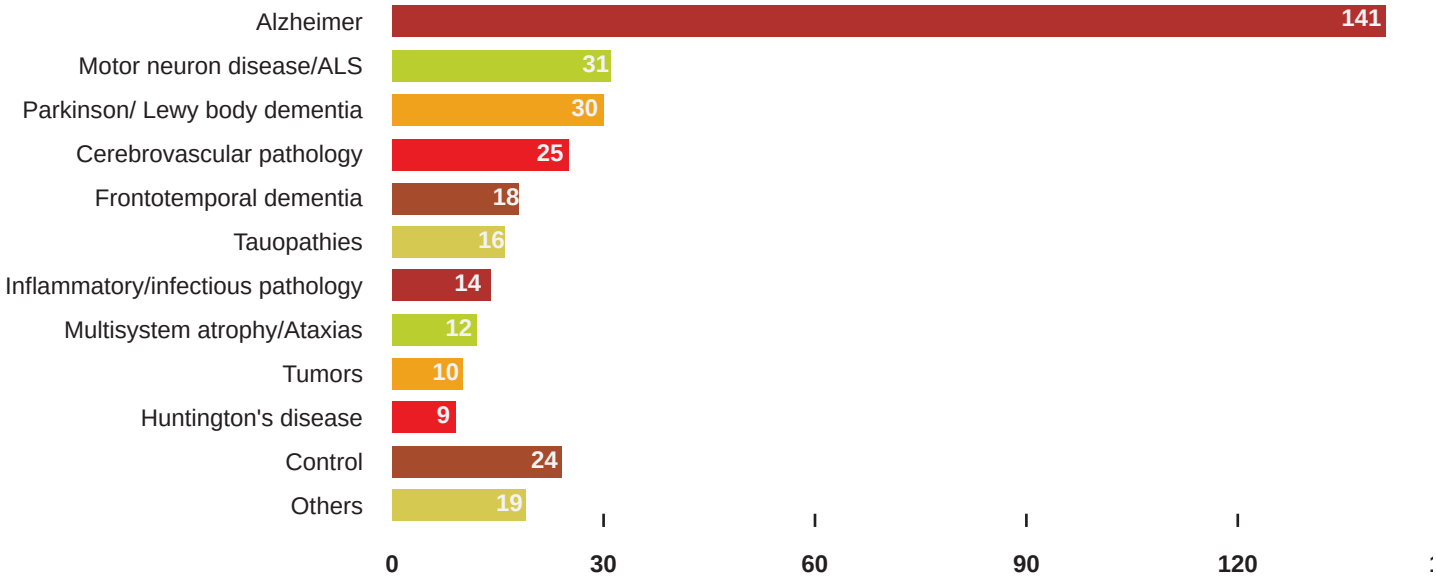
- Center for Molecular Biology "Severo Ochoa", CSIC, Madrid (3 research groups)
- Faculty of Medicine, University of Seville
- Faculty of Medicine, University of Castilla –La Mancha
- Institute of Applied Ophtalmobiology, Valladolid
- Cajal Institute, CSIC, Madrid
- Center of Biomedical Technology (Madrid)Tavhnical University
- Institute of Neuroscience, CSIC, Miguel

Distribution of donation cases by origin in 2013





Distribution of cases by pathology during 2013



Hernández University, Alicante
- Center for Molecular Biology and Neuroscience, Oslo University, Norway
- Royal College of Surgeons, Ireland
- Institute for Health Research I+12
- Institute for Health Research Jiménez Díaz Foundation
- Center for Biomedical Research, CSIC, Madrid
- National Center of Microbiology, ISCIII, Madrid
- Faculty of Medicine, University of Valencia

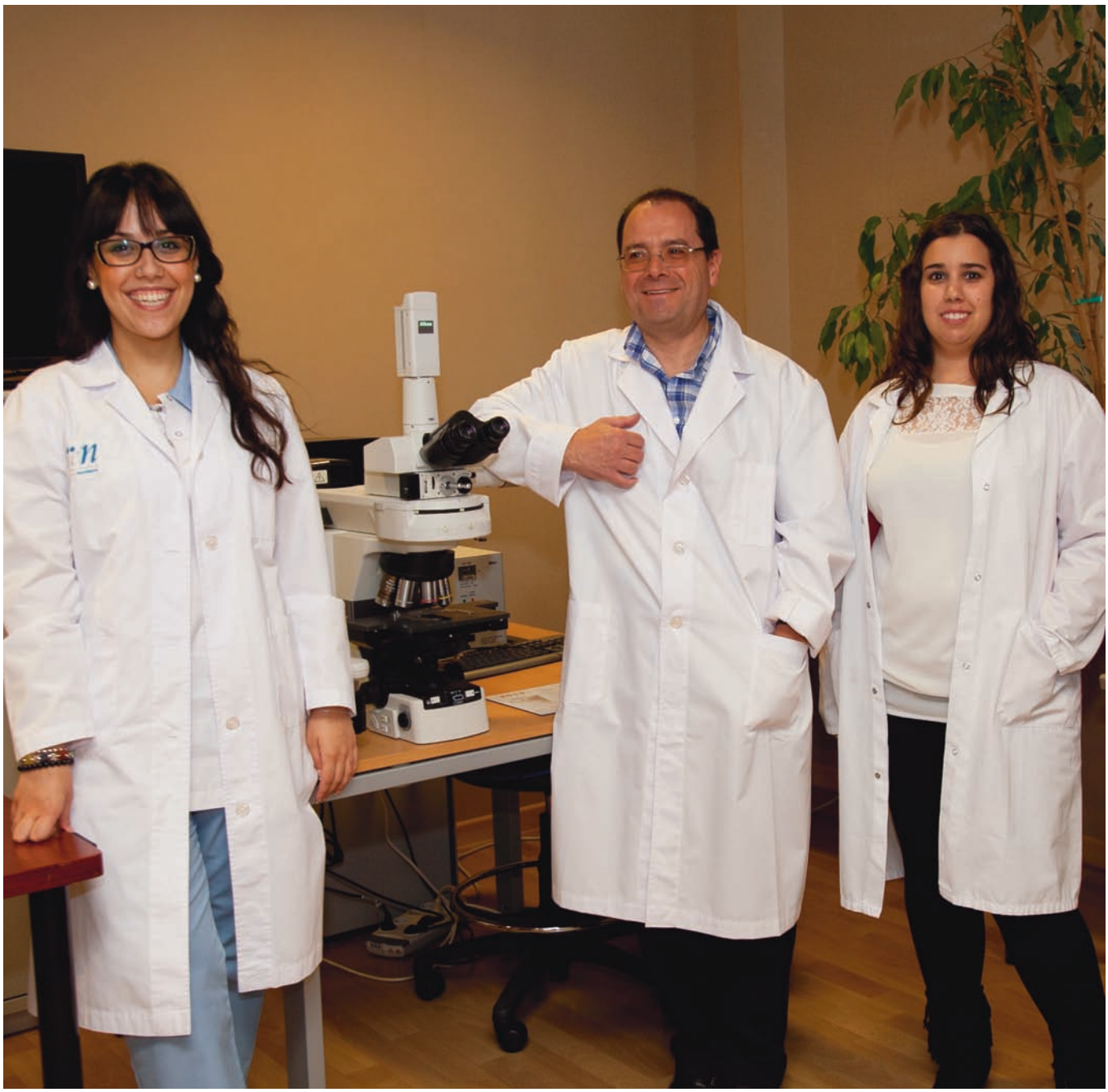
Graph shows the BT-CIEN filed cases breakdown by pathology by the end of 2013.

3.5.4. Team

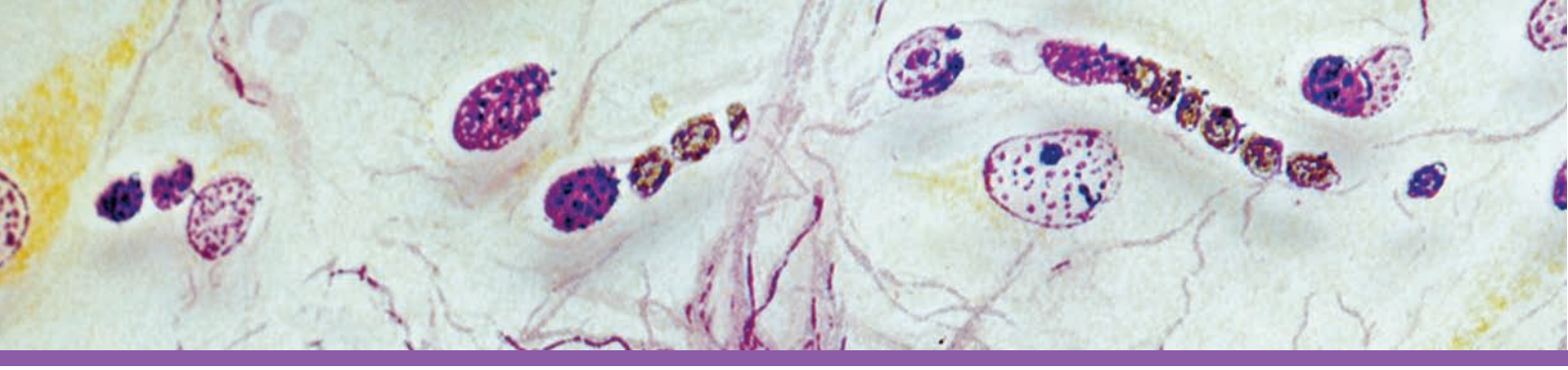
During 2013, the Department of Neuropathology staff was composed of the following professionals:

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

3. SCIENTIFIC ACTIVITY



Neuropathology Team



3.6. Department of Laboratory

From a neuropathological point of view, Alzheimer's disease (AD) is a neurodegenerative disease that affects specific areas of the brain, altering the circuits involved in the catecholaminergic, serotonergic and cholinergic transmission. AD pathophysiology includes the presence of neuritic amyloid plaques, neurofibrillary tangles, neuronal loss and neurochemical abnormalities.

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

- Neurofibrillary tangles (NFT) are intraneuronal bodies composed of paired and helically wound filaments (paired helical filaments, PHF) of a hyperphosphorylated form of the microtubule-associated protein, tau. The NFT appear in many of the dystrophic neurons around amyloid plaques. Currently, many researchers believe that both the development of amyloid plaques and NFT formation represent relatively late events in the progression of the disease, which may or may not reflect the fundamental biochemical-molecular dysfunctions that trigger the disease. Currently, there are no standardized diagnostic tests that can be applied in routine clinical practice to reliably diagnose Alzheimer's disease. The diagnosis is based on clinical criteria that allow an approximation diagnosis of "probability", after ruling out other causes. The accurate diagnosis of the disease is only achieved in 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. This study has the following primary objectives: to gain further insight into the molecular basis of the disease and to develop predictive algorithms that combine information on genetic, biochemical and neuroimaging markers with diagnostic, prognostic or responsive to disease-modifying therapies markers.

For this purpose, the Department's research is connected with the activities of the Multidisciplinary Support Unit, and the Departments of Neuroimaging, Neuropathology and BT-CIEN on the two main research projects in the CIEN Foundation and Queen Sofia Foundation: the Alzheimer project and the Vallecas project.

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

The **Alzheimer Project** (PA, for its acronym in Spanish) focuses on regular and protocolized monitoring of a cohort of CAFRS patients with dementia, ether as residents at the Center or attendants at the Day Center, with the main objective of investigating the final stages of Alzheimer's disease.

Patients are recruited into the monitoring program after signing an Informed Consent (IC) by a family member or guardian. The PCA program consists of i) a biannual clinical and neuropsychological as-

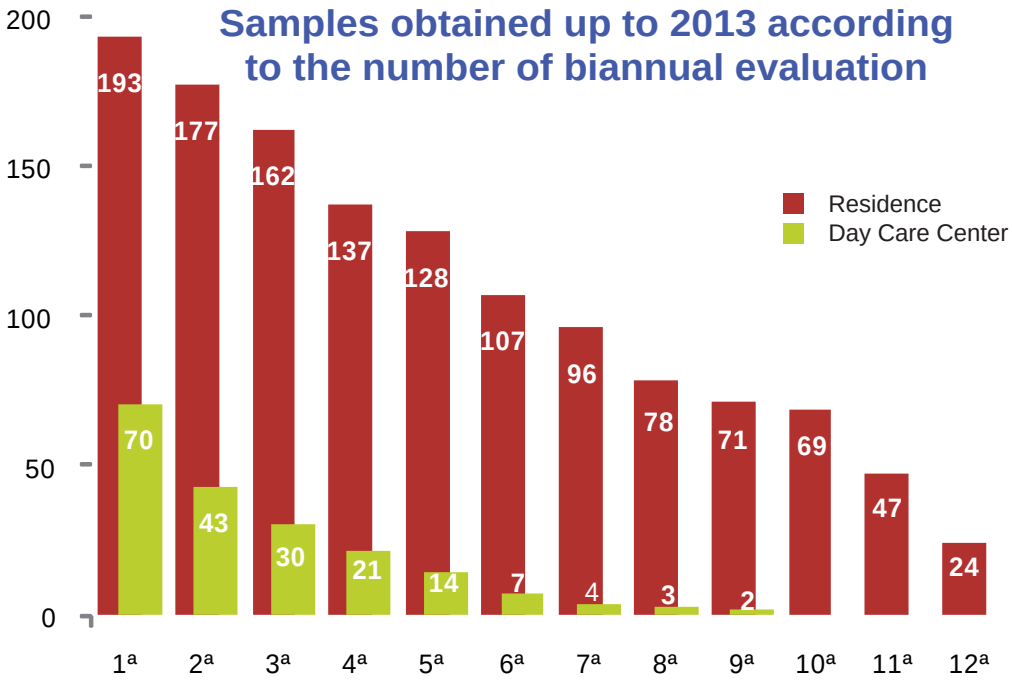
sessment by the Multidisciplinary Support Unit (UMA. for its acronym in Spanish), ii) a biannual sampling blood, coinciding with the usual one taken at the residence, iii) conducting an annual cranial MRI if the patient's condition permits, and iv) donation of brain tissue after death of patient.

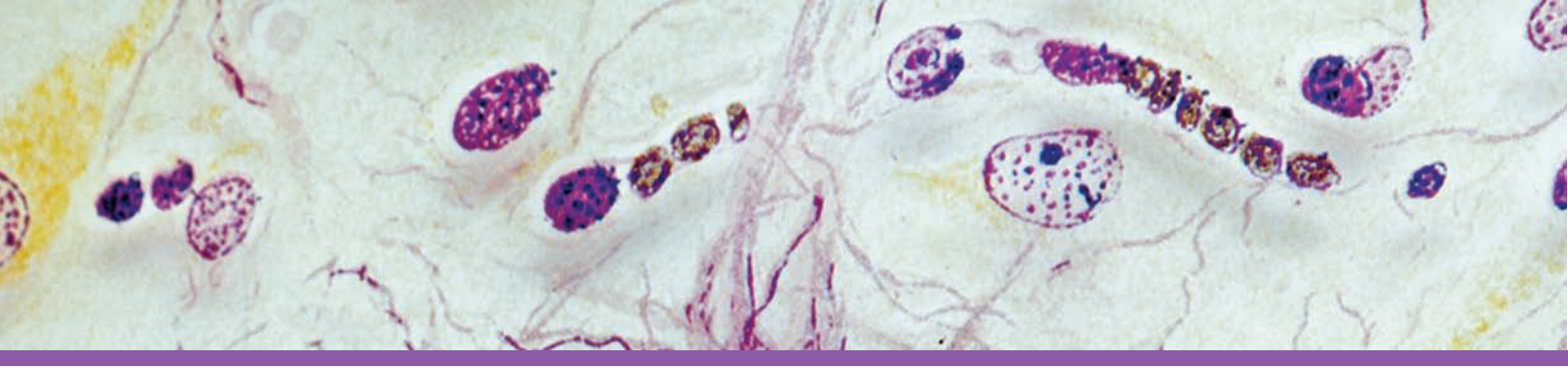
The CAFRS takes care of 156 patients in residence, and 40 patients in the Day Centre. The Alzheimer project monitoring program includes obtaining a blood sample biannually coinciding with the one routinely performed at the Center for conventional analytics.

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

Aliquots obtained from blood samples are incorporated into the CIEN Tissue Bank (BT-CIEN, for its acronym in Spanish) collection according to the protocols of the biobank. The total number of samples incorporated to the BT-CIEN so far, corresponding to the Alzheimer project monitoring program, adds up to 1,483 (13.1% patients corresponding to the Day Centre), which have resulted in a total of 20,762 aliquots.

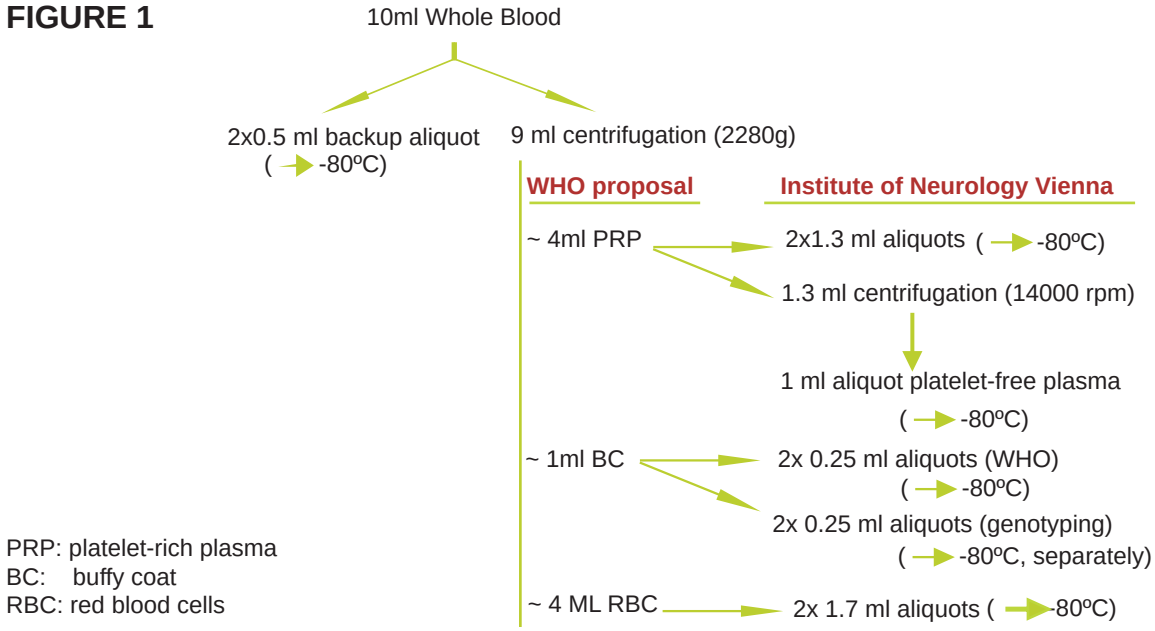
Consistent with other studies, the analysis of the APOE gene polymorphism in CAFRS patients revealed a high presence of allele ε4, that in this population appears to be more prevalent in men. Also, the phenomenon of advancement of the age of onset of Alzheimer's disease associated with the ε4 allele, observed in other cohorts, is noted as it is the reverse phenomenon of delayed age of onset associated with the ε2 allele.





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

FIGURE 1



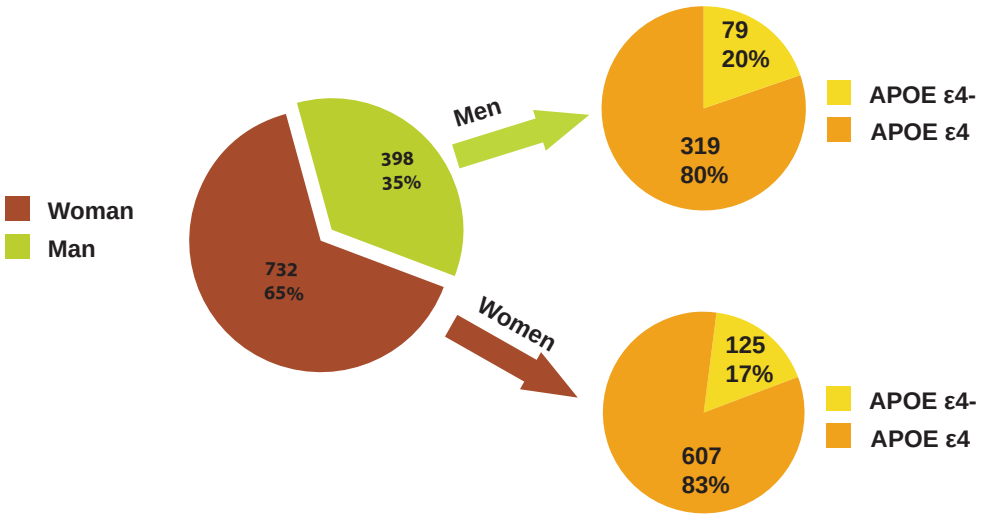
It is currently known that the pathological processes that determine Alzheimer begin many years before the disease leads to the first noticeable symptoms in patients. Years before that future drug treatments preventing or slowing down disease progression could be applied to the "population at risk" who has developed these subclinical lesions, or has a higher risk of developing it than the rest of the population.

In this context it is framed the Vallecas Project, which is constituted as a 5-year longitudinal study specifically aimed at discovering the factors that would allow us to detect this "population at risk" in a phase of potentially treatable pathology.

The phase of recruiting volunteers for participation in the study was finished in December 31, 2013, with its corresponding baseline assessment (n = 1,213). The project includes activities from the Multidisciplinary Support Unit (UMA, for is acronym in Spanish), Neuroimaging, and Laboratory.

Of all patients recruited in the study and having an informed consent, a blood sample is collected and immediately transferred to the laboratory for fractionation into aliquots following the so-called Vienna Institute of Neurology protocol, which allow different types of analysis, as well as classification and storage **(see Figure 1)**. Additionally, one blood tube

Distribution of the APOEε4 allele in Vallecas Project volunteers by gender



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

Within the department of laboratory, the Vallecas Project activity in figures is as follows:

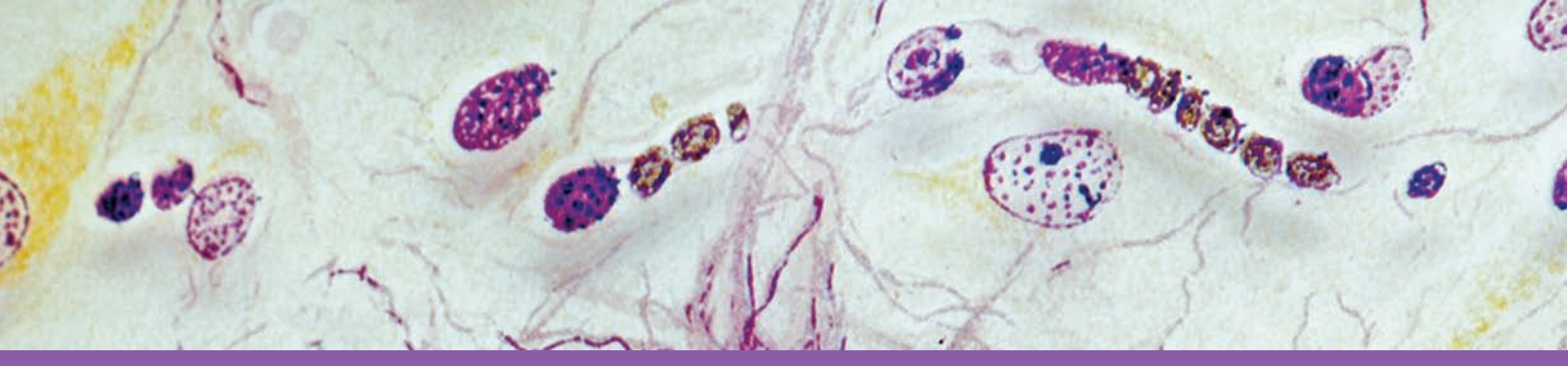
EVALUATION	1ª	2ª	3ª	TOTAL
SAMPLINGS (n)	1.174	684	50	1.908
ALIQUOTS (n)	16.436	9.576	700	26.712

Primary alicuots in duplicate are collected for the following fractions:

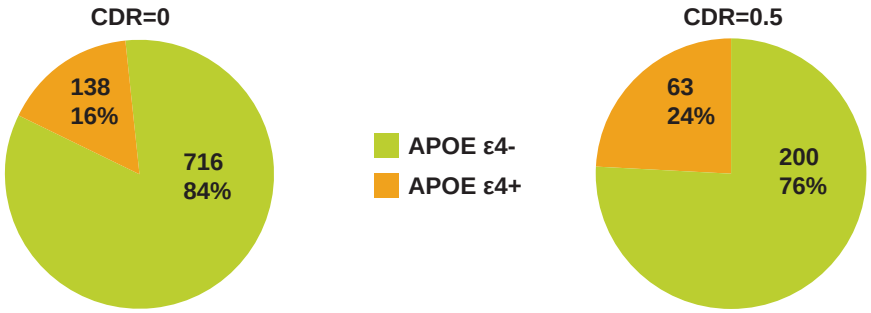
- Whole blood (ST, for its acronym in Spanish)
- Platelets-rich plasma (PRP)
- Platelets-free plasma (PFP)
- Buffy Coat (BC)
- Red blood cells (RBC)
- Serum (Suero, in Spanish)
- Mononucleate leukocytes (LM, for its acronym in Spanish)

Genomic DNA was extracted from whole blood of all participants who have signed informed consent to it and the APOE gene, an important marker of genetic risk for Alzheimer's disease, was analyzed. Also, in order to define different subpopulations of genetic risk, other possible genetic susceptibility genes have also been analyzed in a subset of participants. In all cases, the hematocrit has also been measured in blood samples for their possible relationship with certain brain perfusion imaging studies.

APOE gene analysis has allowed us to determine that, unlike what was observed in patients from the residence, there are no significant differences in the distribution of the ε4 allele between men and women participating in the Vallecas Project.



Distribution of APOE ε4 in Vallecas Project volunteers according to the scale of cognitive impairment (CDR)



However, we observed a clear difference (p = 0.016) in the proportion of the ε4 allele in subjects based on their assessment on the complete scale of cognitive impairment (CDR) or in the specified area of memory, thus confirming the usefulness of this genetic marker to define populations at higher risk of developing Alzheimer's disease or to advance the age of disease onset.

As of December 31, 2013 754 Vallecas project volunteers have been analyzed in a second evaluation. In this study population, there has been conversion to mild cognitive impairment or dementia in 39 people [NORMAL -> amnestic MCI (n=13), NORMAL -> non-amnestic MCI (n=2), NORMAL -> Mixed DCL (n=23), mixed DCL -> Dementia (n=1)].

The study of APOE gene in these converters indicates a higher prevalence of the ε4 allele as expected from a risk and disease advancement factor. Other genes studied showed no significant association, probably due to the low power of the study at this stage. Finally, in this context, it is important to emphasize that the samples obtained from Vallecas Project volunteers aged between 70 and 85 years that include a comprehensive assessment of cognitive, sociological and neuroimaging state are optimal for its use as a control population in various projects related to neurodegenerative diseases, especially Alzheimer's disease. The monitoring for a period of 5 years will allow us to detect early, even before clinical symptoms manifestation, susceptibility factors and biomarkers associated with Alzheimer's disease.

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

- Vascular dysfunction associated with Alzheimer's disease (FIS project)
- Diagnosis of rapidly progressive dementia based on biomarkers (EU Joint Programme – Neurodegenerative Disease Research)
- Development of diagnostic tools for Alzheimer's disease (R&D&i granr, Innpacto program)

Genotype distribution in different gene polymorphisms potentially associated with Alzheimer's disease (www.alzgene.org) in a subset of Project Vallecas volunteers.

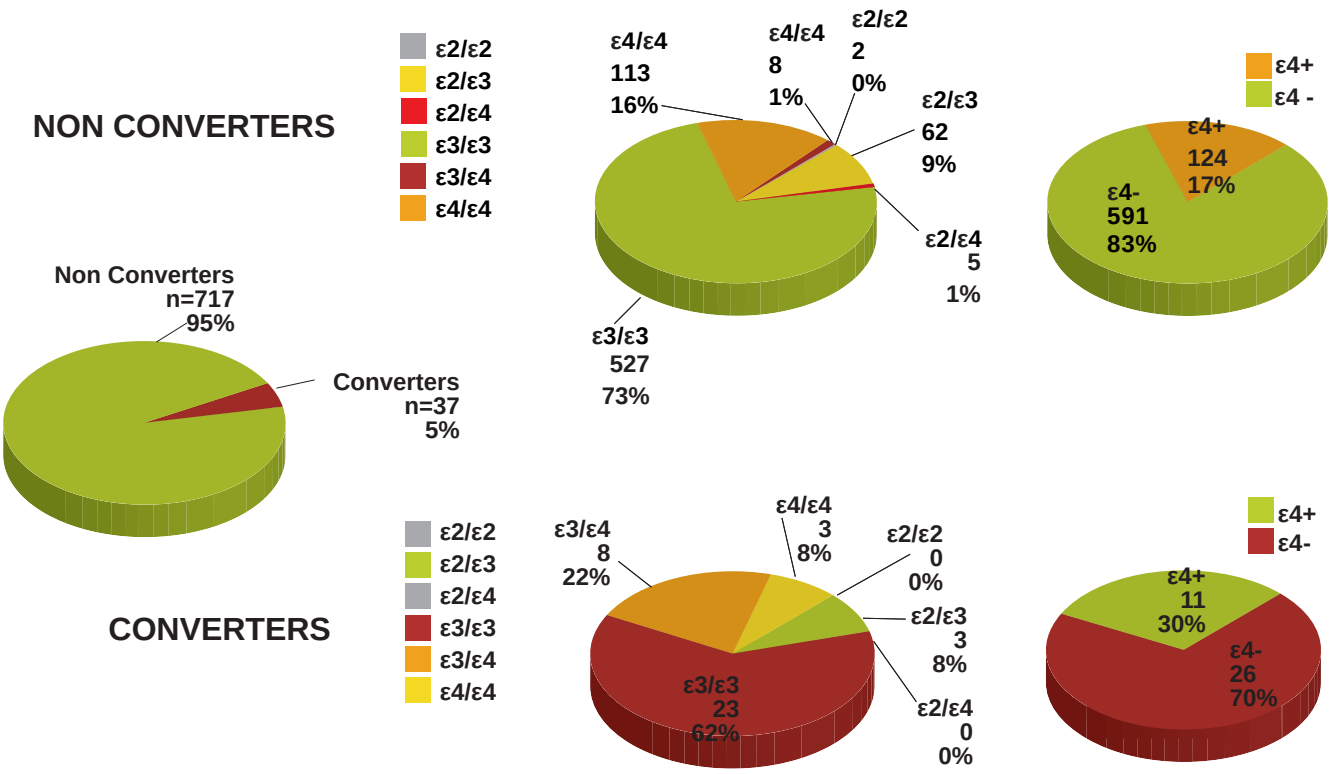
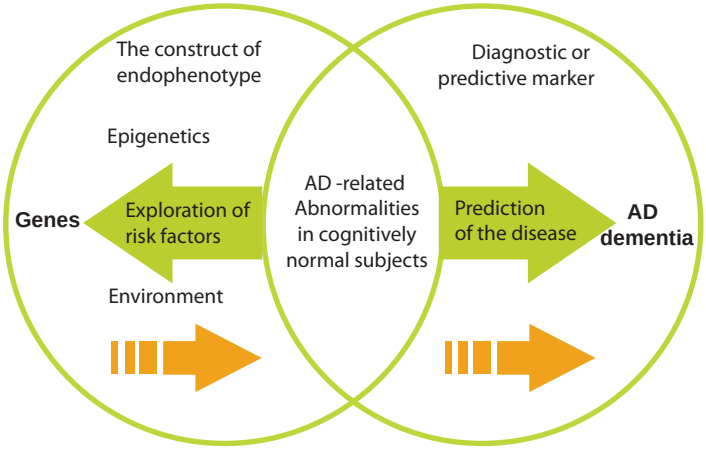
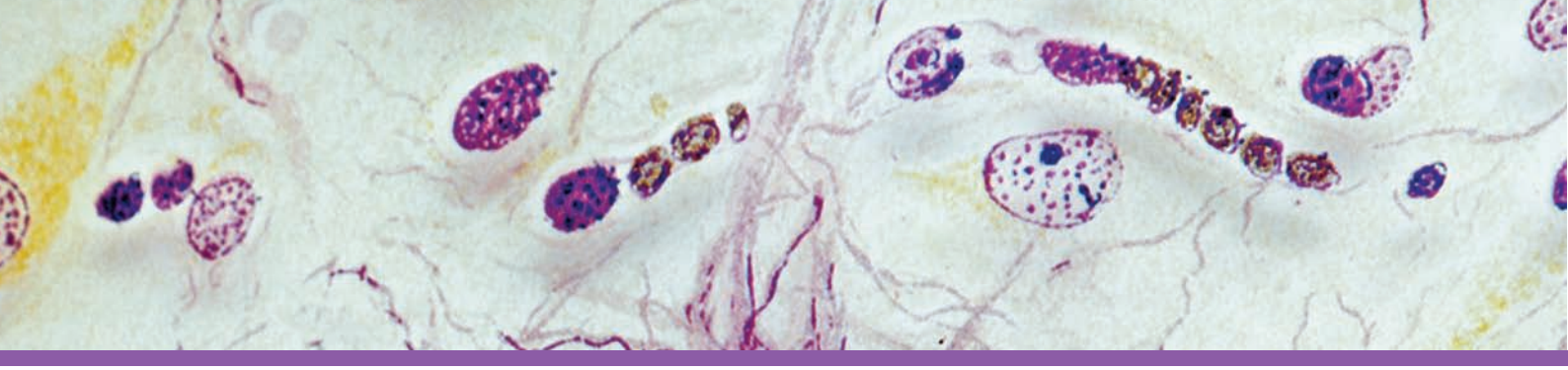


Illustration of the concept of endophenotypes for defining homogenous populations based on certain genetic variants and biomarkers in Alzheimer's disease. Modified from During et al. 2011





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

In the context of research focused on the study of biomarkers and genetic susceptibility factors, the UIPA Department of Laboratory is responsible for obtaining, processing and storing biological samples for research associated with different projects or for depositing in the BT-CIEN, whose ultimate aim is to be used in different areas of research on neurodegenerative diseases.

Gene	Polymorphism	Frequency		
SORL1	rs2070045	TT: 629	TG: 156	GG: 20
SORL1	rs1699102	TT: 211	TC: 198	CC: 42
BIN	rs744373	TT: 276	TC: 135	CC: 38
CR1	rs3818361	TT: 313	TC: 122	CC: 15
ABCA7	rs3764650	TT: 357	TG: 89	GG: 5
PICALM	rs3851179	GG: 221	AG: 161	AA: 39
CLU	rs11136000	GG: 141	AG: 212	AA: 71
BIN	rs744373	TT: 276	TC: 135	CC: 38

At present, the department contributes to BT-CIEN with various biological samples among which 114 cerebrospinal fluid samples have been collected from brain donors.

3.6.2. Team

During 2013, the team of the Laboratory Department was composed of the following personnel:

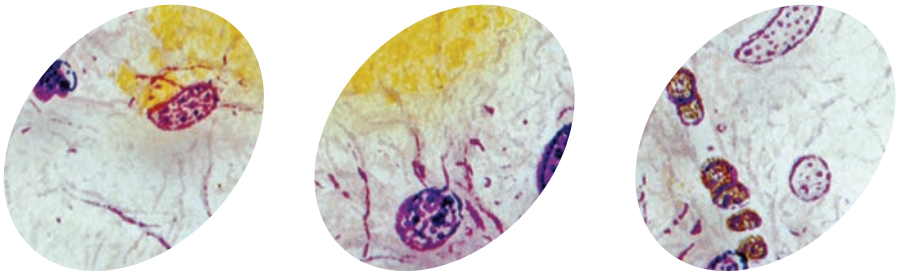
- Miguel Calero Lara (Dr. Chemistry), Head of Department
- Olga Calero Rueda (Dr. Biology)
- Ana Belén Pastor López (Laboratory Technician)
- Andrés Rodríguez Martín (Laboratory Technician, CIEN Foundation-Biocross)

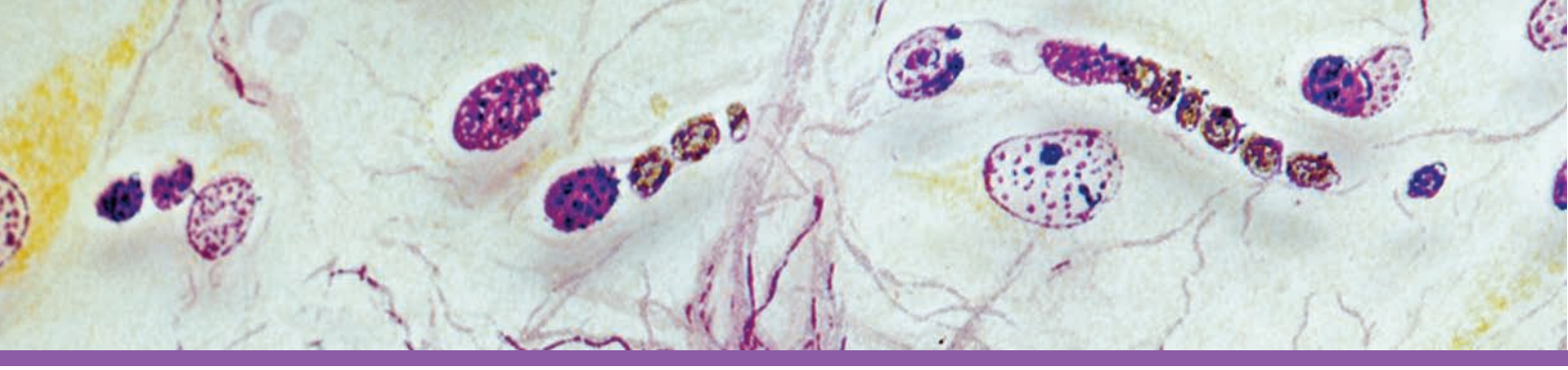
3. SCIENTIFIC ACTIVITY

Laboratory Team

The Vallecas Project

During 2013 it has been completed the volunteer recruitment process to participate in the Vallecas Project. Overall, 1,213 people with certain characteristics will collaborate on the first research study in Spain dedicated to advancing early diagnosis of alzheimer's disease.





4.1. Introduction

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

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

The transit of a cognitively normal individual subject with AD-type dementia is a continuum in which some intermediate states can be recognized. These stages do not meet the consensus criteria for the diagnosis of dementia because some issues are still not fully determined. These are cases where there is a dimly distinguishable mild cognitive disorder. If we had the ideal therapy to largely stop or slow disease progression pre-dementia in these intermediate stages, we could drastically reduce the prevalence of clinically overt AD.

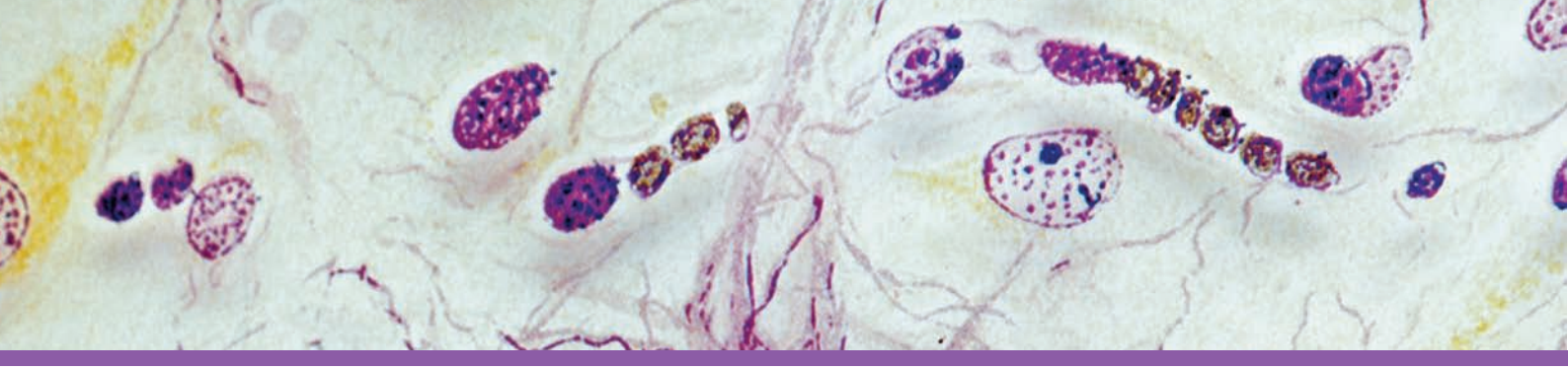
Nowadays, there is no known method to determine which individuals in those pre-dementia states will end up being demented patients (not all convert to severe cognitive impairment), or to accurately identify individuals at high risk of dementia and AD in the general population. With the help of sophisticated,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

The main objective of the population-based study "Vallecas Project" for Early Detection of Alzheimer's Disease, is elucidate, through progression tracking, the best combination of clinical parameters and tests (imaging and laboratory) that allow deciphering what medium- and long-term (3 to 5 years after the baseline observation) features distinguish those who will develop memory impairment (MCI and dementia) from those who will not. Thus, it intends to identify various markers to eventually determine the potential risk that each individual could have to develop the disease in the future.

4.2. Background: Pilot project

A pilot study was conducted between June 2010 and February 2011, prior to the final project, whose first preliminary results are presented in this report. The 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 participated in this phase of the project, of which:

- 95 people were able to participate in the project.
- 80 people were unable to participate because they met at least one exclusion criterion.

4.3. The Vallecas Project

Following the completion and analysis of the pilot study the protocol was amended based on the experience gained and a volunteer recruitment strategy was established (social awareness campaign in the media, visits to centers for seniors, contact pensioner's organizations, etc.). In September 2011, after the "Global Summit on Alzheimer Disease Research" held in Madrid and with the financial support of the Queen Sofia Foundation, began the final implementation of the Vallecas Project, which started its activity gradually in October 2011.

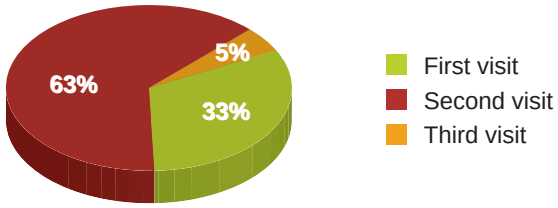
The Vallecas Project, which is being carried out in the Queen Sofia Foundation Alzheimer Center Research Unit by researchers from the CIEN Foundation (Carlos III Institute of Health) aims to develop a probabilistic algorithm to identify individuals at risk for AD-type dementia over the course of a few years. Such an algorithm will be based on a combination of socio-demographic, historical, clinical, neurological and neuropsychological, biological (from blood tests) and neuroimaging (various forms of 3T MRI).

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

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 2013, the project has reached its cruising speed, having completed the initial assessment of all 1,213 volunteers, of which 750 have already made the second annual visit.

Vallecas Project activities during 2013

Number of first visit assessments	311
Number of second visit assessments	614
Number of third visit assessments	48



4.3.1. Baseline 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:

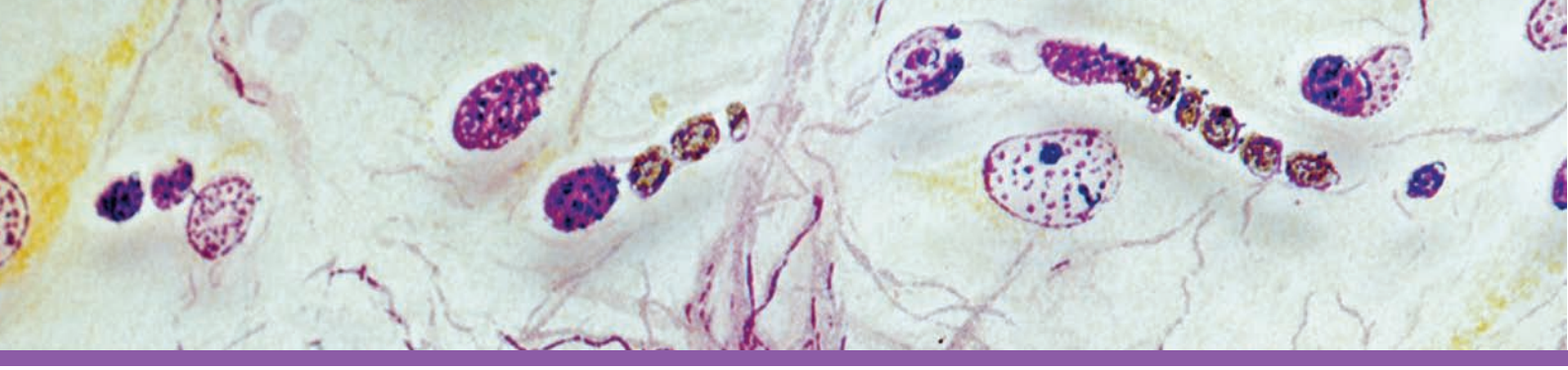
- Informed consent.
- Be aged between 70 and 85 years old.
- Availability and ability to travel to the Alzheimer Centre for visits.
- Visual and hearing abilities that allow performing of the study tests.

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.

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.



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

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

THE VALLECAS PROJECT IN FIGURES	
Recruited sample	1.213
Excluded	47 (3,87%)
Age	
Sample Mean	74,46 años
Age group 69-74	671 (55,32%)
Age group 75-79	379 (31,24%)
Age group > 80	163 (13,44%)
Gender	
Females	780 (64,30%)
Males	433 (35,70%)
Schooling	
Sample Mean	10,35 años
Illiteracy	4 (0,34%)
Read-Write	60 (5,11%)
Minimum studies (numeracy skills)	154 (13,11%)
Primary Education	389 (33,11%)
Senior High School / Professional Training	282 (23,99%)
University Education	286 (24,34%)

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

4.3.4. General examination

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

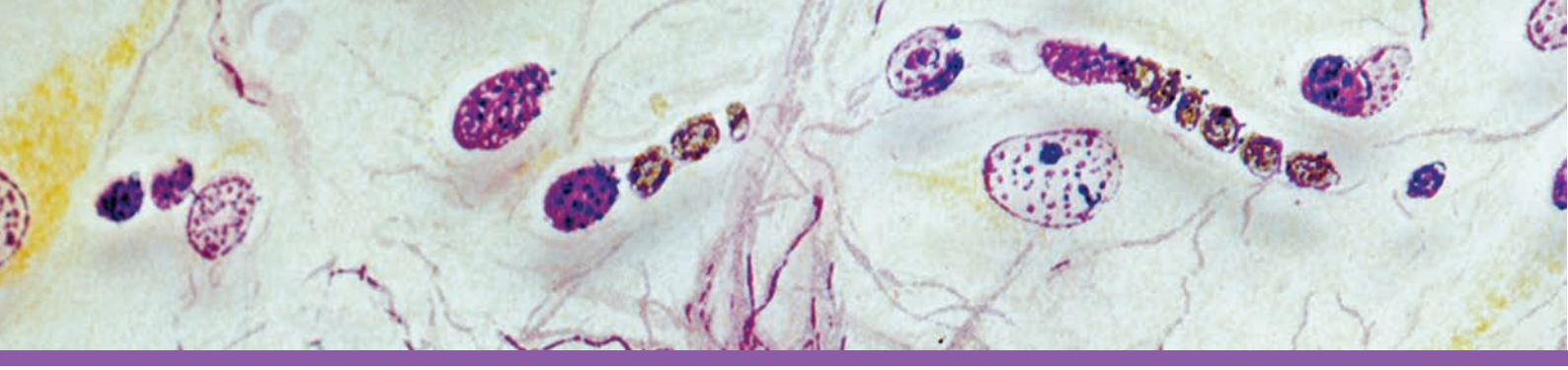
This scale is based on a self-reported test comprising 11 items to assess memory complaints from study participants.

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.

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

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

Clock Drawing Test

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

Reading Test of Intelligence (TELEI)

This test provides a measure of the level of pre-morbid intelligence of the patient through a reading task contained 60 words in the dictionary of the Royal Spanish Academy. An important feature of this test is that the items have a low frequency of use in our country, those who should carry written accent do not carry it and foreign words are also included between them. The subject's task is to read the words in the right way, for what is allowed to rectify if deemed appropriate. The test raw score is the number of words read correctly.

Wechsler Adult Intelligence Scale (WAIS)

This is part of the WAIS scale for assessing intelligence. Natural numbers from 1 to 9, each of them associated with a different symbol, are presented on a test sheet. Below appear random numbers from 1 to 9 without any associated symbol. The task of the subject is to write the symbols for each number as

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

Global Depression Scale (GDS-15)

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

State-Trait Anxiety Inventory (STAI)

This self-reported test evaluates anxiogenic symptoms related to both a specific time and intensity variable period (anxiety state) as well as a more stable personality pattern tending to perceive situations as threatening (anxiety trait). Thus, there are two scales of this test, each consisting of 20 items with 4 response options (scored by a Likert type scale of 0-3).

The total score is the sum of the individual scores for each item. Spain has recently adapted this test in nonclinical populations.

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

This test allows to evaluate the hearing attentional amplitude and the individual's central executive of the working memory. The subject's task consists in repeating the growing sequences of numbers that the evaluator presents at one digit per second.

The test is divided into two separate subtests, so that repetition of the first digit is applied in the same order of presentation (Direct digits) and then in reverse order (Inverse digits). The task ends when the subject is not able to repeat two sequences of the same length of digits. In both subtests, the number of correct repetitions and the maximum amplitude of digits that the subject is able to repeat are counted.

Boston Naming Test (15 items version)

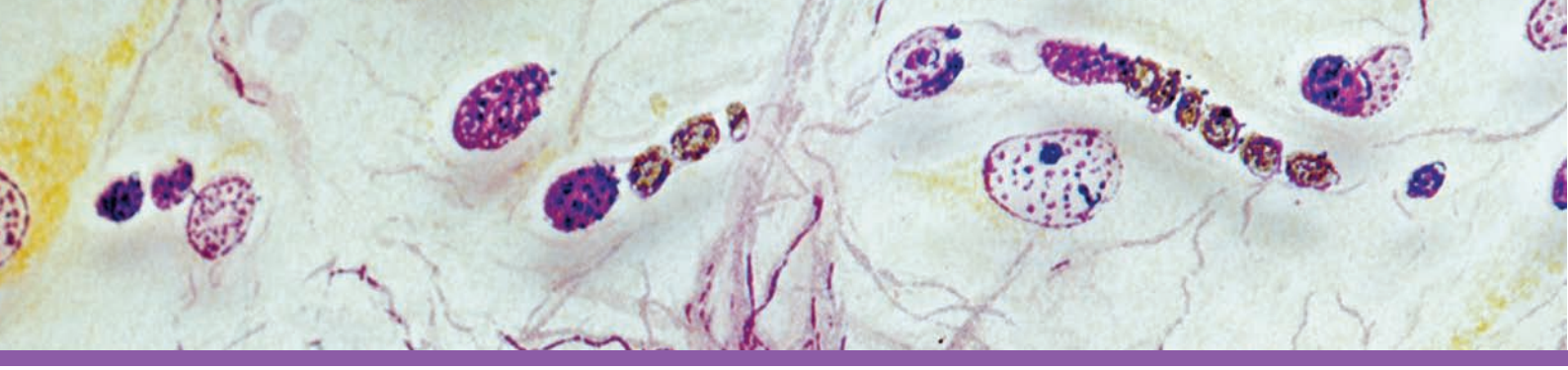
It is a reduced version of the classic subtest included in the Boston test for the diagnosis of aphasia. The Boston Naming Test is used in clinical consultations to assess the ability of naming visual stimuli by visual confrontation. The subject's task is to name each of the 15 drawings that are presented,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

Symbolic gesture (Revised Barcelona Test)

This test explores performing of a series of symbolic gestures of communication. They are simple, intransitive gestures made with a single upper limb. The primary endpoint of the test is the body position in relation to space and the body.

Imitation of bilateral postures (Revised Barcelona Test)

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



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

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

Test of the five points

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

4.3.6. Neuropsychiatric Examination

Depressive symptoms may be a risk factor for the disease, acting as an early manifestation or appearing during its progression. Therefore, it is of interest 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

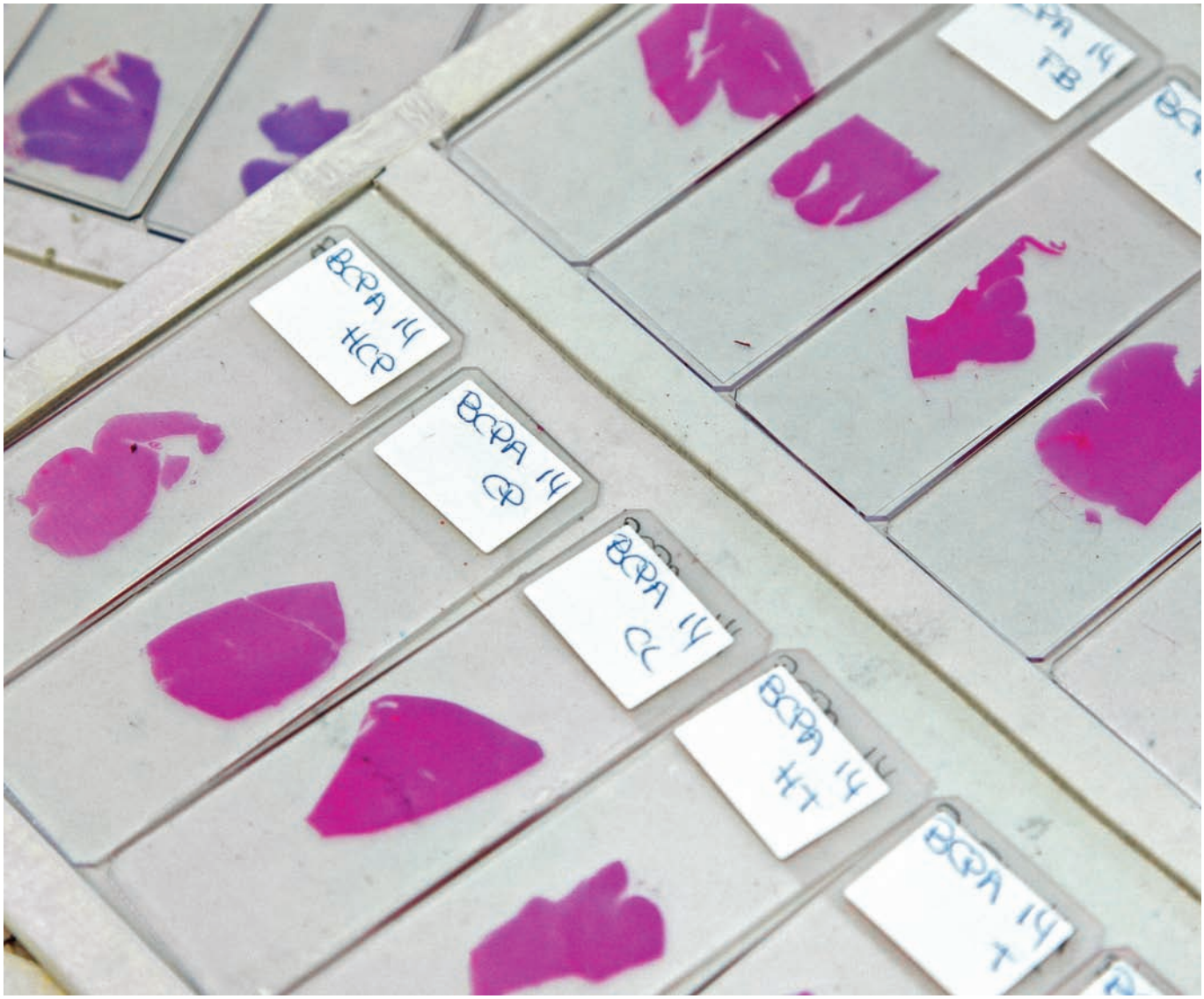
VALLECAS PROJECT CLINICAL EVALUATIONS OCTOBER 2011 - DECEMBER 2013	
First visit	1.175
Excluded during first visit	47
Second visit	614
Third visit	48
Drop outs	193
No compliance with inclusion criteria	30
Decease	9
Diagnosis of neurological disorder	24
Voluntary	130

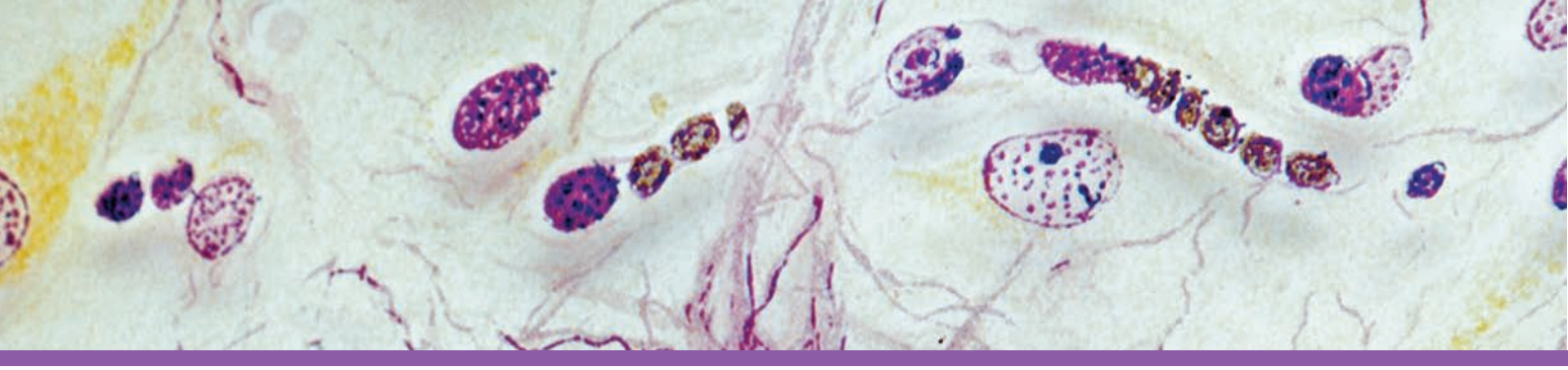
and dementia has been even less explored than that of depression, but may also act as an early manifestation.

The table on the left 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 clini-





cal symptoms. It has been a great interest of the scientific community during recent years in the development of new biomarkers of AD and its utility in risk assessment and early diagnosis of the disease.

Thus, blood samples will be collected within the Vallecas Project for the study of a number of genetic and biochemical markers. Samples are obtained according to the protocol "Collection and Processing of Human Blood Samples in the Vallecas Project" and processed to obtain the fractions indicated in the protocol, which will be stored at -80 ° C. On one hand, DNA is extracted from blood cells to determine, by PCR and sequencing techniques, genetic markers associated with the various polymorphisms of the following genes:

- APOE
- CR1
- 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

EXTRACTIONS	
First visit	1.212
Second visit	668
Third visit	50
TOTAL	1.930
Available samples	
Whole Blood	100%
Platelet-rich plasma	100%
Platelet-poo plasma	100%
Serum	99.%
Buffy Coat	100%
Erythrocytes	100%
Mononuclear leukocytes	99.%
DNA	100%
ApoE	99.50%

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 on the left .

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 postmortem studies of brain tissue. Accordingly, the project aims to conduct a series of studies based on various MRI modern techniques that can provide volumetric quantitative indexes of the morphological changes.

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

Structural Study (3D volumetry, T2 and FLAIR)

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

Diffusion Study (b: 800)

White matter, partly due to Wallerian degeneration and partly to reduced connectivity by decreased cortical activity, presents ultrastructural changes that can be detected with diffusion techniques (DTI).

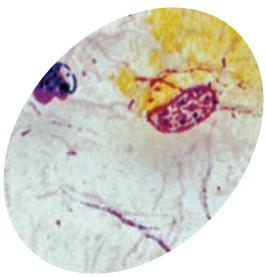
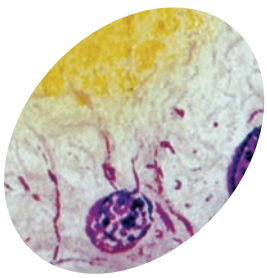
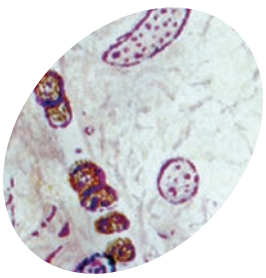
Brain Perfusion Study

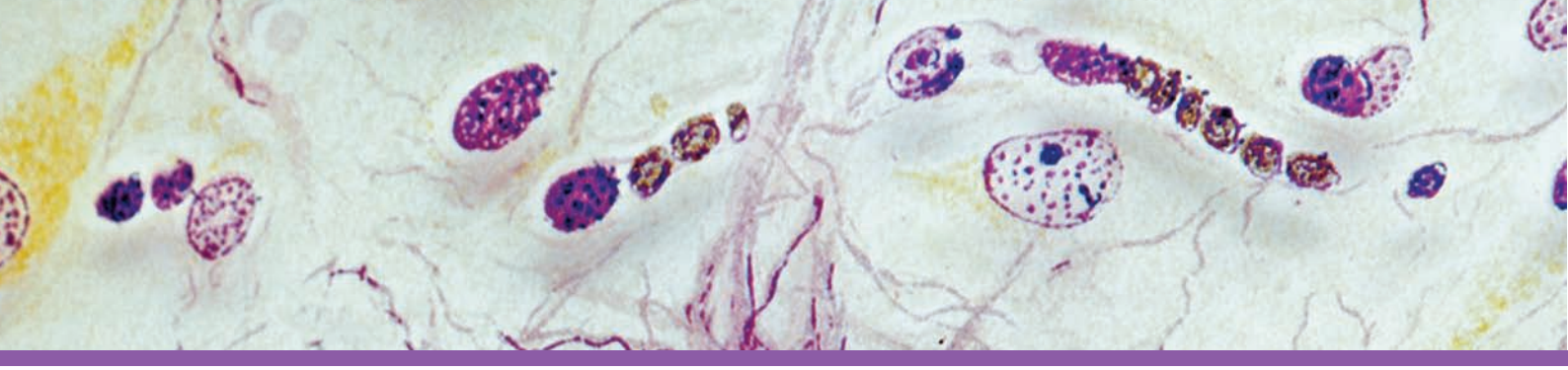
Cerebral perfusion related to cortical activity may be assessed -without needing to inject contrast- through MR sequences (Arterial Spin Labelling, ASL) and therefore hypofunctioning areas will present decreased perfusion.

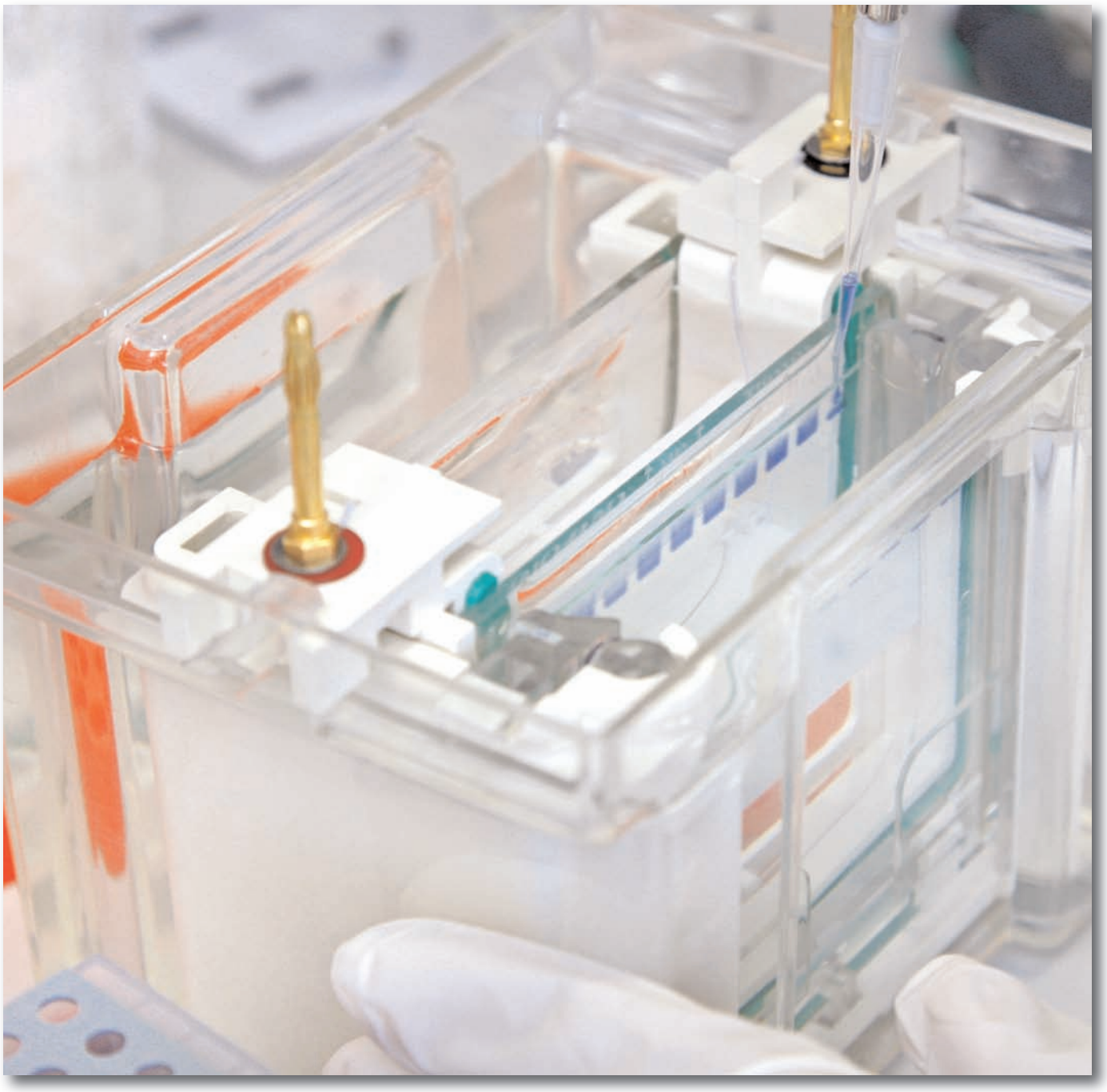
NEUROIMAGING ACQUISITIONS	
Vallecas Project 1	277
Vallecas Project 2 (first review visit)	508
Vallecas Project 3 (second review visit)	40
TOTAL	825

International cooperation activities

In 2013 CIEN Foundation has given a boost to its international relations. besides its active participation together with CIBERNED in the EU Joint Programme for Research in Neurodegenerative Diseases (JPND) and in the International Network of Centres of Excellence in Neurodegeneration (CoEN), it must be added the organization of a round table on dementia jointly with the British Foreign Office and its participation in projects such as the registry project and the "new friends, old emotions" study.





5. INTERNATIONAL COOPERATION ACTIVITIES

5.1. Introduction

Neurodegenerative diseases (ND) are responsible for mitigating states, largely untreated and are closely linked with age. Among these disorders, dementias are responsible for the greatest burden of disease, with Alzheimer's disease and related disorders causing impairment of approximately 7 million people in Europe. This figure is expected to double every 20 years, due to the progressive aging of the population. Currently, healthcare and treatment of patients with some form of dementia in Europe, represents a cost around € 130 billion per year, according to estimations of the European Commission Joint Programme in Neurodegenerative Diseases. This highlights that age-associated neurodegenerative diseases constitute one of the main medical and social challenges facing our society.

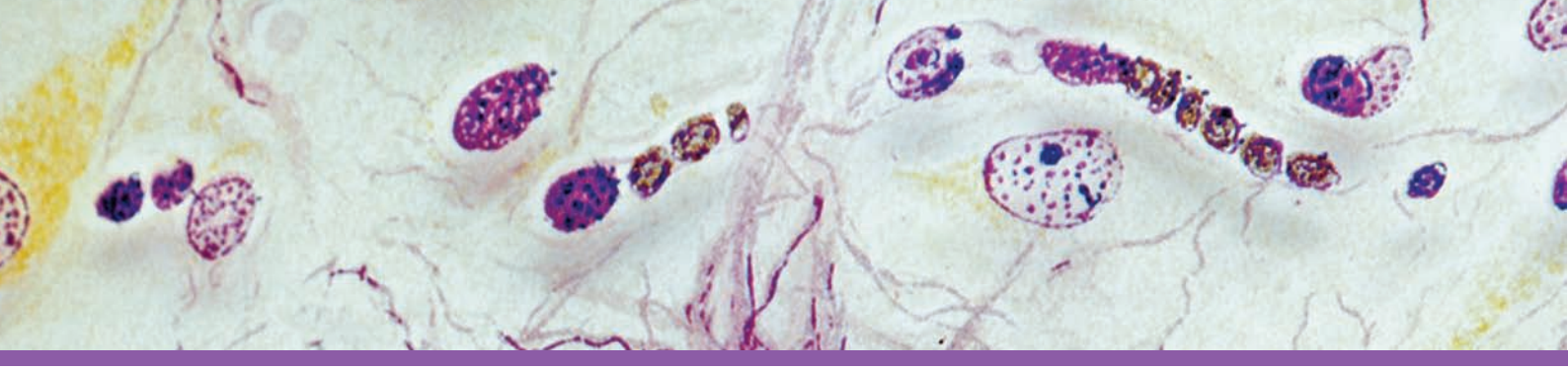
International scientific collaboration increases more and more, not only because of the availability of international funding and the drive of modern communication technologies, but also because science itself has become a truly international collaborative activity. In particular, the scope and scale of the problem of neurodegenerative diseases in today's society require a global response to confront this great challenge and thus has been recognized by various international institutions such as the European Union (EU), the Organization for Economic Cooperation and Development (OECD), the World Health Organization (WHO), etc, and the industrialized countries that constitute the G8. The leaders of governments, businesses and academia also recognize the need for a coordinated strategy to address this major global challenge for health systems. There is consensus among all stakeholders on the need to build capacities, infrastructures and R&D resources in the field of neurodegenerative diseases.

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

In this context, in recent years The CIEN Foundation together with Center for Networked Biomedical research in neurodegenerative Diseases (CIBERNED) has given a boost to its relations with international organizations in the area of research in neurodegenerative diseases such as the EU Joint Programme for Research in Neurodegenerative Diseases (JPND) and the Network of Centres of Excellence in Neurodegeneration (COEN), among other initiatives.

5.2. European Union Joint Programming on Neurodegenerative Disease Research (JPND)

The EU Joint Programming for Research in Neurodegenerative Diseases (JPND) is an innovative collaborative research initiative created to address the growing challenges posed by these disorders. The JPND is a pioneering example of joint programming for the promotion of research within the European Union aimed at scientific challenges requiring a response that exceeds the capacity of a single country, based on the alignment of national research programs devoted to these challenges. Its objective is to enhance the impact of research by aligning existing national research programs and the identification of common objectives whose scope would benefit from joint action. The JPND Scientific Advisory Committee has significant participation of two CIBERNED researchers, Drs. Jesús Avila and Jesús de Pedro, as well as Dr. Ángel Cedazo-Mínguez, from the Karolinska Institute in Stockholm and member of the CIBERNED Scientific External Advisory Committee.



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

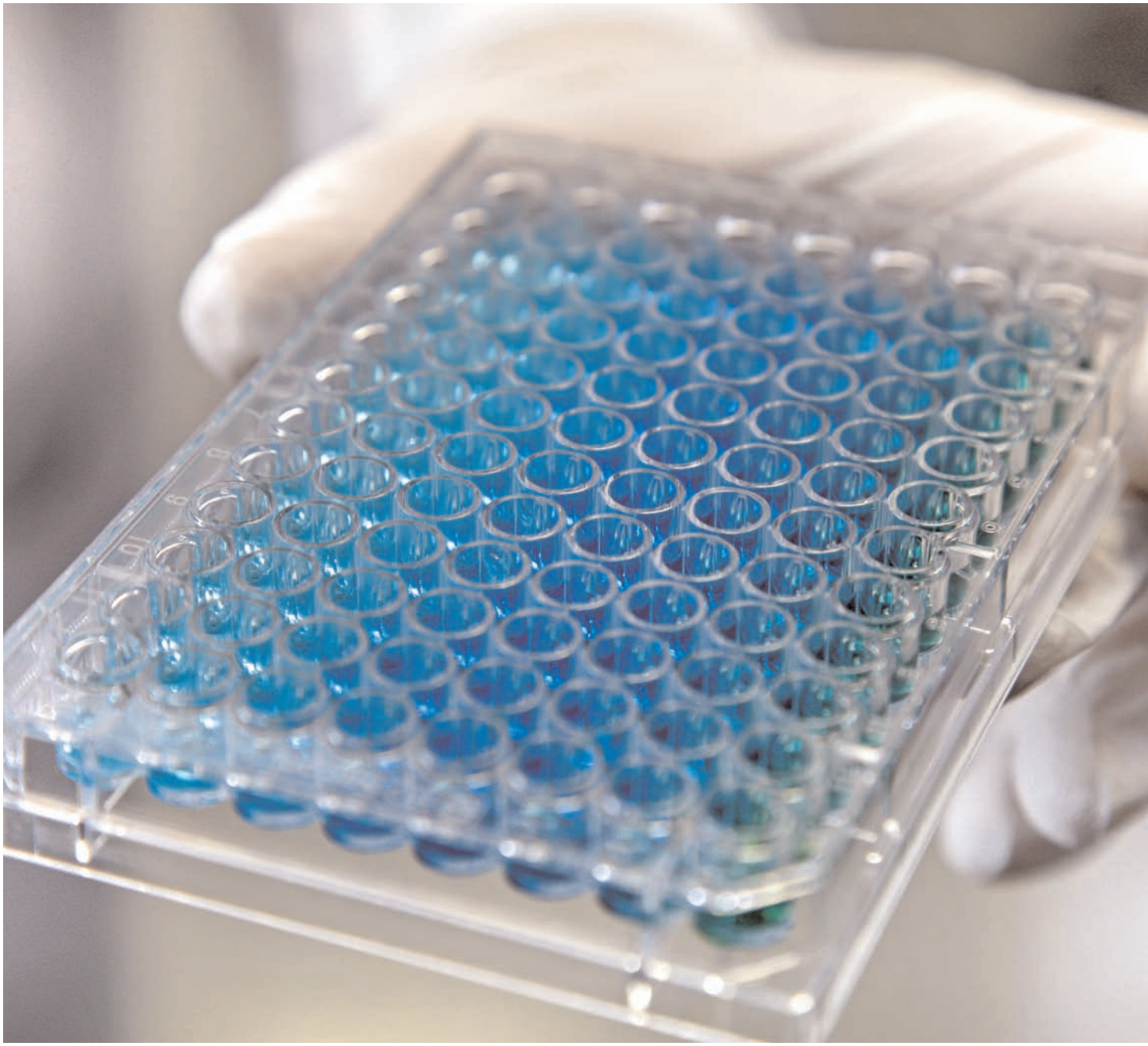
To achieve impact there is a need to encourage novel as well as multidisciplinary approaches, and to strengthen and extend existing capabilities across the full spectrum of basic, clinical, health and social care, and translational research. A number of thematic priorities for future research have been identified:

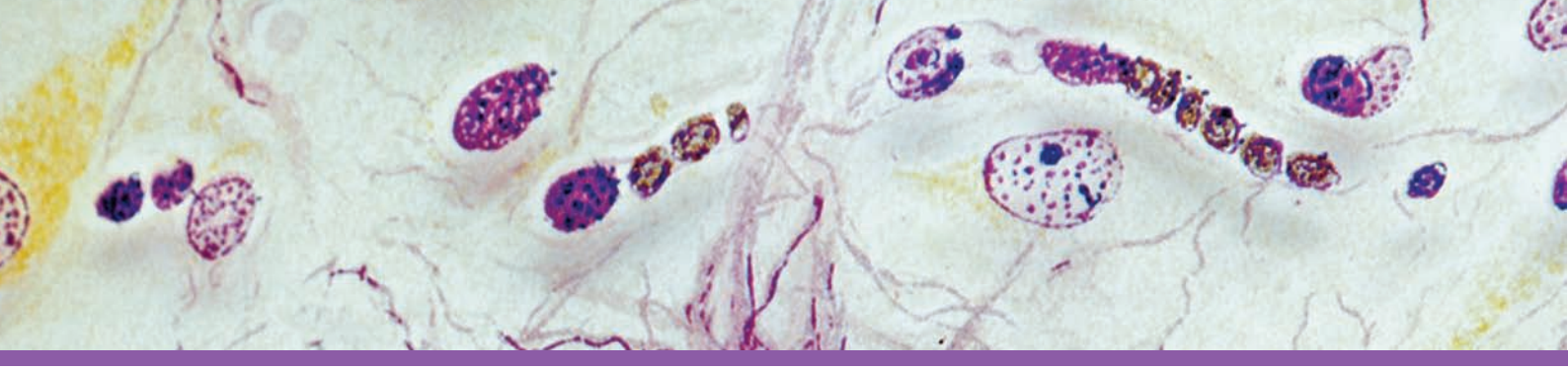
- The origins of neurodegenerative diseases (ND): Further knowledge is needed regarding the causes of specific ND, the factors that determine people's risk and resilience, and the triggering events leading to illness.
- Disease mechanisms and models: A better understanding of the underlying disease mechanisms 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, needing 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 as well as in patients.
- Healthcare and social care: At present there is inefficient co-ordination between health and social care systems in individual countries, needing an evaluation of the equity of access to, as well as the effectiveness and cost-effectiveness of, pathways to diagnosis, treatment, care and support for ND across Europe.

Ensuring progress of the scientific priorities described above will also require the development of a series of complementary activities:

- Knowing our research capability, in order to identify both research gaps and those opportunities that can be addressed through improved co-ordination and investment.
- Supportive infrastructure and platforms, such as integration and harmonisation of data and equipment, and promote an open-access approach to their use.
- Working in partnership with industry, specially from the pharmaceutical, diagnostic and biotechnology sectors.
- Working with regulatory organizations, to promote effective translation of research and find patient benefits.
- International partnership beyond Europe, recognizing that clinical research and the social impact of diseases ND is a global problem, and therefore may be opportunities to join research efforts that are taking place around the world in this area.
- Capacity building, through strengthening of certain areas of research that lack adequate development and the establishment of networks across and between disciplines and researchers
- Education and training, based on 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, by establishing a framework through which they can detect and define relevant issues, to be considered by national policies and their alignment and

5. INTERNATIONAL COOPERATION ACTIVITIES





engagement with major international initiatives.
- Communication and outreach, in order to achieve an effective translation across the different sectors of society.

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

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

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

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

UA 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 a funding initiative to establish a collaborative approach to research in neurodegenerative diseases, called "Centers of Excellence in Neurodegeneration (CoEN)". These founding members were later joined by other European institutions and thus, in December 2011 the CoEN membership application by CIBERNED-CIEN Foundation was approved, recognizing the scientific excellence in both basic and clinical science of the institution which became part of the CoEN Oversight Group.

Current COEN members are:
- Canadian Institutes of Health Research (CIHR)
- Deutsche Zentrum für Neurodegenerative Erkrankungen (DZNE, Germany)
- Medical Research Council (MRC, United Kingdom)
- Flanders Institute of Biotechnology (VIB Flanders, Belgium)
- Health Research Board (HRB) / Science Foundation Ireland (SFI), Ireland
- Ministero della Salute (MDS, Italy)
- Centre of Excellence for Brain Research, Slovakia
- CIBERNED- CIEN Foundation, Spain

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 colla-

borative teams between PIs within the participating national Centers of Excellence.

Since 2012, CIBERNED and CIEN Foundation form part of the Oversight Group to actively participate in the design of CoEN future scientific strategy. Both institutions are represented in the CoEN Oversight Group by Dr. Miguel Medina, CIBERNED Deputy Scientific Director and member of the Scientific Advisory Committee of the CIEN Foundation.

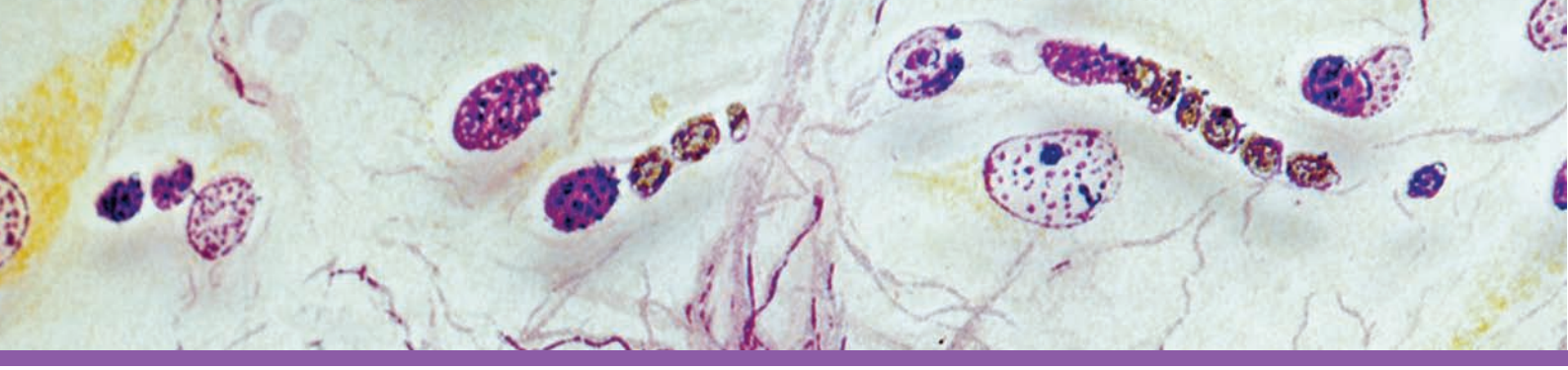
The first phase of the CoEN initiative began in late 2010 and has been aimed at the development of common resources and methodological approaches that underpin future studies. Some of the key issues addressed are: the development and validation of cell and animal models of disease; development of new 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.

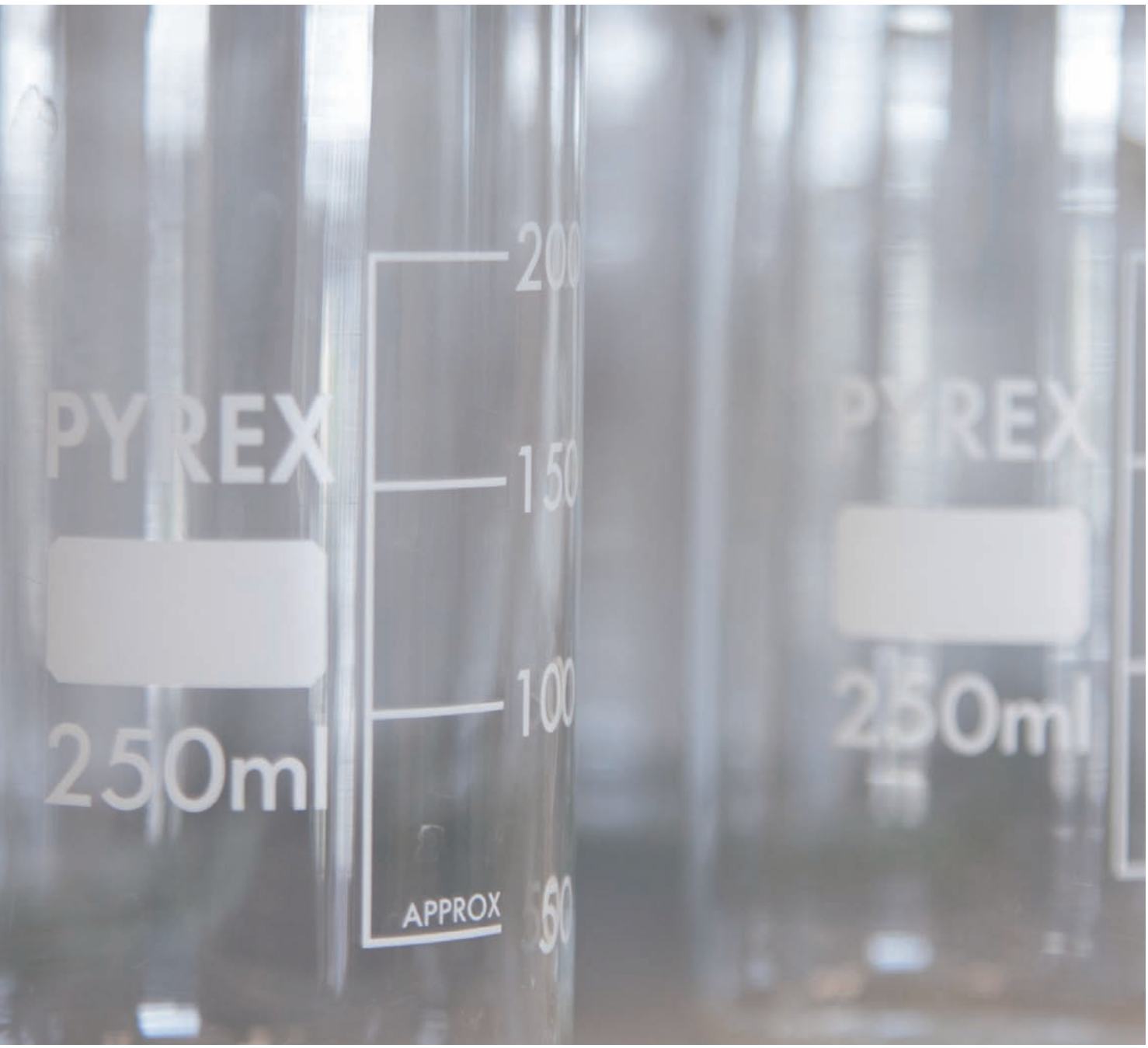
Phase II of the initiative was launched during the year 2013, with the aim of catalyzing collaborative research between centers with a critical mass of resources and expertise to thus promote a radical change in research on neurodegeneration. To do this, the countries participating in CoENs contributed a total amount of 5.5 million euros (of which Spain has provided 600,000 euros) in this call to establish an innovative and progressive research program to address the major challenges in this field. The call is intended to encourage the community to think outside the pre-established frameworks and stimulate new and creative approaches and solutions to the challenges of research in neurodegeneration. This call of Pathfinder projects intends to combine the strengths of research groups through Centers of Excellence in at least two partner countries to provide a truly collaborative effort and value that will advance our approach to research neurodegeneration. The projects would address issues that are not easily financed through standard grant mechanisms from CoEN partners, and is expected to further collaboration between Centers of Excellence, the projects would also serve to provide a platform for future collaboration with industry.

On the other hand, on November 29, 2013, the CoEN Oversight Group brought together leaders of the 15 innovative supported initiatives with representatives of the pharmaceutical industry, including Pfizer, Sanofi, GSK, MSD, Lilly and others. The result of this meeting exceeded expectations. Industry representatives expressed their deep satisfaction of being able to engage in conversation and exchange with academic leaders. They emphasized the fact that innovative collaboration supported by the CoEN initiative research was exactly the type needed to provide new insights and avenues to explore possible solutions to dementia activity, and said CoEN was "an important piece in the overall portfolio of innovation needed to address this critical public health challenge ".

5.4. Other activities of international cooperation

A novelty in 2013 has been the merging of the IX International Symposium on Advances in Alzheimer's disease, which annually promoted the Queen Sofia Foundation and CIEN Foundation, with the 7th Scientific Forum CIBERNED, that each year brings together more than 500 researchers that constitute CIBERNED. Thus, during 23rd and 24th of September 2013, on the occasion of the World Alzheimer's Day on September 21, the first International Congress for Research and Innovation in Neurodegenerative Diseases (CIIIEN) was held in Madrid. A more detailed description of this event can be found on Section 7.1. of this Annual Report.

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On May 8 was held in the Queen Sofia Foundation Alzheimer Center a meeting between representatives and researchers from CIBERNED, CIEN Foundation and Queen Sofia Foundation together with members of the scientific section of the British Foreign Office in which a roundtable was held on dementia attended by Robin Grimes, Head Scientific Advisor of the British Foreign Ministry, Jesús Ávila, CIBERNED Scientific Director, and Pablo Martínez, Scientific Director of the Alzheimer Project Research Unit (UIPA) of the Queen Sofia Foundation.

Dr. Pablo Martínez focused his intervention in the operation and projects associated with the Research Unit he heads, focusing primarily on the Vallecas Project, which for five years is studying volunteers aged between 70 and 85 years, cognitively healthy, to obtain biological, clinical and neuroimaging data in order to try to identify biological markers of disease. In this sense, Martínez wanted to highlight "the need for social collaboration in research in Alzheimer's to move towards early detection of the disease," crucial for improving the quality of life and treatment of those affected by it.

Professor Jesús Ávila, CIBERNED Scientific Director, explained to members of the British Ministry the nature and implications of the association CIEN Foundation-CIBERNED-Queen Sofia Foundation, that complements the institutional and financial support of the latter with the multidisciplinary study of human subjects in CIEN Foundation and basic and translational research on animal models in CIBERNED. Synergies such as this, he said, can make qualitative progress in neurodegeneration research, and specifically Alzheimer's, as it is essential to establish "earliest markers and make the diagnosis in the symptomatic phase to succeed".

Finally, Professor Grimes, Head Scientific Advisor of the British Foreign Ministry, presented attendees with the British program to improve the treatment of dementia in the United Kingdom (UK Dementia Challenge) promoted by British Prime Minister David Cameron last March. In a country in which dementia affects about 670,000 people we are living a "historic" moment, said Grimes, because it is "the first time a Premier makes this problem a priority."

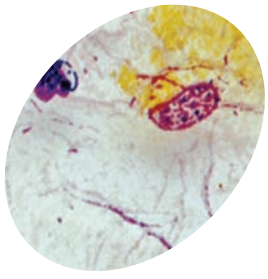
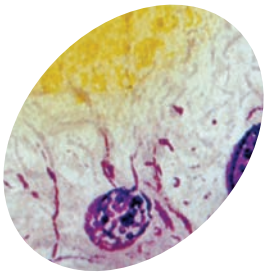
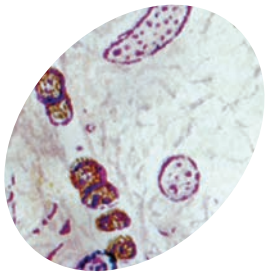
Attendees included also Matthew Desoutter, director of Department of Economic Growth of the British Embassy; Hakim Yadi, head of Life Sciences sector from UK Trade & Investment; Arturo Coello, secretary of the Queen Sofia Foundation; José Ignacio Fernández, program coordinator of the Directorate General of the Elderly of the Department of Social Affairs of the Region of Madrid; M ª Ángeles Pérez, managing director of CIEN Foundation; Miguel Medina, deputy scientific director of CIBERNED; Laura Fernández, managing director of the Alzheimer Center Queen Sofia Foundation; and CIBERNED researchers José Ramón Naranjo and Javier de Felipe. After the panel discussion, attendees visited the facility and met in detail the operation and structure of the Queen Sofia Foundation Alzheimer Center and the Alzheimer Project Research Unit.

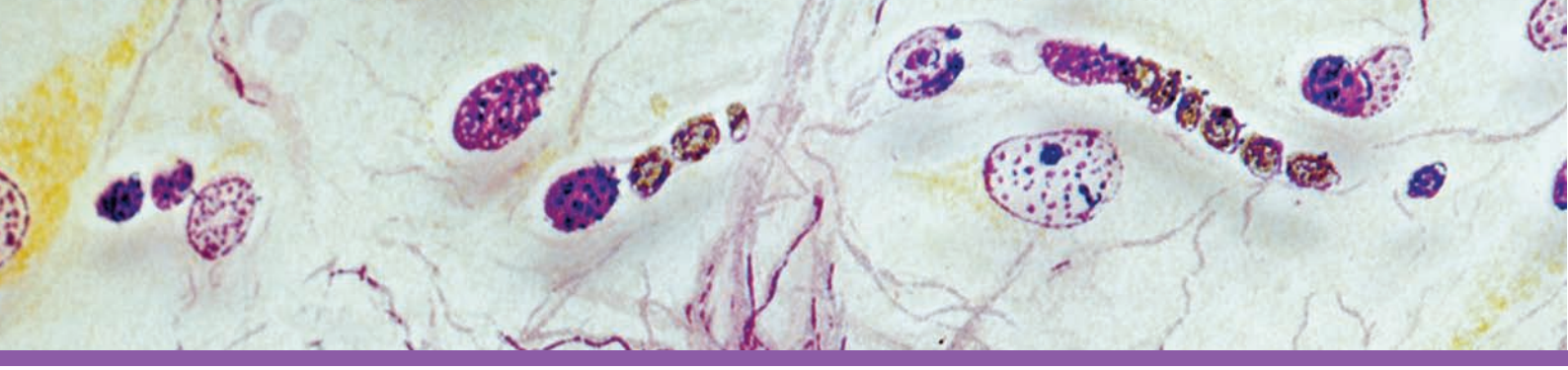
After the panel discussion, which was also attended by a number of CIEN Foundation and CIBERNED researchers, attendees visited the Neuroimaging Department, the CIEN Foundation Tissue Bank (BT-CIEN) and learned in detail, thanks to the explanation of Laura Fernández, operation and distribution of Queen Sofia Foundation Alzheimer Center.

A couple of international scientific projects with the active participation of CIEN Foundation researchers are also worth mentioning: REGISTRY, an international multicenter observational study project coordinated by the European Group on Huntington's disease (more details in Section 3.3.4. of this Report) and the project "New friends, old emotions" which aims at making a guide for the use of animals in robot care for elderly people with dementia, designed for healthcare professionals and caregivers (more details in Section 3.3.8. of this Report).

Scientific productivity

In 2013 CIEN Foundation professionals have produced 85 scientific publications, between articles, books, book chapters and clinical guidelines, representing an increase of 14.9% over the previous year. Over 50% of them are classified in the first and in the second quartile of subject category.

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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. During 2013, for example, CIEN Foundation researchers have produced a total of 85 scientific publications, representing an increase of 14.9% over 2012, of which 81 are to articles in scientific journals, 3 books or book chapters and one specialized clinical guideline. 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.

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

Next type of documents by frequency are communications to conferences. During 2013, there has been a total of 104 contributions to scientific conferences. The distribution by type of contribution has been: oral presentations and communications (56), written as a poster (48), presented in national (54) or international scientific conferences (50).

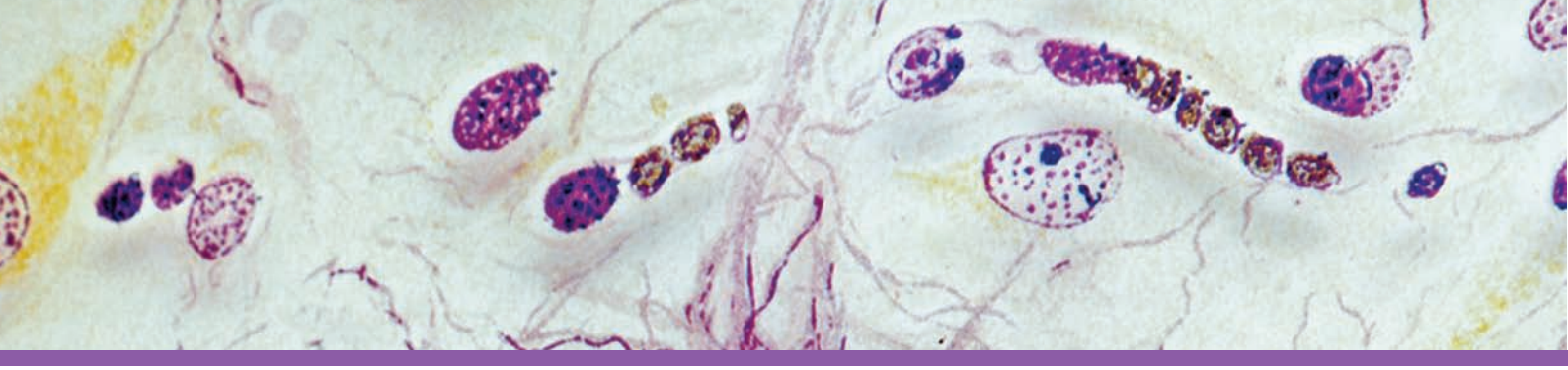
Other noteworthy activities include 80 scientific presentations at various training courses, 24 participations as a reviewer and membership on 7 scientific journals editorial boards The activity carried out in 2013 confirms the continued positive developments in these indicators over recent years at CIEN Foundation.

During 2013 CIEN Foundation researchers have published 85 scientific papers, of which 61 (one 71.8%) were in journals included in the coverage of the Science Citation Index (ISI) Expanded, accessible through the Web of Science (WoS, Thomson Reuters). 48 of those (59.3%) in journals ranked in the first and second quartile within its subject category. This database is able to make distinctions according to the type of documents. Thus, 95.1% of publications in scientific journals (77) correspond to original articles.

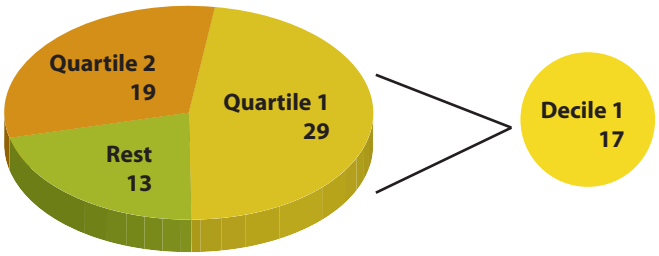
According to their scientific subject category, 87.5% of the publications by the CIEN Foundation profes-

2013 scientific productivity indicators

Total number of publications.....85
Total number of publications in the ISI citation index within the first and second quartile.....48
Cumulative impact factor of publications within the first and second quartile.....217.097
Average impact factor of the publications of the first and second quartile.....4.53
Number of collaborative publications of all kinds (CIBERNED, other national groups, international groups) within the first and second quartile.....29
Number of international collaborative publications within the first and second quartile.....19
Number of national collaborative publications (not FCIEN) within the first and second quartile.....28
Number of collaborative publications with other CIBERs and networks within the first and second quartile.....6



Publications according to the ISI citation index in 2013



sionals included in the ISI citation indexes within the first and second quartiles, have focused on: Clinical Neurology, Gerontology and Neuroscience.

By frequency order, communications to conferences are the following documental type. During the year 2013 there have been a total of 82 contributions to scientific conferences. According to the type of contribution, the overall distribution would be: lectures and oral communications (37), written poster communications (45), either in national (46) or international scientific conferences (36).

Other noteworthy activities include 46 scientific presentations at training courses.

6.2. Publications

Below are referenced the 85 scientific publications by the CIEN Foundation professionals distributed according to type of publication, international or national journals.

6.2.1. International publications

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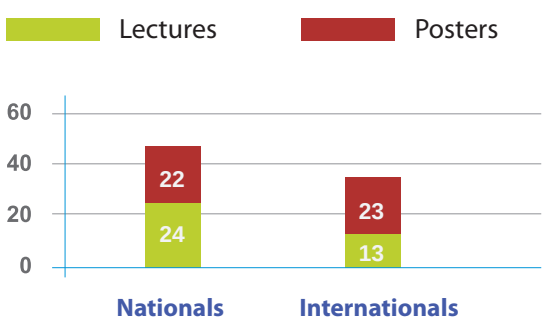
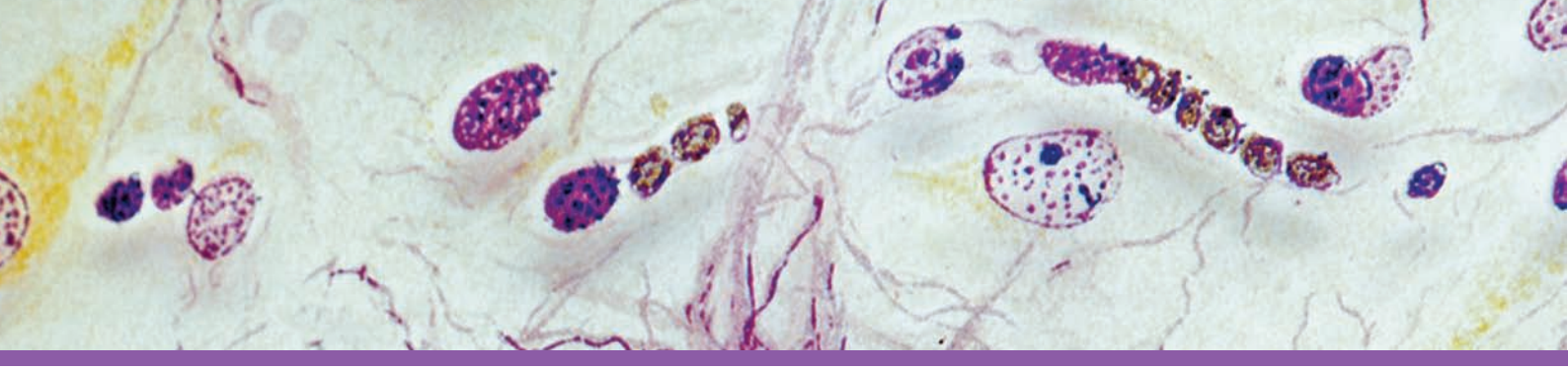
Oral communications in meetings during 2013





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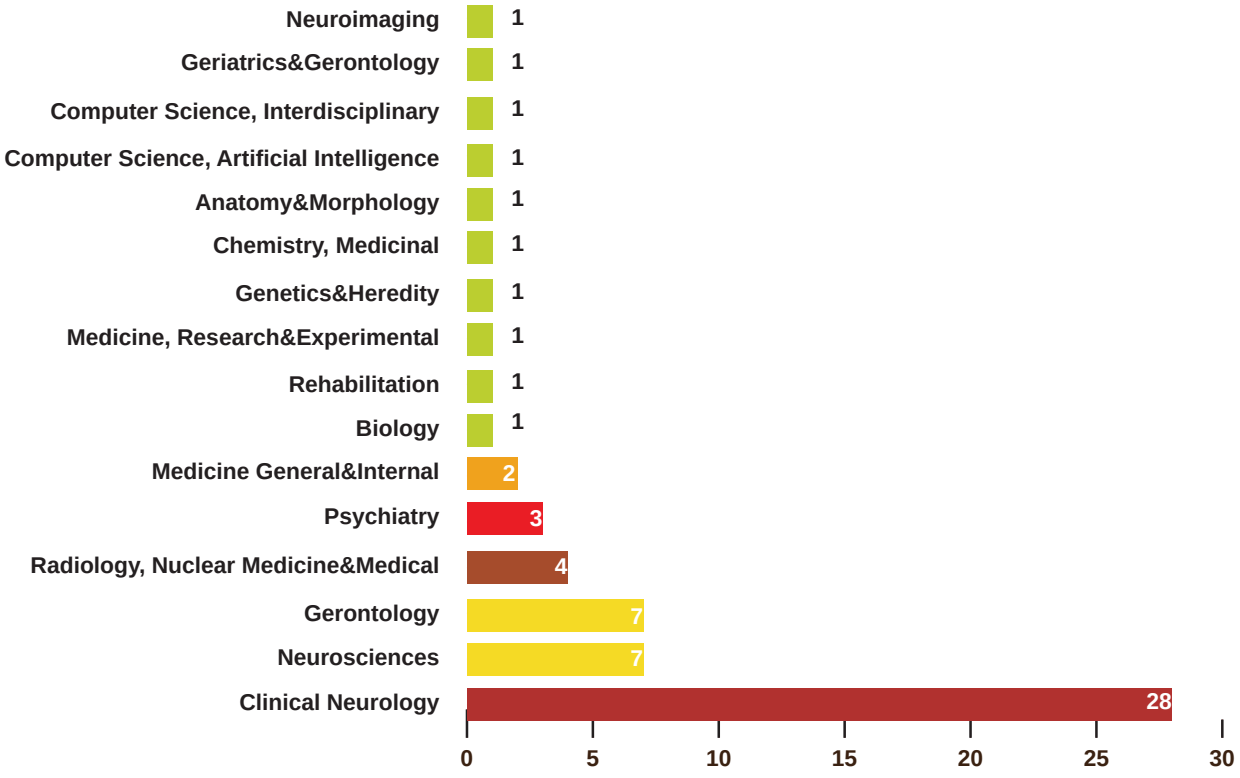
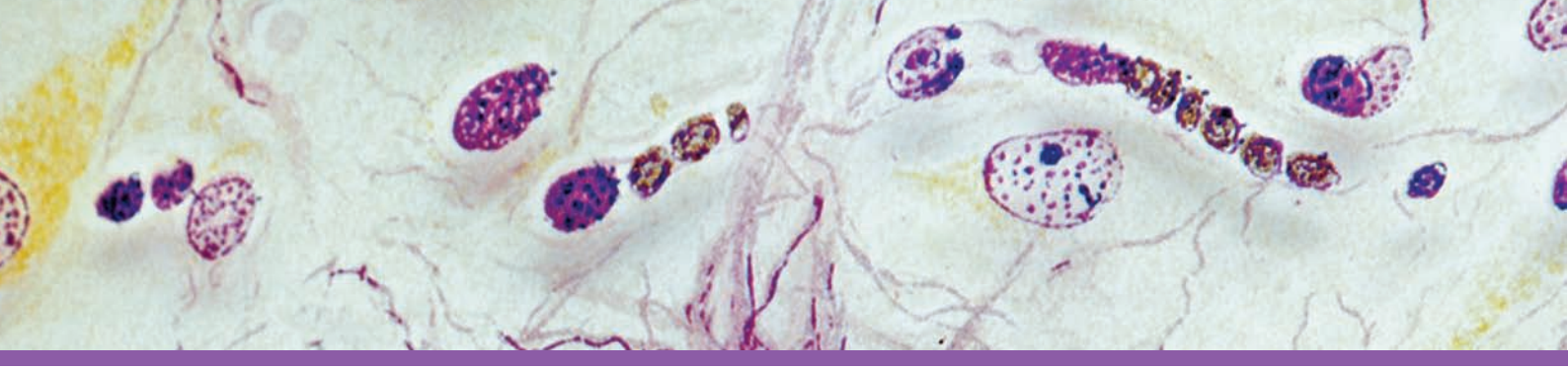
Distribution of publications by scientific category during 2013





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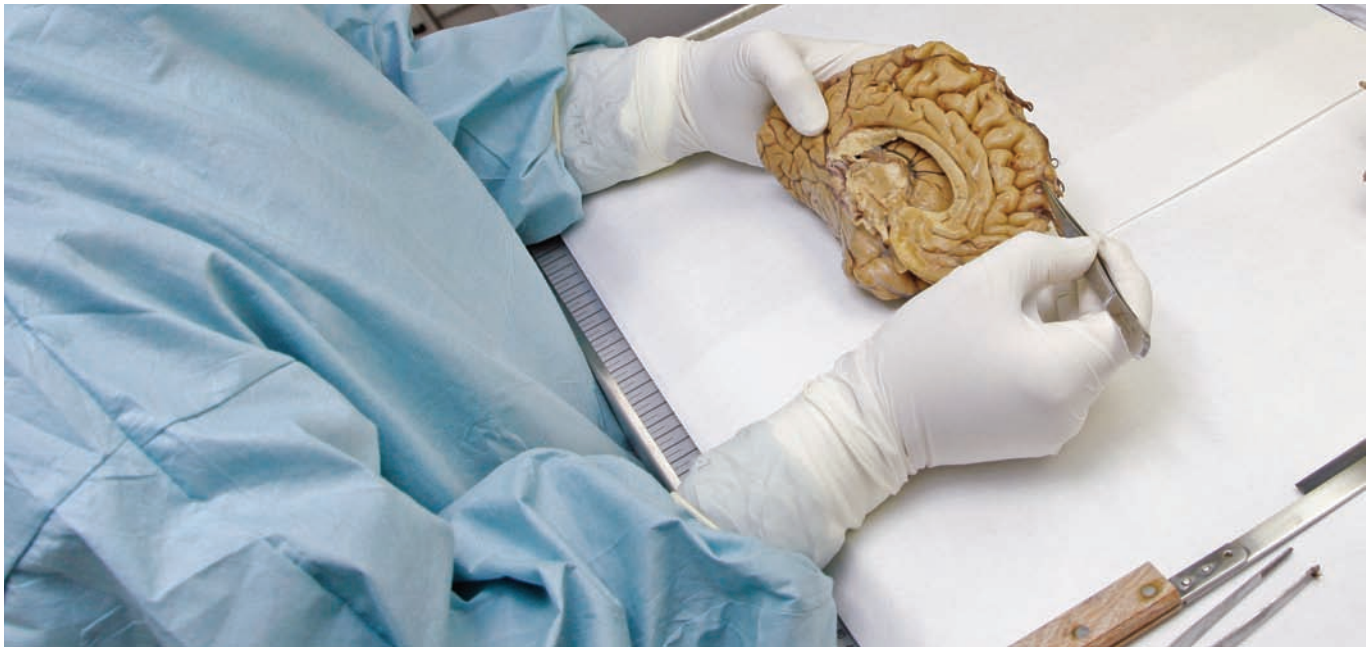

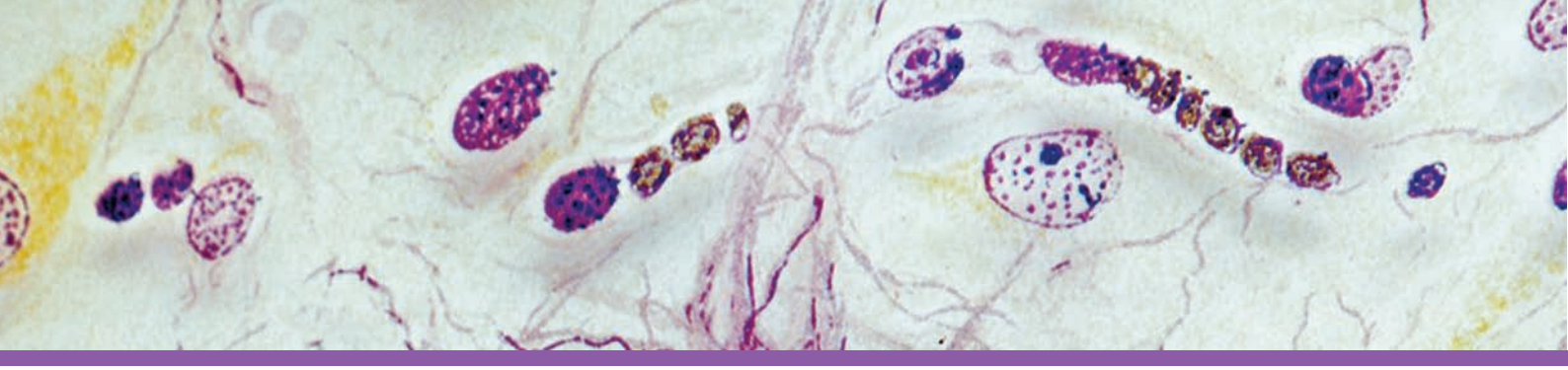

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6.2.4. Clinical guidelines

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6.3. Funded Projects

During 2013 the CIEN Foundation researchers have participated in 11 scientific research projects, of which 8 have been obtained through various national and international competitive calls and are funded by different institutions.

Funded research projects are cited below:

- **Code: FIS PI10/02567**

Principal Investigator: Dr. Pablo Martínez Martín
Title: Robot therapy in dementia
Funding agency: Fondo de Investigación Sanitaria- Carlos III Institute of Health
Duration: 2011-2013
Total budget FCIEN: 33.112,86 €
2013 budget: 2.762,43 €

- **Code: FCIEN-005/11**

Principal Investigator: Dr. Pablo Martínez Martín
Title: Vallecas Project - Alzheimer's disease early detection
Funding agency: Queen Sofia Foundation –CIEN Foundation
Duration: 2011-2016
Total budget: 1.800.000 €
2013 budget: 377.814,93 €

- **Code: 500009**

Principal Investigator: Dr. Marcel Heerink
Title: New Friends, Old emotions (Nieuwe vrienden, oude emoties; Project 2011-3-30 int)
Funding agency: SIA-Raak Project 2011-3-30 int New Friends, Old emotions
Duration: 2012-2014
Total budget FCIEN: 7.200 €
2013 budget: 2.685 €

- **Code: PI12/03018**

Principal Investigator: Dr. Alberto Rábano
Title: Profile of the age-associated Alzheimer pathology (85+CIEN Study)
Funding agency: Carlos III Institute of Health
Duration: 2013-2015
Total budget : 19.965 €
2013 budget : 7.260 €

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

Principal Investigator: Alberto Rábano
Title: Biobank platform
Funding agency: Carlos III Institute of Health
Duration: 2013-2014
Total budget: 46.500 €

- **Code: Proyecto IPT-2012-0769-010000**

Principal Investigator: Dr. Alberto Rábano
Title: Design and manufacture of a system for the diagnosis of Alzheimer's disease based on laser raman spectroscopy
Funding agency: Ministry of Economy and Competitiveness
Duration: 2012-2015
Budget: 720.218 €; CIEN Foundation 93.320 €
2013 budget: 34.962,50 €

- **Code: IMSERSO 231/2011**

Principal Investigator: Dr. Pablo Martínez Martín
Title: Pilot project for the comparative study between social robots-assisted therapy vs standard therapy in patients with dementia
Funding agency: Ministry of Health, Social Policy and Equality - IMSERSO
Duration: 2012-2013
Total budget : 33.000 €

- **Code: METC 11-4-057**

Principal Investigator: Dr. Pablo Martínez Martín
Title: Assessing and diagnosing anxiety in patients with Parkinson´s Disease
Funding agency: Michael J. Fox Foundation
Duration: 2011-2013
Total budget FCIEN: 72.905,96 €
2013 budget: 52.498,68 €

- **Code: Proyecto ARDOUIN**

Principal Investigator: Dr. Pablo Martínez Martín and Prof. Franck Durif (International)
Title: Behavioral Assessment in Parkinson's Disease. Validation of a scale.
Funding agency: Université Clermont-Ferrand (France)
Duration: 2010-2013
Budget: 9.555 €

- **Code: BCR-ALZ-2011**

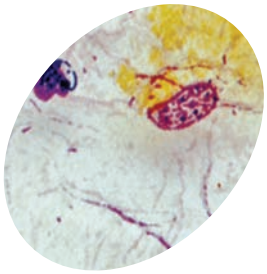
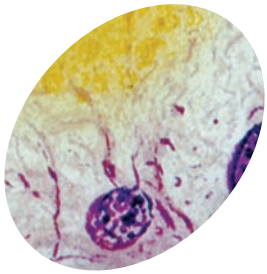
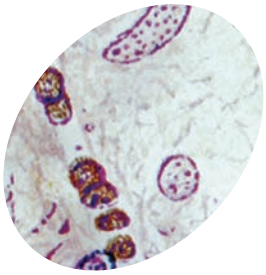
Principal Investigator: Dr. Javier Olazarán
Title: Identification of blood biomarkers for multiparametric diagnosis of Alzheimer's disease
Funding agency: Biocross
Duration: 2011-2013
Budget: 20.000€ (depending of patient r ecruitment. In 2013: 9.200 €).

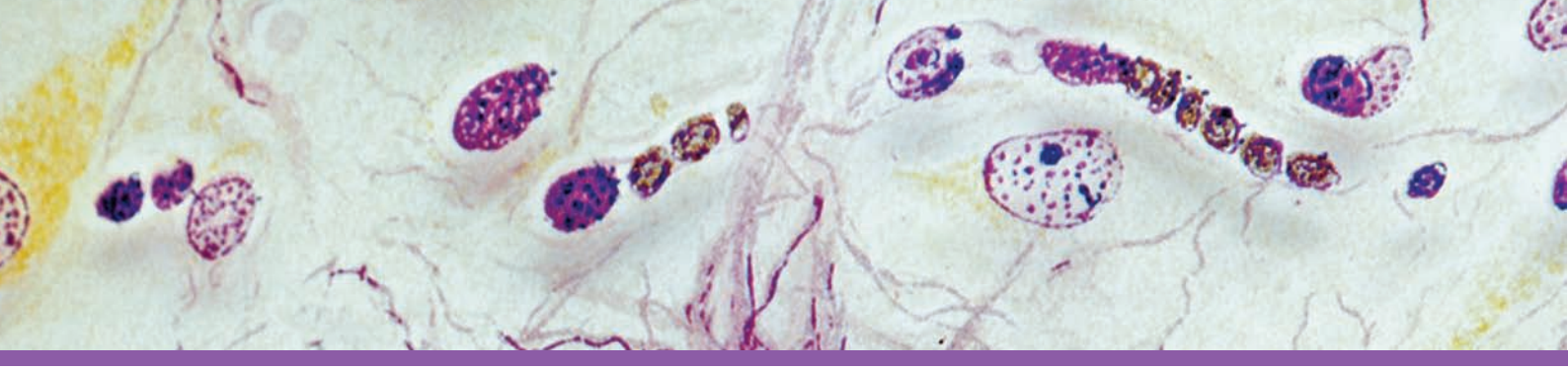
- **Code: Proyecto DENDRIA**

Principal Investigator: Dr. Alberto Rábano
Title: Innovative solutions to accelerate the identification and development of drugs for diseases of the nervous system
Funding agency: Ministry of Science and Innovation
Duration: 2010-2013
Budget CIEN Foundation : 80.000 €
2013 budget: 11.000 €

Social dissemination

One of the commitments of CIEN Foundation is transferring to the scientific community and society the most recent progress in research on alzheimer's and other dementias. In 2013 the first International Congress for Research and Innovation in Neurodegenerative Diseases (CIIIEN) was held, unifying the two largest scientific symposia in this field, promoted by the CIEN Foundation, the Queen Sofia Foundation and CIBERNED.

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Enfermedades Neurológicas
EL PAÍS
Maquinaria del tráfico celular
ABC
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BLOG

7.1. International Congress on Research and Innovation in Neurodegenerative Diseases (CIIIEN)

During 23rd and 24th of September 2013, on the occasion of the World Alzheimer's Day celebrated on September 21, was held in Madrid the first International Congress for Research and Innovation in Neurodegenerative Diseases (CIIIEN) promoted by the Queen Sofia Foundation in collaboration with the CIEN Foundation. The main objective of CIIIEN is to have a meeting forum where to share progress and relevant information about neurodegenerative disease among the scientific community.

The CIIIEN arises from the unifying of the two major scientific conferences on neurodegenerative diseases in general, and in particular Alzheimer's disease, organized in Spain: the IX International Symposium on Advances in Alzheimer's disease, which annually promoted the Queen Sofia Foundation and CIEN Foundation, and the 7th CIBERNED Scientific Forum, which annually brought together more than 500 researchers that constitute CIBERNED. The unification of the two events is a first step in creating a new operating structure in the two main institutions involved in research of neurological and neurodegenerative diseases in Spain: CIEN Foundation and CIBERNED, both under the Ministry of Economy and Competitiveness through the Carlos III Institute of Health. This new structure seeks greater effectiveness and efficiency in research, promoting the interaction of the different research groups.

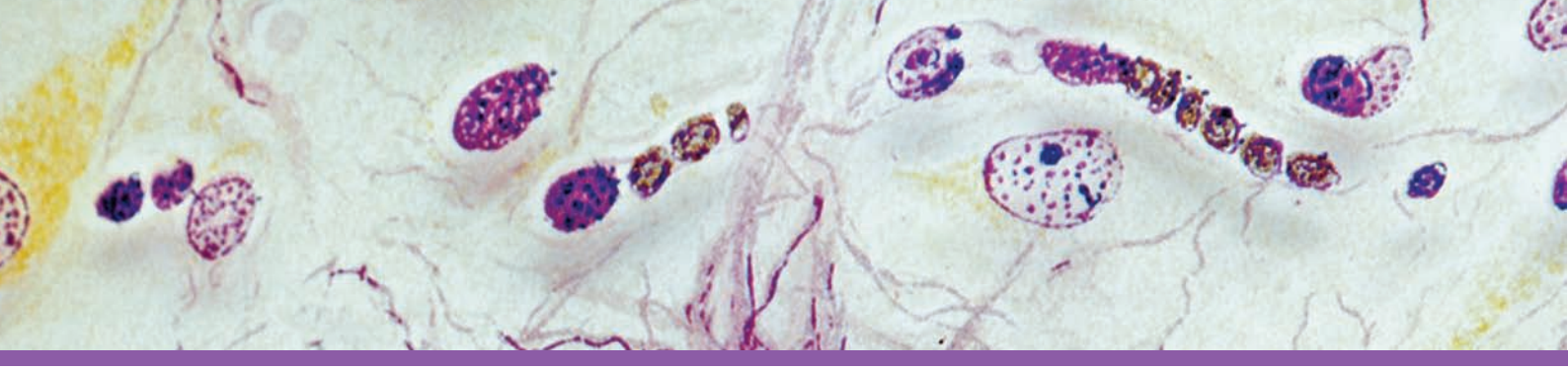
The first edition of CIIIEN was chaired by Her Majesty the Queen and the scientific program consisted of three main blocks: Alzheimer's disease, Parkinson's and Huntington's diseases, and neuromuscular diseases. Among the speakers at the Congress were include some international researchers that are reference in its field of research such as: Kenneth S. Kosik (University of California, Santa Barbara), Lawrence Goldstein (University of California, San Diego), Steven Finkbeiner (University of California, San Francisco), David J. Brooks (Imperial College, London), Davide Pareyson (Neurological Institute C. Besta, Milan) and Yves Agid (Pitié-Salpêtrière Hospital, Paris).

Thus, this event establishes on its first edition as a meeting point for the world's leading experts in neurodegenerative diseases, allowing sharing of knowledge, working methods, new developments and discoveries in a field in which international cooperation between institutions and is becoming increasingly important for obtaining optimal results in research.

7.2. 2013 Alzheimer Social Forum

On the occasion of World Alzheimer's, and in the context of the International Congress for Research and Innovation in Neurodegenerative Diseases (CIIIEN), took place the 2013 Alzheimer Social Forum. The Meliá Castilla Hotel was the place that hosted the meeting between the main associations of families of Alzheimer patients and representatives of research institutions and groups in this field, including CIEN Foundation. CIBERNED, Queen Sofia Foundation, Alzheimer-Salamanca reference Center or IMSERSO-Salamanca.

During the event, presented by the managing director of CIBERNED and CIEN Foundation, María Ángeles Pérez, the documentary "A dialogue about Alzheimer's" focused on conversations between relatives of people with Alzheimer's and neurodegeneration researchers was projected, carried out by the Queen Sofia Foundation, CIBERNED and the CIEN Foundation with participation of the major patient associations. After the screening, a panel discussion was held between researchers and patient groups, moderated by Alberto Lleó, clinical head of the Memory Unit of the Neurology Department in the Santa Cruz and San Pablo Hospital and CIBERNED principal investigator.



7.3. Dissemination activities

One of the objectives of the CIEN Foundation is to convey to society in an accessible manner the progress made in the research on neurological disease As every year, the heads of the CIEN Foundation departments have organized various activities to inform on the research work of its professionals, providing data and information of interest regarding the different neurological diseases studied, while promoting that society gets closer to the scientific community in a friendly manner.

Among the outreach activities undertaken in 2013 can be underlined the following: the Vallecas Project Volunteer's Day and the third edition of the Christmas Tree of Memories.

These activities were complemented with lectures and information days organized by the UIPA to pro-

mote participation in the Vallecas Project and engagement of CIEN Foundation Tissue Bank (BT-CIEN) personnel in various activities organized by patients associations in Spain to promote brain tissue donation as a tool to advance our understanding of neurodegenerative diseases.

Vallecas Project Volunteer's Day

The CIEN Foundation has established February 22 as the Vallecas Project Volunteer's Day in recognition of the invaluable contribution of the 1,213 volunteers who will finally participate in the Vallecas Project, a study designed and carried out by UIPA professionals to look for potential biomarkers that facilitate early diagnosis of Alzheimer's disease.

The first edition of Vallecas Project Volunteer's Day was held in the auditorium of Mutua Madrileña, partner of the event, in Madrid. The success of the initiative is evidenced by the response to this first edition: over 900 volunteers 0f the Vallecas Project attended the happening which was presented by journalist Irma Soriano, patroness of the event.

Among the various activities planned for that day can be highlighted the performance of the play What About Grandma ?, by The Cross Border Project Company, which relates how Alzheimer's disease affects the daily life of an average Spanish family, placing focus on the issues faced by the caregiver.

The Christmas Tree of Memories

In 2013 the "Christmas Tree of Memories" fulfilled its third consecutive year. This action promoted by the CIEN Foundation and Queen Sofia Foundation, seeks to raise awareness in society about the importance of scientific research to advance our understanding of Alzheimer's disease. As in previous editions, this particular Christmas tree was placed in the Queen Sofia Foundation Alzheimer Center, where people who wish so could come and hang on the tree their best Christmas memory.

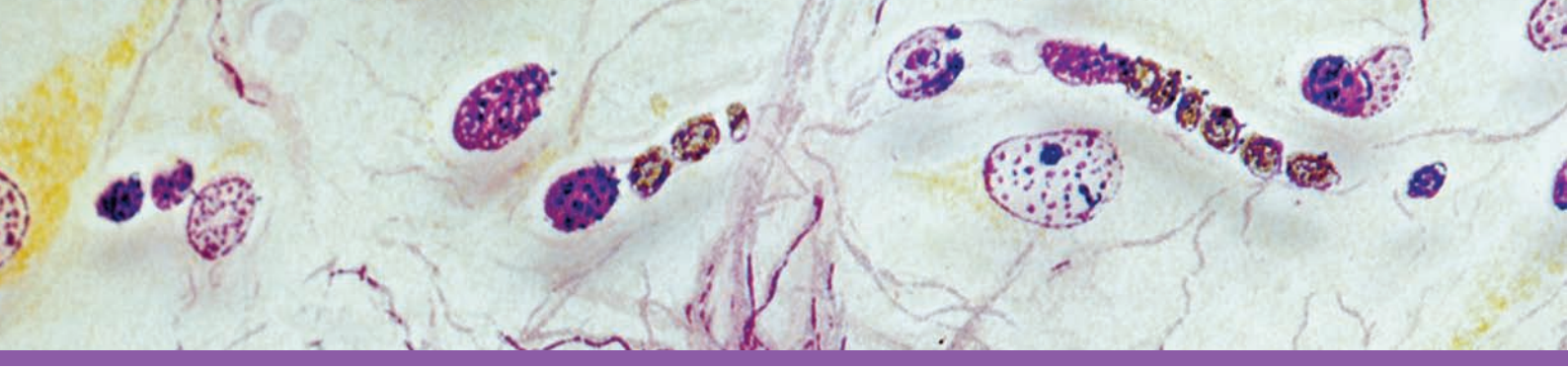
Social networks have once again played a major role in the success of this initiative. Anyone wishing to participate in this project but could not come to the Queen Sofia Foundation Alzheimer Center, could share their best memories on Twitter with the hashtag #ArbolRecuerdos. Thus, in 2013 40 tweets were received for a total of more than 120 memories hanged on the Christmas tree.

Other Outreach Activities

During 2013 the CIEN Foundation has continued to develop other actions to disseminate the research work of its professionals which have resulted so successful in previous editions. Thus, the head of the CIEN Foundation Tissue Bank, Dr. Alberto Rábano, has participated in several informative lectures organized by patient associations in Spain to promote the work done in tissue banks as the BT-CIEN and encourage the donation of brain tissue, essential for researchers to continue advancing in their research projects by having samples that accurately reflect the consequences of neurodegenerative diseases such as Alzheimer's or Parkinson's, among others.

Thus, Dr. Rábano has delivered informative lectures in collaboration with patients organizations in Soria, Valencia, Móstoles and Salamanca. These gatherings have also enabled to bring research closer to the citizens, making them participants in it and answering questions and doubts that may arise.

Likewise, it is noteworthyt the roundtable and panel discussion on dementia with participation of the scientific advisor to the British Foreign Office, held on May 8 in the Queen Sofia Foundation Alzheimer Center, which is described in more detail in the previous block of internationalization activities.



EL PAÍS

EL PERIÓDICO GLOBAL EN ESPAÑOL

FISIOLOGIA O MEDICINA

Maquinaria del tráfico celular

RAFAEL FERNÁNDEZ-CHACÓN
JUAN LERMA

James Rothman (arriba, a la izquierda), Randy W. Scheckman (arriba, a la derecha) y Thomas Südhof. / AFP / EFE / JORGE GUERRERO

Al tiempo que usted lee este artículo, millones de terminales nerviosos liberan sustancias químicas que permiten a las neuronas comunicarse y que, en última instancia, le posibilitarán entender —o al menos eso esperamos— lo que pretendemos contarle. Bernhard Katz (premio Nobel en 1974) reveló que un impulso nervioso aumenta la concentración del ion calcio causando la liberación del neurotransmisor almacenado en pequeños paquetes, las vesículas sinápticas. De manera similar se produce la liberación al torrente sanguíneo de hormonas, como la insulina en las células pancreáticas, o de los mediadores inflamatorios en las células del sistema inmune.

Este año, el Premio Nobel de Fisiología o Medicina ha reconocido los descubrimientos de la maquinaria molecular que hace que las sustancias que una célula fabrica y almacena puedan liberarse de manera precisa y controlada, salvando la membrana celular que separa el interior celular del medio externo. Los galardonados han sido James E. Rothman (Universidad de Yale), Randy Scheckman (Universidad de Berkeley) y Thomas C. Südhof (Universidad de Stanford).

A principios de los años ochenta, Scheckman utilizó un organismo unicelular, la levadura de la cerveza, para identificar genes clave codificadores de proteínas implicadas en el transporte intracelular. Las levaduras se parecen mucho a las células de mamífero y su manipulación genética es sencilla. En levaduras mutantes, Scheckman asoció genes concretos con alteraciones específicas del tráfico intracelular.

Rothman estudió el transporte en las cisternas de un compartimento celular —el aparato de Golgi— de donde purificó proteínas que serían cruciales en los modelos de fusión vesicular, como NSF y SNAP. Vivek Malhotra, hoy en el Centro de Regulación Genómica de Barcelona, estudió con Rothman la proteína NSF.

Las maquinarias moleculares dentro de la célula están formadas por múltiples proteínas que interaccionan entre sí como lo haría la maquinaria de un reloj. En 1993, Rothman, interesado en identificar las piezas de la maquinaria encargada de la fusión vesicular, utilizó, en colaboración con Richard Scheller (hoy en Genentech, EE UU), las proteínas NSF y SNAP como cebos para capturar bioquímicamente otras que engranasen con ellas. Así identificó tres proteínas de los terminales nerviosos previamente descritas por otros investigadores (sintaxina, SNAP25 y VAMP/sinaptobrevina), cuya asociación denominó posteriormente complejo SNARE, y propuso que este podía constituir la maquinaria general para posibilitar la fusión de una vesícula con la membrana celular, igual que dos pompas de jabón de funden cuando se tocan.

Es en el sistema nervioso donde esta maquinaria de relojería ha de tener mayor precisión, pues la transmisión sináptica acontece en milésimas de segundo. En 1985, Südhof inició su carrera con el propósito —en gran parte cumplido— de identificar todas las proteínas de una vesícula sináptica y comprender cómo estas inducen la liberación de los neurotransmisores, utilizando una poderosa combinación de genética y fisiología en ratones. Tanto de manera independiente, como en colaboración con el bioquímico Reinhard Jahn (Instituto Max-Planck, Göttingen) y con el biólogo estructural barcelonés José Rizo (UT Southwestern, Dallas), Südhof identificó y definió el papel de múltiples proteínas clave (incluidas las SNARE) en la fusión de las vesículas con la membrana celular. Una de estas proteínas es la sinaptotagmina, que Südhof demostró ser el sensor de calcio necesario para la liberación rápida de neurotransmisores. En esta demostración, una de las aportaciones clave de Südhof, participaron dos españoles, uno de los autores de este artículo (RF-C) y Rizo. La búsqueda de este sensor de calcio era una pregunta de enorme interés que permanecía abierta en la neurociencia desde hacía 50 años.

> Conocer a fondo el cerebro es esencial para tratar sus enfermedades

> Las investigaciones galardonadas son el paradigma de la investigación básica

La insaciable curiosidad de Südhof le ha llevado a abrir nuevas fronteras en la biología de los terminales nerviosos que han dado lugar al descubrimiento en su laboratorio de otras proteínas, las neurexinas y las neuroliguinas, cuya disfunción está implicada en trastornos cerebrales graves, como el autismo.

Las investigaciones premiadas este año son el paradigma de la investigación básica de excelencia, realizada para saciar la curiosidad humana, motor del progreso y esencial para avanzar en beneficio de la humanidad. En los tiempos que corren, es de esperar que noticias como esta estimulen el apoyo decidido a la investigación básica de calidad. La semana pasada, en la Universidad Internacional de Andalucía en Baeza, al poco de recibir la noticia de la concesión del Premio Nobel, Südhof declaraba que el conocimiento profundo del cerebro es esencial para poder tratar con éxito sus enfermedades. No podemos estar más de acuerdo con esa reflexión.

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ABC

La Reina, junto a la ministra de Sanidad, ayer en Madrid EFE

Congreso Internacional en Madrid

El alzhéimer, una batalla de todos

Su Majestad la Reina inauguró ayer en Madrid el Congreso Internacional sobre Investigación e Innovación en Enfermedades Neurodegenerativas, en el que colabora la fundación que lleva su nombre. La ministra de Sanidad, que acompañó a Doña Sofía durante la apertura de esta cumbre científica, reconoció «la especial sensibilidad» de la Reina «hacia las personas afectadas por la enfermedad de Alzheimer y sus familias, así como el decidido apoyo que les presta a través de su fundación». Ana Mato abogó por la necesidad de trabajar «de manera conjunta» contra una enfermedad que sufren en España 600.000 personas, cifra que podría aumentar notablemente en función del progresivo envejecimiento de la población. El «Proyecto Alzheimer» de la Fundación Reina Sofía, concebido en 2002 a partir del interés personal de la Reina por la necesidad creciente de investigación y sensibilización en torno a esta enfermedad, comprende el Centro Alzheimer Fundación Reina Sofía, inaugurado en 2007, además del apoyo continuado a la Unidad de Investigación del Proyecto Alzheimer, que actualmente gestiona la Fundación CIEN.

7.4. Presence in media

Throughout 2013, the CIEN Foundation has maintained its presence in media as well as its position as benchmark institution for journalists and when it comes to collect information on neurological diseases.

During the year, a total of 32 press releases with information of interest have been sent to journalists. As a result of contacts with media, the CIEN Foundation department of communication has reached a total of 679 impacts achieved compared to 982 a year earlier. Within this coverage obtained in written press, radio, television and online platforms can be highlighted the 40 interviews carried out by CIEN Foundation professionals, mainly focused on two key milestones on the exercise: the "Vallecas project" and the first edition of CIIIEN. Also, some of the interviews have also sought the opinion of CIEN Foundation researchers to evaluate different advances made in the field of neurological diseases, especially Alzheimer's research.

7.5. Presence in social networks

The CIEN Foundation remains giving continuity to the social networks created in 2011 as a channel for disseminating its activities and to communicate with the audience interested in research progress and developments in neurodegenerative diseases.

Thus, the digital presence of the CIEN Foundation has been strengthened by the interaction with the users and stakeholders. Today we can say that we are a gathering point for all those interested in neurological research, also on the Internet.

Facebook

Fiscal year 2012 ended with a total of 1,675 supporters following the page. In late 2013 the CIEN Foundation had over 2,558 followers, reaching to a total of 1,100 people.

Twitter

The year 2012 ended with 4,950 followers, a number that by the end of 2013 grew to constitute a community of over 8,600 followers. In one year, the CIEN Foundation has doubled its reach in this social network and keeps constant interaction with his supporters, receiving numerous comments, re-tweets and publications bookmarked.

Linkedin

In this profile aimed at a professional audience, the CIEN Foundation publishes information of interest in various groups, The profile is aimed at a professional audience, promoting science and public scientific debate.

Google+

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

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