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Fundación Centro Investigación
Enfermedades Neurológicas

10th Anniversary
2007 - 2017



Annual Report 2017

CIEN FOUNDATION

Research Center for
Neurological Diseases Foundation
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*"... ten years rarely run in vain,
and the one who looks back is usually
surprised of the road you walk in a decade. "*

Emilia Pardo Bazán. Los pazos de Ulloa.



Annual Report 2017



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Profile and presentation

The CIEN Foundation is a leading institution in the research of neurodegenerative disorders, especially in Alzheimer's disease. With the support of the Carlos III Institute of Health and the Queen Sofia Foundation, it proposes a model of comprehensive approach to Alzheimer's where applied research is a fundamental mainstay. In the year 2017, the Queen Sofia Foundation Alzheimer Center, headquarters of its research activities, has reached 10 years at the service of society. A decade marked by achievements and milestones that have marked the progress of the CIEN Foundation.





1.1. Who we are



A FOUNDATION FROM THE PUBLIC SECTOR

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

Among its founding objectives are supporting, promoting and coordinating research in neurological diseases, especially neurodegenerative disorders. It also highlights its unifying and coordinating role of leading Spanish research groups in this field.

The CIEN Foundation is based at the Queen Sofia Foundation Alzheimer Center, whose construction was called the Alzheimer Project. Once the Alzheimer Center was built, it was divided into a residence for healthcare and follow-up of the patients and an Alzheimer Project Research Unit of the (UIPA, for its acronym in Spanish), whose main project is the Vallecas Project.

COLLABORATION WITH THE QUEEN SOFIA FOUNDATION

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

As indicated, the headquarters of the CIEN Foundation are located in the Queen Sofia Foundation Alzheimer Center, a pioneering center in Spain in which to comprehensively address the consequences that Alzheimer's disease causes both on patients and their family environment. Since its opening in 2007, at the neighborhood of Vallecas, Madrid, seeks to respond to the social health project proposed by the Alzheimer Project of the Queen Sofia Foundation.



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

Only two institutions in Spain participate in the European Union Joint Programming for Disease Neurodegenerative Diseases (JPND): 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 representatives of this organization after being proposed by the Carlos III Institute of Health.

In addition, both CIEN Foundation as CIBERNED are integrated into the international Network of Centers of Excellence in Research on Neurodegeneration (COEN), mostly composed by European research centers.



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AN INNOVATIVE, INTEGRATED VISION OF THE FIGHT AGAINST ALZHEIMER'S DISEASE

The CIEN Foundation and the Queen Sofia Foundation share a common perspective on action in relation to Alzheimer's disease: This disease requires a comprehensive approach model where research should be one of the fundamental pillars. The leading exponent of this integrative model is the Queen Sofia Foundation Alzheimer Center, where the main backbones of Alzheimer Project converge.

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

The management model implemented by the Queen Sofia Foundation Alzheimer Center has sought to summon the will and interests of all parties involved: Administration (State, Regional and Local) and civil society. For this reason, the management of UIPA, devoted to research, was assigned to the CIEN Foundation, while the Ministry of Family and Social Affairs of the Region of Madrid is responsible for healthcare and training activities.



FOCUSED ON RESEARCH IN NEURODEGENERATIVE DISEASES

The CIEN Foundation is in charge of the following tasks: implement a model of translational research that allows to effectively and efficiently transfer the scientific advances achieved in basic research to clinical practice; promote the continuous training of professionals involved with the research in neurodegenerative diseases through seminars, lectures and doctoral theses; disseminate the calls launched by funding agencies, both nationally and internationally, promoting participation; and encourage the implementation of coordinated research projects in neurodegenerative diseases.

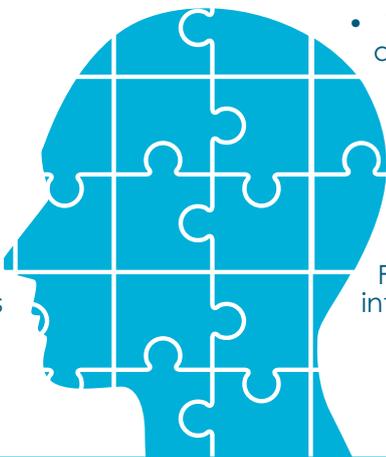
But its function does not end here. From the administrative point of view, the CIEN Foundation is also responsible for managing other centers related to research in neurodegenerative diseases such as the Network Center for Biomedical Research in Neurodegenerative Diseases (CIBERNED, for its acronym in Spanish), maintaining collaboration agreements with the Carlos III Institute of Health for carrying out those management activities.





1.2. The CIEN Foundation in 2017

- During 2017, 31 original articles have been published in specialized journals, 22 of which have been in journals classified in the first and second quartiles, with an average impact factor of 7.56, which represents an increase (11.36%) compared to 2016, following the upward trend in recent years.
- During this year, the CIEN Foundation has continued its international collaborations, so that 50% of the publications were studies carried out in collaboration with foreign institutions, 43.75% with Spanish institutions and the remaining 6.25% were carried out only by researchers from the CIEN Foundation.
- The Clinical Trial Sat-CIEN-02 obtained approval from the Spanish Agency for Medicines and Health Products and the Central Ethics Committee.
- During 2017, the CIEN Foundation maintains its participation as co-owner in two active patent applications, in national phases of different countries, both licensed to Raman Health Technologies.
- In May 2017, the fourth yearly evaluation of the Vallecas Project concluded with 772 participants. At the end of the year, 658 volunteers from the fifth visit have been assessed and the sixth visit has begun, of which 276 have been evaluated.
- Presentation of the canonical brain "Vallecas Brain", a virtual model of the brain obtained from magnetic resonance images of more than 1,000 healthy brains, volunteers of the Vallecas Project, without dementia, aged between 70 and 85 years. The model serves as a reference template with which to compare individual magnetic resonance images and thus identify early on the anomalies characteristic of the onset of Alzheimer's disease and other neurodegenerative diseases.
- Many communications have been presented to national congresses such as the LXIX SEN Annual Meeting and international conferences, such as the Alzheimer's Global Summit or the AAIC2017. Thus, the work carried out by the different departments related to studies such as the Vallecas Project has been made known.
- For the fifth consecutive year, the well established Vallecas Project Volunteer's Day was held, in recognition of the collaboration of these people in favor of research.
- Alzheimer Leon participates in the funding of the Vallecas Project, thanks to the financial support of dozens of sponsors, who in the last edition of the Mano Amiga Awards, joined their efforts to support research projects focused on the disease.
- Throughout 2017, the Tissue Bank reached 800 record cases and the number of donated brains from the Alzheimer Center exceeded 130.
- The Carlos III Institute of Health approved the new development phase of the National Network of Biobanks Platform (2018-2020), to which the BT-CIEN belongs.
- The Scientific Director of BT-CIEN, was appointed Coordinator of the Spanish Group of Neuropathology of the Spanish Society of Neurology and the Spanish Society of Pathology.
- Several educational cooperation agreements have been signed between different public universities and the CIEN Foundation to carry out external internships (curricular and extracurricular).



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- New call for Queen Sofia Foundation-MAPFRE Scholarship 2017 for a PhD in engineering, neuroscience, physics or bioinformatics to work in a research program focused on the study of neurodegenerative disorders using an approach that combines mathematical modeling and computational simulation in order to achieve the characterization of predictive algorithms.
- During 2017 the CIEN Foundation maintains its commitment to the Youth Employment Operative Program of the Council of Education, Youth and Sports of the CAM, through the establishment of a new labor contract for the promotion of youth employment and the implementation of the Youth Guarantee in R+D+I.
- In September, the CIEN Foundation, jointly with the Champalimaud Foundation, the Queen Sofia Foundation and CIBERNED, organized the scientific meeting Global Summit on Alzheimer's Research & Care Lisbon 2017. This special edition of the well established International Conference of Research and Innovation in Neurodegenerative Diseases (CIIEN), brought together prestigious scientists, such as Nobel Prize laureates in Medicine Richard Axel (Columbia University) or John O'Keefe (University College London) at the Champalimaud Center for the Unknown. The CIEN Foundation presented the predictive algorithm based on 5 years of research from the Vallecas Project, to identify conversion variables between a cognitively healthy status and MCI.
- The number of impacts during 2017 on the mass media was around 2,400, increasing by 48% compared to 2016. Thus, for example only during the actions corresponding to the Alzheimer's Global Summit Lisbon 2017 (Lisbon, 18-21 September 2017), more than 350 impacts were generated in the press (national and international agencies and media outlets), 220 in online media, plus the notorious impact on social media, especially Twitter.
- Inauguration of the traditional "Christmas Tree of Memories" that returned in 2017 to be set up in the City of Madrid and the Villa de Vallecas Market.
- In April 2017, an addendum to the 2012 collaboration agreement between the Queen Sofia Foundation and the CIEN Foundation for reinforcing the FCIEN Tissue Bank (BT-CIEN) project was signed.
- In May 2017, we participated in the meeting of the National Dementia Group by contributing to the preparation of Axis IV of the National Alzheimer's Plan.
- On May 22, 2017, H.M. Kings Felipe and Letizia, accompanied by H.M. King Juan Carlos and Queen Sofia together with other personalities, presided over the main celebration of the 40th Anniversary of the Queen Sofia Foundation and the 10th anniversary of the Queen Sofia Foundation Alzheimer Center at the CIEN Foundation headquarters. During the event, the projects carried out by the Queen Sofia Foundation jointly with the CIEN Foundation were highlighted, such as the Vallecas Project and its fight against Alzheimer's.





1.3 Letter from the Managing Director M^a Ángeles Pérez



It is my pleasure to address you at the end of this special year for us, in which the Queen Sofia Foundation Alzheimer Center has completed 10 years, to review the milestones that marked 2017 and strengthened our role as leaders in research in neurodegenerative diseases.

Thanks to the constant support of the Queen Sofia Foundation and the work of those who make up the Cien Foundation, we have continued our work of

applied research in a field of great importance for the health and well-being of our society. Guided by our commitment to a translational research model and the internationalization of our projects, we have contributed new advances in the areas of basic, clinical and epidemiological neurology to the scientific community.

Our scientific activity has turned into the publication of 31 original articles in specialized journals, 22 of them classified in the first and second quartiles. An upward trend that demonstrates the quality of the research carried out at the Cien Foundation. Likewise, 50% of the works published in 2017 are the result of collaboration with prestigious international institutions.

The "Vallecas Project" continues to be one of our main projects. The success of this study to advance the early diagnosis of Alzheimer's disease has made it possible that, at the end of the year, in the fifth follow-up visit, 658 volunteers have participated while we have begun the sixth visit. We want to thank and recognize their work in favor of research to all volunteers, since our work would not be possible without their collaboration.

Together with the results of the "Vallecas Project", other current research activities were presented at the Global Summit Alzheimer's Research Lisbon 2017 organized by the Queen Sofia Foundation and the Cien Foundation jointly with the Champalimaud Foundation and CIBERNED. A special edition of the already well established International Congress of Research and Innovation in Neurodegenerative Diseases (CIIEN), chaired and inaugurated by Queen Sofia and the President of the Portuguese Republic, Marcelo Rebelo de Sousa, convened for the fifth consecutive year with scientists of recognized prestige, including Richard Axel and John O'Keefe, Nobel Laureates in Medicine in 2004 and 2014, respectively to discuss Parkinson's, Alzheimer's and

María Ángeles Pérez Muñoz
Cien Foundation Managing Director

1. PROFILE AND PRESENTATION

other neurodegenerative diseases. In addition, in February we had the honor of organizing in our headquarters the first DEGESCO (Dementia Genetics Spanish Consortium) Symposium on dementia genetics.

On the other hand, the CIEN Foundation Tissue Bank (BT-CIEN) has continued its growth, reaching 800 brain tissue donors for research at the end of the year. More than 130 of these donations come from the Queen Sofia Foundation Alzheimer Center, with which we collaborate closely.

In terms of human resources, we believe in the recruitment, training and retention of talent as a window towards the growth of the CIEN Foundation. Our commitment to the new generations has led us to establish different collaboration agreements with universities and national education centers for the reception of students who want to carry out their internships in our facilities. In addition, we seek to open the Foundation doors to young researchers through the calls for grants for research from the Queen Sofia Foundation-MAPFRE and the youth employment program of the Region of Madrid.

As science communicators, we have continued to strive to make society aware of the importance of research in neurological diseases. Our "Christmas Tree of Memories" accompanied us for another year during the Christmas holidays in the Municipal Market of Villa de Vallecas. Due to its great reception over the years, last Christmas we inaugurated a second Christmas tree of memories in the Madrid City Hall, thus expanding its reach. In spring we also celebrate the tribute to the volunteers of the "Proyecto Vallecas" with the participation of the Radio Televisión Española (RTVE, for its acronym in Spanish) choir. A yearly event to thank their unselfish participation in the project. The media has echoed our news and activities, especially on the occasion of the celebration of the Alzheimer's Global Summit in Lisbon,

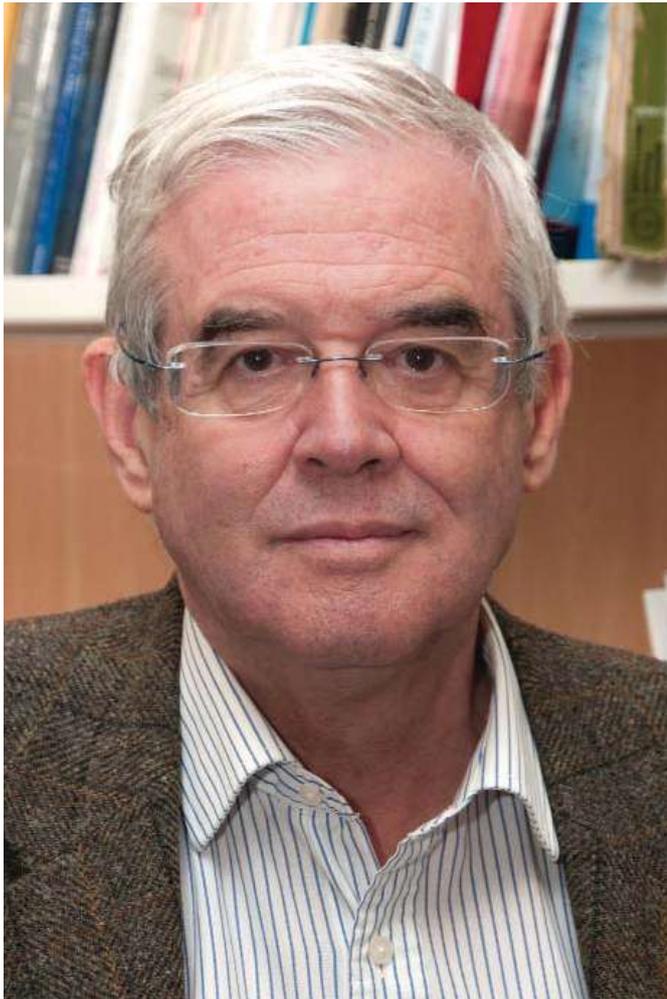
that reached a visibility of more than 500 impacts and a great activity in social media.

The good results of each initiative of the CIEN Foundation, during 2017 and previous years, are the result of the work of all of us who are part of this family, as well as due to the invaluable support of our patrons and benefactors. Together we can build the future of CIEN Foundation and continue the fight to improve the quality of life of people.





1.4. Letter from the Scientific Director Jesús Ávila



Next to reach the ten years of our Queen Sofia Alzheimer Center, I would like to thank H.M. Queen Sofia for its pioneering idea of building this center, and the Queen Sofia Foundation for their constant support, which has been one of the keys to fulfilling this decade. Although tango says that 20 years is nothing, in our case 10 years have fortunately given many fruits that in the near future will be described in more detail.

These achievements are the result of the work of the members of the CIEN Foundation, over the last decade. Therefore, I would like to thank the initial work of Dr. Pablo Martínez (and his collaborators) that allowed the design and launching of the "Vallecas Project" and to all those who have carried out or currently perform their efficient work in the Center through the different departments that make it up. A work that, as mentioned is giving good results as can be seen by reading this report. In this work has been essential the collaboration and dedication of volunteers from the "Vallecas Project" and associations of relatives of patients with Alzheimer's disease.

Now it is necessary to look for that in the next decade of the Center (until reaching the age of 20) we can overcome what has been achieved during this first stage, because it will be good for the society we serve.

Regarding some events carried out in 2017, it is worth mentioning the publication of good scientific articles, some of them in collaboration with other institutions. As well as the celebration at the Queen Sofia Alzheimer Center of the first DEGESCO Symposium, chaired by H.M. Queen Sofia. The Symposium was organized by Drs. Miguel Medina and Miguel Calero, with the aim of bringing together the best national experts on the genetics of neurodegenerative diseases. In addition, we have collaborated in commemorating the 40th Anniversary of the Queen Sofia Foundation and the 10th Anniversary of the Queen Sofia Foundation Alzheimer Center. And, already outside our headquarters, the celebration of a special edition in Lisbon, of the CIEN: the Alzheimer's Global Summit Lisbon 2017, at the Champalimaud Center for the Unknown, chaired by H.M. Queen Sofia.

Thank you all.

Jesús Ávila de Grado
Scientific Director of CIEN Foundation

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1.5. A DECADE OF RESEARCH AT THE QUEEN SOFIA FOUNDATION ALZHEIMER CENTER

On the occasion of the 10th Anniversary of the Queen Sofia Foundation Alzheimer Center, we reflect on the scientific path traced and the achievements made as a reference institution in the research of neurodegenerative diseases.

CIE Foundation professionals review their arrival at the Alzheimer Center, highlighting the reinforcing and specialization of the different research projects over this 10-year period.

SOME HISTORIC MILESTONES 2007-2017

2008



- Launching of the Alzheimer Project Research Unit
- Beginning of activity in the departments of Neurology and Neuropsychology
- Execution of the first Neuroimaging projects such as DEMCAM



2010

- Establishment of the CIE Tissue Bank (BT-CIE, for its acronym in Spanish)
- The Vallecas Project pilot study
- Strengthening of collaborations with private entities

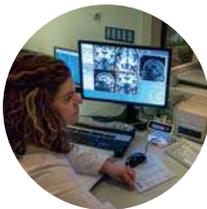


2012

- Launch of the Pathfinder call for projects of COEN
- The Vallecas Project recruitment and basal evaluation reached the first 1,000 volunteers
- BT-CIE obtains the accreditation of its Quality Management system

2007

- Inauguration of the Queen Sofia Foundation Alzheimer Center
- Beginning of activity in the departments of Neuropathology, Neuroimaging and Molecular Genetics
- Celebration at the Center of the Symposium "Advances in Alzheimer's Disease"



2009

- Establishment of the CIE Foundation Training Program
- First clinical trials in Neurology
- Creation of a communication department specialized in health

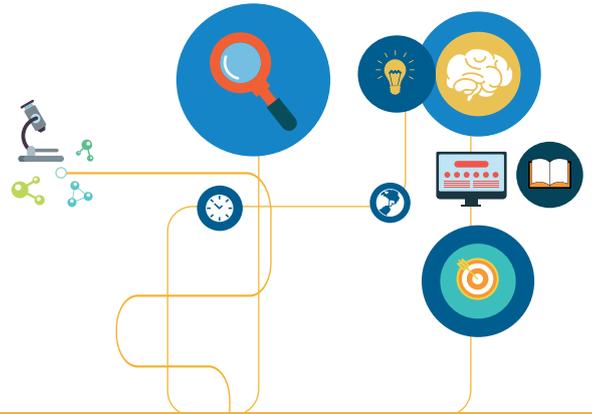


2011

- Start of the Vallecas Project
- Admission into the International Network of Centers of Excellence in Neurodegeneration (COEN)
- Organization of the summit "Alzheimer International 2011"
- Launching of the "Christmas Tree of Memories" campaign



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2014



- BT-CIEN integrates into the National Biobank Network
- II International Congress CIIEN
- Magnetic resonance studies reached over 5700 records



2016



- Delivery of the BT-CIEN brain donor card
- IV International Conference CIIEN
- Completion of the third visit of the Vallecas Project

2013

- First International Congress on Research and Innovation in Neurodegenerative Diseases (CIIEN)
- Institutionalization of the Vallecas Project Volunteer Day



2015

- Launch of the seminar series of the CIEN Foundation
- III International Conference CIIEN
- First publications of scientific results from the Vallecas Project



2017

- Celebration of the 40th Anniversary of the Queen Sofia Foundation and the 10th Anniversary of the Queen Sofia Foundation Alzheimer Center
- Special edition of the CIIEN Conference: Alzheimer's Global Summit Lisbon 2017.

* If you wish to consult the scientific activity data from previous years, the CIEN Foundation has uploaded on its website the annual reports since they began to be published in the year 2009.





INTERVIEW

10th Anniversary Queen Sofia Foundation Alzheimer Center

Eva Alfayate, technical coordinator of the CIEN Foundation Neuroimaging Area

How and in what year does Eva Alfayate arrive at the Alzheimer Center?

On March 7, 2007 I arrived with my laptop to the CIEN Foundation to prepare the visit the next day of their Majesties the King and Queen of Spain,

It seemed to me that a very exciting, novel and singular project was opening for me professionally. After dedicating myself for more than 15 years to Magnetic Resonance in the clinical field, the wonderful world of Neuroimaging research crossed my path. Undoubtedly, the greatest professional challenge I had faced so far.

What do you remember and what would you highlight from the first years at the Alzheimer Center? And today, what would you highlight?

Basically I would like to highlight the illusion of the small team of researchers and managers of the beginning of the Project: Julián, M^ª Ángeles, Almudena, Juan, Pablo, etc.

We worked like a closed circle, with a lot of energy and enthusiasm, with great institutional support and an inescapable responsibility and commitment.

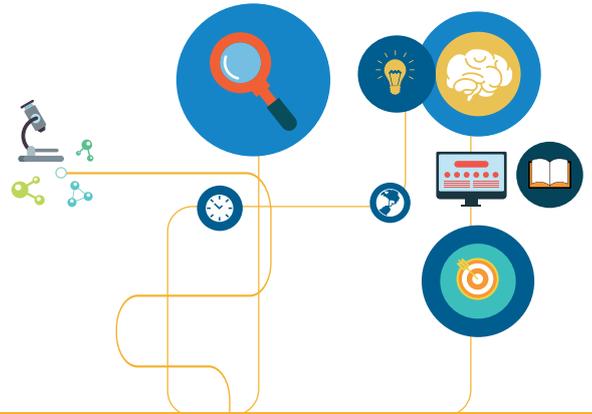
After 10 years, we can say that we have specialized in dealing with the patient and the family member with Alzheimer's disease and other dementias.

On the other hand, I would highlight that our protocols have been consolidated reaching solid quality standards.

In addition, our institutional and personal relationships with the different principal investigators have been strengthened, both by the technical skills in the acquisition, and by the human quality in treating the volunteers.



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What do you think makes a Center like this one become a benchmark in the fight against Alzheimer's?

Without any doubt, the uniqueness of the human team, a group of multidisciplinary professionals with a specific focus on the study of Alzheimer's disease, together with the infrastructure of the facilities; the location of the Research Center annexed to the Patient Residence with this pathology, all this makes the Center undoubtedly a benchmark for the study of Alzheimer's disease.

How do you see the Alzheimer's Center in another 10 years?

With the economic resources necessary to carry out cutting-edge research as well as with updated equipment and a consolidated team of researchers.

With the resources and support to disseminate the work and progress in national and international congresses.

As a reference center where professionals of different categories are trained, specifically dedicated to the areas that the CIEN Foundation has: Neuropathology, Neuroimaging, etc.





INTERVIEW

10th Anniversary Queen Sofia Foundation Alzheimer Center

Alberto Rábano, Director of the CIEN Foundation Tissue Bank

How and in what year does Alberto Rábano arrive at the Alzheimer Center?

I had the opportunity and luck to work with the original group that helped to design the Alzheimer Project Research Unit (UIPA). Several specialists from different fields related to Alzheimer's, clinicians, epidemiologists, basic researchers, neuropathologists, among others, were summoned from the ISCIII to implement this idea. Pablo Martínez, a neurologist affiliated to the National Epidemiology Center, was in charge of coordinating this working group. My role in that group was related to my previous work at the brain bank in Madrid, the Tissue Bank for Neurological Research.

When we started working on the proposed Alzheimer Project, I believe around 2004, I was working at the Alcorcón Hospital Foundation, where we have developed since 1998 a good part of the work of the brain bank. The Neuropathology Unit that I was managing at the hospital at the time had been since 2001 a national reference center for the neuropathological diagnosis of prion diseases. It was a very interesting period in which we all were outlining the characteristics of the Center, its activity, structure, endowment, human resources, etc. This is how the future Department of Neuropathology, with its own facilities, was defined in the Center.

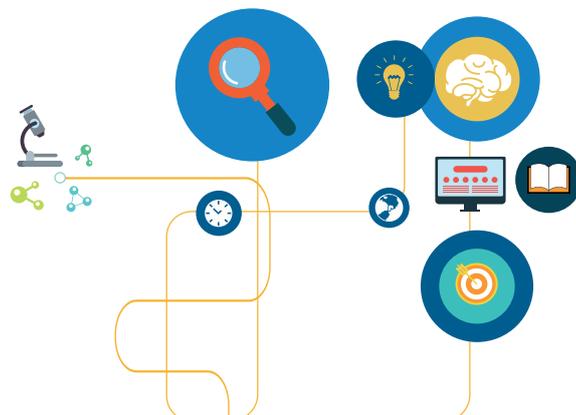
From the beginning, my role was responsible for the line of work of Neuropathology. According to the original development of the Center, the UIPA would have as a main task the multidisciplinary study of institutionalized patients at the Alzheimer Center of Vallecas. Thus, our original mission was to make it possible for the patients of the Center to donate their post mortem brain to the tissue bank, and to perform the extraction and processing of the tissue right there. Consequently, the initial endowment of the Department already allowed to manage a small bank of brains, from the obtaining of the tissue, to the transfer of samples to the investigators who requested them.

As of November 2009, I joined the UIPA full time, and I also incorporated the main activity that we had been doing in the hospital as a Neurological Tissue Bank, except, of course, related to prion diseases, which requires special biosafety facilities. Thus, in 2010 the CIEN Tissue Bank (BT-CIEN) was inaugurated in the Center, which since then incorporates an internal donation program, aimed at residents of the Alzheimer Center of Vallecas, and an external program, aimed at the general population, which is fundamentally the one that was developed in the hospital.

The consequence for the biobank activity is that the annual number of tissue extractions has almost tripled compared to the previous activity, and that step by step a series of brains donated by patients of the residence has been generated, with abundant data and associated samples for many years, which is unique in Spain, and which can be compared with very few series in the world.



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What do you remember and what would you highlight from the first years at the Alzheimer Center? And today, what would you highlight?

As in the launching of any Center, the most relevant of those years, and what I remember best, was all the work of designing the main work processes, the purchase of material and the first processes of selection for hiring personnel. Soon we had a small working group that was able to carry out everything that corresponded to our Department. We all came with the work habits of a hospital, and we had to adapt to a different research environment, and a very special one, because in the social-health dimension of the Center it makes it totally different from any basic research Center. I think that what struck me the most was the possibility of developing the work of the brain bank without the limitations and natural conditioning, derived from the healthcare activity, typical of a hospital.

The current moment of the Center is complex and very interesting. We are a small research Center but very well connected with different research groups, especially CIBERNED. In addition, the activity of the tissue bank keeps us in constant relationship with an extensive set of clinicians interested in the activity of brain donation and in neuropathology. We already have enough experience regarding our ability and also our limitations. I think that now, much more than a few years ago, we are in a position to decide what the best lines of development of the Center may be.

What do you think makes a Center like this one become a benchmark in the fight against Alzheimer's?

Certainly, the singularity of the Center is very important, linked to the Queen Sofia Foundation Alzheimer Center and to the cohort of patients that we have been studying since 2007. Little by little, the increase of data of all kinds on these patients will place us as a unique Center in the world for the study of the advanced stages of the disease. The monitoring of other cohorts, such as the Vallecas project, has undoubtedly contributed to the dissemination of the Center's activity.

How do you see the Alzheimer's Center in another 10 years?

It seems to me probable, and also desirable, that the Center grows, both in its infrastructures and in personnel, and that it incorporates new areas of work in relation for instance with cognitive neuroscience and some lines of experimental work. It would also be desirable for the Center to be more integrated or coordinated with Madrid's public and private healthcare network, and that it could incorporate patients from the network into its study cohorts, both in longitudinal, descriptive studies and in clinical trials.





INTERVIEW

10th Anniversary Queen Sofia Foundation Alzheimer Center

Belén Frades, neuropsychologist at the CIEN Foundation

How and in what year does Belén Frades come to the Alzheimer Center?

I officially started in this Center on April 15, 2010. I previously knew the Foundation as a collaborator in some CIBERNED research projects and had the privilege of participating in the evaluation and evaluation of the first CAFRS patients.

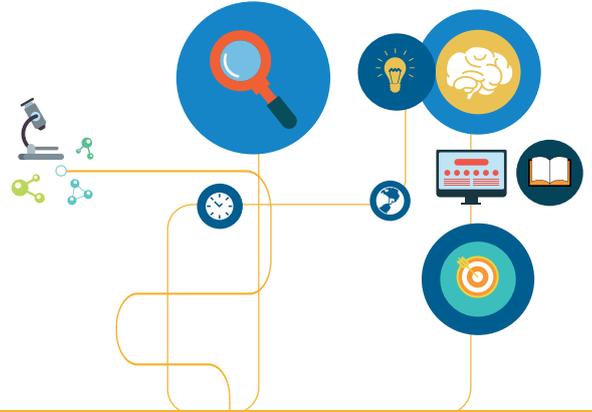
What do you remember and what would you highlight from the first years at the Alzheimer Center? And today, what would you highlight?

I was enthusiastic about the idea of working in a Center that was just starting out and being part of a multidisciplinary and comprehensive professional team. Everything was new and I enjoyed that feeling. Developing and starting the Vallecas Project was a great challenge. As the only neuropsychologist in the Center I proposed the suggestions and ideas that were of my competence. The fact of being the only professional in my field meant that I had to defend firmly the usefulness of the proposals, as well as to debate and convince the other members of the UIPA. The decisions were mostly consensual and that helped in the project and contributed to the fact that we know each other as people. The work scheme was open and dynamic and was completed as the most accurate idea advanced, there was a "warm up" with the pilot project that told us what we should improve.

Currently, we have been with the PV for 7 years and in recent years we have obtained and published interesting results. The neuropsychology team has been consolidated and strengthened within the UIPA.



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What do you think makes a Center like this one become a benchmark in the fight against Alzheimer's?

Have and maintain good ideas and projects; working with multidisciplinary teams; networking, exchange and collaboration with other research groups; the fact of diversifying interests; the dissemination of results at the level of congresses and publications.

How do you see the Alzheimer's Center in another 10 years?

First, I must say that all sectors of science and technology would need more funding than they receive in this country, science is a source of knowledge, economic development and promotes cultural exchange. This Center will advance as long as these requirements are met. Biomedicine is on the rise and this Center can be an important reference in neurology if we encourage teamwork, curiosity, honesty and creativity.





INTERVIEW

10th Anniversary Queen Sofia Foundation Alzheimer Center

Meritxell Valentí, neurologist at the CIEN Foundation

How and in what year does Meritxell Valentí come to the Alzheimer Center?

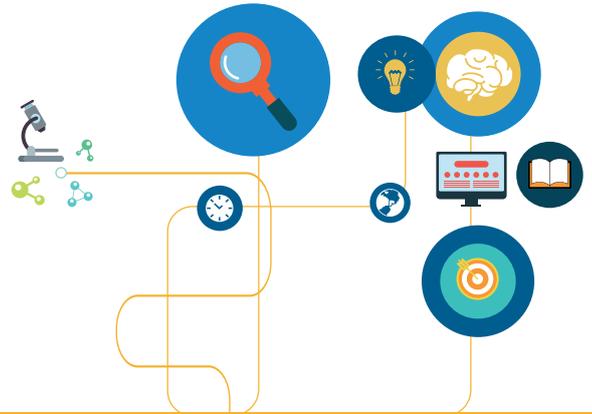
I arrived in the year 2009. I had already collaborated with the Alzheimer Center through the DEMCAM project coordinated by the La Paz University Hospital and in which many Memory, Cognitive Disorders and Dementia Units from the Region of Madrid participated. When the opportunity to work in this Center arose, I applied it in the first moment, because I find the work carried out in it very interesting.

What do you remember and what would you highlight from the first years at the Alzheimer Center? And today, what would you highlight?

The beginnings were difficult, they were tough times because it was about setting up a Center of this style, with the ambition to carry out important projects, but with a long way to go. At present, I see it with a "cruise speed" acquired and stable, with projects that are beginning to give results and with ambition to start new projects.



1. PROFILE AND PRESENTATION



What do you think makes a center like this one become a benchmark in the fight against Alzheimer's?

On the one hand, the high level of many of its members, with a long professional career and a large curriculum behind them that bring experience and prestige to this Center. But most importantly, each of its members (regardless of their level and performance) try to do their job as best and most professionally possible (the greatest asset of an organization are its members).

How do you see the Alzheimer's Center in another 10 years?

I would like that within 10 years, the Alzheimer Center would continue to be a benchmark institution. In addition, this reference has been extended both nationally and internationally, and may collaborate in projects with other international organizations, in projects of a global nature, etc. Furthermore, that the Center would be at the forefront of initiatives and concerns demanded by society, an increasingly digital society, evolving ever so fast, increasingly cognitive and that must know how to adapt, integrate and deal with part of its population that presents difficulties in this aspect.





INTERVIEW

10th Anniversary Queen Sofia Foundation Alzheimer Center

**Almudena Flores Junquera,
CIEN Foundation Secretary of Management**

How and in what year does Almudena Flores arrive at the Alzheimer Center?

I started working at the CIEN Foundation in February 2007. At that time the Foundation was based at the Carlos III Institute of Health, because the Alzheimer Center construction was not yet finished.

That is why my first visit to the Center was on the day of its inauguration, on March 7, 2007, attended by Their Majesties the King and Queen of Spain, relevant authorities and professionals who at that time would be part of the Queen Sofia Foundation Alzheimer's Center. That day we had an overview of the different facilities of the Center. In my case, the tour was more focused on the research unit, a site that the following month, would become my place of work.

I found the building admirable, both from the architectural point of view (modern, with natural lighting, gardens, etc.) and from the social point of view. They had managed to build a Center that combined a research center, a day care center and a residence.

What do you remember and what would you highlight from the first years at the Alzheimer Center? And today, what would you highlight?

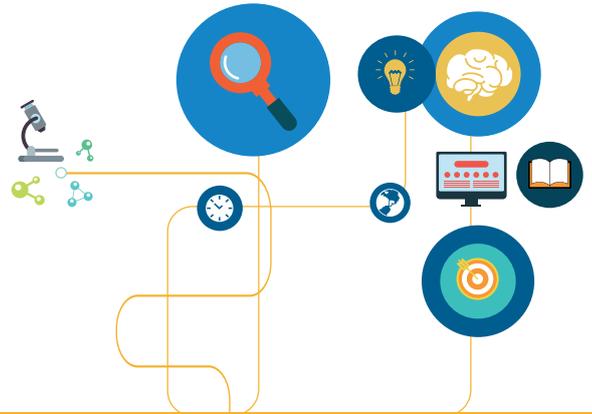
I remember that being a Center recently built and just opened, I still had no life, therefore had not achieved enough temperature inside, also the first months coincided with a spring of not very high temperatures and we experienced quite some cold.

In the Research Unit, there were not many professionals who joined us in their work life. But we all had something in common: a tremendous desire to put the project in motion and to be a Center of reference. The equipment, with which the Center began, was very advanced at the time.

Nowadays, looking back towards the beginning, I would highlight the progress of the Center and the projects carried out in it. In these years it has become a reference model for other Centers.



1. PROFILE AND PRESENTATION



What do you think makes a Center like this one become a benchmark in the fight against Alzheimer's?

The human and professional team, both at the management and research level. In addition, the uniqueness of the Center in which we are, because there are no other Centers in Spain of this type and that makes it a reference.

The different research projects in which we work, including the Vallecas Project (funded by the Queen Sofia Foundation) that has made us known as our society and specifically as elderly people voluntarily come every year without losing the desire and the smile, so that the research can follow a good course towards the prevention of this tough disease; or the Research Program of the Queen Sofia Foundation Alzheimer Center and without forgetting the BT-CIEN Tissue Bank that has become one of the most important banks due to the activity of brain donation.

How do you see the Alzheimer's Center in another 10 years?

I would love to say that I see this Center in a positive evolution very accentuated in terms of research results, compared to the one obtained in the past 10 years; but this advance will be marked by the economic decisions that our country has in front of the research.

Because even if we do not like neurodegenerative diseases, they will affect more people and a Center like this is necessary so that this number can be stopped.





INTERVIEW

10th Anniversary Queen Sofia Foundation Alzheimer Center

Ana Belén Pastor, laboratory technician in the Department of Molecular Genetics of the CIEN Foundation.

How and in what year does Ana Belén Pastor arrive at the Alzheimer Center?

I did a job interview in 2007, it took me a long time to arrive, it was hardly a building surrounded by a wall in the middle of nowhere, I remember a round wooden table, and afterwards, it seemed to me that it would be the last time I visited it. Indeed, at that time I was not selected, but in October of that same year, I received a call from the CIEN Foundation to offer me a position as soon as possible.

What do you remember and what would you highlight from the first years at the Alzheimer Center? And today, what would you highlight?

From the beginning I would highlight the novelty, entering a laboratory where all the equipment was to be used for the first time and there was nobody there to use it. I remember that they told me "you are going to be responsible for the blood samples that enter the laboratory" and "many research groups will come to start their projects" ... However, those first years were very lonely, I have to admit that it was tough, my motivation was low, perhaps because of those expectations that took time to materialize and those samples that came very slowly at first. And ten years later, we have nine ultra-freezers full of samples, we are part of the National Biobank Network, and there are quite a few people among technicians, biologists, students and others who have come and gone, in addition to our characteristic Vallecas project, which is very advanced and many management tasks that are carried out in the Center and that serve the entire scientific community. Maybe we move away from the initial idea of the project, but we already found a place.



1. PROFILE AND PRESENTATION



What do you think makes a Center like this one become a benchmark in the fight against Alzheimer's?

The support of the institutions mainly the Queen Sofia Foundation and its uniqueness based on a research Center directly connected to a healthcare Center.

How do you see the Alzheimer's Center in another 10 years?

Saving the distance, between what I would like it to be and the future that awaits it, it would be good, at least, to continue to be a reference Center and be able to defend it as such, that is, contribute real and significantly to the advancement in knowledge and fight against neurodegenerative diseases through the fruits obtained from 20 years of work and dedication of the people who work, have worked and will work in this Center.





1.6. Organizational structure

1.6.1. Governing and Management Bodies

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

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

At the end of 2017 the Board of Trustees has the following members:

CIEN FOUNDATION BOARD OF TRUSTEES

| POSITION | TITLE | NAME |
|-------------------------------|--|---|
| Honorary chair | Minister of Economy and Competitiveness | Excmo. Sr. D. Luis de Guindos Jurado |
| Chair | State Secretary of Research, Development and Innovation | Excma. Sra. D ^a Carmen Vela Olmo |
| Vice-chair | Director of the Carlos III Institute of Health | Sr. D. Jesús Fernández Crespo |
| Ex-officio Members | President of the Higher Council for Scientific Research State Agency | Sra. D ^a Rosa Menéndez López |
| Ex-officio Members | Director of the Department of National Affairs of the Office of the Prime Minister | Sra. D ^a . Cristina Ysasi-Ysasmendi Pemán |
| Ex-officio Members | Director General of Public Health, Quality and innovation, Ministry of Health, Social Services and Equality | Sra. D ^a Elena Andradas Aragonés |
| Ex-officio Members | Deputy Director General of Evaluation and Promotion of Research, Carlos III Institute of Health | Sra. D ^a Belén Bornstein Sánchez |
| Ex-officio Members | General Director de Scientific and Technical Research, Ministry of Economy and Competitiveness | Sra. D ^a . Marina Pilar Villegas Gracia |
| Member And Secretary | Deputy General Director of Cooperative Research Networks and centers Carlos III Institute of Health General Director of Research, Technology | Sra. D ^a . Margarita Blázquez Herraiz |
| Elected members Andalusia | General Director of Research and Transfer of Knowledge, Department of Economy and Knowledge, Andalusian Government | Sr. D. Manuel García León |
| Elected members Valencia | Director General for Research, Innovation, Technology and Quality, Department of Public Health | Sra. D ^a Ana M ^a Ávila Peñalver |
| Elected members Canary Island | Director General of Welfare Programs, Canary Islands Health Service | Sr. D. Manuel Luis Macías Heras |
| Legal advisor | State Attorney | Sr. D. José Luis Beotas López |
| Invited guests | Scientific Director | Sr. D. Jesús Ávila de Grado |
| Invited guests | Managing Director | Sra. D ^a María Ángeles Pérez Muñoz |
| Invited guests | Queen Sofía Foundation | Sr. D. Jose Luis Nogueira Guastavino |



1. PROFILE AND PRESENTATION

| | | |
|----------------|--|--|
| Invited guests | Advisor to the Office of the Secretary of State for Research | Sr. D. Agustín Larrañaga Elorriaga |
| Invited guests | Assistant to the Secretary | Sra. D ^a M ^a Dolores Donoso Mencía |

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

Cessation in office: Mr. Emilio Lora Tamayo, President of the State Agency of the Higher Council for Scientific Research. Takes the position in his place Ms. Rosa Menéndez López.

Cessation in office: Mr. Bernardo Emilio Macías Gutiérrez from the Region of the Canary Islands, General Director of Assistance Programs of the Canary Islands Health Service. Takes the position in his place Mr. Manuel Luis Macías Heras.

Modification of statutes

In the year 2017 at the meeting of the Board of Trustees, dated December 14, the proposed amendment of the Statutes and its rewriting was unanimously approved, empowering the Secretary of the Board to appear before a Public Notary, submit to the public such modification and rewriting and convey it to the Protectorate and Registry of Foundations.

The proposed modification is as follows:

In accordance with article 29 of the Law 50/2002, of December 26 of Foundations, the CIEN Foundation Board of Trustees has made the following observation: "In accordance with the provisions of article 129 of Law 40/2015, of October 1 of the Legal Regime of the Public Sector, the Statutes of each Foundation will determine the Public Administration to which it will be affiliated. In the text of the Statutes, this affiliation should be made explicit, which is a different matter from the exercise of the Protectorate".

This observation has been included in paragraph 4 of article 1 of the Statutes and has a favorable report from the State Attorney, having been submitted for approval of this Board: "4. The Foundation is of State-wide scope and competence and is affiliated to the General State Administration".

1.6.2 Advisory and participation bodies

External Scientific Advisory Committee

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

- Mr. Joaquín Arenas Barbero. BSc in Pharmacy and PhD in Clinical Biochemistry by Faculty of Medicine of Complutense University of Madrid. He has held the positions of General Director and Deputy General Director of Networks and Cooperative Research Centers within the Carlos III Institute of Health (ISCIII). He is currently Director of the 12 de Octubre Hospital Research.
- Mr. Javier De Felipe Oroquieta. PhD in Biological Sciences by the Complutense University of Madrid. Neurobiologist at the Cajal Institute. He leads the Spanish team of the Blue Brain international project





(Cajal Blue Brain) integrated by scientists from the Technical University of Madrid and CSIC. He belongs to CIBERNED and collaborates actively with the CIEN Foundation.

- Mr. Miguel Medina Padilla. Doctor in Biochemistry and Molecular Biology from the Autonomous University of Madrid. Deputy Scientific Director of CIBERNED.
- Mr. José Ramón Naranjo Orovio. PhD in Pharmacy from the Complutense University of Madrid. Neurobiologist at the National Center for Biotechnology (CSIC). He belongs to CIBERNED and collaborates actively with the CIEN Foundation..
- Mr. Fernando Rodríguez Artalejo. Doctor in Medicine and Surgery from the Autonomous University of Madrid. Professor of Preventive Medicine and Public Health at the Autonomous University of Madrid.

1.7. Vision

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

As the project progresses, a large volume of increasingly rich and relevant information is generated on the most initial phases of cognitive impairment in those subjects who develop it, as well as on the biomarkers (clinical, biochemical and neuroimaging) most suitable for its characterization and identification of the population at greater risk of developing it. In addition to continuing to present our preliminary results in different congresses and scientific meetings, the commitment to publish the results generated from the longitudinal analysis of the Vallecas project in international scientific journals of the greatest possible impact is maintained (see section 6.2.1.).

In recent months, we have initiated the necessary contacts so that the information obtained from the

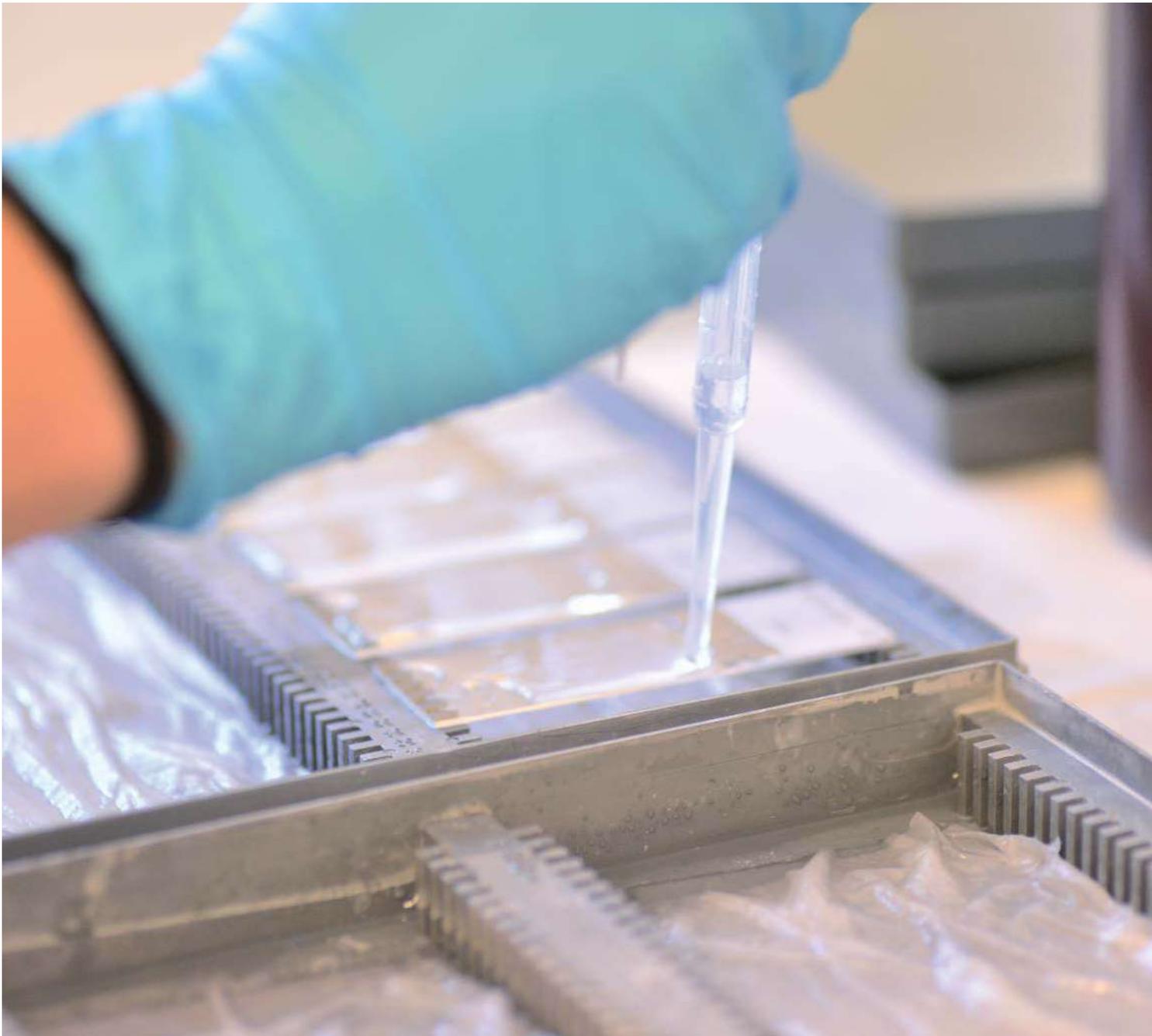
assessments of the volunteers, their biological samples and the neuroimaging studies carried out integrates with that of other national and international cohorts such as the European Medical Information Framework (EMIF), which will significantly increase the potential of each of them as well as the Vallecas Project itself.

In addition, a new agreement is being worked out with the Queen Sofia Foundation in order to establish the framework for collaboration to continue conducting research aimed at identifying individuals at greater risk of developing Alzheimer's dementia in the second phase of the project called "Vallecas 2 Project. Early detection of Alzheimer's disease. Risk and protection factors". This new agreement will allow us to extend the current project activities and update the objectives based on the experience accumulated in recent years as well as maintain a cohort of volunteers whose added value in terms of quantity and quality of data, along with its scientific relevance, increases every year, making it a reference cohort in the study of the factors that determine the onset of mild cognitive impairment and Alzheimer's type dementia in the elderly.

Besides the Vallecas Project, the studies with the patients from the residence will continue in the Queen Sofia Foundation Alzheimer Center and the CIEN Foundation to study dementia in its moderate and advanced stages. As indicated, this longitudinal study, initiated in 2007, aims to monitor and follow up



1. PROFILE AND PRESENTATION

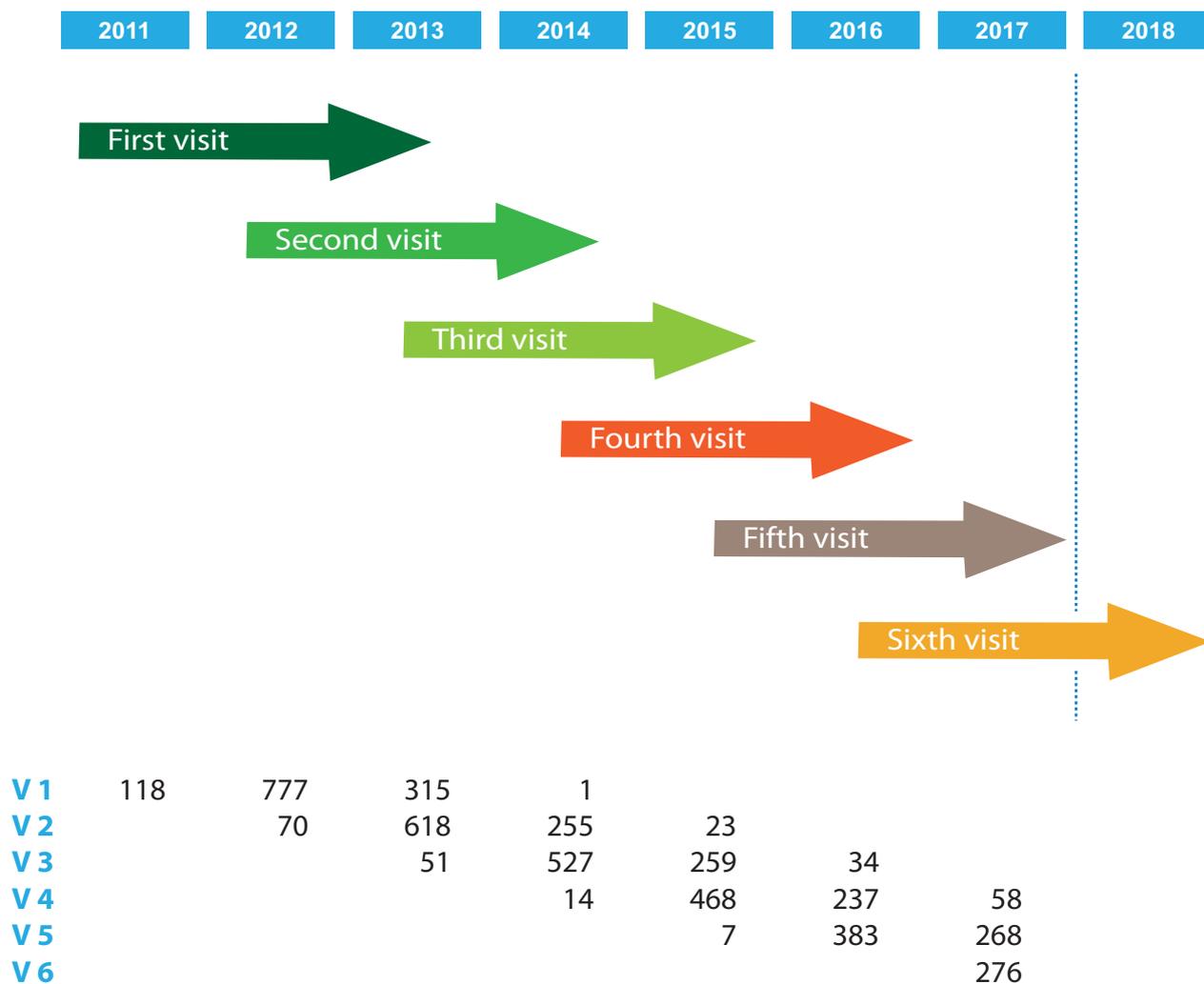




the residents of the Queen Sofia Foundation Alzheimer Center and the users of the Day Care Center.

One of the most important tasks to carry out in this project is the updating and validation of historical data collected so far to integrate them into a single, integrated and anonymized database in order to

ensure the reliability and security of data to enable at the same time a more efficient data analysis. In the coming months and years the information collected from the beginning of the Project will provide important clues about how the two main pathologies that determine dementia in our environment, Alzheimer's pathology and cerebrovascular patho-



December 31, 2017



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

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

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



Mänagement *re*port

Applied research at the CIEN Foundation is guided by a quality management based on leadership, innovation and the responsibility of its staff. By means of an efficient optimization of its resources and the promotion of cooperative and international research, the institution continues betting on progress in the field of neurodegenerative diseases. The continuous training of researchers demonstrates the importance of talent as a pillar for the advancement of the CIEN Foundation.





2.1. General management

CIEN Foundation is a State wide public sector Foundation supervised by the Carlos III Institute of Health under the Ministry of Economy, Industry and Competitiveness.

The CIEN Foundation is governed by its Statutes; by Law 50/2002, of December 26, on Foundations; by Royal Decree 1337/2005, of November 11, which approves the Regulations of the Foundations of State competence; by the provisions of the National Budget Law, in everything that refers to the Foundations of the State Public Sector; by Royal Decree 384/1996, of March 1, on the Registry of Foundations of State Competence; by Law 49/2002, of December 23, on the Tax Status of Non-Profit Organizations and Tax Incentives to Patronage; and for the rest of the legal provisions of an administrative, civil, mercantile or labor nature that apply to it.

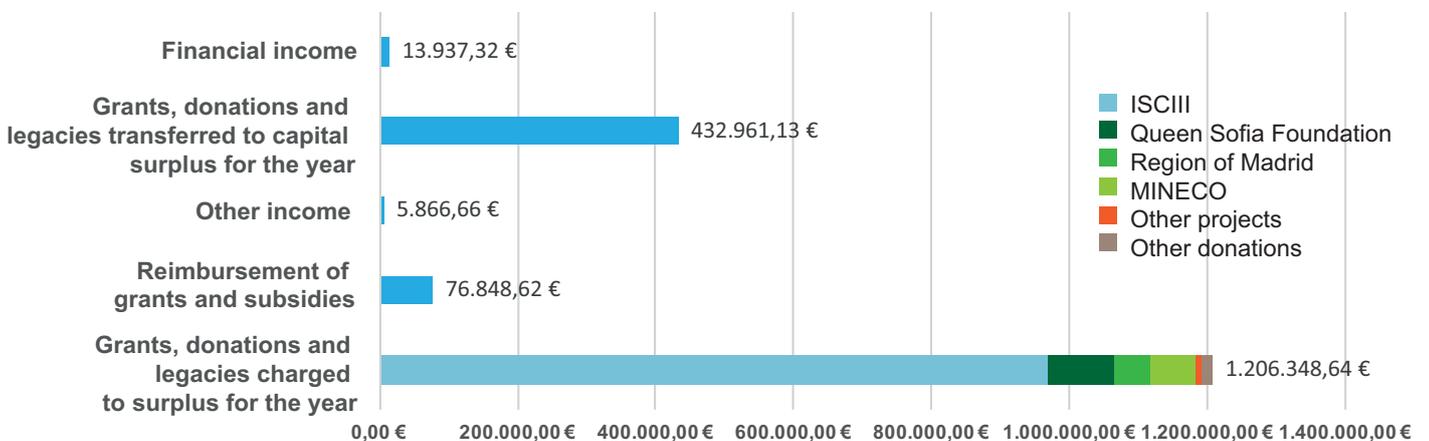
The purpose of the CIEN Foundation is to promote research in all fields of basic, clinical and epidemiological neurology, aspiring to become a Center of national and international reference on research in Alzheimer's disease and other dementias. The alliance between CIBERNED and CIEN Foundation has made possible that they are the only recogni-

zed Spanish institutions within the Centers of Excellence in Neurodegeneration (CoEN), complementary initiative to the JPND to establish a common approach to research in neurodegenerative diseases, promoting collaborative research between recognized national Centers of Excellence in neurodegeneration in order to accelerate progress in understanding the mechanisms of the disease, as well as the identification of new therapeutic approaches.

Particular aims include fostering scientific advances to have an impact on the healthcare system and the well-being of patients. To this end, an offer of services carried out by various Consultation Units and Research Groups of the CIEN Foundation has been articulated and made available to users outside the Center.

- Cerebral tissue sample request service
- Magnetic resonance Imaging acquisition service
- Diagnostic consultation service

Total revenues obtained in 2017





2.2. Management of financial and economic resources

The CIEN Foundation is funded by specific subsidies granted by the State and other local or institutional public entities, as well as by income derived from European and national research projects, contracts for the provision of services and patronage activities.

The annual accounts are prepared from the accounting records of the Entity, having applied the legal provisions in force in accounting matters in order to show the true image of the assets, the financial situation and the results of the CIEN Foundation.

Revenues

In 2017, the CIEN Foundation managed an income budget of over 1.7 million euros. The main source of income comes from the nominative assignment of the Carlos III Institute of Health, which amounts to € 825,000 (representing 47% of total income), aimed at achieving the specific goals and objectives that are materialized in the promotion of research in health sciences, and develop and offer scientific-technical services of the highest quality, aimed at the National Health System and the whole of society.

The breakdown of total revenues obtained in 2017 and 2016 is described in the next page:

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

The Carlos III Institute of Health, by Resolution of July 20, 2017, approves granting a nominative allowance for a total of € 825,000, destined to the fulfillment and development of the aims and objectives of the CIEN Foundation: the promotion of research in the neurological area and the maintenance of the Center.

The contribution of the Queen Sofia Foundation in 2017 was focused in the funding of three main activities: collaboration in the celebration of the Alzheimer's Global Summit Lisbon 2017, financing of the activities of the CIEN Foundation-Tissue Bank and the call for the MAPFRE-Queen Sofia Foundation. Simultaneously, in the items of grants, donations and legacies of capital, a contribution of € 381,758 is recorded. The remaining amount up to the total of this item (€ 432,961) corresponds to the official capital grants received from the ISCIII for financing capital expenditures.

| | |
|---|---------------------|
| ISCIII NOMINATIVE ALLOCATION | 825.000,00 |
| ISCIII ALLOCATION FROM PRIOR YEARS | 86.574,22 |
| OTHER DONATIONS CHARGED TO SURPLUS | 14.436,00 |
| PEJ 2014/MINECO | 61.914,33 |
| PEJ 2015/ CAM | 19.106,47 |
| PEJ 2016/ CAM | 20.999,24 |
| ISCIII-PR.EXCED. JPND-COEN | 8.253,30 |
| ISCIII-PR.EXCED. BIOBANK | 34.464,57 |
| QUEEN SOFIA FOUNDATION | 92.687,53 |
| M+VISION/F.MADRIDMASD PROJECT | 16.539,00 |
| OTHERS | 26373,98 |
| TOTAL | 1.206.348,64 |



2. MANAGEMENT REPORT

The breakdown of total revenues obtained in 2017 and 2016 has been as follows

| | 2017 | 2016 |
|--|----------------------|----------------------|
| Grants, donations and legacies charged to surplus for the year | 1.206.348,64€ | 1.588.467,76€ |
| Reimbursement of grants and subsidies | 76.848,62€ | 131.406,28€ |
| Sales and other income from commercial activity | 5.866,66€ | 4.479,78€ |
| Other income | 432.961,13€ | 506.781,77€ |
| Grants, donations and legacies transferred to capital surplus for the year | 11,64€ | 106,61€ |
| Financial income | 13.925,68€ | 227,85€ |
| TOTAL | 1.735.962,37€ | 2.231.471,05€ |

The rest of the amount corresponding to the subsidies, donations and bequests allocated to the surplus of the year is identified with the projects derived from the Youth Employment Plan, both from the Ministry of Economy, Industry and Competitiveness,

and from the Region of Madrid; the M+VISION project, the Biobank Platform PT13/0010/0045 and the income derived from the realization of the project funded within the framework of the CoEN-Pathfinder 2015 call.

Distribution of CIEN Foundation revenues

| | 2017 | % | 2016 | % |
|---|-----------------------|--------|-----------------------|--------|
| Monetary aid and others | 40.253,30 € | 1,90% | 15.691,23 € | 0,71% |
| Variation of existences of merchandise | 2.696,60 € | 0,13% | -12.708,72 € | -0,57% |
| Supplies | 154.130,42 € | 7,27% | 164.432,45 € | 7,40% |
| Staff costs | 890.134,41 € | 42,01% | 930.045,89 € | 41,87% |
| Other operating expenses | 577.060,15 € | 27,23% | 616.438,80 € | 27,75% |
| Depreciation and amortization | 440.765,97 € | 20,80% | 506.470,99 € | 22,80% |
| Impairment and gains on disposal fixed assets | 0,00 € | 0,00% | 310,78 € | 0,01% |
| Exchange differences | 13.843,41 € | 0,65% | 410,07 € | 0,02% |
| TOTAL | 2.118.884,26 € | | 2.221.091,49 € | |





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

Revenues from provision of services during 2017

Expenditure

The expenses are used for the development of the CIEN Foundation's own activities, which basically correspond to the research and management activities of the Alzheimer's Project Research Unit (UIPA),

2.3. Management of Human Resources

In fulfilling our mission to contribute to the progress of scientific research in society and helping people, from the CIEN Foundation we keep our commitment to become one of the reference centers in neurological diseases research at the international level. To do this, we must be able to attract and retain the best global talent.

People are one of the most valuable strategic resources of our research center. The way to direct and manage this resource becomes one of the keys

Revenues from provision of services during 2017

| | 2017 | 2016 |
|--|-------------------|--------------------|
| Energy production | 11.374,38€ | 10.378,56€ |
| Income from performing MRIs and collaborative research projects | 65.474,24€ | 121.027,72€ |
| TOTAL | 76.848,62€ | 131.406,28€ |

which is part of the Queen Sofia Foundation Alzheimer Project Complex. The Queen Sofia Foundation and the CIEN Foundation formally signed in January 2006, renewed in January 2016, an agreement whereby the former cedes the use of the premises and their equipment, and the CIEN Foundation is committed to the maintenance of the dependencies and equipment, replacing and repairing the one that is necessary. The use of facilities will be used as a priority for the research of Alzheimer's disease and other dementias, and in a complementary manner to other types of research on diseases that are part of the CIEN Foundation's mission.

to the success of the CIEN Foundation; for this reason, from the Human Resources department we work every day to have a competitive human team, professionally respected and identified with our values, strategies and objectives.

One of the objectives of the CIEN Foundation is that its workers develop their research activities in an environment that favors innovation, teamwork, motivating and helps both professional and personal development. For this, we promote policies that allow the reconciliation of work and family life to men and women, which allows not only to develop individual needs, but also a pride of belonging that leads to an improvement in work performance. Likewise, we promote the integral education of our re-



2. MANAGEMENT REPORT

searchers as a basic pillar for the maintenance of quality research, something that has always distinguished our foundation.

Following our human resources strategy, CIEN Foundation's selection processes are aimed at achieving entrepreneurial professionals, capable of adapting to change, ambitious and with a clear vocation for research and for actively participating in the projects managed by the CIEN Foundation.

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

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

During 2017, the CIEN Foundation has counted on a total of 51 professionals, including 30 hired from competitive grants, 11 fellows, 1 in-training Resident Medical Intern in neuropathology, 4 volunteers who have collaborated selflessly with the CIEN Foundation, 4 have developed their activity under signed collaboration agreements, and 3 professionals have been hired through a contract to provide services. The research and technical support staff funded through CIBERNED as well as through the collaboration agreements for research signed by the CIEN Foundation are also part of the staff of the CIEN Foundation.

As every year, CIEN Foundation has continued with its commitment to young researchers and collaboration with public and private institutions. During 2017 has participated in the program "CAM Call for grants

to hire research assistants and laboratory technicians funded by the European Social Fund, through the Youth Employment Operative Program (YEI) PEJ2016/MED/AI-1963" with one formalized hiring. With the aim that young researchers can start their careers and develop their potential, the CIEN Foundation participates in the theoretical and practical training of university students, both in Spain and in other European Union countries, through collaboration agreements carrying out university hands-on training.

Research staff by gender



One more year, the Call for Grants of the Queen Sofia Foundation -MAPFRE Fellowship will allow the incorporation of a specialist in biomedical sciences within the Alzheimer Project Research Unit.

The different departments in which the human resources that make up the CIEN Foundation are located and where our professionals have developed their work are the following:

- Department of Management and Administration
- Department of Neuroimaging
- Department of Neuropathology and Tissue Bank
- Department of Molecular Genetic
- Department of Neurology
- Department of Neuropsychology





2.3.1. Training program

To achieve the goals and objectives of our organization, one of the main tools that the Foundation has defined is the development of the Training Program, adapting it to the needs of its staff, in a way that allows the development of their professional skills in the defined strategic lines and increases the quality of the activities carried out.

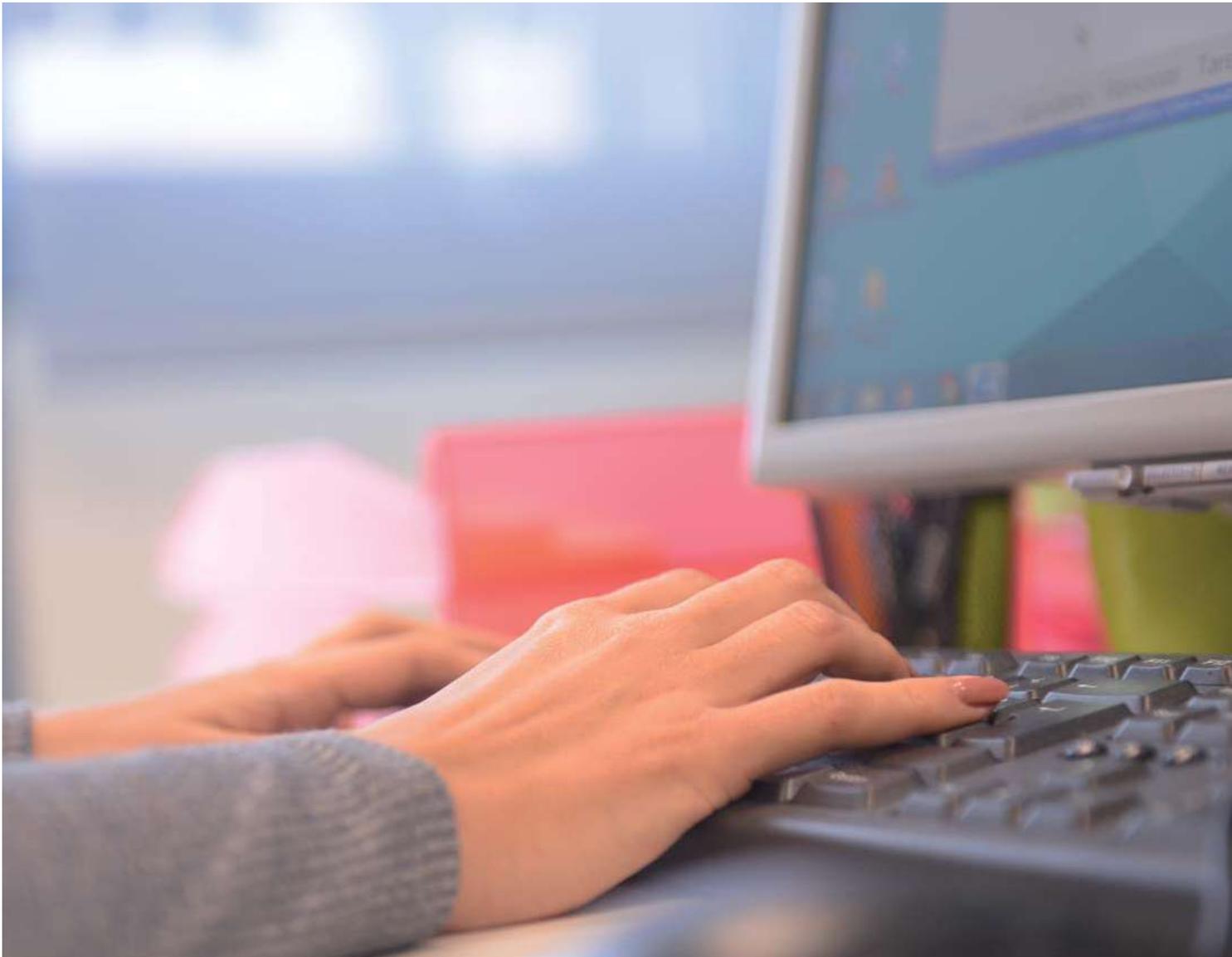
Courses and training actions carried out by our staff

- Intensive Course on Protocol and Organization of Institutional and Corporate Events. ISCE.
- II Edition Sanitas in Dementia "Biomarkers of Alzheimer's disease and other degenerative dementias, present and future." La Moraleja University Hospital.



2. MANAGEMENT REPORT

- International Symposium "Active brains for all: exercise, cognition and mental health". University of Granada
- Alzheimer's Global Summit Lisbon 2017.
- Course on "Update in breast cancer." Ilustrious Official College of Physicians of Madrid-
- Course "Disseminate your Science" Unit of Scientific Culture and Innovation of the Carlos III Institute of Health.
- Course on "PEDIATRIC Health, Education and Parenting and Social Networks" Ilustrious Official College of Physicians of Madrid





- Course on "Management in Radiology SEGECA 2017" Spanish Society of Medical Radiology SERAM.
- Course on "Innovation and Research, in the Department of Diagnostic Imaging BOX-CAMP RADIOLOGÍA" Held at the University of La Laguna and the University Hospital of the Canary Islands.
- "I DEGESCO Symposium on Genetics and Dementia" Held at the CIEN Foundation.
- European Congress of Radiology: "ECR 2017". European Society of Radiology
- European Congress of Radiology: "ECR 2017". European Society of Radiology
- Course on "Advanced Program of European Patent Law". School of Industrial Organization.
- Course on "New approaches to cognitive and behavioral disorders". La Paz University Hospital.
- Course on "Advice and implementation of a quality management system according to ISO 9001: 2015 in biobanks". University of Salamanca.
- Course on "Role of biobanks in the standardization and management of miRNAs from biological samples". Gregorio Marañón Hospital Health Research Institute.
- Course on "ALTMETRICS: Alternative metrics for scientific evaluation". Spanish Association of Documentation and Information – SEDIC.
- Scientific Conference "I Meeting of Scientific Evaluation Services in the Vice-Chancellors". University of Granada.

Internships

- Tutoring of external internships for students in the last year of their Psychology degree:
 - 1 student from the Autonomous University of Madrid
 - 1 student from the Rey Juan Carlos University
 - 4 students from the Complutense University of Madrid
- Final Degree Projects in Biology:
 - A student from the University of Extremadura, Dept. of Neuropathology

- A student from the Complutense University of Madrid, Dept. of Neuropathology
- Final Master Projects:
 - A student from the Technical University of Madrid, Master in Biomedical Engineering
 - A student from the Complutense University of Madrid, Master in Biology

Fellowships

- Queen Sofia Foundation- MAPFRE Fellowship 2017-2018. Linda Zhang

Teaching

- Selection of clinical cases: evaluation and diagnosis of healthy and pathological aging.
- Neuropsychological assessment: Attention, Gnosias, Praxias, Memory, Language and Executive functions.
- Cycle of Scientific Seminars of the CIEN Foundation 2017. Taught by researchers from the CIEN Foundation and other institutions in which the latest scientific works of the researchers are presented and discussed (see more detailed information in section 6 of this report).

2.3.2. Prevention of Occupational Hazards

Following the establishment of the CIEN Foundation's Occupational Health and Safety Policy, which is intended to promote respect for occupational safety and health in the development of our activities, the commitment of the organization expressed is established in the following terms:

- Comply with applicable regulations in the field of occupational health and safety, within the European, national, regional and local regulatory framework.
- Advance in the continuous improvement of our behavior in occupational health and safety.
- Guarantee the protection of the safety and health of workers



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- Promote training and communication both internally and externally.

To guarantee the protection of occupational health and safety, CIEN Foundation has carried out, in coordination with the Prevention Service, various preventive activities during the year 2017, among which the emergency and evacuation drill, in coordination with the Queen Sofia Alzheimer Center, stands out.

In terms of health surveillance, during 2017 a total of 16 medical examinations were carried out. The health exams have included a work history with detailed description of the job, the time spent in it, the risks detected in the analysis of working conditions and the prevention measures taken, anamnesis data, clinical exploration, biological control and complementary studies, directed and chosen according to the risks inherent in the work performed.

Finally, the objectives of improving the safety and health conditions of workers and reducing accident rates taken as a reference by the Mutual Society for Work-related Accidents and Professional Illness have been met, keeping said indexes to zero and, therefore, below of the benchmarks of the Research and Development sector:

2.4. Research projects and grants

CIEN Foundation aims to support, promote and coordinate research in neurological diseases. In order to do this, it focuses its efforts especially in neurodegenerative diseases and in coordinating prominent Spanish research groups. Research projects managed by the Foundation seek to foster research and study in these fields, especially Alzheimer's disease and related disorders.

2.4.1 Research projects

The CIEN Foundation was created with the aim of promoting the creation of a network center that supports, promotes and coordinates research activities. The objectives of the CIEN Foundation are specified in five fundamental activities:

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

| | CNAE reference number | CIEN Foundation | |
|---------|-----------------------|-----------------|---------------|
| | Accident rate | Value | Accident rate |
| INDEX 1 | 6,43 | 0 | 0 |
| INDEX 2 | 0,58 | 0 | 0 |
| INDEX 3 | 0,36 | 0 | 0 |





The Vallecas Project is the main research project carried out by the CIEN Foundation, both in terms of resources used and its social impact. In parallel, the CIEN Foundation is engaged in other research projects on neurodegenerative diseases, among which are the Alzheimer Center Project and the Biobank Platform.

THE VALLECAS PROJECT – Early detection of progressive cognitive impairment and its biomarkers. During

2017, the completion of the fourth year of follow-up (fifth evaluation) of the entire Vallecas Project cohort is expected; in addition, a good part of the participants will carry out the planned sixth evaluation (fifth year of follow-up). The annual follow-up includes the following studies

- Neurological evaluation
- Neuropsychological assessment
- Psychiatric evaluation
- Functional evaluation



2. MANAGEMENT REPORT

- Magnetic resonance imaging
- Blood sampling and analysis of genetic risk factors

For this project, grants have been obtained through public calls for research projects on a competitive basis, which are detailed in Section 6 of this Annual Report.

TISSUE-BANK: Through the Department of Neuropathology of the CIEN Foundation, a biobank of neurological tissue is managed (CIEN Tissue Bank). Contributions to BT-CIEN come, in addition to those obtained in the CAFRS (Internal Donation Program), from donors from the Community of Madrid and other Regions (External Donation Program). In turn, the BT-CIEN, after processing, diagnosis and classification, maintains the biological material in long-term archive conditions and distributes it to researchers and institutions that require it for research projects, in accordance with the application and transfer of biobank samples protocols.

Research Program of the Queen Sofia Foundation Alzheimer Center: Systematic evaluation, by means of a protocol adapted and agreed upon, of the patients institutionalized in the Queen Sofia Foundation Alzheimer Center (CAFRS, for its acronym in Spanish) and attendants to the Day Care Center, after signing an informed consent. This project includes the eventual extraction and neuropathological study of the brains donated by deceased patients. Also in this section, funding has been secured through projects grants obtained in competitive calls (see Section 6).

Other projects and collaborations

Collaboration agreement between the Madridmasd Foundation for Knowledge and the CIEN Foundation to regulate the participation of the Foundation as a host institution in the M+VISION program, within the

framework of the FP7-People-2011-Cofund call. The program, co-funded by the European Union, consider the participation of host institutions as legal entities in which the researchers selected in the calls for the M+VISION program carry out their training activities through research.

The M+VISION program consider two types of grants depending on the type of mobility involved: incoming and outgoing. In the incoming grants the researchers will enjoy the three years of support in Spain. The program offers grants of a total duration of three years, consisting of one year of scholarship and two years of labor contract as well as contributions for research and travel expenses. The first year researchers receive funding from the Region of Madrid and the scholarship is carried out in a primarily academic environment, while the second and third year they are hired directly by the host organizations, conducting a more market-oriented research.

Collaboration agreement signed with King's College London, University of Pennsylvania and University College London, for carrying out the project entitled "Phases 2b-4 Field Validation of the MDS-NMS, the International Parkinson's and Movement Disorders Society Non Motor Scale for Parkinson's disease" funded by The International Parkinson and Movement Disorders Society.

In addition, a specific collaboration agreement has been established between CIBER and CIBERNED for carrying out the project "Search for biomarkers for the early detection of Alzheimer's disease in the Vallcas project cohort", with the active participation of the Neuroimaging department and the CIEN Foundation Tissue Bank.

Actions financed within the framework of Law 18/2014, of October 15, of approval of urgent measures for growth, competitiveness and efficiency and of the Youth Employment Operative Program:





- **PEJ-2014-C-19788:** Grant for the promotion of youth employment and implementation of the Youth Guarantee in R+D+I. Four actions were funded resulting in formalizing 4 labor contracts: 2 research assistants and 2 superior technicians.
- **PEJ15/BIO/AI-0615:** Granting of support for hiring a research assistant in the framework of the call for Grants for the Recruitment of Research Assistants and Laboratory Technicians, 2015 call.
- **PEJ16-MED-AI-1963:** Granting of support for hiring a research assistant in the framework of the call for Grants for the Recruitment of Research Assistants and Laboratory Technicians, call 2016.
- **PEJ-2017-TL-BMD:** Order 4606/2017 of December 14 for which grants are given for the execution of contracts for laboratory technicians corresponding to the 2017 call. Granting of support for the employment of a laboratory technician during 2018.

2.4.2 Fellowships and grants

During 2017 the CIEN Foundation has awarded/carried out the following fellowships and grants:

- **Queen Sofia Foundation - MAPFRE Fellowship 2016-2017:** On December 27, 2016, the Selection Committee decided to grant the scholarship to Mrs. Susana Navas Rutete. A 6-months stay, extendable for the same period, in the Dementia/Alzheimer's disease research program at the Royal College of Surgeons in Ireland (RCSI), Dublin, Ireland, during the first 5 months. The remaining 7 months will be held at the Queen Sofia Foundation Alzheimer Center of the
- **Queen Sofia Foundation - MAPFRE Fellowship 2017-2018:** The fellowship program resolved to grant in this new call to Dr. Linda Zhang. The research program focuses on the study of neurodegenerative disorders using an approach that combines mathematical modelling and computational simulation, in

order to achieve the characterization of predictive algorithms. The duration of the scholarship will be 6 months, extendable for 6 additional months (maximum, 12 months). As part of the scholarship, Dr. Zhang will spend a period of time in the Neuroimaging department of the Queen Sofia Foundation Alzheimer Center and another period at the Eastern University of Finland in Kuopio. This scholarship is an excellent opportunity to actively participate in a joint multidisciplinary research program in both institutions to study the mechanisms of neurodegeneration and dementia.

- **III Pathfinder projects call.:** Collaboration agreement between the ISCIII and the CIEN Foundation for developing the Strategic Research Agenda of the European Union Joint Program on Neurodegenerative diseases, especially Alzheimer's disease (JPND), through the CIEN Foundation's participation in the European Network of Centers of Excellence (CoEN). In 2016 the 3rd Call was resolved, resulting in a project funded by Spanish participation through a CIBERNED research group, entitled "Protection of neurons in vitro and in vivo from Synuclein toxicity by molecular tweezers". This project was completed by December 2017.

2.5. Quality Policy

In this year the procedures and working tools required by the new version of the ISO 9001: 2015 standard have been developed and adapted.

The quality policy aims at guaranteeing and optimizing the processes related to external and internal customer orientation, leadership, staff participation, the process-based approach, continuous improvement and the incorporation of the risk-based process. Thus, it provides greater predictive capacity for the evaluation, administration, elimination and/or minimization of risks.

The following measures are worth highlighting: the adoption of a process-based approach, the manage-



2. MANAGEMENT REPORT

ment of internal and external risks and the planning of quality objectives.

During 2017, the renewal of the Quality Management System certification under the UNE-EN ISO 9001: 2008 standard was successfully passed.

2.6. Data Protection Law

The CIEN Foundation has files containing personal data, for which it is responsible and must be protected in accordance with the provisions of the current regulations on Personal Data Protection (LOPD, for its acronym in Spanish).

These files are contained in the Safety Document, as well as the people involved in their handling and the premises in which they are placed, located at 5 Valderrebollo street, 28031-Madrid.

As the sole responsible for the files, the CIEN Foundation is committed to fulfilling its obligation of secrecy of personal data and its duty to save them, and to adopt the necessary measures to prevent their alteration, loss, or unauthorized access, taking into account at all times the state of the technology, and guaranteeing compliance with the LOPD at all times.



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



Scientific activity

The Alzheimer Project Research Unit (IUPA, for its acronym in Spanish), managed by the CIEN Foundation, continues its multidisciplinary research activity with the purpose of advancing in the knowledge of neurodegenerative disorders, with special emphasis on Alzheimer's disease and related dementias. It is composed of five departments: Neurology, Neuropsychology, Neuroimaging, Neuropathology and Laboratory. In 2017, the continuity of the "Vallecas Project" stands out, among other projects.





3. SCIENTIFIC ACTIVITY

3.1. Overview

On January 18, 2006, the CIEN Foundation signed an agreement with the Queen Sofia Foundation, under which the former assumes the management of the Alzheimer Project Research Unit (UIPA, for its acronym in Spanish). The context in which the UIPA is framed is the Alzheimer Project, promoted by the Queen Sofia Foundation. The main exponent of this project is the Queen Sofia Foundation Alzheimer Center (Alzheimer Complex), located in the Vallecas neighborhood (Madrid), which in 2017 has celebrated its 10th Anniversary. One of the most outstanding aspects of the Alzheimer Complex is that there is a Healthcare Center (formed by a Residence and a Day Center) for Alzheimer's patients and related diseases as well as a Training Center, in addition to the UIPA. This Unit began its activity in April 2007, while the healthcare activity began at full capacity in the second half of that year.

Currently, the UIPA consists of five departments with a clear multidisciplinary approach and with specific objectives, among which are the following: the monitoring and periodic evaluation of patients at the Alzheimer Center; the development of clinical, epidemiological, genetic, research projects as well as on biomarkers in biological samples or neuroimaging, in the field of neurodegenerative diseases, with special focus in Alzheimer's disease and related dementias.

Through this series of studies, new knowledge in genetics and molecular biology that have different applications is generated, that teach the researchers about the pathogenic mechanisms of the disease which can be in turn implemented into the field of diagnosis and, desirably, can result in the development of better treatments.

However, far from promising a simple solution to the problem of neurodegenerative dementias, these advances anticipate an increasingly complex picture, in which the remedies will be achieved through

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

3.2. Department Structure

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

- **Department of Neurology**
- **Department of Neuropsychology**
- **Department of Neuroimaging**
- **Department of Neuropathology**
- **Department of Molecular Genetics**

From the clinical perspective, the UIPA counts with personnel from the Departments of Neurology and Neuropsychology, who are in daily contact with patients who come to the Queen Sofia Foundation Alzheimer Center (CAFRS, for its acronym in Spanish) and with the staff at the healthcare Residence, as well as with the cohort of volunteers from the Vallecas Project (see section 4), playing a role of mediation between basic researchers, relatives and caregivers. This role is critical in making patients, relatives and caregivers aware of the research purpose of the UIPA, give consent and collaborate with the research projects. One of the research activities of these departments consists in carrying out a clinical, syndromic and etiological diagnosis of the patients from the CAFRS, either in the resident regime (Units of Life) or in daycare (Day Center). In addition, a set of clinical data is obtained that will be very useful for the other UIPA scientific areas studies.



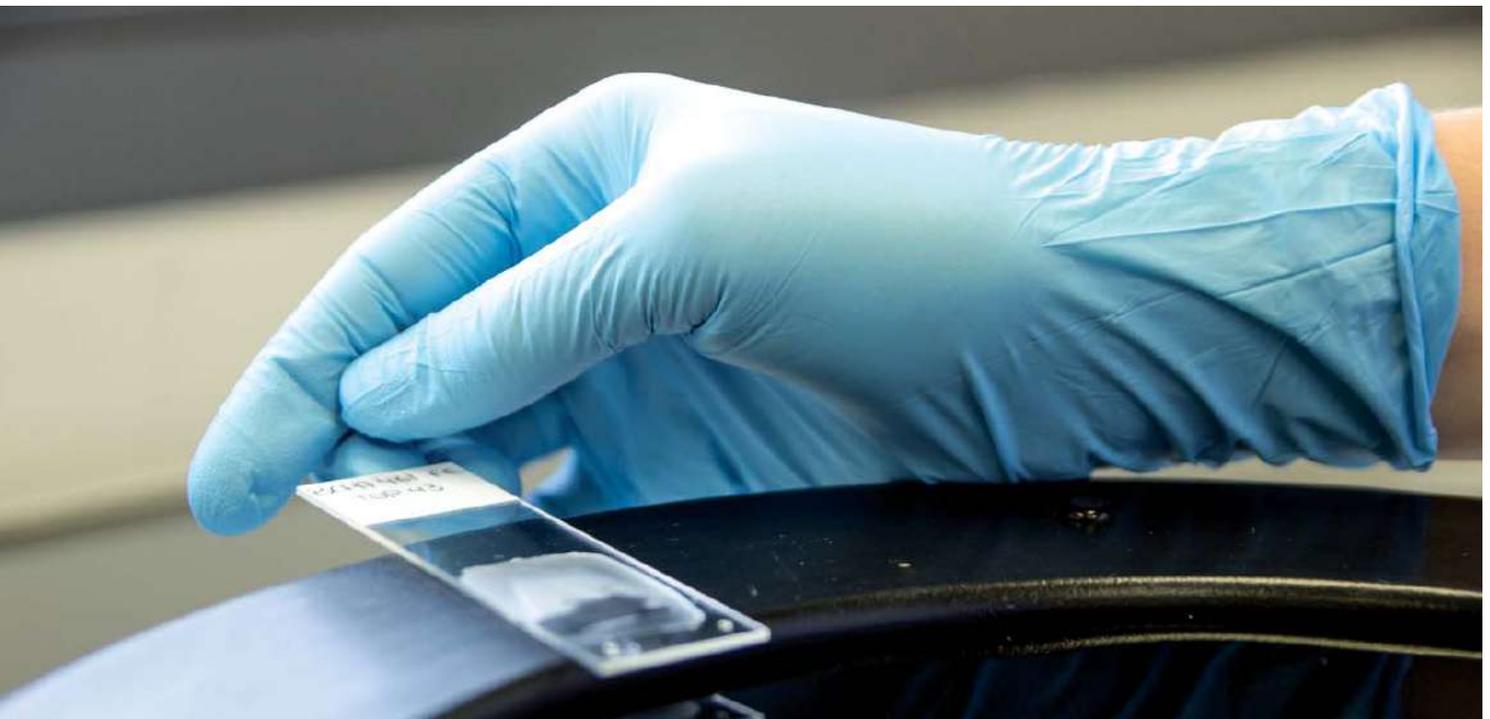


Patients with dementia require specific attention, consisting of an accurate and early diagnosis, an assessment of the affected cognitive areas and its severity, as well as applying and monitoring the treatment. It is essential that various medical disciplines be involved, due to the need to follow the progression, the specific treatment, the overseeing of complications, the application of measures to neutralize them, and the corresponding practice of social health resources. Hence, UIPA responds to a translational vocation to investigate the progression of clinical knowledge in dementias. It is established as an intermediary between basic sciences and the fields of clinical and social sciences related to health, to promote knowledge about neurodegenerative dementias and its application. A team of specialists in Neurology, Psychiatry and Neuropsychology, together with the participation of geriatricians, occupational therapists, physiotherapists and

social workers from the Center's healthcare area make up this part of the Unit. The evaluations carried out in these areas composed the clinical and sociological database that, in addition to its intrinsic interest for research purposes, supports the biological samples and neuroimaging data obtained systematically in the Center.

From the basic research side, UIPA's original project contemplated the creation of departments of Molecular Genetics, Neuropathology, and Neuroimaging. These three areas bring together the most promising fields of research on the biological processes underlying dementia.

The UIPA is characterized by its marked multidisciplinary approach, so that both clinical and basic aspects are in continuous contact, through those five departmental areas, elaborating and contrasting



3. SCIENTIFIC ACTIVITY

hypotheses, and jointly carrying out various research projects. On the other hand, it is from reinforcing these two perspectives, how concepts such as translational research in Medicine have been developed. The scientific activity of the CIEN Foundation is based on this idea: to transfer to the clinical field the advances obtained with basic research.

3.2.1. Department of Neurology

Neurology as a medical-scientific discipline aims to study the structure and function of the nervous system, the identification, description and analysis of its numerous and varied pathologies, the diagnosis of its clinical alterations and the treatment of patients who suffer them. In the field of cognitive impairment, the neurologist must characterize the numerous types and variants of this syndrome through a systematic clinical evaluation of the patient and his/her environment, collaborate with other specialists in psychology, radiology, laboratory, genetics, neurophysiology, etc. make a diagnosis and prescribe and monitor a treatment. In a research group such as the Queen Sofia Foundation Alzheimer Center (CAFRS, for its acronym in Spanish), the Neurology team offers basic clinical support to all studies carried out with volunteers and patients, generates and implements clinical research hypotheses and collaborates with the other teams of specialists in clinical and basic research, in the early detection, prevention and treatment of Alzheimer's disease and other related pathologies. The Department of Neurology develops the following activities:

- General and neurological medical evaluation, and clinical diagnosis of the Vallecas Project participants.
- Detection and management of possible clinical complications
- Preparation of clinical reports.

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

Main lines of research

The activities of this department focus on the following main areas:

1. "The Vallecas Project ": (due to its size, a complete section in this report is dedicated to this study, see block 4). In this project, it is carried out an annual systematic clinical and neurological evaluation of the more than one thousand volunteers participating in the study cohort. This information, together with the data from the neuropsychological assessment, allows establishing the evolutionary diagnosis of each subject and is stored in a large database for carrying out various research projects.

2. Queen Sofia Foundation Alzheimer Center Research Program : (CAFRS): it consists on the systematic clinical evaluation, every six months, of the patients who are in the CAFRS, both in internment regime (Units of Life) and in day care (Day Center). This evaluation, carried out together with the rest of the staff from the Center and healthcare professionals leads to the syndromic and etiological diagnosis and to the protocolled collection of neurological, psychiatric, neuropsychological, demographic, analytical,





therapeutic and neuroimaging data. This systematic gathering of information, from the moment the patient enters the study until it is transferred to another Day Center or passes away, allows for the generation of a large database of clinical data that can be exploited in itself or in relation to the neuroimaging and/or neuropathological data.

In 2017, there were 55 new admissions in the Day Care Center and in the Residence, of which 34 signed the consent to participate in the multidisciplinary periodic evaluations. Together with the 43 baseline evaluations, a total of 455 clinical evaluations (semi-annual frequency), 44 studies of brain MRI (annual frequency) and 344 analytical studies were carry out.

3. Clinical-Therapeutical Research: Progress has been made in the Sat-CIEN-02 project, an academic non-profit academic clinical trial funded by the Alzheimer's Association USA whose Principal Investigator is Dr. Isidro Ferrer and CIBERNED acts as promoter. This double-blind clinical trial consists in the treatment during 26 weeks of a group of 60 patients with cognitive impairment or incipient dementia attributable to Alzheimer's-type degeneration, randomly distributed in 4 arms (one placebo and three doses of active medication). The product that will be evaluated is a cannabinoid mixture that is already registered in the Spanish market for another indica-

tion (treatment of spasticity in patients with multiple sclerosis). The trial will be carried out in nine Spanish healthcare centers (five in Madrid, two in San Sebastián, one in Barcelona and one in Santander). The trial has already been approved by the Ethics Committee and the Spanish Agency for Medicines and Health Products and during this year it has worked on its organization and logistics and on the hiring of participating centers and suppliers.

4. Other ongoing research projects: The Department of Neurology, with its own resources or, more often than not, in collaboration with other CAFRS or external groups, is carrying out several other research projects. Most of them are mainly based on information o from the Vallecas Project or CAFRS databases. In other instances, information provided by various collaborators is used.

- Detection of proteins in the tear as biomarkers of Alzheimer's Disease
- Project REGISTRY. International multi-center observational study conducted by the European Huntington's Disease Group (EHDN). Finished in December 2017.
- Influence of the regular intake of drugs on cognitive performance in the Vallecas Project cohort
- Psychotic symptoms and vascular risk factors in Alzheimer's disease
- Behavioral disorders and neuropathological findings in Alzheimer's disease

PERIODIC MULTIDISCIPLINARY ASSESSMENTS DURING 2017

| | |
|--|-----|
| Admissions in Day Centre and Residence | 55 |
| Informed Consents | 34 |
| Baseline Assessments | 43 |
| Clinical Evaluations | 455 |
| Brain MRI Studies | 44 |
| Blood testing | 344 |



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5. Collaboration with other CAFRS groups in other projects:

- Metabolomic study in patients with Alzheimer's disease or Mild Cognitive Impairment
- PET study with and amyloid tracer in patients with Alzheimer type Mild Cognitive Impairment
- Clinical impact of fungal colonization of the central nervous system in Alzheimer's disease (pending evaluation)

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

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

Team

This department is composed by the following staff:

- Teodoro del Ser Quijano, Dr. Medicine, Neurology. Head of department.
- Meritxell Valentí Soler, Dr. Medicine, Neurology.
- María Ascensión Zea Sevilla, Dr. Medicine, Neurology.



Neurology team





3.2.2. Department of Neuropsychology

Neuropsychology is a scientific field that aims to describe, diagnose and treat cognitive, behavioral and emotional changes that appear as a result of a possible functional or structural impairment of the Central Nervous System. Within the field of dementias

Neuropsychology not only allows to characterize in an accurate way the cognitive state of an individual, but also helps to guide the diagnostic decision, to determine which subjects present a higher risk of developing a future neurodegenerative disorder and propose the appropriate therapeutic intervention.



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Given the multidisciplinary nature of the CIEN Foundation, the purpose of the Neuropsychology department is to contribute to the proper development of ongoing research projects through proper coordination with the rest of the departmental areas. In addition, among its objectives are also the conceptualization and implementation of new research hypotheses in the context of early detection and prevention of Alzheimer's disease.

Among the specific tasks carried out by the Department of Neuropsychology, the following activities are noteworthy:

- Neuropsychological assessment and cognitive diagnosis of the Vallecas Project participants.
- Preparation of clinical reports.
- Management and curation of databases.
- Statistical analysis and preparation of scientific reports.
- Teaching and mentoring of the external training practices of students in the last year of the Psychology Degree at the Autonomous University, the Rey Juan Carlos University and the Complutense University of Madrid.
- Communication in scientific forums of the research work carried out in the department.
- Dissemination to society of the progress of the investigation.

Main lines of research

The interests of the Neuropsychology department focus on four well defined lines of research in the area of its competence. In particular, the following priority research lines can be identified, which are described below.

1. Cognitive markers for the early detection of the prodromal phase of Alzheimer's disease: The professional figure of the neuropsychologist usually handles the application of different evaluation instruments. These include various types of tests, scales and questionnaires useful to measure both the objective cog-

nitive performance and the subjective perception of an individual with respect to aspects such as memory complaints, mood or coping styles. To meet the challenges posed in the context of the Vallecas Project, the neuropsychological test battery focuses especially on the evaluation of memory processes, attention and executive functions as potential early markers of Alzheimer's disease. In addition, the neuropsychological profile of each participant is completed by gathering information related to other cognitive domains such as language, visuospatial ability and visuoconstruction, as well as emotional variables. This is particularly important because it allows identifying the strengths and weaknesses in the cognitive profile and characterize, if appropriate, the type of cognitive impairment that an individual presents. Moreover, the neuropsychological evaluation protocol includes various questionnaires in order to collect information complementary to the cognitive profile. Specifically, we obtain data about the assessment of possible cognitive complaints, as well as different aspects of them such as the time of appearance, the concern generated or the profile of these complaints. In essence, the study of all these cognitive variables, both objective and subjective, together with the rest of the biographical and clinical data, will allow us to establish what role each cognitive parameter plays in the appearance and course of Alzheimer's disease.

1.1. Usefulness of subjective cognitive complaints as an early marker:

Cognitive complaints may appear in preclinical phases of Alzheimer's disease; even a person can often experience this type of complaint though their cognitive performance in a formal neuropsychological examination is within normal parameters. For this reason, there has been renewed scientific interest in recent years for the study of subjective cognitive complaints as a possible marker of future objective cognitive impairment.





The Department of Neuropsychology has carried out different studies to analyze the role of cognitive complaints as a predictor of cognitive impairment in a sample of elderly people from the general population. Specifically, the focus is placed on studying which specific aspects and what type of cognitive complaints show a greater relationship with the development of cognitive impairment.

1.2. Usefulness of various cognitive parameters as early markers:

Numerous studies have shown that there are certain cognitive variables that allow the identification of subjects at higher risk of developing Alzheimer's disease years before their diagnosis. With this idea in mind, we investigate whether certain parameters of the neuropsychological protocol, in the context of a longitudinal research project such as the Vallecas Project, are useful to identify individuals at risk of cognitive impairment. These parameters are analyzed in an evolutionary way together with the rest of clinical and genetic information of each volunteer in order to obtain a classification algorithm that could eventually be generalized to daily clinical practice. In addition, the Department of Neuropsychology is interested in developing new assessment tools that allow examining the role of other cognitive markers not studied in standard neuropsychological evaluations. It is expected that the identification of these markers increase sensitivity and specificity when detecting individuals at risk of dementia.

2. The role of cognitive and functional reserve in the prevention of cognitive impairment: The cognitive reserve is a theoretical construct that formulated several decades ago to explain the lack of correspondence between the degree of brain damage and clinical symptoms sometimes observed among patients. It is presumed as an individual capacity

that develops throughout the life cycle fundamentally through formal education, the type of professional activity performed and the intellectual activity developed. Numerous studies have supported the protective role played by the cognitive reserve in modifying the course of different neurodegenerative pathologies, including Alzheimer's disease. The interest of the Department of Neuropsychology for this construct focuses on analyzing different variables that apparently have the capacity to confer cognitive reserve and therefore could play a protective role against cognitive impairment. Within the Vallecas Project, this set of variables is being studied individually and in groups, with special emphasis on the activities of daily life performed in the middle stages of life. Likewise, different lifestyle variables are examined in order to classify them as risk or protection factors against dementia onset.

3. Clinical and physiopathological mechanisms common to Down syndrome and Alzheimer's disease: A new research program is envisaged in collaboration with the Down Unit of La Princesa University Hospital, the Biomedical Technology Center (CTB), the Complutense University of Madrid (UCM), and the Ramón Castroviejo Ophthalmological Institute. Within this research project, the department of neuropsychology will be specifically responsible for designing a specific protocol for the longitudinal cognitive assessment of a cohort of people with Down syndrome. The purpose of this research program is twofold. On the one hand, characterize clinically and cognitively a cohort of people with Down syndrome, adapting and designing new tools and protocols for the assessment and diagnosis of cognitive impairment in these individuals. On the other hand, the prevalence rate of Alzheimer's disease in Down syndrome will be examined and the association between certain biological and biographical variables with the disease will be studied to determine the dynamics of the disease. Ultimately, the impact of this study is expected to



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

4. Study of non-pharmacological therapies for the prevention and modification of the course of Alzheimer's disease: Non-pharmacological therapies are a set of interventions that are set in place with three specific objectives: to stimulate cognitive processes, promote the level of autonomy and, ultimately, increase the quality of life of individuals. These interventions can be carried out both in healthy elderly people, in order to prevent the onset of cognitive impairment, as well as in patients with cognitive impairment, to try to modify the course of the disease. Among the most used non-pharmacological therapies, cognitive stimulation, physical exercise, occupational activity, music therapy and even diet control stand out.

Although scientific evidence has shown that non-pharmacological therapies have a protective effect against cognitive impairment, there are still some unresolved issues related to this topic. For example, determine what type of intervention is most beneficial or what clinical variables are associated with a better prognosis of the therapy. Taking advantage of the knowledge accumulated throughout the Vallecas Project, the objective of the Department of Neuropsychology is to study the impact that these non-pharmacological interventions have on subjects at risk of developing mild cognitive impairment.

Team

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

Neurology-Neuropsychology Administration

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

CAFRS Collaborators

The following CAFRS staff also collaborated during 2017:

- Irene Rodríguez Pérez
(Occupational therapist, Residence)
- Almudena Pérez
(Occupational therapist, Residence)
- Rocío Rodríguez Casas
(Occupational therapist, Day Center)
- Cynthia Pérez Muñoz
(Training technician and Occupational therapist)
- Emma Osa Ruiz
(Physiotherapist, Residence)
- Sara Esteban Prior
(Physiotherapist, Residence))
- José Luis Muñoz Zarco
(Physiotherapist, Day Center).
Until September 2017.
- Nuria Antón Moreno
(Physiotherapist, Day Center).
Since October 2017.
- Carolina Mendoza Rebolledo
(Grad. Psychology, Neuropsychology, Day Center). Until November 2017.
- Virginia Guerra Martín
(Grad. Psychology, Residence and Day Center)
Since November 2017.
- Gema Melcón Borrego
(Grad. Social Work, Day Center).
Until March 2017.
- Elena Herranz Huerta
(Grad. Social Work, Day Center).
Since March 2017.



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- Lidia Espada Raboso
(Grad. Social Work, Residence)
- Belén González Lahera
(MD, Geriatrics)



Department of Neuropsychology





3.2.3. Department of Neuroimaging

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

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

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

The main objectives Department of Neuroimaging are:

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

- Personnel training related to obtaining, postprocessing or interpretation of advanced neuroimaging techniques

Department activities

UIPA's Department of Neuroimaging primarily deals with the acquisition of MR data (and, where appropriate, the performance of other imaging techniques such as PET or CT through external collaborations) and post-processing and analysis of the data obtained. All studies are monitored and reported by a neuroradiologist.

In addition, the Department provides technical assistance to both the rest of the scientific areas of the UIPA and external research groups. It also searches for new resources and promotes the UIPA research projects and the post-processing of images service among other research groups.

This activity complements the internal seminars and external courses, both nationals and international, on specific neuroimaging techniques.

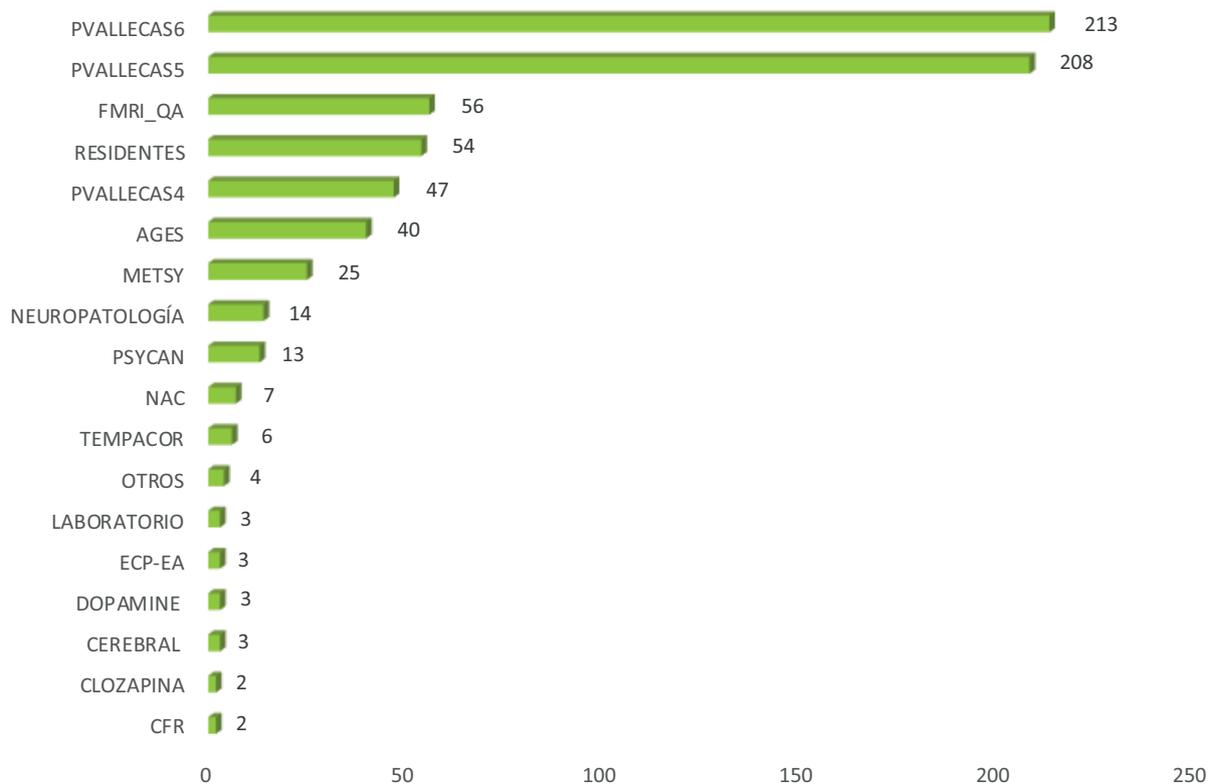
During 2017, the Department of Neuroimaging has participated in MRI studies in the following clinical trials:

- **"Pilot clinical trial to evaluate the efficacy and safety of deep brain stimulation in Alzheimer's disease". Alzheimer**". ECP-EA IP: Dra. Aurora Vilorio Jiménez. Hospital Clínico San Carlos.
- **"NAC"**.Phase III study: "Effect of Adjuvant treatment with N-acetylcysteine for 48 weeks over the loss of gray matter and oxidative metabolism in patients with early onset psychotic episodes". Randomized, Double-blind, placebo-controlled Clinical Trial Code: FIBHGM-ECNC002-2012, EudraCT Number: 2012-005435-87. Promoter Center: Foundation for Biomedical Research Gregorio Marañón Hospital. PI: Celso Arango.



3. SCIENTIFIC ACTIVITY

Number of studies by project 2017



- **"Clozapina** in First Outbreaks of Schizophrenia as Possible Preventive Treatment of Cerebral and Clinical Impairment". Code protocol: CLOZAPINA-1, N° EudraCT: 2006-00200-34. PI: Dr. Francisco Javier Sanz Fuentenebro. 2010-2013. CIBERSAM.

During 2017 the acquisition of MR images from a 706 subjects has been completed. Overall, 4,134 MRI studies have been performed distributed among the different research projects.

52,637 MRI sequences have been conducted since the creation of the department, distributed by year

and type of sequence, as it is shown in the next graph.

Provision of services

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





For Functional MRI studies, the Department has an audio/video system compatible with 3T MRI.

A variety of software packages is used, mainly SPM12, FSL and Freesurfer.

Sequences

Image acquisition of 3D isotropic studies with T1 sequences for VBM. Image acquisition of T2 sequences, DWI, ASL, BOLD and spectroscopy.

Team

The Department of Neuroimaging team, led by Dr. Bryan Strange (MD, PhD, Clinical Neuroscience), has a highly multidisciplinary nature and consists of the following personnel:

Research fellows

- Jaime Gómez Ramírez (PhD, Computer Engineering, Automatics and Robotics).

- Christopher Long (PhD, Engineering, Specialist in Biomechanical Imaging, Madrid Massachusetts Institute of Technology Vision Program). Until May 2017.
- Eva Dueñas Moreno (BSc, Biology). Until December 2017.
- María Molina Matas (BSc, Physics). Until December 2017.
- Linda Zhang (PhD in Radiological Imaging. Grad. Psychology). Collaborator.

Radiodiagnostics

- Mabel Torres Llacsá (MD, Radiodiagnostics)

Image Acquisition

- Eva Alfayate Sáez (Technical Coordinator in Radiodiagnostics)

MRI sequences

| | FUNCTIONAL | VOLUMETRICS | SPECTRA | DIFUSION TENSOR | MISC. | ASL |
|------|------------|-------------|---------|-----------------|-------|-----|
| 2008 | 255 | 339 | 156 | 178 | 312 | 259 |
| 2009 | 337 | 638 | 866 | 423 | 845 | 326 |
| 2010 | 910 | 852 | 1042 | 556 | 1506 | 305 |
| 2011 | 1124 | 845 | 786 | 528 | 1904 | 398 |
| 2012 | 1858 | 1512 | 583 | 1330 | 2938 | 949 |
| 2013 | 1436 | 1276 | 516 | 1116 | 2544 | 950 |
| 2014 | 880 | 937 | 367 | 847 | 1920 | 729 |
| 2015 | 828 | 912 | 309 | 783 | 1985 | 669 |
| 2016 | 739 | 749 | 341 | 618 | 1661 | 572 |
| 2017 | 614 | 648 | 299 | 594 | 1415 | 523 |



3. SCIENTIFIC ACTIVITY

- Felipe García Fernández
(Advanced Technician in Diagnostic Imaging)
- Carmen Rojas Obregón
(Technician in Radiodiagnostics)

Administration

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



Neuroimaging team





3. SCIENTIFIC ACTIVITY

3.2.3. Department of Neuropathology

Neuropathology of neurodegenerative disorders is a specialty in continuous progress with capacity for contrasting clinical judgment and performance of any diagnostic test, including the most recent biomarkers, with the final diagnosis that is still neuropathology ("gold standard"). However, in the field of basic research, neuropathology plays an additional role, providing critical information about the molecular components of the characteristic lesions of each disease, the pathogenic mechanisms and the potential biomarkers.

The post-mortem neuropathological findings observed in donations of brain tissue from patients with neurodegenerative diseases, especially in the case of dementias, have allowed to know in recent decades the epidemiological reality of these diseases in the population, and among other evidences, have revealed the high prevalence of combined pathology (Alzheimer's pathology, Vascular pathology and Lewy pathology, mainly).

The neuropathology of dementia landscape has dramatically changed in recent years. The incorporation to the neuropathological diagnosis of new antibodies for immunostaining and new molecular techniques has helped establishing the boundaries and internal heterogeneity of entities such as dementia with Lewy bodies and frontotemporal dementia, and has also led to the discovery of new entities in this area (DFT-TDP, DFT-FUS, etc.). The neuropathological study of an increasing number of patients with neurodegenerative pathology has allowed identifying new genetic causes of these diseases, thus helping to define new molecular targets for possible therapeutic approaches. In addition, the definition of diagnostic criteria from large series of brains (in biobanks of neurological tissue or brain banks) has allowed us to address the problem of combined and mixed pathology, specifically regar-

ding Alzheimer's disease. The evolution of the diagnostic criteria themselves (e.g. the new criteria for the diagnostic classification of Alzheimer's disease proposed by the National Institute of Aging - Alzheimer's Association, 2012) and molecular techniques are converting the histological diagnosis into an fundamental element in the process of classifying dementias, definitive or quasi-definitive in some cases, but partial or probabilistic in many others. As repeatedly demonstrated in clinical-pathological sessions, made possible in most cases thanks to the donation of brain tissue by patients or their families and the close collaboration of clinicians, the final classification of a case requires the integration of all clinical, neuroradiological, neuropathological and molecular information, when available.

A need for dementia research is the availability of well-diagnosed, classified and long-term preserved brain tissue. Brain banks (biobanks of neurological samples) respond to this need, and the CIEN Foundation has one of the main brain banks in the country, the CIEN Tissue Bank (BT-CIEN, for its acronym in Spanish).

Neuropathology also provides significant support for studies based on animal models of neurological diseases, both for the histological evaluation of transgenic animals and for the search for natural models of the disease. The Department of Neuropathology of the CIEN Foundation participates regularly in the histological evaluation of animal models of different neurodegenerative diseases developed by CIBERNED researchers, as well as in the neuropathological study of elderly mammals of the Madrid Zoo.

Department activities

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





The Department also participates in numerous collaborations in external research projects, mainly with CIBERNED research groups, and carries out its own internal projects, mainly based on series of cases from post mortem donation. Among the active lines of research in the Department are the following:

- Neuropathological and molecular study of tauopathies, including Alzheimer's disease. Pathogenic significance and spread of associated cellular lesions. Argyrophilic grains disease as a model of tauopathy with predominant involvement of the medial temporal lobe.
- Clinicopathological profiles in advanced dementia. Characterization of the combined and mixed pathology and its impact on the clinical trajectories of the patients, with special attention to disease progression rate and survival time.
- Pathological role of fungal colonization and the polymicrobial infection of the Central Nervous System in Alzheimer-type pathology. Risk factors and clinical impact.
- Distinctive features of Alzheimer-type pathology in nonagenarians and centenarians. Neuropathological findings in subjects without cognitive disorder above 90 years of age.
- Characterization and pathogenic study of dementia-associated hippocampal sclerosis.
- Advance age-associated changes in Central Nervous System and cerebral pathology in mammals and non-human primates. Search for natural models of Alzheimer in primates and other mammalian groups.

Provision of services

The range of activities undertaken by the department derives from the ability of its members to collect, process, evaluate and diagnose brain tissue

sample from human or animal origin. All the services provided by the BT-CIEN are accessible to donors and researchers through the website.

- Performing neuropathological autopsies in brain tissue donors, both in the Region of Madrid and neighboring Regions, as well as in other Regions that do not have a brain bank.
- Management of a biobank of neurological samples. Transfer of samples to researchers according to the BT-CIEN standard operating protocols.
- Prospective collection of special biological samples for research projects, at the request of the researchers, once approved in compliance with BT-CIEN protocols (and by the scientific and ethical external committees).
- Diagnostic consultations of neuropathological cases. Among the external consultations, those carried out as support of other biobanks of neurological samples with which BT-CIEN maintains a regular collaboration (Murcia, Salamanca, Leon and Cordoba) stand out. Consultations are also received from different public hospitals and from the Anatomical Forensic Institute of Madrid
- Performing neurohistological and immunohistochemical techniques in neurological samples of human and experimental origin.
- Incorporation in the biobank of samples collections (usually, biological fluids, blood and CSF) from clinical research projects.
- Organization of informative lectures and visits to the biobank for the dissemination and promotion of brain tissue donation among patients and relatives, health professionals and the general population.



3. SCIENTIFIC ACTIVITY

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, which involves residents of the Queen Sofia Foundation Alzheimer Center (CAFRS), and the External Donation Program, that involves donors from the Region of Madrid and other Regions.

There is also an increasing number of research groups applying for biological samples from BT-CIEN,

especially groups from the Center for Networked Research in Neurodegenerative Diseases (CIBERNED). One of the missions of BT-CIEN is to promote the creation of new neurological samples biobanks whenever donors and researchers demand them. The Region of Murcia Brain Bank (BCRM), the Neurological Tissue Bank from the Institute of Neuroscience of Castilla y León (BTN-CyL) and the of Queen Sofia University Hospital Biobank from Cordoba are active examples of this commitment.

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

In January 2014 the Biobanks National Network Platform (PRNBB, for its acronym in Spanish), promoted

Distribution of donation cases by origin in 2017





and funded by the Carlos III Institute of Health (2014-2017) was constituted, with participation of the main biobanks in the country, both hospital and non-hospital, including BT-CIEN. PRNBB mission is to create a stable organizational structure that allows the coordinated activity of participating biobanks in the collection, management and transfer of biological samples of human origin. Before concluding its period of activity in December 2017, the PRNBB renewed its commitment to the ISCIII for a new funding period, 2018-2020. The BT-CIEN has played a prominent role in the R&D&I Program of the PRNBB. Moreover, since 2012 the BT-CIEN has the ISO 9001/2008 quality certification, which was renewed in 2016. The BT-CIEN registry had 656 registered donors by December 31, 2017.

Up to 97 cases were processed in the Neuropathology laboratory during 2017, with the following distribution depending on the origin:

54 donations from the External Program.
24 donations from the Internal Program
19 consultation cases

According to these data, the number of donation cases extracted and processed entirely in the UIPA in 2017 amounted to 78, which is slightly lower than that obtained in 2016. The increase in donations from the Internal Donation Program is noteworthy, with 123 total donations until the end of 2017.

In 2017, the average post-mortem interval obtained is 5.5 hours, which is within the range of those obtained in recent years.

The research centers that have received samples from BT-CIEN during 2017 have been:

- Functional Unit for Research in Chronic Diseases / ISCIII
- School of Medicine. University of Castilla-La Mancha, Albacete.
- School of Medicine. University of La Laguna

- Oviedo University
- Center for Molecular Biology Severo Ochoa
- CEU San Pablo University
- Cajal Institute (CSIC)
- National Center for Biotechnology
- Aragon Health Research Institute
- Georg-August University. Germany

At the end of 2017, the number of donations accumulated by BT-CIEN was 567, of which around 50% correspond to cases with a primary neuropathological diagnosis of Alzheimer's disease.

Team

During 2017, the Department of Neuropathology staff was composed of the following personnel:

- Dr. Alberto Rábano (MD, PhD, Pathology), Head of Department and BT-CIEN
- Elena Gómez Blázquez (Pathology Technician)
- Izaskun Rodal González (Pathology Technician)
- Laura Sáiz Auz (simple management technician).
- Valentina González Álvarez (biologist, quality program and special samples). From February 2017.
- Mario Lozano Enguita (Pathology Technician). Until June 2017.
- María Concepción García Otero (Grad. Psychology, Neuropsychology). Until September 2017.
- Virginia Guerra Martín (Grad. Psychology, Neuropsychology). Until October 2017.



3. SCIENTIFIC ACTIVITY

Collaborators (autopsies):

- Luis Javier Martín Lentijo
(Pathology Technician)
- Ana Sánchez de Castro
(Pathology Technician)
- M^o Cruz Santiago San Marcos
(Pathology Technician).



Neuropathology team





3.2.5. Department of Molecular Genetics

The aging of the population and the growing epidemic of Alzheimer's disease (AD) highlight the importance of research in the molecular mechanisms of pathology, as well as in the development of methods for the early detection of the disease to carry out an adequate evaluation of risk and to be able to implement early and effective therapies. Currently, it is widely accepted that changes at the cellular level associated with AD, including the formation of neurofibrillary plaques and tangles, begin many years before clinical symptoms are evident or the existence significant cell death in the brain. Therefore, the development of biomarkers that allow the identification of patients with incipient AD or asymptomatic people at risk is of great importance, so that treatments aimed at stopping neurodegeneration can be initiated before it becomes irreversible.

The most extensively studied biochemical markers are the tau protein (total levels and different phosphorylated isoforms) and the amyloid β peptide in cerebrospinal fluid (CSF), that are both directly related to neurofibrillary and amyloid pathology, respectively. However, the drawbacks derived from obtaining CSF, together with a limited precision of these assays in early phases, highlight the need to identify new markers. Currently, many researchers believe that both the development of neurofibrillary and amyloid pathologies in AD represent relatively late events in the evolution of the disease, which may or may not reflect the fundamental biochemical-molecular dysfunctions that give rise to the disease. The clinical manifestations of AD are preceded by an asymptomatic preclinical phase, after which the first symptoms appear in the prodromal phase of the disease characterized by mild cognitive impairment (MCI). In this sense, AD can be understood as a continuous process that evolves from the asymptomatic phases to the dementia phase. This

evolution is largely determined by genetic risk variants and is associated with biochemical changes that can ideally serve as early markers of the disease.

Department activities

The activity of the Molecular Genetics Department focuses mainly on the search for biomarkers of early diagnosis of Alzheimer's disease and the study of genetic susceptibility factors of AD and other neurodegenerative disorders. This activity has the following objectives: to deepen the molecular basis of the disease and develop predictive algorithms that combine information on genetic and biochemical markers with diagnostic, prognostic or response value to modifying therapies.

For this purpose, the Department's research is connected with the activities of the Multidisciplinary 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 Vallecas project for early detection of AD and the Basic research project at the Alzheimer Healthcare Center from the Queen Sofia Foundation.

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.



3. SCIENTIFIC ACTIVITY

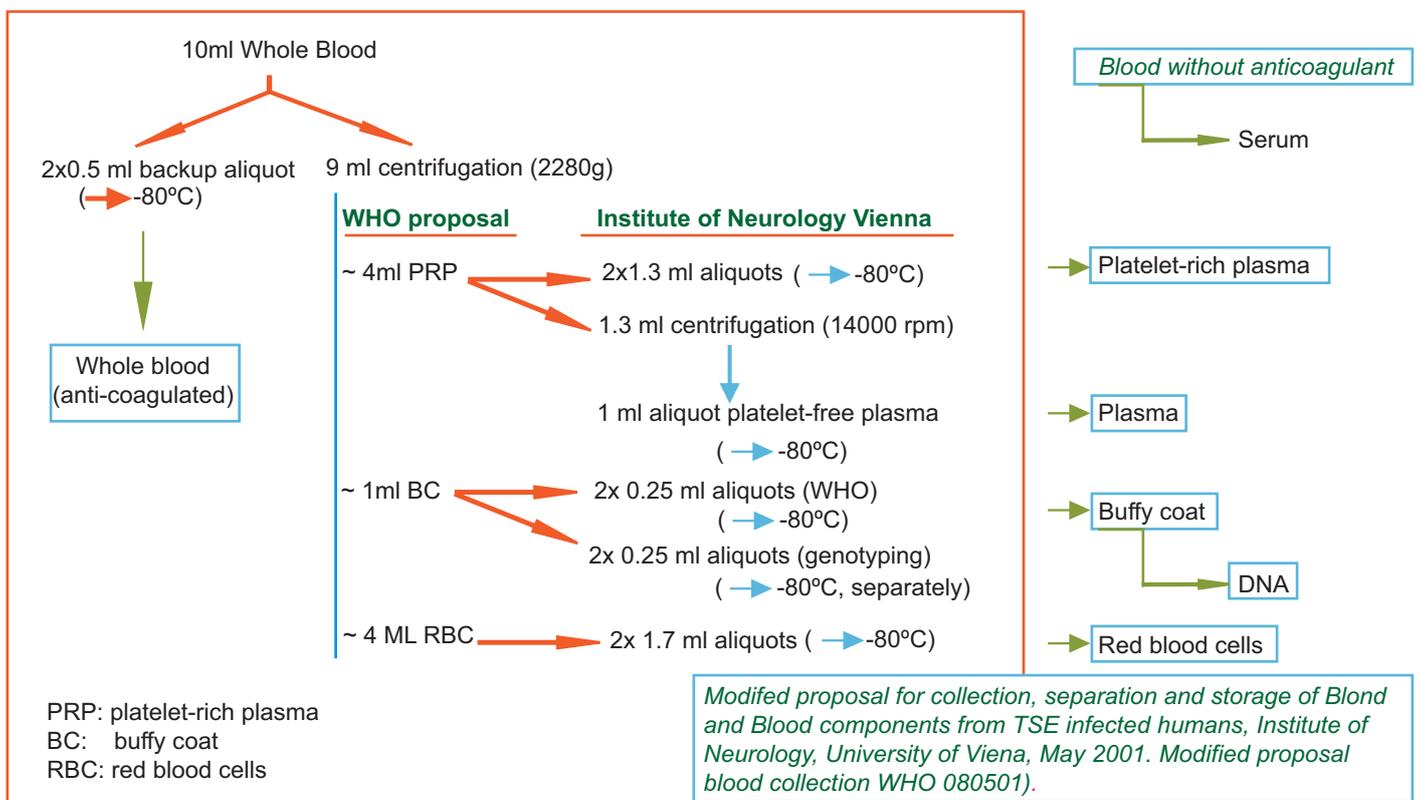
The phase of recruiting volunteers for participation in the study was finished in December 31, 2013, with its corresponding baseline assessment (n=1,169). The project includes activities from the Neurology, Neuropsychology, Neuroimaging, and Molecular Genetics departments. During 2017, we have studied 51 volunteers to complete the fourth follow-up visit, 234 volunteers on the fifth visit, and 249 on the sixth visit.

Of all patients recruited in the study and having an informed consent, a blood sample is collected and immediately transferred to the laboratory for frac-

tionation into aliquots following the so-called Vienna Institute of Neurology protocol, which allow different types of analysis, as well as classification and storage (see Figure below). Additionally, one blood tube (BD-CPT citrate Vacutainer) for the isolation of mononuclear leukocytes, together with another tube lacking anticoagulant to obtain serum are processed..

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

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





The type of primary aliquots that are obtained in duplicate are the following:

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

Genomic DNA was extracted from whole blood of all participants who have signed informed consent to it and the APOE gene, an important marker of genetic risk for Alzheimer's disease, was analyzed. The comparison of the frequency of APOE allele ϵ_4 carriers between CAFRS patients and Vallecas Project volunteers confirms the risk to suffer from Alzheimer's disease with an OR = 3.53 ($p < 0.001$). In addition, in order to define different subpopulations of genetic risk, other possible genetic susceptibility genes have also been analyzed in a subset of participants (see figure).

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

Research Program of the Queen Sofia Foundation Alzheimer Center, This program focuses on regular and protocol-based monitoring of a cohort of CAFRS patients with dementia, either as residents at the Center or attendants at the Day Center, with the main objective of investigating the final stages of Alzheimer's disease. A family member or guardian recruits patients into the monitoring program after signing an Informed Consent. The Alzheimer Project program consists of i) a biannual clinical and neu-

The Vallecas Project activity in figures

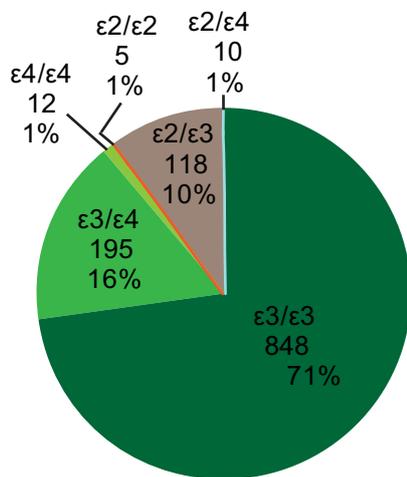
| Evaluation | 1º | 2º | 3º | 4º | 5º | 6º | TOTAL |
|---------------|--------|--------|--------|-------|-------|-------|--------|
| Total samples | 1.169 | 767 | 755 | 648 | 384 | 0 | 3.723 |
| 2017 samples | 0 | 0 | 0 | 51 | 234 | 249 | 534 |
| Total | 1.169 | 767 | 755 | 699 | 618 | 249 | 4.257 |
| Nº Aliquotes | 16.366 | 10.738 | 10.570 | 9.786 | 8.652 | 3.486 | 59.598 |



3. SCIENTIFIC ACTIVITY

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

APOE genotypes



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

The CAFRS takes care of 156 patients in residence, and 40 patients in the Day Centre. The Alzheimer project-monitoring program includes obtaining a blood sample biannually coinciding with the one routinely performed at the Center for conventional analytics. Thus, performing a venipuncture in the patient for research purposes only is avoided. After extraction, each blood sample is processed at once, resulting in 14 aliquots comprising various hematologic derivatives (whole blood, plasma, serum, etc.), including extraction of DNA for genetic studies. Aliquots obtained from blood samples are incorpo-

rated 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 2,420 (14.0% patients corresponding to the Day Centre), which have resulted in a total of 33,880 aliquots of different fractions derived from blood samples.

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

Other projects Currently, several lines of study are being followed up based on the combined use of biochemical markers and genetic data. In 2017, the project entitled "Vascular dysfunction associated with Alzheimer's disease (FIS project)" is concluded, which has continuity in other complementary projects that have begun this year, focused on the study of biomarkers for the early diagnosis of AD and the analysis of genetic risk factors.

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

During 2017, the study of microRNA as potential biomarkers of AD has begun, in collaboration with Dr. Tobias Engel (Royal College of Surgeons, Dublin, Ireland). In this context, funding has been obtained from MINECO (RETOS call for projects) for carrying out the project entitled "miRNA and lipid metabolism markers as potential links between vascular dysfunction and Alzheimer's pathophysiology", whose main

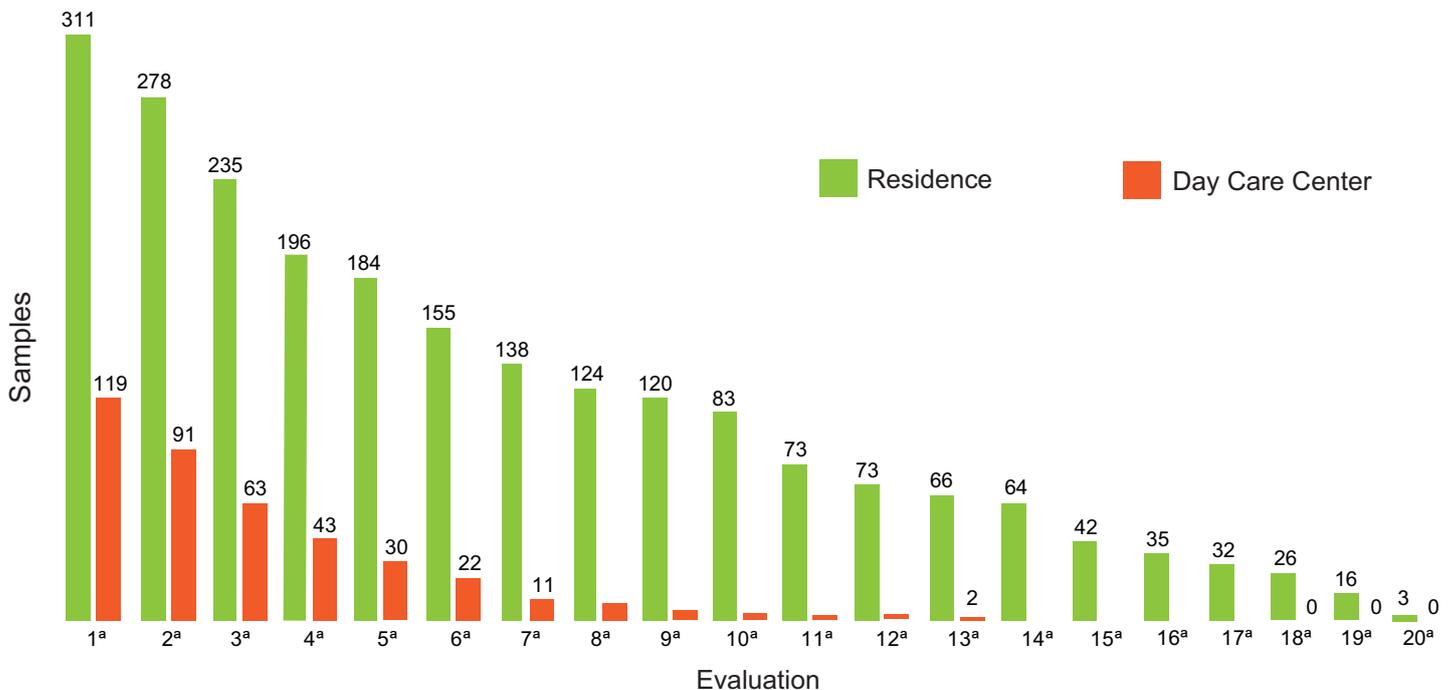




investigators are Drs. Miguel Medina and Miguel Carero. The main objective of this proposal is to explore the possible role of miRNAs and markers of lipid metabolism as possible links between peripheral vascular dysfunction and the pathophysiology of AD. The design of the project is based on a double approach with complementary aims related to the existing cohorts (Vallecas Project and Research Program of the Vallecas Research Center (PICAV) and the CIEN Foundation Brain Bank. The central working hypothesis builds upon the existence of circulating miRNAs and molecules of lipid metabolism in plasma that could differentiate cognitively normal individuals from people with mild cognitive impairment or dementia, either alone or in combination with other parameters being collected from the same individuals

(elderly volunteers) within the Vallecas Project, as well as patients with confirmed AD after autopsy. To this end, we propose to carry out a complementary and synergistic approach to evaluate, validate and standardize the identification, monitoring, quantification and functional validation of miRNAs in plasma samples taken from elderly subjects who are cognitively normal, show deterioration cognitive mild or moderate dementia, in the presence or absence of peripheral vascular pathology. Following a multidisciplinary approach, the analysis of the data obtained will benefit from the availability of other data generated within the Vallecas project (socio-demographic data, clinical history, annual neurological evaluation, neuropsychological evaluation, structural and functional brain MRI, genotyping, etc.)

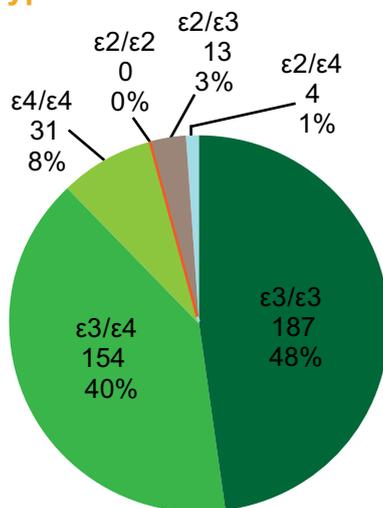
Samples obtained up to December 31, 2017 according to the number of semiannual evaluations



3. SCIENTIFIC ACTIVITY

Distribution of APOE genotypes in the CAFRS patients cohort

APOE genotypes



in order to identify molecular, clinical, or neuroimaging signals that may serve to define populations at higher risk of developing dementia in the future.

Dementia Genetics Spanish Consortium (DEGESCO)

Also, during this year, the CIEN Foundation has continued participating in Dementia Genetics Spanish Consortium (DEGESCO). A number of Spanish research groups share genetic data within this consortium to achieve greater study power in dementia genetics and especially in the Alzheimer's disease. Because of these collaborations, an interesting study on the association of the H1 haplotype of the MAPT gene in non-carriers of the APOE $\epsilon 4$ allele has been published. In the context of DEGESCO, during 2016 several research actions were carried out aimed at defining new genetic risk factors and the participa-

tion of the national consortium in international proposals (see below).

In addition to the study of the APOE gene, using samples from the Vallecas Project (controls) and samples from the Alzheimer Project (AD cases), genetic association studies of the main genes associated with AD have been carried out, including SORL1, LDLR, BIN1, CLU, ABCA7, CR1, PICALM, BACE1 and PRNP. These association studies, in addition to serving as a replication in a Spanish population of studies carried out in other populations, will allow us to determine the most important genetic factors in the development of cognitive dysfunction in our population of the Vallecas Project. It will also allow defining endophenotypes based on genetic variations as well as concrete and measurable characteristics of the patients and controls based on clinical neuroimaging, biochemical or pathological measurements (see figure).

An European DNA bank for deciphering the missing heritability of Alzheimer's disease - EADB (European AD DNA Bank) and GR@ACE project (Genomic Research at Fundació ACE)

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

This initiative will increase the number of AD samples available in Europe more than four times and around the world by almost two-fold. Carrying out



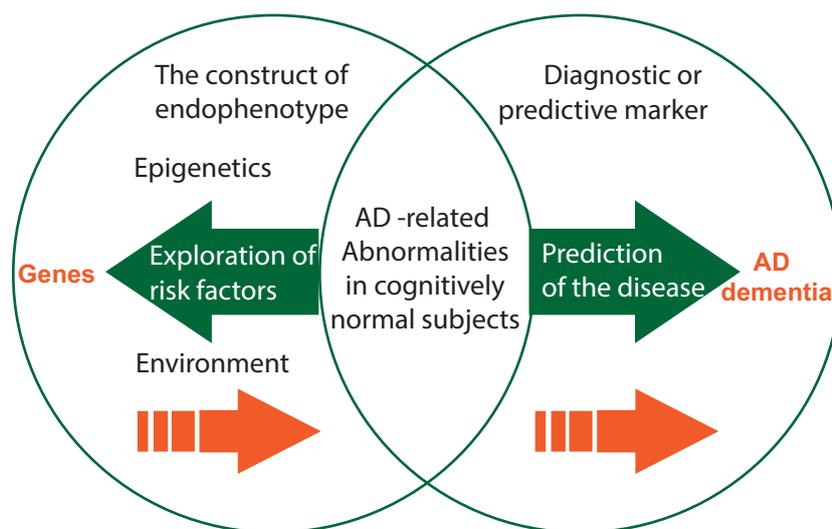


this project will allow us to understand the genetics of AD thus improving our knowledge of the underlying pathophysiological processes in the disease; since the genetic factors seem to represent up to 80% of the attributable risk in AD. In parallel, the EADB will collect DNA samples from the largest European longitudinal cohort of cases of mild cognitive impairment, with the aim of identifying genetic markers that modulate the rate of disease progression and cognitive decline. From a translational perspective, the identification of genetic factors in the pathways that modulate AD risk and increase the rate of disease progression/cognitive decline will be critical for the development and testing of therapeutic approaches.

Additionally, in the context of the DEGESCO consortium, collaboration has begun with the GR@ACE project, led by the ACE Foundation, which will be carried out in three years, and whose objective is the application of high resolution genomic technologies for the identification of a new generation of genes that contribute data in the design of new treatments to deal with Alzheimer's disease.

In relation to the study of biomarkers and the collaborative context with the company Biocross SL and with various Spanish hospitals, we continue with the plasma metabolomic studies of people with Alzheimer's disease, mild cognitive impairment or without cognitive dysfunction. In addition, we also continue

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



3. SCIENTIFIC ACTIVITY

with the development of a non-genetic test adapted to the hospital diagnostic routine for measuring blood ApoE4 as a marker for determining the AD risk.

Contribution to BT-CIEN

The Molecular Genetics department also contributes to the BT-CIEN with processing of various samples, and collaborates on several external projects focu-

sed 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 Molecular Genetics department is responsible for collecting, processing and storing biological samples for research related to various projects or for its deposit in the BT CIEN, whose ultimate purpose is to





use in different research areas on neurodegenerative diseases.

Currently, the department contributes to BT-CIEN with various biological samples including 410 CSF samples from donor's brain and 304 skin samples.

Team

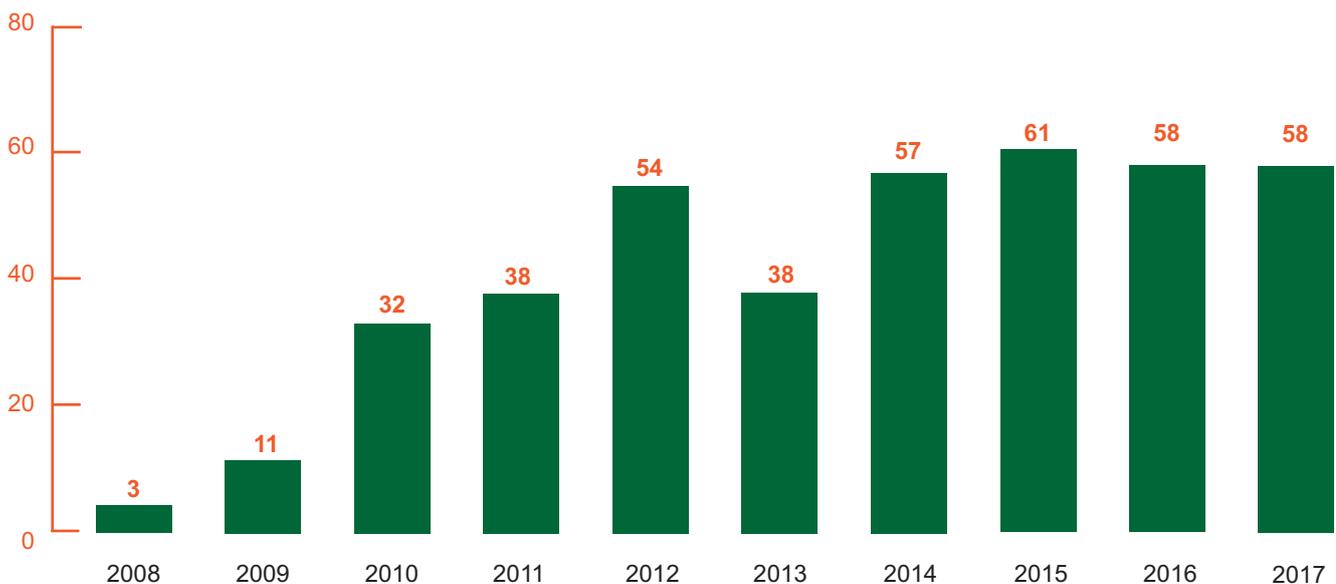
During 2017, the team of the Molecular Genetics Department was composed of the following personnel:

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

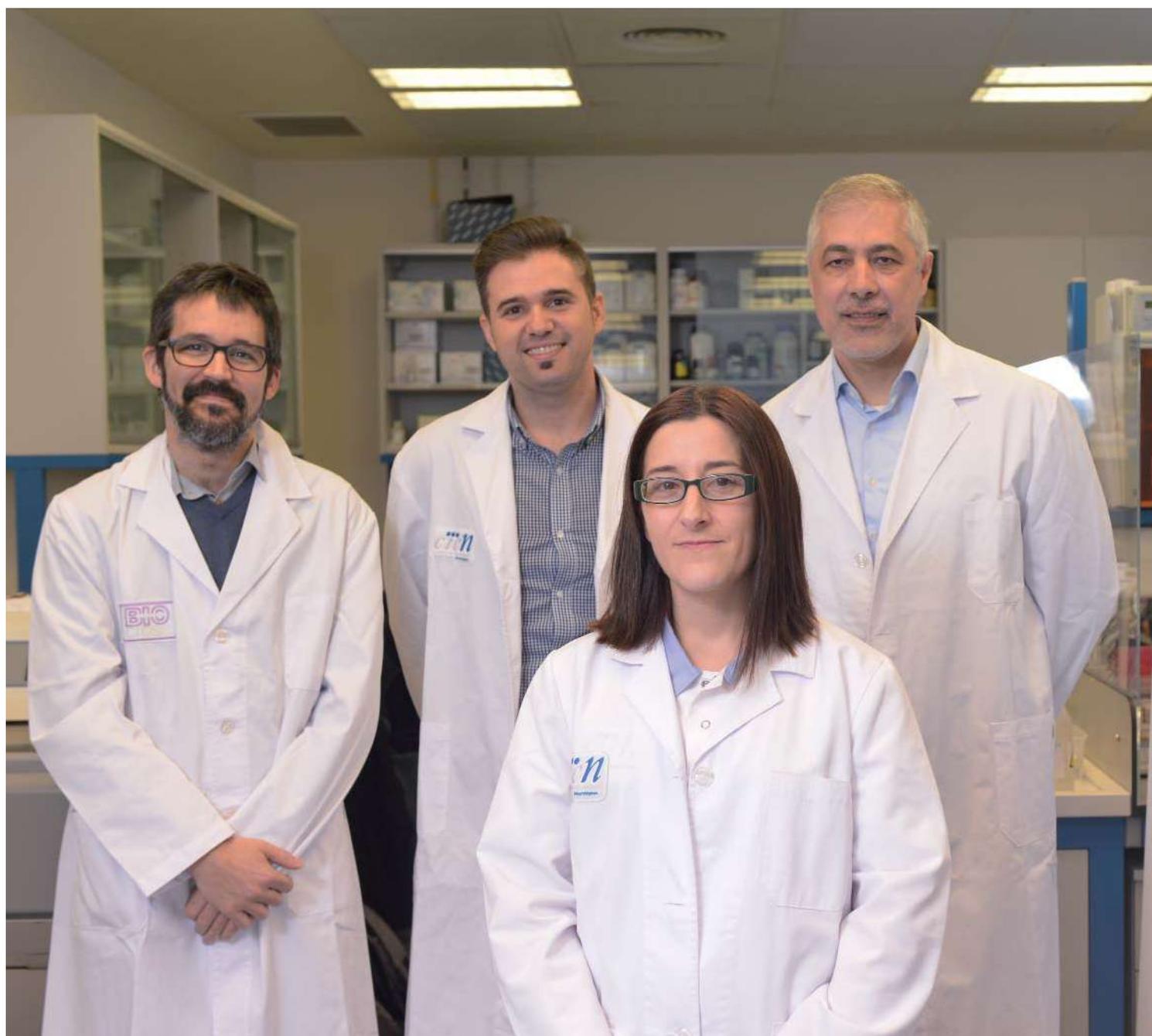
Collaborators

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

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



3. SCIENTIFIC ACTIVITY



Molecular Genetics team



The Vallecas Project

The success of the "Vallecas Project" has allowed the sixth yearly visit of volunteers to begin in 2017. The continuity of this pioneering initiative in the search for answers for the early detection of Alzheimer's results in the publication each year of new data relevant for the scientific community and progress of the research in neurodegenerative diseases.





4. THE VALLECAS PROJECT

4.1. Introduction

Aging is one of the major risk factors for some of the most prevalent diseases such as cancer, cardiovascular disorders or neurodegenerative diseases, but while the number of cases of the first two tends to stabilize, the number of patients with neurodegenerative pathologies, particularly dementia, continues to grow exponentially. According to the demographic estimates of the National Institute of Statistics, in 2017 there are 8.7 million people in Spain aged 65 or over (18.87% of the population) and it is estimated that in 2050 about 15 million Spaniards (approximately one third of our population) will be over 65 years old. In fact, the combination of one of the highest life expectancies in the world and one of the lowest birth rates make the Spanish population the oldest in Europe and one of the oldest in the world after South Korea and Japan.

Dementia is a clinical syndrome characterized by a progressive cognitive impairment severe enough to affect personal and social functioning of an individual. Alzheimer's disease (AD) is the leading cause of dementia in our environment. According to the National Epidemiology Center, 7.3% of the population over 65 years could suffer from this disease nowadays. In total, AD constitutes about 75% of the etiology of dementias, either alone or in combination with cerebrovascular disease. Because of increased life expectancy and the progressive aging of the population in Western countries, dementia represents a huge challenge for public health systems. In our country, it is estimated that by 2050 a third of the population will be over 65 years, so that approximately one million Spaniards could have dementia by then.

According to the Survey of Disability, Personal Autonomy and Dependency Situations developed by the National Institute of Statistics, the rate of disability stands at ninety dementia cases per thousand inhabitants. However, the impact of dementia is not only produced directly on the patient, but also has a

great influence his/her family and social environment concerning affective, organizational and economic aspects. In this sense, dementia should be understood as a social problem that must be approached in a comprehensive manner.

The transition from a cognitively healthy stage to an AD-type dementia is a continuum in which some intermediate stages, preclinical and prodromal can be recognized. These stages are characterized by the presence of an incipient cognitive impairment that increases the probability of conversion to dementia in the future. An effective therapeutic intervention in these phases prior to AD could eventually slow the progression of deterioration and thus reduce the prevalence of the disease. For this reason, one of the challenges currently faced by research is the development of useful tools that allow early diagnosis of AD.

Currently, there is no reliable method to predict safely which individuals in these preclinical stages have an increased risk of converting to dementia. The emergence in the last decade of various diagnostic neuroimaging techniques (eg, brain PET amyloid) has led to considerable progress in research, although its use in regular clinical practice is not feasible due to its high cost.

The most recent descriptive epidemiological research on dementias is allowing us to investigate how prevalence and incidence are changing over time. To establish clear trends, these comparisons should be based on studies that use similar diagnostic and research methods consistently over time. It is important to bear in mind that the main non-genetic risk factors for the development of dementia are related to lifestyle, which makes it particularly important to carry out studies in the Spanish population. Important changes in our society and improvements in living conditions and education in recent decades can have a decisive influence not only on physical





wellbeing, but also mental and cognitive health and therefore on the incidence of dementia in the elderly population. Thus, the analysis of risk factors related to the symptoms of dementia must be accompanied by a comprehensive phenotypic characterization in order to provide a better understanding of the underlying neurobiological mechanisms.

The concept of population studies - that is, the recruitment of participants from community environments to ensure good representations of the entire population - must be incorporated in future neurobiological and neuropathological investigations in dementia. The results of small clinical-based samples, which include only patients from memory clinics or other medical services, have inherently limited generalization and the considerable potential for bias due to highly selective recruitment. In particular, people who are socially disadvantaged are less likely to participate in that research. The integration of neuroscience with population studies and neuroscientific epidemiological approaches is of vital importance and provides the opportunity to integrate the understanding of brain health, neurobiology and neuropathology within the general population to support better prevention, care and cure of dementia.

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

■ 4.2 Background: Pilot project

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

- To verify the feasibility of the working procedure, the cooperation of the target population and the adequacy of screening protocols to the study objectives.
- To obtain early and sufficient information on the characteristics of the recruited volunteers and those that could not be recruited, as well as the limitations of the actual sampling compared to the intended one.
- To get experience in the implementation of the different elements of the protocol and to estimate the burden of the evaluator and the evaluated.
- To promote the Project to achieve the participation of volunteers and attracting enough funds to carry out the Vallecas Project.

175 volunteers were involved in this phase of the project, of which:

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

■ 4.3. The Vallecas Project

Following the completion and analysis of the pilot study the protocol was amended based on the experience gained and a volunteer recruitment strategy was established (social awareness campaign in the media, visits to centers for seniors, contact



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pensioner's organizations, etc.). In September 2011, after the "Global Summit on Alzheimer Disease Research" held in Madrid and with the financial support of the Queen Sofia Foundation.

The Vallecas Project is being carried out in the Queen Sofia Foundation Alzheimer Center Research Unit by researchers from the CIEN Foundation (Carlos III Institute of Health). It aims to develop a proba-

THE VALLECAS PROJECT IN FIGURES

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





bilistic algorithm to identify individuals at risk for AD-type dementia over the course of a few years. Such an algorithm will be based on a combination of socio-demographic, historical, clinical, neurological and neuropsychological, biological (from blood tests) and neuroimaging (various forms of 3T MRI).

The participant recruitment phase for the Vallecas project lasted from October 2011 to December 2013. By then, 1,213 individuals of both genders, aged 70-85 years were recruited and evaluated at baseline. Once included in the study, the project conducts an annual follow-up for five years in order to assess the evolution profile of all participants, specifically identifying those that develop cognitive impairment and/or dementia. At the end of 2016, we are at the end of the fourth visit for the entire cohort, about the middle of the fifth visit and just starting the sixth one (see figure in section 1.6 of this Report).

4.3.1. Baseline evaluation

Before entering the study, volunteers interested in participating in it were subjected to an initial assessment to determine whether they meet the criteria for inclusion and/or whether an exclusion criterion exists. Overall, all volunteers were required to meet four inclusion criteria in order to be considered for entering the study:

- Signing an informed consent.
- Be aged between 70 and 85 years old.
- Availability and ability to reach the Alzheimer Centre for visits.
- Visual and hearing abilities that allow conducting the study tests.

In addition, a number of exclusion criteria were established, including the following: i) suspected or diagnosed dementia; ii) inability to perform neuroimaging studies; iii) alcohol abuse; iv) mental retardation; or v) history of certain psychiatric or

neurological diseases (e.g. schizophrenia, stroke, severe head trauma, Central nervous system infections, uncorrected vitamin deficiencies, etc.).

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

4.3.2. Sociodemographic profile

The following variables are collected through semi-structured interview: gender, date of birth, marital status, number of children, type and amount of income, primary occupation and education level, hobbies and leisure activities, etc.

In addition, each year volunteers also must complete a scale of quality of life and subjective well-being (mobility, personal care, daily activities, pain/discomfort, anxiety/depression, and perceived health status) as well as various questionnaires to gather information related to lifestyle.

4.3.3. Clinical evaluation

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

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



4. THE VALLECAS PROJECT





- Other relevant systemic diseases: hepatic failure, renal failure, Obstructive Sleep Apnea Syndrome (OSA)...
- Family history with special attention to the history of dementia or movement disorders, developmental delay or psychiatric disorders.
- Regular drug treatment during the last 5 years.

4.3.4. General examination

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

- Gait disturbance
- Handwriting
- Instrumental activities of daily living

4.3.5. Neuropsychological Examination

The neuropsychological evaluation allows to explore in a holistic way the various cognitive domains (gnosias, attention, memory, language, praxis and executive functions), as well as a series of variables related to affectivity, behavior and level of autonomy in the daily life of an individual. To do this, the neuropsychologist can use different assessment instruments, including clinical interviews, behavioral observation, cognitive tests and different questionnaires that allow for collecting information from both the individual and a reliable informant.

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

Specifically, although the neuropsychological battery focuses especially on the evaluation of memory processes, attention and executive functions as potential early markers of Alzheimer's disease, the neuropsychological profile is completed by getting information related to other cognitive domains such as language, visuospatial ability and visuoconstruction. All these data allow identifying the strengths and weaknesses in the cognitive profile and characterizing, if necessary, the type of cognitive impairment that an individual presents. Following table lists the different tests that make up the neuropsychological battery of the Vallecas Project, as well as the visit number in which they have been applied to all study participants.

4.3.6. Determination of biomarkers

It is currently widely accepted that the molecular changes associated with AD, including the formation of amyloid plaques and neurofibrillary tangles begin many years before the appearance of clinical symptoms. In recent years, the need to define and develop new early biomarkers of AD that allow us to assess the risk and early diagnosis of the disease has become clear. Thus, blood samples will be collected within the Vallecas Project for the study 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 various fractions indicated in the protocol, which are 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 in the following genes: APOE, CR1, BIN1, CLU, PICALM, ABCA7, SORL1, PRNP, GRM8, and BACE1. These genes are studied using DNA obtained from the extraction of samples from the first visit. Also, in the context of the project funded by the MINECO (Projects RETOS) entitled "miRNA and lipid metabolism markers as potential links between vascular



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dysfunction and Alzheimer's pathophysiology", and whose main researchers are Drs. Miguel Medina and Miguel Calero, in collaboration with the group of Dr.

Tobias Engel (Royal College of Surgeons, Dublin, Ireland) plasma-derived microRNAs are being analyzed as potential biomarkers, as well as molecules

VISITS 1° 2° 3° 4° 5° 6°

Cognitive performance

| | | | | | | |
|--|---|---|---|---|---|---|
| Reading test to evaluate premorbid intelligence | ✓ | | | | | |
| Mini Mental State Examination (MMSE) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Clock Drawing Test | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Free And Cued Selective Reminding Test (FCSRT) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Semantic Lexical Evocation (P, M, R) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Semantic Verbal Fluency (Animals, Fruits and Vegetables, Kitchen Utensils) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Number Key (WAIS-III) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Rey-Osterreith Complex Figure Test | ✓ | | ✓ | ✓ | ✓ | ✓ |
| Forward and reverse digits (WAIS-III) | | ✓ | ✓ | ✓ | ✓ | ✓ |
| Symbolic gesture and Imitation of bilateral postures (TBR) | | ✓ | ✓ | ✓ | ✓ | ✓ |
| Rules Change (BADs) | | ✓ | ✓ | ✓ | ✓ | ✓ |
| Test of the five points | | ✓ | ✓ | ✓ | ✓ | |
| Boston Naming Test (BNT-15) | | ✓ | ✓ | ✓ | ✓ | ✓ |

Cognitive complaints

| | | | | | | |
|--|---|---|---|---|---|---|
| Interview for the assessment of cognitive complaints | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Memory Failures in Everyday (MFE) | | ✓ | ✓ | ✓ | ✓ | ✓ |

Depression and anxiety

| | | | | | | |
|--------------------------------------|---|---|---|---|---|---|
| Geriatric Depression Scale (GDS-15) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| State-Trait Anxiety Inventory (STAI) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |

Functional scales

| | | | | | | |
|---|---|---|---|---|---|---|
| Functional Activities Questionnaire (FAQ) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Clinical Dementia Rating (CDR) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |





related to vascular dysfunction, lipid metabolism and inflammation: Adiponectin/Acrp30, P-Selectin, ICAM-1, IL-6, MMP-9, Serpin E1/PAI-1, TNF-alpha, VCAM-1, CCL2/MCP-1, IL-1 beta, CXCL8/IL-8, E-Selectin, MMP-3, and CRP. The usefulness of these biomarkers is complementary with the information derived from the study of genetic risk markers already mentioned and can define risk factors already revealed in previous studies.

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

| | |
|--------------|--------------|
| First visit | 1.169 |
| Second visit | 767 |
| Third visit | 755 |
| Fourth visit | 699 |
| Fifth visit | 618 |
| Sixth visit | 249 |
| Total | 3.723 |

4.3.7. Neuroimaging Studies

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

MRI is a noninvasive tool that allows the study of normal aging individuals at different moments of his life. However, conventional MRI techniques are unable to detect and quantify age-dependent microstructural changes who have been described in post-mortem studies of brain tissue. Accordingly, the

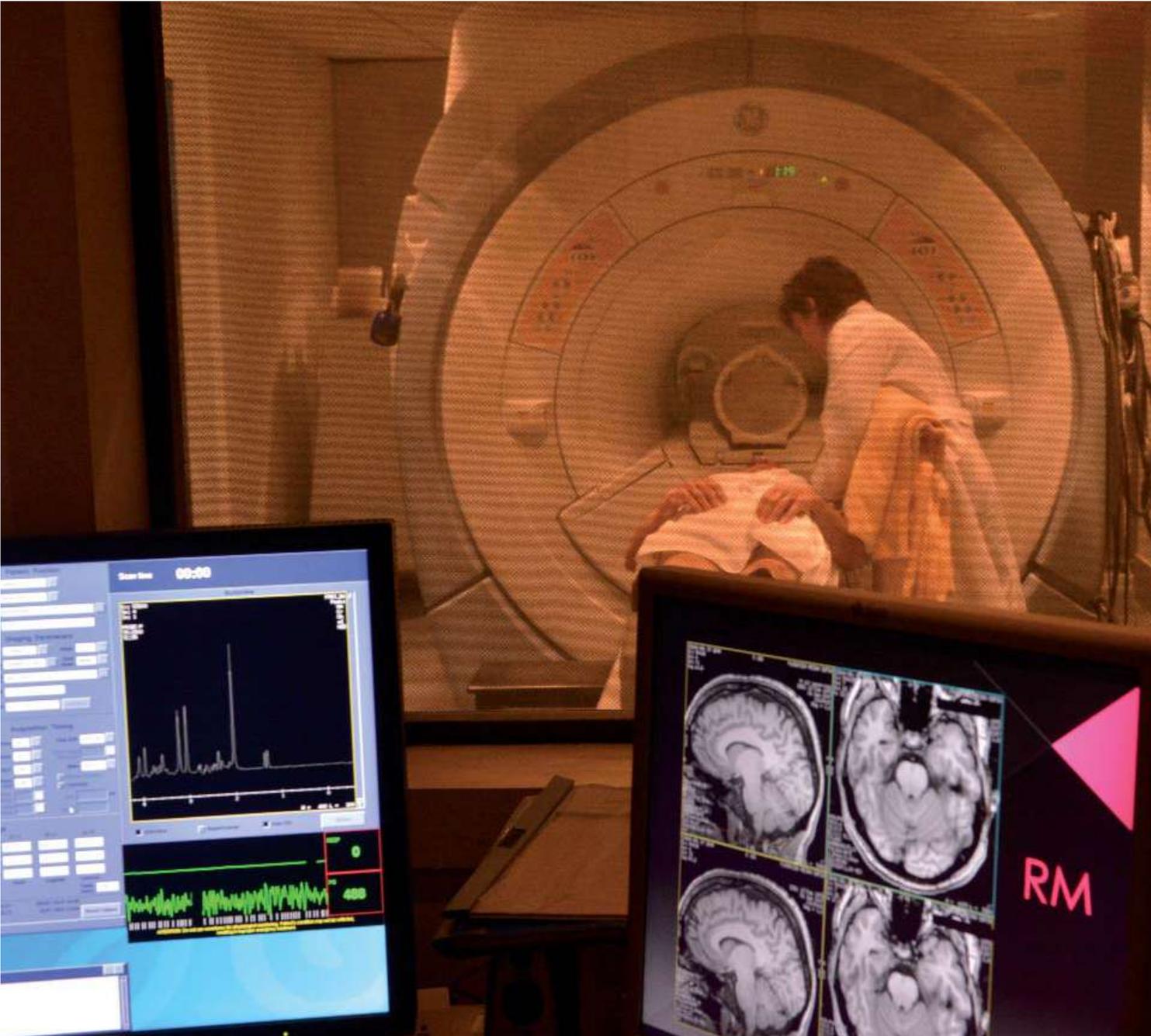
project aims to conduct a series of studies based on various MRI modern techniques that can provide volumetric quantitative indexes of the morphological changes.

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

- Structural Study (3D volumetry, T2 and FLAIR)**
 Determining the progressive loss of brain volume during aging, especially in white matter provides volumetric quantitative indexes of the morphological aging-associated changes. In this sense, the VBM (Voxel-Based Morphometry) techniques, based on creating statistical comparisons of gray and white matter patterns constitute the method of choice, and allows us to determine the volume reduction of the amygdala, hippocampus, entorhinal cortex, etc. técnicas de VBM, basadas en la creación de comparaciones estadísticas de patrones de sustancia gris y blanca, son el método de elección y nos permiten determinar la reducción volumétrica de la amígdala, hipocampo, corteza entorrinal, 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



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contrast-through MR sequences (Arterial Spin Labelling, ASL) and therefore hypofunctioning areas will present decreased perfusion. Throughout 2015 all Neuroradiology reports from every subject and each of the visits from the 'Vallecas Project' have been incorporated in the single project database. Text reports have been encoded, incorporating each item to the database, as well as attaching the report of each visit in pdf format, enabling viewing and downloading to all researchers who have access to the database.

On the other hand, we have organized MRI data corresponding to the 'Vallecas Project' and Queen Sofia Foundation Alzheimer Center subjects, converting the data obtained directly from MRI equipment into the appropriate format for analysis.

A collaborative project with CESVIMA (Supercomputing and Visualization Center of Madrid), a center from the UPM (Technical University of Madrid) has also been established.

As a result, a VBM analysis of T1 sequences from visits 1 and 2 of the subjects 'Vallecas Project' has been performed. The results of this analysis form the basis of a new project awarded to Dr. Bryan Strange by the Alzheimer's Association ("The healthy elderly brain: MRI predictors for developing MCI"), which has allowed the hiring of a new team member, Dr. Linda Zhang. Dr. Zhang, expert in analysis of structural MR images, has examined the white matter in visit 1 of the subjects of the Vallecas Project.

4.3.8. Current status

The Vallecas Project is the main research project conducted at CIEN Foundation, both in terms of resources and social impact. In late 2013, the project completed the recruitment phase and the baseline first visits of volunteers. During 2016 we have combi-

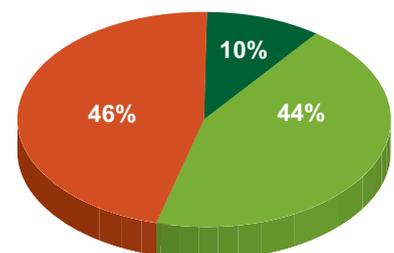
ned the third, fourth and fifth follow-up visits from volunteers.

VALLECAS PROJECT ACTIVITIES DURING 2017

| | |
|------------------------------------|-----|
| Number of fourth visit assessments | 58 |
| Number of fifth visit assessments | 268 |
| Number of sixth visit assessments | 277 |

PERCENTAGE OF VISITS IN THE VALLECAS PROJECT DURING 2017

- Fourth visit
- Fifth visit
- Sixth visit



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

VALLECAS PROJECT CLINICAL EVALUATIONS OCTOBER 2011-DECEMBER 2017

| | |
|---------------------------------------|-------|
| First visit | 1.175 |
| Excluded at baseline | 47 |
| Second visit | 967 |
| Third visit | 870 |
| Fourth visit | 778 |
| Fifth visit | 656 |
| Sixth visit | 277 |
| Drop outs | 465 |
| Do not comply with inclusion criteria | 28 |
| Deceased | 17 |
| Diagnosis of neurological disease | 33 |
| Volunteer withdrawal | 387 |



International *re*lations

With the aim of strengthening and expanding its relations with international organizations, the CIEN Foundation participates in global initiatives that seek to improve our knowledge of neurodegenerative diseases, such as the European Union Joint Program for Research on Neurodegenerative Diseases (JPND) or the Network of Centers of Excellence in Neurodegeneration (COEN). The celebration in 2017 of the international conference Alzheimer's Global Summit Lisbon has highlighted the need to share the new scientific findings and establish new collaborative networks.





5. INTERNATIONAL RELATIONS

5.1. Introduction

The world population is aging. Improvements in health care in the last century have helped people to have longer and healthier lives. However, this has resulted in an increase in the number of people with age-related diseases, including neurodegenerative diseases. Neurodegenerative diseases are responsible for mitigating states, largely untreated and are closely linked with age. Among these disorders, dementias are responsible for the greatest burden of disease, with Alzheimer's disease and related disorders the causes of impairment of approximately seven million people in Europe. This figure is expected to double every 20 years, as the population ages.

Currently, care and treatment of patients with some form of dementia in Europe accounts for a cost of around 130,000 million euros a year, according to estimates by the Joint Programme of the European Union for Research in Neurodegenerative Diseases (JPND). This comes to show that age-related neurodegenerative disorders are one of the leading medical and social challenges facing our society.

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

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

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

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

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





.Supporting research in Alzheimer's disease and related disorders has been and is one of the working priorities of the Queen Sofia Foundation since 2002, the year that promoted the construction of the

Queen Sofia Foundation Alzheimer Center (CAFRS, for its acronym in Spanish), and from which it has continued to support the work of the institutions related to this dementia, both financially as well as



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with the invaluable drive and personal interest of Queen Sofia. In this context, in recent years CIEN Foundation together with the Network Center for Biomedical Research in Neurodegenerative Diseases (CIBERNED, for its acronym in Spanish) has given a boost to its relations with international organizations in the area of research in neurodegenerative diseases such as the EU Joint Programme for Research in Neurodegenerative Diseases (JPND) and the Network of Centers of Excellence in Neurodegeneration (COEN), among other initiatives. These and other internationalization activities carried out during 2016 by CIEN Foundation are detailed below.

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

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

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

To achieve impact there is a need to encourage novel as well as multidisciplinary approaches, and to

strengthen and extend existing capabilities across the full spectrum of basic, clinical, health and social care, and translational research. To that end, a number of priority areas for future research have been identified: The origins of neurodegenerative diseases; Disease mechanisms and models; Disease definition and diagnosis; Treatment and prevention; Health and social care.

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

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

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

A major obstacle to the advancement of research on neurodegenerative diseases is the relative lack of common standards and mechanisms for validation of potentially relevant results in preclinical studies, and clinical studies based on population. One approach to deal with these challenges on a large scale is through a more effective use of large centers





and institutes, where there is already the necessary critical mass of resources and expertise. Increased collaboration between national centers of excellence should also provide the opportunity to accelerate progress in understanding the basic mechanisms of disease, and the identification of new therapeutic approaches.

To this end, on June 10, 2010, the Canadian Institutes of Health Research (CIHR), the German Centre for Neurodegenerative Diseases (DZNE, Germany) and the Medical Research Council (MRC, UK) launched a funding initiative to establish a collaborative approach to research in neurodegenerative diseases, called "Centers of Excellence in Neurodegeneration (COEN)". These founding members were later joined by other European institutions and thus, in December 2011 the COEN membership application by CIBERNED-CIEN Foundation was approved, recognizing the scientific excellence in both basic and clinical science of the institution which became part of the COEN Oversight Group. In 2012, CIEN Foundation and CIBERNED joined this Committee to participate actively in the design of the future COEN scientific strategy. Both institutions are represented by Dr. Miguel Medina, member of the CIEN Foundation Scientific Advisory Board and CIBERNED Deputy Scientific Director. During 2015 the French Agence Nationale de la Recherche (ANR) has also been acknowledged as a new COEN member.

Current COEN members are:

- Canadian Institutes of Health Research (CIHR)
- Deutsche Zentrum für Neurodegenerative Erkrankungen (DZNE, Germany)
- Medical Research Council (MRC, United Kingdom)
- Flanders Institute of Biotechnology (VIB Flanders, Belgium)

- Health Research Board (HRB) / Science Foundation Ireland (SFI), Ireland
- Ministero della Salute (MDS, Italy)
- Centre of Excellence for Brain Research (MESRS), Slovakia
- CIBERNED-Fundación CIEN, Spain
- Agence Nationale de la Recherche (ANR), France

The overall objective of the COEN initiative is to create a collaborative research activity in the field of neurodegeneration beyond national borders, focusing on critical mass and excellence. COEN is aligned with the JPND, although it functions as an independent entity. The overlapping of the COEN group members with those of the JPND will ensure that their complementary objectives progress in close cooperation with each other. This is accomplished through a two-step process, involving expert workshops for the analysis of needs, followed by a call for proposals for collaborative teams between PIs within the participating national Centers of Excellence.

Phase I of the initiative was launched by the end of 2010 and was intended to establish common resources and methodological approaches to support future studies. Some of the key issues addressed have been: the refinement and validation of cellular and animal disease models; the development of new measures to define patient subgroups for clinical trials; the identification of new biomarkers to support translational research; the development and harmonization of cognitive test batteries for diagnosis and follow-up of disease progression; and the establishment of common computer platforms to improve data analysis and exchange.

Phase II of the initiative was initiated in 2013 with the launch of the call for projects called "Pathfinder", completed with successive calls in 2016 and 2017. These three calls for "Pathfinder" research projects



5. INTERNATIONAL RELATIONS

are aimed at catalyzing collaborative research among the different centers with a critical mass of resources and knowledge in order to promote a radical change in the research in the field of neurodegeneration. Pathfinder calls for projects are intended to encourage the community to think outside the pre-established frameworks and stimulate new and creative approaches and solutions to the challenges of research in neurodegeneration, carrying out high risk/high benefit projects and welcoming novel, non-conventional applications.

The scientific scope of the Pathfinder projects is very broad and applications may include studies to improve our understanding of neurodegenerative mechanisms or create technological advances to support new diagnostic or therapeutic approaches. Joint nominations of researchers from recognized Centers of Excellence are invited, and projects must include researchers from two or more countries. The projects should address issues that would not be easily funded through the standard grant mechanisms of COEN partners, and it is expected that, in addition to the collaboration between Centers of Excellence, the projects will also serve to provide a platform for future collaboration with the industry.

■ 5.4. Alzheimer's Global Summit Lisbon 2017

In 2017 CIBERNED held a very special edition of its annual Scientific Forum. This event, which has taken place year after year since 2007, is essential for the proper functioning of CIBERNED, since it allows main researchers, members of their groups, as well as all the rest of attendees, meeting to discuss the findings of their research, present new data and establish collaborations. In 2013, an International Congress of Research and Innovation in Neurodegenerative Diseases (CIIEN) was first established, with great success that has been consolidated in successive yearly editions (2014-2016).

During the days September 18-22, 2017 at the facilities of the Champalimaud Foundation in Lisbon, and coinciding with the celebration of World Alzheimer's Day (September 21), the Alzheimer's Global Summit Lisbon 2017 was held, organized jointly by CIBERNED, the CIEN Foundation, the Queen Sofia Foundation and the Champalimaud Foundation. The Summit took place in the Champalimaud Center for the Unknown, home of the Champalimaud Foundation in Lisbon, and was chaired by Her Majesty Queen Sofia, president of the Foundation that bears her name, and by Ms. Leonor Beleza, president of the Champalimaud Foundation and former Portugal's Minister of Health.

The scientific program consisted of an opening session, three keynote lectures and ten scientific sessions. Renowned scientists such as Richard Axel and John O'Keefe, who received the Nobel Prize in Medicine in 2004 and 2014, respectively, delivered lectures on neurology and the genome (Axel) and brain networks essential for building memories (O'Keefe). International researchers who are world references in their field of research as Rui Costa, expert in neurobiology of actions and movement; António Damásio, Prince of Asturias Research Prize 2005 and author of "The feeling of what happens: the body and emotion in awareness"; Kenneth Kosik (University of California, Santa Barbara, USA) or Maria Grazia Spillantini (University of Cambridge, United Kingdom), among others.

The head of the Neuroimaging Department of the CIEN Foundation, Bryan Strange presented in the VII session results of the Vallecas project to predict the transition to mild cognitive impairment through an algorithm from a battery of tests combined with structural neuroimaging data. Among the written communications, the CIEN Foundation also participated with the work of some of its researchers: Marina Ávila and Miguel A. Fernández from the Department of Neuropsychology; Irene Buendía and





Valentina González from the Department of Neuro-pathology; and Jaime Gómez and Linda Zhang from the Department of Neuroimaging.

In addition, with the additional participation of the State Reference Center for the Care of Patients with Alzheimer's Disease and other Dementias) of the Spain's Ministry of Health, Services and Equality, on September 18-19 the welfare and social health program was also carried out, which was attended by experts such as Takanori Shibata, an expert in artificial intelligence applied to the treatment of neurodegenerative diseases, and Vladimir Hachinski, a professor at the University of Western Ontario and one of the world's leading dementia authorities, both delivered keynote lectures. Also participating, among others, were Mercè Boada, founder and medical director of the ACE Foundation in Barcelona and specialist in early diagnosis of AD, and Pablo Martínez-Lage, Director of Neurology of the CITA Foundation (San Sebastian).

In short, this event has constituted an excellent meeting point for some of the leading national and international experts in neurodegenerative diseases, allowing to share knowledge, working methodologies, new advances and discoveries, in a field in which international cooperation and between institutions is decisive for obtaining optimal results in research.

■ 5.5. Other activities of international cooperation

5.5.1. Collaboration with the Champalimaud Foundation

The CIEN Foundation continues to actively partner with the Champalimaud Foundation in accordance with the collaboration agreement signed in December 2015. In addition to the joint organization of the

Global Summit on Research in Neurodegenerative Diseases, which was held on 21, 22 and 23 September 2017 in Lisbon under the chairmanship of H.M. Queen Sofia, the parties involved are committed to maintain a continuous and active collaboration in the future with the intention of promoting the knowledge of both countries in a field as unknown as that of neuroscience. In this regard, the Summit has highlighted the close links of collaboration between institutions and scientists from both countries, with the aim of promoting a joint European policy of research and treatment of neurodegenerative diseases, a problem of costly economic and social consequences in countries with aging populations.

5.5.2. Alzheimer's Association

The Alzheimer's Association is a non-profit organization that focuses on the care and support of patients with Alzheimer's disease, and which also finances research projects on this field through competitive calls. During 2017, CIEN Foundation researchers in collaboration with CIBERNED and the Technical University of Madrid have received funding from the Alzheimer's Association to carry out two research projects:

1. A multicenter, randomized, double-blind, placebo-controlled, 4-arm, 26 week parallel-group study to evaluate the safety, tolerability and anti-inflammatory effect of three oromucosal doses of Sativex® in patients with mild cognitive impairment of Alzheimer type or early Alzheimer dementia (Sat-CIEN-02). Principal Investigator: Dr. Isidro Ferrer (CIBERNED)

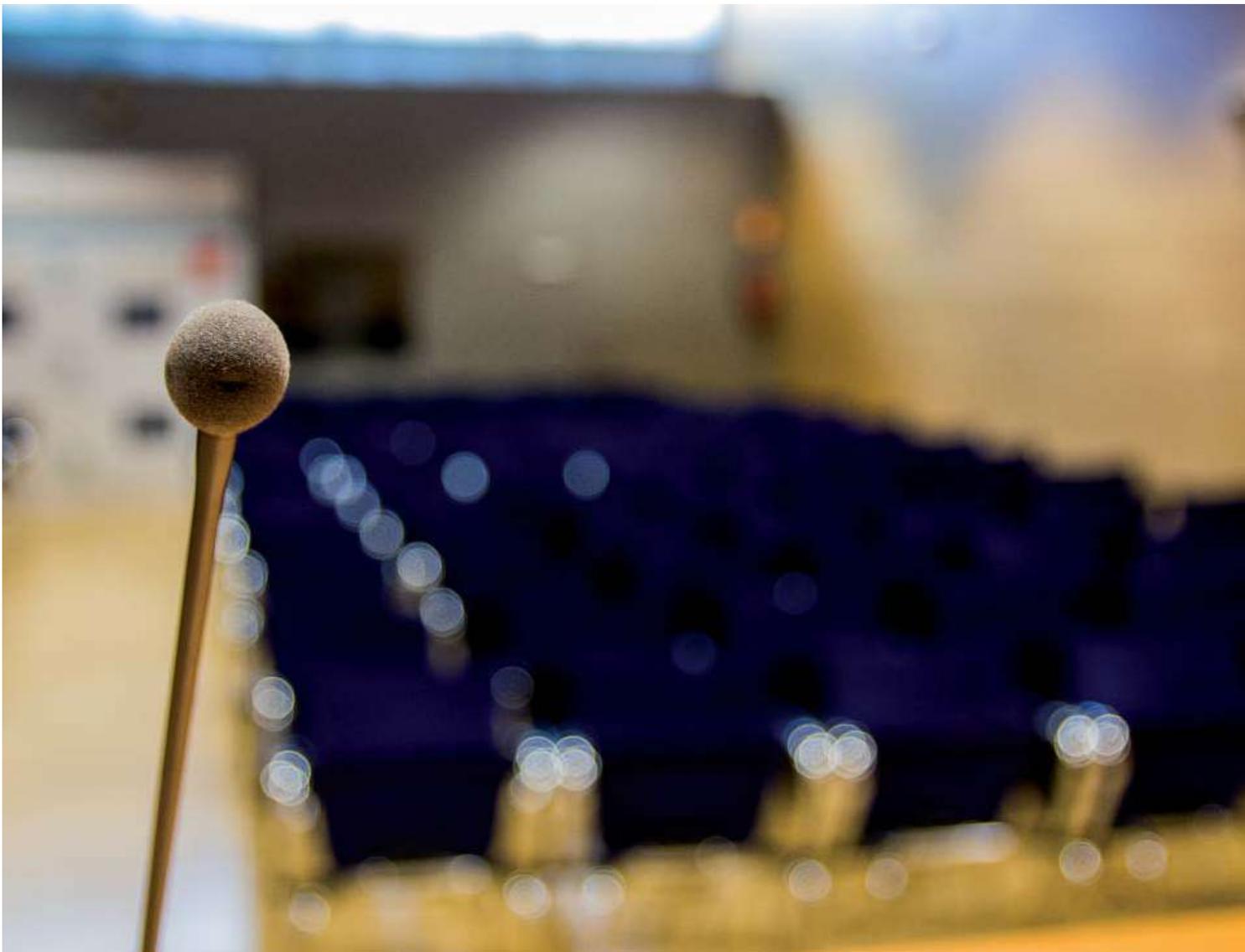
During 2017 the activities of this clinical trial were continued, included in an open and competitive call of the U.S. Alzheimer's Association, which was approved and funded by it to be carried out in Spain during the period of Sept-2016 to Oct-2018.



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The main objective of the trial is to demonstrate the safety and tolerability of cannabinoids in these patients, but it is expected to also gather some indication of their potential therapeutic effect that will serve to design future efficacy studies. The doses selected, based on previous experimental studies in

animals, are low and without psychoactive effects. The use of these drugs in Alzheimer's disease is based on its modulating action on neuronal synaptic activity and its potent anti-inflammatory and neuroprotective effect.





2. The healthy elderly brain: MRI predictors for developing MCI (El cerebro de las personas mayores sanas: predictores de RM para el desarrollo de DCL).

Principal Investigator: Dr. Bryan Strange (UPM and FCEN)

The problem addressed in this proposal is the current lack of a technique to predict whether a healthy elderly individual will develop AD. This is important, given that any treatment for this progressive neurodegenerative disorder is more likely to be successful if administered as early as possible in the disease process. The proposed project will interrogate data from a large sample of 1,213 healthy elderly individuals (70-85 yrs; male and female) as they are followed up in a 5-year longitudinal study. At each yearly visit, volunteers undergo detailed neuropsychological and clinical evaluation, serum biochemistry analysis, as well as a comprehensive magnetic resonance imaging (MRI) protocol, with genetic data acquired on visit 1. On follow-up, some volunteers go from healthy to a state of mild cognitive impairment (MCI). The goal of the project is to retrospectively determine biomarkers in healthy individuals which predict subsequent development of MCI. By contrast to the extensive research effort into determining MRI parameters predicting conversion of MCI to AD, much less is known about specific brain biomarkers that predict the preceding step: going from healthy to MCI. The novelty of this proposal, and the significant advance, is that we will identify changes in the brain present in groups of healthy elderly people that are indistinguishable in the clinical setting, and that differ only subsequently in the development of MCI.

We have acquired structural (T1, T2 weighted), diffusion-weighted (DWI), functional (resting state functional MRI) and perfusion scans (arterial spin-labeling, ASL) in approximately 1,000 volunteers. The first goal of this proposal is to examine the MRI parameters in healthy elderly individuals that predict

later development of MCI. A first analysis comparing whole-brain grey-matter density (GMD) in these "converters" relative to a matched control group selected from the large sample – at visit 1 (when both groups are healthy) – has already shown fascinating differences specific to the entorhinal cortex. The same type of analysis will now be extended to measures of white matter integrity, perfusion and resting functional networks to provide a comprehensive picture of brain abnormalities present before MCI develops.

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

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

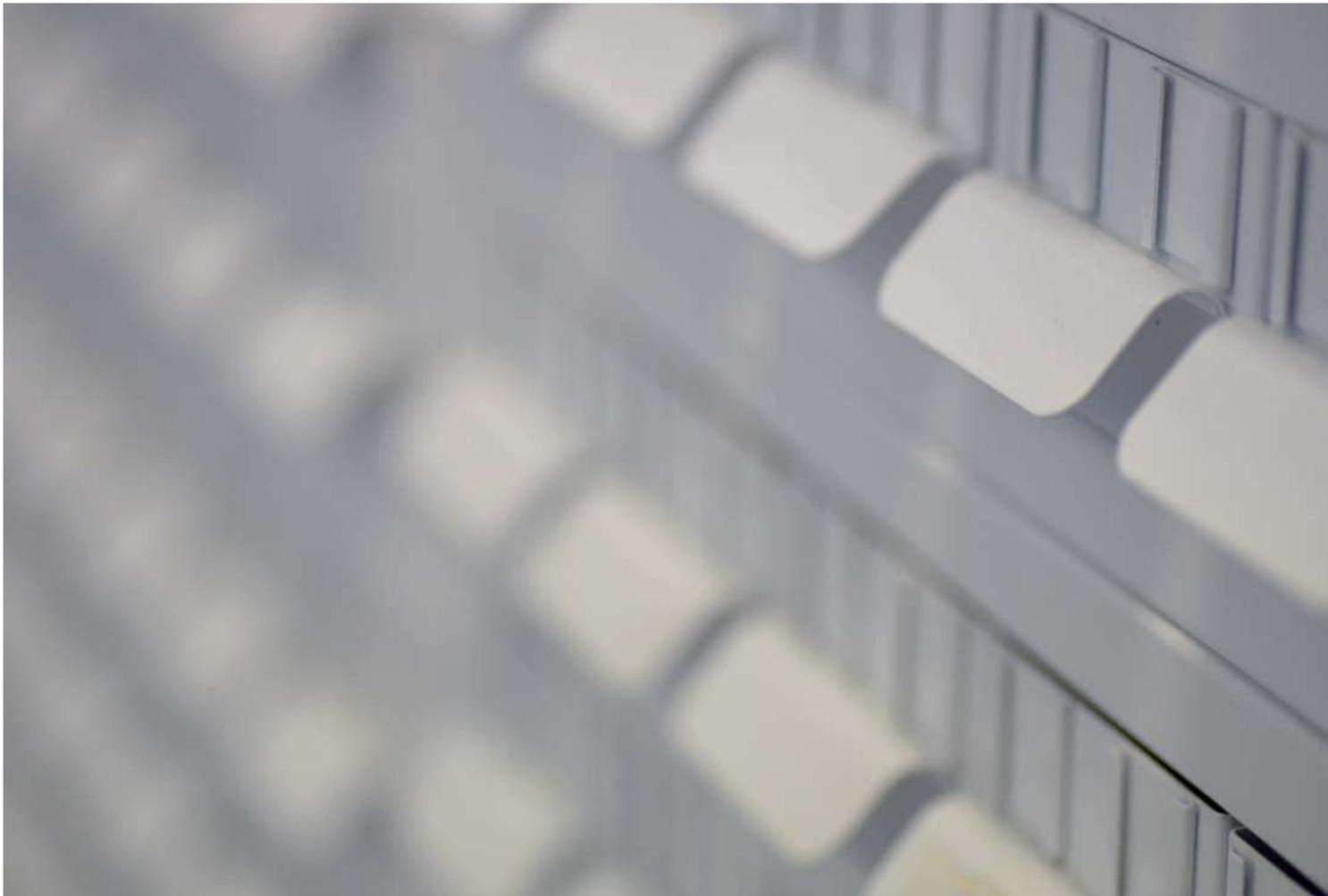
Furthermore, in the hopeful situation that novel dementia treatments will be available soon, it will most likely increase therapeutic efficacy if this treatment



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is started as early as possible in the neurodegenerative process.

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



Scientific productivity

The scientific productivity at the CIEN Foundation continues with the upward trend demonstrated in recent years. In 2017 the quality of the research has been reflected in the publication of various articles in scientific journals of recognized national and international prestige. In addition, productivity has also experienced remarkable growth in terms of internationalization. 50% of the studies presented are the result of collaborative efforts with foreign institutions.





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6.1. Bibliometric analysis

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

During 2017, researchers CIEN Foundation have produced a total of 31 publications, of which 30 have been published in scientific journals of national and international recognition (29 original articles plus one letter) and one book chapter.

The analysis of these publications has allowed studying, through a series of quantitative indicators, both the CIEN Foundation scientific activity as the production, subject, and degree of collaboration and impact of scientific publications. Through this analysis we can note, for instance, that the average impact factor of publications within the first and second quartile has increased from 6.792 in the year 2016 to 7.564 in 2017, which means a 11.36% increase, following the upwards trend of the last years.

In addition, during this year the CIEN Foundation has increased its international collaborations, so that 50%

of the articles corresponded to studies carried out in collaboration with international institutions, 43.75% with Spanish ones, and the rest were performed exclusively by CIEN Foundation researchers. Also noteworthy is the high proportion of collaborative publications with other CIBERS and networks in the first and second quartiles (55,17%).

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

In summary, during 2017 the CIEN Foundation researchers have published 31 scientific papers, of which 24 (77.42%) have been in journals included in the Science Citation Index Expanded, accessible through the Web of Science portal (WoS, Thomson Reuters) and 22 (71%) have been published in journals ranked within the first and second quartile in their category. Considering the type of document, 96.67% of the publications in scientific journals (29) correspond to original articles.

Moreover, according to their scientific subject category 66.7% of the publications within the first and se-

Indicators 2017

| | |
|--|---------------|
| Total number of publications..... | 31 |
| Total number of publications in the ISI citation index within the first and second quartil..... | 22 |
| Cumulative impact factor of publications within the first and second quartile..... | 163,98 |
| Average impact factor of the publications of the first and second quartile..... | 7,564 |
| Number of collaborative publications of all kinds (CIBERNED, other national groups, international groups) within the first and second quartile..... | 21 |
| Number of international collaborative publications within the first and second quartile..... | 11 |
| Number of national collaborative publications within the first and second quartile..... | 9 |
| Number of collaborative publications with other CIBERS and networks within the first and second quartile.... | 16 |





cond quartiles, have focused on the following categories: Neurosciences, Clinical Neurology, Psychiatry, and infectious diseases.

With regards to scientific dissemination activities in meetings and national and international events during the year 2017, there have been a total of 49 participations at scientific conferences, 35 of which correspond to lectures and oral presentations, and 14 correspond to written communications in the form of posters. These communications have been presented at national (22) and international scientific conferences (27).

6.2. Publications

References of the 31 scientific publications from CIEN Foundation personnel are listed below according to type of publication: 30 publications in scientific journals (29 original articles, and one letter) and one book chapter.

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6. SCIENTIFIC PRODUCTIVITY

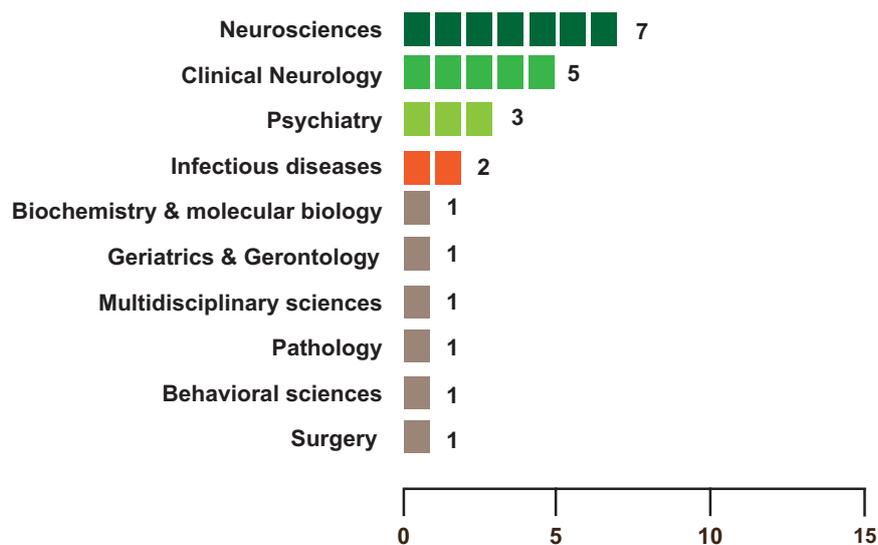
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6. SCIENTIFIC PRODUCTIVITY

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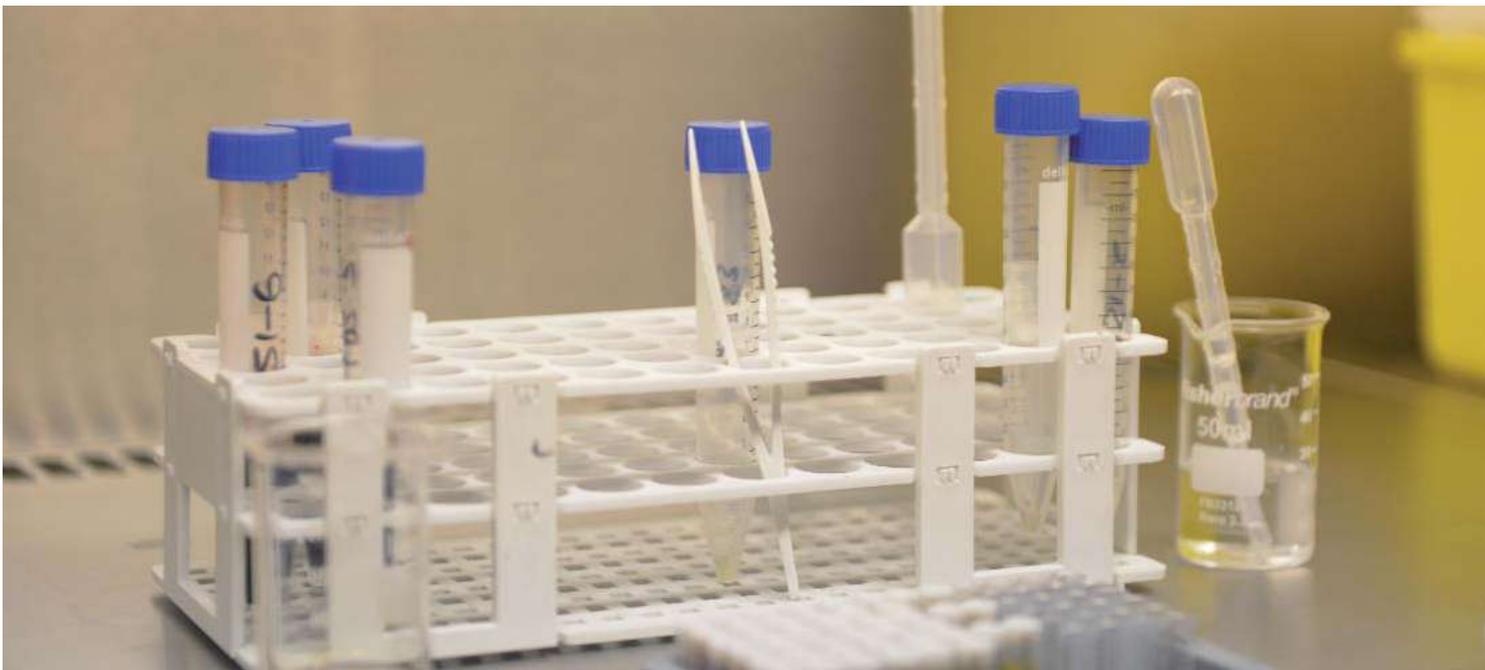


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6.3. CIEN Foundation Seminar Series

The CIEN Foundation has organized this Seminar Series since the beginning of 2015, in which, every Monday afternoon, speakers from both the Foundation and guests from other related institutions, present their work and then the issues are debated. The following are the seminars developed in our Alzheimer Center of Vallecas during 2017:

- Alberto Rábano (Fundación CIEN, BTCIEN): "Rates of progression in neurodegenerative dementia". Monday, January 9.



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- José Luis Cantero Lorente (IP CIBERNED, Universidad Pablo Olavide of Seville): "Biomarcadores subclínicos de diferentes trayectorias de envejecimiento". Monday, January 23.
- Alicia Nadal Solá (Fujirebio) "Relevancia clínica de a-beta y Tau el LCR Firma bioquímica de la enfermedad de Alzheimer". Monday, January 30.
- David Martínez-Gómez (UAM) e Irene Esteban-Cornejo (Universidad de Granada). "Propuesta para la valoración objetiva de la actividad física dentro del Proyecto Vallecas". Monday, February 20.
- Lidia Blázquez (UPM, UNED): "High plasticity of axonal pathology in Alzheimer's disease mouse models". Monday, March 6.
- Irene Goñi, UPM: "Analysis and Quantification of Cerebral Blood Flow as a Possible Biomarker in Early Alzheimer's Disease". Monday, March 13.
- Eva Dueñas (Fundación CIEN): "Efecto de la estimulación transcraneal por corriente directa en pacientes con enfermedad de Alzheimer. Estudio preliminar sobre mejoría de la memoria". Monday, March 27.
- Linda Zhang (Fundación CIEN): "Morphometric brain templates for elderly cohorts: Making the Vallecas Brain". Monday, April 24.
- Aidan Kenny (Department of Physiology and Medical Physics, Royal College of Surgeons in Ireland): "Circulating microRNAs as novel tools for the diagnosis of prodromal Alzheimer's disease". Monday, May 8.
- Miguel A. Fernández y Teodoro del Ser (Fundación CIEN): "Cognitive effects of common prescribed drugs in elderly people. Data from Vallecas Study". Monday, June 12.
- Sergio Veiga, (R&D Manager, Biocross) y Andrés Rodríguez (Research Assistant, Biocross): "ApoE4 blood marker assay. A new non-genetic method to evaluate Alzheimer's Disease risk". Monday, June 26.
- Jussi Tohka, A.I. Virtanen Institute for Molecular Sciences (University of Eastern Finland, Finland): "Machine learning for neuroimaging biomarker discovery - application to Alzheimer's disease". Monday, July 3.
- Elvira Mayordomo, Mónica Hernández y Manuel G Bedia (Universidad de Zaragoza): "Integración de modelos bioinformáticos, cognitivos y de anatomía computacional para la mejora del diagnóstico de enfermedades neurodegenerativas". Monday, September 11.
- Irene Buendía (Trabajo Fin de Master Neurociencia, UCM): "Estudio de los factores asociados al tiempo de supervivencia en una cohorte de pacientes institucionalizados con Enfermedad de Alzheimer". Monday, September 25.
- Monday, November 11 - Communications to SEN 2017:
 - M^a Ascensión Zea - Implicación de los factores de riesgo vascular y la esclerosis del hipocampo en el tiempo de supervivencia de pacientes con enfermedad de Alzheimer. Estudio clínico-patológico. Proyecto Alzheimer.
 - Alberto Rábano - Patología TDP-43(+) en una cohorte de pacientes con demencia (Centro Alzheimer de Vallecas).
 - Belén Frades - Envejecimiento activo en los participantes del Proyecto Vallecas de la Fundación CIEN: estudio longitudinal de las actividades de ocio, cognición y afectividad.
 - Teodoro del Ser - Ensayo clínico de Fase II con cannabinoides de la enfermedad de Alzheimer.

6.4. Funded projects

During 2017 the CIEN Foundation researchers have participated in nine scientific research projects granted through various national and international competitive calls and funded by different institutions.

Funded research projects are cited below:

- **Código FCIEN-005/11**
Principal Investigator: Dr. Miguel Medina





Title: The Vallecas Project – Early detection of Alzheimer's disease
 Funding agency: Queen Sofia Foundation
 Duration: 2011-2017
 Total budget: 1,800,000 €

In February 2018, a new collaboration agreement was signed with the Queen Sofia Foundation, with an expected duration of 4 years, and a contribution of 300,000 € for the 2018 financial year. This agreement regulates the framework of cooperation to carry out the research oriented to the identification of individuals with greater risk of developing Alzheimer's type dementia (AD) within the project called "Vallecas 2, early detection of Alzheimer's disease. Risk and protection factors".

- **Código: PT13/0010/0045**
 Principal Investigator: Dr. Alberto Rábano
 Title: Biobank Platform
 Funding agency: Instituto de Salud Carlos III
 Duration: 2014-2018
 Total budget: 179,934.78 €
 2017 budget: 44,478.26 €

The General Subdirectorate for Evaluation and Promotion of Research of the Carlos III Institute of Health approved the extension of the implementation of the Biobank Platform, extending its execution period until 12/31/2018 without additional funding..

- **Código: K. COLLEGE-MDS-NMS**
 Principal Investigator: Dr. Pablo Martínez
 Title: Phases 2b-4 Field Validation of the MDS-NMS, the International Parkinson's and Movement Disorders Society Non Motor Scale for Parkinson's disease
 Funding agency: International Parkinson and Movement Disorders Society
 Duration: 2016-2018
 Budget: 39,347.65€
- **Código: MDS-NMS_ Rating Scales Program**
 Principal Investigator: Dr. Pablo Martínez
 Title: MDS-NMS_ Rating Scales Program

Funding agency: International Parkinson and Movement Disorders Society
 Duration: 2017-2019
 Budget: 75,000\$

- **PEJ-2014-C-19788 (PLAN EMPLEO JUVENIL)**
 Principal Investigator: Dr. Alberto Rábano
 Title: Grants for Promoting Youth Employment and Implementation of the Youth Guarantee in R+D+i within the framework of the National Plan of Incorporation
 Funding agency: Ministry of Economy and Competitiveness / Secretary of State for Research, Development and Innovation
 Duration: 2015-2017
 Total budget: 150,000 €

In 2017, the four actions funded under this call for Promoting Youth Employment of the State Subprogram of Incorporation were completed.

- **PEJ2015/BIO/AI-0615**
 Principal Investigator: Dr. Alberto Rábano
 Title: Grants for hiring research assistants and laboratory technicians.
 Funding agency: Ministry of Education, Youth and Sports, Region of Madrid
 Duration: 2016-2018
 Total budget: 45,000 €
 2017 budget: 22,500 €

In November 2017, the execution of the action funded in the framework of the call for grants for the execution of contracts for research assistants and laboratory technicians was completed in advance.

- **PEJ16/MED/AI-1963**
 Principal Investigator: Dr. Alberto Rábano
 Title: Grants for hiring research assistants and laboratory technicians.
 Funding agency: Consejería de Educación, Juventud y Deporte Comunidad de Madrid
 Duration: 2017-2019
 Total budget: 45,000 €
 2017 budget: 22,500 €



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In February 2017, the first annuity of the grant within the framework of the call for the execution of contracts for research assistants and laboratory technicians began, which will last until February 2019.

- **Código: PT17/0015/0014**
Principal Investigator: Dr. Alberto Rábano
Title: Biobanks Platform
Funding agency: Carlos III Institute of Health
Duration: 2018-2020
Total budget: 135,000 €

Resolution of the Director of the Carlos III Institute of Health, of December 4, 2017, by which funds are granted for Platforms to support research in health sciences and technologies within the 2017 Call from the Strategic Action in Health.

- **Código: M+VISION**
Principal Investigator: Dr. Bryan Strange
Title: M+VISION
Funding agency: Region of Madrid General Directorate of Universities and Research / Ministry of Education, Youth and Sports.
Duration: 2015-2017
Total budget: 81,077.04 €
2017 budget: 40,538.52 €

Project executed within the framework of the collaboration agreement signed between the Madridmasd Knowledge Foundation and the CIEN Foundation to regulate the participation of the Foundation in the M+VISIÓN project, FP7-People-2011-Cofund, as an receiving institution. The project, co-financed by the European Union, contemplates the participation of host institutions as legal entities in which the researchers selected in the calls for the M+VISION project carry out their training activities through research.

6.5. Patents

During 2017 two patent applications remain active in national and international stages, which have currently a co-ownership agreement with participation of CIEN Foundation and a licensing agreement with Raman Health Technologies:

- **Inventors: Pablo Martínez Martín**, Pedro Carmona Hernández, Adolfo Toledano Gasca, Miguel Calero Lara, Félix Bermejo Pareja.
Title: Infrared analysis of fractions obtained from peripheral blood to indicate cognitive development.
Registration N°: EP128217460, PCT/ES2012/070613.
Application date: 08/08/2011.
Type: Europea/Internacional.
Licensing agreement with Raman Health Technologies.
- **Inventors: Pablo Martínez Martín**, Pedro Carmona Hernández, Adolfo Toledano Gasca, Miguel Calero Lara, Félix Bermejo Pareja, Marina Molina Santos.
Title: Raman analysis, infrared or Raman-infrared of plasma protein structure from peripheral blood and its relationship to the cognitive development in Alzheimer's disease.
Registration N°: EP123823304 PCT/EP/2013/067304.
Application date: 20/08/2012.
Type: National/European.
Licensing agreement Raman Health Technologies.



Social outreach activities

Among the social activities of the CIEN Foundation in 2017, the celebration of the 10th Anniversary of the Queen Sofia Foundation Alzheimer Center, with the presence of Their Majesties the Kings, stands out. This event exalts the importance of the Center's research work. For one more year the Foundation has also carried out activities such as the "Christmas Tree of Memories" or the "Vallecas Project Volunteer's Day", among others. The Global Summit on Alzheimer's disease Research & Care in Lisbon was very well embraced by the press and social media, increasing the visibility of the international event organized by the CIEN Foundation.





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7.1. Dissemination activities

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

In this sense, the CIEN Foundation department heads have organized, as every year, various activities that allow the dissemination of the research work carried out by its professionals. This allows them to bring the scientific field to society in a kinder way, while translating results and relevant information on the various neurological diseases under study. During 2017 the CIEN Foundation has continued to develop dissemination actions of different types, among which we highlight the following.

Educational talks

With the aim of contributing to the welfare of society, from the CIEN Foundation, we want to raise awareness, through the translation of a series of fundamental aspects in the fight against Alzheimer's disease, of the importance of its prevention, the value of donation of tissues for research, or the latest achievements obtained from the study of this condition.

That is why CIEN Foundation professionals, in addition to communications of a purely scientific nature in congresses or seminars, annually schedule informative talks in hospitals, nursing homes or other institutions in different parts of the Spanish geography. Just to cite some examples, M^a Ángeles Pérez, manager of the CIEN Foundation, participated in the conference "Alzheimer challenges", organized to commemorate the 25th anniversary of the San Rosendo Foundation in Orense. Pérez, was responsible for opening the session and provide the vision of the organizations about the dissemination Professor Jesús Ávila, scientific director of the CIEN Foundation, participated in the month of October in the conference series "What do we know about ...?" or-

ganized by the Higher Council for Scientific Research (CSIC, for its acronym in Spanish). In his lecture, entitled "Senile dementia", Ávila disserted about the two types of Alzheimer's disease: the familial form (presenile), whose cause is known and is based on the presence of mutations in specific genes related to the presence of the amyloid beta peptide; and the sporadic form (senile), which is the most common type and whose initial cause remains unknown. In addition, he described how Alzheimer's disease is related to the appearance of two aberrant structures in patients' brains: senile plaques, formed by the beta-amyloid peptide, and the neurofibrillary tangles composed of the tau protein. At the end of the session, the possible relationship of these structures with memory loss was discussed.

In May 2017, Dr. Miguel Medina, member of the scientific advisory committee of the CIEN Foundation and principal investigator of the "Vallecas Project", gave a conference entitled "Recent advances in research on Alzheimer's disease and other dementias" on the Alzheimer's State Reference Center (CRE, for its acronym in Spanish) of Salamanca, in Salamanca, in which he spoke in detail about the main advances in clinical research on these disorders. This training action, which could also be followed in streaming, is part of the Specialized Training Plan in Social Services for the year 2017 programmed by IMSERSO.

Within the Science Week Madrid 2017, the informative day "Research takes off the dressing gown, the most human face of clinical trials" was held on November 7 in the Círculo de Bellas Artes, organized by the More Than Ideas Foundation. Dr. Miguel Calero, responsible for the CIEN Foundation Laboratory area, took part in a colloquium on "Participating in clinical trials: dismantling myths and discovering new challenges" together with Carmen Doadrio (Clinical Trials Section of the Spanish Agency of Medicines and Health Products); Adela Gil, participant in a cli-





nical trial on breast cancer; and Julián Isla, president and founder of Foundation 29 and scientific director of the European Federation of Dravet Syndrome. This session achieved the main objective of this day: to exchange and offer information on the participation of people in clinical trials from regulatory, medical, ethical and human perspectives.

In terms of donations, Dr. Alberto Rábano, director of the Tissue Bank and responsible for the CIEN Foundation neuropathology area, continues to promote the work carried out in the BT-CIEN. The past month of March, 2017 delivered talks in the Queen Sofia Center of Seniors of the Red Cross and in the Red Cross Center on Muguet street in Madrid, one of the main integral centers of the Red Cross, whose facilities count on a Day Center for the Elderly and Alzheimer's patients. In addition, they also carry out training programs both for the general population and internally in the Institution. These talks are aimed at users of centers, patients and relatives of patients with dementia, with the aim of encouraging the donation of brain tissue, within the BT-CIEN program, which is essential for researchers to advance their projects by having samples of brain tissue from healthy or affected donors. Moreover, Rábano was in November in a meeting on dementia in the Valde lasfuentes Sports City of Alcobendas that brought together several prestigious professionals to transfer the latest advances in Alzheimer's disease and other dementias to attendees. Dr. Alberto Rábano was in charge of talking about the importance of brain donation for research and the application of future therapies, highlighting the important achievements made by the Tissue Bank of the CIEN Foundation.

Meetings with Associations of relatives of Alzheimer's patients and other neurodegenerative disorders

During 2017, CIEN Foundation organized and participated in a series of meetings with associations of relatives of Alzheimer's and other neurodegenera-

tive disorders patients, developing joint actions to disseminate advances in the Foundation research activities. This was the case of the VII National Confederation of Associations of Relatives of Alzheimer patients (CEAFA) Congress held in Malaga on November 9-10, 2017 in which M^a Ángeles Pérez, manager of the CIEN Foundation, gave a lecture in the plenary session entitled "The integral dimension of Alzheimer". The Congress was marked by a content of eminently associative and social nature and a clear constructive vocation towards the attendees, so that they could contribute and receive knowledge to adapt and implement them in the confederated associations and other resources providing specialized services to people with Alzheimer's and other dementias.

Likewise, coinciding with the events organized to mark World Alzheimer's Day, M^a Ángeles Pérez spoke at the Henares University Hospital on "The role of organizations in the fight against Alzheimer's disease" during the IX Symposium on Alzheimer's Disease of the Henares. This Conference is organized every year by the Association of Relatives of Alzheimer's, Parkinson's and other dementias patients of the Henares corridor.

Another meeting worth to highlight during 2017 is the Huntington's Family Reunion, which took place on March 11, at the San Pedro de Alcántara Hospital in Cáceres. The last Huntington's Family Meeting, promoted by the Cáceres Association of Huntington and the European Huntington's Disease Network. The conference was based on five conferences delivered by experts, such as Dr. Alberto Rábano, head of the CIEN Foundation neuropathology area and director of the CIEN Tissue Bank (BT-CIEN). In his lecture entitled "Tissue Banks for Neurological Research", he explained the essential role that donation of brain tissue has for research and treated with special attention, the specific logistical problems that involve donations in Extremadura, obstacles that from the



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BT-CIEN is trying to solve. Dr. Verónica Puertas, was in charge of talking about the management of behavioral and cognitive problems in Huntington's disease and Dr. Asunción Martínez gave a vision about the latest developments in Huntington's disease.

Celebration of the 40th anniversary of the Queen Sofia Foundation and the 10th anniversary of the Queen Sofia Foundation Alzheimer Center

On May 22, 2017, Their Majesties the Kings visited the Queen Sofia Foundation Alzheimer's Center in Vallecas, Madrid, accompanied by Their Majesties the King Felipe and King Juan Carlos and Queen Sofia presiding over the central act of these anniversaries,

in which they recalled the projects carried out by the Queen Sofia Foundation and its fight against Alzheimer's.

During the ceremony, King Felipe praised and congratulated Queen Sofia "for this anniversary that highlights your humanity and your commitment to the most disadvantaged people. And thank you from the heart, for the great example that all this entails and on behalf of so many people who throughout all these years have felt that help and support closely - not only materially [...] It has been a long-distance race, full of successes and intermediate targets, in which together with your team you have always had the support of my father King Juan Carlos. It has undoubtedly been worthwhile as demons-



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trated, for example, by this magnificent center, which now turns 10 years old, dedicated to alleviating the effects of Alzheimer's disease".

The King finished his words of recognition and admiration towards Queen Sofia saying "that they are also words of affection from a son to his mother". And with them he underlined and reiterated "the commitment of the Crown, as it cannot be otherwise, with the most vulnerable people. A commitment of which this Foundation is undoubtedly a very dear and endearing expression".

In addition, Her Majesty Queen Sofia took the floor asking to continue supporting "the work that I have tried to do from my Foundation. All together we could overcome the indifference that many times advanced societies have been unable to break. [...] As a new objective, we have decided to expand our activity in the fight against the rest of neurodegenerative diseases, which are probably the most difficult to fight, because they originate in the most unknown part of our body: the brain," emphasized Queen Sofia.

Queen Sofia concluded her speech by remembering "all those who have helped me during these years, both in the execution of projects, and in the financing of our ideas, with the purpose of supporting the most disadvantaged, and with the satisfaction of being able to alleviate the suffering, wherever it is".

Upon their arrival at the center, Their Majesties the Kings and Their Majesties King Juan Carlos and Queen Sofia were received by the Minister of Health, Social Services and Equality, Dolors Montserrat; the Mayor of Madrid, Manuela Carmena; the Secretary of State of International Cooperation and for Ibero-America, Fernando García; the Secretary of State for Research, Development and Innovation, Carmen Vela; and the Councilor for Social Policies and Family of the Region of Madrid, Carlos Izquierdo.

Later, after the official photograph, the Kings enter inside the building, where they received a brief explanation of the Center before a model of it, which included the healthcare and scientific areas. Subsequently, they went to the auditorium, where an institutional video of the Queen Sofia Foundation was screened and Queen Sofia handed out 17 diplomas to the collaborating organizations in recognition of the support received, including the CIEN Foundation.

Then, the previous advertising campaigns of the Foundation were recalled and the new campaign called "The Mission" was presented, which has been seen, heard and read in the major media outlets of our country. A brief meeting with the guests ended the event.

The Queen Sofia Foundation has celebrated the fortieth anniversary in 2017 since its establishment on May 17, 1977 with a small capital contributed by Her Majesty Queen Sofia.

During these years the Foundation has gone through four distinct stages throughout its long life, always with the clear objective of helping those in greatest need:

- ▶ In its first stage, the activities had a discreet work profile and focused on mitigating the precarious personal or family situations that came to their knowledge through the requests of the same people or by parishes, municipalities and other organizations that knew these situations of neglect.
- ▶ Thereafter, in its second stage, in 1994 and as a result of the promulgation of the first Law on Foundations, projects were initiated with the collaboration of renowned organizations and the work of the Foundation was somehow professionalized in different areas of action.



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- ▶ The third stage began with the modification of the Law on Foundations and the incentives for patronage in 2002, and the beginning of the so-called Alzheimer Project that led to the construction of the Queen Sofia Foundation Alzheimer Center, which has been in existence for ten years.
- ▶ The last stage of the Foundation began as a result of the economic crisis, focusing its efforts on projects primarily in Spain, collaborating with the food banks, Caritas, Red Cross, etc. Also, in this period the objective has been extended to help in the research of all neurodegenerative diseases, in

addition to Alzheimer's, such as Parkinson's, Huntington's, etc.

In these 40 years, 153 projects have been allocated to six areas of action: social action, health, women, education, agriculture and the environment. The three main areas are social action with 65 projects, health with 44, including the construction and equipment of the Queen Sofia Foundation Alzheimer Center and research projects in Alzheimer's and other neurodegenerative diseases, and the 29 projects devoted to education.



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The Action Plan for 2017 includes the financing and management of projects related to the fight against Alzheimer's, among which the "Vallecas Project", aimed at searching for biomarkers for early diagnosis, initiatives related to social awareness regarding this disorder, contributions for research scholarships, and the organization of the Global Summit Alzheimer's Research and Care Lisbon 2017. The rest of the Action Plan corresponds mostly to aiding the most disadvantaged groups going hand by hand with the Spanish Federation of Food Banks, Manos Unidas or Bobath Foundation, among others. In addition, an advertising campaign in favor of Alzheimer's research, "The Mission", will be conducted and disseminated through the country's major media outlets, cinemas and other companies.

10th Anniversary Queen Sofia Foundation Alzheimer Center

The Queen Sofia Foundation Alzheimer Center, which has celebrated 10 years since its inauguration on March 8, 2007, is a healthcare complex of reference in Alzheimer's and from which thousands of people have benefited. It addresses the disease simultaneously from three complementary angles: research, training and health care for patients. The Center consists of a residence for 156 people, a day center for 40 people, a training center for health personnel, relatives and volunteers and a research unit. 650 patients have passed through the healthcare area of the Center, between the residence and the day center, since its inception. The average age of the residents is 86 years, the youngest being 63 and the oldest 99 years-old.

The Alzheimer Center has earned the prestigious International Joint Commission accreditation for quality and safety in management and with the user. In Spain there are only 25 centers with this international accreditation counting hospitals, primary care centers and outpatient settings, being the only health-

care residence that has received it in Spain. Also, it has been granted the emblem of the European Green-light Project for environmental care, certified by the European Commission.

Regarding training, 21 symposia have been carried out about the care of the disease, including cognitive stimulation, caregiver program, good practices in residential centers, non-pharmacological interventions, etc.

In the Research Unit, whose management is assigned to the Neurological Disease Research Center (CIEN) Foundation, under the Ministry of Research, Development and Innovation, we must highlight the two calls for research projects that resulted in the award of 15 projects promoted and funded by the Queen Sofia Foundation. In addition, 11 additional projects and 8 further research projects managed by entrustment have been developed in this Unit. A good example of the extent and entity of this research work is the fact that about 50,000 studies of research-oriented magnetic resonance have been performed in the neuroimaging department.

The "Vallecas Project" for the early diagnosis of Alzheimer's disease stands out, a flagship project of the Unit that has been running for the last 6 years, which has been funded by the Queen Sofia Foundation. The "Vallecas Project" follows up a cohort of more than 1,200 volunteers, cognitively healthy people (at the time of recruitment) between 70 and 85 years who undergo a battery of neurological and biological tests to advance in the identification of early markers and risk profiles in Alzheimer's disease.

In addition, 8 international symposia on Alzheimer's research, a genetics symposium on dementia, a World Summit on the occasion of the International Alzheimer Year 2011 and 4 International Congresses on Research and Innovation in Neurodegenerative Diseases have been organized. As well as the Inter-



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national Summit on Research and Care of Alzheimer's Disease Lisbon 2017.

Global Summit Alzheimer's Research and Care Lisbon 2017

LCIEN Foundation was one of the organizing institutions of the Alzheimer's Global Summit that took place in Lisbon on September 18-22, coinciding with the celebration of World Alzheimer's Day (September 21). The Global Summit Alzheimer's Research and Care Lisbon 2017 brought together 80 experts from around the world in the field of scientific research and social-health care related to Alzheimer's and other neurodegenerative diseases. Noteworthy is the participation of Nobel Prize winners in Medi-

cine, such as Richard Axel (Columbia University) and John O'Keefe (University College London) among other prestigious researchers.

The Global Summit Alzheimer's Research and Care Lisbon 2017 was held at the Champalimaud Centre for the Unknown in the Portuguese capital, under the presidency of Her Majesty Queen Sofia, president of the Queen Sofia Foundation, and Ms. Leonor Beleza, president of the Champalimaud Foundation and former Portugal's Health Minister.

The meeting is the result of the collaboration between Spain and Portugal. Five institutions have joined efforts to make the international summit possible: the Spanish Queen Sofia Foundation, CIEN





Foundation and the CIBERNED Network (dependent on the Ministry of Economy and Competitiveness) as well as the CRE Alzheimer (belonging to the IM-SERSO, Ministry of Health, Social Services and Equality), and the Portugal's Fundação Champalimaud.

Vallecas Project Volunteer's Day

CIEF Foundation and Queen Sofia Foundation are aware of the role of the volunteer, crucial to carry out our research projects. Therefore, from CIEF Foundation we feel very grateful for the great generosity of each and every one of the 1,213 people who attended our call and, above all, the fidelity with which year after year keep coming to the corresponding visits of the "Vallecas Project". Hence, since 2013, every year we pay them tribute through the already established "Vallecas Project Volunteer's Day".

The fifth edition of this tribute, celebrated on May 20, 2017 at the Monumental Theater in Madrid, featured the performance of the RTVE Orchestra and Choir, directed by Javier Corcuera, who performed a wide repertoire of popular pieces, such as Verbena de la Paloma, by Tomás Bretón or El Pasodoble de los Sargentos, by Francisco Chueca. The event, which was conducted by the presenter Irma Soriano, also featured a magic show and an emotional video tribute.

The manager of the CIEF Foundation, M^a Ángeles Pérez, as well as the secretary of the Queen Sofia Foundation, José Luis Nogueira, did not want to miss the opportunity to express, once again, words of thanks to the volunteers for their valuable contribution.

Presentation of Dr. Bermejo's book "Alzheimer's, prevention since childhood"

Within the framework of the Madrid Science Week, the CIEF Foundation organized on November 13 in the Auditorium of the Queen Sofia Foundation Alz-

heimer Center the presentation of the book by Dr. Félix Bermejo Pareja entitled "Alzheimer, prevention from childhood" (Editorial ACCI - Iberoamerican Cultural and Scientific Association-, 2017).

The neurologist, psychologist and researcher, Felix Bermejo Pareja, who is currently Director of the Alzheimer's Extraordinary Chair of the Department of Medicine of the Complutense University of Madrid, CIBERNED emeritus professor and consultant neurologist of the 12 de Octubre Research Institute, analyzed in his presentation the bases by which the prevention of Alzheimer's is possible. These include care in pregnancy and the child's first years of life, decisive in establishing what has been called the cognitive reserve of the individual.

After the presentation, a debate was developed around this topic moderated by Dr. Teodoro del Ser Quijano (Coordinator of the CIEF Foundation neurology area) with the participation, in addition to the author of the book, of Drs. Miguel Medina (CIBERNED Deputy Scientific Director and PI of the "Proyecto Vallecas") and Miguel Calero (Coordinator of the CIEF Foundation Laboratory area and CIBERNED researcher).

Christmas Tree of Memories

After the success of the previous campaign, the CIEF Foundation wanted to replicate its traditional "Tree of Memory" placed in CentroCentro building of the Madrid City Hall, located at Cibeles Square. This initiative, which also had the support of the City Council of the capital and the Queen Sofia Foundation, is aimed at raising awareness in society about the effects of Alzheimer's disease in those who suffer from it and giving value into memory through positive emotions, which are the strongest memories in our brain. This "Tree of Memories" planted on December 2016 was intended to be special, on the occasion of the tenth anniversary of the transfer of the



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CIEN Foundation to the Queen Sofia Foundation Alzheimer Center, which will be celebrated in 2017. Therefore, it was the first time that has been installed in the center of the capital, in such an emblematic place as CentroCentro Cibeles, could be seen during the Christmas period by thousands of locals who visited the center and hung their most precious Christmas souvenir in special cards prepared for the occasion as well as through social networks, with the hashtag #arboldelamemoria. The Christmas tree, with a firm trunk holding hundreds of branches, symbolized the idea of continuity of emotions over time, as well as a metaphor of the social nature of

this problem and a call for everyone's involvement, essential to eradicate a disease that potentially affects society as a whole.

In addition, as in previous editions, the original tradition of the Vallecas "Tree of Memory" has been maintained, which since 2011 has been installed throughout Christmas in that district of Madrid. In the last edition, the Villa de Vallecas Market, again welcomed this initiative, with the support of the Queen Sofia Foundation, the Villa de Vallecas District Board of and the Region of Madrid General Directorate for the Elderly.





Other institutional visits

Throughout 2017, the Alzheimer Project Research Unit has received numerous institutional and non-institutional visits, with the aim of showing and disseminating the work carried out in it. We would highlight the visit to the facilities of the Queen Sofia Foundation Alzheimer Center-CIEN Foundation in the month of June, of the the Secretary of State for Research, Development and Innovation, Ms. M^o Carmen Vela Olmo and the Secretary of State for Social Services and Equality, Mr. Mario Garcés Sanagustín, who attended a presentation made by the scientific director of the Foundation, Jesús Ávila, in which he disserted about the incidence of Alzheimer's disease, the current national strategies, the work carried out in the CIEN Foundation and its objectives with studies such as the "Vallecas Project".

In the month of July, we had the honor of receiving H.M. Queen Sofia accompanied by the president of the Congress, Ana Pastor, who visited with great interest the Queen Sofia Foundation Alzheimer Center, the CIEN Foundation Tissue Bank and had the opportunity to exchange views with some of the researchers of the Foundation, such as Dr. Miguel Calero, responsible of the laboratory area, or Alberto Rábano, director of the CIEN Tissue Bank.

7.2. Presence in media

As every year, during 2017, the Communication Area of the CIEN Foundation developed a communication plan, which has been carried out. Constant communications and regular meetings have been maintained with the CIEN Foundation Management regarding media appearances, press releases, reports, programmed initiatives, organization, etc.

It is worth emphasizing in order to formulate and achieve the objectives of the year 2017, a central

event that took place in September was taken into account: the Global Summit Alzheimer's Research & Care Lisbon 2017, organized by the CIEN Foundation in collaboration with the Queen Sofia Foundation, CIBERNED, the CRE Alzheimer of the IMSERSO and Fundação Champalimaud.

The organization and development of this event concentrated the conception and strategy of the communication plan 2017, although several other actions and communication initiatives were carried out. In effect, the communication actions referred not only to the Summit, but also to the activity of the CIEN Foundation. In addition, the constant flow of press releases reflects the updated information on the CIEN Foundation and the "Vallecas Project", its most important project.

A significant international impact has been achieved in the context of the Global Summit, both in terms of dissemination in the press and online media, as well as the extension of the network of contacts with researchers in neurodegenerative diseases throughout the world, which includes international research centers and researchers of the level of Nobel Laureates John O'Keefe and Richard Axel.

In addition, work has been carried out on the dissemination of other already traditional CIEN Foundation events, such as the Vallecas Project Volunteer's Day, held at the Monumental Theater of Madrid, which had the collaboration of the TVE Orchestra and Choir. Also, a new edition of the Christmas Memory Tree was held, with the collaboration of the Madrid City Council, an initiative aimed at raising awareness about the problem of neurodegenerative diseases, and which was installed in December at CentroCentro Cibeles in the capital city.

Regarding the impact on the press, the diffusion of the activities and projects of the CIEN Foundation has been maintained and increased.



En 2050 habrá un millón de casos de demencia en España



El número de casos de demencia en España se estima que llegará a un millón en 2050. La demencia es una de las enfermedades crónicas más frecuentes. Los investigadores creen que el 10 por ciento de la población tendrá algún tipo de demencia en algún momento de su vida. En España, se estima que habrá un millón de casos de demencia en 2050.

El envejecimiento, factor clave
Una de las causas del envejecimiento es el aumento de la esperanza de vida. Esto significa que más personas viven más tiempo, lo que aumenta el riesgo de desarrollar demencia. El envejecimiento es el mayor factor de riesgo para la demencia.



SOCIEDAD

Diario de León

Alzheimer León participa en el proyecto Vallecas



Alzheimer León participa con 12.800 euros en la financiación del Proyecto Vallecas, un estudio de investigación liderado por la Fundación CIEN (Centro de Investigación en Enfermedades Neurodegenerativas). El estudio de Vallecas es el primer estudio de investigación en España que trata de analizar la actividad del cerebro humano antes de que se manifieste la enfermedad de Alzheimer. Este estudio es posible gracias al respaldo financiero de donadores, que en la edición de los Premios Manó Amiga, invierten sus esfuerzos para apoyar la investigación.

La Fundación SARquavitaie dona 10.000 euros a la Fundación CIEN para la investigación del Alzheimer

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La Fundación SARquavitaie dona 10.000 euros a la Fundación CIEN para la investigación del Alzheimer MADRID | EUROPA PRESS

Etiquetas: Mal De Alzheimer, Investigación Médica, Genética, Investigación.
La Fundación SARquavitaie ha hecho entrega de un donativo de 10.000 euros a la Fundación CIEN, que destinará este importe al Proyecto Vallecas de investigación y diagnóstico precoz de la enfermedad de Alzheimer. Esta donación es posible gracias a la campaña "Kilómetros para recordar", una iniciativa que, en esta segunda edición, ha contado con más de 2.000 participantes. La campaña consiste en cambiar los kilómetros recorridos por los participantes por euros para la investigación de enfermedades neurodegenerativas.

La Reina doña Sofía recogerá uno de los premios «Mano Amiga» que entrega Alzheimer León

La gala tendrá lugar el día 11 en el Auditorio «Ciudad de León»



Presentación de la V edición de los Premios Manó Amiga. Elena Ortega - CTA

La Reina doña Sofía recibirá personalmente el premio «Mano Amiga» que cada año, cuando se celebra la gala edición de estos galardones, se ha concedido la asociación Alzheimer León «per se méritos» y distinción personal durante décadas a la lucha contra la enfermedad. La reina doña Sofía ha confirmado su presencia en esta gala, que se celebrará con el patrocinio de la asociación leonesa, y que se celebrará el 14 de noviembre en el Auditorio «Ciudad de León» a partir de las 19:30 horas, una gala que estará presentada por los periodistas Dima Soriano y Iago del Olmo.

Según explicó el presidente del jurado, Miquel Ugeux, también se han dividido los premios «Mano Amiga» en las categorías de Asociación e Individual, que respectivamente han recaído en el Grupo de Trabajo Programa de Promoción e Investigación de Alzheimer Premios, por los «emprendedores leoneses» que asegura que las personas afectadas participan en la tarea de diagnóstico, y el director científico del Centro de Investigación y Clínica de Memoria de la Fundación CITA.



In addition to press releases, reports and information generated around the Global Summit, there have been press appearances and online and audiovisual media that include extensive reports in media such as RTVE, TVE Internacional, El País, El Mundo, El Independiente, Onda Cero, ABC, Telemadrid, La Cuatro, Cadena SER, Diario Médico, ConSalud, El Español and Acta Sanitaria, as well as regular dissemination through the main news agencies.

Five elements have focused the press interventions and appearances:

- The "Vallecas Project", especially the results around the predictive algorithm and the virtual brain model for diagnosis.
- The volunteers of the "Vallecas Project".
- The CIEN Foundation Tissue Bank.

- The Global Summit Alzheimer's Research & Care Lisbon 2017.
- The 40th anniversary of the Queen Sofia Foundation and the 10th anniversary of the Alzheimer Center Queen Sofia Foundation, headquarters of the CIEN Foundation.

In press statements, a protocol of control and prior informed consent has been introduced in 2017, whereby journalists are informed in detail of the CIEN Foundation's assignment to the Carlos III Institute of Health and the Ministry of Economy, Industry and Competitiveness.

The number of impacts during 2017 in media as a whole was around 2,400, increasing by 48% with respect to 2016. Thus, for example, only during the ac-



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tions corresponding to the Alzheimer's Global Summit Lisbon 2017 (Lisbon, 18-21 September 2017), over 350 impacts were generated in the press (national and international agencies and media outlets), 220 in online media (including the traditional digital headers) plus the notorious impact in social media, especially on Twitter.

7.3. Presence in social media

The CIEN Foundation has continued to implement its promotion strategy, which has been rewarded both in the results obtained in social media as well as in the recognition and prestige it has at the national and international level as an organization.

Throughout 2017, the community has received the support and advice of numerous experts who have solved their doubts and queries in real time through social media.

Several campaigns have been promoted from the official accounts of the CIEN Foundation, highlighting above the rest the one referred to the "Vallecas Project" (#ProjectVallecas), the campaign to encourage donation of brain tissue and bring this possibility to users (#HazteDonante) and that aimed at increasing awareness of Alzheimer's disease in the population through the contribution of data and new discoveries (#Alzheimer).

Sporadic campaigns and events have also been covered and disseminated. Among these events are worth mentioning the coverage of the initiative "Christmas Tree of Memory" (#ÁrbolDeLaMemoria), the 1st DEGESCO Symposium held at the Queen Sofia Foundation Alzheimer Center (#DEGESCO), the campaign for the Alzheimer's Global Summit Lisbon 2017 (#GlobalSummit2017) organized in Lisbon or the coverage given to the Seminar Series of the CIEN Foundation 2017 (#Seminar CycleFCIEN).

Analyzing the status of the various official accounts of the CIEN Foundation, we can observe the evolution they have experienced during 2017:

Facebook:

2017 ended with 4,883 followers, who have been increasing progressively and whose positive trend continues constant. This figure represents a 6.22% increase over the previous year.

Twitter:

By the end of 2017, the profile counted on 12,821 followers with whom it has constant interaction, receiving numerous comments, retweets and likes. The number of followers have experienced an increase of 4.68% compared with the previous year.

Google+:

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





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