II Congreso Internacional de Investigación e Innovación en Enfermedades Neurodegenerativas (CIIIEN)

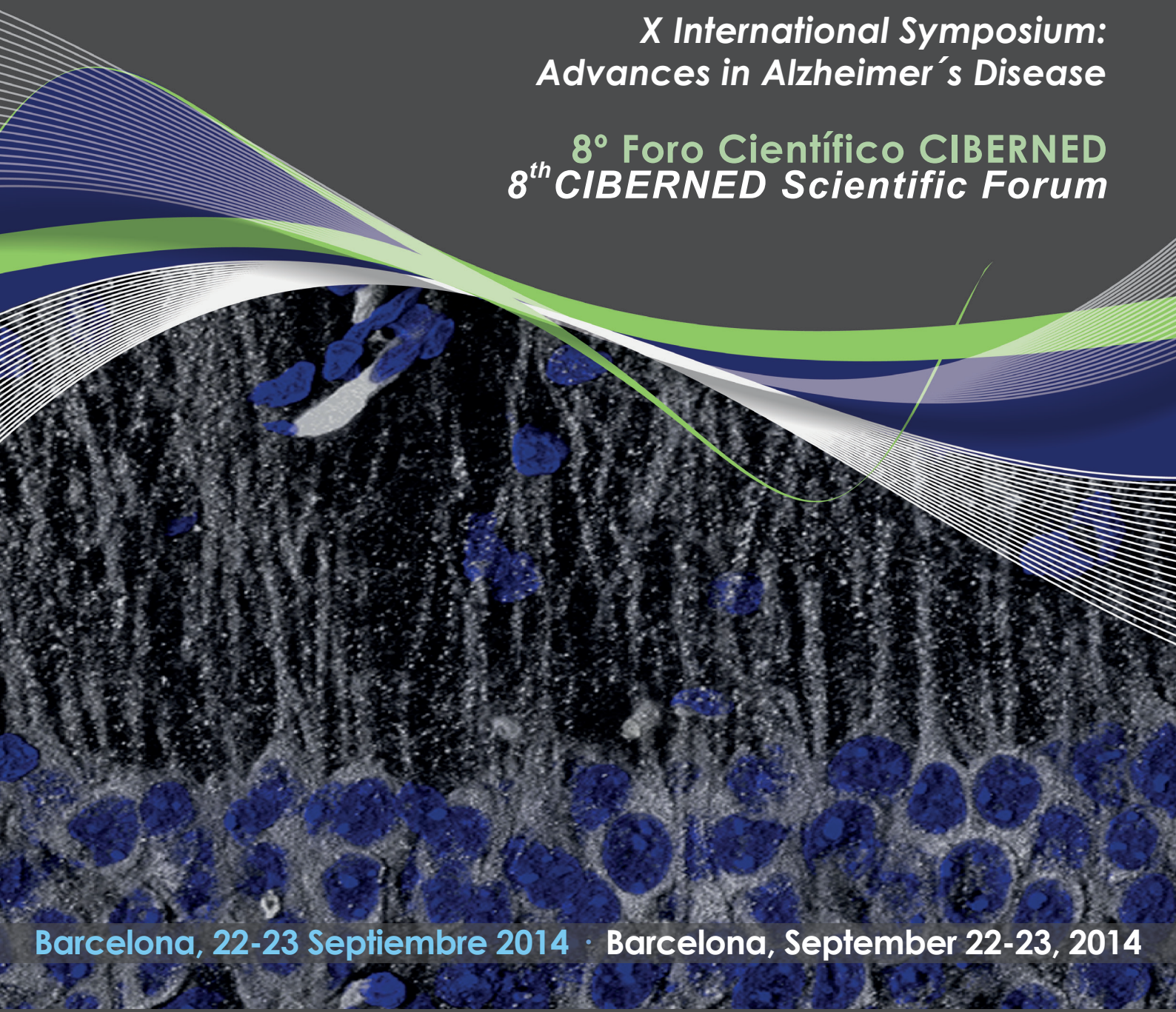
II International Congress on Research and Innovation in Neurodegenerative Diseases

X Simposio Internacional: Avances en la Enfermedad de Alzheimer

X International Symposium: Advances in Alzheimer´s Disease

8º Foro Científico CIBERNED

8th CIBERNED Scientific Forum



Barcelona, 22-23 Septiembre 2014 · Barcelona, September 22-23, 2014

FUNDACIÓN REINA SOFÍA

MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD

Instituto de Salud Carlos III

cien Fundación Centro Investigación Enfermedades Neurológicas

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COVER PICTURE:

Neuronal staining of Tau (white) and nuclei (blue) in CA1 hippocampal region of mouse brain (A. Gamir, C. López-Menéndez and T. Iglesias).

II International Congress on Research and Innovation In Neurodegenerative Diseases

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Centro Investigación Biomédica en Red Enfermedades Neurodegenerativas

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Introduction

This report summarizes the activities carried out around the Second International Congress on Innovation and Research in Neurodegenerative Diseases (CIIIEN). CIIIEN is organized annually by Queen Sofia Foundation, the Center for Research in Neurological Diseases (CIEN) Foundation and the Center for Networked Biomedical Research in Neurodegenerative Diseases (CIBERNED). The Conference took place in Barcelona on 22nd and 23rd of September, 2014 and attracted more than 200 researchers, clinicans and scientists involved in the field of neurodegeneration research.

Under the Presidency of H. M. Queen Sofia, the Congress discussed the main research advances in neurodegenerative disorders, particularly Alzheimer's, Parkinson's and Huntington's diseases, and marked for the second consecutive year, the merger of the X International Symposium on Advances in Alzheimer's Disease and the VIII Scientific Annual CIBERNED Forum.

This annual meeting offers a forum to discuss a range of areas of interest related to basic, clinical and translational aspects of the research in neurodegenerative diseases. It provides opportunities to researchers to discuss and entertain topics that stretch into the future and will be vital to procure the advancement of cooperative research. In addition, there will be many opportunities to meet and network with colleagues from the field to share experiences and learn from each other.

At the end of the scientific sessions, on Tuesday 23rd, a Social Forum was also held consisting of three round tables with the participation of associations, relatives and patients of Alzheimer's, Parkinson's and Huntington.

Participating Institutions

Public Institutions

- **H.E. Ms. Susana Camarero,** Secretary of State of Social Services and Equality.
- **H.E. Ms. María de los Llanos de Luna**, Government Delegate from Catalonia.
- **Dr. Antonio Andreu Periz,** General Director, Carlos III Institute of Health.
- **Ms. Cristina Iniesta Blasco,** Delegate of Health, Barcelona City Council.
- **Dr. Joan J. Guinovart**, Director of the Institute for Research in Biomedicine, Barcelona.
- **Ms. Mª Isabel González Ingelmo,** Manager Director of State Reference Center of Alzheimer Imserso from Salamanca.

Private Institutions

- **Ms. Leonor Beleza,** President, Champalimaud Foundation.
- **Mr. José Luis Nogueira**, Secretary of the Queen Sofia Foundation.
- **Dr. Mercè Boada**, Medical Director of the ACE Foundation.
- **Dr. Jordi Camí**, General Director, Pasqual Maragall Foundation for Research in Alzheimer´s.

Invited Guests

- **Mr. José Fornell,** Institutional Relations and Protocol Advisor, Government Delegation from Catalonia.
- **Ms. Margarita Blázquez,** Deputy General Director of Networks and Cooperative Research Centers, Carlos III Institute of Health.
- **Mr. José Luis Beotas**, State Attorney. Ministry of Education, Social Policy and Sport.
- **Mr. Lluis Tàrraga**, Director of the ACE Foundation.
- **Dr. Galo Ramírez**, Research Professor, CBMSO-CSIC.
- **Dr. Pablo V. Escribá,** Ph. D. Molecular Cell Biomedicine, University of the Balearic Islands
- **Dr. José J. Soto,** Laboratory Technician, University of Alicante
- **Dr. Antonio Páez,** Clinical Operations Sr. Manager, Grifols.

Scientific Conference

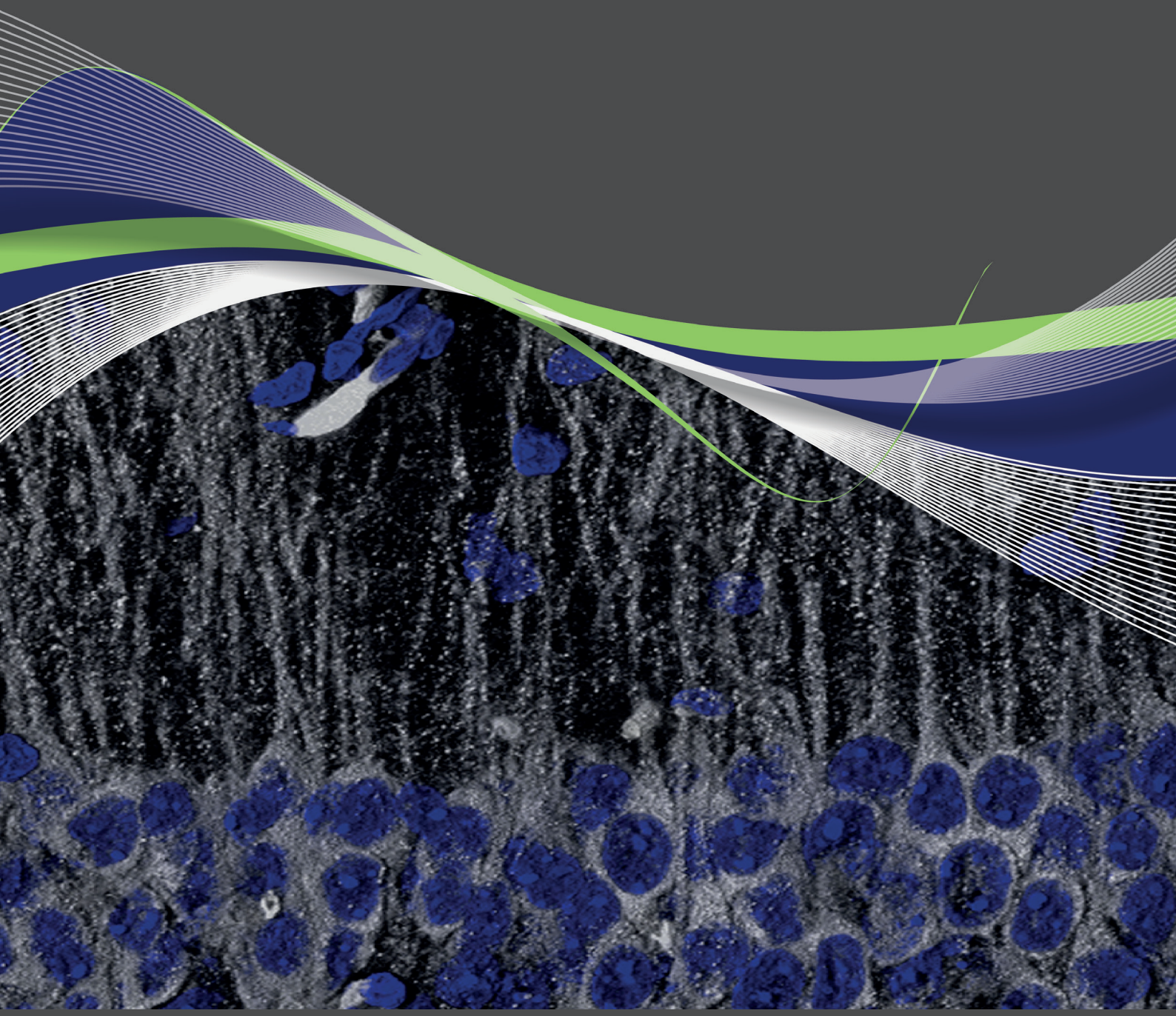
Scientific Organizing Committee

- **Dr. Jordi Alberch**
- **Dr. Joan X. Comella**
- **Dr. Isidre Ferrer**
- **Dr. Alberto Lleó. -** Chairman
- **Dr. Miguel Medina. -** Deputy Scientific Director
- **Dr. Eduardo Soriano**
- **Dr. Eduardo Tolosa**

CIBERNED Steering Committee

- **Dr. Jesús Ávila.** - Scientific Director
- **Ms. Mª Ángeles Pérez.** - Managing Director
- **Dr. Miguel Medina.** - Deputy Scientific Director
- **Dr. Isidre Ferrer**
- **Dr. Alberto Lleó**
- **Dr. Adolfo López de Munaín**
- **Dr. José J. Lucas**
- **Dr. Eduardo Soriano**
- **Dr. Eduardo Tolosa**

SCIENTIFIC PROGRAMME



FUNDACIÓN REINA SOFÍA

MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD

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MONDAY, SEPTEMBER 22

08:00 h.
Welcome and registration.

08:30 - 10:30 h.
SCIENTIFIC SESSION I:
Stem cells in neurodegenerative diseases.
Chairperson : Dr. Antonia Gutiérrez.
CIBERNED, University of Málaga, Spain.

08:30 h.
Adult neurogenesis in animal models of Parkinson´s disease.
Dr. Isabel Fariñas.
CIBERNED, University of Valencia, Spain.

09:00 h.
Stem cells in the carotid body; physiology and biomedical implications.
Dr. José L. López-Barneo.
CIBERNED, Virgen del Rocío University Hospital, University of Sevilla, Spain.

09:30 h.
Stem cells in aging and disease.
Dr. Pura Muñoz.
CIBERNED, Pompeu Fabra University, ICREA, Barcelona, Spain.

10:00 h.
Modeling Parkinson´s disease through patient-specific induced pluripotent stem (iPS) cells.
Dr. Ángel Raya.
Center of Regenerative Medicine in Barcelona, Spain.

Dr. Isabel Fariñas

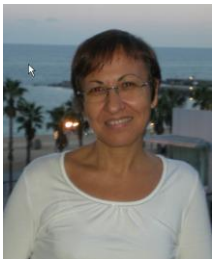
CIBERNED

Isabel Fariñas graduated in Biology from the Universidad Autónoma de Barcelona and did her thesis at the Institute of Neurobiology Ramón y Cajal (CSIC) in Madrid. After a period of three years as an assistant professor at the University of Barcelona, she moved to the University of California at San Francisco (USA), where she became a postdoctoral fellow of the Fulbright and Human Frontier Science Program Organization and later a researcher in the team of Dr. Louis F. Reichardt, and contributed to the characterization of the in vivo actions of neurotrophins in genetically-targeted mutant mice. In 1998, she joined the University of Valencia in Spain where she is currently Professor of Cell Biology and head of the Molecular Neurobiology Lab. Since then, her lab focusses on the mechanisms that regulate self-renewal of stem cells in the adult murine brain with a particular interest in stem cell-niche interactions in normal and diseased brains. Her research group belongs to the Spanish National Network for Cell Therapy and the Center for Biomedical Research in Neurodegenerative Diseases and is Prometeo´s Excellence group of the Comunidad Valenciana. She has won the Fiscam (2007) and Alberto Sols (2009) awards to best publication in biomedicine, is a member of the boards of the Spanish National Stem Cell Bank and the Spanish Society for Gene and Cell Therapy and has served as a board member of the Spanish Society for Neuroscience. She is EMBO member since 2013.

Dr. José López Barneo
CIBERNED

José López Barneo (February 21, 1952), Doctor of Medicine and Surgery, is Professor of Physiology at the Faculty of Medicine of Seville (1986) and Head of Research, at Virgen del Rocío University Hospital (1999). He has held numerous academic positions or in national and international technical committees and currently is Director of the Institute of Biomedicine of Seville (IBIS) charges. His main research lines are related to the cellular responses to hypoxia, neurodegeneration and cell therapy applied to Parkinson's disease. He has authored over 150 international publications and is member of the editorial boards of the most prestigious journals in his field (The Journal of Physiology, Pfluegers Archiv-European Journal of Physiology, Physiological Reviews, among others). He has also been president of the Spanish Society for Neuroscience, president of the Spanish Society of Gene and Cell Therapy and the first director of the Center for Networked Biomedical Research in Neurodegenerative Diseases (CIBERNED).

José López Barneo has received numerous awards for his academic work, among which the following can be highlighted: Juan Carlos I Prize for Scientific and Technical Research (1993), Jaime I Research Award (1998), Maimonides Andalucía Research Award (2002), Lilly Basic Research Award (2003), Javier Benjumea Research Award of the Focus-Abengoa Foundation (2006), FAME Award from the University of Seville (2009) and Santiago Grisolia Chair Prize (2010). He is a member of the "Academia Europaea-Physiology or Medicine" (1997) and "European Molecular Biology Organization" (2000). Dr. López Barneo is Academic of the Royal Academy of Sciences of Seville (2004) and the Royal Academy of Medicine of Seville (2012) and Corresponding Member of the Royal Academy of Natural Sciences (2005). He is a Botín Foundation researcher since 2007.



Dr. Pura Muñoz

CIBERNED

Pura Muñoz-Cánoves studied Pharmacology at the University of Valencia. She obtained her PhD in Biology at the Madrid Autonomous University for work carried out at The Scripps Research Institute, and did postdoctoral work at the University of California-San Diego and The Scripps Research Institute, and in 1994 she joined the Cancer Research Institute in Barcelona as a postdoc, becoming an independent group leader in 1997. In 2002 her group moved to the Center for Genomic regulation in Barcelona, and she became a senior group leader in 2007 in that Institution. In 2009 she moved to the Pompeu Fabra University (UPF), supported by ICREA, as coordinator of the Cell Biology Unit. At present, she is an ICREA Research Professor and Cell Biology Professor in the Department of Experimental and Health Sciences at the UPF and member of CIBERNED.

Dr. Ángel Raya

Center of Regenerative Medicine. Barcelona, Spain

Ángel Raya holds an MD and a PhD from the University of Valencia. He pursued postdoctoral training at the Instituto de Investigaciones Citológicas (currently, Centro de Investigación Príncipe Felipe) in Valencia, from 1995 to 2000. He then was a Research Associate (2000-2004) and a Senior Research Associate (2004-2006) in the Gene Expression Laboratory of the Salk Institute for Biological Studies, La Jolla, CA (USA). He returned to Spain in 2006 as an ICREA Research Professor. He was CMRB´s Scientific Coordinator until 2009, when he joined the Institute for Bioengineering of Catalonia (IBEC) as group leader of the Control of Stem Cell Potency Group. Dr. Raya studies the tissue, cellular and molecular mechanisms that determine the regenerative response in certain species of vertebrates, as well as the genetic and epigenetic mechanisms that control cellular reprogramming. In 2014 he was appointed Director at CMRB.

10:30 - 12:00 h.

SCIENTIFIC SESSION II:

Novel biomarkers in neurodegenerative diseases.

Chairperson: Dr. Alberto Lleó.

CIBERNED, Santa Creu i Sant Pau Hospital, Barcelona, Spain.

10:30 h.

Structural and functional cortical networks in early neurodegeneration

Dr. José Luis Cantero.

CIBERNED, Pablo de Olavide University, Sevilla, Spain.

11:00 h.

Molecular Imaging in Dementia. Its role in clinical practice.

Dr. Pascual Sánchez-Juan.

CIBERNED, Marqués de Valdecilla Hospital, Santander, Spain.

11:30 h.

REM sleep behaviour disorder as an early marker of Parkinson disease.

Dr. Alejandro Iranzo.

CIBERNED, Hospital Clinic of Barcelona, Spain.

Dr. José Luis Cantero
CIBERNED

José Luis Cantero has a PhD in Neuroscience (1999) from the University of Seville with PhD Extraordinary Award in the area of Health Sciences. He did his postdoctoral research at the Department of Psychiatry at Harvard Medical School, Boston, USA (2000-2002). In 2003 he joined the Pablo de Olavide University (Seville), where he is Associate Professor in the area of Physiology from 2012. Currently, he heads the Laboratory of Functional Neuroscience at the Pablo de Olavide University, which he performs research on early detection of Alzheimer's disease by combining biological, electrophysiological and brain imaging markers.

Dr. Cantero is since 2005 responsible of the "Functional Neuroscience" research group (CTS-557) within the Andalusian Research Plan in the area of Science and Health Technologies. Since 2006 he has continuously conducted research projects funded by the National Program of Biomedicine, Andalusian Project Excellence and European Research Projects under Framework Programme. He is principal investigator of the Center for Networked Biomedical Research in Neurodegenerative Diseases (CIBERNED) since 2008 In 2011, he was appointed Corresponding Member of the San Dionisio Royal Academy of Sciences, Arts and Letters.

He has authored over 80 scientific publications, 60 in international journals, some of them in prestigious journals such as Nature Neuroscience, Neuroscience, Journal of Neuroscience, Cerebral Cortex, Neuroimage, Human Brain Mapping, etc. Currently he is a member of the Editorial Board of the journals Brain Structure and Function, International Journal of Clinical and Health Psychology, and American Journal of Neurodegenerative Diseases. In the area of scientific management, regularly collaborates with international (United Kingdom, Italy, Czechoslovakia, Holland and Chile) and national (Ministry of Science and Innovation, Madrid, Community of Navarra, Generalitat Valenciana, Fundación Canaria for Research and Health, Galician Research Plan) research agencies and private foundations (Fondazione Telethon Foundation LOREAL-UNESCO).

Dr. Pascual Sánchez-Juan
CIBERNED

Dr. Sanchez-Juan is a full-time clinical neurologist at the Cognitive Impairment Unit, Marqués de Valdecilla Hospital (HUMV); he is also Scientific Director of the Valdecilla Biobank. Dr. Sanchez-Juan belongs to the CIBERNED group led by Dr. José Berciano. Besides being trained as Neurologist at HUMV, he has specialized in the field of Genetic Epidemiology, pursuing a PhD and Postdoc in this discipline at the Erasmus MC University in Rotterdam (The Netherlands). The main scientific interests of Dr. Sanchez-Juan are neurodegenerative diseases, particularly prion diseases and AD. Dr. Sanchez-Juan has co-authored 79 international publications in indexed journals (index H = 15 (Web of Knowledge July 14, 2014)), including lead postion in pivotal highly cited articles: such as the new definition of the clinical diagnostic criteria of sporadic Creutzfeldt-Jakob disease (Brain, 2009), work in which he is listed as last author; first author in one of the first genome-wide association studies in prion diseases (GWAs) (Neurobiology of Aging, 2012).

In the field of AD biomarkers, Dr. Sanchez-Juan leads several collaborative studies, including being PI of the CIBERNED node im the main European initiative in this field: the EU Joint Programme - NeurodegenerativeDiseaseResearch (JPND). In the same line, the HUMV is the only center in Spain currently performing PIB-PET for the study of *in vivo* brain amyloid deposits. Dr. Sanchez-Juan maintains active collaborations with the UCSF Memory and Aging Center (San Francisco) focused on the clinical utility of PIB-PET, the result of which signs as first author one of the first papers showing the clinical impact of the these molecular imaging techniques (Neurology, 2014).

Dr. Alex Iranzo

CIBERNED

Alex Iranzo graduated in Medicine (1991) and defended his PhD thesis (2002) at the Universidad de Barcelona, Spain. Presently, he is neurologist consultant at the Neurology Service and at the Multidisciplinary Sleep Unit of the Hospital Clinic of Barcelona, Barcelona, Spain. He is investigator of Institute D' Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) and CIBERNED. He is a member of numerous national and international societies such as the American Academy of Neurology, Movement Disorder Society, American Academy of Sleep, World Association of Sleep Medicine, European Sleep Society, International REM Sleep Behavior Disorder Group, European Restless Legs Syndrome Society, European Narcolepsy Network, Spanish Society of Neurology and Spanish Sleep Society. Dr. Iranzo has widely published as first and corresponding author in peer reviewed journals such as The Lancet, The Lancet Neurology, Annals of Neurology, Neurology, Journal of Neurology Neurosurgery and Psychiatry, Movement Disorders, Sleep, and Sleep Medicine. Presently, he is at the editorial board of the journal Sleep Medicine, member of the scientific committee of the European Sleep Society and treasurer of the Spanish Sleep Society.

OPENING SESSIONS

With the Presidency of Her Majesty Queen Sofia

12:00 - 13:45 h.

12:00 h.
OFFICIAL OPENING.

12:05h.
Keynote address.
Dr. Antonio Andreu.
Director of the Carlos III Institute of Health.

12:10 h.
H.E. Ms. Susana Camarero.
Secretary of State of Social Services and Equality

12:15 h.
Opening Session.
Chairperson: Dr. Jesús Ávila.
CIBERNED-CIEN Foundation, Center of Molecular Biology "Severo Ochoa", CSIC-UAM, Madrid, Spain.

Does innate immunity contribute to Alzheimer´s disease pathogenesis?.
Dr. Michael Heneka.
German Centre for Neurodegenerative Disease, University of Bonn, Germany.

13:00 h.
What is normal in normal aging?
The borders between aging and Alzheimer´s disease.
Dr. Anders Martin Fjell.
Research Group for Lifespan Changes in Brain and Cognition, University of Oslo, Norway.

Dr. Michael T. Heneka
University of Bonn, Germany

Michael Heneka completed his medical coursework at the University of Tübingen, Germany in 1996. He obtained his medical degree in 1998 at the Institute of Pharmacology and Toxicology of the University of Tübingen on the topic “The effect of polymerized hemoglobin on cardiovascular and renal parameters in septic shock.” Thereafter he was a postdoc in the laboratory of Prof. DL Feinstein, at the University of Illinois at Chicago, Chicago, USA. In 2002 he passed the board examination in Neurology and qualified as a professor in Neurology in 2003 with a habilitation thesis entitled “Inflammatory mechanisms in Alzheimer’s disease: characterization and development of therapeutic strategies” at the University of Bonn.

He was offered a Fellowship in the Department of Neurosciences, Case Western Reserve University, Cleveland, USA, in the laboratory of Prof. K Herrup and Prof. GE Landreth in 2004, after which he returned to Germany as a senior physician in the Department of Neurology at the University of Bonn.
This was followed by a professorship (C3) for molecular neurology at the University of Münster (WWU) from 2004 to 2008. During this time he was head of the Department of Molecular Neuroscience and of the dementia clinic at the University Hospital MS. In 2008 he was appointed as Professor (W3) for Clinical Neurosciences at the Rheinische Friedrich-Wilhelms-Universität Bonn. Since 2010 Prof. Heneka has been the Neurological Director of the joint Memory Clinic of the Departments of Psychiatry and Neurology (Clinical Treatment and Research Center, KBFZ), University Hospital Bonn and is also affiliated to the German Center for Neurodegenerative Diseases (DZNE).
Beyond his research, reviewer and teaching duties, Michael Heneka serves as head of the Clinical Research Unit 177 (DFG), is a board member of the BMBF Competence Network “Degenerative Dementias” (KNDD) and is a member of the BONFOR Commission. He is also the Organizing Chair of the biennial conference “Venusberg Meeting on Neuroinflammation”.

Dr. Anders M. Fjell
University of Oslo, Norway

Anders Fjell is Professor of Cognitive Psychology in the Department of Psychology at the University of Oslo, Norway and is also affiliated to theDepartment of Neuropsychology, Oslo University Hospital. His expertise and interests include: Memory, Normal development and aging, Alzheimer's Disease, and Neuroimaging. His main research interest is to try to understand how changes in brain structure and activity in development, aging and disease, affect cognitive functions byusing a multi-disciplinary approach, with neuropsychology, cognitive experiments and neuroimaging (MRI, ERP, PET), in addition to CSF biomarkers and genotyping.He is group leader together with professor Kristine B. Walhovd of the Research Group for Lifespan Changes in Brain and Cognition (LCBC). As of February 2014, the groups cosnsists of 4 post docs, 8 PhD candidates, 3 full-time research assistants.

13:45 h.

Poster session.

14:00h.

Lunch and poster session

15:00 – 16:45 h.

SCIENTIFIC SESSION III:

Preclinical changes in neurodegenerative diseases.

Chairperson: Dr. José A. Obeso.

CIBERNED, Center of Applied Medical Research, Univ. Navarra, Pamplona, Spain.

15:00 h.

Update on the Genetics of Parkinson´s disease.

Dr. Vincenzo Bonifati.

Genetics of Parkinson´s disease, Erasmus MC, Rotterdam, The Netherlands.

15:45 h.

The mitocondrial DNA hypothesis of Alzheimer´s Disease.

Dr. Ramón Trullás.

CIBERNED, Institute of Biomedical Research IDIBAPS-CSIC, Barcelona, Spain.

16:15 h.

Reelin rescues amyloid and Tau pathologies in Alzheimer's disease models.

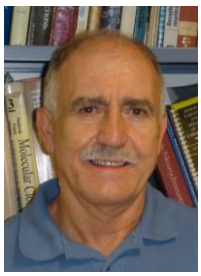
Dr. Lluís Pujadas.

CIBERNED, University of Barcelona, Spain.

Dr. Vincenzo Bonifati

Erasmus MC, Rotterdam, The Netherlands

Vincenzo Bonifati received his MD (cum laude) in 1988 from 'La Sapienza' University of Roma, Italy. In 1992 he completed his residency in neurology at the same University and was appointed staff neurologist. He later moved to the Erasmus University Rotterdam, where he received his PhD in human molecular genetics in 2003. In 2006 he was appointed Associate Professor, and in 2012 he became Professor of Genetics of Movement Disorders in the Erasmus University Rotterdam, Dept. of Clinical Genetics. He has a long-standing research interest in the genetics of the neurodegenerative diseases and movement disorders, with a focus on Parkinson's disease (PD). His work led to the identification of DJ-1 as the gene causing PARK7, one of the Mendelian forms of PD. His group was one of the first to describe the Gly2019Ser mutation, and to characterize the Gly2385Arg variant in the LRRK2 gene, currently considered among the most relevant genetic determinants of PD. In 2009, his group characterized FBXO7 as the gene causing a novel form of autosomal recessive juvenile parkinsonism with pyramidal signs, that they termed PARK15. Recently, his group identified mutations in the SLC30A10 gene causing a novel form of autosomal recessive parkinsonism and dystonia with hypermanganesemia, polycythemia and chronic liver disease, delineating the first human inherited disorder of manganese transport.



Dr. Ramón Trullás

CIBERNED

Ramón Trullás performed predoctoral studies at the Millhauser Laboratories, New York University Medical Center, NY, USA and at the Department of Medical Psychology of the School of Medicine of the Autonomous University of Barcelona (UAB). He obtained the Ph.D. degree in Psychology from the UAB with a thesis on the mechanism of action of antidepressant drugs which received a doctoral award with special distinction. He served as a Postdoctoral Fulbright Fellow with Dr. Phil Skolnick at the Laboratory of Bio-Organic Chemistry, NIDDK, NIH in Bethesda, MD, USA from 1985 to 1988 and continued as a Visiting Associate at the Laboratory of Neuroscience, NIDDK, NIH from 1988 to 1991. Currently, he serves as a Professor of Research at the Institute for Biomedical Research of Barcelona (IIBB/CSIC/IDIBAPS) and as Group Leader at CIBERNED. He has been Chairman of the National Physiology and Pharmacology Grant Evaluation Program (ANEP) and currently is member of the Scientific Advisory Board of EraysBio ERANET for Systems Biology of European Commission and Academic Editor of PLOSone.

Dr. Lluís Pujadas
CIBERNED

Lluís Pujadas is a Junior Researcher from the CIBERNED/University of Barcelona, interested in adult brain functioning and its relation to neurological diseases. He is been working to develop mouse models for studying neurological diseases to understand the molecular basis of development-related processes occurring in adult brain. His recent work was directed to unravel the role of Reelin as a protector factor against amyloid-beta-induced toxicity, and its effect on amyloid-beta aggregation. He started his studies in Chemistry and was graduated in Biochemistry at the University of Barcelona (2000). His thesis was focused in developmental neurosciences studies and he obtained the Ph.D. in Neurosciences from the University of Barcelona in 2006.

16:45 - 17:00 h.
Poster session.

17:00 - 19:00 h
Coffee break and poster session.

17:30 - 19:00 h.
STEERING COMMITEE CIBERNED

19:00 -19:15

2013 Young Investigator Award

María Llorens-Martín, PhD

During the day of Monday 22 September, was presented the Young Researcher Award 2013, that recognizes the work of a researcher under the age of 35 years. This year, the award went to María Llorens-Martín, from the Center for Molecular Biology "Severo Ochoa" (CSIC - UAM) and CIBERNED Research Group led by Jesús Ávila for her publication:

Molecular Psychiatry (2013), 1–10

www.nature.com/mp

ORIGINAL ARTICLE

GSK-3β overexpression causes reversible alterations on postsynaptic densities and dendritic morphology of hippocampal granule neurons *in vivo*

M Llorens-Martín[1,2,8], A Fuster-Matanzo[1,2,8], CM Teixeira[2,3,4,8], J Jurado-Arjona[1,2], F Ulloa[4], J deFelipe[5], A Rábano[6], F Hernández[1,2,7], E Soriano[2,3,4] and J Ávila[1,2,7]

ABSTRACT

Adult hippocampal neurogenesis (AHN) is crucial for the maintenance of hippocampal function. Several neurodegenerative diseases such as Alzheimer's disease (AD) are accompanied by memory deficits that could be related to alterations in AHN. Here, we took advantage of a conditional mouse model to study the involvement of glycogen synthase kinase-3β (GSK-3β) overexpression (OE) in AHN. By injecting GFP- and PSD95-GFP-expressing retroviruses, we have determined that hippocampal GSK-3β-OE causes dramatic alterations in both dendritic tree morphology and post-synaptic densities in newborn neurons. Alterations in previously damaged neurons were reverted by switching off the transgenic system and also by using a physiological approach (environmental enrichment) to increase hippocampal plasticity. Furthermore, comparative morphometric analysis of granule neurons from patients with AD and from GSK-3β overexpressing mice revealed shared morphological alterations. Taken together, these data indicate that GSK-3β is crucial for hippocampal function, thereby supporting this kinase as a relevant target for the treatment of AD.

19:15 – 20:00

CLAUSTRO CIBERNED

08:00 h.

MEETINGS OF COOPERATIVE PROJECTS.

08:30 - 10:30 h.

SCIENTIFIC SESSION IV:

Novel mechanisms of neurodegeneration and neuroprotection.

Chairperson: Dr. José Rodríguez.

CIBERNED, Autonomous University of Barcelona, Spain.

08:30 h.

Protection of neuronal death and axonal degeneration by FAIM-L.

Dr. Bruna Barneda.

CIBERNED, Vall d´Hebron University Hospital, Barcelona, Spain.

09:00 h.

BDNF and STEP: dancing partners in the regulation of synaptic plasticity.

Dr. Ana Saavedra.

CIBERNED, University of Barcelona, Spain.

9:30 h.

Complex regulation of prion biomarkers expression in sporadic Creutzfeldt-Jakob Disease (sCJD).

Dr. Franc Llorens.

CIBERNED, Bellvitge Institute of Biomedical Research, Barcelona, Spain.

10:00 h.

Huntington´s disease as a tauopathy.

Dr. José Javier Lucas.

CIBERNED, Center of Molecular Biology "Severo Ochoa", CSIC-UAM, Madrid, Spain.

Dr. Bruna Barneda
CIBERNED

Obtained her bachelor in biology in 2003. Then joined Dr. J. Rodríguez-Álvarez group at Universitat Autónoma de Barcelona and develop her PhD research focused in mechanisms involved in the control of neuronal survival. In 2009 she obtained her PhD in Biochemistry and molecular biology at the Universitat Autónoma de Barcelona. Next, she moved from neuroscience to epigenetics, and performed a post-doc with Dr. Maribel Parra group at the Epigenetics and Biology of the Cancer Unit at the IDIBELL (2010-2013) where she studied the role of HDAC7, an epigenetic factor, in hematopoietic system development, and the consequences of HDAC7 dysfunction in hematopoietic malignancies progression. In 2013, she returned to neuroscience field by joining the research group Cell signalling and Apoptosis of Dr. J.X Comella at the VHIR, where she develops her research as postdoctoral investigator. Nowadays, her major research interest is study the relevance of neuroinflammation in Alzheimer disease development.

Dr. Ana Saavedra

CIBERNED

Ana Saavedra graduated in Applied Biology (2000) by the University of Minho, Portugal. From September 2001 to December 2006 she was a PhD student at the Center for Neuroscience and Cell Biology, University of Coimbra, Portugal. In January 2007 she joined in Dr. Jordi Alberch's group at the Departament de Biologia Cel·lular, Immunologia i Neurociències, Facultat de Medicina, Universitat de Barcelona-IDIBAPS with a 2 years post-doctoral fellowship from Fundação para a Ciência e Tecnologia (Portugal), followed a one year fellowship from the same institution, and a CIBERNED contract. From January 2011 to April 2014 Dr. Ana Saavedra was a Juan de la Cierva post-doctoral researcher. Presently, she is a CIBERNED investigator at the same department. During the last 7 years most of her work was focused on the study of alterations in the activity of protein kinases and phosphatases in the context of Huntington's disease. Her current research aims include the study of the regulation of striatal- enriched protein tyrosine phosphatase levels/activity by brain-derived neurotrophic factor and its implications for synaptic plasticity and learning and memory.

Dr. Franc Llorens
CIBERNED

Dr. Franc Llorens earned his Bachelor of Biochemistry from Universitat Autonoma de Barcelona (UAB) in 1999. In 2000 he joined the doctoral program “Biochemistry and Molecular Biology” from the UAB obtaining his PhD award in 2005 working on the role of protein kinases in protein synthesis. Meanwhile he was carrying out university teaching activities as associated professor. Subsequently, he shifted his research into the field of neurodegenerative diseases, working in the Centre for Genomic Regulation (CRG), in the Institute for Bioengineery of Catalonia (IBEC) and in the Institute for Biomedical Research of Bellvitge (IDIBELL). Pursuing his interest in the molecular mechanisms leading to neurodegeneration he joined, in 2012, the Prionforschung group in the Department of Neurology of the University Medical School in Göttingen (Germany) and the German Center for Neurodegenerative Diseases (DZNE) where he is currently focused on the epigenetic modifiers involved in the development of rapidly progressive dementias, mixed forms of dementias and co-morbidities. Dr. Llorens has been the recipient of numerous honours and awards including a PhD fellowship from the Generalitat de Cataluña, the Extraordinary PhD award (UAB) and post-doctoral fellowship (Juan de la Cierva) from the Ministry of Science (Spain) among others.

Dr. José Lucas

CIBERNED

Dr. José Javier Lucas has garnered outstanding advances on the etiology and therapeutics of various neuropathologies such as Huntington's disease, Alzheimer's disease, addiction to psychostimulants and pain. His doctoral stage (1990-1993) performed at CSIC Cajal Institute (Madrid) resulted in important advances on the molecular basis of pain regulation (Oncogene 6:223-7 1991; Neuron 10:599-611 1993) while as postdoctoral fellow at Columbia University (N. York) (1994-1998) he obtained important molecular clues on addictive disorders using knockout mice of the serotonin 1B receptor as an animal model (Mol. Pharmacol. 51:755-763, 1997 and Nature 393:175-178, 1998). Since 1998 he works at Centro de Biología Molecular Severo Ochoa, joint center of CSIC and Universidad Autónoma de Madrid where he was appointed Tenuered Scientist in 2000 and since 2008 he is CSIC-Research Professor. Dr. Lucas also is principal investigator of CIBERNED (Centro de Investigación Biomédica en Red sobre Neurodegeneración). He was the first to demonstrate that neurodegenerative disease are susceptible to revert by generating the first conditional mouse mode of one of these diseases, specifically of Huntington (Cell 101: 57-66, 2000). This work has been cited 653 times. The conditional animal model of Alzheimer's disease by GSK-3 overexpression (EMBO J. 20: 27-39, 2001; cited 554 times) allowed to consolidate GSK-3 as a therapeutic target and he also explored ways to facilitate the use of GSK-3 inhibitors such as lithium for Alzheimer's and bipolar disorder (EMBO J. 26: 2743-54, 2007 and J Clin. Invest. 120:2432-45, 2010). In regard to Huntington's pathogenesis, Dr. Lucas has characterized in-depth the ubiquitin-proteasome system (UPS) and the endoplasmic reticulum stress (ERS) (J. Neurosci. 23:11653-61, 2003, Trends Neurosci 27:66 - 70 2004, PNAS 106:13986-91 2009, J. Neurosci. 30:3675-88 2010, Brain 136:577-92 2013 and Brain 136:1161-76, 2013). His most recent contribution is the discovery of the alteration of the splicing machinery in Huntington leading to a toxic role of tau protein. This work has been published in Nature Medicine (20:881-5, 2014) and highlighted in Nature Reviews Neuroscience 15:564, 2014. In summary, the work of Dr. Lucas is reflected in numerous patents and more than 90 publications in international journals, including the most prestigious as Nature, Cell, Nature Medicine, JCI, Neuron, Brain, EMBO J, or PNAS. These papers have been cited more than 4,800 times with an average of 50 citations per article awith an h index of 35.

10:30 h.

Coffee break and poster session.

11:00 - 12:40 h.

SCIENTIFIC SESSION V:

Progress in Huntington's and ALS.

Chairperson: Dr. José Javier Lucas.

CIBERNED, Center for Molecular Biology
"Severo Ochoa", CSIC-UAM, Madrid, Spain.

11:00 h.

Modeling and treatment approaches for Huntington´s disease using stem cells.

Dr. Leslie M. Thompson.

University of California, Irvine, USA.

11:50 h.

What causes ALS?

Dr. Ammar Al-Chalabi.

King´s College London, Institute of Psychiatry, London, UK.

Dr. Leslie M. Thompson
University of California at Irvine, USA

Since becoming a member of the collaborative research team that identified the Huntington's disease (HD) gene, Dr. Thompson has focused much of her scientific career and energies on understanding how the mutant HD gene causes disease and on developing new treatments for this neurodegenerative disease and applications to Alzheimer's and Parkinson's disease. Her role in the HD project involved the identification and characterization of expressed genes from the HD candidate region. Our laboratory now focuses on translational research by understanding pathogenic mechanisms of neurodegenerative diseases with the goal of slowing or stopping progression through target identification and validation in multiple systems. Several potential drug targets have been discovered by our group that are in various phases of target validation and preclinical and clinical trials, including the potential use of HDAC inhibitors for treatment of HD. Our group was instrumental in describing interactions of the Huntingtin (HTT) protein with transcriptional regulatory proteins. We also showed that the interaction of mutant HTT with CREB-binding protein and other acetyltransferases could reduce their activity and that approaches to compensate for that decrease using "transcription-based therapies", in this case HDAC inhibitors, were a rational approach to development of HD treatments. We have continued to study the underlying mechanisms of transcriptional dysregulation in HD, with applications now to induced pluripotent stem cells (iPSCs) derived from HD and control subjects to study HD. We are working closely with a consortium of investigators to use these iPSCs to study CAG dependent phenotypes with the intent of using them as a platform for drug discovery and mechanistic studies. Initial studies show that a number of key molecular alterations are present in the differentiated iPS cells, including transcriptional dysregulation analyzed at the genomic level. We find similar epigenetic patterns in differentiated HD iPS cells, establishing an "ensemble" that may guide transcriptional dysregulation in HD.

Dr. Ammar Al-Chalabi

King´s College London, Institute of Psychiatry, UK

Ammar Al-Chalabi is the Director of the King's Motor Neuron Disease Care and Research Centre at King's College Hospital and Professor of Neurology and Complex Disease Genetics at King's College London. His research and clinical practice focus on amyotrophic lateral sclerosis (ALS, also known as motor neuron disease). He leads the multinational EU (JPND) funded STRENGTH consortium which uses basic and clinical science to find new ways to treat ALS.

12:40 - 13:40 h.

SCIENTIFIC SESSION VI:

Late-breaking news/poster highlights.

Chairperson: Dr. Teresa Iglesias.

CIBERNED, Institute of Biomedical Research CSIC-UAM, Madrid, Spain.

12:40-12:50 h

Dr. Rafael Fernández-Chacón., University of Seville, Spain.

"CSP –alpha is essential to maintain the quiescence of radial-glia like stem cells in postnatal neurogenesis".

Nieto-González J. L., Mavillard F., Linares-Clemente P., Martínez-López J. A., Pardal R. and Fernández-Chacón R.

12:50-13:00 h

Dr. Ignacio Torres. Cajal Institute CSIC, Madrid, Spain.

"Insulin regulates brain glucose handling through cooperation with insulin-like growth factor I signalling".

Hernández-Garzón E., Fernández A. M., Pérez-Álvarez A., Bascuñana P., De la Rosa R. F., Delgado M., Pozo M. A., Miranda-Vizuete A., Guerrero-Gómez D., Moreno E., Canela E., Mc Cormick P. J., Santi A., Genis L., Trueba A., Araque A., Martin E.D. and Torres I.

13:00-13:10 h

Dr. Ana Isabel Rojo. Autonomous University of Madrid, Spain.

"Transcription factor NRF2 as a new therapeutic target in a preclinical model of Alzheimer disease".

Pajares M., Rada P., García-Yagüe A. J., Núñez A., De Ceballos M.L. Cuadrado A. and Rojo A. I.

13:10-13:20 h

Dr. Francisco Molinet. CIMA, University of Navarra, Spain.

"Resemblance of clinical metabolic using pet imaging in a progressive MPTP primate model of Parkinson´s disease".

Molinet F., Iglesias E., Blesa J., Juri C., Collantes M., Prieto E., Peñuelas I. and Obeso J. A.

13:20-13:30 h

Dr. Andrea Ruiz-Calvo. Complutense University of Madrid, Spain.

"Pattern of mutant huntingtin-induced toxicity in D1R vs. D2R-expressing medium-sized spiny neurons of the mouse striatium".

Ruiz-Calvo A., Bellocchio L., Galve-Roperh I., Guzmán M.

13:30-13:40 h

Dr. Rubèn López-Vales. Autonomous University of Barcelona, Spain.

"CSF1R regulates microgliosis and disease progression in Amyotrophic Lateral Sclerosis".

Martínez-Muriana A., Mancuso R., Francos-Quijorna I., Olmos-Alonso A., Osta R., Navarro X., Perry H., Gómez-Nicola D. and López-Vales R

13:40 h.

Lunch & poster session.

15:30 - 16:30 h.

SCIENTIFIC SESSION VII:

Novel genetics factors in neurodegenerative diseases.

Chairperson: Dr. María Jesús Bullido.

CIBERNED, Autonomous University, Madrid, Spain.

15:30 h.

New protein aggregate cardioskeletal myopathy associated with combined MuRF1 and MuRF3 mutations.

Dr. Montserrat Olivé.

CIBERNED, Bellvitge Institute of Biomedical Research, Barcelona, Spain.

16:00 h.

The primary pathogenic role of muscle stem cells in a new type of muscular dystrophy.

Dr. Carmen Paradas.

CIBERNED, University of Sevilla, Spain.

Dr. Montse Olivé
CIBERNED

Montse Olivé (MD, PhD) did her residence in Clinical Neurophysiology and then trained on clinical and pathology of muscle disorders. She joined the Institute of Neuropathology, at the Bellvitge University Hospital in 2001 where she is in charge of the analysis of muscle biopsies. In collaboration with the Department of Neurology she is also responsible for the clinical and electrophysiological evaluation of patients suffering from muscle disorders. Both the the Institute of Neuropathology and Department of Neurology are referral centres for diagnosis of neuromuscular disorders. Most of her work is dedicated to the clinical and morphological identification and characterisation of genetic neuromuscular diseases in the adult patients. Her main research interest is focused on protein aggregate myopathies and rare structural myopathies. Membership of the World Muscle Society, Société Française de Myologie and Protein Aggregate Myopathies and Rare Structural Myopathies consortiums at the European Neuromuscular Centre. She has over 75 publications in international peer-reviewed journals.

Dr. Carmen Paradas
CIBERNED

Carmen Paradas, MD, PhD is a Neurologist and Clinical Researcher in the Neuromuscular Diseases Unit at Hospital Universitario Virgen del Rocio and Instituto de Biomedicina de Sevilla (HUVR-IBiS), Universidad de Sevilla where she trained as a neurologist. After a one year neuromuscular research training in Dr. Illa's lab at Hospital de Sant Pau (Barcelona), she completed her PhD thesis on dysferlin myopathies and worked as a neurologist with special interest in neuromuscular diseases at HUVR. Her research is focused on the description of new muscular dystrophy phenotypes and identification of the responsible genes. She is leading several research projects, supported by public funding, as an associated researcher at IBiS, and she collaborates with Luis Escudero ("Ramon y Cajal" Investigator at IBiS, and Spanish member in the COST program) in the description of a quantifiable imaging method through network analysis for the diagnosis and follow-up of neuromuscular disorders. As a member of CIBERNED, she is one of the curators of the Spanish neuromuscular diseases database. During two years as postdoc (2012-2013) at Columbia University Medical Center, she has been involved in the North American Mitochondrial Disease Consortium (NAMDC), patient registry and biorepository for the mitochondrial patients in USA and Canada. Her main areas of research are: muscular dystrophies, distal myopathies, identification of new genes in neuromuscular disorders and imaging in neuromuscular disorders (muscle MRI and quantifiable imaging method through network analysis).

16:30 h.
Coffee break.

17:00 - 18:00 h.
SCIENTIFIC SESSION VIII:
Other institutions.
Chairperson: Dr. Ramón Trullás.
CIBERNED, Institute of Biomedical Research
IDIBAPS-CSIC, Barcelona, Spain.

17:00 h.
Genome-wide analysis of Alzheimer´s disease (AD): A huge international effort to uncover genetic factors linked to AD etiology.
Dr. Agustín Ruiz & DEGESCO.
ACE Foundation.

17:20 h.
Analysis of the genetic influence in brain structure and function: the ALFA (Alzheimer and Families project).
Dr. Juan D. Gispert.
Barcelonabeta Brain Research Centre. Pasqual Maragall Foundation.

17:40 h.
The Vallecas Project for early detection of Alzheimer´s disease (CIEN Foundation and Queen Sofia Foundation).
Dr. Miguel Medina.
CIBERNED-CIEN Foundation, Madrid, Spain.

Dr. Agustín Ruiz

ACE Foundation

Dr. Agustin Ruiz is the current Director of Research and CSO of ACE Foundation. Barcelona Alzheimer Treatment & Research Center (Barcelona, Spain). Born in Utrera, Sevilla (August 10, 1969), he graduated in Medicine and Surgery and earned a Ph.D. in Molecular and Cell Biology from the University of Seville. For eight years he performed research tasks in the Unit of Medical Genetics and Prenatal Diagnosis of the Virgen del Rocío University Hospital, Seville (1993-2001). There he received the Extraordinary Doctoral Award by the University of Seville (2000) for his thesis work. Later on, he promoted and founded six biotechnology companies receiving the 50K Award for Best Business Idea and Best Business Plan in the field of Biotechnology by the San Telmo International Institute. The result of this activity with their partners received the 2008 Award for Business Excellence in Innovation by the Region of Andalusia. In 2011 he moved to Barcelona to direct the research programs at the ACE Foundation Barcelona Alzheimer's Treatment and Research Center. Agustín Ruiz has published 111 articles in indexed journals such as: JAMA;,JCEM, Annals of Internal Medicine, Journal of Experimental Medicine, Nature Genetics, Lancet Neurology, Molecular Psychiatry, Nature Protocols, Hypertension or Genome Medicine among others. He is co-author of seven patents related to the molecular diagnosis of complex diseases and bioinformatics tools for genomic research. He has received 34 projects awarded for funding by regional, national and European competitive agencies. He has participated in the drafting of several chapters in scientific books and reviews in national journals. He is a reviewer of projects of the European Commission and is on the scientific projects review panels in several European countries and in high impact journals. His research interests focus on the application of genomic technologies in medicine. He has participated in the identification of numerous genetic factors linked to different diseases and cloning of 14 genes related to Alzheimer's disease.

Dr. Juan D. Gispert

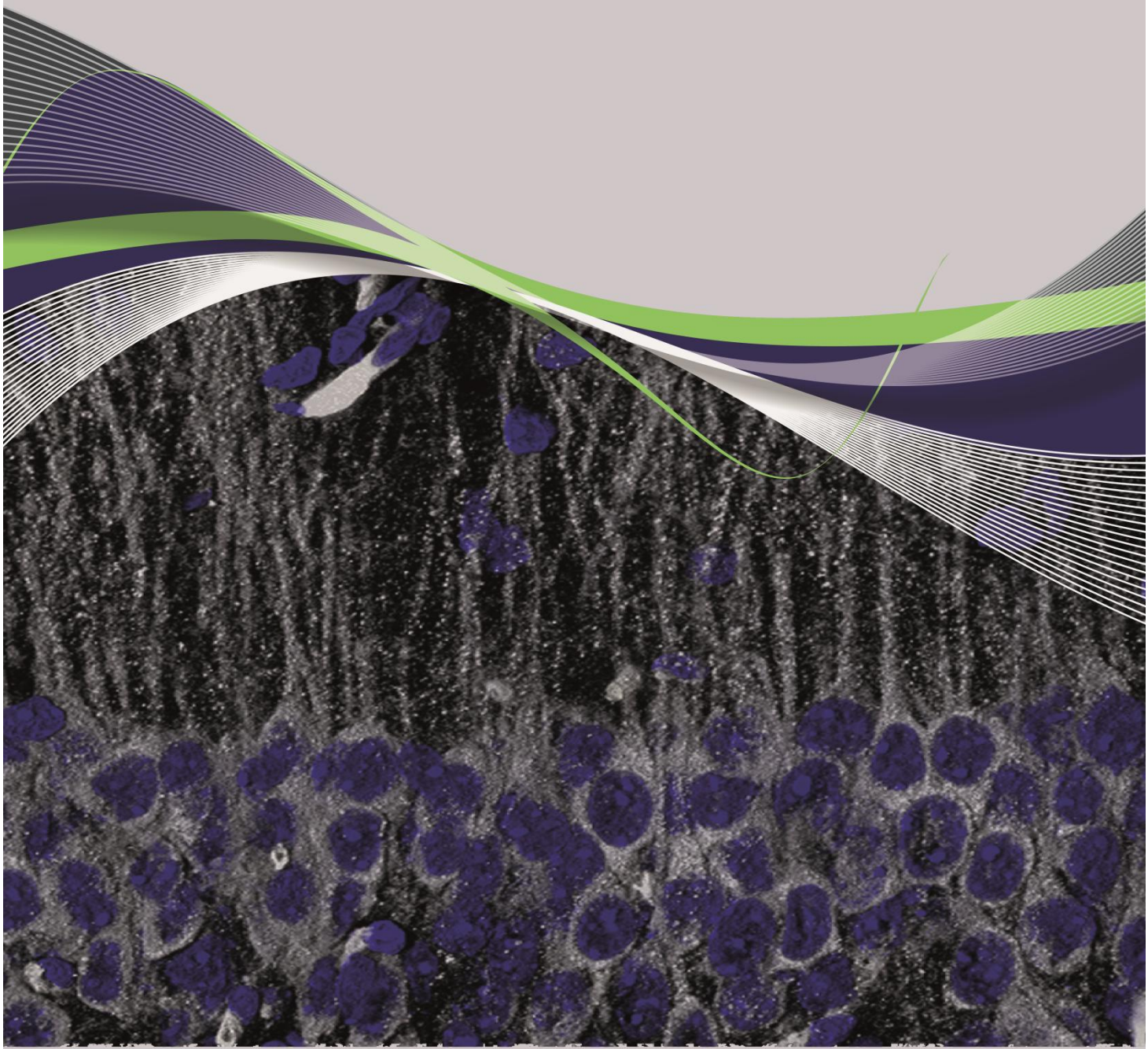
Pasqual Maragall Foundation

Juan D. Gispert is since 2011 the scientific responsible for neuroimaging in the BarcelonaBeta Brain Research Center - Pasqual Maragall Foundation and he is an expert in acquisition, processing and analysis of neuroimages. Previously, Dr. Gispert was scientific director of the Institut d'Alta Tecnologia, a center for molecular imaging where different radiotracers were developed for both clinical, for example, several ligands for beta-amyloid plaques, as preclinical research, studying different models of brain pathology and aging. Dr. Gispert has coauthored more than 60 scientific articles, usually serves as reviewer in the field of neuroimaging for scientific journals and funding agencies and has participated in various clinical trials.

Dr. Miguel Medina
CIBERNED

Dr. Miguel Medina earned his PhD in Biochemistry and Molecular Biology from the Universidad Autónoma of Madrid. After a few years of postdoctoral work in the field of virology and animal health, Dr. Medina became interested in the field of neuroscience and human pathology and since then has acquired extensive research experience in the study of the molecular basis of neurodegenerative diseases. He has worked in various academic centers of maximum scientific prestige, having been a postdoctoral fellow at the Center of Molecular Biology "Severo Ochoa" in Madrid (1993-1995), and then at the Center for Neurologic Diseases, Harvard Medical School in Boston (1996-2001), where he was appointed as a Harvard Junior Faculty, as well as an independent Senior Scientist at the Cavalieri Ottolenghi Scientific Institute of the University of Turin (2001-2003). From 2003 until 2007 he headed the Drug Discovery Department of the Spanish biopharmaceutical company Noscira S.A., where he built from scratch and spearheaded a solid scientific platform for searching, identifying and isolating compounds (both synthetic and natural from marine organisms) as potential therapeutic agents for the treatment of neurodegenerative diseases, in particular Alzheimer's disease (AD). In November 2007 he became Research Director at Noscira, leading a research team that moved two novel compounds from early discovery into phase II proof of concept clinical trials for AD and progressive supranuclear palsy (PSP). In March 2012 he was appointed as Deputy Scientific Director of CIBERNED (Center for Networked Biomedical Research in Neurodegenerative Diseases). He is the Spanish representative in the COEN (International Network of Centres of Excellence in Neurodegeneration) Oversight Group and serves as a member of the External Scientific Advisory Board of the CIEN Foundation and the Research Ethics Committee of the Human Brain Project. He is also a member of the editorial advisory boards of the international journals Recent Patents on Biothecnology, Recents Patents on CNS Drug Discovery (Regional Editor), Journal of Bioequivalence and Bioavailability, Aging & Neurodegeneration, and Journal of Alzheimer's disease (Senior Editor). Dr. Medina has authored over 75 peer-reviewed scientific publications and is listed as co-inventor of 25 patents.

Abstracts



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P 1

EARLY EPIGENETIC MODULATION IN FEMALE SAMP8 ON THE BASIS OF ACCELERATED SENESCENT

C.Griñan-Ferre, E. Apostolopoulou, S. Toffoletto, A. Camins, M. Pallàs

With the increasing of life expectancy, ageing and age-related cognitive impairments are becoming one of the most important issues for human health. Adult neurogenesis is directly implicated in brain ageing, and both neurogenesis and ageing seem to be controlled at the epigenetical level. This epigenetic mechanisms act during the development of the nervous system, in which the play an important role in switching on genes related to a particular phenotype and in permanently silencing those genes directly involved in the development of others cell lineages. In fact, neurogenesis takes place by desinhibition of neurogenic genes, which are inactive in progenitors cells. In this context, repressor complex REST inhibits the expression of neurogenic genes not only by binding to their cis-elements but also by upregulating histone deacetylase (HDAC) activity. In addition, neurogenic gene transcription is reduced due to the demethylation and deacetylation of histones caused by several proteins that form part of repressor complex REST.

In this work, we focus on the participation of the repressor complex REST in the senescence process and in particular in the neurogenesis formation at 1 month in SAMP8 mice, a model of accelerated senescence, that presenting symptoms associated with aging processes at an early age. Through western blotting analysis we found that levels REST and the components of REST-complex are increased at 1 month old SAMP8 compared to age-matched SAMR1 mice and decreased levels of doublecourtin (DCX) a selective marker of cells committed to the neuronal lineage and through real-time PCR analysis we found changes in HDAC2 another component of REST complex also in BRAF35/HMG20b, activator of REST complex and Neurod6 that is a REST-responsive gene, the overexpression of which results in neural differentiation of murine embryonic stem (ES) cells. The increase in LSD1 level was confirmed also by immunohistochemistry. Besides SAMP8 mice display decreased NeuN staining and increased GFAP. Together with this we reported a marked deficit in memory tasks for SAMP8 mice.

These evidences could be a preliminary clue about the involvement of epigenetic through repressor complex REST in ageing and neurogenesis process.

ACKNOWLEDGEMENTS: SAF2012-39852, SAF-2011-23631-"Ministerio de Educación y Ciencia"

P 2

ALTERATIONS IN ENERGY METABOLISM IN THE BRAIN OF APPSwe/PS1dE9 MOUSE MODEL OF ALZHEIMER'S DISEASE

Ignacio Pedrós, Dmitry Petrov, Francesc Sureda, Mercè Pallàs , Manuel Vázquez-Carrera, Jaume Folch and Antoni Camins Dept. Pharmacology & Therapeutic Chemistry. Institute of Biomedicine. School of Pharmacy. University of Barcelona. SPAIN. Unitats de Bioquímica i Farmacologia, Facultat de Medicina i Ciències de la Salut, Universitat Rovira i Virgili, Reus (Tarragona), Spain.

Background: The present study had focused on the behavioral phenotype and gene expression profile of molecules related to insulin receptor signaling in the hippocampus of 3 and 6 months-old APPswe/PS1dE9 (APP/PS1) transgenic mouse model of Alzheimer's disease (AD).

Results: Elevated levels of the insoluble Aβ (1-42) were detected in the brain extracts of the transgenic animals as early as 3 months of age, prior to the Aβ plaque formation (pre-plaque stage). By the early plaque stage (6 months) both the soluble and insoluble Aβ (1-40) and Aβ (1-42) peptides were detectable. We studied the expression of genes related to memory function (Arc, Fos), insulin signaling, including Insulin receptor (Insr), Irs1 and Irs2, as well as genes involved in insulin growth factor pathways, such as Igf1, Igf2, Igfr and Igfbp2. We also examined the expression and protein levels of key molecules related to energy metabolism (PGC1-α, and AMPK) and mitochondrial functionality (OXPHOS, TFAM, NRF1 and NRF2). 6 months-old APP/PS1 mice demonstrated impaired cognitive ability, were glucose intolerant and showed a significant reduction in hippocampal Insr and Irs2 transcripts. Further observations also suggest alterations in key cellular energy sensors that regulate the activities of a number of metabolic enzymes through phosphorylation, such as a decrease in the Prkaa2 mRNA levels and in the pAMPK (Thr172)/Total APMK ratio. Moreover, mRNA and protein analysis reveals a significant downregulation of genes essential for mitochondrial replication and respiratory function, including PGC-1α in hippocampal extracts of APP/PS1 mice, compared to age-matched wild-type controls at 3 and 6 months of age.

Conclusions: Overall, the findings of this study show early alterations in genes involved in insulin and energy metabolism pathways in an APP/PS1 model of AD. These changes affect the activity of key molecules like NRF1 and PGC-1α, which are involved in mitochondrial biogenesis. Our results reinforce the hypothesis that the impairments in both insulin signaling and energy metabolism precede the development of AD amyloidogenesis.

This work is supported by grants: SAF2011-23631; 2009/SGR00853 and CB06/05/00 24,CIBERNED.

P 3

MDMA is not able to produce a classic dopaminergic toxicity in the APPswe/PS1dE9 striatum but potentiates the Aβ deposition

Abad, S.; Ramón, C.; Camarasa, J.; Pubill, D.; Camins, A.; Escubedo, E.

Background: MDMA, a recreational drug commonly used by adolescents, causes neurotoxicity and may alter the performance in some behavioral tests. In mice is a relatively selective dopaminergic neurotoxin. Many patients of Alzheimer's disease (AD) develop parkinsonian symptoms and constitute a worse prognosis, with a faster cognitive decline. The aim of the present study was to elucidate whether MDMA favors the nigrostriatal dysfunction in a model of AD.
Methods: Male mice C57BL/6, wild type (WT) or double transgenic APPswe/PS1dE9 (APP), 1-month-old were treated simulating a recreational pattern using the following dose schedule: 3 s.c. doses/day (3 h), once/week for 8 weeks. Mice at 3 or 6 month old were submitted to the open field test (OF). Animals were killed for measurement of neurotransmitters levels by HPLC-EC and determination of tyrosine hydroxylase (TH), dopamine transporter (DAT), and 4-hydroxynonetal (4-HNE) by western blotting in striatum. Also, Immunofluorescent of TH was performed in the Substantia Nigra (SN). Thioflavin S staining was performed for amyloid-β (Aβ) deposition.
Results: We measured the neurotransmitters levels in the striatum at 3 and 6 month old and we observed a decrease of dopamine and its metabolite DOPAC at 3 months old in MDMA wild-type (WT) animals but did not in MDMA transgenic mice, that ran in parallel with the lower locomotor activity showed in MDMA-WT animals. All these parameters were recovered at 6 months old. MDMA produced a decrease of the number the TH-positive neurons in the SN at 3 months old APPswe/PS1dE9 that remained constant at 6 months. The amphetamine derivate did not cause a decrease either TH or dopamine transporter (DAT) at 3 or 6 months in MDMA-treated animals. However, MDMA increased the amyloid plaque deposition in the striatum at 6 month old detected by Thioflavin S staining.
Conclusions: This study suggests that MDMA is not able to produce the classic dopaminergic toxicity in transgenic mice APPswe/PS1dE9, nevertheless potentiates the Aβ deposition. Together, the present findings suggest that both mechanism nigroestriatal dysfunction and Aβ deposition are not correlated each other.
This work is supported by grants: SAF2010-15948; 2009/SGR977 ; SGR00853. Also SAF2011-23631; 2009/SGR00853 and CB06/05/00 24,CIBERNED.

P 4

Anatomical substrate of impaired cortical oscillatory coupling in mild cognitive impairment.

Gonzalez-Escamilla G, Atienza M, Cantero JL
Our current knowledge about the anatomical substrate of impaired cortical oscillatory coupling in mild cognitive impairment is still rudimentary. Here, we show that both resting-state oscillatory coupling and its anatomical correlates clearly distinguish healthy older (HO) adults from individuals with amnestic mild cognitive impairment (aMCI). aMCI showed failures in neural-phase coupling of resting-state electroencephalographic alpha activity between fronto-temporal and parietal regions. We further investigated whether plasma concentrations of Abeta oligomers (Aβ40 and Aβ42) accounted for impaired patterns of oscillatory coupling in aMCI. Results revealed that decreased plasma Aβ42 was associated with augmented coupling of parieto-temporal regions in HO subjects, but no relationship was found in aMCI. Oscillatory coupling of frontal regions was also significantly reduced in aMCI-ApoE ε4 carriers compared to noncarriers, although neither neuroanatomical nor plasma Aβ changes accounted for this difference. However, failures of oscillatory coupling in aMCI were negatively related to volume of the angular gyrus, and positively related to volume of the precuneus and the splenium of the corpus callosum. Previous evidence suggests that all these regions are neuropathological targets of AD. Together, these data shed light on how the MCI status modifies anatomo-functional relationships underlying coordination of large-scale cortical systems in the resting-state.

P 5

APOE ?4 in mild cognitive impairment affects compensatory neural networks during associative encoding

Prieto del Val L, Cantero JL, Atienza M
Elderly subjects with amnestic mild cognitive impairment (aMCI) benefit less from semantic congruent cues at encoding, and the presence of the apolipoprotein E (APOE) ε4 makes this benefit even smaller. However, neural correlates of this deficit are unknown to date. This work was aimed at investigating cortical oscillatory correlates of successful encoding of face-location associations preceded by either semantically congruent or incongruent cues, in healthy old (HO), aMCI APOE ε4 carriers and noncarriers. Differences in beta-oscillatory dynamics indicated that aMCI ε4 carriers are unable to activate right temporal regions involved in associative memory and congruency benefit in HO subjects. Interestingly, the activation was extended to further cortical regions in aMCI through alpha/beta oscillations, regardless of the ApoE genotype. Enhanced memory in ε4 noncarriers was only paralleled by activation of a distributed fronto-temporo-parietal network. On the contrary, the redundant prefrontal activation shown by aMCI ε4 carriers did not prevent impaired memory performance. All together, these results reveal that functional network dynamics are constrained by the presence of APOE ε4 in aMCI subjects. While the lack of this allele promotes activation of perceptual and semantic compensatory networks, its presence is linked to reduced processing efficiency and capacity in aMCI status.

P 6

Characterization of the TNF?-induced Fas expression and activation in neuroblastoma cells: implications for its use in the treatment of neuroblastoma tumors

Koen M.O. Galenkamp, Paulina Carriba, Laura Planells-Ferrer, Jorge Urresti, Elena Coccia, Joaquín Lopez-Soriano, Bruna Barneda-Zahonero, Miguel F. Segura, Joan X. Comella

Development of new treatments against neuroblastoma (NBL) tumors is desirable due to the high mortality rate in the high-risk groups. Here, we set out to study the possible anti-tumor effects of TNFα and FasL, which have been rarely studied in a NBL setting. We show that TNFα is able to increase FasL-induced cell death by a mechanism that involves NFκB-mediated Fas mRNA transcription. This increase in Fas mRNA is translated in an increment in Fas protein levels, which in turn, concurs with an increased exposure of Fas on the plasma membrane. Thereby, TNFα is able to sensitize NBL cells to FasL-induced cell death. Next, we explore the possibility to use TNFα in combination with established NBL treatments that have been reported to induce cell death through the Fas / FasL pathway. We demonstrate that TNFα is able to increase cisplatin and etoposide-induced caspase-8 cleavage, which correlates with an augmentation in cell death. Lastly, we assess the heterogeneity of Fas expression in NBL cells. We show that, within the studied NBL cell lines, there is a population that responds to TNFα treatment with an increase in Fas expression that primes for FasL-induced cell death. This increase in Fas expression is only observed in cell lines that show TNFα-induced sensitization to treatment with the chemotherapeutics cisplatin and etoposide. These finding reveal the underlying mechanism that explains the priming to cisplatin and etoposide-induced cell death by TNFα in NBL. In conclusion, our study proposes that TNFα and FasL have the potential to be used in the treatment of NBL patients.

P 7

BCl-xL is required for protection from etoposide-induced cell death by Liefuard/FAIM2

Jorge Urresti, Stéphanie Reix, Rana Moubarak, Laura Planells-Ferrer, Koen Galenkamp, Joaquin López-Soriano, Bruna Barneda & Joan X. Comella

Death receptors (DRs) are members of the tumor necrosis factor receptor superfamily. They are mainly involved in the extrinsic apoptotic pathway but they are also able to regulate other cellular processes such as cell proliferation and differentiation. LFG is a DR antagonist that specifically blocks Fas induced apoptosis, although its mechanism of action is still unknown. Here, we perform an extensive analysis of LFG subcellular localization. LFG localizes mainly to the ER and Golgi. This pattern of subcellular localization is characteristic of TMBIM family proteins, which LFG belongs to. Members of this family have been found to interact with Bcl-2 family members and modulate its activity. In this regard, we show that LFG interacts with Bcl-xL and Bcl-2 but not with Bax or Bak. We also report that LFG is able to protect only Type II cells from Fas induced apoptosis a process that usually needs an amplification step through the mitochondria involvement. However, LFG itself is not located at the mitochondria, which opens the question of a possible role of LFG in the ER in FasL induced type II cell death. Indeed, we find that LFG inhibits calcium release from the ER after FasL stimulation, and this process correlates with LFG protection of Fas induced apoptosis. Thus, our data suggests the existence of an initiation step in the induction of cell death in type II cells that involves calcium mobilization from the ER, and that this step can be modulated by LFG.

P 8

SYNAPTIC PATHOLOGY IN PS1/APP ALZHEIMER MICE HIPPOCAMPUS

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Cognitive impairment in Alzheimer's disease (AD) is likely caused by synaptic dysfunction prior to neuronal loss. We have previously characterized the neuronal/axonal vulnerability in PS1M146L/APP751SL mice hippocampus. Plaque-associated abnormal swellings of neuronal processes represent the first indicator of disease development and might compromise neuronal integrity and hippocampal synaptic function. Here, we examined by cellular and molecular approaches the axonal/synaptic nature of dystrophic neurites, and the loss of vesicles density in presynaptic terminals along with the progressive accumulation of autophagic structures and Abeta within hippocampal synaptosomes in our transgenic AD model. Neuritic pathology occurred from early ages associated to amyloid pathology onset in the hippocampus and worsened during the model lifetime. All fibrillar amyloid deposits were decorated with dystrophic neurites of axonal nature. Our ultrastructural study showed large dystrophic presynaptic elements that displayed a considerable accumulation of of autophagic vesicles and on contrary fewer synaptic vesicles. In concordance, axonal dystrophies were immunopositive for the autophagic marker LC3, some of them exhibited both LC3-II and synaptophysin labeling in varying degrees. Moreover, quantitative Western-blots revealed a progressive increase in levels of LC3-II and monomeric Abeta within PS1/APP synaptosomes during the aging. Our findings are consistent with early impaired autophagy proteolysis leading to the LC3-II vesicles build-up within dystrophic axons/synapses, which might contribute to both Abeta accumulation and presynaptic efficiency reduction. Moreover, extracellular amyloid deposits may have a deleterious area of influence with a synaptotoxic effect. Therefore, this work emphasized the structural and functional pathology within axons and synaptic terminals in the hippocampus of our AD model, and their contribution to amyloid accumulation. Supported by grants FIS-PI12/01439 (JV) and FIS-PI12/01431 (AG).

P 9

RELATIONSHIP BETWEEN AMYLOID PLAQUE PATHOLOGY AND GLIAL CELLS IN ALZHEIMER MICE HIPPOCAMPUS

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Amyloid-beta plaques are a defining neuropathological hallmark of Alzheimer's disease (AD) and their development is intimately linked to activated astrocytes and microglia. However, the role of these activated glial cells in AD pathogenesis is unclear. Here we examined plaque-glia interactions in the hippocampus of PS1M146L/APP751SL transgenic mouse model by immunohistochemistry at both light and electron microscopy. In addition, we studied the effect of chronic oral lithium treatment on plaque/glia relationship and plaque toxicity in the same AD model. This model develops plaques at early ages (3-4 months) typically surrounded by axonal/synaptic dystrophies, intermixed with both microglial and astroglial processes. The number and size of plaques increased with age. Oligomeric Abeta forms a halo around plaques and this toxic halo showed a plaque size-dependent increase. The ultrastructural analysis revealed numerous microglial processes in intimate contact with the fibrillar component of the plaque. Also, astroglial cytoplasmic processes interdigitated with fibrillar extensions of plaques, especially in larger ones. The astrocyte-plaque contact area was characterized by a virtual lack of glial filaments and other organelles. Lithium treated animals developed smaller plaques characterized by higher Abeta compaction, reduced oligomeric-positive halo and therefore with attenuated capacity to induce neuronal damage. This switch of plaque quality by lithium could be mediated by astrocyte activation and the release of heat shock proteins, which concentrated in the core of the plaques These results highlight the therapeutic potential of glial cells to modulate plaque toxicity which might constitute a novel promising and innovative approach to develop a disease-modifying therapeutic intervention against AD. Supported by grants FIS-PI12/01439 (JV) and FIS-PI12/01431 (AG).

P 10

Normal ageing in the rat and pathological ageing in human Alzheimer's disease decreases FAAH activity: Modulation by cannabinoid agonists

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Anandamide (AEA) is an endocannabinoid involved in several physiological functions including neuroprotection. AEA is synthesized on demand and its endogenous level is regulated through its degradation, where fatty acid amide hydrolase (FAAH) plays a major role. The aim of this study was to characterize AEA breakdown in physiological and pathological ageing and its regulation by CB1 and CB2 agonists. FAAH activity was analysed in an independent cohort of human cortical membrane samples from control and Alzheimer's disease (AD) patients, and in membrane and synaptosomes from adult and aged rat cerebrocortical. Our results demonstrate that FAAH activity: (a) Decreases in frontal cortex from patients with AD and this effect is mimicked by Aβ1-40; (b) Increases and decreases in aged cerebrocortical membrane and synaptosomes, respectively; (c) In the presence of JWH-133, a CB2 selective agonist, c.i) increases slightly in human controls; c.ii) decreases in adults and it is completely abolished in aged rat cerebrocortical membrane; and c.iii) decreases in adult and aged rat cerebrocortical synaptosomes; (d) In the presence of WIN 55,212-2, a mixed CB1/CB2 agonist, d.i) decreases in controls and increases in AD patients; and d.ii) decreases in adult and aged rat cerebrocortical membrane and synaptosomes. Although a similar profile is observed in FAAH activity between aged synaptic endings and AD brains, it is differently modulated by CB1/CB2 agonists. This modulation leads to a reduced availability of AEA in AD and to an increased availability of this endocannabinoid in ageing.

P 11

Amyloid beta oligomers regulate oligodendrocyte differentiation and myelination

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Amyloid beta (Abeta) oligomers are key peptides involved in Alzheimer´s disease (AD) pathogenesis. The effects of these oligomers on white matter, and specifically on oligodendrocytes (OLG) are still poorly understood, even though their damage may contribute to cognitive decline in AD. Here, we have investigated the role of Abeta oligomers in OLG differentiation and myelination in vitro and in vivo. Using a panel of developmental stage-specific antigenic markers, we observed that Abeta oligomers modified the differentiation pattern, regulating the transition of early progenitors to the late progenitor stage (O4 positive cells) and to the inmature to mature OLG stage (MBP positive cells) in OLG in vitro. To further investigate the pathway underlying Abeta-mediated OLG differentiation, we analyzed the phosphorylation levels of three key proteins involved in myelin synthesis, AKT, ERK and CREB. We found that Abeta oligomers promoted a sustained AKT dephosphorylation, and ERK and CREB phosphorylation and the specific pharmacological inhibition of these pathways reduced the Abeta-induced MBP upregulation in cultured OLGs. Furthermore, Abeta oligomers increased the MBP levels in cultured cerebellar slices in control and in lysolecithin-induced demyelination conditions. This Abeta-mediated myelin upregulation was confirmed in the corpus callosum of a mouse model of AD. Our data suggest that Abeta oligomers induce OLG differentiation through MAPK/ERK, PI3K/AKT and PKA/CREB signaling pathways, which may be relevant to understand AD pathophysiology.

P 12

Adenosine A1 Receptor Inhibits Neurogenesis But Sustains Astrogliogenesis in Multipotent Neural Cells from Post-Natal SVZ

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Excitotoxic concentration of extracellular purines is among the factors inhibiting adult neurogenesis during neurodegenerative diseases. We previously demonstrated that extracellular ATP released during oxygen and glucose deprivation inhibited adult neurogenesis from subventricular zone (SVZ) through the activation of specific P2X receptors. Here we wanted to study the effect of adenosine, the natural product of ATP hydrolysis, in modulating neuronal differentiation and neurogenesis from the SVZ. We demonstrated by immunofluorescence and citofluorimetry that high concentration of adenosine (100□M) can reduce neuronal differentiation of neurospheres cultures generated from postnatal SVZ. All the adenosine receptors (A1, A2a, A2b and A3) are expressed in this cells but only A1 is involved in the inhibition of neuronal differentiation, as demonstrated by qRT-PCR, Western blot and specific gene silencing. Furthermore, activation of A1 receptor induced the downregulation of a multitude of genes related with neurogenesis as demonstrated by genomic analysis.

We found that the mechanism by which adenosine inhibits neuronal differentiation involves the release of IL10 and further activation of the Bmp2/SMAD3 pathway sustaining indeed astrogliogenesis.

In vitro data were confirmed also in in vivo neurogenesis. After intra cerebral ventricular infusion of the A1 agonist CPA we found a drastic reduction of neurogenesis and the parallel increase of astrogliogenesis in the olfactory bulb of adult rats. With this work we contribute to the knowledge of the purinergic mechanisms that regulate adult neurogenesis, especially in pathological condition when purines are released at citotoxic concentrations. Moreover, we also suggest a critical role of IL10, independent of the neuroinflammation, in balancing the differentiation to neurons or astrocytes.

P 13

CRTC1 nuclear translocation is critical for hippocampal-dependent associative memory

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Associative learning deficits are common in dementia patients but the molecular mechanisms underlying impairments of associative emotional memory in neurodegeneration remain largely unknown. In this study, we examined the effects of context-dependent learning on nuclear translocation and function of the transcriptional effector CREB regulated transcription coactivator 1 (CRTC1). By using fear conditioning, we found that contextual fear learning triggers rapid translocation of CRTC1 from the cytosol and dendrites to the nucleus of CA3 hippocampal neurons. CRTC1 nuclear translocation by context fear learning is associated with CRTC1 dephosphorylation at Ser151, a residue critical for transcriptional activation. Contextual fear learning induces a differential expression of the CREB target genes, including the Nr4a family members Nr4a 1, 2 and 3. Notably, reduced CRTC1 nuclear translocation and transcription is associated with long-term memory deficits in a mouse model of neurodegeneration lacking the presenilin-1 and -2 genes, while adeno-associated viral-mediated CRTC1 overexpression rescues contextual fear memory and transcriptional deficits in PS mutant mice. Taking together, our results suggest a critical role of CRTC1 nuclear translocation and transcriptional function in contextual memory encoding, and provide evidence that enhancing CRTC1 function ameliorates associative memory deficits during neurodegeneration. This study was supported by the following grants from the Ministerio de Economia y Competitividad: SAF2010-20925, SAF2013-43900, CIBERNED CB06/05/0042 and Generalitat de Catalunya (SGR2009-1231).

P 14

The carboxyl-terminal domain of tetanus toxin could prevent Alzheimer's disease

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Several therapeutic strategies have been proposed to prevent Alzheimer's disease (AD). Recently it has been shown the carboxyl-terminal domain of the heavy chain of tetanus toxin (Hc-TeTx), a non-toxic protein prevent neuronal death by activation of signaling cascades as neurotrophins do. Neurotrophins might have therapeutic relevance to AD, but there are several disadvantages that complicate their administration. Hc-TeTx is able to elude many of the problems associated with neurotrophin administration, and might therefore be used as a therapeutic agent in AD treatment.

The objectives of the present study were first to investigate the effect of local hippocampal administration of Hc-TeTx on spatial memory and neuronal death of Aβ(25-35)-treated rats and second, to investigate its effects in early spatial memory deficits and some specific AD markers in APPSwe,Ind transgenic mice. To this end, confocal imaging analysis of the hippocampus was used to compare pathological markers in APPSwe,Ind mutant mice and wild type mice, with and without previous administration of Hc-TeTx. Our results suggest that acute intrahipocampal microinfusion of Hc-TeTx may protect neurons against Aβ(25-35)-caused neurotoxicity by inhibiting inflammatory process and neuronal death. Morever, APPSwe,Ind transgenic mice that received intraperitoneal Hc-TeTx injections from the age of 3 months show a significant reduction of β-amyloid (Aβ) levels in the hippocampal cornu ammonis 1 (CA1) region. Hc-TeTx might therefore be used in early stages of AD to halt disease progression. In both animals models Hc-TeTx improve spatial memory, and taking into consideration the well-established properties of neurotropism, retrograde axonal transport, and half-live within the CNS, Hc-TeTx might prove to be a good therapeutic tool in Alzheimer's disease.

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P 15

cLTD mediated changes in synaptic AMPA receptors is associated to changes in postsynaptic density scaffold proteins.

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Abstract: Excitatory synaptic transmission is tightly regulated by total number and activation of AMPA receptors (AMPAR) present at the synapse. Synaptic AMPARs localization is closely related with NMDA receptor (NMDAR) activity. Current evidences suggests that AMPARs are inserted into the postsynaptic membrane during LTP and could be removed from the membrane during LTD. Dephosphorylation of GluA1 at Ser845 and enhanced endocytosis could be critical events in the modulation of LTD. Moreover, changes in scaffold proteins from the postsynaptic density (PSD) could be also related to AMPAR regulation in LTD. In the present study we have analyzed the effect of chemical LTD (cLTD) on AMPAR and AKAP150 levels in cultured cortical neurons. cLTD reduces surface expression of GluA1 and GluA2 AMPAR subunits and GluA1 phosphorylation at Ser845. Moreover cLTD induces concomitant changes in AKAP79/150 and PSD95 protein levels that are dependent on calcineurin (CaN) and proteosome activation since pharmacological inhibition of CaN or proteosome activity revert cLTD-mediated changes in AKAP79/150 and PSD95. Since PSD95 and AKAP79/150 are synaptic proteins that has been proposed to function as a signaling scaffold that regulates phosphorylation, channel activity, and endosomal trafficking of AMPAR, the cLTD-mediated changes in these proteins could be related to a deregulation of synaptic AMPA receptors in LTD.

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P 16

Characterization of the cerebrospinal fluid proteome in the search for biomarkers of preclinical Alzheimer's Disease

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Background: Synaptic loss is central to early Alzheimer's Disease (AD) pathogenesis. We hypothesize that markers of synaptic loss could be used to diagnose AD at the preclinical stage. Methods: In order to identify putative synaptic biomarkers, we first sought to characterize the cerebrospinal fluid (CSF) proteome of 10 cognitively healthy controls and 10 age-matched AD patients (mean age=67). Prior to their proteomic analysis, samples were pooled and subjected to immunodepletion, enabling detection of less abundant proteins. To achieve proteomic profiling, samples were digested with trypsin, separated by liquid chromatography and analysed by tandem mass-spectrometry (LC-MS/MS). Results: Using MASCOT software, 1,260 proteins were identified, 260 of which had not been previously reported in human CSF. Parallel to the experimental study we performed a systematic literature search to create a database of proteins identified in human CSF. The combination of proteins identified experimentally with those retrieved from the literature resulted in a dataset of 3,229 CSF proteins. A gene ontology (GO) analysis of the CSF proteome revealed significant enrichment for proteins involved in cell adhesion (n=261 proteins), transcription (n=109), metabolism (n=960), development (n=428) and complement activation (n=32), among others. To identify putative markers of synaptic loss, we searched the dataset of CSF molecules for proteins predominantly expressed at cortical synapses. This revealed 34 proteins that had a GO related to synapse organization/transmission (n=19) or were previously identified in mouse and/or human postsynaptic density (n=28) and were expressed mainly in the cortical neuropil (as described by the 'Human Protein Atlas' database). These putative synaptic markers will be quantified in CSF from cognitively healthy controls and age-matched AD cases using targeted mass spectrometry. Conclusions: Detailed characterization of the human CSF proteome has allowed us to identify 34 proteins primarily expressed at the synapse that, if confirmed as biomarkers of synaptic loss, could be invaluable for the diagnosis of preclinical AD.

P 17

Cerebrospinal fluid ?-amyloid and phospho-tau biomarker interactions affecting brain structure in preclinical Alzheimer disease.

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OBJECTIVE: To assess the relationships between core cerebrospinal fluid (CSF) biomarkers and cortical thickness (CTh) in preclinical Alzheimer disease (AD).

METHODS: In this cross-sectional study, normal controls (n = 145) from the Alzheimer's Disease Neuroimaging Initiative underwent structural 3T magnetic resonance imaging (MRI) and lumbar puncture. CSF β-amyloid1-42 (Aβ) and phospho-tau181p (p-tau) levels were measured by Luminex assays. Samples were dichotomized using published cutoffs (Aβ+ /Aβ- and p-tau+ /ptau-). CTh was measured by Freesurfer. CTh difference maps were derived from interaction and correlation analyses. Clusters from the interaction analysis were isolated to analyze the directionality of the interaction by analysis of covariance.

RESULTS: We found a significant biomarker interaction between CSF Aβ and CSF p-tau levels affecting brain structure. Cortical atrophy only occurs in subjects with both Aβ+ and p-tau+ . The stratified correlation analyses showed that the relationship between p-tau and CTh is modified by Aβ status and the relationship between Aβ and CTh is modified by p-tau status. p-Tau-dependent thinning was found in different cortical regions in Aβ+ subjects but not in Aβ- subjects. Cortical thickening was related to decreasing CSF Aβ values in the absence of abnormal p-tau, but no correlations were found in p-tau+ subjects.

INTERPRETATION: Our data suggest that interactions between biomarkers in AD result in a 2-phase phenomenon of pathological cortical thickening associated with low CSF Aβ, followed by atrophy once CSF p-tau becomes abnormal. These interactions should be considered in clinical trials in preclinical AD, both when selecting patients and when using MRI as a surrogate marker of efficacy

P 20

Dopamine-induced striatal cell death in Huntington's disease is dependent on Cdk5-mediated mitochondrial fission.

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Huntington's disease (HD) is characterized by motor disturbances associated to dysfunction and degeneration of the medium spiny neurons within the striatum. The molecular mechanisms underlying striatal vulnerability are still unknown, but growing evidence suggests that mitochondrial dysfunction occurs during the pathogenesis of the disease. We previously described that deregulation of cyclin-dependent kinase 5 (Cdk5) activity induced by mutant huntingtin (mHtt) increases the susceptibility of striatal neurons to dopamine via D1 receptor activation. Interestingly, Cdk5 acts as a mitochondrial regulator during neuronal apoptosis. Therefore, we investigated whether aberrant Cdk5 signalling contributes to striatal neurodegeneration by altering mitochondrial dynamics processes. We observed that striatal cells expressing mHtt exhibit increased mitochondrial fragmentation that worsens after dopaminergic stimuli. These mitochondrial defects can be completely rescued by Cdk5 inhibition with roscovitine or Cdk5 knockdown with siRNA transfection. Moreover, we found that mHtt deregulates the levels and the subcellular distribution of fission/fusion proteins while activation of D1 receptors promotes an increase in the levels of the fission protein Drp1 and its translocation to the mitochondria. We demonstrate that mHtt-induced Cdk5 activation is involved in the deregulation of the Drp1 GTPase activity since its inhibition prevents the aberrant activation of Drp1. Altogether our findings support the hypothesis that Cdk5 plays a crucial role in mitochondrial defects involved in the striatal neurodegeneration in HD.

P 21

Fingolimod (FTY720) enhances hippocampal synaptic plasticity and memory in Huntington's disease by preventing p75NTR/TrkB imbalance

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Abstract: Huntington's disease (HD) is a hereditary neurodegenerative disorder characterized by motor and cognitive impairments. Striatal atrophy is the main pathological hallmark, but degeneration in other regions of the brain, like the cerebral cortex and the hippocampus, has been reported. HD mouse models display low levels of brain-derived neurotrophic factor (BDNF) and altered expression of its receptors TrkB and p75NTR, which have been involved in the regulation of synaptic plasticity and cognitive function. Fingolimod (FTY720), an agonist of sphingosine-1 phosphate receptors commonly used as an immunomodulator in Multiple Sclerosis patients, has recently been shown to increase BDNF levels. Here, we have investigated whether FTY720 improves synaptic plasticity and memory dysfunction in the R6/1 mouse model of HD through regulation of BDNF signaling. Chronic administration of FTY720 from pre-symptomatic stages prevented long-term memory deficits and dendritic spine loss in CA1 hippocampal neurons from R6/1 mice. FTY720 increased BDNF mRNA in the hippocampus, without altering pro-BDNF processing. However, FTY720 chronic treatment prevented p75NTR up-regulation and promoted TrkB phosphorylation in the hippocampus of R6/1 mice, supporting a role for FTY720 in the enhancement of synaptic plasticity. FTY720 modulated p75NTR expression likely by decreasing astrogliosis and tumor necrosis factor α (TNFα) levels within the hippocampus of R6/1 mice. Our findings define a new mechanism for the action of FTY720 in neurodegenerative diseases and propose this drug as a suitable candidate for treating cognitive dysfunction in HD.

P 22

Histamine H3 receptors negatively modulate glutamate-induced neuronal excitation by forming heteromers with glutamate mGlu5 receptors.

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Group 1 metabotropic glutamate receptors (mGlu1R and mGlu5R) are required for both persistent forms of memory and persistent synaptic plasticity, suggesting that can be target for memory and plasticity-related disorders. We hypothesized that one way to target mGluR might be via receptor heteromers. Heteromers are complexes between different receptors with biochemically distinct properties from the single receptors. Thus, we investigated potential mGlu5R partners in the hippocampus. Here by co-immunoprecipitation, Bioluminescent Resonant Energy Transfer and Proximity Ligation Assays, we report a novel receptor heteromer between mGlu5R and the histamine H3 receptors (H3R) in transfected cells and in rat hippocampus. A sharp inhibition of signaling by the agonist of either receptor in the presence of the agonist or the antagonist of the other receptor was seen. These results indicate a negative cross-talk in signaling when heteromers are activated with both agonists and also a cross-antagonism between receptors that might be attributed to an allosteric interaction between receptors in the H3R-mGlu5R heteromers. Heteromer formation leads the H3R-mediated modulation of mGlu5R signaling. The cross-antagonism and the negative cross-talk at the level of signaling in hippocampal slices were also seen at the level of extracellular field potential recordings and on pyramidal neuron Ca+2 mobilization and excitation. Thus, targeting H3R-mGlu5R heteromers by H3R ligands might be an efficient and potent way to modulate mGlu5R-mediated neuronal signaling and excitability as well as neuronal plasticity. The results point out that H3R-mGlu5R heteromers are new targets to treat neurocognitive diseases where reduced mGlu5R signaling is desired

P 23

Neuronal calcium binding proteins NCS-1 and calneuron interact and modulate striatal adenosine A2A-dopamine D2 receptor heteromers signaling.

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It is known that adenosine A2A (A2AR) and dopamine D2 (D2R) receptors form heteromers in which A2AR activation inhibits D2R ligand affinity and signaling, but the variables that control this negative crosstalk under physiological conditions are presently unknown. Here we demonstrate that a local change in Ca2+ concentrations regulates the receptor heteromer function. The neuronal Ca+2 binding proteins NCS-1 and calneuron-1 interact with A2AR-D2R heteromers in transfected cells and in primary cultures of rat striatal neurons. The binding of NCS-1 or calneuron-1 to the A2AR-D2R heteromers, which depends on low or high concentrations of Ca2+, respectively, transduces differential effects on A2AR-induced inhibition of D2R-mediated adenylyl-cyclase and MAPK signaling. Binding of NCS-1 or calneuron-1 to the A2AR-D2R heteromer impairs A2AR agonist-induced inhibition of D2R-mediated adenylyl-cyclase signaling, allowing D2R activation to inhibit adenylyl-cyclase signaling. This results in low cAMP accumulation upon co-activation of A2AR and D2R. On the other hand, the binding of calneuron, but not NCS1, potentiates A2AR-agonist induced inhibition of D2R-mediated MAPK signaling, which results in low levels of phosphorylated ERK1/2 upon co-activation of A2AR and D2R. Our results show that Ca+2 levels, by promoting binding of different Ca+2-binding proteins to the heteromer, determine functional selectivity within A2AR-D2R heteromer upon co-activation of A2AR and D2R.

P 24

Targeting Dopamine D1-D3 receptor heteromers fpr L-DOP-induced dyskinesias in the 6-OHDA rat model.

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Parkinson's disease (PD) is a progressive neurodegenerative disorder caused by the degeneration of the pigmented neurons of the substantia nigra pars compacta that provide dopamine input to the striatum. Chronic dopamine replacement therapy leads to involuntary aimless movements known as L-DOPA-induced dyskinesia (LID), due to an increased of dopamine D1 receptors (D1R) signaling promoted by an up-regulation of D3R. In this study, we investigate by radioligand binding techniques changes in D1R and D3R protein expression in the striatum of a unilateral PD rat model. We determine the receptor levels in the right (lesioned) side and in the left (non-lesioned) side of the striatum in control, 6-OHDA-lesioned and in non-dyskinetic and dyskinetic L-DOPA-treated rats. A high increase in D3R is observed in both striatum sides only in dyskinetic rats. We also investigate the presence of cross-talk between D1R and D3R as fingerprint of the D1R-D3R heteromer by competition binding experiments. Lesioned side of dyskinetic rat striatum is the only case showing positive cross-talk of D3R on D1R. In all cases, left side shows higher D1R affinity than right side and positive cross-talk is not longer observed. By in situ proximity ligation assay, we detect the higher number of positive cells containing D1-D3 receptor heteromers in striatum of dyskinetic animals. All these results show that the increase of D3R expression in dyskinetic rats induces heteromerization in both striatum sides. In this case, D3R activation increases D1R affinity in right side and catch up the high affinity detected in left side. This fact can be responsible of the dyskinetic pattern in rats.

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Adenosine A1 and A2A receptor heteromers form dynamic but stable tetrameric complexes with two different G proteins

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G-protein-coupled heteromers serve as unique protein complexes that allow cells to sense the environment in a variety of ways. The dynamics and structural characteristics underlying their functional diversity are not known. Studying the model heteromer of adenosine A1 and A2A receptors, we show here by single particle tracking experiments, that heteromers can form dynamic but stable heterocomplexes. Using biophysical energy transfer techniques and single molecule microscopy, together with molecular models of protein oligomerization, we provide experimental evidence to support a model of these A1-A2A receptor complexes to be heterotetramers formed by two transmembrane helix-4-interacting A1 and A2A homodimers bound together via transmembrane helix 5. The resulting non-square heterotetramer forms a complementary interface that can simultaneously accommodate two separately bound abg heterotrimeric G proteins (Gs and Gi) only if the g but not a subunits face the inside of the heterotetramer.

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Role of PrPC expression in tau protein levels and phosphorylation in Alzheimer's disease.

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Alzheimer's disease (AD) is characterized by the presence of amyloid plaques mainly consisting of hydrophobic □-amyloid peptide (A□) aggregates and neurofibrillary tangles (NFTs) composed principally of hyperphosphorylated tau. A□ oligomers have been described as the earliest effectors to negatively affect synaptic structure and plasticity in the affected brains, and cellular prion protein (PrPC) has been proposed as receptor for these oligomers.

The most widely accepted theory holds that the toxic effects of A□ are upstream of change in tau, a neuronal microtubule-associated protein that promotes the polymerization and stabilization of microtubules. However, tau is considered decisive for the progression of neurodegeneration, and indeed tau pathology correlates well with clinical symptoms such as dementia. Different pathways can lead to abnormal phosphorylation, and, as a consequence, tau aggregates into Paired Helical Filaments (PHF) and later on into NFTs.

Reported data suggest a regulatory tendency of PrPC expression in the development of AD, and a putative relationship between PrPC and tau processing is emerging. However the role of tau/PrPC interaction in AD is poorly understood.

In this study we show increased susceptibility to □-amyloid derived diffusible ligands (ADDLs) in neuronal primary cultures from PrPC knock-out mice, compared to wild-type, which correlates with increased tau expression. Moreover, we found increased PrPC expression that paralleled with tau at early ages in an AD murine model, and in early Braak stages of AD in affected individuals. Taken together, these results suggest a protective role for PrPC in AD by down-regulating tau expression, and they point to this protein as being crucial in the molecular events that lead to neurodegeneration in AD.

P 27

Semaphorin-3E/Plexin-D1 regulates the migration of Cajal-Retzius cells in developing cerebral cortex.

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During the development of the cerebral cortex, pioneer Cajal-Retzius (CR) cells settle in the preplate and coordinate the precise growth of the neocortex. Indeed, CR-cells migrate tangentially from specific proliferative regions of the telencephalon (e.g., the cortical hem) to populate the entire cortical surface. This is a very finely tuned process regulated by an emerging number of factors that has been sequentially revealed recent years. However, the putative participation of one of the major families of axon guidance molecules in this process, the Semaphorins, was not explored. Here, we show that Semaphorin-3E (Sema3E) is a natural negative regulator of the migration of PlexinD1-positive CR-cells originating in the cortical hem. Our results also indicate that Sema3E/PlexinD1 signalling controls the motogenic potential of CR-cells in vitro and in vivo. Indeed, absence of Sema3E/PlexinD1 signalling increased the migratory properties of CR-cells. This modulation implies negative effects on CXCL12/CXCR4 signalling and increased ADF/Cofilin activity.

P 28

Changes in the endocannabinoid signaling system in CNS of TDP-43 transgenic mice: relevance for a neuroprotective therapy in TDP-43-related disorders

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There is robust evidence supporting that the endocannabinoid signaling system serves as an endogenous protective system in the CNS, so that its malfunctioning, in particular a deficiency in the generation of endocannabinoids and/or the down-regulation of CB1 receptors in neurons, might be associated with the initiation and/or progression of different chronic neurodegenerative diseases. By contrast, the up-regulation of CB2 receptors in glial cells, as well as an elevated generation of endocannabinoids, appear to protect neurons and glial cells against different insults that operate in these disorders. Interestingly, these responses may be corrected and/or elicited by pharmacologically targeting specific elements of this signaling system. Our group has contributed to the study of the role of this signaling system mainly in basal ganglia disorders, e.g. Huntington's disease, Parkinson's disease, but recently we have been extended our interest to other neurodegenerative disorders such as amyotrophic lateral sclerosis (ALS) using the model of SOD1 mutations in mice (Moreno-Martet et al., CNS Neurosci Ther, 2014). We have also initiated some experiments in transgenic mice for TDP-43, another ALS-related gene. TDP-43 is a nuclear DNA-binding protein which has been found in the cytosol in the form of protein aggregates in ALS and other neurodegenerative disorders, for example, frontotemporal lobar dementia (FTLD-TDP). Alterations in TDP-43 protein represent a new type of proteinopathy similar to tauopathies, α-synucleinopathies or polyglutaminopathies. TDP-43 transgenic mice develop motor deficits and damage of spinal motor neurons reminiscent of ALS, but they can also develop some cognitive deficits derived from the damage of cortical neurons. We concentrated in motor deficits that were observed in our animals, using the rotarod test, at early ages (70 and 80 days of age), consistent with previous data reported in the literature. The analysis of the spinal cord of these TDP-43 transgenic mice revealed a lower number of Nissl-stained cells, as well as a reduction in the number of TDP-43-positive cells, in parallel to an important increase in the levels of CB2 receptors with no changes in the expression of other endocannabinoid genes, e.g. CB1 receptors, degrading and synthesizing enzymes. Some of these responses were also found in the cerebral cortex of TDP-43 transgenic mice. In conclusion, our data support the idea that the endocannabinoid signaling system, in particular the CB2 receptor, may serve for the development of a neuroprotective therapy in TDP-43-related disorders, such as ALS and FTLD-TDP. We are presently engaged in pharmacological experiments to investigate this possibility.

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P 29

G2019S LRRK2 fibroblasts show a susceptibility to the MPP+ neurotoxin by a mTOR-dependent autophagy

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Parkinson's disease (PD) is a neurodegenerative disorder characterized by mitochondrial dysfunction, oxidative stress and later neuronal death. Several genetics and environmental factors have been implicated in the pathogenesis of PD.

MPP+ is a neurotoxin widely used to induce parkinsonian cellular model, it is responsible for cellular damage at different levels, apoptotic death, depletion of mitochondrial potential membrane and deregulation of cellular recycling machinery.

In this study, we characterized the MPP+-induced toxicity in fibroblasts from PD patients with G2019S LRRK2 and control individuals without this mutation. Obtained results show that MPP+ induces a mTOR-dependent autophagy in both fibroblasts cells. Further, cell death to MPP+ was higher in mutant fibroblasts which exhibited a basal level of mTOR-independent autophagy due to the G2019S LRRK2 mutation.

Inhibition of autophagosome-lysosome fusion by Bafilomycin A1 exacerbated the response to MPP+ exposure in both cell lines, but inhibition of early state autophagy by 3-methyladenine lessened this difference between both cell types.

This finding confirms the important implication of the interaction of genetics and environmental factors in the PD etiology and may help to get a better understanding in the pathogenic mechanism of this disease.

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P 30

Sulforaphane fail in the protection of mouse embryonic fibroblasts against MPP+/PQ- induced oxidative stress

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Several studies have demonstrated the ability of Nrf2 transcription factor to control the cytoprotective adaptive response in the brain using PD models. In this sense, brain samples from animals with neurodegeneration by oxidative stress have shown that increased nuclear Nrf2 may have a protective effect on dopaminergic neurons in the SNpc, and on the other hand, in MEFs it is has been observed the induction of antioxidant defenses from this pathway after exposure to inducing agents. The chemical characteristics of the agents which have the ability to interact with the Nrf2/Keap1 pathway show differences from each other in the chemical structure or how to interact (directly or indirectly) with the pathway. Sulforaphane (SFN) is a naturally isothiocyanate presents in cruciferous plants. This substance shows in its structure a highly electrophilic central carbon (-N = C = S) which can easily react with the sulfhydryl groups of Keap1 to form dithiocarbamates, so in this fact lies its ability to promote the translocation of the transcription factor Nrf2 to the nucleus. However, it has been found that this substance can play a dual role, as a chemotherapeutic agent or as a promoter of antioxidant defenses.

Based on this powerful cellular defense of Nrf2 factor against oxidative stress and based on the chemical features offered by SFN, the aim of this work was to determine whether the activation of this axis exerted a protective effect or not against MEFs induced PQ and MPP+ cytotoxicity and on the other way, if that substance could modulate another celular processes such as autophagy, apoptosis or acetylation, thinking that this model could be used to elucidate the Nrf2 potential role as a molecular therapeutic target value.

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P 31

Pattern of mutant huntingtin-induced toxicity in D1R vs. D2R-expressing medium-sized spiny neurons of the mouse striatum.

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Huntington's disease (HD) is a devastating neurodegenerative condition that is caused by an aberrant polyglutamine expansion in the N-terminal region of the huntingtin protein. Neuronal intranuclear protein inclusions are characteristically found in HD patients, in which the basal ganglia stands as the brain structure that is primarily affected. Within this area, medium-sized spiny neurons (MSNs), the projecting and large majority of cells, are particularly sensitive. Some MSNs express D1 dopamine receptors (D1Rs) and constitute the direct pathway of corticostriatal circuitry, while other MSNs express D2 dopamine receptors (D2Rs) and constitute the indirect pathway of corticostriatal circuitry. Most of the evidence accumulated to date supports that D2R-MSNs are more vulnerable to mutant huntingtin-induced toxicity than D1R-MSNs. However, a precise mechanistic monitoring of mutant huntingtin expression and neurotoxicity in D1R-MSNs vs. D2R-MSNs has not been conducted so far. Here, by using bacterial artificial chromosome (BAC) transgenic mice expressing reporters driven by specific promoters (BAC-D1R-tomato and BAC-D2R-GFP), together with viral gene transfer strategies (CFP-tagged mutant huntingtin harboring a pathogenic polyQ repeat of 94 residues), we sought to explore the selective neurotoxic properties of mutant huntingtin in those two populations of MSNs.

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Involvement of CB1 cannabinoid receptor signalling in focal cortical dysplasia

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The endogenous cannabinoid system exerts a neurodevelopmental regulatory role that controls the expansion and identity of neural progenitors and regulates neuronal differentiation. Here we investigated the expression and function of CB1 cannabinoid receptor signalling in focal cortical alterations associated to an over activation of the mammalian target of rapamycin complex 1 (mTORC1) pathway. Confocal microscopy analyses were performed in focal cortical dysplasia and tuberous sclerosis samples. Gene expression analyses of different elements of the endogenous cannabinoid system was undertaken to determine their differential expression when compared to control tissue. In addition, primary dysplastic cortical neuron cultures were employed for pharmacological manipulation experiments. The results indicate that there is a selective enrichment in the expression of the CB1 cannabinoid receptor in FCD cases that correlate with the activation status of the mTORC1 pathway. CB1 cannabinoid receptor was observed in dysplastic cells showing undifferentiated neural marker expression suggesting its potential involvement in FCD type 2 malformations. Ongoing experiments are aimed to identify the consequences of CB1 receptor manipulation in neuronal differentiation and activity in FCD derived cultures. In conclusion embryonic alterations of CB1 cannabinoid receptor signaling may be involved in the pathology of focal cortical malformations that results in pharmacoresitant children epilepsy and in particular with those cases associated to the expression of undifferentiated neuronal markers. These results point to the endocannabinoid system as a novel extracellular signaling system involved in developmental alterations associated to overactive mTORC1 pathway.

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Papel de la Proteina Kinasa D (PKD) en supervivencia neuronal y neurodegeneración

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La proteína quinasa D (PKD) es una serina-treonina quinasa que participa en multitud de procesos biológicos, sin embargo, se desconoce qué papel tiene esta proteína en la patofisiología neuronal. Mediante experimentos de hibridación in situ en nuestro laboratorio comprobamos que PKD se expresa de manera muy marcada en el giro dentado de ratones de 2 meses de edad sugiriendo que PKD podría tener un papel en aquellas funciones reguladas por ésta estructura cerebral. Por otro lado, estudios en cultivos primarios de neuronas corticales de rata, indican que tratamientos excitotóxicos con NMDA, producidos por una exposición crónica de los receptores de tipo NMDA a este agonista, inducen una rápida activación de PKD, dependiente de PKCs, seguida de una fuerte desfosforilación de la proteína en tratamientos más prolongados. Comprobamos además, que este proceso está regulado por receptores de tipo NMDA, en concreto por la subunidad GluN2B. Teniendo en cuenta que la excitotoxicidad está asociada al desarrollo de ciertas enfermedades neurodegenerativas como son las enfermedades de Alzheimer, Parkinson o Huntington, pensamos que PKD podría estar jugando algún papel en procesos asociados a supervivencia neuronal o neurodegeneración. En este sentido, nuestros resultados muestran que la inhibición de PKD induce una mayor muerte neuronal, la activación de proteínas implicadas en rutas de muerte, como p38MAPK, así como la fragmentación nuclear y del aparato de Golgi de manera basal y en condiciones excitotóxicas. Como conclusión, podemos decir que PKD parece participar en la supervivencia neuronal y su modulación podría mediar mecanismos de protección frente al daño excitotóxico asociado a diversas enfermedades neurodegenerativas.

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Light and electron microscopic detection of GPCR heteromeric complexes in the macaque brain using the in situ proximity ligation assay

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Light and electron microscopic detection of GPCR heteromeric complexes in the macaque brain using the in situ proximity ligation assay. Jose L. Lanciegoa,*, Iria G. Dopeso-Reyesa, Alberto J. Ricoa, Salvador Sierra-San Nicolasa, Elvira Rodaa, Maria Lanza, Diego Pignataroa, Diego Sucunzaa, Daniel Farreb, Rafael Francob:

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Here the in situ proximity ligation assay (PLA) was used to characterize a number of G proteincoupled receptor heteromeric complexes across different basal ganglia nuclei in macaques, comprising control animals as well as animals rendered parkinsonian (with and without levodopainduced dyskinesia) following the chronic treatment with the specific dopaminergic neurotoxin MPTP. The PLA technique enabled us to demonstrate the presence of a number of GPCR receptor heteromers in both the input and the output basal ganglia nuclei. At the level of the caudateputamen (input nuclei), different types of GPCR heteromers were found, those comprising dopaminergic D1-D3 and cannabinoid CB1-GPR55 receptor heteromers. When considering the internal division of the globus pallidus (GPi, output nucleus), we focused on cannabinoid CB1-CB2 heteromers as well as on receptor heteromers made of adenosine 2A (A2A) and cannabinoid receptor types 1 and 2 (CB1 and CB2). The putative changes in the number of all these types of GPCR heteromers in the different diseased states was qualitatively assessed with the confocal microscope. Most importantly, ultrastructural confirmation of the pre- and/or post-synaptic localization of cannabinoid receptor heteromers was provided. To the very best of our knowledge, this represents the first time in which the PLA technique was taken to the electron microscope. Throughout these studies, we took advantage of different technical recipes for the PLA assay, including: (i) fluorescent detection by labeling secondary antibodies with PLA probes, (ii) fluorescent detection following direct labeling of primary antibodies and (iii) ultrastructural detection of PLA-labeled primary antibodies using peroxidase-labeled oligonucleotides, the latter incubated with colloidal gold-tagged goat anti-peroxidase antibody and finally visualized with a silver enhancement solution. Supported by grants from Ministerio de Economia y Competitividad (BFU2012-37907, SAF2008-03118-E and SAF39875-C02-01), Eranet-Neuron, CiberNed (CB06/05/0006), and by Departamento de Salud, Gobierno de Navarra.

P 35

L-DOPA treatment selectively restores spine density in D2R-expressing projection neurons in dyskinetic mice

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Background: L-DOPA-induced dyskinesia is an incapacitating complication of L-DOPA therapy which affects most patients with Parkinson's disease. Previous work indicating that molecular sensitization to D1 dopamine receptor (D1R) stimulation is involved in dyskinesias prompted us to perform electrophysiological recordings of striatal projection "medium spiny neurons" (MSN). Moreover, because enhanced D1R signaling in drug abuse induces changes in spine density in striatum, we investigated whether the dyskinesia is related to morphological changes in MSNs.

Methods: Wild type and BAC transgenic mice (D1R-tomato and D2R-GFP) mice were lesioned with 6-hydroxydopamine and subsequently treated with L-DOPA to induce dyskinesia. Functional, molecular and structural changes were assessed in corticostriatal slices. Individual MSNs injected with Lucifer-Yellow were used for DAB-derived 3-D reconstructions with Neurolucida software. Intracellular current-clamp recordings with high-resistance micropipettes were used to characterize electrophysiological parameters.

Results: Both D1R-MSNs and D2R-MSNs showed diminished spine density in totally denervated striatal regions in parkinsonian mice. Chronic L-DOPA treatment, which induced dyskinesia and aberrant FosB expression, restored spine density in D2R-MSNs but not in D1R-MSNs. In basal conditions, MSN are more excitable in parkinsonian than in sham mice, and excitability decreases towards normal values following L-DOPA treatment. Despite this normalization of basal excitability, in dyskinetic mice, the selective D1R agonist SKF38393 increased the number of evoked action potentials in MSNs, compared to sham animals.

Conclusions: Chronic L-DOPA induces abnormal spine re-growth exclusively in D2R-MSNs and robust supersensitization to D1R-activated excitability in denervated striatal MSNs. These changes might constitute the anatomical and electrophysiological substrates of dyskinesia.

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Role of mutations N370S and L444P of the GBA gene in autophagy and its involvement in Parkinson's disease

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There is now a well-established clinical association between mutations in the glucocerebrosidase gene (GBA) that encodes the lysosomal hydrolase glucosylceramidase and the development of Parkinson's disease (PD) in the general population. The mechanisms by which GBA mutations predispose to neurodegeneration remain unclear. To study the role of heterozygous GBA mutations in the pathology of PD, we generated fibroblast lines from skin biopsies of five PD patients with heterozygous GBA mutation carriers (N370S and L444P) and four controls. Both GBA mutations demonstrated a significantly reduced level of GCase protein and enzyme activity and retention of glucocerebrosidase isoforms within the endoplasmic reticulum (ER). We have observed that this ER retention overload activates ER stress pathway leading to the activation of signaling events known as the unfolded protein response (UPR), resulting in increased autopaghy demand. Our results also showed that this was associated with enhanced expression of the lysosomal markers Lamp1 and Lysotracker and a significant accumulation of lamellar bodies (as pathology maker for lisosomal storage disorder) detected by electron microscopy. In addition, using flow cytometry we demonstrated that GBA mutations not only were associated with evidence of endoplasmic reticulum but also oxidative stress. Related to this, these mutations showed significant decline in mitochondria membrane potential. To sum up, our results demonstrated that N370S and L444P induce autophagic flux and carry out impairment in lysosomal function due to an accumulation of misfolded proteins in ER.

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Resemblance of clinical metabolic changes using pet imaging in a progressive mptp primate model of Parkinson´s disease

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Parkinson´s disease (PD) is characterized by progressive loss of dopaminergic neurons in the substantia nigra causing dopamine depletion in the striatum. This triggers a succession of compensatory changes delaying the appearance of motor manifestations, leading to a prolonged pre-motor period of disease evolution. Here, we describe the metabolic pattern associated with progressive nigro-striatal lesion in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) monkey model.

Aim: To define the metabolic changes associated with dopamine striatal depletion. Methods: Twenty-four monkeys (Macaca fascicularis) were administrated MPTP using 0.5 mg/kg weekly to obtain different groups: Basal, asymptomatic, mild and severe parkinsonian, according to Kurlan scale assesments. An additional recovered group was performed after L-Dopa treatment. PET imaging was performed using monoaminergic (11C-dihydrotetrabenazine; 11C-DTBZ) and metabolic (18F-fluorodeoxyglucose; 18F-FDG) radiotracers. Regions of interest (ROI) analysis were done for 11C-DTBZ PET (striatum) and Statistical Parametric Mapping (SPM) analysis for 18F-FDG studies (whole brain). Results: 11C-DTBZ PET images showed a progressive decrease of Binding Potential (BP) values in the striatum throughout MPTP administration and the ensuing of parkinsonian signs (1.43 BP basal, 0.85 BP asymptomatic, 0.40 BP mild, 0.27 BP severe, 0.45 BP recovered). 18F-FDG PET images revealed a metabolic pattern recognized by hypometabolism in caudate, posterior parietal, lateral premotor and frontal cortex, and hypermetabolism in the thalamus, globus palidus and cerebellum. Conclusions: Progressive dopaminergic striatal depletion in this MPTP monkey model led to recognizable metabolic patterns that resemble largely the clinical changes observed on patients and can provide useful in-vivo information about compensatory mechanisms.

P 38

The role of GluN2A subunit on the levodopa-induced dyskinesias and its potential therapeutic role

Hernandez LF, Gardoni F, Iglesias E, Hirsch, EC, DiLuca M, Obeso JA

Over-activation of cortico-striatal synapse occurs in Parkinson´s Disease (PD) patients and in animal models. The administration of levodopa (L-DOPA) which temporarily restores the excitation balance of striato-thalamo-cortical loop, leads to dyskinesias, which is one major therapeutic problem in PD. On the other hand, it has been shown that altered striatal NMDA receptor function in the postsynaptic compartment make also important contributions both to motor manifestations of the disease and to treatment response to dopaminergic drugs. Here we analyze the composition of the glutamatergic subunits receptors in two PD animal models (rat and non-human primate) and in a group of Parkinson´s disease patients. Moreover, analysis of the expression of the GluN2A subunits in striatal NMDAR was performed in samples coming from dyskinetic and non-dyskinetic 6-OHDA rats, MPTP non-human primates and PD patients and their respective controls. Overall, there is a modification of the molecular composition of NMDA receptor at striatal synapses in the PD models studied here as well as in the striatum of post-mortem tissue from PD patients. Additionally, since an increased expression of GluN2A subunits was also found in dyskinetic animal models and PD patients, we assessed the potential antidyskinetic effect of the peptide TAT2A in the non-human primate model. TAT2A binds to the GluN2A subunit avoiding its functionality in the membrane surface.

These results suggest the existence of pronounced changes in the expression of glutamatergic receptor subunits, which likely reflect maladaptive plasticity of the striatal circuit in PD and upon L-DOPA treatment. Furthermore, we demonstrate aberrant increase of the expression of GLuN2A subunits at synaptic site in both dopamine depleted and levodopa-induced dyskinesias, suggesting that alteration in the GluN2A subunit expression may be a key pathogenic element in the glutamatergic synapse in the parkinsonian state.

P 39

Nurr1 blocks the mitogenic effect of fgf-2 and egf, inducing olfactory bulb neural stem cells to adopt dopaminergic and gabaergic neuronal phenotypes

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The transcription factor Nurr1 is required for the development of mesencephalic dopaminergic neurons (DA neurons) and to obtain these neurons from cultured stem cells (1-3). Although Nurr1 is expressed in the mouse olfactory bulb (OB), it remains unknown whether it influences the generation of DA neurons from neural stem cells (NSCs) isolated from the OB (termed OBSCs) (4,5). We found that expressing Nurr1 in OBSCs produces a marked inhibition of cell proliferation and the generation of immature neurons immunoreactive for tyrosine hydroxylase (TH) concomitant with marked up-regulations of Th, Dat, Gad, and Fgfr2 transcripts. In long-term cultures, these cells develop neurochemical and synaptic markers of mature-like mesencephalic DA neurons, expressing GIRK2, VMAT, DAT, calretinin, calbindin, synapsin-I, and SV2. Furthermore, the dopamine D1 receptor agonist SKF-38393 induced c-Fos in TH+ cells supporting their functional capacity to respond to dopaminergic stimulus. Concurring with the increase in Th and Gad expression, a subpopulation of induced cells was both TH- and GAD-immunoreactive indicating that they were DA-GABAergic neurons. Indeed, these cells could mature to develop VGAT+ boutons suggesting their ability to uptake and storage GABA in synaptic vesicles. These results indicate that Nurr1 overexpression in mouse OBSCs induces the formation of two populations of DA neurons with features of the ventral mesencephalon and of the OB. They also suggest that upregulation of Fgfr2 by Nurr1 in OBSCs may be involved in the generation of DA neurons.

Key words: Transcription factors, neural stem cells, dopaminergic neurons, GABAergic neurons, Fgfr2.

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6. Supported by grants from CIBERNED (ISCIII), MINECO, and the Comunidad de Madrid.

P 40

Generation of dopaminergic neurons from ips cells derived from patients having parkinson´s disease with mutations in the glucocerebrosidase (GBA1) gene

Autores: -----

Human neurons can be obtained from induced pluripotent stem cells (iPS cells or iPSCs) derived from fibroblasts reprogrammed by overexpressing four transcription factors: OCT3/4, KLF4, SOX2 and c-MYC (OKSM or Yamanaka factors). The neurons can be used as a model to study the cellular and molecular mechanisms of neurodegeneration or for transplantation studies. In fact, several groups have reported the generation of neurons from patients having Parkinson´s disease (PD). Mutations in the glucocerebrosidase (GBA1) gene, which encodes a lysosomal enzyme that is deficient in Gaucher´s disease (GD), are risk factors for PD and Lewy body dementia. The objective of our study was to produce iPSC-derived dopaminergic neurons from PD patients having GBA mutations to investigate the impact of the mutations in neuronal survival and maturation. We have used non-integrative Sendai viral vectors to transduce the transcription factors OKSM as a mean to reprogram dermal fibroblasts from PD patients carrying the N370S/wt and the L444P/wt mutations in the GBA1 gene. The use of these vectors allowed us to obtain vector-free iPSC colonies by performing the first passages under clonal conditions. The reprogrammed cells maintained the original GBA genotype, presented the typical iPSC morphology, and expressed endogenous pluripotency markers (Nanog, Oct4, Sox2, TRA-1-60, and SSEA-4). Moreover, they differentiated into endodermic, mesodermic and ectodermic cells, and maintained overall genomic integrity up to passage 15, although they can be expanded for at least 40 times in culture. We are currently analysing the phenotype of dopaminergic neurons generated from the GBA-derived iPSCs and controls using cellular, molecular, genetic and functional assays.

Supported by grants from CIBERNED (ISCIII). MINECO, the Comunidad de Madrid and CSIC, Spain.

P 41

Characterization of transgenic mice with neuronal overexpression of CPEB4

Parras A, Lucas JJ

Several neurological syndromes have been correlated with aberrant regulation of translation (one important example is fragile X mental retardation syndrome). Translation in CNS is regulated by multiple mechanisms and factors. Among these, the family of Cytoplasmic Polyadenylation Binding Proteins (CPEBs) is the main group implicated in local translation.
CPEB-family is composed by four sequence-specific RNA-binding proteins that play an essential role in translational control by modulating the length of poly (A) tails of specific mRNAs. All CPEBs in vertebrates are expressed in the brain suggesting their potential roles in regulating neuronal functions.
Although CPEB1 and CPEB3 have been shown to play an important role in brain function, the role of CPEB2 and CPEB4 remains elusive. We have thus decided to generate a conditional transgenic mouse overexpressing CPEB4 in the brain during adulthood by using the tet-off regulated system. We are characterizing this transgenic mouse by histological and proteomic assays and performing several behavioral tests.

P 42

Huntington's disease is a four-repeat tauopathy with tau-nuclear rods

Marta Fernández-Nogales Jorge R. Cabrera, María Santos-Galindo, Jeroen J.M. Hoozemans, Isidro Ferrer, Annemieke J.M. Rozemuller, Félix Hernández, Jesús Avila and José J. Lucas

A disbalance in tau isoforms containing either three or four microtubule-binding repeats causes frontotemporal dementia with parkinsonism linked to chromosome (FTDP-17) in families with intronic mutations. Here we report equivalent disbalance at the mRNA and protein level and increased total tau levels in the brains of Huntington's disease (HD) subjects together with rod-like tau deposits along neuronal nuclei. These so called tau-nuclear rods (TNRs) show ordered filamentous ultrastructure and can be found filling the neuronal nuclear indentations previously reported in HD brains. Finally, alterations in the splicing factor SRSF6 coincide with tau-missplicing and a role of tau in HD pathogenesis is evidenced by the attenuation of motor abnormalities of HD transgenic mice in tau knock-out backgrounds.

P 43

Transcription factor NRF2 as a new therapeutic target in a preclinical model of Alzheimer disease.

Marta Pajares, Patricia Rada, Ángel J García-Yagüe,,ÁngelNuñez, M L de Ceballos,Antonio Cuadrado and Ana I Rojo

Current therapies for Alzheimer´s disease (AD) ameliorate the symptoms but it is urgent to find new molecular targets that could delay the degenerative process. We propose the transcription factor NRF2 as a novel therapeutic target. NRF2, considered the master regulator of redox homeostasis, regulates the expression of more than 100 anti-oxidant and anti-inflammatory genes. We have generated a new AD model consisting in bigenic APP(V717I)/TAU(P301L) (biAT) and trigenic APP(V717I)/TAU(P301L)/Nrf2-KO (triAT) mice. Firstly, we showed that deficiency of NRF2 impaired cognitive behavior and spatial memory analyzed using Morris Water Maze test and long term potentiation (LTP). In accordance, synaptic dysfunction was detected. PSD-95 and synaptophisin levels were misbalance in both genotypes but interestingly NRF2-null animals were more sensitive than biAT. We analyzed GFAP and CD11b as markers of astroglial and microglial activation respectively. As expected, both genotypes exhibited microglial activation in cortex, hippocampi and subicullum. However, triAT animals evidenced higher microglial M1-activated and an increase in pro-inflammatory markers. Regarding Aβ plaques, the oldest mice (13-14 months) showed a slight and reproducible plaque formation, preferentially in subicullum and cortex. Analysis of Aβ-plaques distribution by immunohistochemistry and quantification by ELISA revealed that deficiency of NRF2 reduces the Aβ load in hippocampi.These animals will be an excellent tool to study AD due to: (1) the slow development of amyloidosis and TAUpathy, with a very useful time window to analyze preclinical events such as early inflammation, (2) the possibility to analyze the role of oxidative stress and proteinopathy in the evolution of AD neurodegeneration and neuroinflammation and (3) the comparison of biAT vs. triAT allows to determine the relevance of NRF2, drug design and analysis of off-target effects.

P 46

CSP-alpha is essential to maintain the quiescence of radial-glia like stem cells in postnatal neurogenesis

J.L. Nieto-González, L. Gómez-Sánchez, F. Mavillard, P. Linares-Clemente, J. A. Martínez-López, R. Pardal and R. Fernández-Chacón

Cysteine String Protein-alpha (CSP-alpha) is a synaptic co-chaperone that prevents activity-dependent degeneration of nerve terminals. Mutations in the human CSP-alpha gene cause neuronal ceroid lipofuscinosis characterized by progressive dementia and seizures. Synapses formed onto granule cells by parvalbumin (PV)-expressing basket cells progressively degenerate in CSP-alphaKO mice. Using electrophysiology, we have found dysfunctional GABA release from basket in CSP-alpha KO mice. At the dentate gyrus of CSP-alpha KO mice, calretinin-expressing neurons are significantly increased. We have systematically used BrdU injections and specific markers to uncover a severe deregulation of adult neurogenesis. We have observed that the pool of radial-glia like stem cells becomes progressively depleted due to hyper-proliferation, likely caused by a loss of stem cell quiescence. Surprisingly, part of these alterations occurs before basket cell synaptic dysfunction is established, suggesting that proliferation increase is partly due to a cell autonomous mechanism. Our data are compatible with two types of alterations in adult neurogenesis: circuit-independent and circuit (PV neurons)-dependent mechanisms. Remarkably, our study uncovers an unanticipated requirement of CSP-alpha to maintain the quiescence of radial-glia like cells in postnatal neurogenesis.

Support: BFU2010-15713, ERA-NET NEURON EUI2009-04084, ISCIII and FEDER. We are grateful to A. Arroyo and M. C. Rivero for excellent technical assistance.

P 47

Caracterización molecular de un modelo experimental progresivo de enfermedad de Parkinson: inyección intraventricular de 6-O HDA

Belén Gago, Ana Quiroga, Guadalupe Mengod, Roser Cortés, Elena Iglesias, José A. Obeso, Concepción Marin, Maria Cruz Rodriguez-Oroz

La enfermedad de Parkinson (EP) se caracteriza principalmente por una degeneración progresiva de las neuronas dopaminérgicas en la sustancia negra pars compacta (SNc) y por una depleción dopaminérgica estriatal. Existen varios modelos para estudiar esta enfermedad pero ninguno imita una pérdida de las células de la SNc progresiva, puesto que la mayoría de ellos inducen una inmediata y casi completa degeneración, al contrario de la evolución progresiva lenta que se observa en los pacientes de EP. La administración del neurotóxico 6-OHDA en el tercer ventrículo a lo largo de un intervalo de tiempo (1 a 10 días) podría constituir un nuevo modelo de desarrollo progresivo de la neurodegeneración. En estos animales se observa una disminución significativa de los niveles de de tirosina hidroxilasa (TH) en sustancia negra, así como el desarrollo de acinesia, de manera progresiva. El objetivo de este trabajo es la caracterización temporal de los cambios en los niveles de ARNm de los receptores dopaminérgicos D1 y D2 y de los péptidos opioides encefalina y dinorfina en el estriado, y del enzima ácido glutámido descarboxilasa (GAD67) en la sustancia negra en animales que han recibido 1, 5, 7 y 10 inyecciones de 6-OHDA en días consecutivos. No se observan cambios significativos en la expresión de ninguno de los marcadores en el estriado respecto a los grupos control ni entre los distintos puntos temporales. Este modelo, por la inducción progresiva de la degeneración dopaminérgica podría servir para estudiar mecanismos compensatorios que ocurren en la fase temprana de la enfermedad.

P 48

CSF1R regulates microgliosis and disease progression in Amyotrophic Lateral Sclerosis.

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3 Laboratory of Genetic Biochemistry (LAGENBIO-I3A), Aragon Institute of Health Sciences, Universidad de Zaragoza. Zaragoza, Spain.

Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disorder that affects motor neurons (MNs) in the brain and spinal cord. ALS has a complex pathophysiology involving glutamate-induce cytotoxicity, protein aggregation, cytoskeletal abnormalities and glial cell activation. Although microgliosis is an important hallmark of neurological diseases, the study of microglia in ALS has generated controversial results. In the present study we found that microglia expansion in the spinal cord of SOD1G93A mice correlates with the upregulation of the components of the CSF1 receptor (CSF1R) pathway. In order to evaluate whether CSF1R contributes to microgliosis in this ALS model, we treated SOD1G93A mice with GW2580, a selective CSF1R inhibitor. We found that daily treatment with GW2580, starting at the pre-symptomatic stage of the disease (day 60), reduced microglial cell proliferation in the lumbar spinal cord of SOD1G93A. Moreover, inhibition of CSF1R also reduced microglial cell activation but did not interfere with cell polarization. Interestingly, we observed that targeting CSF1R slowed disease progression and increased lifespan of the mice, correlating with an increased preservation of spinal motoneurons. Our findings support that CSF1R plays a crucial role in microgliosis and disease progression in ALS, and suggest that CSF1R inhibitors might be a good therapeutic candidate for the treatment of ALS patients.

P 49

Mechanisms Involved in Retrograde Motoneuron Degeneration and Survival

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2 Institut de Recerca Biomèdica de Barcelona, Barcelona, Spain.

Traumatic axotomy or mechanical traction (avulsion) of the nerves near the spinal cord is caused by accidents that cause irreversible dysfunction and/or monoplegia. In patients who have been subjected to surgical reconnection of the injured nerves, only minor recovery of function is achieved, in part due to early primary loss of avulsed motoneurons (MNs) by retrograde degeneration. In our experimental model of nerve root avulsion in the adult rat, up to 80 % of MNs are progressively lost by still unknown mechanisms. On the other side, after axotomy and surgical repair of the nerve at a distal site, MNs are able to survive and regenerate their axons. It is not known how MNs can cope with this axotomy stress in the latter but not in the former case. In order to shed light into this, we have carried out proteomic analysis to compare these models. Besides, we generated protein-protein interactomes from 331 protein-seeds that defined 19 motives chosen by manual curation of the literature as main biological processes related with either regenerative or degenerative events in adult spinal MNs. We performed GSEA bioinformatic analysis to confront our proteomic data to these specific interactomes. We validated some results by immunohistochemistry and western blot analysis. Among significant motives, networks associated with autophagic- related events together with those of anti-anoikis are strongly linked to the endogenous neuroprotective mechanisms triggered in MNs to survive in vivo after axotomy. This accurate information can be also a useful platform to develop effective neuroprotective therapies.

Foro Social

Asociaciones de familiares de pacientes

Participantes

- **Dª Inmaculada Fernández**, Federación Catalana de Alzheimer
- **Dª Flor De Juan,** Alzheimer León
- **Dª Mercedes García**, Alzheimer León
- **Dª Carmen José Ruiz Pareja**, Alzheimer Soria
- **Dª Juana García Tomás,** AFA Valencia
- **Dª Ana Morón Esteban,** AFA Valencia
- **D. Pere Isart**, AFA Tárrega
- **Dª Ramona Moix,** AFA Tárrega
- **Dª Montserrat Segarra,** AFA Tárrega
- **Dª Catalina Rotger Callonch,** AFA Pollença
- **Dª María Morro Cifre,** AFA Pollença

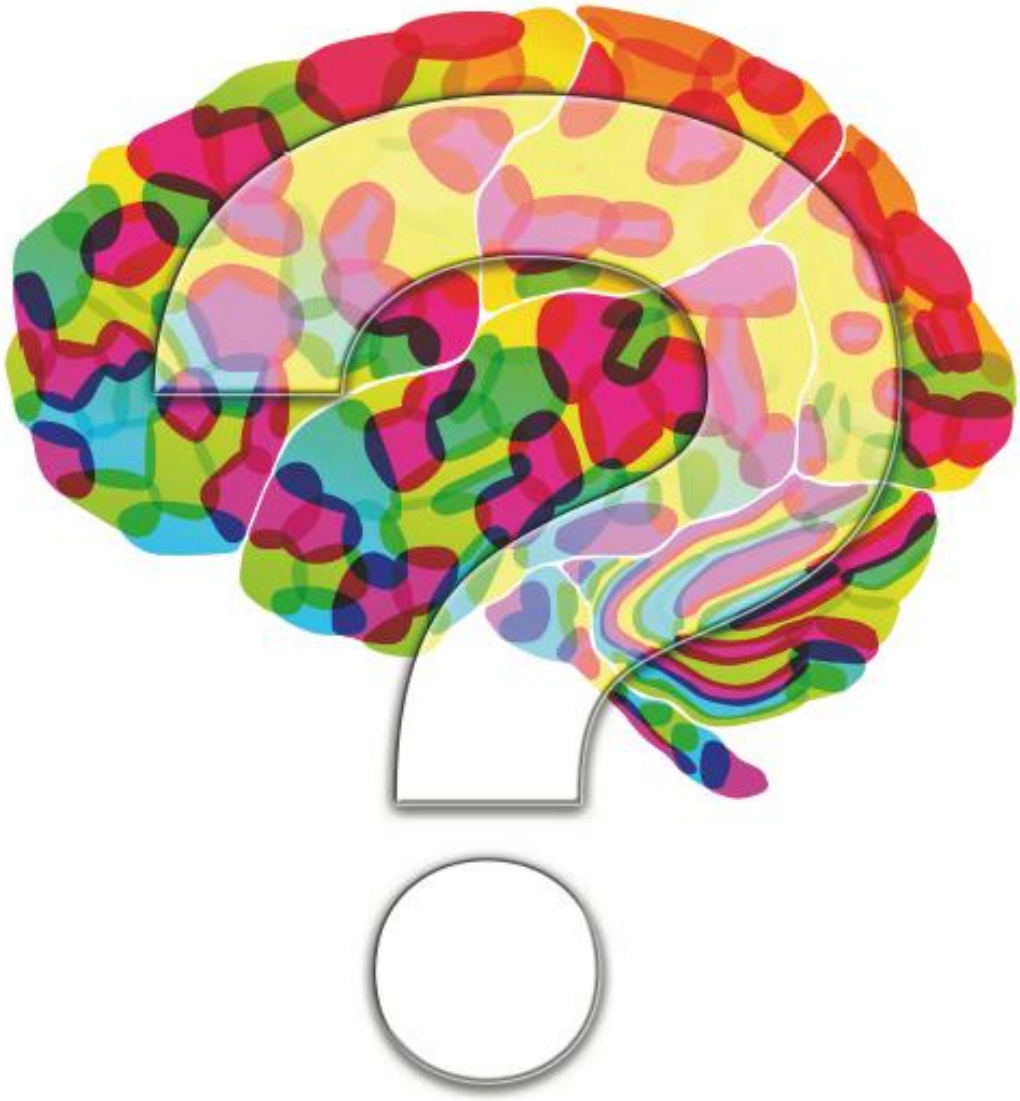
Invitados

- **D. Koldo Aulestia**, CEAFA
- **D. Jesús Mª Rodrigo**, CEAFA
- **Dª Ascensión Gómez Valero**, Asociación Alzheimer San Rafael, Córdoba
- **D. Antonio Anguita**, Asociación Alzheimer San Rafael, Córdoba

Participantes Mesa Redonda

- **D. Emilio de Benito** – Moderador
- **Dr. Alberto Lleó** – Neurólogo e investigador
- **D. Manel Martí** – Enfermo de alzhéimer
- **Dª. Mª Carmen Pardina Sierra** – Familiar
- **Dª. Carmen Ponce** – Cuidador no familiar
- **Dra. Mercè Agustí Pareda** – Médico de atención primaria
- **Dª Inmaculada Fernández Verde** – Representante de asociación de familiares

Tú tienes un papel en la lucha contra el alzhéimer



Foro Social CIIIEN 2014

23 septiembre 2014 - Barcelona

Foro Social CIIEN 2014

23 septiembre 2014 - Hotel Barceló Sants

Con motivo del **Día Mundial del Alzhéimer**, el 21 de septiembre, **Fundación Reina Sofía, Fundación CIEN y CIBERNED** van a realizar un debate abierto a pacientes, familiares, médicos, asociaciones, investigadores y todas las personas interesadas.

En el debate se contestarán una selección de las preguntas publicadas en Twitter con el hashtag **#PapelAlzheimer.**

Recuerda, unidos podremos avanzar en la lucha contra esta enfermedad silenciosa.

Tú tienes un papel en la lucha contra el alzhéimer

Programa:

18:30 h. Presentación y bienvenida.

18:35 h. Proyección del vídeo sobre alzhéimer

18:45 h. Debate.

Modera: Emilio de Benito, periodista especializado en sanidad y ciencia.

Participan:

Neurólogo e Investigador – **Alberto Lleó**

Enfermo de alzhéimer - **Manel Martí**

Familiar - **Mª Carmen Pardina Sierra**

Cuidador no familiar - **Carmen Ponce,**

Médico de atención primaria - **Mercè Agustí Pareda**

Representante de asociación de familiares - **Inmaculada Fernández Verde**

20:00 h. – 20:45 h. Enfermedades de Huntington y Parkinson.

Ponencia enfermedad de Huntignton:
"Pasado, presente y futuro de la investigación en la EH".
Saül Martínez-Horta, Unidad del Parkinson y Trastornos del Movimiento, Hospital de la Sants Creu i Sant Pau. Coordinador del Grupo Europeo para la enfermedad de Huntington.

Ponencia enfermedad de Parkinson:
"El papel de los pacientes en la investigación"
Eduardo Tolosa, Unidad de Párkinson y Trastornos del Movimiento del Hospital Clinic de Barcelona. IP de CIBERNED.

Organizan:

Colaboran:

Preguntas Formuladas

- ¿Qué papel juega la herencia genética en los factores de riesgo para desarrollar alzhéimer?
- ¿Por qué unos desarrollan la enfermedad y otros teniendo taupatías cerebrales no la desarrollan? ¿Seguimos pensando en la reserva cognitiva o son más potentes los factores externos como el estrés u hábitos de vida?"
- ¿Cuál es el componente hereditario en el alzhéimer esporádico?
- Se oye mucho hablar del diagnóstico temprano, pero ¿De qué vale si no hay cura para la enfermedad?
- Si tienes un hijo con 41 años, y a los 66 te diagnostican la enfermedad de Alzheimer, ese hijo tiene más probabilidades de desarrollar el Mal de Alzheimer que los hijos que han nacido primero?
- ¿Cómo de alto es el riesgo de que mis hijos puedan heredar esta enfermedad pues mi esposa inicio a los 47 años?
- Tengo entendido que las personas que toman somníferos para dormir, a largo o corto plazo puede derivarse en un Alzheimer. ¿Es cierto?
- ¿Cómo se puede detectar a temprana edad el Alzheimer?
- ¿Pueden provocar los problemas de sueño el deterioro cognitivo?
- ¿Por qué la gente se preocupa tanto del cuerpo y bastante menos del cerebro, cuando debería de ser totalmente al revés?

- Con el deterioro de las neuronas que producen el alzhéimer se deterioran los órganos de los sentidos ¿Cuál de ellos es el que menos se ve afectado?
- ¿Cómo paliar que el 50% de cuidadores no profesionales termine con depresión, ansiedad o agotamiento?
- ¿Por qué adelgazan los enfermos de alzhéimer? porque mi mamá come de todo menos pollo y además toma calcio y vitaminas.
- ¿Se podrá crear una vacuna contra el alzhéimer?
- ¿Pueden sufrir deterioro cognitivo las personas con problemas de sueño?
- ¿Qué se puede hacer para prevenir el alzhéimer?
- ¿Es normal perder la memoria al hacerte mayor o hay que pensar que se puede estar desarrollando una demencia?
- ¿Está aumentando el número de personas con enfermedad de Alzheimer?
- ¿Qué signos o síntomas deben alertarnos sobre la existencia del alzhéimer?
- ¿Son conscientes los pacientes del inicio del alzhéimer?
- ¿Me puedo apuntar al Proyecto Vallecas o a alguna investigación sobre Alzhéimer?
- ¿Cuánto puede vivir una persona a la que le acaban de diagnosticar alzhéimer?
- ¿Podemos esperar a corto o medio plazo que seamos capaces de revertir parcial o totalmente los daños producidos por la enfermedad de Alzheimer?

Difusión

Notas de prensa

Convocatoria de prensa

El próximo jueves 18 de septiembre, en el Centro Alzheimer Fundación Reina Sofía

La Fundación Reina Sofía y la Fundación CIEN presentan el congreso internacional en enfermedades neurodegenerativas

- **El Congreso sobre Investigación e Innovación en Enfermedades Neurodegenerativas (CIIIEN) analizará las enfermedades de Alzheimer, Parkinson y Huntington, principalmente.**
- **Previamente se presentará el cupón de la ONCE dedicado a la campaña "Edición Recuerda", de sensibilización sobre alzheimer.**

(Madrid, 16 de septiembre de 2014). **La Fundación Reina Sofía**, junto con la Fundación Centro de Investigación en Enfermedades Neurológicas (Fundación CIEN) y el Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas (CIBERNED), **presentará el próximo jueves 18 de septiembre** el **Congreso Internacional sobre Investigación e Innovación en Enfermedades Neurodegenerativas (CIIIEN),** que tendrá lugar los próximos 22 y 23 de septiembre en Barcelona.

El doctor **José Ramón Naranjo Orovio, investigador del Centro Nacional de Biotecnología del CSIC (CNB) y CIBERNED** atenderá a los medios en rueda de prensa con el objetivo de avanzar algunos de los principales contenidos que se tratarán en el Congreso, coincidiendo con la conmemoración del Día Mundial del Alzheimer –21 de septiembre-

Previamente, tendrá lugar la **presentación del Cupón de la ONCE del próximo sábado 20 de septiembre**, cuya imagen contribuye a la difusión de la campaña de sensibilización y recaudación de fondos para la investigación en alzheimer, **"Edición Recuerda"**. A la misma asistirán **Alberto Durán**, vicepresidente 1º ejecutivo de la Fundación ONCE; José Luis Nogueira, secretario de la Fundación Reina Sofía; **José Ramón Menéndez Aquino**, Director General del Mayor de la Comunidad de Madrid; y **Mª Ángeles Pérez,** directora gerente de la Fundación CIEN y CIBERNED.

Fecha y hora: **Jueves, 18 de septiembre de 2014**

11,00 h - Presentación del cupón ONCE dedicado a "Edición Recuerda"

11,30 h - Presentación del Congreso Internacional sobre Investigación e Innovación en Enfermedades Neurodegenerativas (CIIIEN)

Lugar: **Centro Alzheimer Fundación Reina Sofía** (C/ Valderrebollo, 5, 28031 Madrid)

Contacto: Ida de la Hera 91 545 01 96/667 148 353 idelahera@servimedia.net

Nota informativa

Los próximos 22 y 23 de septiembre, en el Hotel Barceló Sants (Barcelona)

Barcelona acogerá la próxima semana un congreso internacional de investigación en neurodegeneración

- **Bajo la presidencia de S.M. la Reina Doña Sofía el Congreso sobre Investigación e Innovación en Enfermedades Neurodegenerativas (CIIIEN) analizará las enfermedades de Alzheimer, Parkinson y Huntington, principalmente.**
- **Como clausura, el martes 23 de septiembre se celebrará un Foro Social con asociaciones, familiares y pacientes de estas enfermedades**

(Madrid, 18 de septiembre de 2014). La Fundación Reina Sofía, junto con la Fundación Centro de Investigación en Enfermedades Neurológicas (Fundación CIEN) y el Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas (CIBERNED), celebrarán los próximos **22 y 23 de septiembre** el **Congreso Internacional sobre Investigación e Innovación en Enfermedades Neurodegenerativas (CIIIEN),** que contará con la **presidencia de S.M. la Reina Doña Sofía**.

La directora gerente de la Fundación CIEN, Mª Ángeles Pérez, ha aprovechado la presentación para mostrar su agradecimiento **"por el interés personal"** que tanto la Ministra de Sanidad, Asuntos Sociales e Igualdad, **Ana Mato** -quien acompañará a la Reina Doña Sofía en la inauguración oficial del Congreso- **como la Reina Doña Sofía, "han mostrado en esta y anteriores ocasiones por este congreso que, sin el apoyo de su Fundación, no sería posible".**

El doctor **José Ramón Naranjo Orovio,** investigador del Centro Nacional de Biotecnología del CSIC (CNB) y CIBERNED, ha adelantado hoy en una rueda de prensa celebrada en el Centro Alzheimer Fundación Reina Sofía algunos de los principales contenidos que se tratarán en el Congreso, que coincide con la conmemoración del **Día Mundial del Alzheimer, el próximo 21 de septiembre.**

Estructurado en ocho sesiones trabajo y dos conferencias plenarias, se trata de un congreso de **"altísimo nivel científico",** aseguró Naranjo, gracias al gran **"nivel en neurociencia existente en España",** en que destacan centros como CIBERNED, "único centro español junto con la Fundación CIEN que forma parte de las **redes europeas de excelencia en investigación**".

Durante el congreso, explicó Naranjo, se abordarán principalmente "tres bloques fundamentales en la investigación en neurodegeneración, como son la **identificación de biomarcadores, las terapias celulares y los mecanismos neuroprotectores**".

En cuanto al primero de los bloques, el estudio e identificación de biomarcadores en enfermedades neurodegenerativas, Naranjo afirmó que los investigadores están buscando

"biomarcadores lo más sensibles y precoces posibles", ya que "**cuando las enfermedades neurodegenerativas dan la cara normalmente no hay nada que hacer"**.

Así, se ha referido también a la importancia del desarrollo de **terapias celulares**, "menos aplicables a alzheimer ya que "son muchas áreas se van degenerando de manera progresiva y cuando aparece el cerebro está muy dañado", pero que representan una esperanza en enfermedades como el **párkinson**, "ya que **la sustitución de neuronas es más factible al ser menor la cantidad afectada y distribuirse de forma más localizada"**.

Con respecto al avance en el desarrollo de **mecanismos de neuroprotección**, el doctor Naranjo se ha referido a su idoneidad en estas enfermedades, "que tienen un **componente genético y hereditario cada vez más conocido**", con lo que la inducción de las funciones compensadoras del cerebro que suponen estas estrategias "es una de las líneas fundamentales de trabajo, ya que **puede ralentizar la aparición de estas enfermedades**", además de atenuar sus efectos.

Por último, Naranjo ha destacado la parte final del congreso, en que, con un tinte más social, la Fundación Reina Sofía, la Fundació ACE - Instituto Catalán de Neurociencias Aplicadas y la Fundación Pascual Maragall presentarán **sus "proyectos estrella, como es el caso del Proyecto Vallecas de la Fundación Reina Sofía"**.

Tras esta sesión, el Congreso concluirá con la celebración de un Foro Social consistente en tres mesas redondas que contarán con la participación de asociaciones, familiares y pacientes de las enfermedades de Alzheimer, Parkinson y Huntington.

Tema: **Barcelona acogerá la próxima semana un congreso internacional de investigación en neurodegeneración**

Contacto: Ida de la Hera
91 545 01 96/667 148 353 idelahera@servimedia.net

Convocatoria de prensa

El próximo lunes 22 de septiembre, en el Hotel Barceló Sants (Barcelona)

S.M. la Reina Doña Sofía inaugurará el congreso internacional en enfermedades neurodegenerativas

- **El Congreso sobre Investigación e Innovación en Enfermedades Neurodegenerativas (CIIIEN) se celebrará los próximos 22 y 23 de septiembre en Barcelona y analizará las enfermedades de Alzheimer, Parkinson y Huntington, principalmente**

- **S.M. la Reina Doña Sofía inaugurará oficialmente el congreso acompañada de la Ministra de Ministra de Sanidad, Servicios Sociales e Igualdad, Ana Mato, y el director del Instituto Carlos III, Antonio Andreu**

(Barcelona, 18 de septiembre de 2014). **S.M. la Reina Doña Sofía,** acompañada de la Ministra de Ministra de Sanidad, Servicios Sociales e Igualdad, **Ana Mato, y** el director del Instituto Carlos III, **Antonio Andreu**, inaugurará el **próximo lunes 22 de septiembre** el **Congreso Internacional sobre Investigación e Innovación en Enfermedades Neurodegenerativas (CIIIEN),** que tendrá lugar los próximos 22 y 23 de septiembre en Barcelona.

Los medios de comunicación interesados en cubrir informativamente este acto deberán solicitar acreditación para sus representantes enviando la petición **por correo electrónico a premsa.catalunya@seap.minhap.es antes de las 15.00 horas del viernes 19 de septiembre** en la que consten nombre y apellidos, DNI o pasaporte y medio al que representan.

Los periodistas acreditados deberán presentarse en el **Hotel Barceló Sants a las 11.15 horas**.

El congreso, organizado por la **Fundación Reina Sofía**, junto con la Fundación Centro de Investigación en Enfermedades Neurológicas (**Fundación CIEN**) y el Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas (**CIBERNED**), analizará los principales avances en la investigación en enfermedades neurodegenerativas, especialmente las enfermedades de Alzheimer, Parkinson y Huntington.

Fecha y hora: **Lunes, 22 de septiembre de 2014, 11,15 h.**

Lugar: **Hotel Barceló Sants** (Plaça dels Països Catalans s/n, Barcelona)

Contacto Fundación Reina Sofía – Fundación CIEN - CIBERNED: Ida de la Hera

91 545 01 96/667 148 353 idelahera@servimedia.net

Nota de prensa

El congreso tiene lugar en Barcelona hasta mañana martes 23 de septiembre

S.M. la Reina Doña Sofía inaugura el II Congreso Internacional en Enfermedades Neurodegenerativas

- **El Congreso sobre Investigación e Innovación en Enfermedades Neurodegenerativas (CIIIEN) está celebrando su segunda edición hasta mañana 23 de septiembre en Barcelona**
- **Centrado en las enfermedades de Alzheimer, Parkinson y Huntington, principalmente, reúne a casi 200 investigadores nacionales e internacionales del campo de la neurociencia**

(Madrid, 18 de septiembre de 2014). **S.M. la Reina Doña Sofía,** acompañada de la Secretaria de Estado de Servicios Sociales e Igualdad, **Susana Camarero, y** el director del Instituto Carlos III, **Antonio Andreu**, ha inaugurado oficialmente hoy en Barcelona el **II Congreso Internacional sobre Investigación e Innovación en Enfermedades Neurodegenerativas (CIIIEN),** que tendrá lugar los próximos 22 y 23 de septiembre en Barcelona.

El congreso, organizado por la **Fundación Reina Sofía**, junto con la Fundación Centro de Investigación en Enfermedades Neurológicas (**Fundación CIEN**) y el Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas (**CIBERNED**), analiza los principales avances en la investigación en enfermedades neurodegenerativas, especialmente las enfermedades de Alzheimer, Parkinson y Huntington.

La Secretaria de Estado de Servicios Sociales e Igualdad, **Susana Camarero,** ha agradecido a las instituciones organizadoras su esfuerzo por **"consolidar un foro de referencia internacional"** como es el actual congreso. Camarero ha querido hacer mención especial a la **"sensibilidad, apoyo y compromiso personal de S.M. la Reina Doña Sofía** con las personas afectadas por enfermedades neurodegenerativas", quien, "a través de la labor que realiza la fundación que lleva su nombre pone de manifiesto la **voluntad de la Casa Real, y de la suya propia, de continuar al lado de los que sufren",** "promoviendo la investigación y la información" en este ámbito, y promoviendo su puesta "a disposición de familiares y enfermos".

La Secretaria de Estado ha destacado asimismo el importante trabajo que se está desarrollando en el campo de la neurodegeneración en España, con iniciativas como la puesta en marcha de la Estrategia para el abordaje de la cronicidad, o la **Estrategia Nacional para la Investigación en Enfermedades Neurodegenerativas**, puesta en marcha el pasado mes de marzo y que se espera esté definida, tras el trabajo conjunto con investigadores, asociaciones y enfermos, a finales de año.

Antonio Andreu, director del Instituto de Salud Carlos III, ha destacado la necesidad de estos encuentros "para que investigadores básicos, trasnacionales y clínicos pongan en común no sólo

sus aciertos, sino también sus errores", que constituyen los **"elementos cosustanciales de la verdadera ciencia"**. Instituciones, investigadores y asociaciones participantes en el congreso, ha continuado, que "comparten el objetivo común de trabajar por un sistema en que la ciencia desvele las claves de cómo **luchar de forma eficiente contra una de los mayores retos de nuestra sociedad",** que son las enfermedades neurodegenerativas.

"**Vosotros sois nuestra esperanza** para que un día cercano podamos **desarrollar estrategias eficaces para la prevención, el diagnóstico y sobre todo el tratamiento** que nos permitan combatir este gran problema social", ha señalado Andreu refiriéndose a los investigadores de CIBERNED, un grupo que, prosiguió, supone un espacio de colaboración y agregación del conocimiento que ha supuesto "**avances espectaculares que nos sitúan en la antesala de un nuevo horizonte de la neurociencia**".

Por segundo año consecutivo, este congreso **supone la unión del X Simposio Internacional "Avances en la enfermedad de Alzheimer" y el VIII Foro Científico CIBERNED,** y cuenta con la participación y presencia de numerosos investigadores nacionales e internacionales.

Durante el mismo, se abordarán principalmente tres bloques principales en la investigación en neurodegeneración, como son la **identificación de biomarcadores, las terapias celulares y los mecanismos neuroprotectores.**

Al término de las sesiones científicas el martes 23, **tendrá lugar un Foro Social** consistente en tres mesas redondas que contará con la participación de asociaciones, familiares y pacientes de alzhéimer, párkinson y Huntington.

Contacto Fundación Reina Sofía – Fundación CIEN - CIBERNED: Ida de la Hera

91 545 01 96/667 148 353 idelahera@servimedia.net

Nota de prensa

Concluye el II Congreso Internacional sobre Investigación e Innovación en Enfermedades Neurodegenerativas

- **Centrado en las enfermedades de Alzheimer, Parkinson y Huntington, principalmente, el congreso ha reunido a alrededor de 200 investigadores nacionales e internacionales del campo de la neurociencia**

(Madrid, 23 de septiembre de 2014). – La Fundación ACE - Instituto Catalán de Neurociencias Aplicadas, la Fundación Pasqual Maragall y la Fundación CIEN han clausurado hoy con la presentación de **tres proyectos innovadores en alzhéimer** el II Congreso Internacional sobre Investigación e Innovación en Enfermedades Neurodegenerativas, que ha tenido lugar en Barcelona los días 22 y 23 de septiembre.

Durante la clausura, **Agustín Ruiz,** director de la Fundación ACE - Instituto Catalán de Neurociencias Aplicadas, ha explicado a los asistentes el trabajo que desde su fundación se hace en investigación en alzhéimer. Ruiz, quien ha destacado que **"la prevalencia del alzhéimer se duplica en cada intervalo de 5 años desde los 65 años de edad",** ha expuesto el trabajo que su Fundación realiza en el estudio genético de la enfermedad de alzhéimer.

En este campo, se ha referido a las investigaciones realizadas como parte del **consorcio español DEGESCO** (Consorcio Español de Genética de Demencias) –al que pertenecen asimismo diversos investigadores de CIBERNED- **que el pasado año identificó 11 nuevos genes relacionados con el alzhéimer,** lo que ha supuesto el inicio de la investigación en nuevas dianas para la investigación farmacológica, además de la **confirmación del papel del sistema inmunológico en la enfermedad de Alzheimer –**gracias a la identificación de genes relacionados con la enfermedad en la región HLA-DRB5/DRB1 del complejo mayor de histocompatibilidad; familia de genes fundamentales en la defensa inmunológica del organismo-.

Por su parte, **Juan D. Gispert**, de la Fundación Pasqual Maragall, ha presentado el trabajo del Centro de Investigación Barcelonaβeta, un proyecto que, impulsado por la fundación, integra investigación básica, clínica e innovación tecnológica para el estudio del cerebro, con el objetivo de contribuir al conocimiento científico que provea soluciones efectivas a la enfermedad de Alzheimer y a los problemas cognitivos asociados al envejecimiento. Gispert se ha centrado en el estudio de la atrofia hipocampal –el cambio en la morfología del hipocampo- y sus efectos en las demencias y en particular en alzhéimer.

Asimismo, **Miguel Medina,** director científico adjunto de CIBERNED e investigador principal del **Proyecto Vallecas de la Fundación CIEN - Fundación Reina Sofía,** ha expuesto los resultados parciales del Proyecto Vallecas, un estudio longitudinal a 5 años que está estudiando neuropsicológica y biológicamente a **1.213 sujetos de entre 75 y 85 años, con el objetivo de comparar sus resultados e historias una vez concluido este intervalo**, en el momento en que algunos de ellos hayan desarrollado demencia y otros no. Así, se pretende establecer mayores relaciones biológicas y

neuropsicológicas con la demencia, y en particular con la enfermedad de alzhéimer, para contribuir al **diagnóstico precoz de la enfermedad.**

Medina ha agradecido **el apoyo "de la Fundación Reina Sofía, sin la que este proyecto no sería posible",** además de el trabajo del equipo multidisciplinar –neurólogos, psicólogos y técnicos- que trabajan en el proyecto.

II Congreso Internacional sobre Investigación e Innovación en Enfermedades Neurodegenerativas

Por segundo año consecutivo, el **Congreso Internacional sobre Investigación e Innovación en Enfermedades Neurodegenerativas (CIIIEN) ha supuesto la unión del X Simposio Internacional "Avances en la enfermedad de Alzheimer" y el VIII Foro Científico CIBERNED,** y cuenta con la participación y presencia de numerosos investigadores nacionales e internacionales.

Organizado por la Fundación Reina Sofía, la Fundación Centro de Investigación en Enfermedades Neurológicas (Fundación CIEN), y el Centro de Investigación Biomédica en Red en Enfermedades Neurodegenerativas (CIBERNED), el congreso ha reunido a más de 200 investigadores y personas relacionadas con el ámbito de la neurodegeneración, en un encuentro centrado en el análisis de las enfermedades neurodegenerativas.

Bajo la presidencia de S.M. la Reina Doña Sofía, la primera de las jornadas estuvo centrada en la aplicación de las terapias con células madre en enfermedades neurodegenerativas, el análisis del envejecimiento normal frente a la neurodegeneración patológica y los cambios preclínicos habituales en las enfermedades neurodegenerativas.

Durante esta jornada, se ha hecho entrega del Premio Joven Investigador 2013, que reconoce la labor de personas menores de 30 años, y que en esta edición recayó en la investigadora María Llorens Martín, del Centro de Biología Molecular "Severo Ochoa" (CSIC- UAM) y perteneciente al grupo de CIBERNED liderado por Jesús Ávila de Grado-, en reconocimiento a su trabajo "GSK-3b overexpression causes reversible alterations on postsynaptic densities and dendritic morphology of hippocampal granule neurons in vivo", publicado en febrero del pasado año por la revista Molecular Psychiatry, demuestra que los daños en neuronas granulares asociados al alzhéimer son reversibles.

La **segunda de las jornadas** ha estado centrada en los mecanismos de neuroprotección del cerebro y su estimulación –beneficiosos para el combate, prevención y tratamiento de las enfermedades neurodegenerativas-, el progreso en el conocimiento de la enfermedad de Huntington y la Esclerosis Lateral Amiotrófica (ELA) y los nuevos factores genéticos descubiertos recientemente en algunas enfermedades neurodegenerativas.

Tema: Concluye el II Congreso Internacional sobre Investigación e Innovación en Enfermedades Neurodegenerativas

Contacto Fundación Reina Sofía – Fundación CIEN - CIBERNED: Ida de la Hera

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La Reina Sofía inaugura el Congreso Ciiien

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El congreso internacional de enfermedades neurodegenerativas arranca con el apoyo de la reina Sofía

22.09.14 | 13:29h. EUROPA PRESS | BARCELONA

Durará dos días y reunirá a numerosos expertos de internacionales

La reina Sofía ha inaugurado este lunes en Barcelona la segunda edición del Congreso Internacional en Innovación e Investigación en Enfermedades Neurodegenerativas, que durará dos días y reunirá a numerosos expertos internacionales que ahondarán en el Alzheimer, el Parkinson y otras patologías relacionadas.

En el primer acto en la capital catalana al que acude tras la abdicación del rey Juan Carlos I, la reina Sofía ha estado acompañada por la secretaria de Estado de Servicios Sociales e Igualdad, Susana Camarero, –que ha sustituido a la ministra del ramo, Ana Mato, por motivos de agenda– y la delegada del Gobierno en Catalunya, Llanos de Luna, entre otros.

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La reina Sofía inaugura el II Congreso de enfermedades neurodegenerativas y alzhéimer

Se trata del segundo de los compromisos de la nueva agenda que seguirá a partir de ahora, que incluirá "actos puntuales y concretos". La reina Sofía se ha trasladado a Barcelona para inaugurar el II Congreso Internacional sobre Investigación e Innovación en Enfermedades Neurodegenerativas (Ciiien), organizado, entre otros, por la Fundación Reina Sofía, y ha asistido a varias sesiones en las que expertos internacionales han presentado y han debatido sobre patologías como el alzhéimer. Doña Sofía ha seguido la

Lunes 22-09-2014 archivo semanal: Lunes

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La reina Sofía inaugura congreso enfermedades neurodegenerativas y alzhéimer

EFE 22/09/2014 (15:17)

Barcelona, 22 sep (EFE).- La reina Sofía ha inaugurado hoy en Barcelona el II Congreso Internacional sobre Investigación e Innovación en Enfermedades Neurodegenerativas (Ciiien), organizado, entre otros, por la Fundación Reina Sofía, y ha asistido a varias sesiones en las que expertos internacionales han presentado y han debatido sobre patologías como el alzhéimer.

Doña Sofía ha seguido la presentación del doctor Michael Heneka, investigador de la Universidad de Bonn, y uno de los grandes expertos en alzhéimer, quien ha explicado que la inflamación tiene un papel activo en esta enfermedad.

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El congreso internacional de enfermedades neurodegenerativas arranca con el apoyo de la reina Sofía

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Durará dos días y reunirá a numerosos expertos de internacionales

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BARCELONA, 22 (EUROPA PRESS)

La reina Sofía ha inaugurado este lunes en Barcelona la segunda edición del Congreso Internacional en Innovación e Investigación en Enfermedades Neurodegenerativas, que durará dos días y reunirá a numerosos expertos internacionales que ahondarán en el Alzheimer, el Parkinson y otras patologías relacionadas.

En el primer acto en la capital catalana al que acude tras la abdicación del rey Juan Carlos I, la reina Sofía ha estado acompañada por la secretaria de Estado de Servicios Sociales e Igualdad, Susana Camarero, –que ha sustituido a la ministra del ramo, Ana Mato, por motivos de agenda– y la delegada del Gobierno en Catalunya, Llanos de Luna, entre otros.

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Miercoles, 15 de Octubre 2014

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DOS DÍAS

La reina Sofía inaugurará el lunes en Barcelona un congreso de enfermedad neurodegenerativas

Directorio: Barcelona Enfermedades Congreso Innovación

Foto: FOTO DE ARCHIVO REUTERS

BARCELONA, 18 Sep. (EUROPA PRESS) -

La reina Sofía inaugurará el lunes a las 12.00 en Barcelona el II Congreso sobre Investigación e Innovación de Enfermedades Neurodegenerativas, que durará dos días y reunirá a numerosos expertos internacionales, ha informado la Delegación del Gobierno en Catalunya en un comunicado.

12 | 1 | ? | 0

DIARIO MEDICO
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PÁGINAS: 1,9
TARIFA: 966 €
ÁREA: 232 CM² - 30%
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24 Septiembre, 2014

El papel de la inflamación de la microglía cobra más peso en Alzheimer

BARCELONA
KARLA ISLAS PIECK

El vínculo entre la inflamación y la enfermedad de Alzheimer es cada vez más evidente, por lo que se debe poner especial atención a los procesos inflamatorios, especialmente en las personas con factores de riesgo, según ha quedado de manifiesto durante el II Congreso Internacional en Enfermedades Neurodegenerativas que se ha celebrado estos días en Barcelona.

Jesús Ávila, director científico del Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas (Ciberned) y profesor del CSIC, ha

Según Ávila, estas nuevas evidencias refuerzan las teorías que apuntan la importancia de la inflamación en el desarrollo del Alzheimer, que cada vez cobran más peso en la investigación sobre esta enfermedad.

Otro de los estudios destacados que se han abordado en el congreso

Jesús Ávila, director científico del Ciberned

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ÁREA: 336 CM² - 30%
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23 Septiembre, 2014

Arrenca a Barcelona el congrés sobre malalties neurodegeneratives

▶ La reina Sofia inaugura una cita on experts d'arreu del món analitzen els últims avenços científics en la lluita contra l'Alzheimer o el Parkinson

BARCELONA | EFE/ACN/DdG

■ El II Congrés Internacional en Innovació i Investigació de Malalties Neurodegeneratives va començar ahir a Barcelona i reunirà durant dos dies destacats investigadors d'arreu del món. El congrés analitzarà els principals avenços científics en malalties neurodegeneratives, especialment en Alzheimer, Parkinson i Huntington i abordarà 3 blocs fonamentals en la investigació d'aquestes patologies que són la identificació de biomarcadors, les teràpies cel·lulars i els mecanismes neuroprotectors.

La reina Sofia va ser l'encarregada d'inaugurar la cita, acompanyada de la secretària d'Estat de Serveis Socials i Igualtat, Susana Camarero, i del director de l'Institut Carles III, Antonio Andreu. El congrés ha estat organitzat per la Fundació Reina Sofia, la Fundació Centre d'Investigació en Malalties Neurològiques (Fundació CIEN) i el Centre d'Investigació Biomèdica en Xarxa de Malalties Neurodegeneratives (CIBERNED).

Els experts participants en la cita

ANDREU DALMAU (EFE)

La reina Sofia va ser l'encarregada d'inaugurar la trobada de científics.

teràpies cel·lulars i els mecanismes neuroprotectors. Per tancar el congrés, tindrà lloc avui la celebració d'un Fòrum Social que consistirà en tres taules rodones que comptaran amb la participació d'associacions, familiars i pacients d'Alzheimer, Parkinson i Huntington.

secretària d'Estat, qui va subratllar que per aconseguir-ho és important portar hàbits de vida que evitin els factors de risc d'aparició i desenvolupament d'aquestes malalties.

Així, va explicar que l'actual repte de la sanitat és preveure o retardar el desenvolupament de les

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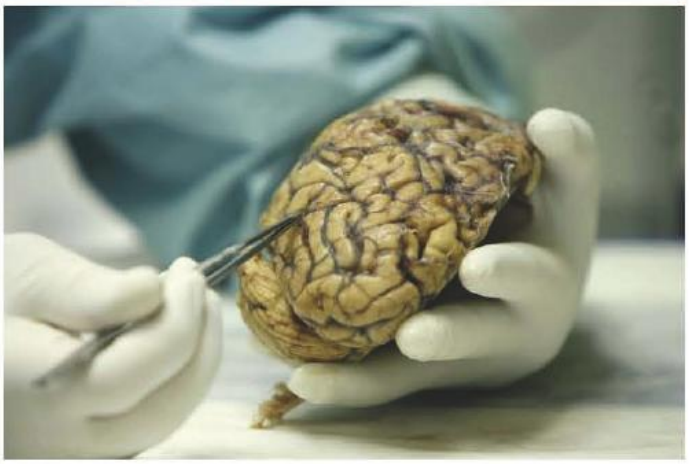
Barcelona reúne a 200 científicos para analizar los avances en alzhéimer, huntington y párkinson

Barcelona acogerá el 22 y 23 de septiembre el II Congreso Internacional de Investigación e Innovación en Enfermedades Neurodegenerativas, al que asistirán unos 200 científicos, nacionales e internacionales, y en el que se pondrá de manifiesto el "alto nivel" de la ciencia española en este campo.

EFEFUTURO MADRID | JUEVES 18.09.2014



EFE/Fernando Alvarado

El congreso, **dividido en ocho** sesiones de trabajo, **ha** sido presentado **hoy en Madrid, en el** Centro Alzhéimer Fundación **Reina Sofía**, y en él **se analizarán los últimos avances relacionados con esta enfermedad**, el párkinson y **huntington**, **principalmente**.

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