

Alzheimer 2011 Internacional



GLOBAL ALZHEIMER'S RESEARCH SUMMIT, MADRID 2011

BASIC AND CLINICAL RESEARCH

*Present and Future
of Alzheimer's Research*

ABSTRACT BOOK



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GLOBAL ALZHEIMER'S RESEARCH SUMMIT, MADRID 2011

Dear researchers,

Due to the International Year on Alzheimer's Research 2011, the Queen Sofia Foundation and the Pasqual Maragall Foundation organize the **Global Alzheimer's Research Summit, Madrid 2011** Congress.

This Event will congregate experts, professionals, scientists and researchers from around the world to present the latest advances in Alzheimer's Research with a view to advance our understanding of its causes and to improve the quality of life to the people affected and their caregivers.

Global Alzheimer's Research Summit, Madrid 2011 gathers in a unique program the health and social care and the basic and clinical research. It is also a platform for experts and neuroscientists from around the world to exchange their global experiences and knowledge.

From the Queen Sofia Foundation and the Pasqual Maragall Foundation we would like to show our most sincere gratitude to collaborators, associations of relatives, diagnosed people and the support of more than 1900 attendees for being part of this event.

Thanks to all of them, this Summit is a reality today.

Yours sincerely,



Arturo Coello
Vocal-Secretary
Fundación Reina Sofía



Jordi Camí
General Director
Fundación Pasqual Maragall

PROGRAMME

GLOBAL ALZHEIMER'S RESEARCH SUMMIT, MADRID 2011

THURSDAY SEPTEMBER 22nd

- 08.15–09.00** **Reception**
- 09.00–09.30** **Welcome**
Jordi Camí, Pasqual Maragall Foundation
Jesús Ávila, responsible of Basic and Clinical Area
Juan Carlos López, Nature Medicine
- 09.30–11.00** **Session 1 - “Molecular Mechanisms I”**
Chair: George Perry
Speakers: Sangram Sisodia
 Christian Haass
 Mony de Leon

Discussion
- 11.15–12.10** **Session 2 - “Molecular Mechanisms II”**
Chair: Juan Carlos López
Speakers: Virginia Lee
 Jesús Ávila

Discussion
- 13.00–13.45** **Keynote Lecture: Dennis Selkoe - “Deciphering the molecular basis of Alzheimer’s disease predicts novel therapies”**
- 15.00–16.00** **Session 3 - “Genetics”**
Chair: Eduardo Soriano
Speakers: Alison Goate
 Sandra Barral

Discussion
- 16.15–17.45** **Session 4 - “Therapeutic Advances”**
Chair: Bengt Winblad
Speakers: Dale Schenk
 Martin Citron
 Jeffrey Cummings

Discussion
- 18.00–18.30** **Presentation of the “International Network for knowledge and good practices Exchange”**
- 18.45–19.25** **Screening of Pasqual Maragall “Bicycle, Spoon, Apple”**

FRIDAY SEPTEMBER 23rd

09.00-10.30

Session 5 – “*Translational Research*”

Chair: Khalid Iqbal
Speakers: George Perry
Lennart Mucke
Bengt Winblad

Discussion

11.00-12.30

Session 6 – “*Biomarkers and Diagnosis*”

Chair: Jesús Ávila
Speakers: Bruno Dubois
Kaj Blennow
Khalid Iqbal

13.30-14.15

PLENARY TALK: Kenneth Kosik- “*Stalking an Alzheimer’s Gene in the Colombian Countryside*”

15.30-17.00 H

Session 7 – “*Novel Aspects of Basic Research in AD*”

Chair: Juan Carlos López
Speakers: Eduardo Soriano
Ángel Cedazo Mínguez
Javier de Felipe

Discussion

15.30-17.00 H

Session 8 – “*Novel Aspects of Clinical Research in AD*”

Chair: Pablo Martínez - Martín
Speakers: Philippe Amouyel
Juan Álvarez-Linera
José Luis Molinuevo

Discussion

17.10-18.20 H

PRESENTATION OF SELECTED POSTERS

Moderated by: Eduardo Soriano

18.20–18.30 H

CONCLUSIONS

KEYNOTE LECTURE

KEYNOTE LECTURE

Deciphering the molecular basis of Alzheimer's disease predicts novel therapies

Dennis Selkoe

Harvard Medical School, Brigham and Women's Hospital, Boston MA, USA

Research focused on the pathogenesis of human disease has often provided novel insights into fundamental mechanisms of cell biology. The study of Alzheimer's disease (AD) provides a salient example: the discovery of intramembrane proteolysis as a widespread protein processing and signaling mechanism arose in part from the identification of presenilin as an unusual aspartyl protease that cleaves APP within the membrane to release the amyloid β -protein ($A\beta$). The contemporaneous discovery that Notch receptors are cleaved by presenilin/ γ -secretase in an indistinguishable manner suggests how AD arose in the human population: a conserved proteolytic mechanism required for life in all metazoans can also generate a small hydrophobic peptide ($A\beta$) that accumulates with age in the limbic and association cortices of all primates and can progressively impair synaptic function. A key step towards proving the identify of a causative agent in human disease is to isolate the suspected agent from affected tissues of patients and recapitulate the disease phenotype by administering it to an experimental animal (Koch's postulate). Whereas many studies have examined synthetic and cell-derived $A\beta$ oligomers, the neural effects of $A\beta$ assemblies obtained directly from AD patients have not been established. We isolated soluble $A\beta$ oligomers (principally dimers) and insoluble amyloid plaque cores from the cerebral cortex of patients with typical AD but not from patients with non-AD dementias. The soluble oligomers dose-dependently inhibited long-term potentiation (LTP), enhanced long-term synaptic depression (LTD) and reduced dendritic spine density in normal rodent hippocampus. Further, the human oligomers potently disrupted the memory of a learned behavior in normal adult rats. These effects were specifically attributable to soluble low-n $A\beta$ oligomers at low nanomolar concentrations in the absence of amyloid fibrils; $A\beta$ monomers were inactive. Mechanistically, activation of metabotropic glutamate receptors was required for the LTD effect and of NMDA receptors for the spine loss. Therapeutically, immunodepleting oligomers from the AD brain isolates reversed all effects, and co-administering antibodies to the N- (but not C-) terminus of $A\beta$ prevented

both the LTP and LTD deficits. Insoluble amyloid plaque cores from AD cortex did not impair LTP unless they were first solubilized to release A β dimers, suggesting that plaque cores are themselves largely inactive but sequester A β dimers that are potentially synaptotoxic. We conclude that A β oligomers extracted directly from AD brains potently impair synapse structure and function in hippocampus and that soluble dimers are the minimal synaptotoxic species. These findings fulfill a key criterion for establishing disease causation in AD.

PLENARY TALK

PLENARY TALK

“Stalking an Alzheimer’s Gene in the Colombian Countryside”

Kenneth S. Kosik

University of California, Santa Barbara, Santa Barbara, California, USA

Beyond the point in southern Colombia where the Andes split into the Cordillera Central and the Cordillera Occidental, the conquistador Jorge Robledo founded the town of Santa Fe de Antioquia in 1541, which later became the capital of the state of Antioquia until 1826 when the capital was moved to Medellin. Somewhere in the turmoil of this tectonic cultural clash between the Spanish and the indigenous people, a story, forever lost, of either romance or rape resulted in a genetic event that eventually marked numerous families across this rugged mountainous terrain with a form of Alzheimer’s disease that begins in the mid-forties. Even more remarkable is that now, having endured this scourge for generations, the people of this remote land may help to solve the global toll of Alzheimer’s disease.

As the family trees of the people with early onset Alzheimer’s grew by piecing together genealogies from birth and death records in churches throughout the region, it became clear that the root cause of the disease was a gene mutation. This mutation, which we now know changes one nucleotide out of the three billion in the genome, sits quietly in nearly every cell until one reaches the fifth decade when the insidious deterioration of memory begins to erode one’s personality.

Today these Colombian families number over 5000 people. Among them are children and young adults who carry the deadly mutation. With gene testing it is possible to know who will get the disease and when. As this story has unfolded, Alzheimer trialists have increasingly shifted trial designs toward individuals with the earliest symptoms and even pre-symptomatic preventive treatments. This thinking about Alzheimer’s prevention has converged with an opportunity to conduct a treatment trial in the Colombian population in which the outcome measure is a delay in the age of onset beyond the very tight mean of 47 years. The many gene carriers approaching the age of risk makes conducting a trial statistically feasible. The key individual behind all of the family studies in Colombia is Francisco Lopera, a neurologist who comes from the same region of Antioquia where many of the families reside. Lopera and

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his nurse Lucia Madrigal have worked tirelessly to assemble family trees, follow the patients, and care for them. Most recently Eric Reiman and Pierre Tariot have joined our group and are making the possibility of a clinical trial, which the Colombian families welcome, a reality.

SESSIONS

SESSION 1

"Molecular Mechanisms I"

PRESENILIN FUNCTION IN HEALTH AND DISEASE

Sangram S. Sisodia,

The University of Chicago, Chicago, Illinois, USA

Inheritance of mutant PSEN genes encoding presenilins (PS1 and PS2) variants cause autosomal dominant, familial Alzheimer's disease (FAD). PS is the catalytic subunit of the γ -secretase complex that is essential for intramembranous processing of APP, Notch and several type I membrane proteins and we will present recent efforts aimed at elucidating the structure and activity of the γ -secretase complex. In addition, we will summarize experiments that test the proposal that PSEN deficiency leads to deficits in autophagy. Finally, studies will be presented that extend our earlier report that ubiquitous expression of FAD-linked PS1 variants exhibit impairments in enrichment-mediated proliferation and neurogenic differentiation of progenitors (NPCs) in the hippocampal niche in a non-cell autonomous manner. For these experiments, we will describe the analysis of mice with a mutant knockin allele in the PSEN1 locus, and in a transgenic line in which an FAD-linked PSEN transgene can be conditionally inactivated in a cell-specific and/or temporal manner to assess enrichment-mediated effects of FAD-linked PS1 variants on NPC phenotypes in in vivo settings.

Supported by NIH AG027854 (SSS), the Edward H. Levi Fund, CINN Foundation, Adler Foundation and Cure Alzheimer's Fund (CAF). SSS is a paid Consultant of Nocira, Inc. and Eisai Research Labs Inc.

MODULATION OF γ -SECRETASE ACTIVITY

Christian Haass

German Center for Neurodegenerative Diseases - Munich (DZNE) & Adolf Butenandt Institute, Biochemistry, Ludwig-Maximilians-University Munich, Munich, Germany

Secretase plays a pivotal role in Amyloid β -peptide ($A\beta$) generation. Secretase is a protease complex composed of the four essential components, presenilin, nicastrin, aph-1, and Pen-2. We cannot confirm other reported components of the secretase complex. Presenilin contains the active site domain comprised by a GxGD motif, which defines a novel class of intramembrane cleaving aspartyl proteases including signal peptide peptidases (SPPs) and their homologues (SPPLs) as well as the prepilin peptidases. We provide evidence that sequential cleavage of substrates is a common feature of secretase as well as SPPLs. Similarly presenilin autoactivates itself by sequential endoproteolysis. Inhibition of secretase leads to unwanted side effects mostly due to blocking of its essential function in Notch signaling and clinical trials were consequently cancelled. Modulation of secretase activity, instead of its inhibition is therefore a more hopeful therapeutic approach. However, first generation γ -secretase modulators (GSM) such as a subset of the non-steroidal anti-inflammatory drugs (NSAIDs) failed to prove efficacy in a clinical trial. Nevertheless, high affinity second-generation GSMs have been generated. The high therapeutic potential of these compounds is demonstrated by their ability to lower $A\beta_{1-42}$ produced from a number of very aggressive PS1 and PS2 mutations, whereas conventional NSAID-type GSMs fail to do so. Little is known how γ -secretase activity may be regulated. We therefore conducted a genome-wide RNAi screen in *Drosophila* S2 cells to identify secretase regulators/modulators. Several proteins will be presented, which via different cellular mechanisms affect $A\beta$ generation.

BIOMARKERS FOR PRESYMPTOMATIC DIAGNOSIS OF AD AND MECHANISM DISCOVERY

M. J. de Leon

New York University School of Medicine, New York, NY, USA

The detection of Alzheimer's disease (AD) in its presymptomatic stages is a reality. Our recent studies show this capacity using imaging modalities that include: FDG-PET and high resolution serial MRI. However, while FDG-PET

and MRI studies of the hippocampal formation show sensitivity for early features of AD at both the normal and MCI stages of cognition and show good correlation with clinical progression, these measures alone are not specific for AD. Additional valid markers for the neurofibrillary and amyloid plaque pathology of AD are required for diagnostic confidence. Our recent studies show that CSF measures of hyperphosphorylated (P) P-tau contribute this diagnostic potential and also correlate with the brain changes found in presymptomatic AD. CSF and PET biomarkers of amyloid beta (Ab) to a lesser extent show diagnostic and correlative potential. Overall, the data suggest that a combination of both sensitive and specific markers is useful for advance diagnosis. Moreover, as recent studies show that AD specific biomarkers do not show meaningful progression effects, sensitive imaging modalities will be of continued value for following the course of AD. We will present longitudinal evidence supporting the combined use of imaging and AD specific biomarkers in the presymptomatic diagnosis of AD.

Perhaps the most important objective for imaging and biomarkers is the identification of new mechanisms of AD risk and progression in presymptomatic subjects. In a series of longitudinal NL aging studies we observe evidence two emergent mechanisms: 1) presymptomatic subjects with a maternal history of AD show reduced glucose metabolism cross-sectionally and longitudinally as well as evidence for brain amyloid deposits; and 2) using MRI-ASL, NL elderly with elevated plasma Ab40 levels show impaired CO₂ induced vasodilation of hippocampal blood vessels. This impaired reactivity is independent of vascular reactivity deficits associated with cerebrovascular disease.

In summary, FDG-PET and MRI imaging have provided sensitive measures for the detection of AD in MCI and presymptomatic stages. Both FDG-PET and MRI imaging when combined with AD specific biomarkers improve diagnostic classifications at all stages of AD. Thus, the presymptomatic recognition of AD is a realistic goal. However, biomarkers and imaging have also provided new evidence for two potential mechanisms related to AD: 1) the reduced metabolism and increased AD risk in the offspring of a mother affected by AD suggests the inheritance of defects in mitochondrial DNA and 2) a vascular amyloid mediated alteration of cerebral vascular reactivity suggests basis for progressive brain damage.

SESSION 2

“Molecular Mechanisms II”

TAU FOCUSED DRUG DISCOVERY FOR ALZHEIMER'S DISEASE (AD) AND RELATED TAUOPATHIES

Virginia M.-Y. Lee

University of Pennsylvania School of Medicine, Philadelphia, PA, USA

The microtubule (MT) binding protein tau is the major constituent of neurofibrillary tangles (NFTs), a hallmark of AD and other related disorders including neurodegenerative tauopathies that manifest as sporadic and familial frontotemporal dementias (FTDs). Thus, tau pathology is a critical underlying abnormality that links AD and these disorders to a shared mechanism of neurodegeneration. NFTs are composed of tau assembled into paired helical filaments (PHFs) known as PHFtau, and when tau is transformed into PHFtau, less normal tau is available to stabilize MTs. Since MTs are essential for intracellular transport, when MTs are destabilized and axonal transport is compromised, neurodegeneration follows. Several interventions focusing on correcting losses of normal tau function and reversing gains of toxic function by PHFs/NFTs have been suggested for development as disease modifying therapies for AD and related FTD tauopathies. Plausible targets for tau focused drug discovery are briefly summarized, and recent efforts to develop MT stabilizing, PHFtau anti-fibrillization and neuroprotection compounds as disease modifying therapy for AD and related FTD tauopathies are reviewed.

A ROLE FOR GSK3 IN IMPAIRED NEUROGENESIS AND MEMORY LOSS IN ALZHEIMER DISEASE

Jesús Avila

Centro de Biología Molecular “Severo Ochoa” (CSIC-UAM), C/ Nicolás Cabrera 1, Universidad Autónoma de Madrid, Campus Cantoblanco, Madrid, Spain.

The functional decline of a tissue during aging could be related to a decrease in its regenerative potential due to the diminishing capacity of their resident stem cells to maintain the tissue structure. Adult neurogenesis takes place in two brain regions in which resident stem cells are mainly present: the subventricular zone and the subgranular zone of the dentate gyrus (DG) in the

hippocampus. New neurons, from the DG, integrate with preexisting neurons to play an important role in learning and memory.

It has been suggested that aging or depletion of dentate gyrus stem cells could be a cause for the loss of learning and memory observed in elderly or in AD patients. Indeed, lack of memory is an early feature in Alzheimer disease (AD). In familiar Alzheimer disease, mutations in app, ps-1 or ps-2 genes promote the onset of the disease that could be dependent of an increase in the amount (and/or oligomerization) of beta amyloid peptide. The increase in beta amyloid peptide could promote GSK3 activation. In sporadic Alzheimer disease (SAD), a possible increase in GSK3 activity has been also suggested, being aging the main risk for SAD.

We have addressed the role of GSK3 β in adult neurogenesis in a conditional transgenic mouse model overexpressing GSK3 β at the DG, and testing DG neurogenesis in young and old mice. Our data indicate that adult neurogenesis is impaired in the transgenic mice in correlation with a decrease in DG volume and impaired memory. These defects in memory impairment could be reversed at those ages in which neuronal stem cells are present at the DG but not after depletion of those cells, a feature that occurs in older animals.

We speculate with the possibility that a similar mechanism could take place in the DG of Alzheimer disease patients and that it is the explanation for the loss of episodic memory found in those patients.

SESSION 3

"Genetics"

NEW FINDINGS IN THE GENETICS OF LATE ONSET ALZHEIMER'S DISEASE

Alison M. Goate

Washington University School of Medicine, St. Louis, MO USA

The first mutations to be associated with AD were observed in the most severe form of the disease: familial cases with an early onset of disease (<60yrs). Subsequently, APOE genotype was found to be a major risk factor for sporadic AD. Despite these advances 50% of AD cases carry no known genetic risk factors. In order to identify the remaining heritability two general approaches

have been taken that are based on differing hypotheses. The first is that multiple common variants modestly increase or decrease risk for AD while the second hypothesis proposes that much of the genetic risk results from rare variants of moderate effect. To identify the common variants several large genome-wide association studies (GWAS) have been performed in AD cases and elderly non-demented controls. These studies have provided evidence for nine novel risk genes and demonstrated that the increase in risk conferred individually by these genes is approximately 10-15% compared to the 3-8 fold increase in risk associated with APOE genotype. We have also used CSF biomarkers of AD as endophenotypes to identify genes that influence levels of these proteins. Genes that influence AD risk also influence CSF A β 42 levels whereas genes that are associated with CSF tau/ptau levels are associated with rate of progression of AD but not risk. A sequencing approach is required to identify rare variants associated with AD. Technological advances in next-generation sequencing have now made whole genome or whole exome studies feasible. To identify rare functional variants we have sequenced individuals from population extremes including LOAD cases from densely affected families and individuals with low/high biomarker measurements. Both approaches have identified pathogenic variants in known genes and are now being applied to identify pathogenic variants in novel genes.

GWAS AND BEYOND: RISK LOCI, BIOLOGICAL CANDIDATES AND BIOMARKERS

Sandra Barral

Columbia University, New York, NY, USA

Late onset Alzheimer's disease (LOAD), defined by the onset of symptoms after age 60, evolves slowly from mildly impaired memory to severe cognitive loss. Identification of genes that contribute to LOAD risk could reveal basic pathogenic mechanisms, identify proteins and pathways for drug development, and provide methods for determining who is at greatest risk when preventative measures become available. A substantial fraction of LOAD is attributable to genetic factors. A family history of dementia is one of the most consistent risk factors for LOAD, with heritabilities of 58% to 79%. Relatives of individuals with LOAD are at increased risk for dementia, but the distribution of secondary cases is not consistent with Mendelian inheritance.

Numerous large pedigrees with autosomal dominant, early-onset AD (EOAD; late 40's, early 50's) led to the discovery of rare mutations in amyloid precursor protein (APP), presenilin 1 (PSEN1) and presenilin 2 (PSEN2). These studies suggested

a common pathogenic mechanism involving enhanced generation and aggregation of amyloid peptide.

In LOAD, rare genetic variants associated with increased risk have been found in SORL1 and ADAM10. Also, more recently, exome sequencing of large multiplex families with LOAD has identified rare variants in APP, PSEN1 and PSEN2.

A current theme underlying research for genetic influences in complex diseases such as LOAD is the "common disease, common variant" hypotheses. This theory posits that multiple common variants underlie the cause of LOAD. The common variant most clearly associated with LOAD is the $\epsilon 4$ allele of apolipoprotein E (APOE), a gene with three common alleles ($\epsilon 2$, $\epsilon 3$, and $\epsilon 4$). The $\epsilon 2$ allele is considered protective and $\epsilon 3$ neutral. The $\epsilon 4$ allele influences age at onset in a dose-dependent manner. However, more than half of the patients with LOAD do not have the high-risk $\epsilon 4$ allele and the population attributable risk of LOAD due to APOE may be as low as 10 to 15%. Recent GWA studies identified associations of LOAD with common variants in CLU, PICALM, CR1, BIN1, MS4A4A cluster, ABCA7, CD2AP, CD33, and EPHA1 associations that have been confirmed in other Caucasian and Hispanic cohorts. The odds ratios (OR) for these genes are much lower than for APOE (OR = 3.2 and 14.9 for $\epsilon 3/\epsilon 4$ and $\epsilon 4/\epsilon 4$, respectively), and range from 1.16 to 1.20 for CR1, CLU, and PICALM. Further characterization of the effects of the genes, in terms of risk assessment and sequence variation, is essential to clarify the clinical impact for people at risk of LOAD.

SESSION 4

“Therapeutic advances”

CONQUERING ALZHEIMER'S DISEASE: A NEED FOR EVENTUAL ACCEPTANCE OF BIOMARKERS AS READOUTS IN THE CLINIC

Dale Schenk

Elan pharmaceuticals, South San Francisco, CA, USA and Janssen Alzheimer's Immunotherapy, South San Francisco, CA, USA

Enormous efforts to understand and treat Alzheimer's disease (AD) have occurred over the last 30 years. These efforts have focused on both the pathology and the genetics of the disease. It is highly instructive that both of these research areas have repeatedly identified two key proteins and their gene products, namely beta amyloid peptide (A β) and microtubule associated protein tau. These findings have also resulted in a number of biomarkers such as low A β 42 or elevated tau in CSF of those suffering from the disease. Most importantly, very significant efforts have resulted in a number of investigational agents targeting primarily A β for treatment of AD. Despite the enormous increase in our understanding of the molecular, genetic and pathological characterization of the disease, our clinical understanding and characterization of AD has changed only modestly. In part, this is due to the absence of significant treatments that alter the course of the disease and secondly, a general lack of detailed understanding of what constitutes cognition and memory. Fortunately, a solution to this dilemma is beginning to emerge. For example, some data suggests that a reduction CSF A β 42 or increase in PIB retention is a potential predictor of later dementia. In addition, in those with the disease, a reduction in CSF tau might be a predictor of an effective treatment. Thus, biomarkers appear to predict or correlate with clinical outcome. This fact, together with the observation that both A β and tau-the two biomarkers in question, also happen to be the two pathophysiological and genetic hallmarks of the disease, creates a reasonable scenario to link the entire disease process. Why is this essential to produce more effective treatments? For the simple reason that biomarkers are more reliable, have less variance and have no translation or reporter bias. Indeed, when one examines very mature therapeutic areas such as cardiovascular disease or oncology, these areas are

driven almost entirely by the readout of biomarkers both for clinical studies and in the practice of medicine. With this in mind, it is imperative that the connection between pathology, biomarkers and clinical outcomes be understood and embraced as thoroughly and as soon as possible.

CENTRAL INHIBITION OF ALZHEIMER'S BETA-SECRETASE IN HUMANS: PROOF OF CONCEPT WITH LY2811376

Martin Citron

Eli Lilly & Company, Indianapolis, Indiana, USA

Cerebral deposition of amyloid- β peptide ($A\beta$) is critical in Alzheimer's disease (AD) pathogenesis. $A\beta$ generation is initiated when β -secretase (BACE1) cleaves the amyloid precursor protein. For more than a decade BACE1 has been a prime target for designing drugs to prevent or treat AD. However, development of such agents has turned out to be extremely challenging with major hurdles in cell

penetration, oral bioavailability/metabolic clearance, and brain access. Using a fragment-based chemistry strategy, we have generated LY2811376, the first orally available non-peptidic BACE1 inhibitor that produces profound $A\beta$ -lowering effects in animals, and importantly, translates into strong and long-lasting $A\beta$ reduction in human CNS. Our studies with LY2811376 demonstrate that BACE1 is a tractable small-molecule target with promise for the development of AD therapeutics.

DRUG DEVELOPMENT FOR ALZHEIMER'S DISEASE: THE ROLE OF BIOMARKERS

Jeffrey Cummings

University of California, Los Angeles, Los Angeles, CA, USA

Alzheimer's disease (AD) has reached epidemic portions, affecting 35 million people worldwide. If new treatments are not found, AD will affect nearly 100 million persons by the year 2050. New therapies to prevent, delay the onset, slow the progression, or improve the symptoms of AD are urgently needed. AD progresses slowly and it takes time and large number of patients in a clinical

trial to determine if the agent is working when clinical outcomes are used. Documenting target engagement and demonstrating disease modification with biomarkers can show effects with smaller numbers of patients, can be used in Phase 2 to increase confidence in a candidate therapy, and can de-risk Phase 3 making success more likely in late stage development. Target engagement biomarkers are linked directly to the mechanism of action of the drug. For example, beta-secretase inhibition might be used to assess target engagement of a BACE inhibitor or decreased amyloid production might be used to assess the pharmacokinetics of a gamma secretase inhibitor. MRI is the most likely candidate for demonstrating disease modification in multi-center trials. Linking target engagement and disease modification biomarkers is a promising approach to accelerating new drug development for AD.

SESSION 5

“Translational Research”

OXIDATIVE AND MITOCHONDRIAL ABNORMALITIES IN ALZHEIMER DISEASE

George Perry

College of Sciences, University of Texas at San Antonio, San Antonio, TX, USA;

Mitochondrial dysfunction is a prominent and early feature of Alzheimer disease (AD). Recent studies demonstrate that mitochondria are dynamic organelles that undergo continual fission and fusion events which regulate their morphology and distribution, and also serve a crucial physiological function. Morphometry showed a small but significant reduction in mitochondria number in AD. Additionally, the average size of mitochondria was significantly enlarged in AD vulnerable neurons. Levels of the fission/fusion proteins DLP1, OPA1, Mfn1 and Mfn2C were significantly decreased in AD, yet levels of Fis1 were significantly increased. Interestingly, although all these proteins demonstrate even distribution in the cytoplasm and processes of pyramidal neurons in age-matched control hippocampus, they appeared to accumulate in the soma but not in the processes of pyramidal neurons in AD hippocampus. Given that OPA1, Fis1, and Mfn1/2 are all mitochondrial membrane proteins, the changes in their distribution to soma in AD neurons, suggest changes in mitochondria

distribution in these neurons. The expression of fission/fusion proteins was manipulated in M17 cells and primary hippocampal neurons in a way that mimicked their expression changes in AD (i.e., reduced expression of DLP1, OPA1, Mfn1/2 or increased expression of Fis1). These manipulations all reduced mitochondrial density in the cell periphery (M17

cells) or neuronal processes (primary neurons) which correlated with reduced spine numbers (primary neurons).

A β PP and A β caused reduced expression of DLP1 and OPA1 while increasing expression of Fis1, consistent with our findings in AD brains. Through time lapse study, we were able to demonstrate that mitochondria were able to fuse with each other but at a much slower rate in A β PP overexpressing cells.

Overall, we concluded that A β PP, through amyloid- β production impairs mitochondrial fission/fusion balance through regulation of expression of mitochondria fission and fusion proteins.

STRATEGIES TO PREVENT NEURAL NETWORK DYSFUNCTION IN ALZHEIMER'S DISEASE

Lennart Mucke

Gladstone Institute of Neurological Disease and University of California, San Francisco, California, USA

Amyloid-(A) peptides are widely thought to cause Alzheimer's disease (AD), but the underlying mechanisms remain to be fully elucidated. Human amyloid precursor protein (hAPP) transgenic mice are informative models of A-induced neuronal dysfunction. Although these mice develop typical neuritic amyloid plaques, their cognitive impairments are caused by A oligomers, which elicit an intriguing combination of synaptic depression and aberrant excitatory network activity. The microtubule-associated protein Tau and tyrosine kinases play critical roles in the A oligomer-induced abnormalities. Even partial reduction of Tau effectively prevents A-induced neuronal and cognitive dysfunction in different lines of hAPP transgenic mice, most likely by preventing aberrant neuronal activity and A-induced changes in the intracellular transport of factors that regulate synaptic functions. Modulation of the src family kinase Fyn modulates A-induced neuronal deficits in ways suggesting synergism among A, tau and Fyn. A oligomers bind directly to the receptor tyrosine kinase EphB2, promoting EphB2 degradation in the proteasome. Because EphB2 regulates the function of synaptic NMDA-type glutamate receptors, EphB2 depletion could contribute to A-induced synaptic deficits. Indeed, knockdown of EphB2 in

neurons of nontransgenic mice caused synaptic deficits similar to those seen in untreated hAPP mice. More importantly, normalization of neuronal EphB2 levels in hAPP mice reversed their deficits in synaptic functions as well as their impairments in learning and memory. Ongoing studies aim to unravel the intriguing relationships among these diverse molecules with the ultimate goals of blocking copathogenic interactions and improving cognitive functions in the context of AD.

Supported by the National Institutes of Health.

RE-THINKING ALZHEIMER DISEASE THERAPY: LESSONS LEARNED FROM ONGOING CLINICAL TRIALS

Bengt Winblad

Karolinska Institutet Alzheimer Disease Research Center, Huddinge, Sweden

Research into Alzheimer disease (AD) has been at least partly successful in terms of developing symptomatic treatments, but has also had several failures in terms of developing disease-modifying therapies. These successes and failures have led to debate about the potential deficiencies in our understanding of the pathogenesis of AD and potential pitfalls in diagnosis, choice of therapeutic targets, development of drug candidates, and design of clinical trials.

Many clinical and experimental studies are ongoing, mainly based on beta-amyloid (A β) strategies, but the exact role played by A β in AD pathogenesis is not yet clear. We need to acknowledge that a single cure for AD is unlikely to be found and that the approach to drug development for this disorder needs to be reconsidered.

Preclinical research is constantly providing us with new information on pieces of the complex AD puzzle, and an analysis of this information might reveal patterns of pharmacological interactions instead of single potential drug targets. The first signs of a shift away from linear "one protein - one drug thinking" have already appeared: research is moving from proteins to focus on organelles (eg mitochondria) and also multi-target-directed ligands.

Despite the recent negative results of RCTs on AD, increased collaboration between pharmaceutical companies, basic and clinical researchers will bring us closer to developing an optimum pharmaceutical approach for the treatment of AD. A better understanding of the disease pathogenesis, but also solving methodological problems in clinical trials on AD - eg standardized diagnostic

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criteria to identify homogenous group of patients, appropriate treatment duration and measures of disease-modifying effects - will help finding a cure for AD.

SESSION 6

“Biomarkers and diagnosis”

NEW CONCEPT AND NEW DIAGNOSTIC CRITERIA FOR ALZHEIMER'S DISEASE

Bruno Dubois

INSERM-UPMC UMRS 610, Federation of Neurology, Salpêtrière Hospital;
University of Paris 6, Paris, France

The incremental growth of scientific knowledge around the pathogenic events and course of AD has significantly advanced our view of the disease and its defining boundaries. In 2007, the International Working Group for New Research Criteria for the Diagnosis of AD proposed a new diagnostic framework intended to move beyond the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA) criteria. Indeed, distinctive and reliable biomarkers of AD are now available through structural brain imaging with Magnetic Resonance Imaging (MRI), molecular neuroimaging with Positron Emission Tomography (PET) and cerebrospinal fluid (CSF) analyses. According to these new research criteria, the diagnosis of AD is made when there is both clinical evidence of the disease phenotype and in-vivo biological evidence of Alzheimer's pathology. By relying on the specific clinical and biological features of the disease, the newly proposed algorithm permits diagnosis of AD with a high level of accuracy, even at the stage of earliest clinical manifestations (prodromal stage). Although successfully stimulating scientific discussion, the proposal of a “dual clinico-biological entity” that can be diagnosed during life also raises new questions about the definition of AD that will be addressed. We consider that the definition of Alzheimer's disease should refer to the clinical expression of the disease and that it should encompass the whole spectrum of the clinical course, including the prodromal pre-dementia stage.

The timeliness of these criteria is underscored by the myriad of drugs currently under development that are directed at altering the disease pathogenesis, particularly at the production and clearance of amyloid β as well as at the hyperphosphorylation state of tau. The strength of these proposed research criteria was the introduction of neurobiological measures onto the clinically based criteria. Their usefulness will be determined in the future as investigators

apply the criteria in a variety of research studies and clinical trials as key issues in their application are resolved.

BIOCHEMICAL MARKERS – TOOLS TO STUDY DISEASE PATHOGENESIS AND MONITOR NOVEL THERAPIES IN AD PATIENTS

Kaj Blennow

Clinical Neurochemistry Laboratory, Inst. of Neuroscience and Physiology, The Sahlgrenska Academy at University of Gothenburg, Sahlgrenska University Hospital, Mölndal, Sweden

Cerebrospinal fluid biochemical markers (CSF biomarkers) have been developed that can be used to monitor the central disease mechanisms in Alzheimer's disease (AD). These include total tau (reflecting neuronal degeneration), A β 42 (reflecting plaque pathology), and phosphorylated tau (reflecting tau phosphorylation state and tangle pathology). Numerous studies have shown that these CSF biomarkers have high diagnostic accuracy to identify AD, and several large recent multi-centre studies also show that they can identify prodromal AD with high accuracy. Thus, CSF biomarkers will be useful in clinical trials to enrich

the patient cohort with AD cases, which will increase the possibility to identify a clinical effect of the drug. Further, since lumbar puncture easily can be introduced as a routine procedure, CSF biomarkers will be important tools for accurate and early diagnosis of AD if the new types of disease-modifying drug candidates, such as secretase inhibitors, prove to be effective.

CSF biomarkers are also valuable tools to validate findings from preclinical studies on biochemical changes with possible relevance for AD pathogenesis directly in living patients with the disease. Especially, genetically engineered mice are commonly used to assess new drug candidates, but an effect of a compound on A β plaque burden in such transgenic mice has a low predictive power for a clinical effect in AD patients. Therefore, it might be wise to verify an effect on A β metabolism, or plaque burden, in patients with AD before launching large clinical trials. Biomarkers used in drug development may be called theragnostic markers. In this context, a primary biomarker (such as A β 42) is used to monitor the central biochemical effect of an A β modulatory drug, while a downstream biomarker (such as T-tau) monitor downstream effects on the intensity of the neuronal degeneration. By CSF analyses, many aspects of the APP/A β metabolism can be monitored, including specific A β isoforms, APP isoforms (-sAPP and -sAPP), and secretase (BACE1) activity.

One example is the shorter A β isoforms A β 1-15 and A β 1-16, which have been found to be sensitive biomarkers for γ -secretase inhibitor treatment, even at doses that do not affect CSF A 1-42 or A 1-40. Intense research efforts are ongoing to identify new CSF biomarkers for additional pathogenic processes in AD. Recent data show that there is a marked increase in CSF A β oligomers in AD. This novel biomarker may thus be of great value, both for clinical diagnosis and to monitor treatment effects.

ALZHEIMER DISEASE THERAPEUTICS: CHALLENGES, OPPORTUNITIES, AND PROMISING APPROACHES

Khalid Iqbal

New York State Institute for Basic Research in Developmental Disabilities
Staten Island, New York, USA

Alzheimer disease (AD) is a chronic, progressive, neurodegenerative disorder with an average progression of 7–10 years. Though histopathologically characterized by neurofibrillary degeneration associated with abnormal hyperphosphorylation of tau and by β -amyloidosis of the brain, AD is a multifactorial disorder that involves several different disease mechanisms. The familial form of AD accounts for less than 1% of the cases and is caused by certain missense mutations in APP, presenilin (PS)-1 or PS-2 genes. The causes of the sporadic form of AD, which represents over 99% of the cases, are at present not understood. While the prolonged chronicity and the involvement of different disease mechanisms offer enormous opportunities to treat this disease, the lack of practical means to identify various subgroups of AD and to stratify test patients in clinical trials poses a formidable challenge. Increasing evidence favors inhibition of neurofibrillary degeneration as one of the most promising therapeutic approaches. The elevated level of abnormally hyperphosphorylated tau in the lumbar CSF can both facilitate the stratification as well as help monitor the efficacy of the treatment in AD patients. A cause of abnormal hyperphosphorylation of tau in sporadic AD is a decrease in the activity of protein phosphatase (PP)-2A, which is a major regulator of the phosphorylation of tau. I2PP2A, also known as SET, which is a potent endogenous negative regulator of PP2A is both upregulated and translocated from its primary nuclear location to the cytoplasm where it interacts with the catalytic subunit of PP2A and causes tau abnormal hyperphosphorylation. Memantine, which can restore PP2A activity by interacting with I2PP2A, has

been found to decrease the CSF level of pThr181 tau in patients with AD. Memantine-like drugs,

but with increased capacity to enter the affected neurons, are needed to inhibit neurofibrillary degeneration. While inhibition of neurodegeneration can help arrest further cognitive decline, drugs that can enhance neurogenesis and neuronal plasticity are required to achieve the necessary balance between neurodegeneration and regeneration of the affected areas of the brain to reverse cognitive impairment in patients with AD.

Supported in part by the New York State Office of People with Developmental Disabilities and NIH/NIA grants AG019158 and AG028538.

SESSION 7

“Novel Aspects of Basic Research in AD”

ROLE OF REELIN IN ADULT BRAIN PLASTICITY AND IN ALZHEIMER'S DISEASE

Eduardo Soriano

IRB Barcelona, University of Barcelona and CIBERNED-ISCIII, Barcelona, Spain.

Reelin is an extracellular matrix protein essential for neuronal development that signals through the APOE2R/VLDLR receptors and the adaptor protein DAB1. Moreover, Reelin is also widely expressed in the adult brain. To unravel the function of Reelin in the adult forebrain, we generated transgenic mice that overexpress this protein under the control of the CaMKIIalpha promoter (CAMKII/Reelin). Overexpression of Reelin increased adult neurogenesis and impaired the migration of adult-generated neurons. Retroviral tracing of these neurons in the hippocampus demonstrated that Reelin levels control dendritogenesis and the functional integration of adult-born neurons. Remarkably, inactivation of the Dab1 gene specifically in adult progenitors resulted in granule cells displaying basal dendrites in the hilus.

In the hippocampus, the overexpression of Reelin produced an increase in synaptic contacts and hypertrophy of dendritic spines. Induction of long-term potentiation (LTP) in alert behaving mice showed that Reelin overexpression evokes a dramatic increase in LTP responses. In addition, we demonstrate that

while NMDA NR2B-mediated synaptic transmission is significantly reduced in Reelin-overexpressing mice. Taken together, these findings suggest that Reelin acts as a “homeostatic” factor in the regulation of glutamatergic neurotransmission, structural and physiological plasticity, and adult neurogenesis.

We also show that Reelin expression controls GSK3 activity and Tau phosphorylation and that Reelin accumulates in amyloid plaques. Together with in

vitro B-42/Reelin aggregation experiments and PICUP cross-linking experiments, our data suggest that the Reelin pathway exerts a protective effect in Alzheimer's Disease. To test this hypothesis, we crossed mice expressing mutated hAPP with CAMKII/Reelin mice. Our preliminary results indicate that overexpression of Reelin partially prevents some neuropathological and behavioral deficits in hAPP-overexpressing mice. On the basis of our results, we propose that the Reelin activation cascade protects against some pathological manifestations of Alzheimer's disease in mouse models of this pathology.

THE IMPORTANCE OF SIDE-CHAIN OXIDISED OXYSTEROLS IN ALZHEIMER DISEASE PATHOGENESIS

Ángel Cedazo-Mínguez

Karolinska Institutet, KI-Alzheimer disease research center. Huddinge, Sweden

Alzheimer's disease (AD) is considered a multi-factorial disorder and several risk factors are likely to contribute to the probability of developing the disease. The prevalence for AD is associated to cholesterol levels, altered cholesterol metabolism, cardiovascular disease and hypertension. Specially, the association of AD with disrupted cholesterol metabolism has been confirmed by numerous epidemiological and genetic studies. However, the underlying molecular mechanisms by which risk factors contribute to AD pathogenesis are still unknown.

Brain cholesterol is separated from the blood cholesterol by the blood-brain barrier (BBB). Thus it is intriguing how serum cholesterol could influence the prevalence of AD. Side-chain oxidized oxysterols are cholesterol metabolites that are able to cross the BBB. The most important mechanism for cholesterol excretion from the brain is by conversion into 24(S)-hydroxycholesterol (24S-OH). On the other hand, extracerebral homeostasis is maintained by the formation of 27-hydroxycholesterol

(27-OH). We have investigated the biological roles of 24S-OH and 27-OH in the brain.

We have shown that 27-OH has a suppressive effect on the generation of long-term potentiation and the induction of activity regulated cytoskeleton associated protein (Arc), compromising memory consolidation. In an extensive study, we have demonstrated that both 24S-OH and 27-OH upregulate the activity of brain renin-angiotensin system (RAS), through a Liver X receptor-dependent mechanism. Furthermore, increased 27-OH levels are intimately related to increased RAS activity in brains of individuals with AD or mild cognitive impairment (MCI).

Overall, our results suggest that side-chain oxidized oxysterols are not subproducts of cholesterol metabolism, and that their biological functions could be of importance in AD pathogenesis. Disturbances in cholesterol metabolism could contribute to memory impairment as well as to the over activation of brain RAS, which further suggest mechanistic links between two well-known risk factors for AD: hypercholesterolemia and hypertension.

DENDRITIC SPINES AND ALZHEIMER'S DISEASE

Javier De Felipe

Laboratorio de Circuitos Corticales (CTB), Universidad Politécnica de Madrid, Campus Montegancedo S/N, 28223 Pozuelo de Alarcón; Instituto Cajal (CSIC), Avda. Doctor Arce 37, 28002 Madrid; and Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Spain

Dendritic spines of pyramidal cells represent the main postsynaptic elements of cortical excitatory synapses and are fundamental to memory, learning and cognition. In turn, pyramidal cell axons constitute the main source of these synapses. Furthermore, since the discovery in the 1970s that dendritic abnormalities in cortical pyramidal neurons are the most consistent pathologic correlate of several brain diseases, including mental retardation, research has focused on how dendritic alterations are related to reduce intellectual ability. The recent introduction of powerful sophisticated tools in the field of microanatomy has led to a growth in the studies of these disorders.

Abnormal phosphorylation of the microtubule-associated protein tau in the brain forms paired helical filaments (PHF), which are the major components of intraneuronal neurofibrillary tangles (NFT) typically observed in Alzheimer's disease (AD) patients and other neurodegenerative disorders. We examined the microanatomy of pyramidal cells showing either diffuse phosphotau in a

pre-tangle state or tau aggregation forming NFT. Anti-PHF-tau antibodies AT8 and PHF-1 were used since it has been shown that immunostaining with these antibodies is more frequently observed in neurons of patients at an early and later stages of the disease, respectively. We injected pyramidal neurons with Lucifer Yellow mostly in the hippocampal formation and adjacent cortex obtained at autopsy of AD patients. Following the intracellular injections, sections were doubly immunostained with anti-Lucifer Yellow and either anti-PHF-tauAT8 or anti-PHF-tauPHF-1 antibodies. Thereafter, we measured the dendritic diameter, the dendritic spine density, and the dendritic spine length and volume in 3D of thousands of dendritic spines that were scanned by confocal microscopy. We observed no significant changes in the microanatomical characteristics of the dendrites of Lucifer Yellow-injected pyramidal neurons showing early stages of neurofibrillar pathology (presence of diffuse phosphotau in a pre-tangle state), whereas the presence of tau aggregation forming NFT (more advanced neurofibrillar alterations) displayed significant changes in the number and shape of spines. These changes include, in the earliest neurofibrillar pathological stages, a decrease in the dendritic diameter and in the length and volume of dendritic spines. In intermediate and more advanced stages of NFT accumulation, there is a reduction in the dendritic diameter and a dramatic decrease or a virtual lack of dendritic spines. Thus, our results indicate that in AD patients the presence of diffuse phosphotau in a pre-tangle state does not induce changes in the dendrites of pyramidal neurons, whereas the presence of tau aggregation forming NFT gives rise to a progressive dendritic atrophy and loss of dendritic spines (synaptic disconnection) of pyramidal neurons, depending on the degree of tau aggregation.

SESSION 8

“Novel Aspects of Clinical Research in AD”

INTERNATIONAL COLLABORATION ON ALZHEIMER'S DISEASE RESEARCH: FROM GENOMICS TO EUROPEAN JOINT PROGRAMMING INITIATIVE

Philippe Amouyel

UMR744 Inserm-Lille North of France University-Institut Pasteur de Lille, Lille, France Alzheimer's disease (AD) is a highly complex multifactorial disease. The ultimate goal of research in this field is to find a cure of the disease and to enable early diagnosis for early, targeted treatments, but the time necessary to reach this goal is not predictable. However, an international mobilization of researchers on this topic would accelerate the provision of solutions.

For instance, the first genetic susceptibility factor for late-onset sporadic AD, APOE, was identified in 1993. Since then, hundreds of other genetic associations have been suggested from single groups but almost none of them could be replicated. It is only in 2009 that the constitution of large international consortia, gathering more than 30 laboratories from several countries, allowed large genome wide association studies to deliver new hits, opening new research avenues. So, AD understanding requires more extensive exchanges of the best researchers from different fields and countries.

To progress in that direction, a new concept of collaboration among owners of national research programmes emerged in Europe: the joint programming initiative. It can be defined as a process in which countries sharing a common vision build together a common strategic research agenda, to address a major societal challenge for which the scale and the scope of their national programmes alone may not reach adequate proportions. Participation in such a process is carried out on a voluntary basis and according to the principles of variable geometry and open access. Thus, the Joint Programming initiative on Neurodegenerative Diseases and Alzheimer's disease in particular (JPND) has been created officially in 2009 and joined today by 23 countries. An international scientific advisory board is preparing the common SRA submitted to stakeholder's view that will be released in the third quarter of 2011. As case studies, two calls have been launched one aiming at linking research centers within 6 countries and another one on the optimisation of biomarkers and

harmonisation of their use between clinical centres gathering 20 countries. These two experiences will help to identify limits and hurdles for individual national funding bodies to work within their existing frameworks to deliver a coordinated pan-European research programme and to prepare the implementation of the future European strategic research agenda.

YOUNG ONSET DEMENTIA

Florence Pasquier

National Reference Centre for Young Onset Dementia, Memory Clinic,
Universiy Hospital, Lille, France

Alzheimer's diseases (AD) and related disorders are often considered as diseases of the elderly by the general public and even the medical profession. In young patients (under-65s), AD is often diagnosed well after disease onset and after several medical opinions, due to atypical clinical forms or delicate differential diagnoses. The initial symptoms are often wrongly attributed to psychological or psychiatric conditions. In fact, even though AD is the most frequent cause of dementia, many other aetiologies are possible in young subjects; dementia thus constitutes a more difficult diagnostic problem here than in the elderly. In addition to late diagnosis, young patients pose specific problems concerning the differential diagnosis, socioprofessional impact and management of the disease (youngest patients may not be eligible for the state support given to old patients).

The prevalence of dementia was estimated at up to 50 per 100,000 in the 30-64 age class and 100 per 100,000 in the 45-64 age class. These problems have now been acknowledged and a National Reference Centre for young patients suffering from AD or a related disorder (CNR-MAJ) has been set up (Measure 19 of France's 2008-2012 National Alzheimer's Plan), notably in order to improve the diagnosis and management of these individuals. A few surveys have been performed. There was no difference between young AD patients with (10% have an autosomal dominant transmission) or without family history for diagnostic delay, but the family burden was higher in patients with a family history. Vascular risk factors and white matter lesions (both ischemic and hemorrhagic) on MRI were surprisingly frequent in young onset AD. It has been showed that most young patients live at home. The main risk factors for entry an institution are the absence of partner, and the presence of

a frontal lobe syndrome. Specific needs for young patients, their family and professionals involved are not yet met. Young patients are often very keen to participate in research, but are currently often excluded from studies because of their young age, although they do not usually suffer from multiple diseases, and are not receiving multiple medications. Most of young patients present with “pure” diseases (e.g. no cerebrovascular pathologies on top of a degenerative disease) and are thus a good target for basic research and clinical trials. They deserve as much as older patients the attention of clinicians, researchers, and decision makers.

MRI MARKERS IN EARLY ALZHEIMER'S DISEASE

J. Alvarez Linera

Ruber International Hospital

Neurobiological changes in Alzheimer's disease (AD) occur in a stereotypical pattern that begins in the medial temporal lobe (MTL) years before the clinical manifestation (brain reserve). Brain atrophy is a marker of neurodegeneration that reflects the neurobiological disorder and is correlated with the neuropsychological changes at all stages of the disease. Other imaging markers may reflect changes in microstructural (diffusion), functional (perfusion) or metabolic (MRS) domains that would provide additional information but are awaiting wider validation. In the early stages of AD, the most effective MRI markers are those that reveal atrophy in MTL, particularly the measures of the hippocampus. The MTL atrophy measures are helping to propose new diagnostic criteria for AD, allowing a diagnosis of probable AD in predementia stages, when memory loss criteria are attached to Imaging criteria (MRI or PET) or measures of amyloid/tau in CSF. The use of atrophy markers (global or MTL) increases the effectiveness in clinical trials (both by reducing the size of the sample and increasing the statistical power) and is therefore contributing significantly to the development of new treatments. The association of multiple markers of structural and functional imaging (MRI and PET) and the use of advanced computational analysis techniques will allow better management of AD but it needs a broader validation and know the most efficient combination of biomarkers at each stage of the disease, including the preclinical period.

WHEN DOES ALZHEIMER'S DISEASE REALLY START?

José L Molinuevo

Director of the Early Detection Program of the Pasqual Maragall Foundation.
Disease and Other Cognitive Disorders Unit, Hospital Clinic i
Universitari, Barcelona, Spain.

Alzheimer's disease (AD) has been traditionally conceptualized as a clinic-pathological disease, requiring its definite diagnosis the presence of a characteristic pathology together with a dementia clinical picture. The fact that certain AD biomarkers show an acceptable sensitivity and specificity to detect AD pathology, has shifted the diagnostic paradigm towards a clinico-biological approach. Furthermore, recent consensus papers have addressed the possibility of detecting the preclinical stage, setting a conceptual frame to extend the research into this phase of the disease.

The objective of this talk is to present recent data that shows how CSF AD biomarkers behave in the preclinical stage of the disease and its relation with cognition and cortical thickness. These studies, following the new lexicon, have been performed in both presymptomatic subjects (PreS) and asymptomatic subjects at risk for the disease (AsymR). In brief, the results show that memory performance was related to A β 1-42 levels in AsymR subjects and presented a positive correlation with time to disease onset to reach floor levels when symptoms appear in PreS. By contrast, memory was associated with higher t-tau and p-tau in the clinical (prodromal) stage of the disease. Furthermore, an increased in cortical thickness of typical AD areas was observed when mean A β 1-42 levels were still in the normal range in preS, while they presented transitional values in AsymR subjects. Overall, this suggests that this increased in cortical thickness may be a very early event happening when amyloid is starting its deposition, and preceding atrophy.

SPEAKERS & CHAIR

SPEAKERS & CHAIR



Juan Álvarez-Linera Prado

Head of Neuroradiology at the Riber International Hospital since 1994 and Head of the Department of Neuroimage at the Alzheimer Project Investigation Unit (UIPA, CIEN Foundation, Reina Sofia Foundation) since 2007.



Philippe Amouyel

Professor of Epidemiology and Public Health at the University of Lille in France. Since 2008, he has been the Managing Director of the French National Research Foundation on Alzheimer's Disease and Related Disorders and the coordinator of the European Joint Project Neurodegenerative Disease. His field of study is the genetics of Alzheimer's disease.



Jesús Ávila

Research Professor at CSIC's "Severo Ochoa" Centre for Molecular Biology, where he used to be Director. His work is centred on the study of tau protein function in neurodegenerative processes and on the search for axonal regeneration processes. Ávila studies the molecular bases of memory loss and the appearance of dementia in Alzheimer's disease. His studies have primarily focused on the function of the tau protein in these neurodegenerative processes.



Sandra Barral

Expert in genetic mapping of the susceptibility to Alzheimer's disease and other neurodegenerations.



Kaj Blennow

specialist in general psychiatry and clinical chemistry, is Head of Laboratory for the Clinical Neurochemistry at the Sahlgrenska University Hospital in Sweden and Professor of Clinical Neurochemistry. His research interests revolve around the search for biomarkers for Alzheimer's disease, other cerebral disorders in cerebrospinal fluid and in the neurochemical pathology of Alzheimer's disease. Blennow has received numerous prizes, including the Alois Alzheimer Research Prize.



Ángel Cedazo Mínguez

Co-director of the Alzheimer's Disease Research Centre and Deputy Director of the Department of Neurobiology, Healthcare Sciences and Society at the Karolinska Institute in Sweden. He studies the molecular mechanisms related to the appearance of Alzheimer's disease, such as the influence of one form of cholesterol transporter, in the appearance of the disease.

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Martin Citron

Leader of the Research and Discovery Group on Alzheimer's Disease at the pharmaceutical company Eli Lilly and Company, Indianapolis (USA), where he directs the programme aimed at validating compounds with possible therapeutic properties to treat Alzheimer's. Citron is an eminent scientist in the pharmaceutical industry who is directly interested in the development of drugs capable of curing Alzheimer's disease.



Jeffrey Cummings

Andrea and Joseph Hahn Neurology Professor at the Cleveland Clinic Lerner School of Medicine and Director of the Lou Ruvo Center for Cerebral Health in Las Vegas, United States. His work is centred on the carrying out of clinical examinations and in the development of new treatments for neurodegenerative diseases and other neurological illnesses. Dr. Cummings' scientific interests include the study of dementia, neuropsychiatry, neurotherapy and the interface between neuroscience and society.



Javier de Felipe

Research Professor at CSIC-Institute Cajal and the Co-director of *Cajal's Blue Brain Project*. He is also the Director of the Cajal Cortical Circuits Laboratory at the Polytechnic University of Madrid. He has conducted outstanding anatomical studies of the brain of Alzheimer's patients in which he described some of the differences between people with and without dementia.



Mony de León

Professor of Psychiatry at the University of New York's Medicine Faculty and a scientist at the Nathan Kline Institute in New York State. His doctoral thesis described cortical atrophy in Alzheimer's disease in living patients for the first time. For over 25 years, de León has conducted visualisation and biological biomarker studies for the early diagnosis of Alzheimer's disease, a field in which he is a world leader.



Bruno Dubois

Professor of Neurology at the Neurological Institute of the La Salpêtrière Neurological University Hospital at the Pierre et Marie Curie University in Paris. He is Leading Director of the Department of Behavioural Neurology and for the Centre of Research on Dementia at the same Hospital. His interests revolve around the clinical and pharmacological aspects of Alzheimer's disease.



Alison Goate

Samuel & Mae S. Ludwig Professor of Genetics in Psychiatry and a Professor of Genetics and Neurology at the Medical School at Washington University in Saint Louis, Missouri, United States. Goate is internationally renowned for her studies of genetic anomalies in Alzheimer's disease. Two of her studies were the first to report on the first genetic mutation associated with families with Alzheimer and identified mutations in four other genes related to Alzheimer's disease and dementia. She is currently focusing on molecular genetics of neuropsychiatric diseases, including new genetic risk factors for late-onset Alzheimer's.

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Christian Haass

Professor at the Faculty of Medicine of the Ludwig Maximilians University in Munich. The emphasis of his work is on molecular and cellular biology in Alzheimer's and Parkinson's. Christian Haass, together with **Sangram Sisodia** and **Lennart Mucke** (who will also take part in the summit), are leading researchers in the study of the molecular changes which occur in Alzheimer's disease in relation to the beta-amyloid protein.



Khalid Iqbal

Biochemistry Doctor at the University of Edinburgh, he is Professor in the Department of Neurochemistry at the New York Institute for the Basic Investigation on Development Disabilities. He has performed pioneering research into the composition of the neurofibrillary tangles present in the brains of Alzheimer's patients, discovering the abnormal behaviour of the tau protein, as well as the involvement of different kinases and phosphates in the process. More recently, he has proposed a classification of Alzheimer's disease based on specific biomarkers in the cerebrospinal fluid of patients.



Kenneth Kosik

Professor in the department of Molecular and Cellular Biology and Development at the University of California in Santa Barbara, United States. **Kosik** conducts molecular biology studies of the tau protein and other critical targets in neurodegeneration in Alzheimer's disease. He also has a distinguished career as a scientific author of a range of titles. Particularly noteworthy is a book written recently on the effect of lifestyle on neurodegenerative diseases.



Virginia Lee

Director of the Center for Neurodegenerative Disease Research at the University of Pennsylvania (USA). In addition to being an authority on Alzheimer's, Lee is also an authority on Parkinson's disease, frontotemporal dementia and age-related neurodegenerative disorders.



Juan Carlos López

Degree in Basic Biomedical Research from the National Autonomous University of Mexico and a Doctorate from the University of Columbia in New York, where he studied neuronal plasticity processes. In 2000, Juan Carlos López set aside experimental science to become Editor of *Nature Reviews Neuroscience* in London. He is currently Editor in Chief of *Nature Medicine*.



Pablo Martínez Martín

Doctor of Medicine, has been Scientific Director of the Alzheimer's Project Research Unit of the Queen Sofía Foundation and the CIEN Foundation since 2006. He is also a member of the Networked Biomedical Research Centre on Neurodegenerative Diseases (CIBERNED) and the Carlos III Health Institute (MCINN). Martínez Martín has a special interest in clinical assessment methodology, self-assessment and the analysis of results.



José L. Molinuevo

Director of the Early Detection Program of the Pasqual Maragall Foundation Neurologist and Doctor of Medicine, is currently Director of the Alzheimer's Disease and Other Cognitive Disorders Unit at Hospital Clinic in Barcelona, where he runs a genetic counselling program for monogenic dementias (PICOGEN). Molinuevo is an expert in dementias, with a special interest in early diagnosis, clinical symptoms and therapeutics for Alzheimer's disease and other dementias.

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Lennart Mucke

Distinguished Joseph B. Martin Professor of Neurosciences in the Department of Neurology at the University of California in San Francisco, and Director of the Gladstone Institute for Neurological Diseases in San Francisco (USA). Dr. Mucke has established a strenuous interdisciplinary programme focussed on the fundamental processes related to the origin and evolution of Alzheimer's disease. Mucke has created experimental models of a range of diseases which have been used to identify new strategies for preventing neurological decline associated with neurodegeneration.



Florence Pasquier

Medical doctor with a Doctorate in Cognitive Psychology and is Director of the Memory Clinic in the Neurology Department of Lille University Hospital and the French Reference Centre for Young-Onset Dementia in France. His field of research focuses on early detection of Alzheimer's disease in young patients (under the age of 65).



George Perry

Dean and Professor of Biology at the University of Texas, in San Antonio, USA. He is currently President of the American Association of Neuropathologists. Perry is an expert in the study of oxidative stress in neurodegenerative processes. This approach aims to discover the protective effect which antioxidant molecules may have on the brains of people with Alzheimer's.



Dale Schenk

Executive Vice-president of the pharmaceutical company Elan since 2007, he is known worldwide for his work in trying to develop a method of vaccination for the treatment of Alzheimer's disease. His work in this area, as well as early detection and alternative treatment strategies, has led to new approaches to the treatment of Alzheimer's disease.



Dennis Selkoe

Leader in the research of Alzheimer's disease for the past 25 years, is the Vincent and Stella Coates Professor of Neurological Diseases at the Brigham and Women's Hospital, affiliated with the University of Harvard, USA. Selkoe is widely considered to be the creator of the amyloid hypothesis of Alzheimer's disease.



Sangram Sisodia

Expert in molecular pathology in Alzheimer's disease, is the director of the Molecular Neurobiology Centre at the University of Chicago. He was educated at the University of Georgia (USA) and at *Johns Hopkins University*, where he attained the position of tenured professor of Pathology and Neurosciences. He has received numerous distinctions, including the Potamkin Prize for Research on Alzheimer's Disease from the *American Academy of Neurology* (1997) and the *Metropolitan Life Foundation* award for Medical Research (1998).

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Eduardo Soriano

Received his doctorate in Developmental Neurobiology from the University of Barcelona in 1986. He is currently Director of the “Developmental Neurobiology and Neural Regeneration” laboratory at IRB Barcelona; member of the Executive Committee of the Networked Biomedical Research Centre on Neurodegenerative Diseases (CIBERNED); Coordinator of the Biomedicine Programme (ANEP, MICINN) and Vice-chairman of the Neurosciences Panel (LS5. Advanced grants) of the European Research Council. Soriano has described reelin, a protein related to the organisation of the cerebral cortex, and is currently studying this protein’s role in Alzheimer’s disease.



Bengdt Winblad

Professor of Geriatrics at the Karolinska Institute (Sweden), is co-president of the European Alzheimer’s Disease Consortium and chairs the Medical and Scientific Advisory Panel of Alzheimer Disease International. He is also member of the Nobel Assembly for the Prize for Medicine and Physiology. Winblad is a world leader in epidemiology, genetics and treatment of dementias, especially Alzheimer’s disease.

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