Introduction to Session 2
Lewy body dementias: DLB and PDD

Co-Chairs: Dennis W. Dickson, MD and Karen S. Marder, MD, MPH
NIH Liaisons: Debra Babcock, MD, PhD and Beth-Anne Sieber, PhD
Prioritized Recommendations

1. Create longitudinal clinical, biological, and imaging resources from earliest (prodromal) stages and culminating in autopsy studies (5-10 y)
2. Discover disease mechanisms through unbiased genomics, expression arrays, metabolomics, & proteomics of tissues from patients (5-10 y)
3. Identify novel common and rare genetic variants as well as epigenetic changes that influence risk and clinical features (1-10 y)
4. Develop imaging approaches to enhance diagnostic accuracy, detect prodromal disease, and to monitor disease progression (1-10 y)
5. Develop biofluid biomarkers for Lewy-related pathology, as well as concurrent Alzheimer pathology, for diagnosis at earliest stages (1-5 y)
6. Develop models (animal, cellular, in vitro) for key features to understand selective vulnerability, mechanisms of neurotoxicity, and factors that determine disease progression (transmission and propagation) (1-10 y)
7. Initiate symptomatic (1-5 y) and eventually disease-modifying (5-10 y) clinical trials that address key signs and symptoms using approved therapeutic approaches and newly developed therapies

Schedule change

Session 2 logistics:

Presentations

Clinical studies  1. Create longitudinal clinical, biological, and imaging resources from earliest (prodromal) stages and culminating in autopsy studies (5-10 y)
Autopsy studies  2. Discover disease mechanisms through unbiased genomics, expression arrays, metabolomics, & proteomics of tissues from patients (5-10 y)
Genetics  3. Identify novel common and rare genetic variants as well as epigenetic changes that influence risk and clinical features (1-10 y)
Imaging biomarkers  4. Develop imaging approaches to enhance diagnostic accuracy, detect prodromal disease, and to monitor disease progression (1-10 y)
Biofluid biomarkers  5. Develop biofluid biomarkers for Lewy-related pathology, as well as concurrent Alzheimer pathology, for diagnosis at earliest stages (1-5 y)
Modeling  6. Develop models (animal, cellular, in vitro) for key features to understand selective vulnerability, mechanisms of neurotoxicity, and factors that determine disease progression (transmission and propagation) (1-10 y)
Therapeutics  7. Initiate symptomatic (1-5 y) and eventually disease-modifying (5-10 y) clinical trials that address key signs and symptoms using approved therapeutic approaches and newly developed therapies

Schedule change
PDD and DLB have more similarities than differences

• ‘Lewy body disease’ is an umbrella term for studying biology of PD, PDD and DLB

• Common pathobiology related to misfolding and toxic aggregation of α-synuclein – ‘Lewy Body Disorders’

• For clinical care and clinical research, the distinction between those with primary symptom complex of dementia (DLB) and those with a primary movement disorder is important (PDD), and the ‘one year rule’ should be used.
Overlapping clinicopathologic syndromes

**AD**: Neuritic type senile plaques (SP) and neurofibrillary tangles (NFT)

**PD**: Lewy bodies in substantia nigra → nigrostriatal DA loss

**DLB and PDD**: Cortical Lewy bodies & Lewy neurites; Diffuse type SP; fewer NFT

**PD**: Lewy bodies in substantia nigra → nigrostriatal DA loss
The Lewy Body Dementias: Dementia with Lewy bodies (DLB)

Ian G. McKeith, MD, Newcastle University
What do we know about DLB?

- Common – 15% prevalence in post-mortem samples of all dementias but under-diagnosed clinically
  - 4% in community
  - 7.5% in secondary care

- Clinical and pathological diagnostic criteria for DLB are well established and in global use

- Poor patient/carer experience
  - 78% received non-DLB first diagnoses

- Greater disability and worse quality of life than AD
  - 1 in 4 caregivers rate DLB QoL as worse than death

- DLB patients and families have
  - Different management needs
  - Different research requirements
  - Their own carer support organisations

- Different underlying pathophysiology than AD
  - Abnormal accumulation of α-synuclein – with amyloid and tau as secondary pathologies
• Cognitive decline & reduced social/occupational function
  • Attentional, executive and visuospatial dysfunction prominent

• CORE features
  • Fluctuation
  • Recurrent visual hallucinations
  • Spontaneous parkinsonism

• Suggestive features
  • REM sleep behaviour disorder
  • Neuroleptic sensitivity
  • Dopaminergic abnormalities in basal ganglia on SPECT/PET

At least one core + one suggestive or 2 core features for Probable DLB

One core or suggestive feature sufficient for Possible DLB

Clinical diagnosis is to be incorporated into DSM V
What do we need to know about DLB?

- How to diagnose it better and earlier
- Clinical diagnosis alone is unlikely to be adequate – need biomarker profiling

- We particularly need to understand
  - the prodromal syndrome and the factors influencing risk and progression of DLB
  - how to use existing agents for optimal symptomatic treatment

- We need better outcome measures
- We need to know how to optimally organize care pathways for DLB
Presynaptic alpha-synuclein aggregates, not Lewy bodies, cause neurodegeneration in dementia with Lewy bodies

Kramer ML and Schulz-Schaeffer WJ. Journal of Neuroscience 2007 27;6 1405-1410

Main $\alpha$-synuclein burden (50-92%) is in the synaptosomal fraction (peak III) and shown to be trapped inside the synaptosomes.

Golgi–Cox–Davenport staining of brain slices for visualization of dendrites and their spines show extensive pathology in DLB (F,H) compared with aged control (E,G).
How will we find out?

• Longitudinal studies of DLB cases from the prodromal stage to death and autopsy
  – to enable an at-risk platform for evaluation of biomarkers and early interventions
• Likely that this will include both DLB and PDD cases
  – needs integration of dementia/movement disorder and other constituencies

• DLB research
  – is essential to address a common disorder that currently has no specific research “home”
  – will facilitate synergy between AD and PD clinicians and scientists
  – can rapidly deliver improvements in diagnosis and management of DLB
  – is well placed to benefit from patient/public participation
The Lewy Body Dementias: Parkinson’s Disease with Dementia (PDD)

Dag Aarsland, MD, Karolinska Institute
Parkinson’s disease: new concept

• Traditional view:
PD is a motor disorder due to loss of nigrostriatal dopaminergic neurons

• New concept:
PD is a multisystem, multi-transmitter disease with motor and non-motor symptoms
What do we know about cognition in PD?

- Dementia is common in PD:
  - The majority of PD patients have Dementia after > 10 years
  - Wide variation in time from onset of motor symptoms to dementia

Hely et al 2008
What do we know about cognition in PD?

- 20-25% of non-demented PD have MCI, even at diagnosis.
- Cortical atrophy, Lewy bodies, amyloid, and tau-pathology are associated with dementia at autopsy.
- Consensus criteria for PDD and PD-MCI available (Litvan et al 2013).
- PD-MCI is a risk factor for PDD.
- Other clinical risk factors for PDD:
  - REM-sleep disorder, visual hallucinations, old age, non-tremor dom. PD.
- Biomarkers of cognitive decline:
  - Cortical atrophy on MRI, reduced CSF ab42, hypometabolism on PET.
- Treatment of PDD: symptomatic effect of rivastigmine and possibly donepezil and memantine (Emre et al 2004).
What do we need to know about cognitive impairment in PD?

- Mechanisms of early cognitive decline
- Which patients are at risk for early rapid cognitive decline?
- Are some cognitive deficits stable and others progressing?
- Genetic correlates and predictors of cognitive decline in PD
- Role of α-synuclein on cognition: CSF and imaging markers
- Therapy:
  - Can AChEIs and memantine delay progression in PDD?
  - Find disease-modifying treatments to delay / prevent progression to PDD
How will we find out

- Prospective Study with Biomarkers (genes, blood, CSF, multiple imaging modalities) in early PD (PPMI)
- Make existing cohorts (CAMPAIGN, ParkWest, etc) and resources publicly available (PPMI)
- Run trials in PD-MCI with anti-dementia drugs & novel potentially disease-modifying molecules with primary outcome to prevent PDD
Overview and Discussion

Dennis W. Dickson, MD, Mayo Clinic
Jacksonville
Carol F. Lippa, MD, Drexel University
College of Medicine
Autopsy-based studies

Need for unbiased profiling studies of DLB & PDD

• Systematically profile disease-specific changes in the brain, spinal cord and peripheral autonomic nervous system using unbiased methods in new and well established cohorts of DLB and PDD.
  • Genomics
  • Expression array
  • Metabolomics
  • Proteomics

• Develop an open access DLB and PDD BioBank and database for clinical data and biomaterial.
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Genetics Overview and Opportunities

Presenter: Ellen Sidransky, MD, NHGRI, NIH
Discussants: David K. Simon, MD, PhD, Harvard Medical School
John Hardy, PhD, University College London
The Genetics of Lewy Body Dementias: What We Know

• There are likely multiple different genes involved, some identified, while most remain to be discovered.
• Most known genes are associated with lysosomal or mitochondrial pathways.
• As with other complex disorders, genes include rare alleles with large effect size and common alleles with small effects.
• Genes known to cause Parkinson disease and Alzheimer disease are also implicated in DLB and PDD (SNCA-A53T, E46K & triplication, GBA1).
• Families with multiple affected individuals may identify rare Mendelian forms, whereas GWAS can help find common variants.
Rare alleles cause Mendelian, “single gene” disease

Contribution of several low frequency variants with moderate effect

Common variants contributing to common disorders

For Parkinson disease
For Alzheimer disease

Family studies

SNCA, LRRK2, PARK2, PINK1, DJ1, FBXO7, PLA2G6, ATP13A2

TREM 2, APOE4, GBA, LRRK2

Whole exome sequencing

SNCA, LRRK2, MAPT, PARK16, BST1, HLA-DRB5, GAK, ACMSD, STK39, LAMP3, SYT11, HIP1R, STBD1, GPNMB

GWAS

For Lewy body disorders
few genes are known, but there is likely overlap with both PD and AD
Pathways to Parkinsonism

Combining known genes to formulate a story

Many of the genes identified fall into lysosomal and mitochondrial pathways.

Both could be critical in the pathogenesis of Lewy body disorders.

JHardy-UCL
Multicenter study of *GBA1* mutations in Dementia with Lewy Bodies  

(JAMA Neuro: April 2013)

- Included *GBA1* genotypes from 11 centers
  - 721 cases with DLB, 1962 controls.
  - 450 cases were autopsied, 80% of cases had full GBA sequencing

- Odds ratio = 8.28 (95%CI = 4.78 – 14.88)

- Age at diagnosis ~5 years earlier in *GBA1* carriers with DLB.

- Mutations associated with higher PD scores (H&Y, UPDRS).

- Even in studies of PD, *GBA1* carriers had earlier dementia.

*GBA1* mutations play an even greater role in DLB than in PD!  
*GBA1* appears to be a risk factor for dementia.
The Genetics of Lewy Body Dementias: What We Don’t Know

• What are the novel genes and pathways that account for the missing heritability in the Lewy body dementias? Fewer genes are known than in PD and AD.
• To what extent are DLB and PDD genetically different from PD?
• What is the risk for developing dementia in patients with PD, and to what extent can genes be used to predict whether a patient with PD will develop early dementia?
• Does environment play a role?
• What is the contribution of epigenetic modifications?
• Are there genetic variants that can be used to predict clinical course or therapeutic response (pharmacogenomics)?
How will we find out

• Identify novel common and rare genetic variants and epigenetic changes that influence the risk and clinical features of DLB and PDD.
• Perform GWAS in large cohorts as well as whole exome/genome sequencing of families with multiple affected members.
• Identify genetic factors that influence the risk of PDD, DLB, or the risk of Lewy body pathology in other degenerative diseases (e.g., AD).
• Develop a panel of common genetic variants or gene expression profiling to stratify patients in terms of diagnosis, prognosis (e.g., rate of progression), and response to treatment.
• Examine gene-environment interactions.
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Imaging Diagnostics

Presenter: David Eidelberg, MD,
The Feinstein Institute for Medical Research
Discussant: Karen S. Marder, MD, MPH,
Columbia University Medical Center
Imaging Diagnostics: What We Know

- A variety of radioligands have been developed for the evaluation of the specific neurotransmitter changes associated with cognitive dysfunction.
- Substantial progress has been made in the development of radioligands binding to abnormal cortical protein aggregates.
- Imaging has been used to assess brain dysfunction at the systems-level (spatially distributed neural networks).
- Today’s imaging technology is generally “mature” enough to support the development of comprehensive multicenter databases for natural history studies.
- Currently available imaging tools often have signal-to-noise (SNR) characteristics that are sufficient for reliable assessments in single subjects.
Imaging Diagnostics: What We Don’t Know

- The mechanisms that mediate cognitive dysfunction in DLB are varied and probably involve multiple neurotransmitters.
- Dementia is not simply associated with cortical amyloid deposition, and specific radiotracers for α-Syn aggregates are not available.
- It is unknown whether these measures provide sensitive biomarkers of neurocognitive progression in individuals.
- It is not known whether functional network descriptors will have sufficient sensitivity/specificity for the classification of individual cases and monitoring progression and treatment responses.
- The optimal imaging modality/analytical algorithm for systems-level assessments is not known.
Co-Localization of Metabolic Network Activity and Cortical Protein Aggregates in PD-MCI Subjects

PD-Related Cognitive Pattern (PDCP)

Precuneus, pre-SMA, Cerebellum/DN, PMC, Parietal

Eidelberg *TINS* 2009
Alzheimer’s Disease Parkinson’s Disease

MCI(-) 20
MCI(+) 22
AD 20
NL 20
PDD 14

Network Expression

Feinstein Institute

***
p=0.007

P<0.001, **P<0.01, *P<0.05 (vs. normal, Tukey HSD)
Network Expression

Discovery  

Validation

Alzheimer’s Disease

***P<0.001, **P<0.01, *P<0.05 (vs. normal, Tukey HSD)
Imaging Diagnostics: Unmet Research Needs

- Develop imaging approaches for improved diagnostic accuracy and sensitivity to progression of the underlying disease process.
  - Create a "minimal data set" with emphasis on imaging modalities demonstrating high replicability across populations, scanning sites, and imaging platforms.
  - Integrate strategies to evaluate emerging technologies / analytical approaches for feasibility and value added in a multicenter trial environment. Establish firm "go - no go" criteria for further study.

- Enhance scope of longitudinal PDD / DLB studies by incorporating imaging metrics as potential outcome variables.
  - Obtain quantitative assessments of "systems-level" progression rates in individuals with "prodromal" disease.
  - Explore synergistic multi-modal approaches to enhance the accuracy and reliability of diagnostic and progression biomarkers at early disease stages.
  - Incorporate modern computational algorithms to optimize individual subject measurements.
Biofluid Biomarkers

Presenter: Clemens R. Scherzer, MD, Harvard Medical School
Discussant: Karen S. Marder, MD, MPH, Columbia University Medical Center
DEVELOP AND VALIDATE BIOLOGICAL MARKERS: What’s in the pipeline?

AD

- Aβ42
- t-tau
- p-tau

Entering:
- APP processing: e.g.
  - sAPP-β, BACE1, sAPP-α
  - SORL1/LR11
- Aβ oligomers
- Synapse loss: e.g., calbindin
- Apolipoproteins
- Neuroinflammation
- miRNAs
- Metabolites

PD

- s-urate
- ? t-α-synuclein

Entering:
- c-urate, purine metabolites
- 25[OH]D₃
- c-phosphoS129-α-synuclein
- c-o-synuclein
- c-glucocerebrosidase
- p-EGF
- b-mRNAs, splice variants
- c-DJ1
- p-glutathione, 8-OHG

Fagan, A. et al., 2012

Parnetti, L. et al., 2013
DEVELOP AND VALIDATE BIOLOGICAL MARKERS FOR DLB: What we don’t know

[Brain pathology diagram with stages: Prodromal markers, Early diagnostic, Progression/response, Clinical diagnosis, Pre-clinical DLB, DLB, Course of disease, Age]
DEVELOP AND VALIDATE BIOLOGICAL MARKERS FOR PDD: What we don’t know
BIOFLUID MARKERS FOR DLB/PDD: Unmet needs

- **Identify Lewy body- & Alzheimer-type pathology-related markers** detectable in biological fluids

- **Unbiased Biomarkers Discovery**: Systematically map disease-specific changes in brain of patients with DLB or PDD using unbiased methods including genomics, epigenomics, metabolomics and proteomics in order to identify novel disease-linked biomarkers (as outlined in Priority #3)

- **Translate, Develop, and Validate** these novel leads, as well as LB-pathology-, and AD-pathology-linked markers as biofluid laboratory tests useful for enabling clinical trials and improving clinical care
  - For tracking disease progression
  - For early or even prodromal diagnosis
  - For monitoring molecular disease processes
  - For response to therapies
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Modeling mechanisms of disease in DLB and PDD

Presenter: Eliezer Masliah, MD, UC San Diego School of Medicine
Discussant: Pamela McLean, PhD, Mayo Clinic, Jacksonville
Modeling DLB & PDD: What we know

- Over-expression of wt and mutant α-synuclein in invertebrate and mammalian models reproduce some of the behavioral, biochemical and neurodegenerative pathology observed in LBDs.

- Accumulation of α-synuclein in the synapses is an early event in neurodegenerative process in LBD that is reproduced by the models.

- α-Synuclein spreads in vivo from neuron to neuron and neuron to glial cells leading to neurodegeneration and neuro-inflammatory responses.

- α-synuclein seeds might act in a prion-like fashion in wild-type mice resulting neurodegeneration and motor deficits similar to LBD.

- Abeta and Tau interact with α-synuclein leading to worsening of the LBD-like phenotype in experimental animal models.

- The BAC α-synuclein tg rat models reproduce features of DLB/PDD.
Modeling DLB & PDD:
What we don’t know

• What are the pathological species of α-syn leading to neurodegeneration in vivo, are the species formed in the models similar to those seen in LBD brains?
• What is the functional significance of α-syn spreading?
• Does α-syn follows the neuro-anatomical spreading predicted by the Braak staging system?
• How does accumulation of α-syn is involved in the neuronal vulnerability of dopaminergic and non-dopaminergic neurons responsible for non-motor deficits in LBD-like models?
• What is the contribution of other susceptibility genes (eg: GBA, HLA, Tau, LRRK2) to the progression of LBD in experimental models and how do they interact with α-syn in vivo?
• How environmental factors (e.g., pesticides) intersect with α-syn aggregation and spreading in vivo leading to LBD-like pathology in the various models?
• Are the LBD iPS derived neuronal and non-neuronal models predictive of the in vivo effects, can they be used in conjunction with the in vivo models?
Modeling DLB & PDD: Unmet research needs

• To develop more complete rodent models that reproduce in a differential manner the non-motor deficits of DLB and PDD.

• To develop models that incorporate the contribution of genetic polymorphisms of α-syn, GBA and other susceptibility genes.

• To develop better knock in models that express α-syn at basal levels

• Develop models of sporadic forms of DLB/PDD that combine interactions of susceptibility genes with environmental factors.

• Discover tractable biomarkers in the experimental animal models that will mimic and predict therapeutical responses in patients with LBDs.
Therapeutic approaches for DLB and PDD

Bernard Ravina, MD, Biogen Idec
Discussants: Pamela McLean, PhD, Mayo Clinic, Jacksonville
James Galvin MD, MPH, New York University
Carol Lippa, MD, Drexel University
What is known about the treatment of Lewy body dementias?

• Little
• DLB and PDD subjects generally excluded from PD and AD trials
• Adverse effects more common due to
  – specific features – autonomic impairment, psychosis, falls
  – non-specific comorbidities
• Dementia, psychosis rate limiting steps in caring for PDD
• Cholinesterase inhibitors show efficacy in PDD and DLB
  – offer modest but real symptomatic benefits on cognition and behavior, mostly psychotic features \(^1,^2\)
  – PDD is established indication

\(^1\) Rolinski, 2012; \(^2\) Mori, 2012
What is unknown?

- Most of the key ingredients for a successful development program
- Differences between PDD and DLB in clinical symptoms and course
- Biological Target – mixed pathology
  - Temporal evolution
  - Relationship of clinical course to pathology
- Fluid and imaging biomarkers
  - Target engagement
  - Pharmacodynamic effects
  - Progression
- Genetic and other modifiers of pathology and progression
- Adequate clinical measurement tools
An Example of Disease Evolution: Hypothesized Cascade of Biomarkers in Familial AD

Bateman, 2012
Therapeutics - Recommendations

- Overall goal - develop clinical trials that address key signs and symptoms of LBD
  - Drugs, biologics, devices, other
  - Academic-Industry-Government

- Near term – symptomatic therapies

- Longer Term – disease modifying therapies
  - Understanding disease mechanisms, modeling disease process and clinical course, developing biomarkers will enable therapeutics
  - Require longitudinal cohorts

- An example – Pimavanserin for PD Psychosis
  - NINDS, NIH workshop on diagnostic criteria\(^1\)
  - Academic-Industry collaboration to refine SAPS scale\(^2,3\)
  - Academic- Industry collaboration – successful phase III trial\(^4\)

\(^1\)Ravina, 2007; \(^2,3\) Voss, 2010 and 2013; \(^4\) clinicaltrials.gov - NCT00658567
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General Discussion
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