ASK THE EXPERT
LBDA is proud to feature this presentation as part of its LBD University program.
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Biomarkers in LBD

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Disclosures

Research Support

- Alzheimer’s Association
- Department of Defense
- GE Healthcare
- Lewy Body Dementia Association
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- National Institute of Health
- Sanofi

Recent consulting work

- Avid Radiopharmaceuticals
- Axovant
- Bracco Diagnostics
- GE Healthcare
- Takeda Pharmaceuticals
Overview

• Definitions
  • Precision medicine
  • What’s a biomarker?
• Dementia with Lewy Bodies Consortium (DLBC)
  • Why a consortium?
  • Details
Definitions – Precision Medicine

- Precision Medicine
  - Medical model
    - Customization of healthcare
    - Tailored to the individual patient
    - Diagnostic testing employed to select appropriate and optimal therapies
  - Tools
    - Biomarkers
    - Molecular diagnostics, imaging, analytics
Definitions – Precision Medicine

• Cancer
  • Breast CA
    • Genetic testing of patient
    • Genetic testing of tumor
    • Molecular characteristics of tumor
    • Tumor histology and distribution

All determine therapeutic approach
Definitions – Biomarker

“ A measurable substance in an organism whose presence is indicative of some phenomenon such as disease, infection, or environmental exposure”
Definitions – Biomarker

• Why?
  • Accurate diagnosis
  • Cause, progression, symptoms
  • Predict disease
• Guide therapy
  • Optimal treatment
  • Response to treatment
• New insights into disease
Neuropathology of Community Based Dementia

Leverenz et al, JAMA Neurol, 2002; Rieke et al JAGS, 2004; Leverenz et al, Brain Path, 2008
Definitions – Biomarker

• Biomarkers

• Biofluids
  • Blood, urine, saliva, cerebrospinal fluid
  • Proteins, enzymes, genetics

• Imaging
  • Structure, proteins, function

• Other
  • Clinical characteristics
  • Neuropsychology
AD and PD Consortia

- Alzheimer’s Disease Research Centers (ADC/ADRC)
  - 32 Centers nationwide
  - Systematic collection of data, biofluids, autopsy
- Alzheimer’s Disease Neuroimaging Initiative (ADNI)
  - 59 sites
  - Systematic collection of neuroimaging data
  - Over 600 publications
- Parkinson’s Progression Marker Initiative (PPMI)
  - 33 sites
  - Systematic collection of neuroimaging and biomarker data
National Alzheimer’s Project Act (NAPA)

2016 Lewy Body Dementias Recommendations

- Initiate clinical trials for motor and non-motor manifestations of LBD
- Create longitudinal clinical, biological, and imaging resources for LBD
- Characterize disease-specific changes in brain and other tissues
- Identify common and novel gene variants, epigenetic changes, environmental influences
- Develop imaging approaches to enhance diagnosis, detect latent/prodromal disease, and monitor progression
- Develop biomarkers (using samples from recommendation 2)
- Develop animal, cellular, in vitro models for synucleiopathies
- Develop disease modifying therapies
“Biomarkers for the Lewy Body Dementias”
RFA-NS-16-022

• Expand the collection of clinical data and biologic specimens in the NINDS PDBP to include patients with LBD

• Support hypothesis-driven clinical research to discover biomarkers that will improve efficiency and outcome of Phase II clinical trials for LBD
Dementia with Lewy Bodies Consortium

- Nine Centers with extensive LBD experience
  - All members of the LBDA Scientific Advisory Council
  - Cleveland Clinic coordinating site
  - LBDA support for annual meetings
- Focus on developing a longitudinal study sample with compatibility with multiple programs:
  - Parkinson’s Disease Biomarker Program (NINDS)
  - National Alzheimer’s Center program (NIA)
  - Alzheimer’s Disease Neuroimaging Initiative (NIA)
- Submitted 5/10/16
- Awarded 9/30/16 (end date 9/29/21)
Study Design
Study Visits

Baseline
6 mo ±45 days
12 mo ±45 days
24 mo ±45 days
36 mo ±45 days
48 mo ±45 days
60 mo ±45 days

Imaging

Lumbar Puncture

Cognitive Assessment

Biofluids Collection
Dementia with Lewy Bodies Consortium

• Benefits:
  • Large longitudinal study with matching clinical and biomarker data
  • Open to all investigators
  • Potential to collaborate with Canadian and European programs
  • Resource for years beyond the grant
Dementia with Lewy Bodies Consortium

Thanks!
Dementia with Lewy Bodies Consortium

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Molecular Imaging for Classifying Types of LBD

Kirk A Frey, MD, PhD
Thu University of Michigan
Disclosures

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• Common Stock ownership: Merck, Johnson & Johnson, General Electric, Novo Nordisk, Bristol Myers Squibb
LBD – Current Status and Challenges

- LBD is a complex syndrome – variable clinical symptoms, variable course, limited therapies
- LBD pathology can include several distinct changes in individual brains, suggesting that more than one disease pathway or process is involved
- Discovery of approaches in living LBD patients that allow classification of the pathologies will be essential to identification and testing of new therapies
LBD – Lewy Body Pathology
LBD – Amyloid Plaque Pathology
LBD – Neurofibrillary Tangle Pathology
- Lewy Body Pathology: alpha-synuclein (α-Syn) deposition
- Amyloid Plaque Pathology: amyloid beta (Aβ) deposition
- Neurofibrillary Tangle Pathology: \textit{tau} protein deposition
Positron Emission Tomography of Monoaminergic Vesicular Binding in Aging and Parkinson Disease
Bohnen NI, Albin RL, Koepppe RA, Wernette KA, Kilbourn MR, Minoshima S, Frey KA
Use of Florbetapir-PET for Imaging β-Amyloid Pathology

*JAMA* (2011) *305*:275-283
Aβ-Amyloid Deposition in Patients with Parkinson Disease at Risk for Development of Dementia
Petrou M, Bohnen NI, Müller MLTM, Koepp RA, Albin RL, Frey KA
Neurology (2012) 79:1161-1167
Pharmacokinetic Evaluation of the Tau PET Radiotracer $^{18}$F-T807 ($^{18}$F-AV-1451) in Human Subjects

University of Michigan LBD Project

- 100 Subjects with LBD (DLB or PDD)
- Research Brain Imaging: MRI / PET DTBZ / PET Aβ / PET tau

Goals:
- Classify individual subjects by imaging results
- Determine clinical correlates of brain imaging classifications
- Determine clinical courses of individual subjects
University of Michigan LBD Project

“Lewy Body Dementia Biomarkers”

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Targeting Lewy Body Specific Pathology Using Biomarkers

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Columbia University Medical Center
Disclosures

- Grants from NIH, MJ FOX, CHDI, HDSA
- Clinical trials: TEVA, Vaccinex
- LBDA Scientific Advisory Committee
Mission

Clinical care and the design of clinical trials would benefit from earlier diagnosis and more accurate diagnosis of DLB.

Our goals:

• To identify the extent to which Lewy body versus Alzheimer disease (AD) pathology contributes to the phenotype and underlying biology of DLB

• To discover new molecular targets that are specific to DLB
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

**Brainstem LBs**

**α-synuclein**

**Amyloid stain + thioflavin S**

**Cortical LBs**

**α-synuclein**
Gaps in Knowledge

- **DLB may be underdiagnosed in African Americans and Hispanics.**
  - LB pathology is more common in AA than Whites
    - AA are equally likely to receive a diagnosis during life.

- **Difficult to clinically detect co-existing AD pathology in DLB**
  - >AD pathology = harder to diagnose DLB
  - Fewer hallucinations and reduced diagnostic accuracy of DLB
    - 75% to 39%.

- **Challenge: Clinical trial design due to mixed AD+DLB pathology**
  - Early biomarkers of LB pathology needed
    - Blood or CSF.
Specific Aim 1

- Recruit an ethnically diverse cohort (White, Hispanic, African American)
  - 40 DLB cases/year for each of 4 years
    - Clinic visits at 6 months, then annually.
- Recruiting from memory centers, movement disorders centers and primary care
- Expanded battery to capture features of both DLB and AD
Genetic analyses of DLB

Genetic analysis implicates APOE, SNCA and suggests lysosomal dysfunction in the etiology of dementia with Lewy bodies

Jose Bras1, Rita Guerreiro1, Lee Darwent1, Laura Parkkinen4, Olaf Ansorge4, Valentina Escott-Price5, Dena G. Hernandez6, Michael A. Nalls6, Lorraine N. Clark7,8, Lawrence S. Honig7,9, Karen Marder7,9, Wiesje M. Van Der Flier10, Afina Lemstra10, Philip Scheltens10, Ekaterina Rogaeva11, Peter St George-Hyslop11,12, Elisabet Londos13, Henrik Zetterberg1,14, Sara Ortega-Cubero15,16,17, Pau Pastor15,16,17, Tanis J. Ferman16,19, Neill R. Graff-Radford20, Owen A. Ross21, Imelda Barber22, Anne Braae22, Kristelle Brown22, Kevin Morgan22, Walter Maetzler22, Daniela Berg23, Claire Troakes24, Safa Al-Sarraj24, Tammaryn Lashley2, Yaroslau Compta2,30, Tamas Revesz2, Andrew Lees2, Nigel Cairns25,26, Glenda M. Halliday27,28, David Mann29, Stuart Pickering-Brown29, Dennis W. Dickson21, Andrew Singleton6 and John Hardy3

Clinical and neuropathological similarities between dementia with Lewy bodies (DLB), Parkinson’s and Alzheimer’s diseases (PD and AD, respectively) suggest that these disorders may share etiology. To test this hypothesis, we have performed an association study of 54 genomic regions, previously implicated in PD or AD, in a large cohort of DLB cases and controls. The cohort comprised 788 DLB cases and 2624 controls. To minimize the issue of potential misdiagnosis, we have also performed the analysis including only neuropathologically proven DLB cases (667 cases). The results show that the APOE is a strong genetic risk factor for DLB, confirming previous findings, and that the SNCA and SCARB2 loci are also associated after a study-wise Bonferroni correction, although these have a different association profile than the associations reported for the same loci in PD. We have previously shown that the p.N370S variant in GBA is associated with DLB, which, together with the findings at the SCARB2 locus, suggests a role for lysosomal dysfunction in this disease. These results indicate that DLB has a unique genetic risk profile when compared with the two most common neurodegenerative diseases and that the lysosome may play an important role in the etiology of this disorder. We make all these data available.
Current Progress – Genetics

• Major progress:
  • Large scale genetic association study and analysis of heritability
  • Overlap between genetics of PD with DLB and AD with DLB
    • Some of the same loci are involved in PD as in DLB
    • Potentially different flavors of genetic variability at those loci
  • Supports lysosomal dysfunction as a mechanism of disease
  • Once APOE is excluded, the genetic correlation between a) DLB and PD and b) DLB and AD is equal

• Ongoing research:
  • Large whole genome association
  • Whole exome sequencing
  • Targeted resequencing studies
Specific Aim 2

- Determine Lewy body specific differences in gene expression
  - To identify targets for therapy
  - To identify potential biomarkers
- RNAseq technology to identify DLB specific changes
  - 50 DLB/AD brain donors compared to 50 AD donors.
- Brain regions being compared
  - Cingulate cortex - common spot for LB
  - Frontal cortex - more likely to have AD pathology.
- Comparing DLB/AD to
  - Pure DLB (without AD)
  - controls.
RNA-Seq

Samples of interest
- Condition 1 (e.g. tumor)
- Condition 2 (e.g. normal)

Isolate RNAs
- Poly(A) tail

Generate cDNA, fragment, size select, add linkers

Map to genome, transcriptome, and predicted exon junctions

Unsequenced RNA

RNA reads

Short insert

100s of millions of paired reads
10s of billions bases of sequence

Downstream analysis

https://en.wikipedia.org/wiki/RNA-Seq#Fusion_gene_detection
Specific Aim 3

Develop biomarker assays in blood and CSF, including at RNA and protein levels.

• Plasma from subjects with autopsy diagnoses
  • Plasma from subjects with clinical diagnosis
  • Plasma from the cohort subjects recruited in AIM #1

• Exploratory analysis of cell-free DNA methylation patterns and protein biomarkers in CSF samples
  • Source: Columbia ADRC CSF bank and from PDBP resources.
Conclusions

• Challenges in DLB clinical trials:
  • Inclusion of participants with varying amounts of AD pathology
  • Can’t easily assess how AD pathology affects diagnosis and progression.
• Genetic studies are still at an early stage
  • Data suggests unique genetic contributions to DLB
• RNA expression studies may identify:
  • Biomarkers
  • Targets for therapeutics.
• Goal: Identify early biomarkers of LB disease that are:
  • Easy to analyze (e.g. blood tests)
  • Cost effective and
  • Target the underlying cause of DLB
Columbia University LBD Project:

“Targeting Lewy Body Pathology Using Biomarkers”

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Ask the Expert
Q&A
Interested in Joining a Research Study or Clinical Trial?

Find a Study Near You
https://www.lbda.org/participate-in-research

Also:
https://pdbp.ninds.nih.gov/projects-we-support
https://clinicaltrials.gov/
The Lewy Body Dementia Association is the only organization in the United States solely dedicated to improving the lives of LBD families.

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LBDA is a 501(c)3 organization