

National Institute on Aging (NIA) Penn U19 “Center On Alpha-synuclein Strains In Alzheimer Disease & Related Dementias”. Principal Investigator: John Q. Trojanowski

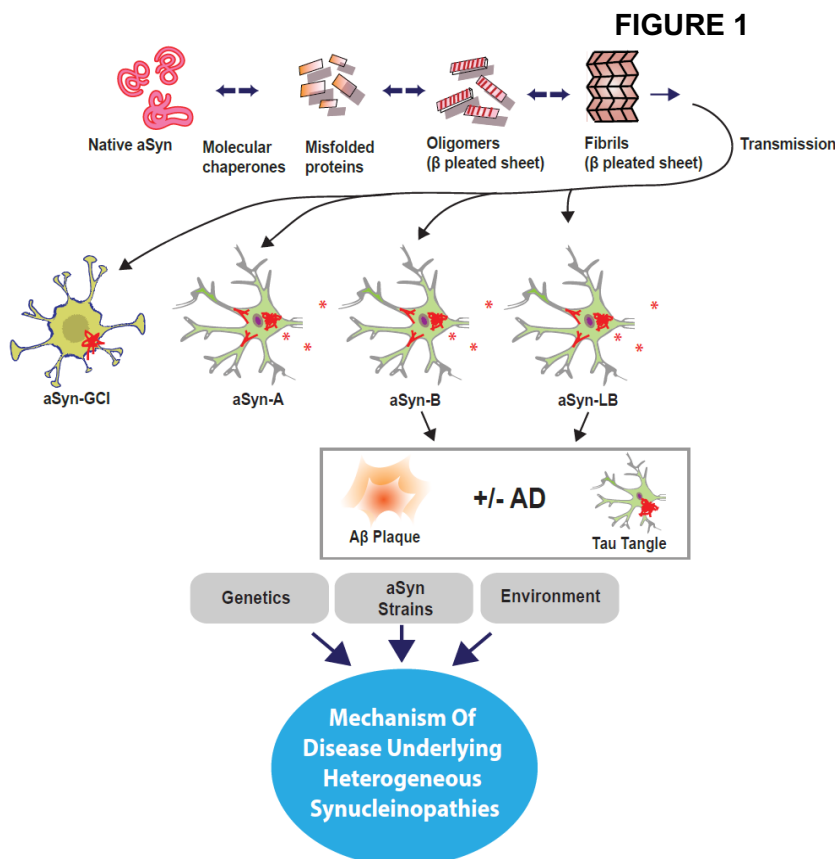
As described below under Resources Made Available Through This U19 Center To Outside Investigators In Cooperation With NIA

The U19 Center and Penn biosample bank that the Penn team has developed over the past 20 years will be a valuable resource to other investigators beyond Penn who pursue research on amyloid polymorphisms and strain. Thus, we will work on this closely with NIA Progm. U19. Details on available data and resources as well as plans for sharing these resources are briefly described in the summaries of Cores A, C and D. Please contact Mr. Kevin Davies or Lisa Toole at 215-662-6399 if you would like to discuss biosampels or research strategies with Virginia Lee or John Trojanowski or other investigators in this U19.

Research Strategy

Significance

The goals of this Penn U19 “**Center On Alpha-synuclein Strains In Alzheimer Disease & Related Dementias**” at the University of Pennsylvania (Penn) Perelman School of Medicine (PSOM) are to elucidate mechanisms of progressive neurodegeneration and dementia in AD+aSyn/PD/PDD/DLB and MSA. We refer to PDD and DLB collectively as LB dementias (LBD). We hypothesize that cellular dysfunction and death result from transmission of distinct pathologic alpha-synuclein (aSyn) strains leading to toxic Lewy bodies (LBs) and neurites (LNs) in AD+aSyn and LBD. We contrast these aSyn strains with those forming glial cytoplasmic inclusions (GCI) in multiple system atrophy (MSA) and rarely associates with dementia or AD pathology as control aSyn strains in our studies. Further, aSyn strain diversity leads to heterogeneity in AD+aSyn and LBD. Thus, Projects I and II seek to elucidate the mechanisms underlying heterogeneity of AD+aSyn/LBD, hypothesizing that different biochemically and milieu-influenced strains formed by misfolded aSyn underlie the spectrum represented by AD+aSyn and LBD compared with the more virulent MSA aSyn stain (see Figure 1 below). Projects III and IV complement these first 2 Projects by focusing on patient-oriented studies of LBD and AD to examine clinical and pathological heterogeneity with multimodal clinical, genetic, and biomarker assessments, with follow up to autopsy which will reveal those patients with AD+aSyn versus pure AD (AD-aSyn). Taken together, these Projects will advance more precise approaches to understanding AD+aSyn and LBD.



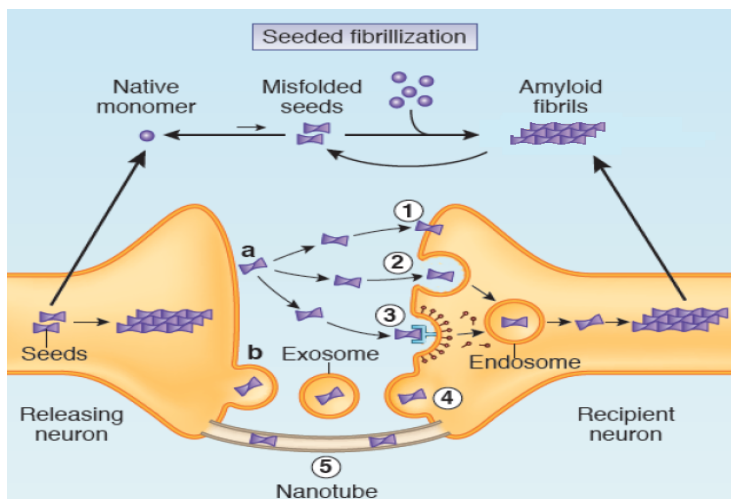
LEGEND: The upper portion of this figure illustrates hypothetical mechanisms of how distinct LB (aSyn-LB) and GCI (aSyn-GCI) aSyn strains lead to the onset and progression of heterogeneous synucleinopathies. Genetic and environmental factors (lower portion of the figure) contribute to this process. Normal quality-control systems (chaperones, proteasomes, phagosomes, lysosomes) that eliminate misfolded proteins are overwhelmed. Growing evidence suggests progression of AD+aSyn/LBD may be linked to the cell-to-cell spread of pathological aSyn. This provides a conceptual basis for understanding disease progression, mediators of neurodegeneration and heterogeneity in AD+aSyn and LBD. Elucidating these mechanisms will lead to more precise diagnosis and optimal therapies for AD+aSyn/LBD. The aSyn-A and aSyn-B strains are distinct synthetic strains that induce aSyn pathology alone or tau>aSyn pathology, respectively, as

described by Guo et al³ and below on the next page.

AD+aSyn/LBD, like most neurodegenerative diseases (NDs), share mechanisms involving protein misfolding and progressive accumulations of these proteins as aggregates that are diagnostic of AD+aSyn and LBD versus MSA.^{13, 18-29} Figure 2 on the next page illustrates hypothetical steps in this process including CNS spread of pathological aSyn consistent with the staging of aSyn pathology^{30, 31} and imaging studies.³²⁻³⁴ Early clues that pathological aSyn could spread from cell-to-cell in PD came from studies showing formation of LBs in fetal neurons grafted into PD patients.^{35, 36} This concept was extended when we showed that striatal injections of synthetic aSyn preformed fibrils (PFFs) into aSyn transgenic (Tg) and wildtype (WT) mice induced PD-like LBs and LNs in brain regions neuroanatomically connected to striatum, including the substantia nigra (SN) pars compacta (SNpc) in association with SN neuron loss, but without any statistically significant astrogliosis or microgliosis at early post-injection survival times.^{37, 38}

Although the concept of disease protein transmission in AD+aSyn, LBD and MSA is still emerging, using an integrative approach like we propose in our U19 Center, prion investigators have provided important mechanistic insights into, as well as an in-depth understanding of, diverse clinical and pathological phenotypes in sporadic human prion diseases linked to distinct prion strains.³⁹⁻⁴⁶ Because of the relevance of this to our U19 Center studies, we briefly review key findings from the prion field. First, normal cellular prion proteins (PrPc) may misfold into pathological conformers (PrPSc) through a templating mechanism. Second, more than 20 different pathological PrPSc strains have been reported. Third, different PrPSc strains show differential toxic consequences and abilities to spread, correlating with heterogeneous clinical and pathological phenotypes of prion diseases. Importantly, prion strains were defined by rigorous experimental, molecular and biochemical methods like those used in Projects I and II, as well as clinicopathological strategies like those used in

FIGURE 2



LEGEND: This figure illustrates the template-directed protein misfolding, seeded aggregation, release and uptake of misfolded aSyn enabling its cell-to-cell transmission and spread of pathological aSyn in AD+aSyn and LBD. Converging evidence suggests that disease progression is driven by a process involving template-directed protein misfolding, seeded aggregation and release of small aSyn fragments from inclusions followed by their uptake by normal cells to enable the cell-to-cell transmission of pathological aSyn culminating in progressive CNS dissemination of pathological aSyn.⁴⁷⁻⁵²

Project III and IV.^{39, 41, 42, 45} Thus, over the last several decades, different PrPSc strains have been defined by their molecular and biochemical features, as well

as by their transmissible properties and clinicopathological manifestations. Notably, unlike prion diseases synucleinopathies are not communicable.^{53, 54} Through the collaborative efforts of Projects I-IV and Cores A-D in the Penn U19 Center, we propose to use strategies similar to those exploited in the prion field to implement our studies of aSyn strains based on biochemical, morphological, transmissible, clinical, and pathological features.

Studies of the existence of strains of pathologic proteins involved in non-prion transmissible NDs mediated by proteopathic aSyn, tau, A β and other ND protein seeds are in the early stages compared to prions.^{27, 47, 50, 51, 55-64} Project I and II present compelling preliminary data for the existence of strains of synthetic aSyn PFFs. For example, we first defined synthetic aSyn strains A and B following serial passaging of aSyn PFFs,³ and now characterize distinct aSyn strains derived from the brains of AD+aSyn, LBD and MSA patients.¹ Thus, similar to prion diseases wherein multiple PrPSc strains and clinicopathological phenotypes have been defined, we hypothesize that different transmissible pathological aSyn strains underlie the phenotypic heterogeneity and progression seen in AD+aSyn, LBD and MSA. Indeed, understanding PrPSc strains has significant practical relevance because these insights may explain the heterogeneity of human prion disorders, and we predict the same will be true of AD+aSyn, LBD and MSA. Accordingly, Projects III and IV will work closely with Cores B-D to develop and analyze deep phenotyping data on AD+aSyn and LBD subjects. Indeed, to advance our U19 Center mission together, all Projects/Core work in unison on a shared goal to correlate deep phenotypic data from Projects III/IV with strain data from Projects I/II in collaboration with the Cores to determine for the first

time the correspondence of clinicopathological phenotypes with novel aSyn strains as suggested by our preliminary data.¹ In fact, our work on transmission of AD tau strains versus frontotemporal dementia (FTD) tau strains shows propagation of AD-like versus FTD-like tau pathologies, respectively, in our mouse models which provides compelling support for the feasibility of this approach,⁶⁵⁻⁶⁷ in addition to our preliminary data on brain derived aSyn strains.¹ Indeed, our recent transmission of postmortem FTD brain derived TDP-43 in mice further strengthens the view that cell-to-cell spread of disease proteins is a feature of most non-prion NDs.⁶⁸

A unique aspect of this U19 is that Projects III and IV aim to understand the heterogeneous presentation and progression of AD and LBD by investigating them through the framework of the aSyn strain model developed in Projects I and II. In particular, Project III will assess the association of aSyn strains in aSyn-AD compared to aSyn+AD pathology, compare this with AD+aSyn pathology in autopsy studies of patients with PDD /DLB and AD, examine the anatomic distribution of aSyn strains and associated aSyn, tau and A β pathology in human brains, and relate these strains and their accompanying misfolded proteins to antemortem cognitive deficits. Project III also will use autopsy-validated CSF measures obtained in living patients followed to autopsy to assess the anatomic distribution and spread of these pathologies in clinical LBD and AD patients using longitudinal imaging, and to define the accompanying cognitive deficits. On the other hand, Project III will focus on *cognitive heterogeneity* within a cohort of PD patients by defining the molecular signatures of individuals who do versus do not develop cognitive decline, and comparing these signatures to those found in DLB and AD. In particular, Project III will utilize both unbiased proteomic screening approaches and aSyn-conformation-based approaches to define these molecular signatures. Project IV will focus on heterogeneity of aSyn strains in AD and LBD from a human *cognitive, imaging* and *neuropathological* perspective. Thus, these patient oriented studies are complemented the focus on *biochemical* heterogeneity at the protein and cellular aSyn strain level in Project I, and the use mouse models in Project II to understand whether heterogeneity of *transmissibility* occurs for different aSyn strains in an *in vivo* context.

We note that emerging data suggest that progression of aSyn pathology may be determined by at least 4 key factors: (1) the templated spread of pathological aSyn, (2) the intrinsic vulnerability of cells to develop aSyn inclusions followed by their differential susceptibility to neurodegeneration, (3) the anatomical connectome of affected CNS regions and (4) interactions of aSyn pathology with tau and A β pathology.^{37, 38, 47, 49, 51, 52, 61, 69} Recognition of these common pathogenic mechanisms opens up fresh opportunities to pursue novel disease-modifying treatments for AD+aSyn and LBD.^{26, 27, 56-58, 70-74} Abundant neuronal accumulations of aSyn in LBs/LNs are the pathological signatures of sporadic PD/PDD/DLB and some forms of familial PD/PDD, while these pathologies affect ~50% of AD patients. Normal aSyn is a 140 amino acid heat-stable protein expressed especially in neurons, and although its function is not well understood, its enrichment at synapses suggests it has synaptic functions, while pathological aSyn in AD+aSyn, LBD and MSA is characterized by insolubility to detergents, post-translational modifications (proteolytic cleavage, nitration, hyperphosphorylation, ubiquitination, oxidation) and the conformation of amyloids.^{18, 26, 27, 69, 75-79}

PD exemplifies many features of NDs, is the second most common ND after AD affecting ~1,000,000 Americans, but is increasing more rapidly than AD which affects 5,500,000 Americans.^{26, 64, 80-84} Non-motor symptoms (NMS), including cognitive impairments (CI), olfactory dysfunction, constipation, REM behavior disorder and depression present at any stage of PD.⁸⁵⁻⁹⁵ MSA is uncommon and is often misdiagnosed as PD in living patients, but does not progress to dementia with AD co-pathology like PD.^{28, 29, 96-100} Dementia adds to the cost of PD and increases mortality while there are no disease-modifying therapies for AD or LBD.^{19, 88-91, 101, 102} About 80% of PD patients progress to dementia, and genetic factors are implicated, including variants in *COMT*, *MAPT*, *BDNF* and *APOE*.^{94, 101, 103, 104} Motor signs are more prominent in PD and PDD, but motor signs are relatively subtle in DLB while cognitive and neuropsychiatric features are much more common, including REM sleep behavior disorder, hallucinations and fluctuations. DLB shows LBs and AD pathology with dementia occurring before parkinsonism, unlike PDD wherein dementia emerges >1 year after onset of parkinsonism,^{87, 88, 90, 93, 94, 105} although recent studies from our group challenge this concept.⁹⁴ While genetic factors underlying DLB overlap in part with AD and PD,¹⁰⁶⁻¹¹⁰ rare *SNCA* mutations cause PD and there are ~30 PD risk loci.^{104, 111-113} Indeed, some of these mutations cause significant oligodendroglial aSyn deposition and morphological phenotypes that resemble MSA,^{114, 115} but specific genetic factors underlying MSA are not clear.¹¹⁶ Notably, the A53T *SNCA* mutation induces abundant tau as well as aSyn pathology,^{117, 118} consistent with reports that aSyn cross-seeds tau pathology.^{2, 3, 119-122}

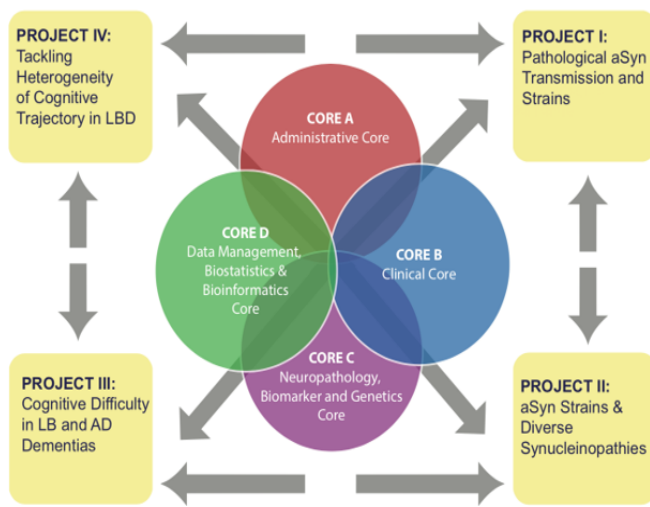
The molecular mechanisms underlying transmission of pathological aSyn likely begin with unifocal or multifocal aSyn misfolding events which adopt abnormal conformations with amyloid properties that may define different aSyn strains.^{18, 27, 47, 50, 51, 56-58, 61, 64} Proteopathic aSyn seeds template normal aSyn to adopt pathological conformations that progressively seed aggregation to form LBs/LNs and GCIs. These may

fragment to release “daughter” seeds followed by cell-to-cell transmission likely involving specific mechanisms of secretion or release and uptake via receptors, thereby enabling pathological aSyn to spread to neighboring or distant cells via axonal, dendritic or other modes of conveyance followed by an autocatalytic chain reaction-like iterative process (Fig. 1 and 2).^{47, 49, 51, 52, 55, 61, 123-130} To elucidate the onset and progression of AD+aSyn and LBD, the U19 Center builds on remarkable progress in understanding aSyn-mediated neurodegeneration since the discovery of *SNCA* mutations pathogenic for PD, the identification of aSyn as the disease protein that forms LBs/LNs and GCIs, and the growing experimental evidence that progression of AD+aSyn, LBD and MSA may result from the cell-to-cell spread of aSyn strains.^{26, 37, 38, 48, 52, 112, 129, 131-134} Projects I-IV work with Cores A-D to elucidate the differential progression of AD+aSyn and LBD, as well as mechanisms of aSyn-mediated neurodegeneration in these disorders, including studies of model systems (Projects I/II) and patients (Projects III/IV) to understand mechanisms of disease AD+aSyn /LBD and identify more precise approaches to therapy.^{80, 135-138} Unique to the Penn U19 Center is that this Center will work with Austin Yang, NIA Program Officer for this U19, to provide qualified investigators with existing and new biofluids, DNA/RNA, autopsy tissue and data collected from ADRD patients over the past 20 years at Penn, in addition to aSyn strains. The archived biologicals collected from ADRD patients (AD, PD/PDD, DLB, FTD, and related tauopathies, synucleinopathies and TDP-43 proteinopathies) at Penn together with synthetic and brain-derived aSyn strains are unique ND resources that the Penn U19 Center will provide to qualified investigators through a review process similar to that used in the AD Neuroimaging Initiative (ADNI) ADNI in partnership with NIA.^{139, 140}

The following key questions about the pathobiology of AD+aSyn/LBD and proteopathic aSyn seeds remain to be addressed to elucidate the molecular mechanism of disease progression and link these insights back to an understanding of disease progression in living patients in order to develop better ways to diagnose and treat AD+aSyn/LBD through rigorously designed and precise approaches: **1)** Is the progression of AD+aSyn/LBD mediated by the cell-to-cell spread of aSyn seeds? **2)** How do proteopathic aSyn seeds spread from cell to cell? **3)** Do different conformational strains of aSyn account for AD+aSyn and LBD versus MSA as well as the heterogeneity within these disorders? **4)** If different aSyn strains are the source of disease heterogeneity, how do they arise, propagate and mediate their effects? **5)** Can understanding cell-to-cell spread of aSyn strains lead to insights into mechanisms of disease progression in patients with AD+aSyn/LBD and MSA? **6)** Do aSyn strains cross-seed other ND proteins and might this account for the common convergence of LBD and AD as well as the rare co-occurrence of AD in MSA? **7)** How are aSyn strains modified by genes and environment? **8)** How can addressing the foregoing questions be translated into developing biomarkers and disease-modifying therapies for AD+aSyn/LBD? **9)** Can we track spreading aSyn pathology in LBD, and does the pattern of spreading pathology differ in AD+aSyn versus LBD? It is beyond the scope of any single group to address all of these questions, but Projects I-IV work synergistically Cores A-D to elucidate many of them and thereby advance the overall goals of our Center.

Innovation

The Penn U19 Center innovates by elucidating mechanisms underlying the heterogeneous progression of cognitive impairment to dementia in LBD compared to AD+aSyn in addition to neurodegeneration mediated by progressive accumulations and cell-to-cell spread of pathological aSyn strains. Thus, the Penn U19 Center seeks to understand the molecular mechanisms that underlie AD+aSyn/LBD heterogeneity. Together the Center Projects will work with the Center Cores to rigorously test the aSyn strain hypothesis from perspectives that span from individual patients to model systems of alpha-synucleinopathies including AD+aSyn and LBD. Finally, the Penn U19 Center is unique in that it will work with Austin Yang and NIA Program to provide outside investigators new and existing biofluids, DNA/RNA, autopsy tissue and data collected from ADRD patients over the past 20 years and in this U19 Center in addition to aSyn strains through mechanisms described in Core A.



Approach

The Penn U19 Center consists of 4 Cores that support 2 experimental and 2 patient-oriented Projects. Figure 3 illustrates the interactions of the Cores and Projects while the U19 organizational chart is shown in Figure 4 on the next page. The 4 Penn U19 Center Cores are summarized first followed by the 4 Projects.

FIGURE 3

LEGEND: The Project and Cores of the Penn U19 Center and their interactions are shown in here.

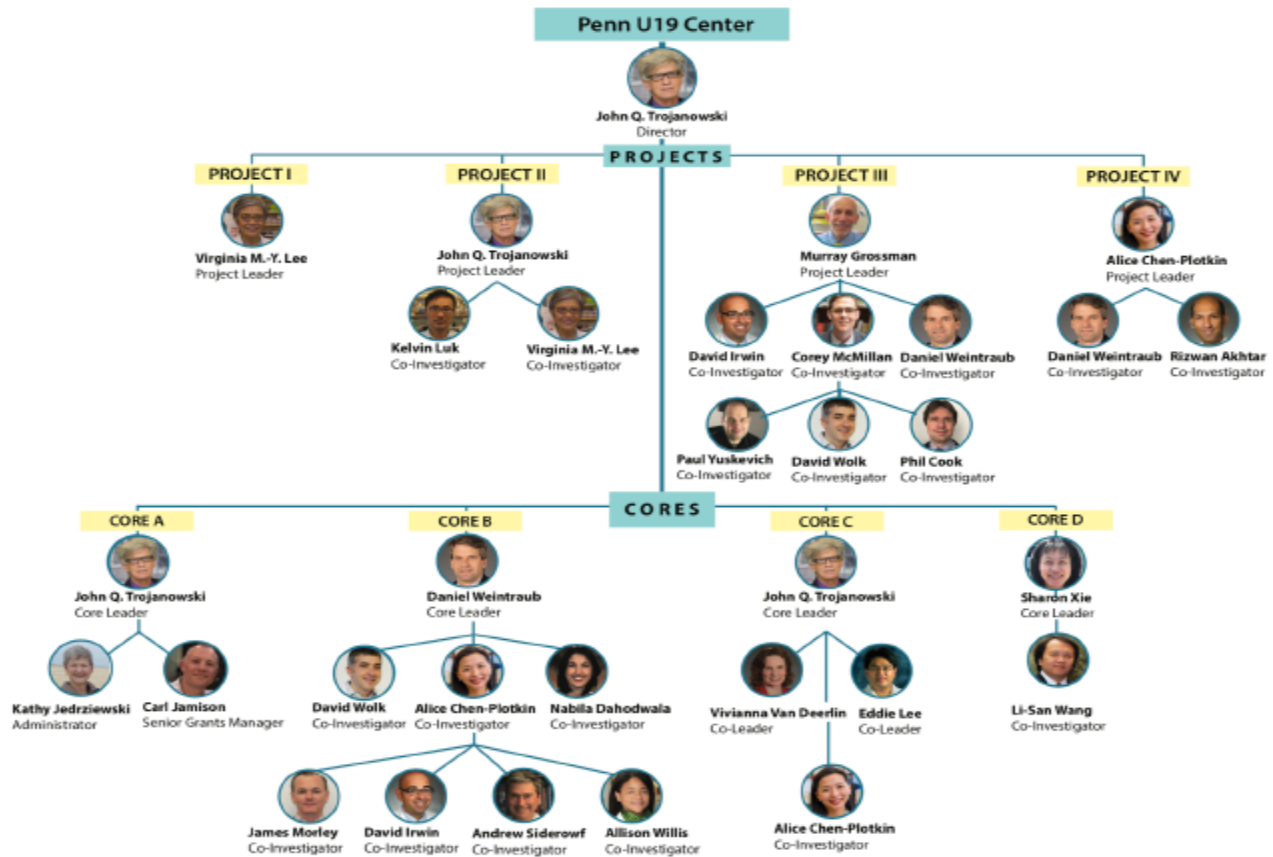
CORE A: Administrative Core - Core A Leader: John Q. Trojanowski

Core A facilitates accomplishing the goals of this multidisciplinary Penn U19 Center research program. Accordingly, the Aims of Core A are to oversee budgetary and fiscal aspects of this Center; promote/foster interactions between Cores and Projects, as well as interactions of Penn U19 investigators with scientists outside the U19 Center at and beyond Penn; convene U19 External Advisory Committee meetings; serve as an information resource for outreach to the patient community and general public regarding AD+aSyn, LBD and MSA; monitor progress of Cores/Projects; facilitate sharing of data/reagents/resources of the Penn U19 Center with other researchers in partnership with the NIA; participate in national and international meetings on ADRD as well as Penn symposia to accelerate the pace of advances in understanding ADRD and related synucleinopathies as well as promote outreach to the public; train the next generation of AD+aSyn and LBD investigators; enhance the careers of junior faculty; host and train outside investigators who wish to visit our Center to learn methods required for transmission studies of pathological tau and aSyn. An Internal Executive Committee (IEC) composed of Core and Project Leaders will work with NIA to respond to and adjudicate applications for U19 resources and data. Thus, Core A plays a key role in the mission of this U19 Center with considerable institutional support, as described in Core A and in the letters of support from PSOM Dean Larry Jameson, Vice Dean for Research Jon Epstein and other PSOM leadership.

CORE B: Clinical Core - Core B Leader: Daniel Weintraub; Co-Investigators: Alice Chen-Plotkin, Nabila Dahodwala, David Irwin, James Morley, Andrew Siderowf, Allison Willis and David Wolk

Core B recruits and evaluates patients with LBD and supports assessments of AD patients through the Penn AD Core Center (ADCC), some of whom will have AD+aSyn on autopsy, for research conducted by the U19 Center's Projects. Core B also is an essential link to the other Cores for collaborative studies and support of education, outreach, training and career enhancement, collection of blood (for DNA extraction and plasma biomarkers), CSF, structural MRIs, and brain tissue/DNA, and data collection, biostatistics and management (see Core D). Core B will use NINDS Common Data Elements (CDEs) and components of ADNI and NACC DLB assessment protocols for collection of clinical and cognitive data, and work with NIA to send biosamples to qualified investigators outside the U19 who are approved through mechanism described in Core A, work with Core D to upload all data to the Penn Integrated Neurodegenerative Disease Database (INDD), and collaborate with the ADCC and other AD and LBD focused research programs on multi-center studies. Finally, the PD Research, Education and Center (PADRECC) at the Philadelphia Veterans Affairs (VA) Medical Center is an integral part of Core B. This PADRECC is

FIGURE 4



LEGEND: This schematic shows the Penn U19 Center Organization Chart with the names and photographs of the Project and Core Leaders, Co-Leaders and Co-Investigators as well as Core A staff.

one of 6 VA Centers of Excellence specializing in the diagnosis and management of PD and related movement disorders, and it offers clinical, research, and educational services for Veterans, 20% of whom are minorities. Thus, this PADRECC adds racial and socioeconomic diversity to our U19 Center.

CORE C: Neuropathology, Biomarker & Genetics Core - Core C Leader: John Q. Trojanowski; Co-Core Leaders: Alice Chen-Plotkin, Edward B. Lee and Vivianna Van Deerlin

The Neuropathology, Biomarker & Genetics Core C supports the mission of the Penn U19 Center by banking and characterizing postmortem brain tissue from clinically assessed AD and LBD cases, some of whom will have pure AD and MSA, respectively, at autopsy as well as banking biofluids and extracting DNA for studies. Core C supports the U19 Center goals by implementing postmortem diagnostic criteria for all subjects followed in Core B who come to autopsy using state-of-the-art methods, while also assessing the utility of antemortem diagnostics, including studies of potential genetic, biofluid and structural imaging signatures. Core C also works closely with the Projects to identify the best cases for isolation of pathological aSyn from postmortem brains associated with detailed phenotypic data to enable correlations of pathological aSyn stains with subtypes of AD and LBD. To accomplish this, Core C works closely with all Center Cores/Projects by improving diagnostic methods and providing thoroughly characterized fresh, unfixed frozen and fixed CNS tissues, biofluids and DNA to investigators at and beyond the U19 Center in partnership with NIA program.

CORE D: Data Management, Biostatistics & Bioinformatics Core - Core D Leader: Sharon Xie, Co-Investigator: Li-San Wang

Core D is responsible for maintaining a relational database of demographic, clinical, genetic, biomarker, imaging and neuropathology data gathered by the Center. The Center database is linked with the INDD developed by Xie et al¹⁴¹ which allows cross disease comparative studies with other NDs such as AD with and without LBs followed in other NIH-funded studies as exemplified by the NIA-funded Penn ADCC (P30 AG010124-27) wherein Sharon Xie leads a core similar to Core D here. Notably, the Penn ADCC has a NACC

DLB Module led by Dave Irwin that will foster collaborations between the U19 Center and the ADCC. It also has a NACC FTD Module led by Murray Grossman so there is extensive cross-talk between investigators in this U19 and the Penn ADCC. Core D provides database, computing, biostatistical and bioinformatics support to Center investigators as well as to outside collaborators with the Center, including data sharing between the Penn U19 Center and the NIA funded AD Centers (ADCs) and NINDS-funded Udall centers and other qualified investigators. It provides biostatistical training to the next generation of ADRD researchers.

These 4 Penn U19 Center Cores support the following 4 Projects:

PROJECT I: Pathological Alpha-Synuclein Transmission - Project I Leader: Virginia M.-Y. Lee

The diversity of misfolded aSyn pathology in AD+aSyn/LBD/MSA supports the aSyn strain hypothesis wherein pathological aSyn adopts different conformations that account for disease in these disorders. Since aSyn pathology progressively spreads in brains of AD+aSyn/LBD/MSA patients, we propose the strain transmission hypothesis to explain the heterogeneity of these disorders and the spreading of pathological aSyn. Indeed, Projects I and II have advanced beyond the use of Tg mice and synthetic aSyn PFFs to study the spread of pathological aSyn in WT mice for modelling AD+aSyn and LBD versus MSA using aSyn strains isolated from AD+aSyn, LBD and MSA brains characterized genetically and neuropathologically by Core C from patients followed by Core B and studied in Projects III and IV. We demonstrated the existence of human brain-derived aSyn strains through the analyses of pathological aSyn isolated from AD+aSyn and LBD brains harboring abundant LNs/LBs (aSyn-LB) and MSA brains with abundant GCIs (aSyn-GCI).¹ We showed that aSyn-LB (from AD+aSyn and LBD brains) and aSyn-GCI from MSA brains are conformationally and biologically distinct, and that aSyn-GCI is ~1,000-fold more potent than aSyn-LB in seeding pathological aSyn aggregation. Moreover, other recent studies suggest the intracellular environment plays a deterministic role in aSyn strain specification.¹ Thus, going forward, we will identify the determinants of cell type specificities for AD+aSyn and LBD brain derived aSyn-LB compared to MSA brain derived aSyn-GCI strains and elucidate mechanisms for the templated propagation of these and other aSyn strains we uncover. This will include cryo-electron microscopy (Cryo-EM) studies with Vera Moiseenkova-Bell PhD, the new Director of the Beckman Center for Cryo-EM which will launch May, 2019 so we will collaborate with Vera Moiseenkova on these Cryo-EM studies of brain derived aSyn stains (see letter of support). Thus, Project I works closely with all U19 Center Cores/Projects, especially Project II, to provide LB-aSyn and GCI-aSyn strains for strain-specific transmission studies in mouse models.

Project II: Alpha-Synuclein Strains & Diverse Synucleinopathies - Project II Leader: John Q. Trojanowski; Co-Investigators: Virginia M.-Y. Lee and Kelvin Luk

Here we test the hypothesis that pathological aSyn in AD+aSyn, PD, PDD and DLB (i.e., LBD) brains represent the emergence and spread of different aSyn strains in neurons to form LBs and LNs. We compare these strains to each other and with aSyn strains in MSA brain derived GCI-aSyn strains. Testing this hypothesis will advance understanding of if/how distinct aSyn strains drive clinical and pathological heterogeneity in these diverse synucleinopathies. Since dementia in PDD and DLB frequently is accompanied by AD pathology (aSyn+AD), we will test the hypothesis that aSyn strains from AD+aSyn and LBD brains (aSyn-LB) induce A β and tau pathologies compared to pathological aSyn from MSA brains (aSyn-GCI) which rarely show comorbid AD. Project II works closely with all U19 Center Cores/Projects to determine if aSyn-LB and aSyn-GCI strains differentially induce pathological aSyn in neurons versus glia as well as recruit AD-like plaque and tangle pathology following intracerebral injections into Tg mice that model A β plaque and/or tau pathologies compared to WT and Tg mice that model MSA-like GCIs. These studies will open up new pathways to explore how LB versus GCI aSyn strains contribute to the distinct and heterogeneous clinical and pathological features of AD+aSyn/LBD versus MSA as well as interact with AD pathologies.

Project III: Cognitive Difficulty in Lewy Body & Alzheimer Dementias - Project IV Leader: Murray Grossman; Co-Investigators: Phil Cook, David Irwin, Corey McMillan, Daniel Weintraub, David Wolk and Paul Yuskevich

Our recent autopsy studies of a large number of clinically diagnosed PDD and DLB patients showed that aSyn pathology, when accompanied by tau and A β co-pathology (i.e. aSyn+AD), is relatively more abundant in cortex than striatum and associates with more rapid clinical decline as well as more cognitive difficulties.¹⁴² In contrast, aSyn pathology consistent with LBD but without AD pathology (i.e. aSyn-AD) is equally abundant in cortex and striatum, and patients have longer survival with less cognitive difficulties. In our living cohort, we also found that LBD patients with abnormal CSF A β ₁₋₄₂, consistent with likely aSyn+AD, have greater MRI

cortical atrophy and cognitive difficulties while patients with normal CSF A β , consistent with likely pure aSyn (i.e. aSyn-AD), have more prominent striatal atrophy with less cognitive, but greater motor, difficulties.¹⁴³ We build on these findings with all the U19 Cores to study the nature and anatomic distribution of ND pathologies and associated aSyn strains, and examine the corresponding clinical, cognitive, and anatomic features of LBD versus AD during life. This will be done by collaborating with Core C through pathologic evaluation of LBD and AD using a validated digital histology (DHist) approach with superior sensitivity to quantify the anatomic distribution of aSyn, A β and tau pathology in a 2X2 design comparing LBD (aSyn-AD, aSyn+AD) and AD (AD-aSyn, AD+aSyn), relate these pathologies to antemortem clinical features from Core B as well as with Project IV, and use DHist to assess mAbs characterized by Projects I and II to correlate aSyn strains defined in these Projects with human pathology in aSyn-AD vs. AD+aSyn. We also compare aSyn+AD with pure AD (i.e. AD-aSyn), and expect different anatomic distributions of pathology and corresponding clinical differences that are related to specific aSyn strains. We extend these studies into living patients with autopsy-validated CSF to define likely pathology in aSyn-AD vs. aSyn+AD, and AD-aSyn vs. AD+aSyn. Using cross-sectional and longitudinal multimodal structural MRI, we study the spread of cerebral atrophy and examine associated cognitive decline in executive, language, memory and spatial domains. We expect to find relatively different patterns of progressive atrophy and related cognitive impairments depending on likely aSyn+AD pathology compared to pure aSyn (i.e. aSyn-AD) pathology, and compare these to pure AD pathology (i.e. AD-aSyn) and AD+aSyn pathology. We will also relate the anatomic and cognitive profiles to aSyn strains in CSF from Project IV. These multimodal studies will elucidate how aSyn pathology is modified by A β and tau co-pathology in aSyn+AD versus AD+aSyn and pure AD, identify related clinical phenotypes, assess the contribution of aSyn strains to pathologic and clinical heterogeneity of AD and LBD, and improve diagnosis and prognosis as treatments emerge for these conditions.

Project IV: Tackling Heterogeneity Of Cognitive Trajectory In LBD - Project III Leader: Alice Chen-Plotkin; Co-investigators: Rizwan Akhtar and Dan Weintraub

To tackle the problem of heterogeneity of PD/PDD/DLB compared to AD+aSyn in a manner that is likely to yield both biological insight and practical tools, Project IV will develop biochemical and genetic biomarkers of differential PD/PDD cognitive progression. In the past 5 years, we have collected DNA and baseline biofluids from ~400 Penn LBD and AD+aSyn patients assessed on an annual/biennial schedule with motor and cognitive measures. We have generated data suggesting that multiple plasma-based biochemical markers predict differential cognitive progression, as reflected by change in the Mattis Dementia Rating Scale-2 (DRS-2). While some baseline biochemical biomarkers predict subsequent decline along both motor and cognitive trajectories, others are selectively informative with respect to motor or cognitive outcomes.

We now propose to confirm our Penn-discovered, PDBP-replicated lead proteins in additional cohorts of PD/PDD/AD+aSyn patients, and to develop assays that can translate into clinical or clinical trial use. We will additionally relate common genetic variants to expression levels of top biomarker candidates using (1) publicly available resources such as the Genotype-Tissue Expression (GTEx) project to perform expression quantitative trait locus (eQTL) analyses, and (2) Penn-based datasets of genome-wide genotyping and protein profiling in the same patients to conduct protein quantitative trait locus (pQTL) analyses. We will test the hypothesis that genetic variants nominated through these eQTL and pQTL analyses will predict progression in LBD using cohorts at Penn and elsewhere. Finally, we will use antibodies to the aSyn strains defined in Projects I and II to develop biomarker assays to characterize biofluids from our Penn cohort to test the hypothesis that distinct aSyn strains result in differential development of cognitive features in clinical PD/PDD/DLB and AD+aSyn patients.

Finally, all of the Penn U19 Center investigators worked very closely together to design and formulate the research plan described in this application by pursuing NIA research priorities in "Recommendations of the Alzheimer's disease-related dementias conference",¹³ and especially the priorities that address AD and RD including LBD (DLB and PDD), as well as the new guidelines on the biological definition of AD.¹⁴⁻¹⁷ We incorporate these NIA recommendations in each of the Projects and Cores of the U19 Center, while all Project and Center investigators also deliberately designed the plans for interacting closely and frequently across all the Projects and Cores to ensure that all Center investigators interact synergistically with a very deliberate common purpose to implement the goals of the U19 Center (see Fig. 5 on the next page). In addition, we will implement a unique U19 data and biosample sharing program described below and in Core A in partnership with our U19 NIA Program Officer, Austin Yang. The interaction grid in Figure 5 on the following page briefly summarizes how each Project and each Core interacts to implement the U19 Center mission.

Preliminary Data For The Penn U19 Center

These preliminary derive in part from a Udall Center that was not renewed and other NIH grants. We highlight the strong record of productivity from our group as a whole, as well as the studies from each Project/Core leader that establish feasibility of the work proposed in this U19 application.

Project I: Project I obtained significant preliminary data supporting feasibility of the our proposed Aims by testing the aSyn transmission and strain hypotheses of pathological aSyn which included studies showing: **1)** cell-to-cell transmission of LB/LN-like pathology *in vitro* and in Tg as well as WT animals (including non-human primates; Kordower et al, in review)^{37, 38, 52, 130, 144-148} following CNS inoculation of mouse (Ms) aSyn (Ms-aSyn) PFFs (and human aSyn-PFFs); **2)** reduction in PD-like LB/LN pathology in our Ms-aSyn transmission neuron-based cell culture transmission and WT mouse models following exposure to/injection of Ms-aSyn and treatment with aSyn specific MAbs;⁷⁰ **3)** induction of distinct aSyn strains *in vitro* by human aSyn PFFs;³ **4)** identification of distinct LB-aSyn and GCI-aSyn strains with novel MAbs,¹⁴⁹ as well as by isolating these strains from human post-mortem LBD and MSA brains;¹ **5)** possible interactions of aSyn positive LBs/LNs and other neuropathological lesions in LBD and subjects with co-incidental AD and LB pathology.^{87, 94, 150-152} Finally, cryo-EM studies of these strains will launch soon in the new Penn Cryo-EM Center led by Vera Moiseenkova-Bell. This has been done for AD and Pick's disease brain derived tau and recombinant aSyn, but not on brain derived aSyn strains.¹⁵³⁻¹⁵⁸

Project II: Working closely with Project I, Cores A-D in addition to partnering with Projects III and IV as well as with many collaborators at other Centers and institutions beyond Penn, Project II demonstrated feasibility of its 3 Aims by: **1)** Identifying unique synthetic aSyn PFF strains A and B³ that differentially transmitted aSyn positive PD-like LBs/LNs with strain B cross-seeding tau positive AD-like neurofibrillary tangles and dystrophic neurites following injection of Ms-aSyn strain B PFFs into the brains of previously described PS19 tau Tg mice expressing human mutant P301S tau.¹⁵⁹ Notably, this combination of aSyn and tau pathology showed greater verisimilitude to LBD and AD pathology than that seen in aSyn or tau Tg mice.³ **2)** Developing a WT mouse model of aSyn transmission using synthetic Ms-aSyn PFFs;³⁸ **3)** Showing that LB-aSyn and GCI-aSyn are distinct aSyn strains biochemically, immunologically and neuropathologically;¹ **4)** Demonstrating preclinical efficacy of immunization with anti-aSyn MAbs in model systems of aSyn transmission;⁷⁰ **5)** Facilitating best practices for the use by us and others of aSyn and tau PFFs under the leadership of Kelvin Luk to model AD+aSyn/LBD working with the Michael J. Fox Foundation (MJFF) as summarized in Projects I and II, Core D and elsewhere,^{62, 69, 160, 161} all of which we will do in partnership with our NIA Program Officer Austin Yang.

FIGURE 5

Interactions between Penn U19 Center Projects and Cores

	Core A	Core B	Core C	Core D	Project I	Project II	Project III	Project IV
Core A		Oversees administrative matters, collaborates on training, outreach & interactions with other Centers	Oversees <u>administrative matters</u> , collaborates on training & outreach & interactions with other Centers	Oversees <u>administrative matters</u> , collaborates on training & outreach & interactions with other Centers	Oversees <u>administrative matters</u> , collaborates on training & outreach & interactions with other Centers	Oversees <u>administrative matters</u> , collaborates on training & outreach & interactions with other Centers	Oversees <u>administrative matters</u> , collaborates on training & outreach & interactions with other Centers	Oversees <u>administrative matters</u> , collaborates on training & outreach & interactions with other Centers
Core B	Provides annual progress reports to Core A & CL is member of the Center Executive Committee (EC)		Recruits patients, collects DNA & biofluids to bank in Project I, enrolls patients for autopsy & recruits subjects for studies in Projects I-IV	Contributes clinical data for integration with data from other Cores/Projects for analysis by Core D	Characterizes subjects followed to autopsy in Core C which provides brains for Project I studies	Recruits & characterizes subjects for studies of brain derived aSyn in Project II	Recruits & characterizes subjects for studies of brain derived aSyn in Project I	Characterizes subjects followed to autopsy in Core C which provides samples for Project IV studies
Core C	Provides annual progress reports to Core A and the CL is member of the Center EC	Performs autopsies, DNA banking & genetics for Udall subjects & these data inform studies in Projects I-IV		Provides genetic and neuropathology data to integrate with data from other Cores/Projects for analysis by Core D	Provides genetic and neuropathology data for Project I studies	Provides genetic & neuropathology data plus CNS tissues for Project II studies	Provides genetic & neuropathology data or Project III studies	Provides genetic & neuropathology data and CNS tissues for Project IV
Core D	Provides annual progress reports to Core A and the CL is a member of the Center EC	Manages & analyzes Core B data in conjunction with data from Projects I-IV and Core C	Manages & analyzes Core C data in conjunction with data from Projects I-IV and Core B		Manages & analyzes Project I data & collaboratively <u>provides</u> study design input	Manages & analyzes Project II data & collaboratively provides study design input	Manages & analyzes Project III data & collaboratively provides study design input	Manages & analyzes Project I data & collaboratively <u>provides</u> study design input
Project I	Provides annual progress reports to Core A and the PL is a member of the Center EC	Integrates phenotypic data with cell model data to elucidate <u>Syn</u> strains	Uses brains from Core C to generate <u>Syn</u> strains and integrates data from Core C with cell model data to elucidate <u>Syn</u> strains	Collaborates with Core D in all analyses of human, mouse and cell culture model data to <u>elucidate Syn</u> strains		Project I metrics are also applied for interpreting Project II data	Project I data informs Project II-IV data to define different <u>Syn</u> strains based deep phenotyping data	Project I data inform Project IV studies to define <u>Syn</u> strains in patients <u>and</u> <u>model</u> studies
Project II	Provides annual reports to Core A and the PL is a member of the Center EC	Provides input on aSyn strains for Core B studies	Provides input on aSyn strains for Core C studies	Provides data for integration with data from other Cores/Projects for analysis by Core D	Helps guide study development and shares animal model data with Project I		Informs <u>interpretation of studies</u> on different <u>Syn</u> strains by Project III	Informs <u>interpretation of studies</u> on different <u>Syn</u> strains by Project IV
Project III	Provides annual progress reports to Core A and the PL is a member of the Center EC	Integrates clinical data from Core B with mouse model data to elucidate features of <u>Syn</u> strains	Guides future sample and autopsy recruitment efforts for Core C and partners with Core C in Project III studies	Provides data for integration with data from other Cores/Projects for analysis by Core D	Uses <u>all Project I</u> data for integration with patient and cell model data to elucidate <u>Syn</u> strains	Uses all Project II data for integration with patient and cell model data to elucidate <u>Syn</u> strains		Integrates all Project IV data to elucidate <u>Syn</u> strains, and interpret all <u>Syn</u> strain data
Project IV	Provides annual progress reports to Core A and the PL is a member of the Center EC	Integrates clinical data from Core B with mouse model data to elucidate features of <u>Syn</u> strains	Integrates all data generated from Core C with model data to elucidate <u>Syn</u> strains	Collaborates with Core D in all data analysis to <u>elucidate Syn</u> strains	Collaborates with Project I to elucidate features of transmitted <u>Syn</u> strains	Collaborates with Project II to integrate model data to elucidate <u>Syn</u> strains	Collaborates with Project III to integrate mouse model data to elucidate <u>Syn</u> strains	

LEGEND: This grid summarizes the interactions of each U19 Center Core and Project listed in the far left margin of this grid. Thus, by reading the grid from the left margin to the right in each row, the interaction between the Core or Project in the left margin and the Core or Project listed at the top across the horizontal margin can be found in each box or cell of each column under the corresponding Core and Project.

Project III: Following up our autopsy studies of clinically diagnosed PDD,^{87, 150, 162} we examined a large autopsy series of PDD and DLB (n=213).⁹⁴ A medium to high level of AD co-pathology was found in 51% of LBD. This also was associated with higher burden of aSyn pathology compared to patients with low levels of AD co-pathology. The presence of medium to high levels of tau and Aβ co-pathology each worsened cognitive functioning relative to patients with low levels of AD co-pathology, and shortened survival in a dose-dependent manner. However, we could not identify clinical or neuropathological cutpoints to reliably distinguish PDD and

DLB which also share prodromal symptoms, clinical features, biomarker changes and genetic risk factors.^{19, 25, 88, 90, 104, 163-167} Thus, we contend that PDD and DLB exist on a clinical-pathological spectrum more meaningfully defined by the status of AD co-pathology. We investigated the basis for these differences by examining two aSyn strains identified by Projects I/II: Strain A induces only aSyn pathology, while Strain B induces tau>aSyn pathology. Examining relatively distinct reactivity of Strain A mAb Syn7015 and Strain B mAb Syn9029 in serial sections of temporal cortex, we found higher Strain A mAb than Strain B mAb staining in pure aSyn-AD; but in aSyn+AD, the ratio of Strain B mAb to Strain A mAb immunoreactivity is significantly higher than in aSyn-AD. Moreover, if tau tracks the anatomic distribution of aSyn in LBD with Strain B pathology, then the locus of tau may differ in LBD (i.e. aSyn+AD) compared to pure AD (i.e. AD-aSyn). In fact, while tau pathology is denser in pure AD compared to aSyn+AD, we found different relative distributions of tau in these two groups: tau is a higher fraction of total pathology in superior temporal cortex in aSyn+AD, but tau is a higher fraction of total pathology in mid-frontal cortex in AD-aSyn. Moreover, category fluency is reduced in aSyn+AD vs. pure aSyn-AD, and category fluency in aSyn+AD is related to tau pathology in midfrontal cortex and Boston naming test is related to tau in superior temporal cortex, emphasizing the anatomic specificity of tau pathology in LBD; none of these cognitive tests correlates with regional A β or aSyn pathology.

We extended these findings to *in vivo* studies using autopsy-validated markers of aSyn+AD compared to aSyn-AD.^{7, 11, 168} In LBD with normal CSF A β (i.e. aSyn-AD), GM atrophy was primarily in striatum; in LBD with abnormal CSF A β and t-tau levels (i.e. aSyn+AD), we found significantly greater frontal and temporal cortical atrophy.^{19, 169, 170} Measures of decision-making^{99, 100}, language¹⁰¹⁻¹⁰³ and discourse^{98, 104-106} were related to frontal, temporal and parietal atrophy, mediated by abnormal CSF A β and tau levels. aSyn+AD has significantly greater longitudinal decline in frontal and temporal cortex and striatum than aSyn-AD, related to CSF A β . We also found differences in the anatomic locus of atrophy in aSyn+AD compared to pure AD-aSyn. Finally, in medial temporal lobe (MTL) subfields, pathologic assessment shows that AD-aSyn has higher absolute tau in all MTL subregions than aSyn+AD, yet we find that AD-aSyn has higher relative tau in CA1/entire MTL but aSyn+AD has higher relative tau in entorhinal cortex/entire MTL. Using our novel, autopsy-validated MRI algorithm to quantify MTL subfield volume, we find that CA1 is significantly smaller in AD-aSyn and aSyn+AD and aSyn-AD, and smaller in aSyn+AD than aSyn-AD. However, BA35 is smaller in AD-aSyn than aSyn-AD ($p=0.002$), but does not differ from aSyn+AD. In aggregate, these findings emphasize the important role of AD co-pathology in our autopsy series, the relationship of these pathologies to distinct aSyn strains (one of which induces tau co-pathology), the use of validated CSF biomarkers of AD so that we can examine progressive AD co-pathology in LBD in life, as well as the potential scientific and clinical implications of this knowledge for understanding the progression of disease pathology and more precise approaches to treatment of these disorders.

Project IV: Project IV leader Alice Chen-Plotkin has worked extensively in the genetic and biochemical biomarker field in neurodegeneration, laying the groundwork for her proposed U19 Project to biochemically and genetically characterize living PD patients who do vs. do not develop cognitive decline with and without AD pathology.¹⁷¹ In particular, we have pioneered the use of unbiased, large-scale screens to identify novel protein biomarker candidates,¹⁷¹ finding that (1) low levels of plasma epidermal growth factor (EGF) correlate with cognition in PD/PDD,¹⁷² and (2) low levels of plasma apolipoprotein A1 (ApoA1) correlate with earlier age at onset in PD and greater motor severity.¹⁷³ Importantly, we subsequently replicated both findings in national/international cohorts.^{174, 175} With respect to Project IV's proposed genetic studies, we have recently shown that (1) in PD, *APOE* and *SNCA* genotypes correlate with longitudinal cognitive and motor decline, respectively,^{110, 176} and (2) in FTD, common variants at the *TMEM106B* locus modify *TMEM106B* expression levels, lysosomal function, and clinical outcomes, attesting to our expertise in the areas of human genetics and functional genomics.^{177, 178} Finally, complementing the use of unbiased screens to nominate lead biomarkers are Project IV's proposed studies focused on aSyn. Here, we note that Project IV investigators have already begun studies of plasma and CSF aSyn strains as PD biomarkers using newly developed anti-aSyn strain specific MAbs^{63, 179}, thereby establishing feasibility and opening the way to do the same in AD.

Core A: This Core effectively supports the mission of the Penn U19 Center by: **1)** overseeing fiscal matters, **2)** organizing monthly (and more often as needed) U19 Center Core/Project meetings and external reviews of the Center by an External Advisory Committee, **3)** fostering dissemination of research findings from the Penn U19 Center to scientists at and beyond Penn and to the public, **4)** ensuring compliance with NIH/NIA policies on human subjects, **5)** sharing data and resources from the U19 Center as well as distributing Center data from

INDD to investigators outside the Center and beyond Penn in partnership with the NIA, **6**) training the next generation of ADRD investigators, **7**) working with the Internal Executive Committee (IEC) to set the direction of the U19 Center, provide biosamples to others in partnership with the NIA, guide Center programs and promote interactions of Center investigators with key stakeholders including other ADRD Centers, the NIA ADCs, DLB UO1 and NINDS Udall Centers, ADNI, the MJFF PPMI, and other related NIH as well as public/private agency supported initiatives focused on ADRD as exemplified by facilitating the participation of Penn U19 Center investigators in the 4th DLB Consensus report,¹⁸⁰ the NIA and NINDS recommendation conferences, PPMI, ADNI and PDBP.^{13, 139, 171, 181-184} Thus, Core A is designed to serve as the administrative unit of the Penn U19 Center.

Core B: Core B will collaborate extensively with all Cores/Projects and other investigators beyond Penn in studies that focused on biomarkers (CSF, plasma, genetics, PET imaging, structural imaging), neuropathology, and patterns or predictors of cognitive impairment and decline, and rating scale development in AD+aSyn/LBD. This is exemplified by the following highlights of preliminary data for Core B: **1**) Recognition of the contribution of co-morbid AD and aSyn pathology to cognitive decline in AD+aSyn and LBD.^{7, 142, 169, 185-187} Specifically, co-morbid A β and tau neuropathology, APOE ϵ 4 genotype, lower CSF A β 1-42 levels, and increasing A β amyloid burden on PET imaging are all associated with CI in PD, and LBs contribute to CI in AD. **2**) Establishing that plasma biomarkers are predictors of both CI in PD.^{174, 188, 189} **3**) Recognition that progression from incident MCI to dementia in established PD is nearly universal, which prompted us to examine the rates and predictors of progression from normal cognition to either MCI or dementia in our U19 cohort using standardized neuropsychological methods.¹⁹⁰ Briefly, this study showed that the transition from normal cognition to CI, including dementia, in PD occurs frequently and quickly. In addition, certain clinical and cognitive variables may be useful in predicting progression to CI in PD. **4**) We also examined the importance of genetically-moderated subtypes of PD, including the differential effects of genetic factors on cognition, and showed that APOE ϵ 4 genotype and glucocerebrosidase (GBA) mutations are associated with CI in PD.¹⁹¹⁻¹⁹³ **5**) Other studies demonstrated the importance of non-motor symptoms in early and prodromal PD, including cognitive performance.¹⁹⁴⁻¹⁹⁶ This research includes recognition that cognitive decline may be present in prodromal PD such that as many as 20% of *de novo* PD patients may have some cognitive deficits, and that certain non-motor symptoms are associated with CI in early PD. **6**) Finally, we developed and validated assessment instruments for cognitive abilities in AD and PD, and helped design the new NACC module for LBD (DLB and PDD).¹⁹⁷⁻²⁰⁰

Core C: Core C pursues neuropathology, biomarker and genetic studies of AD+aSyn and LBD in collaborative partnerships for studies summarized in Projects I-IV and Core C. Table 1 in Core C summarizes the autopsies on ADRD patients we have obtained in the past 5 years for studies of aSyn strains in AD+aSyn and LBD and they are suitable for other studies we conduct,²⁰¹ including the average PMI of our cases.²⁰¹ Notably, since 1985, Penn has banked CNS tissues from >1,700 subjects with a primary diagnosis of AD, LBD, related disorders and normal control (NC) as described in more detail below and elsewhere.^{140, 151} Core C preliminary data show that it will collaborate effectively with other investigators at and beyond the Penn U19 to publish patient-oriented neuropathology studies,^{20, 87, 94, 151, 202-208} genetic studies^{108, 164, 165, 191, 192, 203, 209-217} and biomarker studies.^{9, 11, 163, 175, 188, 218-220} Other Core C preliminary studies relevant to this U19 include establishing and validating neuropathology criteria for AD with/without comorbid LBD,^{20, 221} developing digital microscopy methods for use in AD+aSyn/LBD studies²⁰², measures of PD behavioral deficits,^{190, 197, 198, 222-224} modelling aSyn transmission,^{37,3,38} successful passive anti-aSyn and anti-tau immunotherapy studies in mice,^{70, 225} collaborations with other Centers on transmission of aSyn pathology in rats^{145, 226} and developing a model of prodromal PD in mice.¹⁴⁴ Finally, Core C and other Penn U19 Center investigators worked with Ian McKeith on the 4th revision of consensus criteria for DLB¹⁰⁵ as in the prior criteria update,⁹⁰ but recent studies from our group challenge the concept of DLB distinct from PDD.⁹⁴ In summary, Core C will implement all of its proposed Aims in this U19 Center.

Core D: Core D will provide database, biostatistics and bioinformatics support to U19 Center investigators, including support for NIH investigator initiated research grant and K-award applications on ADRD as exemplified by Core D preliminary data from studies highlighted here with investigators within and outside the U19 Center that resulted in Core D co-authored papers on the pathobiology of AD and LBD. In particular, Core D will provide statistical mentoring for U19 Center trainees.

Database: Core D released a second version of the INDD for U19 investigators that was described earlier¹⁴¹ as well as a web-querying system for INDD called INQuery, which is a web-based database querying tool that enables researchers to query and extract data directly from INDD without the need of IT specialists. INQuery is a fully self-contained database querying system built in-house at Penn by current and former Core D members and other U19 Center investigators that allows users to merge, sort, and filter data from the entire INDD and export it into Excel format files.

Biostatistics and Bioinformatics: Core D will perform statistical analyses, bioinformatics consultation, interpretation of the findings, and manuscript writing for manuscripts as exemplified by publications in which the Core D Leader, Sharon Xie, or Core D co-investigator Li-San Wang were co-authors. For example, Core D used mixed-effects modeling for longitudinal data, receiver operating characteristic (ROC) analysis, and Cox regression models to examine factors associated with cognitive decline in AD and LBD, clinical and pathological correlations in AD and LBD, as well as evaluations and development of scales measuring dementia and functional impairment of AD and LBD patients.^{87, 142, 174, 185, 186, 188, 197, 198, 212, 215} Sharon Xie and her doctoral students developed innovative statistical methodology to account for large variability of biomarker measurements in diagnostic performance evaluations to improve early detection of ADRD and other ND,²²⁷ new statistical approaches to monitoring ND disease progression that may improve clinical trial design for disease modifying-therapies of dementia in AD and LBD,^{228, 229} and accounting for selection bias/missing data in autopsy-confirmed ND studies.²³⁰

Resources Made Available Through This U19 Center To Outside Investigators In Cooperation With NIA

Finally, a unique ADNI-like resource component of this U19 is the use of procedures we developed over the past 20 years to share biologicals obtained through this U19 Center and from prior collections of CSF, plasma, serum, DNA/RNA and brain samples from AD and LBD patients who have been followed through NIH-funded programs. In addition, we will provide aSyn and tau pre-formed fibrils (PFFs) to outside investigators some of whom may elect to visit our U19 Center to learn best practices for aSyn and tau PFF generation and isolation of brain-derived AD tau and LBD aSyn, as well as best practices for injection of pathological tau and aSyn into the brains of mice as described.^{1, 3, 60, 66, 160, 231} Thus, this U19 Center and Penn biosample bank that the Penn team has developed over the past 20 years will be a valuable resource to other investigators beyond Penn who pursue research on AD+aSyn and LBD. We will work on this closely with Austin Yang, our NIA Program Officer for the U19. CNDR is the home base of this U19 as well as the ADCC and the PO1 mentioned earlier and below. Details on available data and resources as well as plans for sharing these resources are described in Cores A, C and D.

Concluding Remarks

The preliminary data reviewed above indicates that the Penn U19 Center is superbly positioned to achieve its mission, including ADNI-like biosample and NACC-like data distribution to qualified investigators outside the U19 Center in partnership with NIA. We believe the Penn U19 Center will contribute significantly to the field of AD and LBD research both with regard to collaborative efforts within the U19 Center at Penn and beyond to other AD, ADRD and PD centers throughout the nation and globally. Moreover, an additional strength of the Penn U19 Center is that it works so seamlessly with the Penn ADCC (P30 AG-10124-27) led by John Trojanowski, which has a DLB module led by Dave Irwin, and an NIA funded Program Project Grant entitled "Frontotemporal Dementias (FTD): Genotypes and Phenotypes" led by Virginia Lee (P01 AG-17586-16). Indeed, ten U19 Center investigators also are formally investigators in the ADCC and/or P01 (see other support for details), thereby illustrating the close working relationship between the U19 Center and these other NIA-funded studies. In summary, we will develop a better understanding of a paradigm shift in thinking about AD and LBD by focusing our studies in this U19 Center on aSyn strains and their mechanistic roles in AD and LBD. We also create unique ADNI-like mechanisms for biological resource sharing and NACC-like mechanisms for data sharing in partnership with NIA. Taken together, the strengths of our team, our science and our collaborative efforts across this U19 Center as well as beyond with other ADRD centers will make the Penn U19 Center a significant contributor to NIH/NIA-funded ADRD research programs.

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