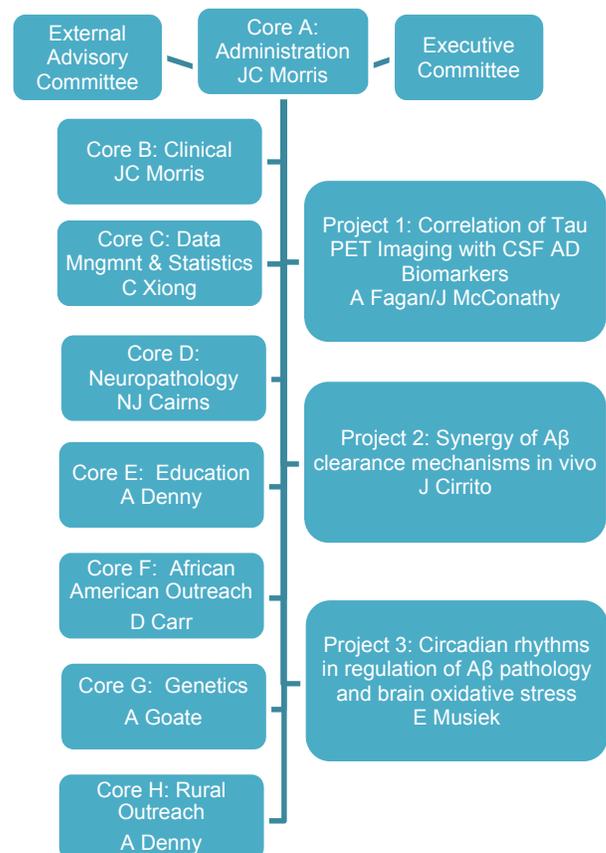


Overall Specific Aims

The goals of the Knight ADRC at Washington University are to foster and facilitate the performance of innovative research on Alzheimer disease (AD) and related topics, with emphasis on research that explores the preclinical stage of the illness as identified by biomarker abnormalities antecedent to symptoms, examines the mechanisms and indicators that underlie the transition from preclinical to symptomatic AD, and improves the understanding of the pathobiology of the illness. The following Overall Specific Aims are proposed to continue our current efforts to achieve these goals.

1. Coordinate and integrate an interdisciplinary group of clinical and biomedical investigators with the skills and experience to conduct cutting edge research on AD and related topics.
2. Provide investigators with well characterized, longitudinally studied research participants, both cognitively normal and those with early-stage symptomatic AD.
 - a. Assure that these participants reflect the ethnic and racial diversity of the St. Louis region.
 - b. Obtain from participants standard clinical, behavioral, and cognitive data, at baseline and annually thereafter, with the Uniform Data Set and transmit these data to the National Alzheimer's Coordinating Center.
 - c. Obtain from participants imaging (MRI, florbetapir PET, tau [T807] PET) data and biofluids (blood, cerebrospinal fluid) and other tissue (e.g., dermal fibroblasts) to support the biomarker studies of the ADRC investigators.
 - d. Obtain voluntary autopsy consent to allow the collection of postmortem tissue to confirm clinical diagnoses and to support research.
3. Foster new lines of research and provide a rich training environment for fellows and junior faculty and to support their career progression in transdisciplinary AD research.
4. Work collaboratively with other AD research programs, including the Alzheimer Disease Cooperative Study and the Alzheimer Disease Neuroimaging Initiative, and with community organizations such as the Alzheimer's Association.
5. Provide the environment and resources to maintain the coherence and productivity of the Knight ADRC, which will be organized with 5 mandatory Cores (Administration, Clinical, Data Management and Statistical, Neuropathology, and Outreach, Recruitment, and Education) and 3 additional Cores (Genetics, African American Outreach, and Rural Outreach) and with 3 R01-type science projects (see Figure at right). All Cores will support the Projects, which all use Core resources. The Administration Core provides budgetary coordination and administrative support for all Projects and provides for their annual review (External Advisory Committee). The Clinical Core enrolls, follows, and characterizes participants who will be enrolled in Project 1 for tau PET imaging and who provide CSF for Projects 1 and 3, and collaborates with the Neuropathology Core (NPC) in obtaining autopsy consent in deceased participants to allow human brain tissue for Project 2. The Outreach, Recruitment, and Education Core (OREC), together with the African American Outreach Core (AAOC) and the Rural Outreach Core (ROC), works closely with the Clinical Core to ensure that the cohort is of sufficient size to meet the needs of all Projects and that it appropriately reflects the diversity of the metropolitan St. Louis population. The NPC assures the accuracy of the clinical diagnosis for autopsied participants and provides human brain tissue to Project 2. The Genetics Core provides each Project with ApoE genotype data and the Data Management and Statistics (DMS) Core provides each Project with data management regarding participants and biospecimens, conducts analyses, and provides statistical expertise.

Knight ADRC 2015-2020



Overall Research Strategy

A Glossary of abbreviations commonly used in this application is provided here.

Washington University (WU) Grants

ADRC: Alzheimer Disease Research Center (P50 AG05681; JC Morris, PI); endowed in 2010 by Charles F and Joanne Knight (**Knight ADRC, KADRC**)

HASD: Healthy Aging and Senile Dementia Program Project Grant (**PPG**), (P01 AG03991, JC Morris, PI)

ACS: Antecedent Biomarkers for AD: The Adult Children Study PPG (ACS; P01 26276, JC Morris, PI)

DIAN: Dominantly Inherited Alzheimer Network (U19 AG032438; JC Morris, PI)

Multicenter Collaborative Grants

ADNI: Alzheimer Disease Neuroimaging Initiative (U01 AG024904; MW Weiner, PI); the ADNI Neuropathology Core is at WU (JC Morris, Core Leader; NJ Cairns, Co-Core Leader)

ADCS: Alzheimer Disease Cooperative Study (U01 AG010483; PS Aisen, PI)

LOAD: Genetics Consortium for Late onset Alzheimer Disease (U24 AG026395; R Mayeux, PI)

ADGC: Alzheimer Disease Genetics Consortium (U01 AG032984, G Schellenberg, PI)

NCRAD: National Cell Repository for Alzheimer Disease (U24AG21886; T Foroud, PI)

NACC: National Alzheimer Coordinating Center (U01 AG016976; W Kukull, PI): the data repository for all National Institute on Aging (**NIA**)-funded Alzheimer Disease Centers (**ADCs**)

Definitions

AD: Alzheimer disease, the brain disorder regardless of clinical status

Preclinical AD: the brain disorder prior to clinical expression; here operationalized as CDR 0 (**CN:** cognitively normal)

Symptomatic AD: the clinically expressed stage of AD, with symptoms ranging from subtle (very mild AD dementia, prodromal AD, mild cognitive impairment [**MCI**]) to severe; here operationalized as CDR>0 in individuals meeting clinical diagnostic criteria¹

A β : Amyloid-beta protein, generated by cleavage of the amyloid precursor protein (**APP**)

APOE/APOE: the gene and protein, apolipoprotein E; the ϵ 4 allele confers susceptibility for AD

CL/PL: Core and Project Leader

ESI: Early stage investigator

AAOC: African American Outreach Core

DMS: Data Management and Statistics Core

NPC: Neuropathology Core

OREC: Outreach, Recruitment, and Education Core

ROC: Rural Outreach Core

Procedures/Instruments

CDR: Clinical Dementia Rating; the CDR-SumBox (**CDR-SB**) is a more quantitative representation, with a range from 0 (no impairment) to 18 (severe impairment)

CSF: Cerebrospinal fluid, obtained by lumbar puncture (**LP**)

MRI: Magnetic resonance imaging, here performed at 3 Tesla (**3T**)

PET: Positron emission tomography

PIB: Pittsburgh Compound B, [¹¹C] amyloid tracer

Florbetapir: [¹⁸F] amyloid tracer, also known as AV45 and Amyvid ®

T807: [¹⁸F] tau tracer

UDS: Uniform Dataset, the standard clinical and cognitive assessment protocol used by ADCs

[Note: Unless otherwise stated, the reporting period used here is from 5/1/09-2/28/14]

Introduction

Responses to the 12/22/09 Summary Statement follow:

1. Large sizes of the Executive and Tissue Committees. **Response:** Our integrated Executive Committee adjudicates the ADRC and its 3 major affiliated grants, obviating the need for duplicative Committee meetings for each grant alone. The Executive Committee approves the Biospecimens Committee's decisions regarding biospecimen requests (25 in 2013) and evaluates additional requests for participants and their data (49 in 2013).

The composition of both Committees is designed to provide the expertise to evaluate the broad range of topics and tissue (DNA, plasma, dermal fibroblasts, CSF, fixed and frozen brain tissue) addressed by the requests. We balance careful stewardship of our precious resources with expeditious review and fulfillment

of requests. The growing number of total requests (from 51 in 2009 to 74 in 2013) indicates that our many collaborators appreciate our rapid responses and do not find our Committees to be cumbersome or slow. Dr. Morris holds a weekly Leadership Meeting with his Associate Directors (Goate, Holtzman, Johnson) and Executive Directors (Buckles, Moulder). This group is empowered to respond to urgent requests if circumstances require, rather than await the next Executive Committee meeting.

2. Difficult to compare and generalize findings. **Response:** We now routinely classify all our participants with the diagnostic criteria of ADNI-2 (while still separately maintaining our long-established CDR-based diagnostic approach). We now generate the diagnostic categories of “Significant Memory Concern”, “early MCI”, “late MCI”, and “AD dementia”¹ so that our cohort is readily comparable to cohorts at other ADCs.
3. Detail familial and nonAD dementia. **Response:** The Clinical Core collaborates with the Genetics Core in assessing members of families with dominantly inherited dementing illnesses; many of these individuals are assessed only once and thus are not entered into the Clinical Core, but those who are followed longitudinally are entered (see Clinical Core). During this reporting period the Genetics and Clinical Cores published 2 papers addressing FTLD (granulin mutation),^{2,3} 1 addressing Kufs disease (DNAJC5 mutation),⁴ and 1 addressing AD (presenilin 1 mutation).⁵ Because the ADRC evaluates a large number of familial FTLD individuals, it was included as one of 8 performance sites in the Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects (LEFFTDS) grant that begins 7/1/14 (AG045390, B Boeve, PI). Also in this reporting period, the Clinical Core published reports on a wide variety of nonAD dementia, including familial Creutzfeldt-Jakob disease,⁶ variably protease-sensitive prionopathy,⁷ Dementia with Lewy Bodies,⁸ HIV-associated neurocognitive disorder,⁹⁻¹¹ and Whipple’s disease¹² (see Clinical Core).
4. Very large budget for Clinical Core; small cohort. **Response:** In this renewal application, the requested first-year budget for the Clinical Core is at the median for Clinical Core budgets for the 15 currently funded ADRCs: 7 other Clinical Core budgets are higher than ours and 7 are lower. This requested budget is \$20,000 less than our requested first-year Clinical Core budget 5 years ago. The anticipated cohort size of ~350 participants will be sufficient for the needs of the Projects included in this application and to foster other Alzheimer research. The value of our cohort is best measured by the 70 projects that directly used our participants and the 140 publications that used Core resources in this reporting period.
5. Neuropathology Core Leader unable to sign out cases. **Response:** Richard Perrin, MD, PhD, an established neuropathologist who leads Project 1 in the current ADRC budget period, is Assistant NPC Leader in this renewal application.
6. Most autopsies occurred.....in CDR 3. **Response:** Most deaths occur in CDR 3 individuals as deaths are associated with severity of illness. Moreover, autopsy rates are higher in CDR 3 individuals as families have time to prepare for end-of-life issues, whereas death generally is unanticipated in CDR 0, 0.5, and 1 individuals and families may not consider autopsy in this acute setting. Beginning at the baseline visit, we discuss voluntary consent for autopsy with all participants and their families and re-discuss at each follow-up assessment. We are completing an analysis of our autopsy consent process (see OREC) to determine how we can be more successful.
7. Most [participants] are CDR0 and CDR 0.5 but trials enroll CDR1s; process to coordinate clinical trial participation. **Response:** In the reporting period, the Clinical Core enrolled and followed over 100 participants in industry-sponsored trials of experimental agents developed against AD (Pfizer, Wyeth, Eli Lilly, Bristol-Myers Squibb, Elan/Janssen Immunotherapy). All but one trial enrolled individuals with symptomatic AD at either CDR 0.5 or CDR1 level, the one exception (BMS-708163) was limited to CDR 0.5. The Clinical Core cohort met recruitment goals for each study. As an example, we participated in a single site Lilly-sponsored study of solaneuzumab to determine if a single infusion of the drug might produce a measurable change in plasma A β levels to serve as a possible diagnostic. Our screening methods were efficient. Between 8/2010 and 2/2012 our Clinical Core screened 65 people for the study, including 11 healthy young volunteers (1 screen fail). All remaining volunteers were from the Clinical Core cohort, including 37 CDR 0 individuals (7 screen fails) to yield 15 CDR 0 florbetapir-positive and 15 CDR 0 florbetapir-negative persons and 15 CDR 0.5/1 symptomatic AD individuals (2 screen fails). Post-solaneuzumab infusion, participants returned at weekly intervals to provide plasma samples. All 43 participants completed the study which ended 8/2012. We now are participating in the ADCS trials of intranasal insulin in symptomatic AD, enrolling CDR 0.5/1, and solaneuzumab in older adults, enrolling older CDR 0. The composition of the Clinical Core cohort is appropriate for both studies.
8. Specificity of biomarkers with other disorders. **Response:** To evaluate the specificity of our AD biomarkers, we collaborate with other ADCs. For example, our ADRC investigators performed analyte measurements on 239 CSF samples from the Penn ADC, including 28 individuals with FTLD, 8 with DLB,

12 with Parkinson disease dementia, 5 with progressive supranuclear palsy (PSP), and 4 with corticobasal syndrome. We received CSF samples from the ADRC at University of California, San Francisco, from individuals with FTL, DLB, and PSP to optimize the differentiation of AD and nonAD dementias using our novel CSF AD biomarker, VILIP-1.

9. “[Weak] psychometric developmental research”. **Response:** David Balota, PhD, and colleagues in the Department of Psychology have a longstanding interest in measures of attentional control as an indicator of early symptomatic AD and preclinical AD.¹³⁻¹⁵ Dr. Balota’s research has been supported for many years in the PPG, “Healthy Aging and Senile Dementia”, and more recently in the related PPG, “Adult Children Study”. Dr. Balota, in collaboration with Dr. Martha Storandt, developed the ELSMEM, a computerized battery to assess Executive, Linguistic, Spatial and Memory abilities for the DIAN study.¹⁶ The Clinical Core’s cognitive battery now includes two computerized measures from Dr. Balota’s work that are sensitive to preclinical and early stage symptomatic AD:^{15,17} the Continuous Tapping Test (CTT) and the Color-Word Interference Test (CWIT), which is based on a switching version of the classic Stroop task (see Dr. Balota’s Letter of Support in Clinical Core).

Dr. Martha Storandt retired in June of 2012. The ADRC Director recruited the neuropsychologist, Jason Hassenstab, PhD, to the ADRC in late 2010 so that he could train with Dr. Storandt, who then transitioned the psychometric leadership of the ADRC to him upon her retirement. Dr. Hassenstab has been awarded a K23 mentored career development award in which he studies cognitive and neuroimaging outcomes in insulin resistant older adults. In addition to co-authoring or leading several ADRC-related publications,¹⁸⁻²¹ he also will be able to contribute to psychometric developmental research efforts.

10. “Operational application of NINDS-ADRDA criteria”. **Response:** Our Clinical Core has adopted the 2011 revised criteria for “AD dementia”.¹ We use all information obtained with the UDS (including the health history, medication inventory, neuropsychiatric inventory, and depression scale), and findings from the neurologic examination and from the review of the participant’s records, including imaging studies (requested from the participant’s primary physician prior to the baseline assessment to permit this review). The clinician who conducts the UDS assessment, including “bedside” mental status tests such as the Mini Mental State Examination, also completes the neurological exam and medical record review, then synthesizes all information to generate the CDR score and (as appropriate) the dementia diagnosis for UDS Form D1, in accordance with standard criteria for AD and nonAD disorders.

A. Significance

1. The Knight ADRC has a long track record of successfully developing and promoting transdisciplinary research into the etiology, pathogenesis, diagnosis, treatment, and now the prevention of Alzheimer disease (AD). With its well-established infrastructure, integrated approaches, and stable leadership all contributing to its “centeredness”, the whole of the Knight ADRC represents far more than the sum of its parts. It is the acknowledged nidus for AD-related research at Washington University and is recognized locally, regionally, nationally, and internationally for its productivity and impact. The Knight ADRC has introduced concepts such as preclinical AD,²²⁻²⁶ approaches such as the Clinical Dementia Rating (CDR),^{27,28} methodologies such as stable isotope labeling kinetics (SILK) to measure production and clearance of central nervous system (CNS) proteins such as A β ,²⁹ instrumentation such as cerebral microdialysis to measure CNS proteins in the interstitial fluid (ISF) of awake behaving animal models,³⁰ and has pioneered the first-ever anti-A β secondary prevention trials in asymptomatic individuals at certain risk to develop symptomatic AD.³¹ In all these ways and more, the Knight ADRC has changed clinical and basic science paradigms for the entire AD research field.

The major scientific themes of the ADRC have been to distinguish the earliest symptomatic stage of AD from healthy cognitive aging, to characterize the preclinical stage of AD antecedent to the onset of symptoms using multimodal imaging and biofluid markers of AD, and to investigate the pathobiology of AD. To pursue these themes the ADRC supports investigator-initiated projects. However, the R01-type projects supported by the ADRC’s P50 mechanism are low-budget and cannot be renewed after their 5 years of funding. We thus established independently-funded longitudinal research initiatives to enable us to successfully pursue our major research themes. The program project grants, “Healthy Aging and Senile Dementia” (HASD; P01 AG03991, JC Morris, PI) and “Antecedent Biomarkers for AD: The Adult Children Study” (ACS; P01 AG026276; JC Morris, PI) represent cerebrospinal fluid (CSF) and imaging biomarker studies of preclinical AD at different ages: HASD (7/1/14-6/30/19) focuses on the indicators that mark the transition from cognitively normal (CN) aging to symptomatic AD in individuals 65y and older, whereas ACS explores the initial onset of biomarker abnormalities and their rate of change in CN individuals, age 45y and older, who have an affected parent with AD. [Note: the ACS cohort already serves as the optional “higher risk” cohort allowed by the RFA, obviating the need for the ADRC to add this option.] A special group of adult children are those whose affected

parent had a single gene mutation causing AD. Our international “Dominantly Inherited Alzheimer Network” (DIAN; U19 AG032438, JC Morris, PI) investigates the pathochronology of AD biomarker changes in asymptomatic mutation carriers who are destined to develop AD dementia. In addition to these 3 large, multicomponent research grants (HASD, ACS, DIAN), the Knight ADRC provides critical support to many other investigator-initiated, independently funded projects that address important questions relevant to our overall scientific themes and thus are included under the ADRC’s “umbrella” (see 3. below).

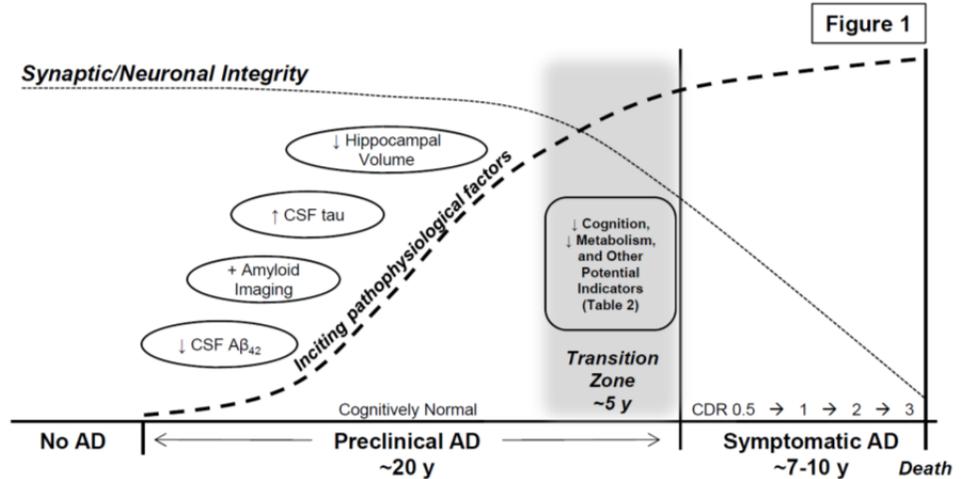
2. The current Knight ADRC budget period supported innovative science led by three individuals who in 2010 were all early-stage investigators

(ESI) (see Progress, below). In this renewal application, the Knight ADRC continues to foster the development of new lines of research conducted by young to mid-career investigators. All 3 Projects directly use participants and/or their tissue from the Knight ADRC’s Clinical and/or Neuropathology Cores, and all 3 use genotype data from the ADRC’s Genetics Core.

The innovative scientific initiatives in the 3 proposed projects address the hypothetical

model developed by the ADRC (Figure 1). This model proposes that: 1) the pathophysiological process of AD begins up to 2 decades before symptoms appear. Although the triggering event(s) remain unknown, dysregulation of A β homeostasis is likely to be involved; 2) in addition to A β dysregulation, other pathophysiological factors slowly accumulate in the brain, initially without substantial neuronal dysfunction (hence, cognitive function remains normal); and 3) at some point, the AD pathology breaches synaptic and neuronal integrity and a continuous process of neuronal deterioration ensues that results in symptomatic AD. Project 1 (Fagan and McConathy [ESI], Co-PL) focuses on the final phase of this model by using a new PET tau tracer, [18 F] T807, to characterize tau burden in the brain in participants who are 1) healthy (CN, CSF biomarker-negative), 2) have preclinical AD (CN, CSF-biomarker-positive), or have 3) early-stage symptomatic AD (CDR 0.5, CSF biomarker-positive). In addition to correlating tau imaging results with CSF levels of tau and phospho-tau, Project 1 will examine the cognitive correlates of cerebral tau burden (assessed by T807) through the transition from preclinical AD to symptomatic AD. Project 2 (Cirrito, PL) addresses the early stage of the model using a novel micro-immuno-electrode technique to explore potential deleterious influences on A β clearance, including competition from α -synuclein, that disrupt steady-state A β concentrations, with a subset of experiments in postmortem AD brain \pm Lewy bodies. The Project also proposes that at least some of these A β clearance mechanisms may demonstrate circadian oscillation. Project 3 (Musiek [ESI], PL) extends the study of circadian rhythms in the middle stage of the model, as circadian disruption might not only augment A β dysregulation but also cause oxidative damage that threatens synaptic and neuronal integrity. The Project will use actigraphy data and CSF from participants to assess isoprostane levels as a marker of oxidative stress. Using the ADRC’s infrastructure, the Projects aim to identify key mechanisms that underlie neuronal dysfunction in AD as well as potential indicators (tau burden, circadian disturbances, impaired A β clearance, oxidative stress) that may signal the change from preclinical to symptomatic AD. These indicators also may serve as novel therapeutic targets for future intervention trials that aim to prevent the transition from CN to symptomatic AD.

3. Each ADRC Core materially supports the 3 proposed Projects. The Administration Core provides budgetary coordination and administrative support for all Projects and provides for their annual review (External Advisory Committee). The Clinical Core enrolls, follows, and characterizes participants who will be enrolled in Project 1 for tau PET imaging and who provide CSF for Projects 1 and 3, and collaborates with the Neuropathology Core (NPC) in obtaining autopsy consent in deceased participants to allow human brain tissue for Project 2. The Outreach, Recruitment, and Education Core (OREC), together with the African American Outreach Core (AAOC) and the Rural Outreach Core (ROC), works closely with the Clinical Core to ensure that the cohort is of sufficient size to meet the needs of all Projects and that it appropriately reflects the diversity of the metropolitan St. Louis population. The NPC assures the accuracy of the clinical diagnosis for

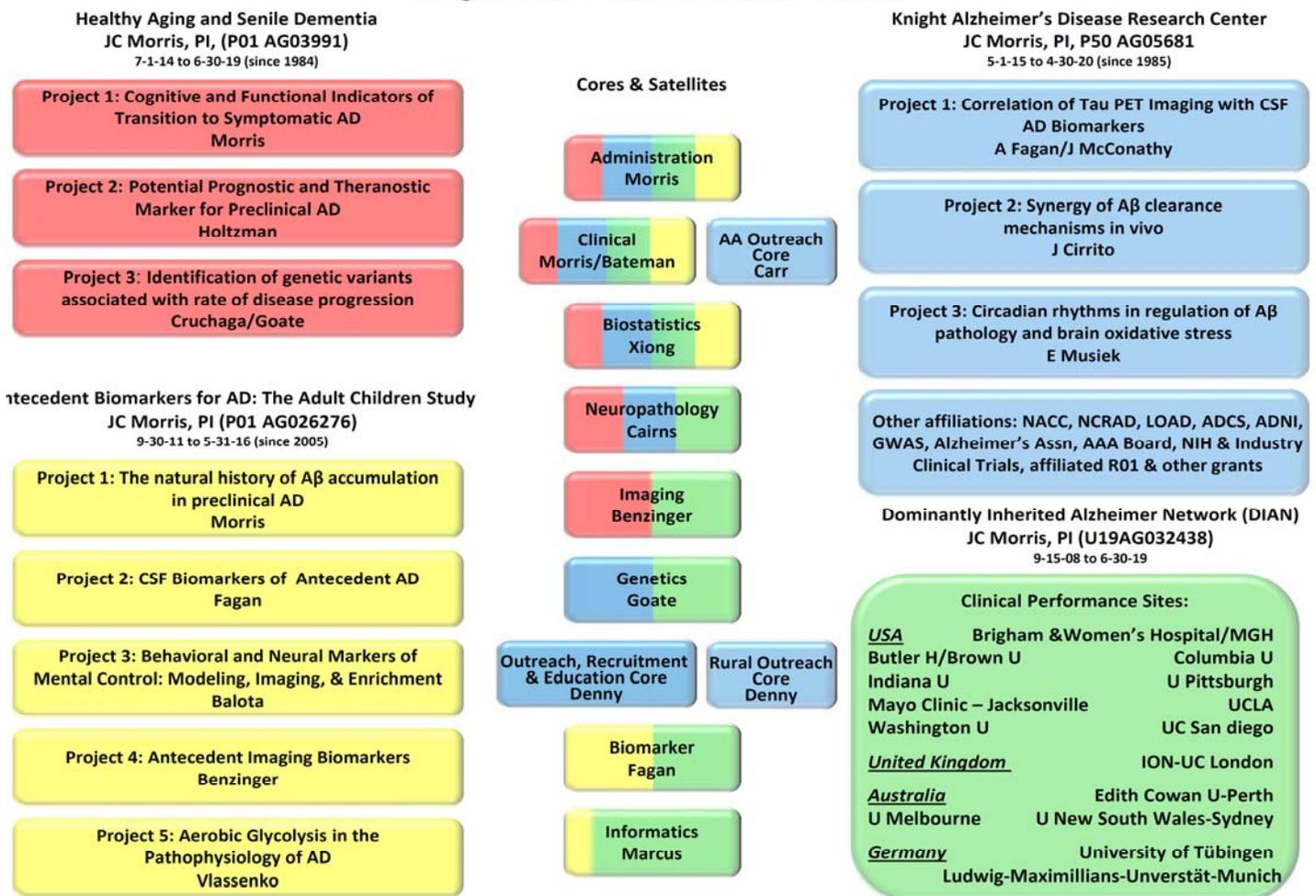


autopsied participants and provides human brain tissue to Project 2. The Genetics Core provides each Project with ApoE genotype data and the Data Management and Statistics (DMS) Core provides each Project with data management regarding participants and biospecimens, conducts analyses, and provides statistical expertise.

The aggregate resources of the ADRC Cores provide a rich environment to support Alzheimer and related research at WU and beyond, outside of the P50 mechanism. Details of the funded research supported by the ADRC in this reporting period are noted in the Administration Core, but includes ADRC support for 126 federally-funded, 125 non-federally-funded, and 30 industry-funded studies (total 281); the federal awards total \$146,755,402 and the nonfederal awards total \$12,093,587. In addition to these 281 studies, the ADRC's Pilot Grant program is highly successful, as 17 of the 23 (74%) pilot awards subsequently generated 27 new grants that totaled an additional \$20,768,526. Currently active (as of 4/15/14) grants at WU that derived from and/or are supported by the ADRC include 10 NIH R01, 1 Alzheimer Association, 1 Department of Defense, 3 Bright Focus, 3 Alzheimer Drug Discovery Foundation, 1 Ellison Foundation, 1 Cure Alzheimers Foundation, and 1 CART awards. ADRC investigators additionally have industry-sponsored research (non-clinical trial) funded by Abbott, Biogen-Idec, and Pfizer. Four of the R01 grants are collaborations with other ADCs: AG034119, C. Xiong, PI, with Rush University Medical Center; AG038656, K. Kryscio, PI, University of Kentucky; C. Xiong, WU site leader; AG029672, P Crane, University of Washington, PI, C. Xiong, WU site leader; and AG045390, B. Boeve, PI, Mayo Clinic; N. Ghoshal, WU site leader. Altogether, there were 626 publications that were supported by the Knight ADRC in this reporting period, including 238 directly resulting from ADRC investigators and initiatives and 388 resulting from use of ADRC resources (participant, data, tissue, etc.). This number is notably higher than that reported 5 years ago (n=368, see Overall Progress Report Publication List).

Figure 2

Knight ADRC and Affiliated Grants



Finally, directly affiliated with and benefitted by the ADRC and its Cores are the HASD and ACS PPGs and the DIAN; the organizational structure of all 4 grants is shown in Figure 2. The Knight ADRC Director, Morris, currently is PI for these 4 grants but will transition the leadership of the DIAN grant in 2015 to his colleague, Randall J. Bateman, MD. Morris also will transition the leadership of the Knight ADRC in its next budget period

to another colleague, David M. Holtzman, MD. Planning for these transitions already is well underway. Morris, Holtzman, and Bateman meet weekly. Subsequent to the leadership transitions, Morris will assure continuity by serving as Associate Director and as Clinical Core Leader for both ADRC and DIAN. He also will remain as PI of the 2 PPGs, HASD and ACS. Morris, Holtzman, and Bateman have worked productively together for many years (indeed, Morris and Holtzman co-mentored Bateman during his ADRC postdoctoral fellowship from 2004 to 2006) and together constitute a remarkable leadership team for AD research at WUSM.

4. The Knight ADRC is a major contributor to the national network of ADCs.

- a. Morris is the founding Chair of the Clinical Task Force of the ADCs and was instrumental in the development and implementation of the Uniform Dataset (UDS) that is the clinical and cognitive assessment protocol for all ADCs. The UDS has been successful: since the UDS was implemented in September 2005, 30,327 UDS Initial Visit Packets and 89,880 Follow-up Visits have been submitted to the National Alzheimer Coordinating Center (NACC) through 4/21/14. The number of investigator requests to NACC for UDS data has risen from an annual average of 14 from 2006 through 2009 to 65 from 2010 through 2013. Also, 373 publications have used UDS data.
- b. ADRC Associate Director Alison Goate serves on the NACC Steering Committee and ADRC Associate Executive Director, Krista Moulder, serves on the ADC Administrators Steering Committee.
- c. Morris chairs the External Advisory Committees for 8 ADRC/ADCCs.
- d. Morris and Moulder, with support from NACC and the Alzheimer Association, developed and led the LP Survey in which 18 of the 27 ADCs participated.
- e. The ADRC and its Genetics Core are key contributors to national AD genetics initiatives, including LOAD, ADGC, and the NCRAD; the ADRC provided more samples to NCRAD for GWAS than any other ADC (See Letter of Support, Tatiana Foroud).
- f. The ADRC is an actively participating site in two clinical trials, SNIFF and A4, supported by the ADCS and its industry partners.
- g. A total of 34 ADNI participants have been enrolled and 19 are actively followed; the ADNI NPC; (JC Morris, CL; NJ Cairns, Co-CL) is directly supported by the ADRC NPC; 7 of our ADNI participants have died and all 7 have come to autopsy, making the ADRC the largest current contributor to ADNI autopsies.

5. The Knight ADRC has a long tradition of multi- and transdisciplinary research at Washington University. ADRC investigators at the School of Medicine represent 12 Departments, Divisions, or Programs: Neurology, Neurosurgery, Psychiatry, Pathology, Medicine [Geriatrics], Biostatistics, Ophthalmology, Occupational Therapy, Nursing, Emergency Medicine, Cell Biology, and Developmental Biology. Additional investigators come from the Schools of Engineering, Social Work, Law, and Arts and Sciences (Chemistry, Political Science, and Psychology). The wide range of disciplines represented in the ADRC bring different and often illuminating perspectives to our scientific initiatives. As an example, in exploring the cognitive and biomarker correlates of preclinical AD, colleagues in the Program of Occupational Therapy asked in an ADRC pilot study whether there may also be noncognitive correlates and found that CN older adults who were amyloid positive by PET PIB had a greater risk of falls than CN older adults who were negative with PET PIB.³² Another example relates to our interest in learning the wishes of our CN participants regarding their individual research results (such as amyloid imaging) and whether an educational intervention regarding the limitations and potential risks of such disclosure (e.g., inability to use the results for individual-level prediction of symptomatic AD; possible effects on eligibility for long term care insurance) altered the person's wish to know. We are completing analyses of our Disclosure Survey data from 345 participants; the survey development and implementation was supported by a University Research Strategic Alliance grant awarded to ADRC Director, Dr. Morris, and Professor Matthew Gabel from the Department of Political Science. Professor Gabel expanded the survey's scope to include queries about such attributes as the participant's political and religious beliefs, reasoning that adherents to certain groups perceive the value of "science" differently than others and may have varying levels of trust in medical professionals, and that these views might influence responses to the survey questions.

6. The Knight ADRC continuously and actively fosters new lines of research, as represented by the proposed 3 R01-type projects in this renewal application that: 1) use a novel *in vivo* tracer of cerebral tau burden to track the transition from CN aging to preclinical AD to symptomatic AD; 2) innovatively explore abnormalities in A β clearance pathways as a contributor to dysregulation of A β homeostasis in a mouse model of AD; and 3) investigate novel mechanisms of neurodegeneration and oxidative stress that relate to perturbations of circadian rhythms. Other new lines of research supported in the reporting period include the characterization of AD biomarkers in HIV neurocognitive disorder,^{10,33} developing antisense oligonucleotides to modify tau in mouse models,³⁴ developing a noninvasive method that does not require arterial blood sampling for

quantitative PET imaging,³⁵ and correlating driving performance in CN older adults as a function of the presence or absence of preclinical AD.

7. The Knight ADRC provides an exceptionally rich, varied, and productive training environment for ESIs, postdoctoral fellows, residents, medical and undergraduate students, and visiting scholars (see also OREC).

a. ESIs: Our ADRC pilot grant success was discussed in 3. (above), generating in this reporting period almost \$21 million in external grant support subsequent to the pilot award. The pilot grant mechanism is used to encourage highly promising investigators to develop careers in AD research. Each pilot grant awardee regularly meets with the ADRC leadership group (Morris, Goate, Holtzman, Johnson, Buckles, Moulder) to ensure the grant's successful completion and to receive mentoring. This approach also extends to promising pilot grant applicants who are not awarded. For example, **Liviu Mirica, PhD**, Associate Professor of Chemistry, was new to AD research when he unsuccessfully applied in 2010 for pilot funding to study novel metal chelators of soluble A β oligomers. The leadership group reviewed with him the critiques of his application, discussed how to respond, and encouraged him to resubmit. He reapplied for an ADRC pilot and was awarded from 5/1/11-4/30/12, and then leveraged the pilot into an Alzheimer Association New Investigator Research Grant (NIRG), "Bifunctional chemical agents as theranostic tools for A β aggregation" (1/1/12-12/31/13).

Other ESIs who were not originally AD investigators include: 1) **Beau Ances, MD, PhD**, who received an ADRC pilot award (5/1/09-4/30/10) shortly after being recruited to WU in 2008 as an Assistant Professor of Neurology to study brain integrity in older HIV+ adults. His pilot, "Interaction between HIV and aging using PIB", attracted him to AD research where he investigates the disruption of resting state networks in AD using fMRI. Now Associate Professor of Neurology, he received an Alzheimer Association NIRG ("Resting state network signature of AD", 1/1/12-12/31/13) and increasingly is publishing his findings in AD;³⁶⁻³⁸ 2) **Tim Miller, MD, PhD**, did his doctoral thesis with Associate Director Eugene Johnson and, after neurology residency and postdoctoral training in neuromuscle disease at University of California, San Francisco, was recruited back to WU in 2007 as Assistant Professor of Neurology. His interests in amyotrophic lateral sclerosis motivated his laboratory to develop antisense oligonucleotides to decrease mRNA levels of SOD1 and, eventually, tau. His ADRC pilot grant (5/1/09-4/30/10), "Developing antisense oligonucleotides to modify tau in mouse models of dementia", led directly to his current ADRC R01-type project, "Treating tauopathies with antisense oligonucleotides", that demonstrates that these novel therapies to reduce tau can protect mouse models against seizures.³⁴ Now Associate Professor of Neurology, Dr. Miller has an R21 AG044719, "Does a shift from 4R to 3R tau protect against A β -induced cognitive deficits?"; and 3) **Jon McConathy, MD, PhD**, came to WU as Assistant Professor of Radiology in 2010 in the Division of Nuclear Medicine. Originally interested in applying novel PET tracers for oncological imaging, he began consulting with Eli Lilly and Company in 2011 and was introduced to neuroimaging tracers, most recently [¹⁸F] T807 for tau, through their subsidiary, Avid Radiopharmaceuticals. Introduced to the ADRC through its PET amyloid imaging program, he was encouraged to apply for pilot funding by ADRC leadership and has been awarded the pilot grant, "Preclinical imaging of tau pathology with the novel PET imaging agent, T807" (5/1/14-4/30/15). His developmental work on this pilot application led to discussions with David Holtzman and Anne Fagan in the ADRC and culminated in Dr. McConathy serving with Dr. Fagan as Co-Project Leaders for the proposed Project 1 in the renewal application, "correlating tau imaging with CSF tau".

The ADRC pilot awards in this reporting period also furthered the career development of several other ESIs who already were interested in AD research. Only 3 are described here: **John Cirrito, PhD**, received the pilot grant, "Effect of endogenous A β on synaptic plasticity" (5/1/10-4/30/11) that was leveraged into his R01 AG042413, "Synaptic regulation of ERK-mediated A β metabolism" (8/12-4/17) and then into Project 2 of this renewal application, "A β clearance pathways", JR Cirrito, PL. **Catherine Roe, PhD**, used her pilot grant, "Driving performance in preclinical AD", to successfully apply for an identically named R01 AG043434 (9/12-5/17). **Erik Musiek, MD, PhD**, in 2013 completed his ADRC postdoctoral fellowship in the laboratory of David Holtzman where he investigated circadian clock dysfunction as a mediator of neurodegeneration (K08 NS079405), received an Alzheimer Association NIRG ("The circadian clock as a therapeutic target", 3/14-2/16) and successfully applied for an ADRC pilot grant for 5/14-4/15, "Circadian regulator of A β clearance" which in turn resulted in proposed Project 3 of this renewal application, "Circadian regulation of neurodegeneration", ES Musiek, PL.

b. The ADRC has offered a postdoctoral fellowship program, led by Dr. Morris, since 1985. A variety of funding sources support this program, including an endowed philanthropic gift to Dr. Morris. Some fellows have clinical research interests and train entirely with Morris (e.g., Jeffrey Burns, MD, currently Edward H. Hashinger Professor of Neurology and Associate Director of the University of Kansas ADC), but more often

they pursue a basic or translational science project in the laboratory of another ADRC investigator while also training with Morris in clinical aspects of aging and dementia. In this reporting period, 18 trainees were successful in obtaining the following training awards: 3 K01, 2 K08, 2 K23, 1 K25, 3 K12, and 2 American Brain Foundation/American Academy of Neurology/Alzheimer Association Clinical Research Training Fellowships. (See Table 4 in Administration Core Appendix).

c. The OREC describes the many educational opportunities provided by the ADRC for residents (neurology, psychiatry, medicine) and students in nursing, social work, medical school, St. Louis College of Pharmacy, and undergraduate students. Additionally, international visitors come for several purposes. With sponsorship from their institutions, 6 neurologists and 1 psychiatrist from South Korea and China in this reporting period completed an ADRC mini-fellowship for a year or longer to learn specific clinical, neuropathological, or neuroimaging research skills and to work on a research project. An example is Jee-Hoon Roh, MD, PhD, who began a visiting scholarship in the laboratory of David Holtzman with sponsorship from Asan Medical Center in Seoul, South Korea, and was able to extend his stay with a Clinical Research Training Fellowship from the American Brain Foundation (American Academy of Neurology) to complete his project.³⁹ Other international scholars visit for shorter periods of time (days to months) to focus on a specific objective, such as an “introduction to dementia and aging” (medical student from the Kingdom of Saudi Arabia, 2013), effective leadership of dementia research (6 neurologists from Japan, 2013), and administration and interpretation of our dementia screening instrument, the AD8⁴⁰ (5 neurologists from Taiwan, 2013).

8. The ADRC provided well characterized participants, brain tissue, and biospecimens to investigators, within and outside the ADRC, in this reporting period. The individual Cores (Administration, Clinical, NPC, Genetics) detail the types and numbers of participants provided to investigators, but in aggregate the ADRC supported with the above-listed resources 126 federally-funded, 125 non-federally funded, and 30 industry-sponsored studies (total=281). The Genetics Core provided much more than APOE genotypes: CLU, PICALM, CR1, BDNF, TOMM40, PSEN1, MAPT, COMT, ACE genotypes and GWAS data were provided to 11 ADRC investigators and 5 outside investigators, including one at Nanjing University, China.

9. The ADRC has advanced the development of novel therapeutics for AD.

a. Dr. Holtzman’s laboratory discovered the therapeutic potential of the anti-A β mouse antibody, m266. This antibody was licensed to Eli Lilly and Company, and the humanized antibody is being actively evaluated as solanezumab in several AD trials.

b. The laboratories of Dr. Holtzman and Dr. Marc Diamond developed anti-tau antibodies that have shown promise as therapeutic agents in preventing the spread of tauopathy within the brain of genetically modified mice that develop tauopathy. Some of these antibodies have been licensed. One of them has been humanized and has entered phase I clinical trials. Holtzman and Diamond have an active program to generate additional anti-tau antibodies that have therapeutic potential utilizing novel cellular and animal models and techniques. Dr. Diamond also is performing high throughput cellular screens to block the prion-like propagation of tau in the brain.

c. Dr. Miller’s Project 2 in the current ADRC budget period is developing an antisense oligonucleotide-based method of lowering tau mRNA or the 4R isoform of tau mRNA, and has demonstrated that this approach is effective in protecting against chemically-induced seizures in a non-transgenic mouse.³⁴ He next will explore whether lowering mouse tau will protect A β -induced cognitive deficits in the PSAPP mouse model.

d. Dr. Holtzman and Dr. Bateman co-founded a company, C2N Diagnostics, that uses the SILK assay to measure the production and clearance of CNS proteins.²⁹ This assay allows much faster *in vivo* assessment of a drug’s effectiveness against its target than traditional assays. This technique has been utilized by many drug companies to assess compounds targeting A β , ApoE, and other targets. Dr. Bateman’s lab has tested the mechanistic effect of beta-secretase and gamma-secretase inhibitors in a macaque CSF SILK model⁴¹ and in human SILK studies.^{42,43}

e. The DIAN-Trials Unit (TU) is developing novel therapeutics by testing proposed disease modifying therapeutics in dominantly inherited AD by testing prevention and also the development of novel theranostic biomarkers.^{26,31,44} The DIAN-TU trial platform tests multiple drugs in an adaptive fashion, accelerating evaluation of novel AD therapeutics.

B. Emphasis

The overall emphasis of this renewal application remains unchanged: to characterize the preclinical stage of AD, examine the factors involved in the transitions from healthy brain aging to preclinical AD to symptomatic

AD, and elucidate the pathobiology of the disorder. As discussed in Significance (above), each of the Projects in this application address different stages of the model shown in Figure 1.

C. Innovation

The innovation of the Knight ADRC is reflected in the 3 proposed R01-type science Projects (novel tau imaging correlation with CSF tau biomarkers; micro-immunoelectrodes to explore A β clearance pathways; characterize the role of disrupted circadian rhythms in neurodegeneration) and in their relation to different stages of preclinical AD as proposed in Figure 1. The Knight ADRC also innovatively maximizes the integration and research potential of its affiliated multicomponent grants (particularly HASD) by maintaining uniformity of leadership, personnel, procedures, and protocols. This approach allows the science supported by these grants to be remarkably complementary and synergistic while remaining budgetarily distinct (See Administration Core).

D. Approach

1. Progress

a. Current Projects

- 1) Project 1 "Novel protein biomarkers for AD in CSF", R Perrin, PL. Using targeted ELISAs and multiplexed immunoassays (Rules Based Medicine/Myriad/Luminex), Project 1 evaluated over 200 proteins in the CSF of ADRC participants for their potential as AD biomarkers. One non-neuronal protein, YKL-40, predicts clinical progression in AD⁴⁵ and small panels of proteins distinguish CDR 0 from CDR >0.^{46,47} Project 1 also developed a powerful non-targeted approach, Quantitative Label Free Proteomics (QLFP), to apply to the ADRC CSF samples.⁴⁸ The QLFP method also is being applied to CSF from DIAN participants to integrate the time courses of novel biomarkers into those of "established" biomarkers with the support of a Bright Focus Foundation grant to Dr. Perrin. Dr. Perrin is also participating in a NACC-funded collaborative study with Dr. William Hu (Emory ADRC) and Dr. Steven Arnold (Penn ADCC) to move novel CSF biomarkers closer to clinical application.
- 2) Project 2 "Changing protein levels and isoforms in mouse models of dementia", T Miller, PI. This project establishes antisense oligonucleotide methods to target tau mRNA, then demonstrated that lowering tau in a non-transgenic adult mouse model protected against chemically induced seizures.³⁴ Current experiments are testing whether lowering mouse tau will protect PSAPP tg mice from A β -induced cognitive deficits. A cohort of Tau N279K mice have been developed with antisense oligos that reduce human 4R tau mRNA without lowering total tau. Project 2 findings were instrumental for the R21 AG044719, "Does a shift from 4R to 3R tau protect against A β -induced cognitive deficits?", T. Miller, PI.
- 3) Project 3 "ApoE metabolism in AD and controls", RJ Bateman, PI. Quantitation of CSF is ongoing to test the hypothesis that the absolute amount of ApoE4 is lower in human CSF compared to the ApoE3 isoform. For processed cases (n=18 ApoE3/3, 1 ApoE4/4, and 9 ApoE3/4 individuals), the amount of ApoE3 and ApoE4 isoforms is similar in heterozygotes; however, a slight increase in ApoE4-specific peptide was observed relative to ApoE3-specific peptide in these cases. Total ApoE for ApoE33 individuals, as estimated by the detection of peptides common to both isoforms as well as the E3 specific peptide, is similar to what is observed in heterozygotes. The protocol for measuring ApoE in CSF has been optimized and validated. Processing of 60 metabolic labeling curves (30 each of amyloid positive and negative cases) is ongoing. All samples for brain ApoE quantitation will be processed together in a single experiment and additional frozen samples obtained from the Neuropathology Core.

b. Selected Other Studies

1) Biomarkers

- a) In 241 CN participants age 45-88 years PET amyloid imaging with Pittsburgh Compound B (PIB) was completed; 168 (70%) of these participants also had CSF assays for A β , tau, and p-tau, and all were genotyped for ApoE. The frequency of elevated PIB levels rose in an age-dependent manner and there also was a gene dosage effect for ApoE4 with greater PIB retention and lower CSF A β ₄₂. There was no ApoE effect on CSF tau. Increasing cerebral A β deposition with age is the pathobiological effect of ApoE4. A substantial number of CN older adults have preclinical AD.⁴⁹
- b) The ability of AD biomarkers (PIB PET amyloid imaging, CSF levels of A β ₄₂, tau, and p-tau) to predict incident cognitive impairment was examined in 201 CN participants, age 45-88 years, who were followed for up to 7.5 years. Abnormal levels of all biomarkers were associated with faster time to cognitive impairment. These data indicate that biomarkers signal underlying AD pathology

years prior to onset of cognitive impairment and that biomarker-positive CN individuals are at elevated risk for future symptomatic AD.¹⁹

- c) In 311 CN participants 65y and older, CSF biomarkers were used to classify participants in accordance with proposed stages of preclinical AD.⁵⁰ The participants with normal levels of CSF A β ₄₂ and tau had a 5-year progression rate to symptomatic AD of only 2%. The 5-year progression rate for individuals with reduced CSF A β ₄₂ but normal CSF tau levels was 11%, for individuals with both reduced CSF A β ₄₂ and elevated CSF tau was 26%, and for persons with reduced CSF A β ₄₂, elevated CSF tau, and poorer memory performance was 56%.²⁰ These data will be useful in prevention trials to stratify participants by preclinical AD stage.

2) Disease mechanisms

- a) The kinetics of A β production and clearance in the central nervous system were compared in 12 CN participants versus 12 individuals with symptomatic AD who had hourly CSF sampling for 36 hours after intravenous infusion of 13C6-leucine. Tandem mass spectrometry quantified the 13C6-leucine incorporation and removal rates from CSF A β . The average A β ₄₂ production rate did not differ between controls and symptomatic AD. However, the average clearance rate of A β ₄₂ was slower for persons with symptomatic AD. Late onset symptomatic AD is associated with a 30% impairment in the clearance of A β ₄₂, suggesting that clearance mechanisms may be important in the pathogenesis of late onset AD.⁵¹
- b) Performing *in vivo* microdialysis in a mouse model of amyloidosis expressing human ApoE isoforms (PDAPP/TRE) demonstrates that the concentration and clearance of soluble A β in the brain is ApoE isoform-dependent. The ApoE isoform-dependent differences in soluble A β metabolism occur in both aged and young (prior to A β deposition) PDAPP/TRE mice. The ApoE isoforms differentially regulate A β clearance from the brain, suggesting that A β clearance pathways may be useful therapeutic targets.⁵² The findings are particularly relevant for Project 2 in this application.
- c) Whole-exome sequencing was carried out in 14 large families with late onset AD. A rare variant in *PLD3* (phospholipase D3) segregated with disease status in 2 of the families and doubled the risk for AD in 7 independent case-control series. In cell-based studies, overexpression of *PLD3* resulted in decreased intracellular APP whereas knockdown of *PLD3* resulted in increased intracellular APP. These genetic and functional data show that *PLD3* influences APP processing and that *PLD3* coding variants have a two-fold increased risk for AD.⁵³

3) Therapy development

In young PS1APP transgenic mice with unilateral microdialysis probes in the hippocampus, brain interstitial fluid (ISF) levels of A β were decreased by 25% following administration of selective serotonin reuptake inhibitor drugs. Direct infusion of serotonin into the hippocampus also reduced ISF A β levels. Chronic treatment with citalopram caused a 50% reduction in A β plaque load in the mice. In CN older adults who underwent PET PIB imaging, the use of antidepressant drugs within the past 5 years correlated with reduced amyloid load.⁵⁴ A manuscript indicating that citalopram slows A β production by 37% and reduces CSF A β concentrations in young healthy humans is now in press at Science Translational Medicine.⁵⁵

- c. Collaborations (a brief synopsis; for the full range of collaborations see Table 5 in Administration Core Appendix)

ADRC investigators collaborate extensively; the Genetics Core alone is very active in national and international genetics consortia.^{53,56} Other examples include studies with ADNI⁴⁷ and with other ADCs⁵⁷ as well as with NACC investigators and NACC data.^{58,59} ADRC investigators are involved in national^{1,50,60,61} and international⁶² efforts to improve the diagnosis of AD and to standardize biomarker platforms.⁶³

2. Bringing new investigators into the field. See A.7. (above) regarding Drs. Mirica, Ances, Miller, and McConathy. Additionally, in this reporting period, the Knight ADRC provided \$960,000 to the Department of Neurology to serve as start-up funds for Drs. Cirrito, Diamond, Hassenstab, and Musiek, all of whom were new investigators and/or new recruits to Washington University.

3. Stimulate non-ADC funded research. See A.3. (above) that reports the 126 federally-funded, 125 non-federally-funded, and 30 industry-sponsored studies that have been stimulated by the ADRC outside of our P50 mechanism in this reporting period.

4. Leveraging funds from donors

The current total endowment supporting the Knight ADRC is \$12.5 million. The majority of the endowed funds come from philanthropic gifts provided by Charles and Joanne Knight and by a grateful patient of Dr. Morris. The Knights also endowed a Distinguished Professorship that supports Dr. Bateman. Expendable

philanthropic gifts to the Knight ADRC are on the order of \$500,000 or more annually and come from other grateful patients, friends and families of deceased participants, and individuals who support the ADRC's mission and investigators. These funds are used to support research initiatives, such as "extra" pilot grants beyond the 3 funded each year by the P50 mechanism, and investigators, such as the start-up funds described above.

5. Interrelationship with other relevant research projects.

The complementary and synergistic interactions of the Knight ADRC with its affiliated multicomponent grants (HASD, ACS, and DIAN) have been described in the Significance and the Innovation Sections above. Another interaction with a multicenter grant is The Human Connectome Project (HCP) partnership between Washington University and the University of Minnesota. The HCP aims to generate the most complete and accurate description of the connections among gray matter locations in the human brain at the millimeter scale, using complementary magnetic resonance (MR) imaging methods. While the original HCP focused on young adults aged 22-35y, a Lifespan Pilot Supplement was recently awarded to test and optimize HCP scanning protocols in children and in older adults. The Knight ADRC is collaborating with HCP to serve as the referral source for ~30 individuals aged 65-75y for the Lifespan Pilot project; our affiliated ACS grant will also provide ~30 individuals aged 45-55y. The longitudinal clinical, cognitive, and biomarker data from our participants are a tremendous asset to the HCP imaging analyses.

6. Relationship with Washington University; Institutional Support

The Chair (Dr. Holtzman) of the Department where the ADRC is administered is an Associate Director of the ADRC. The Knight ADRC enjoys exceptional support from the School of Medicine and from the University as a whole (see Letters of Support from Chancellor Wrighton and Dean Shapiro). The School of Medicine in 2012 provided \$1.6 million to acquire, renovate, and furnish 3400 square feet of new space for the ADRC that is in the same building that houses the Administration and Clinical Cores along with OREC, AAOC, and ROC (see Administration Core). This new space was justified by the expansion of the ADRC's research portfolio, including DIAN and DIAN-TU. As further demonstration of institutional support, the School of Medicine has pledged to provide \$100,000 annually in the next budget period to support ADRC research initiatives (see Letter of Support, Dean Shapiro); this will be supplemented by an additional \$30,000 annually from the School's McDonnell Center for Systems Neuroscience (see Letter of Support, Dr. Petersen). These funds will be used to support acquisition of biomarkers in Projects that are underfunded (e.g., tau imaging in proposed Project 1 of this application) and to "catch up" missed biomarker visits (because of past budgetary restrictions) by our participants.

7. Leadership and Career Progression.

The Knight ADRC benefits from stable leadership. Dr. Morris has led the Clinical Core since 1991 and shared co-leadership of the ADRC with Eugene Johnson from 1997 until 2003, when Morris became Director and Principal Investigator. The Leaders of all Cores but one in the last renewal continue as Leaders of their respective Cores in this renewal. The exception is the Education Core, which now is led by Andrea Denny after former Core Leader James Galvin left Washington University in 2010. Two Satellites in the 2009 application now are Cores and have new Leaders, Ms. Denny for the Rural Outreach Core (replacing Satellite Leader Galvin) and David Carr for the African American Outreach Core (replacing Satellite Leader Monique Williams).

Dr. Morris benefits from his Associate Directors, Eugene Johnson, David Holtzman, and Alison Goate. Morris and Johnson have worked together in the ADRC since it was initially funded in 1985 and both have interacted very productively with Holtzman and Goate in the ADRC for over 20 years; Morris, Holtzman, and Goate are frequent scientific collaborators.⁶⁴ Morris also benefits from Executive Director, Virginia Buckles, PhD, and Associate Executive Director, Krista Moulder, PhD. Dr. Buckles has worked with Dr. Morris since 1992; Dr. Moulder joined the ADRC in 2010.

The Knight ADRC is committed to the career development of its junior investigators. The model is that each Core Leader identifies his or her future successor, mentors that individual for an appropriate period of time, and then transitions Core leadership when both are ready. For example, Dr. Chengjie Xiong was recruited to Washington University in 2001 as Research Assistant Professor of Biostatistics to train with then-DMS Core Leader, J. Philip Miller. The training period enabled Dr. Xiong to successfully develop his career: he was awarded a K25 from 2005-2009 with Dr. Morris as his mentor to ensure that his statistical methods served the needs of the ADRC; became Research Associate Professor in 2006, in 2009 moved to Investigator (tenure) Track, and was promoted to Professor on the Investigator track in 2013; currently is PI on 2 R01s. The training period also positioned him to assume the leadership of the DMS Core for the past two funding cycles. Another example is Jason Hassenstab, who after completing his postdoctoral fellowship in neuropsychology at

Brown University was recruited in 2010 to Washington University to train with Martha Storandt, who had led the psychometric component of the ADRC since its inception but then was planning for retirement. Dr. Hassenstab was successful in obtaining a K23 award (Dr. Morris is a co-mentor) to further his career development while being mentored by Dr. Storandt in the ADRC's psychometric program, for which he assumed leadership when Dr. Storandt retired in 2012. Another example is Randall Bateman, MD. Dr. Bateman was the ADRC postdoctoral fellow from 2004 to 2006, when he was co-mentored by Drs. Holtzman and Morris. Dr. Bateman was awarded a competing revision (supplement) to Dr. Morris' ACS PPG from 2007-2010 that addressed dominantly inherited AD; this revision and the ACS were the infrastructure that helped to establish the international Dominantly Inherited Alzheimer Network (DIAN; U19AG032438, JC Morris PI) for which Dr. Bateman serves as Leader of the Clinical Core. The application to renew the original DIAN funding period (2008-2014) will be awarded July 2014; at the end of the first year of the renewal period, Dr. Morris will transition the leadership of the DIAN grant to Dr. Bateman.

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