**Background:** Early, minimally-invasive, accurate detection of Alzheimer’s disease (AD) could facilitate screening and enrollment of better defined participants into clinical trials, and enable disease progression and treatment response monitoring. Neurodegenerative diseases (NDs), including AD, Parkinson’s disease (PD), and frontotemporal degeneration (FTD), may begin with a prolonged asymptomatic stage. Further, many NDs can present with similar clinical manifestations at early stages. While early stages of NDs affect different brain regions, most NDs are characterized by early synapse dysfunction/loss. We have developed a novel approach for early detection and monitoring of neurodegeneration based on targeted selection and quantitative analysis of microRNA (miRNA) biomarkers enriched in certain brain regions, present in synapses, and detectable in plasma. Effective miRNA biomarker “pairs” are comprised of one miRNA enriched in synapses of brain regions affected by disease (e.g. hippocampus for AD) and a miRNA enriched in different brain regions. **Methods:** RNA was extracted from patient and control plasma samples. Plasma concentrations of miRNAs were analyzed by individual RT-qPCR and statistical analysis of miRNA ratios was performed using customized software, essentially as described in Sheinerman et al. Aging 2013. **Results:** Recent, unpublished data will be presented. In collaboration with Washington University, plasma samples from 30 cognitively normal (CDR 0) amyloid negative subjects and 29 amyloid positive subjects with very mild/mild dementia, CDR 0.5-1, were analyzed and differentiated with 86% accuracy. In the second study, 84 plasma samples from donors cognitively normal at enrollment were analyzed. 42 subjects later have progressed to CDR >0 (“progressors”), and 42 have remained cognitively normal during 3-12 years observation period (“non-progressors”). miRNA biomarkers differentiated “progressors” from “non-progressors” with 78% accuracy, and amyloid positive and negative “progressors” with 79% accuracy. In the cohort recruited at University of Pennsylvania, levels of miRNAs were measured in plasma of 250 subjects with AD, PD, FTD, amyotrophic lateral sclerosis (ALS), and controls. miRNA pairs capable of effectively differentiating each ND from control with >90% accuracy and from each other with 87%-98% accuracy have been established. **Conclusions:** These data strongly support applicability of the proposed approach to early detection and differential diagnosis of AD. Larger, longitudinal studies are ongoing.

**THURSDAY, JULY 28, 2016
ORAL SESSIONS**

**O5-06 PROTEIN-PROTEIN INTERACTIONS: CROSS-TALK BETWEEN PROTEIN AGGREGATION AND DISEASES**

**O5-06-01 TDP-43 SUPPRESSES TAU EXPRESSION VIA PROMOTING ITS MRNA INSTABILITY**

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**Background:** Tau pathology is a histopathological hallmark of Alzheimer’s disease (AD) and related tauopathies. Recent studies suggest that the pathological changes of tau appear to be essential to neurodegeneration and to the propagation of neurofibrillary pathology in AD. Inhibition of tau expression in some mouse models protects them from cognitive impairment. In the brains of patients with AD and chronic traumatic encephalopathy, tau pathology is accompanied by intracellular aggregation of trans-active response DNA-binding protein 43 (TDP-43). However, the role of TDP-43 in tau pathogenesis is not understood. **Methods:** We overexpressed or knocked down TDP-43 and determined tau expression at mRNA and protein levels by real-time PCR and Western blots. GFP followed by 3’-terminal untranslated region (3’-UTR) of tau mRNA was constructed for the study. The role of truncations and neurodegenerative mutations of TDP-43 in tau expression was investigated. The level of tau and TDP-43 and their relationship in control human brains and AD brains were analyzed. **Results:** We found that TDP-43 suppressed tau expression by promoting tau mRNA instability. TDP-43 binds on the UG repeats of tau mRNA 3’UTR. The C-terminal region of TDP-43 was required for this function. TDP-43 mutations that cause frontotemporal lobar degeneration or amyotrophic lateral sclerosis did not promote tau mRNA instability. TDP-43, the level of which is decreased in AD brains, was correlated negatively with tau level in human brain. **Conclusions:** TDP-43 suppresses tau expression by promoting the instability of its mRNA. Down-regulation of TDP-43 could be involved in tau pathology in AD and related neurodegenerative disorders.

**O5-06-02 PROTEOMIC NETWORK ANALYSIS TO FIND COMMON MECHANISMS UNDERLYING ALZHEIMER’S DISEASE AND PD**

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**Background:** A common theme among neurodegenerative diseases is the co-occurrence of diverse disease protein aggregates in the same patient, underscoring the need to delineate common pathways associated with related neurodegenerative diseases. For example, greater than 50% of Alzheimer’s Disease (AD) cases have Lewy bodies comprised of aggregated α-synuclein, whereas co-morbid AD pathologies, including amyloid beta (Aβ) plaques and tau pathology, are often found in Parkinson’s Disease (PD) patient brains at autopsy. Despite this overlap in neuropathology, the cellular and molecular mechanisms that link AD and PD are poorly understood. To overcome this limitation we present a systems biology approach to define specific protein co-expression networks from postmortem brain tissue of patients with AD, PD and co-morbid AD/PD pathologies. **Methods:** Employing liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) on an Orbitrap Fusion mass spectrometer we comparatively analyzed the total brain proteome of post-mortem frontal cortex samples (Brodmann Area 9) representing four groups (n=10 cases each): i) pathology free controls, ii) AD, iii) PD and iv) AD/PD cases with co-morbid pathologies. Using both label-free and isobaric tandem-mass tags (TMT) approaches we were able to identify and quantify over 4,000 proteins across all 40 individual cases. **Results:** Weighted Co-expression Network Analysis (WGCNA) defined protein modules linked to cell-type that were specific to AD as well as those shared with PD, the latter representing common mechanisms associated with neurodegeneration. **Conclusions:** These results highlight the utility
Cerebrovascular accumulation of the amyloid beta-protein (Abeta), a condition known as cerebral amyloid angiopathy (CAA), is a common pathological feature of patients with Alzheimer’s disease. Additionally, familial forms of Abeta mutations, such as Dutch E22Q and Iowa D23N, cause severe cerebral vascular accumulation of amyloid that serves as a potent and early driver of vascular cognitive impairment and dementia (VCID). The distinctive features of vascular amyloid that underlie its unique pathological properties remain unknown. Here we investigated how cerebral vascular fibrillar amyloid seeds influence the assembly, accumulation, and structure of Abeta.

Methods: A combination of biochemical and biophysical approaches were used to study amyloid fibril formation in vitro. Transgenic mice were then used in conjunction with quantitative pathological, biochemical and structural analyses to study how CAA mutant and wild-type Abeta interact in brain to drive vascular amyloid formation. Results: In the in vitro that CAA mutant amyloid fibril seeds can adopt a parallel or anti-parallel configuration and that both can promote rapid fibril assembly of wild-type Abeta peptides that adopt corresponding fibrillar signatures. In the in vivo studies we first show that intrahippocampal administration of biotin-labeled wild-type Abeta peptides strongly accumulate on pre-existing cerebral microvascular amyloid deposits in Tg-SwDI mice, a model that preferentially develops early-onset CAA mutant microvascular amyloid. Subsequently, we crossed Tg-SwDI mice with Tg2576 mice, a model that produces high amounts of human wild-type Abeta in brain. The bigenic mice exhibited markedly elevated accumulation of microvascular fibrillar amyloid in brain compared to either single transgenic line that was largely composed of human wild-type Abeta. Further, isolated microvascular amyloid seeds from Tg-SwDI mice drive assembly of human wild-type Abeta into distinct anti-parallel amyloid fibrils. Conclusions: These findings indicate that cerebral vascular amyloid can serve as an effective scaffold to promote rapid assembly and strong deposition of Abeta into a unique structure that likely contributes to its distinctive pathology.