BOSTON UNIVERSITY

School of Medicine

10th Annual

Alzheimer's Research Day

Tuesday, September 25, 2012

Keynote Speaker:

Dr. Reisa Sperling

Professor of Neurology, Harvard Medical School
Director, Center for Alzheimer's Research and Treatment

Can we detect Alzheimer's disease a decade before dementia – and why would we want to?

HIEBERT LOUNGE, L-BUILDING, 14th FL

12:00p LECTURE

1:15p LUNCH & POSTER SESSION

Host: Carmela Abraham, Ph.D., Department of Biochemistry

Free and open to all | Wheelchair Accessible

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http://bu.edu/alzresearch/researchday

This event is sponsored by the Boston University Alzheimer's Disease Center, the Departments of Biochemistry and Pharmacology, and the Graduate Program for Neuroscience.

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LIST OF ABSTRACTS

Brain regions associated with baseline cognitive function and subsequent decline in normal aging and mild cognitive impairment as measured with MRI and FDG-PET.

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In order to better understand cognitive function in normal aging and mild cognitive impairment (MCI) it is important to understand the brain regions associated with them. In this study we set out to identify these regions using MRI morphometry and FDG-PET. MRI, FDG-PET, and neuropsychological test scores from 306 subjects were obtained from the ADNI database. Volume, cortical thickness, and FDG-PET uptake were calculated. Z-scores were calculated for annualized percent change (APC) of neuropsychological test scores. MRI and FDG-PET variables predicting baseline neuropsychological test scores and ACP in neuropsychological performance were identified using separate stepwise linear regression. Significant predictors from each imaging modality were combined for the multi-modal models.

Each MRI, FDG-PET, and multi-modal model predicting baseline neuropsychological test scores was significant ($p < 0.0001$, adjusted R-squared between 0.1052 and 0.4660). MRI models predicting the APC of the neuropsychological test scores were significant ($p < 0.0001$, adjusted R-squared between 0.0391 and 0.2560). Each multimodal model of APC was significant ($p < 0.0001$, adjusted R-squared between 0.0398 and 0.2200). FDG -PET on its own was not a good predictor of APC ($p < 0.05$, adjusted R-squared between 0.0043 and 0.0626). Adding FDG-PET to MRI morphometry did not consistently increase the R-squared values.

High-Resolution Multi-Elemental Metallomic Mapping of the Brain in the Tg2576 Transgenic Mouse Model of Alzheimer's Disease

Noel Casey[1,3],Juliet Moncaster[1], Amanda Gaudreau[1,2,3], Mark Wojnarowicz[1], Tim Connelly[1,2,3-], Andrew Fraine[1,2], Olga Minaeva[1,2], Rob Webb[1,2], Lee E. Goldstein[1,2,3]

Interaction of the Alzheimer's disease (AD) amyloid-β peptides (Aβ) and biometals in the brain represent a major pathogenic pathway in Alzheimer's disease (AD) and provide the basis for clinical effective disease-modifying therapy. Mapping the microanatomical distribution of essential and trace elements and isotopes in the brain is essential for understanding AD pathobiology and designing new disease-modifying therapies. To date, mapping the brain metallome has been limited by technical barriers. Here we developed a new technique, High-Resolution Metallomic Imaging Mass Spectrometry (HR-MIMS), to perform the first high-resolution multi-elemental and isotopic distribution maps of the brain metallome in the Tg2576 transgenic AD mouse model compared to wild-type control mice. Mice were procured from the Boston University Alzheimer's Disease Center Transgenic Mouse Facility. Mouse brains were flash frozen and analyzed by metallomic imaging mass spectrometry (MIMS mapping) at the Boston University Center for Biometals & Metallomics, Boston, MA. High resolution metallomic maps generated from Tg2576 (Tg) and wild-type (Wt) mouse brain demonstrated unique elemental and isotopic distribution patterns. Zinc (Zn) brain maps revealed a distinctive distribution pattern marked by cortical lamination, prominent allocortical (hippocampus, amygdala) deposition, and isotopic (64Zn, 70Zn). Simultaneous metallomic maps of the same Wt and Tg brains revealed distinctive elemental and isotopic distribution patterns for other important biometals, including copper (Cu), iron (Fe), selenium (Se), molybdenum (Mo), manganese (Mn), and others. This study strongly supports a role for zinc in AD-linked brain pathology.

Elucidating the Function of the Anti-aging Protein Klotho in the Brain

Ci-Di Chen and Carmela R. Abraham
Boston University School of Medicine, Department of Biochemistry

We have previously shown that myelin abnormalities and loss characterize the normal aging process of the brain and that an age-associated reduction in Klotho is conserved across species. Predominantly generated in brain and kidney, Klotho overexpression extends life span whereas loss of Klotho accelerates the development of aging-like phenotypes. While the function of Klotho in brain is unknown, loss of Klotho expression leads to cognitive deficits. In this study, we found significant effects of Klotho on oligodendrocyte functions including induced maturation of primary oligodendrocytic progenitor cells (OPC) *in vitro* and myelination through Akt and ERK signal pathways. Klotho knockout mice have a significant reduction in major myelin protein and gene expression compared to control mice. By immunohistochemistry, the number of total and matured oligodendrocytes were significantly lower in Klotho knockout mice. Striking, Klotho knockout mice exhibited significantly impaired myelination of the optic nerve and corpus callosum by electron microscopy. Moreover, these mice also displayed severe abnormalities at the nodes of Ranvier. In order to decipher the mechanisms by which Klotho affects oligodendrocytes, we used luciferase pathway reporters to identify the transcription factors involved. Taken together, these studies provide novel evidence for Klotho as a key player in myelin biology, which may thus be a useful therapeutic target in efforts to protect brain myelin against age-dependent changes that are also seen in Alzheimer's disease white matter.

Three Highly Correlated Scoring Systems of the Clock Drawing Test are Affected by Age and Education

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The clock drawing test (CDT) can measure qualitative aspects of executive functioning. It is unclear whether more in-depth rating scales can provide more accurate results. The Mendez scoring system, 21 point-item scale, is one of the larger accredited scoring methods. The Freund scoring system, 8 point-item scale, is also a reliable, time-efficient method. A four point-item scale on the Montreal Cognitive Assessment (MoCA) test, the MoCA scoring system, is possibly the most widely used method for measuring executive dysfunction.

There is no single method currently proven to predict dementia as defined by the new 2011 criteria. Furthermore, the influence on CDT performance and executive functioning in a relatively highly educated population is not completely clear. The aim of this study is to determine correlation between the three scoring methods, and whether education and age affect the various scoring systems used for assessing the CDT.

191 CDTs from TheAlzCenter.org memory clinic were studied. Each CDT was scored on MoCA, Freund, and Mendez scales. Education, age and other factors were analyzed to determine their relationship to CDT scoring systems. All CDT scoring systems were highly correlated. In multivariate models, the MoCA scoring system was affected primarily by education ($p < 0.05$), while age affected Freund ($p < 0.001$) and Mendez ($p < 0.05$) scoring systems. While one scoring method is not better than the other, clinicians may prefer to use the smaller scoring scale for time conservation. However, it is important to recognize that demographic factors may mask cognitive deterioration.

Chronic Traumatic Encephalopathy in Blast-Exposed Military Veterans and a Blast Neurotrauma Mouse Model

A Fisher[1,3], C Tagge[1,3], M Wojnarowicz[1], O Minaeva[1,3], S Sarangi[1,3], J Moncaster[2,3], N Casey[2,3], C Nowinski,[6] R Stern,[2,6] R Cantu,[6,7] J Geiling,[8] J Blusztajn,[2] B Wolozin,[2] T Ikezu,[2] T Stein,[2,9] C Abraham,[2] A Budson,[2,9] N Kowall,[2,9] D Chargin,[10] A Sharon,[10] S Saman,[11] G Hall,[11] W Moss,[12] R Cleveland,[3] R Tanzi,[5] P Stanton,[4] N Kowall[2], A McKee[2,11], L Goldstein[1,2,3]

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Traumatic brain injury (TBI) resulting from exposure to explosive blast affects ~12-23% of the 2.4 million U.S. military servicemen and women deployed to Iraq and Afghanistan. We recently reported the first case series of postmortem brains from U.S. military veterans with blast exposure (Goldstein, 2012). We found evidence of chronic traumatic encephalopathy (CTE), a tau protein-linked neurodegenerative disease associated with repetitive concussive injury in athletes (McKee, 2009, 2010). In the same study, we replicated CTE-linked neuropathology, axonopathy, microvasculopathy, and neurodegeneration in C57BL/6 mice exposed to a single blast. Blast-exposed mice developed learning and memory deficits that correlated with impaired axonal conduction and defective long-term synaptic plasticity.

Our results identify common determinants leading to CTE in blast-exposed military veterans and head-injured athletes, and additionally, provide mechanistic evidence linking blast-induced head acceleration to persistent neurobehavioral deficits.

An N-Terminal Cleavage Fragment Of The Prion Protein Binds To Specific Assemblies Of The Amyloid-Beta Peptide And Blocks Their Neurotoxic Effects

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Alzheimer's disease (AD) is associated with progressive dementia and accumulation in the brain of the amyloid-β (Aβ) peptide, a cleavage product of the amyloid precursor protein (APP)[1]. Compelling evidence suggest that soluble, oligomeric assemblies of Aβ are primarily responsible for the synaptic dysfunction underlying the cognitive decline in AD[2]. So far, the identity of the cellular receptors to which these oligomers bind to exert their neurotoxic effects has remained enigmatic. Recently, the cellular prion protein (PrP^C) has emerged as a novel and unexpected candidate receptor for Aβ oligomers[3]. Several reports also suggest that PrP^C could directly mediate the synaptotoxic effects of Aβ oligomers, although this evidence is still controversial[4-6]. Interestingly, the two putative binding sites for Aβ oligomers identified in PrP^C (residues 23-27 and 95-110) are both encompassed within the flexible, N-terminal tail of the molecule (residues 23-111)[7]. This region is proteolytically released as part of the normal, cellular processing of PrP^C, to produce a soluble fragment called N1[8]. An artificial, secreted form of PrP^C was previously reported to suppress cognitive impairment in a mouse model of AD[9]. Therefore, regardless of whether PrP^C mediates the neurotoxicity of Aβ oligomers, soluble forms of PrP^C such as the N1 fragment could sequester oligomers in the extracellular space and show therapeutic benefit in AD.

Here, by applying several in vitro and in vivo assays, we show that N1 binds to specific assemblies of Aβ oligomers with nanomolar affinity. We also report that N1 fully abrogates the synaptotoxic effects of Aβ oligomers in cultured hippocampal neurons and in a novel toxicity assay using the nematode *C. elegans*.

Collectively, these data provide strong experimental evidence supporting the idea that N1, or small peptides derived from it, could be potent inhibitors of Aβ oligomer toxicity and represent an entirely new class of therapeutic agents for AD.

References:
1. D. J. Selkoe et al., 2011 Cold Spring Harb Perspect Biol, 3.
2. D.M. Walsh et al., 2007 Neurochem. 101, 1172.
3. K. Lauren et al., 2009 Nature 457, 1128.
4. D.A. Gimbel et al., 2010 J Neurosci 30, 6367.
5. C. Balducci et al., 2010 Proc Natl Acad Sci U S A 107, 2295
6. E. Biasini et al., 2011 Trends Neurosci, (Epub ahead of print)
7. S. Chen et al., 2010 J Biol Chem 285, 26377.
8. D. A. Harris et al., 1993 Biochemistry 32, 1009.
9. A. M. Calella et al., 2010 EMBO Mol Med 2, 306.

How do Memory Screening Tools Compare to Florbetapir PET Scan Results? A Pilot Study

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Objective: In light of the recently FDA approved Amyloid PET scan, the use of clinical screening tools such as the Montreal Cognitive Assessment and Mini Mental Status Examination must be reassessed. We retrospectively analyzed the ability of the MoCA and MMSE to differentiate between individuals attending TheAlzCenter.org memory clinic who received positive and negative scan results.

Methods: Clinic charts of 19 de-identified patients with memory complaints from TheAlzCenter.org who received amyloid PET scans were retrospectively studied. Patients included 10 individuals with negative scans and 9 individuals with positive scans. MoCA and MMSE scores were identified for all patients except for one. A t-test, univariate, and multivariate models were conducted to evaluate the relationship between testing scores and scan positivity.

Results: Individuals with positive scan results had lower MMSE and MoCA scores compared to individuals with negative scans after analyses adjusted for age and sex.

Conclusion: Commonly used clinical tools such as the MMSE and MoCA differed among amyloid PET scan positives and scan negatives in a memory clinic population. Further study is needed to see if paper-pencil test can improve patient selection of Amyloid PET scans in the memory clinic.

Inhibition of APP dimerization as a therapeutic approach to reduce levels of amyloid-beta peptide

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Alzheimer's disease (AD) is the most common neurodegenerative disorder and is characterized neuropathologically by the presence of amyloid plaques and neurofibrillary tangles. Amyloid plaques are primarily composed of aggregated amyloid-beta peptide (Aβ). Production of Aβ results from amyloidogenic processing of amyloid beta precursor protein (APP), where APP is sequentially cleaved by β-secretase and g-secretase. APP also undergoes non-amyloidogenic processing, which does not result in production of Aβ. APP is a transmembrane glycoprotein that can dimerize to itself as well as to other proteins such as Notch or amyloid precursor like proteins. Homodimerization of APP has been shown to affect production of Aβ, although findings from different groups conflict in whether this homodimerization induces or reduces production of Aβ. Previously, this laboratory has identified a compound that inhibits APP dimerization, and also reduces Aβ production. The proposed projects will examine the mechanism of this reduced homodimerization and Aβ production, as well as aim to identify compounds of similar structure that inhibit dimerization and more efficiently inhibit Aβ production. Identification of compounds that efficiently inhibit dimerization and Aβ production may lead to a potential novel therapeutic approach for AD if successful in animal models of disease.

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High-Resolution Multi-Elemental Metallomic Mapping of the Human Eye in Alzheimer's Disease and Normal Aging

Juliet Moncaster[1], Noel Casey[1,3], Amanda Gaudreau[1,2,3], Mark Wojnarowicz[1], Tim Connelly[1,2,3-], Andrew Fraine[1,2], Olga Minaeva[1,2], Rob Webb[1,2], Lee E. Goldstein[1,2,3]

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We previously identified amyloid-β (Aβ) deposition, amyloid pathology, and co-localizing supranuclear cataracts in the lens of the eye in Alzheimer's disease (AD) and Down Syndrome (DS) (Goldstein, 2003; Moncaster, 2010). Interaction of Aβ and biometals represent a major pathogenic pathway in AD and provide the basis for clinical effective disease-modifying therapy. To date, mapping the ocular metallome has been limited by technical barriers. Here we developed a new technique, High-Resolution Metallomic Imaging Mass Spectrometry (HR-MIMS), to perform the first high-resolution multi-elemental and isotopic distribution maps of the metallome of the adult human eye in AD and age-matched controls. Human eyes were obtained through the Boston University Alzheimer's Disease Center and NDRI (Philadelphia, PA). High -resolution maps generated from AD and age-matched control eyes demonstrated unique elemental and isotopic distribution patterns. Zinc was confirmed in the subequatorial supranucleus of the lens, the same region implicated in AD-linked Aβ accumulation and cataractogenesis. Simultaneous metallomic maps of the same lenses revealed distinctive elemental and isotopic distribution patterns for other important biometals, including copper (Cu), iron (Fe), selenium (Se), molybdenum (Mo), manganese (Mn), and other elements. This study supports a role for zinc in AD-linked lens pathology.

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The Interaction between the ApoE Genotype and Angiotensin Converting Enzyme Inhibitors on the Risk of Developing Alzheimer's disease

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Departments of Pharmacology & Experimental Therapeutics[1], Psychiatry[2], and Alzheimer's disease Center[3], Boston University School of Medicine; Department of Public Health and Family Medicine[9], Tufts University [4]; Urban Indian Health Institute, Seattle, WA[5]

Objective: The effect of Angiotensin converting enzyme (ACE) inhibitors on Alzheimer's disease (AD) remains unclear, with conflicting results reported. We investigated the interaction of the Apolipoprotein E (ApoE) genotype and ACE inhibitors on AD.

Methods: We used cross-sectional data from the Nutrition and Memory in the Elderly (NAME) with an AD diagnosis and documentation of medications taken as well as longitudinal data from the National Alzheimer's Coordinating Center (NACC). ApoE genotype in both studies was determined. The ACE inhibitors in the NACC study were divided into central and peripheral ACE inhibitors; ACE inhibitors in the NAME study were pooled.

Findings: Cross-sectionally using the NAME study, we found that ApoE4 carriers treated with ACE inhibitors had a greater frequency of AD diagnoses compared with those who did not have the treatment (28% vs. 6%, p = 0.01) or with ApoE4 non-carriers treated with an ACE inhibitor (28% vs. 10%, p = 0.03). AD was significantly associated with an interaction between ApoE4 and ACE inhibitor use. In the NAME study, subjects with both the ApoE4 genotype and using ACE inhibitors were at significantly increased risk of having AD (OR = 20.85, 95% CI = 3.08, 140.95, p = 0.002) after adjusting for age, gender, ethnicity and education. We thus further used the longitudinal the NACC study to determine two bi-directional possibilities for ACE inhibitors on AD in ApoE4 carriers: delaying or accelerating the AD onset. We found that among ApoE4 non-carriers, both central (OR = 1.45, 95% CI = 1.16, 1.81, p = 0.001) and peripheral (OR = 1.77, 95% CI = 1.22, 2.56, p = 0.003) ACE inhibitors were associated with a reduced risk of AD onset. In contrast, among those ApoE4 carriers, both subclasses of ACE inhibitors were not associated with the risk of AD onset significantly although the central ACE inhibitors had a trend to reduce the onset of AD (OR = 1.31, 95% CI = 0.96, 1.78, p = 0.09).

Conclusion: ACE inhibitors may reduce the risk of developing AD but the effect may depend on ApoE4 genotype. ACE inhibitors, especially peripheral ones, may not delay AD development effectively when ApoE4 allele is present.

Characterization And Modulation Of Alzheimer's Disease Amyloid-B (Aβ) Protein Aggregation Monitored By Quasi-Elastic Light Scattering

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[1] Boston University School of Medicine, MA; [2] Boston University Photonics Center, MA; [3] Boston University College of Engineering, [4] The Center for Biometals and Metallomics, Boston University, MA.

Alzheimer's disease (AD) is characterized by age-related cerebral deposition of amyloid-β peptides (Aβ). We discovered that Aβ accumulates in the supranuclear region of the lens in patients with AD (Goldstein, 2003) and Down Syndrome (DS), Moncaster, 2010), a common chromosomal disorder that carries 100% risk of early-onset AD. In AD and DS lenses, Aβ accumulates as electron-dense intracellular aggregates that distribute heterogeneously within the cytoplasm of supranuclear and deep cortical lens fiber cells. These Aβ lens aggregates qualify as Raleigh scattering centers that clinically manifest as distinctive AD-specific supranuclear lens opacities. Aβ aggregates identical to those detected in human lenses can be generated in vitro by controlled incubation of human lens protein extract with synthetic Aβ peptide. This aggregation process can be studied by quasi-elastic light scattering (QLS). QLS analyzes time-dependent light scattering intensity fluctuations from which autocorrelation functions can be derived. We are investigating the properties and mechanisms

The neuropathology of Alzheimer disease in the setting of chronic traumatic encephalopathy

Thor D. Stein, Victor Alvarez, Ann C. McKee

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease induced by repeated mild traumatic brain injuries (TBIs). It is a tauopathy characterized by neurofibrillary tangles and glial tau inclusions that preferentially involve the cortical sulci, medial temporal lobe, diencephalon, and brainstem. Trauma is also a known risk factor for Alzheimer disease (AD), and we hypothesize that multiple mild TBIs play a causative role in the development of AD as well as CTE. In CTE the tau pathology is markedly perivascular and occurs in the cortical sulci where the stresses on vessels are likely greatest. This tau pathology may be due to vascular damage and disruptions of the blood brain barrier (BBB)- alterations that also have been linked to AD. Out of 64 cases of CTE diagnosed in athletes at autopsy, 24 (38%) had CTE with various degrees of beta-amyloid deposition; 15 (23%) had CTE and cerebral amyloid angiopathy; and 7 (11%) had AD and CTE. Within those subjects with both AD and CTE, the percent of beta-amyloid plaque burden is greatest within the sulcus as compared to the gyrus of the inferior frontal cortex. This increased beta-amyloid deposition is accompanied by increased numbers of GFAP-positive reactive astrocytes and IBA -1-positive microglia as well as increased NFTs and tau-positive astrocytes within the sulcus compared to the crest of the gyrus. These differences are not present in subjects with AD alone, and the increased GFAP and beta-amyloid immunostaining does not occur in subjects with CTE alone. Furthermore, there is a marked increase in GFAP-positive astrocytes in a perivascular distribution within the white matter of subjects with AD and CTE. In conclusion, the pathologies of AD occur predominantly within the sulcal depths of individuals with CTE and a history of head trauma and may be a result of vascular and axonal injury that occurs there.

Modeling And Elucidating The Pathobiology Of Impact Induced Traumatic Brain Injury In The Mouse

C Tagge[1,2], A Fisher[1,2], M Wojnarowicz[1], O Minaeva[1,2], S Sarangi[1,2], J Moncaster[1,3], N Casey[1,3], N Kowall[3,4], A McKee[4], LE Goldstein[1,2,3]

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Traumatic brain injury (TBI) resulting from exposure to explosive blast affects ~12-23% of U.S. military servicemen and women. We recently reported the first case series of postmortem brains from U.S. military veterans with blast exposure (Goldstein, 2012). We found evidence of chronic traumatic encephalopathy (CTE), a tau protein-linked neurodegenerative disease associated with repetitive concussive impact injury in athletes (McKee, 2009, 2010). Based on our findings of possible similar pathology in blast and impact brains, we hypothesize that biomechanical forces transmitted to structures in the brain during closed-head impact-induced TBI, generate shearing forces that disrupt microvascular integrity, activate neuroinflammatory responses, and initiate pathogenic cascades that trigger persistent TBI and late-emerging CTE. To investigate this hypothesis, we are developing mouse models that closely mimic trauma conditions associated with impact and blast head injury (Goldstein et al., 2012). The model allows for varying of intensity and recurrence of impact and characterizes trauma biomechanics and biological endpoints, including focal tauopathy, neuroinflammation, neurodegeneration, and disruption of blood-brain barrier. Results of this study will advance understanding and comparison of impact- and blast-induced TBI and CTE and provide translational technologies urgently needed for blast- and impact-induced TBI and sequelae.

Changes In Klotho Trafficking And Function Associated With Polymorphisms

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Klotho (KL) is an anti-aging protein named after the Greek goddess who spins the thread of life. Mice deficient in KL are normal throughout development, but rapidly degenerate displaying a variety of aging-associated abnormalities including atherosclerosis, mineral homeostasis deficits, osteoporosis, and cognitive decline. These abnormalities lead to an early death with a mean life expectancy of 60.7 days. In contrast, KL overexpressing mice have a 20-30% extension in lifespan. Although the precise mechanisms necessary for its anti-aging effects remain a point of debate, KL is involved in many pathways implicated in aging including FGF-23 signaling, suppression of insulin/IGF-1 and wnt signaling, and ion channel trafficking.

While multiple genetic association studies have identified KL polymorphisms linked with changes in disease risk, there is a paucity of concrete mechanistic data to explain how these two amino acid substitutions alter KL protein function. One such polymorphism, the KL-VS is associated with altered lifespan, increased risk of coronary artery disease, decrease in cognitive ability, and changes in bone mineral density. Our studies have sought to investigate the functional differences in the KL-VS variant that result in increased risk of many age-related diseases. The single nucleotide polymorphisms lead to differences in half-life of the protein, changes in trafficking, as well as a difference in its enzymatic activity compared to wild type KL. Preliminary results also suggest that KL-VS leads to differences in its ability to function as a co-receptor for FGFR1. Further studies will further elucidate the functional changes in KL associated with this variant in order to better understand how variations in only one gene can so dramatically impact lifespan and disease risk.

Towards the Development of a Blood Test for Early Stages of Alzheimer's Disease Using Enzyme Levels in Human Serum

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The levels of enzymes responsible for the clearance of amyloid β (Aβ) from the brain hold promise as biomarkers for the early diagnosis of Alzheimer's disease (AD), for monitoring its progress, and for developing drugs. The goal of this study was to examine two such enzymes, angiotensin-converting enzyme (ACE) and insulin-degrading enzyme (IDE), in cerebral spinal fluid (CSF) and serum.

We obtained pared CSF and blood samples from 30 cognitively normal surgical patients (16 male, 14 female, ages 40-60, mean age 46.7) before their operations. Control serum came from a healthy male researcher (age 38). Using fluorogenic substrate V, fluorescent antibody-tagged amyloid-β (FAM-Aβ), and two substrates specific for ACE, we tested the proteolytic activities in the pared CSF and serum samples. Both human serum and CSF had proteolytic activities cleaving substrate V and also FAM-Aβ. We found that the proteolytic activities in serum and CSF were correlated, with stronger correlation among women for substrate V but stronger correlation among men for FAM-Aβ. We found no correlation between the enzyme activities and age.

Since the activities of serum IDE and ACE are low in subjects with probable AD, and our study showed a link between proteolytic activities in central nervous system and peripheral blood, blood IDE and ACE may become useful biomarkers for AD.

G3BP protects against pathological tau and Ab42-induced neurotoxicity

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AD is a devastating neurodegenerative disease that was originally diagnosed over 100 years ago, yet no disease modifying treatment strategies currently exist. The two hallmarks of AD are neurofibrillary tangles of hyperphosphorylated tau and plaques composed of amyloid-β peptide (Aβ42). Recently, the Wolozin lab also identified stress granules (SG) as a major component of AD pathology. SGs accumulate in the brains of subjects with MCI and AD, and are physically distinct from classic markers of AD. RNA binding proteins are a large group of proteins that regulate RNA translation through formation of RNA/protein complexes. Stress, such as that occurring during neurotoxicity or inflammation, induces alterations in the pattern of protein synthesis, and these stress-induced regulatory events are mediated in part by SGs. This project focuses on RasGAP Binding Protein (G3BP); an RNA binding protein that nucleates SG assembly. G3BP accumulates in neurons that are largely free of classic markers of tau pathology. Previous research on G3BP has almost entirely centered on its oncogenic activity, as it activates the Ras family of GTPases to control genes for cell growth, differentiation and survival. However, bio-informatics points to a potential role for G3BP in neurobiology. G3BP stabilizes many transcripts, including tau mRNA, prompting us to investigate whether G3BP exhibits similar actions in neurodegeneration. We now report that G3BP exhibits protective effects against Aβ42 and tau-induced changes in AMPA receptor activity.

The neuroprotective role of Klotho protein on brain-derived primary cells.

Ella Zeldich and Carmela R. Abraham
Boston University School of Medicine, Boston

The Klotho (KL) gene was identified in 1997 as a gene mutated in the KL mouse, which displays extremely shortened life span with multiple disorders resembling human aging KL is mainly expressed in brain and kidney, but the precise function of KL in the brain is unknown. Our lab previously determined that KL is decreased in the brain white matter of aged non-human primates, rodents and mice and KL knockout mice exhibit significantly impaired myelination of the optic nerve and corpus callosum. In addition, it has been demonstrated recently that KL protein also protects cells from oxidative stress, which is involved in the pathogenesis of various disease conditions including ischemia, inflammation and many neurodegenerative disorders including Alzheimer's and Parkinson disease. To further understand the potential neuroprotective role of KL in brain tissues, our lab performed a high throughput screen to identify small molecules that can modulate KL expression. Two compounds were identified that elevate both KL transcription and KL protein expression. These compounds, as well as recombinant mouse KL, were able to rescue the neuronal cells from oxidative stress induced by glutamate. In addition, our preliminary results showed an effect of these compounds on oligodendrocytes maturation and differentiation. Taken together our results demonstrated the ability of endogenous KL protein, recombinant KL and KL induced by the compounds to alleviate oxidative stress and to affect neural cell maturation. Our results could be the first step toward the development of therapeutic agents that will act through the neuroprotective properties of KL.

Understanding the functional connectivity in Alzheimer's disease with optogenetic approach

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Most cognitive functions are orchestrated by brain activities across a large-scale neural network, rather than within a single isolated brain region. Accordingly, cognitive dysfunctions observed in Alzheimer's disease (AD) patients are not only due to the damage within an individual brain region, but also due to the damage of functional connectivity, the temporal coupling of neural activities between spatially remote brain regions. In the current study, the functional connectivity between prefrontal cortex (PFC) and hippocampus were studied in AD transgenic mice (APPPS1 mice) not only because PFC- and hippocampus-related functions (e.g. reversal learning and episodic memory) are compromised in AD, but also because that one presumable culprit of AD, amyloid-beta, accumulates in these regions at the early stage of AD. Electrophysiological activities in both regions were recorded simultaneously in head-fixed awake 12-month-old APPPS1 mice and wild-type control. Functional connectivity, calculated by multi-taper coherence analysis, showed a trend of an increase in APPPS1 mice, compared to the wild-type mice. Moreover, we are investigating the detail mechanism of functional connectivity with optogenetic tools, which can selectively activate or silence neurons with light. An automated mice behavior chamber adapted for ontogenetic has also been built to record and manipulate the neural activities in real time during cognitive behavior tests, such as a visual discrimination reversal test. Combining the electrophysiological, behavioral, and optogenetic approaches, this study will advance our understanding in the role of functional connectivity in AD-related cognitive dysfunction soon.