afar american federation for aging research

NIH National Institute on Aging

The Rosalinde and Arthur Gilbert Foundation

NEW INVESTIGATORS IN ALZHEIMER'S DISEASE GRANTEE MEETING

WEDNESDAY, SEPTEMBER 25 – FRIDAY, SEPTEMBER 27, 2019

UCLA Luskin Conference Center
Los Angeles, California

@AFARorg

OBJECTIVES

- Provide an introduction to the grantees funded by The Rosalinde and Arthur Gilbert Foundation and the National Institute on Aging
- Gain a better understanding of how this support influences the career development and research progress of these investigators
- Provide an opportunity for the grantees to share and disseminate their research and experiences as new investigators
- Discuss opportunities for linking Alzheimer's disease research with treatment, clinical management, prevention, and policy change
- Build a learning community to facilitate sharing of research and professional networking.

WEDNESDAY, SEPTEMBER 25

3:00 – 3:30 p.m.	**Registration, group gathers**	*Centennial Prefunction*
3:30 – 4:00 p.m.	**Welcome and Opening Remarks**	*Centennial CD*

George M. Martin, MD
Professor Emeritus, University of Washington

Nina Silverberg, PhD
Director, Alzheimer's Disease Centers Programs
Division of Neuroscience
National Institute on Aging, National Institutes of Health

Liz Schwarte, MPH
Ad Lucem Consulting

4:00 – 5:30 p.m. **DataBlitz! Session**

The academic equivalent of speed dating – a fast-track vehicle to understand research and possible synergies with others. Each session involves a research theme, with current grantees each presenting their research in eight minutes or less – the time limit will be strictly enforced. Groups will be arranged by content area. Meeting participants who are not presenting are encouraged to join any of the groups. Alumni will moderate the sessions.

Pinnacle Room - Group 1
Roberto Fernandez, moderator

Innovation Room – Group 2
Todd Cohen, moderator

Odyssey Room – Group 3
Kim Green, moderator

Pathways Room – Group 4
Catherine Kaczorowski, moderator

5:30 – 7:30 p.m. **Networking Reception** (heavy hors d'oeuvres) *Courtyard South*

THURSDAY, SEPTEMBER 26

7:30 – 8:30 a.m. **Breakfast** *Plateia A*

8:30 – 9:00 a.m. **DataBlitz! 'Wrap-up'** *Centennial CD*

Presented by alumni moderators, highlighting new and exciting research.

9:00 – 9:15 a.m. **Welcome from The Rosalinde and Arthur Gilbert Foundation**

Martin H. Blank, Jr.
Trustee & COO

Richard S. Ziman
Trustee & CEO

9:15 – 10:15 a.m. **The IDEAS Study: Translating Research Advances into Clinical Practice**

Gil Rabinovici, MD
Edward Fein & Pearl Landrith Distinguished Professor
Departments of Neurology, Radiology and Biomedical Imaging
University of California, San Francisco

10:15 – 10:45 a.m. Break *Centennial Prefunction*

10:45 a.m. – 12:15 p.m. **Available Resources through NIA Centers**

Walter A. Kukull, PhD
Professor of Epidemiology, University of Washington
Director, **National Alzheimer's Coordinating Center (NACC)**

Gerard D. Schellenberg, PhD
Professor of Pathology and Laboratory Medicine
Perelman School of Medicine, University of Pennsylvania
PI: **The National Institute on Aging Genetics of Alzheimer's Disease Data Storage Site (NIAGADS)**

Tatiana Foroud, PhD
Joe C. Christian Professor and Chair of the Department of Medical and Molecular Genetics
Indiana University School of Medicine
Director, **National Centralized Repository for Alzheimer's Disease and Related Dementias (NCRAD)**

12:15 – 12:30 p.m. Break

12:30 – 1:30 p.m. Networking Lunch *Plateia A*

1:30 – 3:00 p.m. **Career development breakouts: Consultancies and Aims Page workshops**

Legacy A – Consultancies – Group 1
Legacy B – Consultancies – Group 2
Illumination Room – Aims Page Workshop – Group 1
Enlightenment Room – Aims Page Workshop – Group 2

3:00 – 3:30 p.m. Break *Centennial Prefunction*

3:30 – 5:00 p.m. **NIA Funding Initiatives in Alzheimer's Disease** *Centennial CD*
Nina Silverberg, PhD
Director, Alzheimer's Disease Centers Program
Division of Neuroscience
National Institute on Aging, National Institutes of Health

Partha Bhattacharyya, PhD (via Zoom Online Meetings)
Program Director
Division of Behavioral and Social Research (DBSR)
National Institute on Aging, National Institutes of Health

Lisa Opanashuk, PhD (via Zoom Online Meetings)
Program Officer
Division of Neuroscience
National Institute on Aging, National Institutes of Health

5:00 – 6:30 p.m. **Free time/one-on-one mentoring (sign up in advance)**

6:30 – 8:30 p.m. Dinner *Plateia A*

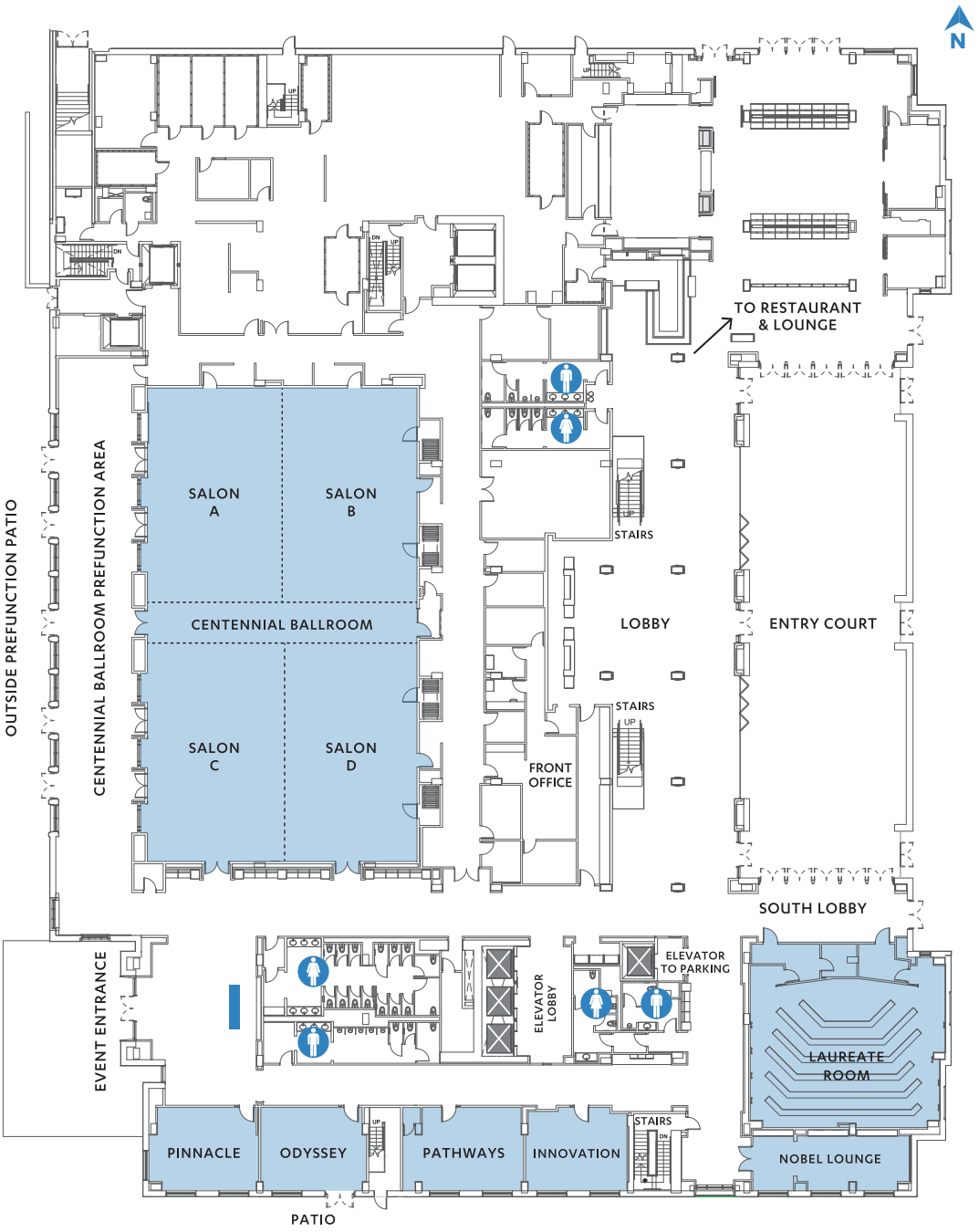
FRIDAY, SEPTEMBER 27

7:00 – 8:30 a.m. Breakfast *Plateia A*

Adjourn

MEETING SPACE: LEVEL 1

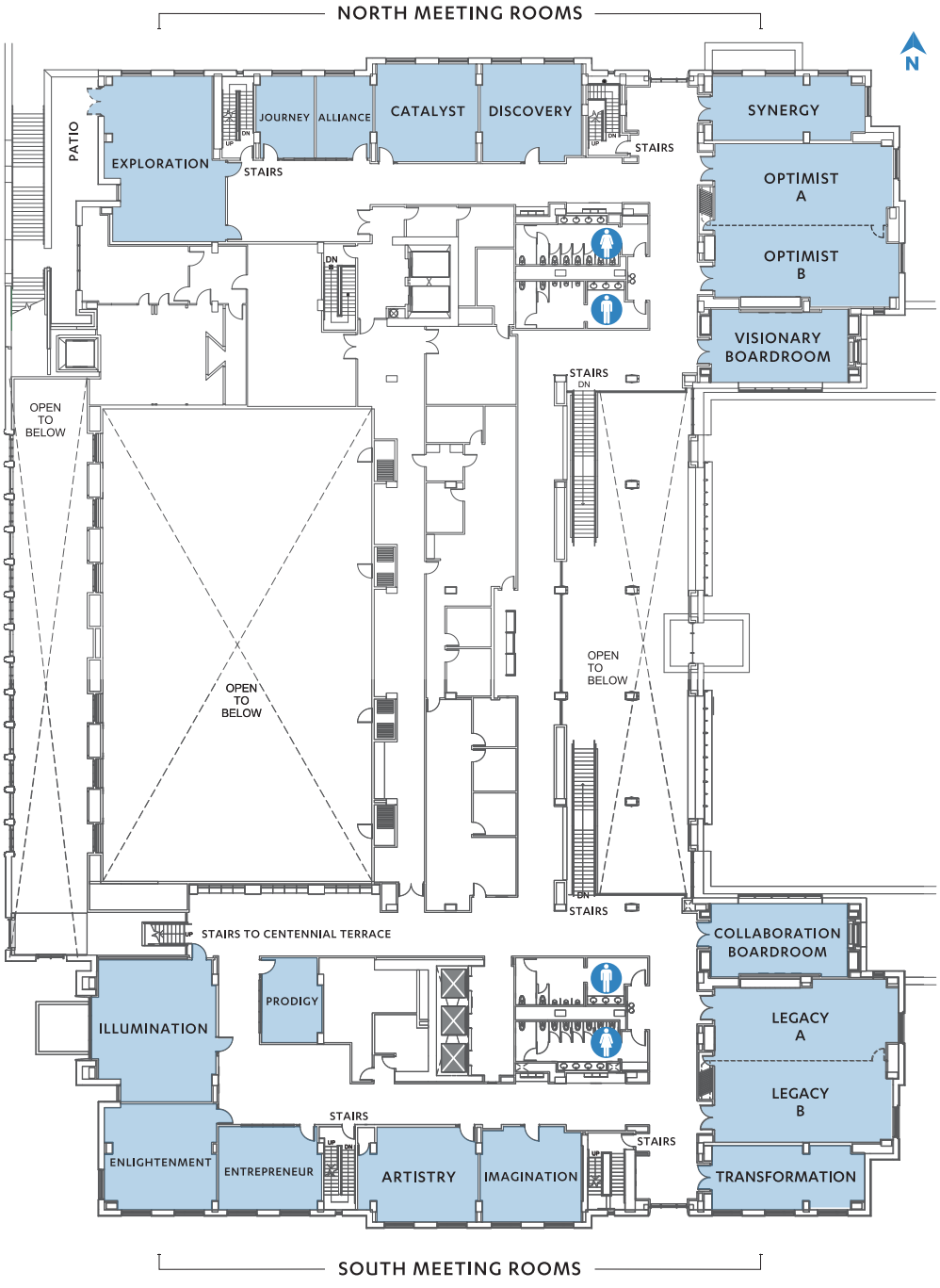
UCLA LUSKIN CONFERENCE CENTER



For information on advance reservations for the UCLA Meyer and Renee Luskin Conference Center, please call 855-LCC-UCLA (855-522-8252) or visit LuskinConferenceCenter.UCLA.edu

MEETING SPACE: LEVEL 2

UCLA LUSKIN CONFERENCE CENTER



For information on advance reservations for the UCLA Meyer and Renee Luskin Conference Center, please call 855-LCC-UCLA (855-522-8252) or visit LuskinConferenceCenter.UCLA.edu

2019 New Investigator in Alzheimer's Disease
Meeting Participant List

Role	FIRST:	LAST:	INSTITUTION:	E-MAIL:
NIA Grantee	Halima	Amjad	Johns Hopkins University	hamjad1@jhmi.edu
NIA Grantee	James	Andrews	University of Washington	jsa1@uw.edu
NIA Grantee	Alicia	Arbaje	Johns Hopkins University School of Medicine	aarbaje@jhmi.edu
NIA	Partha	Bhattacharyya	National Institute on Aging, National Institutes of Health	bhattacharyyap@mail.nih.gov
foundation	Martin	Blank, Jr.	The Rosalinde and Arthur Gilbert Foundation	www.thegilbertfoundation.org
NIA Grantee	Siu-Hung (Wallace)	Chick	University of Colorado Denver	WALLACE.CHICK@CUANSCHUTZ.EDU
Alumni scholar	Todd	Cohen	University of North Carolina at Chapel Hill	toddcohen@neurology.unc.edu
NIA Grantee	Constanza	Cortes	Duke University	constanza.cortes@duke.edu
NIA Grantee	Dana	Crawford	Case Western Reserve University	dana.crawford@case.edu
foundation	Robbie	Diamond	The Rosalinde and Arthur Gilbert Foundation	www.thegilbertfoundation.org
NIA Grantee	Sudipto	Dolui	University of Pennsylvania	sudiptod@pennmedicine.upenn.edu
Alumni scholar	Roberto	Fernandez-Romero	The University of Tennessee Medical Center	rfernandez@utmck.edu
SPEAKER	Tatiana	Foroud	Indiana University School of Medicine	tforoud@iu.edu
Alumni scholar	Kim	Green	University of California, Irvine	kngreen@uci.edu
current scholar	Congcong	He	Northwestern University	congcong.he@northwestern.edu
Staff	Hattie	Herman	American Federation for Aging Research	hattie@afar.org
Alumni scholar	Jason	Hinman	UCLA	jhinman@mednet.ucla.edu
Alumni scholar	Fenghua	Hu	Cornell University	fh87@cornell.edu
Alumni scholar	Catherine	Kaczorowski	The Jackson Laboratory	Catherine.Kaczorowski@jax.org

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Meeting Participant List

Role	FIRST:	LAST:	INSTITUTION:	E-MAIL:
Alumni scholar	Daniel	Kaganovich	Hebrew University of Jerusalem	dan@cc.huji.ac.il
SPEAKER	Walter	Kukull	University of Washington	kukull@uw.edu
NIA Grantee	Lei	Liu	Brigham and Women's Hospital	lliu35@bwh.harvard.edu
SPEAKER	George	Martin	University of Washington	Gmmartin@uw.edu
foundation	Janis	Minton	The Rosalinde and Arthur Gilbert Foundation	www.thegilbertfoundation.org
Alumni scholar	Robert	Morrison	Loyola University	rmorrison@luc.edu
NIA Grantee	Nathan	Mortimer	Illinois State University	ntmorti@ilstu.edu
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NIA Grantee	Karen	Nuytemans	University of Miami, Miller School of Medicine	knuytemans@med.miami.edu
NIA	Lisa	Opanashuk	National Institute on Aging, National Institutes of Health	lisa.opanashuk@nih.gov
foundation	Sean	Ostrovsky	The Rosalinde and Arthur Gilbert Foundation	www.thegilbertfoundation.org
NIA Grantee	David	Plante	University of Wisconsin-Madison	dplante@wisc.edu
Alumni scholar	Ling	Qi	The University of Michigan Medical School	lingq@med.umich.edu
SPEAKER	Gil	Rabinovici	University of California, San Francisco	Gil.Rabinovici@ucsf.edu
NIA Grantee	Annalise	Rahman-Filipiak	University of Michigan	rahmanam@med.umich.edu
NIA Grantee	Martin	Riccomagno	University of California, Riverside	martinmr@ucr.edu
Alumni scholar	Subhojit	Roy	University of California, San Diego	sroy@ucsd.edu
Alumni scholar	Yonatan	Savir	Technion	yoni.savir@technion.ac.il
SPEAKER	Gerard	Schellenberg	Perelman School of Medicine, University of Pennsylvania	gerardsc@pennmedicine.upenn.edu

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Meeting Participant List

Role	FIRST:	LAST:	INSTITUTION:	E-MAIL:
staff	Liz	Schwarte	Ad Lucem Consulting	liz@adlucemconsulting.com
NIA Grantee	Ophir	Shalem	Children's Hospital of Philadelphia	shalemo@upenn.edu
Alumni scholar	Yin	Shen	University of California, San Francisco	Yin.Shen@ucsf.edu
NIA	Nina	Silverberg	National Institute on Aging, National Institutes of Health	silverbergn@mail.nih.gov
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NIA Grantee	Manju	Subramanian	Boston University School of Medicine	manju.subramanian@bmc.org
current scholar	Vivek	Swarup	University of California, Irvine	vswarup@uci.edu
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NIA Grantee	Tobias	Ulmer	University of Southern California	tulmer@usc.edu
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Alumni scholar	Marc	Vermulst	University of Southern California	vermulst@usc.edu
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NIA Grantee	Zhen	Zhao	University of Southern California	zzhao@usc.edu
foundation	Richard	Ziman	The Rosalinde and Aurthur Gilbert Foundation	www.thegilbertfoundation.org
NIA Grantee	Megan	Zuelsdorff	University of Wisconsin-Madison	mlzuelsd@wisc.edu

Data Blitz!
Group 1: Pinnacle Room
Moderator: Roberto Fernandez

First	Last	Institution	Project
Halima	Amjad	Johns Hopkins University	Acute care utilization in older adults living undiagnosed or unaware of dementia
James	Andrews	University of Washington	Sarcopenia and the Development of Hospital-Associated ADL Disability Among Older Adults in the Health ABC Study
Alicia	Arbaje	Johns Hopkins University School of Medicine	Medication management during hospital-to-home transitions of older adults with Alzheimer's Disease and related dementias (ADRD)
Karen	Nuytemans	University of Miami, Miller School of Medicine	Genetics of frontotemporal dementia in diverse cohort enriched for Hispanic patients
Annalise	Rahman-Filipiak	University of Michigan	Development of a Culturally-Informed Measure of Alzheimer's Risk Disclosure Needs and Preferences: Stage I of the SHARE(D) Project
Judith	Tate	The Ohio State University	A Problem Solving Intervention for Post-ICU Cognitive Impairment in Older Adults
Megan	Zuelsdorff	University of Wisconsin-Madison	Social-biological dimensions of ADRD risk and resilience in a Native American cohort

Data Blitz!
Group 2: Innovation Room
Moderator: Todd Cohen

First	Last	Institution	Project
Siu-Hung (Wallace)	Chick	University of Colorado Denver	Development of a screening strategy to identify Aß-resistance genes
Jason	Hinman	UCLA	Ischemic axonal injury up-regulates MARK4 in cortical neurons and primes tau phosphorylation and aggregation.
Lei	Liu	Brigham and Women's Hospital	A Novel Cellular Complex of BACE1 and γ-Secretase Sequentially Generates Aβ from APP
Tal	Nuriel	Columbia University Medical Center	Investigating the effects of APOE4 expression in AD-relevant brain regions
Andrea	Soranno	Washington University in St. Louis	Single-molecule conformational analysis of Apolipoprotein E
Manju	Subramanian	Boston University School of Medicine	Association of Cognition to Amyloid- β and Tau in the Vitreous Humor
Tara	Tracy	The Buck Institute	Impact of KIBRA signaling on memory in tauopathy
Ching-On	Wong	UTHealth Medical School	An Endolysosomal Transmembrane Protein Regulates Glial Cell Metabolism and ApoE Secretion
Zhen	Zhao	University of Southern California	Genetic interaction of PICALM and APOE in Alzheimers disease

Data Blitz!
Group 3: Odyssey Room
Moderator: Kim Green

First	Last	Institution	Project
Dana	Crawford	Case Western Reserve University	T-cell receptor repertoires and Alzheimer's disease
Congcong	He	Northwestern University	Autophagic regulation of microglial activation and neuroinflammation
Daniel	Kaganovich	Hebrew University of Jerusalem	Stress Granules mediate lipid metabolism by inhibiting fatty acid oxidation and directing fatty acid import into Lipid Droplets
Nathan	Mortimer	Illinois State University	A Drosophila Model to Understand the Role of Innate Immunity in Alzheimer's Disease
Ling	Qi	The University of Michigan Medical School	The Sel1L-Hrd1 complex manages endoplasmic reticulum-mitochondria contacts and mitochondrial dynamics
Yonatan	Savir	Technion	The effect of cellular aging on the unfolded protein response in changing environments
Ophir	Shalem	Children's Hospital of Philadelphia	Dissecting the mechanisms that underlie mislocalization and aggregation or RNA binding proteins in neurodegenerative diseases using marker based CRISPR screens

Data Blitz!
Group 4: Pathways Room
Moderator: Catherine Kaczorowski

First	Last	Institution	Project
Constanza	Cortes	Duke University	Enhanced Skeletal Muscle Proteostasis as a Modulator of CNS Aging and Alzheimer's Disease
Sudipto	Dolui	University of Pennsylvania	Analysis Strategies for ADNI ASL Data
Martin	Riccomagno	University of California, Riverside	Novel combinatorial approaches to selectively target reactive astrocytes
Subhojit	Roy	University of California, San Diego	Functional synaptic interacting partners for alpha-synuclein
Yin	Shen	University of California, San Francisco	Charting the 3D epigenome in Human Neural Cells to Reveal Contributions of Genetic Variants to Complex Neurological Disorders
Vivek	Swarup	University of California, Irvine	Integrative genomics approach identifies conserved transcriptomic networks in Alzheimer's disease
Tobias	Ulmer	University of Southern California	Structural basis of CD33 receptor signaling in Alzheimer's disease

Aims Page Workshops
Thursday, September 26, 1:30 - 3:00 pm

Group 1
Room: Illumination

Moderators:
Jason Hinman
Fenghua Hu
Ling Qi

Participants
Connie Cortes
Vivek Swarup
Tobias Ulmer
Wallace Chick
Tara Tracy

Group 2
Room: Enlightenment

Moderators:
Bud Kukull
Yin Shen
Todd Cohen

Participants
David Plante
Lei Liu
Annalise Rahman-Filipiak
Karen Nuytemans
James Andrews

Consultancies
Thursday, September 26, 1:30 - 3:30 pm

Moderator Group 1: Robert Morrison
Room: Legacy A

Participants:

Halima Amjad	Johns Hopkins University
Sudipto Dolui	University of Pennsylvania
Congcong He	Northwestern University
Judith Tate	The Ohio State Univresity
Megan Zuelsdorff	University of Wisconsin-Madison
Martin Riccomagno	University of California, Riverside

Other Attendees

Roberto Fernandez-Romero	The University of Tennessee Medical Center
Catherine Kaczorowski	The Jackson Lab
George Martin	University of Washington
Yonatan Savir	Technion
Manju Subramanian	Boston Univeristy School of Medicine

Moderator Group 2: Subhojit Roy
Room: Legacy B

Participants:

Alicia Arbaje	Johns Hopkins University
Nathan Mortimer	Illinois State University
Ophir Shalem	Children's Hopsital of Philadelphia
Cing-On Wong	UT Health Medical School
Dana Crawford	Case Western Reserve University
Tal Nuriel	Columbia University Medical Center

Other Attendees

Kim Green	University of California, Irvine
Daniel Kaganovich	Hebrew University of Jerusalem
Liz Schwarte	Ad Lucem Consulting
Nina Silverberg	NIA
Marc Vermulst	University of Southern California
Andrea Soranno	Washington University in St. Louis

How a Consultancy Session works:
This is a popular and effective group problem-solving activity known as a "consultancy." This is structured to enable a set of people with a variety of knowledge and expertise to provide support, new perspectives, and ideas to one another, particularly around an important or difficult challenge.

Each Scholar will get approximately 10 minutes: 2-3 minutes or so to present what he/she views as **the major career challenge he/she is facing (or will soon face)**. This may include, but is certainly not limited to:

- Time Management
- Balancing Career and Family
- Strategies for promotion
- Balancing research, clinical, teaching and administrative responsibilities
- Issues related to your lab/team members (supervision, quality control, hiring, firing, disciplinary action, etc.)
- Transitioning relationship with your mentor(s).
- Finding/solidifying your niche, area of expertise

Following each Scholar's presentation, the group will ask clarifying questions for the next one-two minutes. For the bulk of the remainder of the time, the Scholar will receive feedback and advice from the group. In the last minute or so, the Scholar will then have a chance to respond to the ideas presented.

We will follow a strict timetable, so that each person will have the same opportunity for constructive feedback.

Acute care utilization in older adults living undiagnosed or unaware of dementia

Halima Amjad, David L. Roth, Jennifer L. Wolff, Julie P.W. Bynum, Quincy M. Samus
Johns Hopkins University School of Medicine
Division of Geriatric Medicine and Gerontology
MFL Center Tower, Room 719
5200 Eastern Avenue
Baltimore, MD 21224

Background: Most individuals with dementia are undiagnosed or they/their families are unaware of the diagnosis. Implications of dementia diagnosis and awareness are poorly understood. Our objective was to determine whether undiagnosed dementia or unawareness increases risk of hospitalization or emergency department (ED) visits, outcomes with recognized risk in diagnosed dementia.

Methods: We linked National Health and Aging Trends Study (NHATS) data to fee-for-service Medicare claims for 4,311 community-living participants in the nationally representative cohort. Based on self or proxy report of diagnosis, a proxy dementia screening questionnaire, cognitive testing, and presence of a Medicare claims diagnosis, participants were classified as having no dementia or probable dementia for which they were (1) undiagnosed, (2) unaware but diagnosed, or (3) aware and diagnosed. Cox proportional hazards models evaluated hospitalization and ED visit risk by time-varying dementia diagnosis and awareness status, adjusting for sociodemographic characteristics, functional impairment, medical comorbidities, and prior hospitalization.

Results: Compared to no dementia, persons with dementia who were unaware but diagnosed had greater risk of hospitalization (HR 1.66, 95% CI 1.26-2.19) and ED visits (HR 1.63, 95% CI 1.28-2.08). Persons unaware but diagnosed also had greater risk compared to persons aware and diagnosed (hospitalization HR 1.34, 95% CI 0.98-1.82; ED HR 1.38, 95% CI 1.05-1.83). Persons with undiagnosed dementia demonstrated hospitalization risk similar to persons with no dementia (HR 1.02, 95% CI 0.79-1.31) and similar or potentially lower than persons aware and diagnosed (HR 0.82, 95% CI 0.61-1.10); ED visit findings were similar.

Conclusions: Results suggest that being unaware of diagnosed dementia may affect healthcare utilization while undiagnosed dementia does not. Strategies to improve communication and understanding of dementia upon diagnosis could potentially reduce hospitalizations and ED visits in a vulnerable population.

Key words: Alzheimer’s disease, dementia, health care utilization

Title: Sarcopenia and the Development of Hospital-Associated ADL Disability Among Older Adults in the Health ABC Study

Authors: James S. Andrews[1], Ellen Caldwell[1], Catherine Hough[1]

Affiliations: [1]University of Washington

Keywords: Sarcopenia, Hospitalization, Activities of Daily Living, Disability

Abstract:
Half of all physical disability among older adults arises during hospitalization. We examined whether sarcopenia is a risk factor for hospital-associated activity of daily living (ADL) disability in the Health ABC Study. Individuals hospitalized during the first 5 years of follow-up were analyzed (n=938 men, 841 women). Low appendicular lean mass to body mass index ratio (ALM_{BMI}; <0.789 men, <0.512 women) and low grip strength (<26 kg men, <16kg women) were assessed at the annual visit prior to hospitalization. Hospital-associated ADL disability was defined as becoming unable or needing help to perform any of 5 ADLs (walking 1/4 mile, climbing 10 steps, getting in/out of bed/chairs, bathing, and dressing) or death at the next annual visit following hospitalization. Logistic regression modeled associations of pre-hospitalization low ALM_{BMI} and low grip strength with development of ADL disability following hospitalization with and without adjusting for covariates (age, race, cognitive function, physical activity, smoking status, falls, and medical comorbidities). 17 % of men and 19% of women developed the primary outcome, including 10% of men and 8% of women who died. Low grip strength was associated with increased risk of worsening ADL function or death in men (adjusted OR: 2.1 (1.2-3.7)), but not in women (aOR: 1.2 (0.7-2.1). Low ALM_{BMI} was not associated with worsening ADL function or death in men (aOR: 1.0 (0.6-1.5) or women (aOR: 1.1 (0.7-1.9). While future studies are needed, low grip strength appears to be an important risk factor for the development of hospital-associated ADL disability among older men.

Medication management during hospital-to-home transitions of older adults with Alzheimer's Disease and related dementias (ADRD)

Arbaje AI, Keita M, Keller SC, Gurses AP, Samus Q.
Johns Hopkins University School of Medicine, Baltimore, Maryland

Background: Care transitions are the movement of a person from one healthcare setting to another. The hospital-to-home transition is a high-risk period, especially for medication errors and adverse events and for persons with Alzheimer's disease and related dementias (ADRD). There is relatively little research to guide care transition improvement efforts for the ADRD population. An area of particular risk for older adults with ADRD during the hospital-to-home transition is role ambiguity regarding medication management (MM). Role ambiguity in MM occurs when the roles of older adults with ADRD, informal caregivers, and healthcare providers remain without a clear definition of who is responsible for completion of MM-related tasks, such as medication reconciliation.

Objectives: The goal of the current study is to: (1) identify issues related to role ambiguity regarding medication management that threaten the safety of older adults with ADRD during hospital-to-home transitions, (2) increase situational awareness by alerting skilled home health care organizations and providers in real time of risky care transitions possibly resulting in poor patient satisfaction or rehospitalization, and (3) engage stakeholders to develop a set of strategies specific to ADRD to decrease role ambiguity and support MM during this high-risk transition.

Methods: The current study utilizes a prospective cohort design and a participatory ergonomics approach from the field of human factors engineering. Older adults with ADRD, who were recently discharged from the hospital and referred to receive home health care, and their caregivers are being enrolled in the study. While in the home, researchers observe the start of care visit with the older adult, caregiver, and home health clinician. During this visit, researchers obtain data on critical MM tasks and categorize factors shaping older adult and informal caregiver expectations for MM task distribution. During this visit, researchers also administer the Index of Home Health Transition Quality to identify threats to older adults' safety. The clinician overseeing the start of care visit also completes the survey. Over a two-week period, beginning at the end of the start of care visit, the older adult and caregiver complete a diary on MM tasks.

Post enrollment of the initial cohort of older adult and caregiver dyads, researchers form an intervention refinement team (IRT) consisting of older adults with ADRD, informal caregivers, and healthcare providers involved in hospital-to-home transitions. The IRT meets three times over the course of 3 to 6 months to develop strategies on improving MM and rate each strategy according to (1) importance to reducing role ambiguity, (2) likelihood of effectiveness in supporting MM, and (3) level of actionability.

Results: We began recruitment in August, 2019 and will report on the following items and lessons learned thus far: ongoing status of recruitment and consent; lessons learned about identifying ADRD patient in the electronic medical record; use of observation instrument and taking of photographs in the home; acceptance and use of solicited participant diaries; participants' preferred methods for diary completion; and care transitions ratings by clinician and patients/caregiver dyads.

Conclusions/Policy Implications: Results support the need for ongoing work to develop and test a behavioral or technological solution to address unmet needs and safety risks during the hospital-to-home transition for older adults with ADRD. Study findings can inform the development of policies to address medication errors for older adults with ADRD transitioning from the hospital to home.

Key words: older adults, care transitions, medication management, dementia

Development of a screening strategy to identify Aß-resistance genes

Chick WS[1], Link CD[2], and Potter H[3].

[1] Department of Cell and Developmental Biology, [3] Department of Neurology, University of Colorado Anschutz Medical Campus, [2] Department of Integrative Physiology, University of Colorado Boulder

ABSTRACT

Genetic factors play an important role in the pathogenesis and progression of Alzheimer's disease (AD). One hallmark of AD is the development of amyloid ß (Aß) neuritic plagues and fibrils, which is believed to play a central role in neuronal cell loss. Most people of advanced age develop amyloid plagues and fibrils in their brains, but only a subset of the aging population develops clinical signs of AD. This finding suggests the existence of gene regulatory pathways controlling disease development and potentially disease severity. Protective mechanisms against AD appear to exist, but have not been characterized at the genetic or molecular level. Herein, we propose to screen for genes/pathways in mammalian cells that confer protection against AD by using resistance to Aß cytotoxicity as a surrogate. Our laboratory has generated a library of mouse mutant embryonic stem (ES) cells, comprising 42,000 independent mutants mutagenized by *piggyBac* (*PB*) transposon-mediated gene entrapment. We will utilize Aß42 oligomers for the selection of resistance mutants in a forward genetic screen via a high-throughput ES cell platform. This novel approach will allow for an unbiased interrogation of the genome, potentially revealing novel functional pathways protective against AD, which may provide new insights into therapeutic targets for AD treatment. Our long-term plan is to screen the entire library (42,000 mutants) to isolate Aß resistance mutants and identify the underlying genes and pathways. In this application, we will establish the necessary techniques required to select Aß resistance and to identify resistance genes; a pilot screening will be conducted as a proof of principle. Aß affects neurons, so we will differentiate our mutant ES cells into neurons, followed by selection for Aß resistance in 96-well plates. Mutants showing a significant increase in survival in the presence of Aß will be isolated for extensive characterizations, including the identification of the mutated gene(s), the nature of the mutational events (null, partial loss of function, or gain of function), and the confirmation of the causal relationship between the disrupted gene and the Aß resistance phenotype. Once those genes are identified, their functions can also be confirmed in human neurons by engineering the mutations using CRISPR. This study pursues an innovative approach encompassing the use of stem cells, a transposon, and forward genetics to identify genes/pathways protective against AD. Furthermore, the ES cells carrying AD-protective mutations may be used in subsequent experiments to generate the corresponding mice for *in vivo* studies.

Enhanced Skeletal Muscle Proteostasis as a Modulator of CNS Aging and Alzheimer's Disease

Presenting Author: Cortes CJ[1],

Co-Authors: Wertman VD[1], Matthews I[1], Gromova A[1,4], Bai K[1], Tucker HA[1], LA Spada AR[1-3].

Affiliations: Departments of Neurology[1], Neurobiology[2], Cell Biology[3], Duke University School of Medicine, Biomedical Sciences Graduate Program[4], University of California San Diego

Keywords: aging, autophagy, proteostasis, skeletal muscle, myokine

Proteostasis is essential for cell health and viability, and involves complex and highly conserved networks that regulate protein translation, protein folding, and protein degradation. A decline in proteostasis function is one of the features of aging tissues, particularly of the central nervous system (CNS). Indeed, the aging brain is particularly sensitive to proteotoxic stress, as demonstrated by the high number of age-associated neurodegenerative disorders characterized by protein misfolding and aggregation, including Alzheimer's disease (AD). The regulation of non-cell autonomous proteostasis has recently arisen as a novel mechanism for the modulation of systemic homeostasis in worms and flies, and is postulated to have important organismal effects on metabolism and aging. However, to date, there are no studies addressing the existence and activity of these pathways in mammals, and their potential effects on the aging brain. Transcription Factor E-B (TFEB) is a powerful master transcription factor regulator of proteostasis, integrating autophagy and bioenergetics. We recently derived transgenic mice that moderately overexpress TFEB in skeletal muscle, and discovered that the resulting enhanced skeletal muscle proteostasis function can significantly ameliorate proteotoxicity in the aging CNS and also improve cognition and memory in aging mice. Our current work aims address muscle-to-brain cell-nonautonomous proteostasis signaling in the context of healthy brain aging and in Alzheimer's disease, and uncover novel peripheral pathways promoting neuroprotection in the context of AD.

T-cell receptor repertoires and Alzheimer's disease

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Alzheimer's disease (AD), a progressive neurodegenerative disease characterized by memory loss and impaired mental function, affects approximately 5.7 million residents and is the sixth leading cause of death in the United States. The number of AD cases is expected to increase two to three fold in the near future as the number of older adults increases in this aging population. The cause of AD remains unknown, but several risk factors have been identified including poor vascular health status, physical and mental inactivity, depression, smoking, low education attainment, among other modifiable risk factors. Known non-modifiable (genetic) risk factors for late-onset AD include the *APOE* e4 allele and at least 19 common variants identified from genome-wide association studies.

The strongest of the known genetic risk factors is the *APOE* e4 allele. *APOE* normally encodes a product that regulates cholesterol in the brain, and it is known to bind to the amyloid-β peptide, the major component of amyloid plaques found in AD patients. Carriers of the e4 allele have increased brain amyloid-β plaque deposition compared with non-carriers. Based on these observations, beta amyloid deposition is a major target for the development of therapies and secondary prevention strategies for AD. To date, strategies targeting the progression of AD dementia among pre-clinical AD patients have been disappointing.

The lack of effective treatment strategies may be due to an incomplete biological understanding of the basis of AD risk and disease development and progression. Recently, both genetic and experimental data have established the importance of innate and adaptive immunity in AD risk. In studies of model organisms, immune deficient mice (characterized by lack of T, B, and natural killer cells) exhibit an increase in amyloid-β pathology, a phenotype ameliorated with bone marrow transplantation. Despite the strength of this emerging evidence, no studies have yet characterized AD risk or progression using both known AD-risk variants and adaptive immune response profiles in humans.

To fill this gap in knowledge, we are characterizing the T-cell receptor repertoire representing current and past adaptive immune responses among cases of AD and controls to further the biological understanding of the AD process. Cases and controls are being drawn from a larger existing study of AD and successful aging in the Amish residing in Ohio and Indiana. We are in the process of selecting participants for somatic TCR sequencing who have been cognitively screened with the modified mini-mental state exam (3MS) education adjusted examination score who also have genome-wide genotyping or sequencing data. We expect that AD cases will have a greater genetic burden for AD compared with controls and a poor adaptive immune response as reflected by restricted T-cell receptor repertoires, either as an independent AD risk factor or modifier of the known genetic risk for AD.

Key words: T-cell receptor, Alzheimer's disease, Amish, sequencing, genome-wide, adaptive immune response

Analysis Strategies for ADNI ASL Data

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Introduction: The etiology of Alzheimer's disease (AD) is likely multifactorial and appears to interact with vascular pathologies.[1] Cerebral blood flow (CBF, expressed in ml/100g/min) provides a surrogate biomarker of cerebrovascular function. Moreover CBF and glucose metabolism are tightly coupled;[2] hence, CBF also reflects neurodegenerative effects on synaptic activity. Arterial Spin Labeled (ASL) perfusion MRI[3] provides non-invasive quantification of CBF and can readily be acquired along with structural MRI, which is almost universally carried out in patients with suspected neurodegenerative conditions. However, ASL has low signal to noise ratio and can have severe artifacts with sub-optimal acquisitions. Alzheimer's Disease Neuroimaging Initiative (ADNI) is a multisite study with the goal of validating biomarkers[4] and included ASL MRI in both the ADNI 2 and 3 phases of the study. However, ADNI used multiple ASL sequences in multiple scanning platforms to exploit the advantage of using scanner product sequences, which are not always of optimal or comparable quality. We aim to develop strategies of automated quality control, data cleaning, and analysis to take full advantage of this dataset. This will enable our main goal of the project, which is to study the longitudinal trajectory of CBF across the AD continuum. We present some preliminary results here.

ASL data processing: We developed two signal processing strategies, SCORE[5] and SCRUB,[6] for 2D pulsed ASL, which is one of the Siemens product ASL sequences and the only sequence used in ADNI2. Fig. 1 shows CBF maps where SCORE and SCRUB successfully removed artifacts that other algorithms, such as simple averaging (SA), mean and standard deviation (MSD) based filter, and Huber's M Estimation (HME) based filter[5] failed to remove. The novel algorithms provided better test-retest reliability and improved control-patient group difference compared to other methods[5, 6].

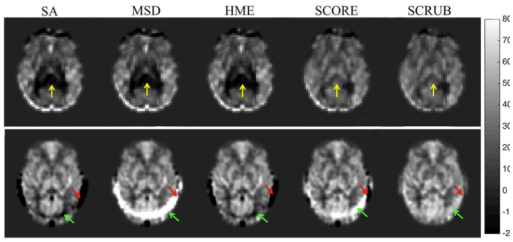

Figure 1. Visual comparison of CBF maps obtained using SCORE and SCRUB and the reference algorithms for two subjects (top and bottom row).

Automated ASL quality evaluation metric: Manual quality evaluation of CBF maps is subjective, has the potential for bias, and requires significant effort to perform in large studies such as in ADNI. We proposed a quality evaluation index (QEI) for automated objective quality evaluation of CBF maps,[7] that mimic rating of artifacts by a neuroradiologist. The left subplot of Fig. 2 shows examples of four CBF maps with neuroradiologist rating and the QEI. The QEI provided correlation value of 0.83 ($p<0.0001$) with average of two manual ratings which was comparable to that obtained between the raters (0.81, $p<0.0001$). The proposed measure correlated with test-retest reliability (right subplot of Fig. 2); scans with higher QEI showed higher intersession reliability as evident from lower coefficient of variation (CV).

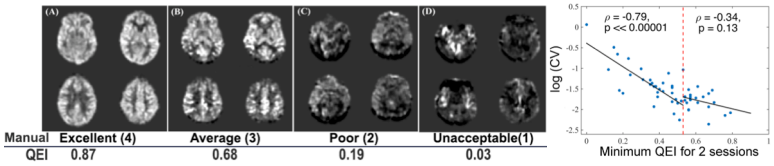

Figure 2: Left: Examples of (A) Excellent (QEI = 0.87) (B) Average (QEI = 0.68) (C) Poor (QEI = 0.19) and (D) Unacceptable (QEI = 0.03) CBF maps where the ratings are based on consensus of the two raters. Right: Scatter plot of minimum of QEI for the two sessions (worse of the two CBF maps) versus logarithm of Coefficient of Variation (CV) between CBF data obtained 3 months apart.

ASL CBF in preclinical AD: Although some previous studies with ADNI did not show CBF changes in preclinical subjects (subjects with high cerebral amyloid, but normal cognition), we reassessed the relationship using SCRUB data processing. We used a method of iteratively discarding data with poor quality as measured by QEI and computing the effect size of the difference between the amyloid positive (Aβ+) and amyloid negative (Aβ-) groups (Fig. 3). Although there was no group difference when considering all the subjects (leftmost point of Fig. 3), removal of few subjects with poor quality CBF maps showed significantly higher CBF in the Aβ+ subjects.[8] This suggests an inverse u-shaped curve of CBF from Aβ- cognitively normal adults to preclinical AD to the advanced stage of the disease, suggesting a possible compensatory CBF response to early amyloid deposition.

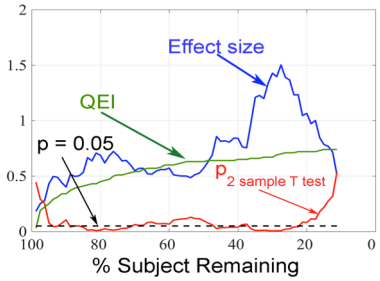

Figure 3: Effect sizes (blue) with Aβ+> Aβ- grey matter CBF, p values (red) corresponding to 2 sample T tests, and automated Quality Evaluation Indices (QEIs; green) of discarded subjects as a function of number of subjects remaining after discarding subjects with the poorest CBF scans measured using the QEI.

Discussion and conclusion: This work in progress aims at studying CBF changes along the AD continuum using novel signal processing methods. The preliminary data suggests potential of extracting useful information from the ADNI CBF maps, which are not always of optimal quality, but provide a large sample size and plethora of other useful biomarkers and cognitive scores.

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Title: Autophagic regulation of microglial activation and neuroinflammation

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Co-authors: Robert Vassar[1,2], Yoon-Jin Kim[1], Hongxue Shi[1], Meng Wang[1], Tong Xiao[1]

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Keywords: autophagy; Becn1; microglia; mitochondria; cytokine; amyloid

This ongoing research project focuses on demonstrating how autophagy, the lysosome-mediated self-degradation pathway, promotes amyloid clearance and reduces neuroinflammation in Alzheimer's disease (AD). We are able to genetically increase autophagy activity in mouse microglia, the macrophages that engulf toxic amyloids in the brain, via knocking in a point mutation in Becn1, an essential autophagy gene. Using this tool, we found that the autophagy level in microglia determines the amount of amyloid uptake and removal: high autophagy activity enhances the uptake and removal of amyloids from the environment; whereas decreasing autophagy by autophagy-blocking drugs inhibits the phagocytic capacity of microglia. Alzheimer's mouse models expressing this high-autophagy mutation show reduced inflammatory cytokine expression and neuroinflammation, which is one of the most important causal factors in AD progression. Furthermore, we found pilot evidence that hyperactive autophagy increases the biogenesis and the respiratory function of mitochondria. At the molecular level, we identified candidate proteins that act as receptors to specifically bring amyloids to the autophagy machinery for degradation. These results advanced our earlier findings to better understand how autophagy regulates amyloid metabolism and how to increase autophagy activity to improve brain function and reverse memory deficits in AD. The exciting next step is to reveal the underlying molecular mechanism by which autophagosomes target amyloid-containing secretory/phagocytic vesicles and to pharmacologically test it using autophagy-inducing compounds.

Title: Ischemic axonal injury up-regulates MARK4 in cortical neurons and primes tau phosphorylation and aggregation.

Authors: Eric Y. Hayden, Jennifer Putman, Stefanie Nunez, Woo Shik Shin, Mandavi Oberoi, Malena Charreton, Suman Dutta, Zizheng Li, Yutaro Komuro, Mary Teena Joy, Gal Bitan, Allan MacKenzie-Graham, Lin Jiang, Jason D. Hinman

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Abstract

Ischemic injury to white matter tracts is increasingly recognized to play a key role in age-related cognitive decline, vascular dementia, and Alzheimer's disease. Knowledge of the effects of ischemic axonal injury on cortical neurons is limited yet critical to identifying molecular pathways that link neurodegeneration and ischemia. Using a mouse model of subcortical white matter ischemic injury coupled with retrograde neuronal tracing, we employed magnetic affinity cell sorting with fluorescence-activated cell sorting to capture layer-specific cortical neurons and performed RNA-sequencing. With this approach, we identified a role for microtubule reorganization within stroke-injured neurons acting through the regulation of tau. We find that subcortical stroke-injured Layer 5 cortical neurons up-regulate the microtubule affinity-regulating kinase, Mark4, in response to axonal injury. Stroke-induced up-regulation of Mark4 is associated with selective remodeling of the apical dendrite after stroke and the phosphorylation of tau in vivo. In a cell-based tau biosensor assay, Mark4 promotes the aggregation of human tau in vitro. Increased expression of Mark4 after ischemic axonal injury in deep layer cortical neurons provides new evidence for synergism between axonal and neurodegenerative pathologies by priming of tau phosphorylation and aggregation.

Stress Granules mediate lipid metabolism by inhibiting fatty acid oxidation and directing fatty acid import into Lipid Droplets

Triana Amen and Daniel Kaganovich

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Hebrew University Jerusalem

Metabolic flexibility allows cells to survive starvation by reconfiguring energy producing routes in accordance with changing fuel availability. Starvation response spans several orders of operational complexity and temporal regulation. Short term starvation leads to PPAR-driven transcription activation, which in turn results in increase in fatty acid metabolism in mitochondria. During long term starvation, however, cells face the consequences of Fatty Acid Oxidation, such as oxidative damage, and must therefore reroute fatty acids towards Lipid Droplets. Stress Granules appear following long-term starvation. Their precise function in starvation, however, is not known. Our data provide evidence that Stress Granules both upregulate and downregulate Fatty Acid metabolism during stress. We show that Stress Granule formation is triggered by the PPAR response, which is in turn regulated by Stress Granules. Over longer periods of starvation, Stress Granules recruit the mitochondrial porin VDAC2, thereby blocking Fatty Acid import into mitochondria and promoting Lipid Droplet biogenesis. The subsequent decrease in FAO during long-term starvation reduces oxidative damage and rations fatty acids for longer potential use.

Title: A Novel Cellular Complex of BACE1 and γ-Secretase Sequentially Generates Aβ from APP

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Keywords: RIP, protein complex, sheddase, Alzheimer's disease, β-secretase, γ-secretase

Background:

Intramembrane proteolysis of transmembrane substrates by the presenilin–γ-secretase complex is preceded and regulated by shedding of the substrate's ectodomain by α- or β-secretase. We recently discovered that substrate processing by α- and γ-secretases can occur in a large, multi-protease fraction that mediates sequential cleavages of substrates within a high molecular weight (HMW) complex stabilized by members of the tetraspanin web. We now asked whether β- and γ-secretases also interact to mediate efficient sequential processing of APP, generating the amyloid β (Aβ) peptides that initiate Alzheimer's disease.

Methods:

We used coimmunoprecipitation (coIP), non-denaturing FPLC, and novel Aβ ELISAs to identify an endogenous high MW complex in HEK293 cells and normal mouse and human brains that contains β- and γ-secretases. We then designed a new experimental system in which incubation of FPLC fractions containing this native complex at 37°C generated a range of Aβ peptides from endogenous holo-APP, a paradigm we refer to as de novo Aβ generation.

Results:

An endogenous HMW complex (~5 MD) containing mature, proteolytically active β- and γ-secretases and holo-APP was catalytically active in vitro and generated a full array of Aβ peptides, with physiological Aβ42/40 ratios. The isolated complex responded properly to γ-secretase modulators in vitro. Alzheimer's-causing mutations in presenilin altered the Aβ42/40 peptide ratio generated by the HMW β/γ-secretase complex in vitro

indistinguishably from that observed in the medium of the whole cells. We also discovered roburic acid, a natural compound which decreases Aβ production in HEK293 cells and iPS-derived neurons (iNs) by partially disrupting the HMW β/γ-secretase complex without inhibiting either β or γ-secretase activity per se.

Conclusion:

Aβ is generated from holo-APP by a BACE1/γ-secretase complex that provides sequential, efficient regulated intramembrane proteolysis (RIP) of full-length substrates to final products. We are currently exploring the subcellular localization of this HMW β/γ-secretase complex through super-resolution microscopy and searching for therapeutic compounds similar to roburic acid with better potency for dissociating the β/γ-secretase complex to reduce Aβ production without inhibiting either β or γ-secretase activity.

Title: A *Drosophila* Model to Understand the Role of Innate Immunity in Alzheimer's Disease

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Key words: *Drosophila*, innate immunity, β-amyloid, autoinflammation, parasitology, virulence

Abstract:

Despite clear links to Alzheimer's Disease (AD) progression, the physiological role of the amyloid β (Aβ) peptide is incompletely understood. In the disease state, Aβ aggregation leads to the formation of β-amyloid plaques, and both soluble Aβ peptides and β-amyloid plaques have been linked to cytotoxicity and AD pathogenesis. Recent research suggests that in non-disease states, Aβ plays a role in the innate immune response to infection. Accordingly, pathogen infection history has been associated with increased levels of Aβ and the subsequent formation of β-amyloid plaques during disease progression.

Our research seeks to test the link between Aβ and innate immune responses using the *Drosophila melanogaster*-parasitoid wasp model system. In this system, *Drosophila* are infected by wasps and mount a genetically conserved cellular innate immune response to kill the invading parasite. We find that loss of the *Drosophila* Aβ precursor protein *APPL* blocks the production of a successful immune response. More specifically, our findings suggest that Aβ functions as an opsonin, acting to target immune cell activity against the invading parasite. We further find that the overexpression of human Aβ in *Drosophila* leads to an infection dependent autoinflammatory response, in which Aβ appears to target *Drosophila* immune cells against self-tissue, leading to immune induced tissue damage. Taken together, these findings suggest that Aβ may play an evolutionarily conserved role in host defense.

Furthermore, during infection parasitoid wasps transfer venom proteins into the *Drosophila* host. This venom contains virulence factors that allow the parasite to overcome the host immune response. We find that infection by two evolutionarily distant parasitoid wasp species is sufficient to block the self-directed immune damage mediated by human Aβ expression. In host-parasite relationships, parasites often evolve virulence activities that specifically target host immune mechanisms. The ability of these parasite species to inhibit Aβ-mediated autoinflammation suggests that they utilize virulence proteins that target human Aβ.

Investigating the effects of *APOE4* expression in AD-relevant brain regions

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The ε4 allele of apolipoprotein E (*APOE*) is the dominant genetic risk factor for late-onset Alzheimer's disease (AD). However, the reason why the *APOE4* variant is associated with increased risk of AD remains a source of debate. In order to obtain an unbiased view of *APOE4*'s effects on neurobiology, we performed a systems biology level analysis on aged *APOE* targeted replacement mice that were devoid of overt AD pathology, focusing mainly on the entorhinal cortex (EC), one of the first regions affected in AD pathogenesis. We observed that *APOE4* expression results in age-related dysregulation of neuronal activity and bioenergetics regulation in the EC, as well as a more global dysregulation of endosomal-lysosomal function. Follow up studies are currently underway to investigate the underlying cause of these unique observations, as well as the downstream consequences. Included in this analysis is a large-scale single-nucleus RNA-sequencing study, which was funded with the help of this Next Generation of Researchers in Alzheimer's disease R03. We anticipate that further elucidating the distinct effects that *APOE4* expression has in the EC and other AD-related brain regions will greatly increase our understanding of why *APOE4* increases the risk of AD and how to prevent or slow the progression of AD among this crucial population.

PROJECT SUMMARY

Title: Genetics of frontotemporal dementia in diverse cohort enriched for Hispanic patients

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Keywords: Genetics - dementia – health disparity – Hispanic population

Frontotemporal dementia (FTD) is often described as an Alzheimer disease (AD) related dementia due to clinical, pathological and genetic overlap. Genetic research has identified several genes contributing to FTD pathogenesis. However, these genes do not explain disease in many familial and sporadic FTD cases and are mostly identified in non-Hispanic white (NHW) populations; indicating a clear gap in our knowledge of underlying genetic factors, especially in diverse population groups. Recent research in AD has identified disease variants and/or variant effects specific to certain population groups (e.g. ABCA7 deletions in African Americans (AA)[5] and reduced APOEε4 effect on African background in AA[6] and Hispanic (HI) patients (Rajabli et al, under review), warranting research in these diverse populations to assess the full disease variant spectrum. The underrepresentation of HI and AA in biomedical research also represents a major source of health disparity. Additionally, a recent study in the large AD Sequencing Project (ADSP) consortium indicated contribution of FTD known disease genes in a portion of adjudicated AD cases, supporting a true genetic overlap between two disorders. Taken together, these data suggest missing data on potentially shared genetic factors and warrant further analyses of FTD genes in FTD and AD cohorts, especially those encompassing HI patients.

To assess the contribution of known FTD disease genes and identify novel FTD disease variants in diverse populations of FTD and AD patients, we will complete the following goals: (1) we will establish a local Miami FTD cohort representative of the population proportions in Miami. This Caribbean enriched cohort will have a wide variety of different levels of ancestral contribution (European, African or American Indian), allowing it to inform on variants in those backgrounds. (2) We will perform GSA genotyping and imputation to obtain data on known FTD variants in the local diverse cohort. Local ancestry across these loci will be determined and variant frequencies in cases will be compared to controls (derived from ADSP/FUS efforts) within population group and within ancestral origin of the variant. (3) We will perform whole genome sequencing in FTD families, prioritizing HI patients and families with early onset disease, and perform sharing analyses to identify novel disease variants. Identified variants of interest will be screened in the remainder of the patients and in collaborative HI FTD cohorts (UCSF, Miller). Additionally, we will extract these novel variant positions from already available data in ADSP/FUS cohorts; including Puerto Rican, Peruvian and African American datasets, to assess genetic overlap with AD.

This proposal will leverage all genomic expertise, pipelines and data that are available through the ADSP/FUS consortium efforts, extending on the analyses already performed within the ADSP datasets and expanding the utility of the data generated within ADSP and related projects to AD related dementia research. We will aim to extend this pilot into the current established ADSP collaborations in Puerto Rico and Peru.

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The Sel1L-Hrd1 complex manages endoplasmic reticulum-mitochondria contacts and mitochondrial dynamics

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ABSTRACT

The mechanism underlying interorganellar communication and physiological consequences of miscommunication remain largely unclear. Here, using three-dimensional high-resolution imaging techniques, we show that the Sel1L-Hrd1 protein complex, the most conserved branch of endoplasmic reticulum (ER)-associated protein degradation (ERAD), exerts a profound impact on ER-mitochondrial contact and mitochondrial dynamics. *Sel1L* deficiency in brown adipocytes increases the number of ER-derived mitochondria-associated membranes (MAMs) per mitochondrion with closer membrane apposition, leading to attenuated mitochondrial fission and the formation of pleomorphic “megamitochondria” in response to acute cold challenge. Remarkably, in some cases, there are ER tubules penetrating the mitochondrion in parallel fashion, with radiating and interconnecting cristae folds. Mitochondria of *Sel1L*-deficient adipocytes exhibit dysfunctional respiration after cold challenge, and brown adipocyte-specific *Sel1L*- and *Hrd1*- deficient mice are cold sensitive. Our study identifies Sel1L-Hrd1 ERAD as a critical determinant of MAM contacts, thereby managing mitochondrial dynamics and function.

Development of a Culturally-Informed Measure of Alzheimer's Risk Disclosure Needs and Preferences: Stage I of the SHARE(D) Project

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Keywords: Risk Disclosure, Health Disparities, Concept Mapping, Health Belief Model

Introduction & Objectives: The recent adoption of the amyloid, tau, neurodegeneration (A/T/N) staging model of Alzheimer's disease (AD) and advances in genotyping and neuroimaging provide better characterization of research participants and patients. However, there are no clear guidelines for providing feedback about Dementia-Alzheimer's Type (DAT) risk, especially for ethnic minority patients and families disproportionately impacted by DAT. The *Sharing Alzheimer's Risk Estimates in Diverse Populations*, or SHARE(D) study, aims to (1) investigate the preferences and needs of racially and clinically diverse participants and associated caregivers in regards to DAT risk disclosure (Stage I); and (2) develop and pilot person-centered, culturally-informed protocols for risk disclosure for research and clinical settings (Stage II).

Methods: In Stage I, 50 patient-caregiver dyads (25 African-American, 25 White) who are diagnosed as cognitively normal or with mild cognitive impairment (MCI) through the Michigan Alzheimer's Disease Research Center's (MADRC) consensus process will complete a risk disclosure needs assessment. Given the psychological, social, and economic complexity of health decision-making, concept-mapping was employed to develop the needs assessment interview. Prior to recruitment, our interdisciplinary panel of experts generated concepts, themes, and ideas associated with the decision to engage in DAT risk disclosure, identifying commonalities and relationships among these constructs, and representing these relationships visually to allow for a more comprehensive definition.

Results: The SHARE(D) Interview evaluates whether patients and caregivers want to receive risk feedback, what experimental information they would wish to be included, and rationale for requesting this information. Furthermore, as a means of exploring any racial differences that may exist, it assesses how individuals' health beliefs (perceived threat of DAT, perceived benefits and barriers) around DAT risk disclosure shape risk disclosure preferences in both African American and White families. In addition to structured questions about these facets, open-ended and broader questions are included to avoid potential bias and improve knowledge of cultural factors impacting critical risk disclosure decisions.

Conclusions: The SHARE(D) Interview is a novel approach to assessing the complex psychological and sociocultural factors critical to DAT risk disclosure preferences in diverse older adults and their families. This measure will be implemented starting in September 2019. As part of the larger SHARE(D) study, Stage I results will inform Stage II feedback piloting, in which a subset of 10 of the Stage I dyads will engage in personalized DAT risk disclosure. Initial outcomes including satisfaction, comprehension and recall, and emotional reactions will be measured immediately and at one- and six-weeks following feedback.

Novel combinatorial approaches to selectively target reactive astrocytes

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Astrocytes are the most abundant glial cell in the brain, and a critical part of its immune response. When the brain is challenged with an injury or infection astrocytes become reactive. While this response appears to be universal, much remains to be learned about the role reactive astrocytes serve. Recently, several genes were identified whose expression in the central nervous system is restricted to reactive astrocytes. Using this knowledge, we have developed a transgenic mouse which expresses Cre in a reactive astrocyte-specific manner (RA Cre). The RA-Cre mouse is a powerful new tool that will allow the examination of reactive astrocytes across many disease models. To validate this tool, we have characterized the expression of Cre-dependent reporters using models of neuroinflammation. By combining the RA-Cre mouse with viral approaches, we will determine the role of reactive astrocytes on Alzheimer's Disease progression.

Title: Functional synaptic interacting partners for alpha-synuclein

Subhojit Roy, UCSD

Abstract: The small presynaptic protein alpha-synuclein has established roles in the pathogenesis of Parkinson's disease, but the normal role of this cytosolic protein remains enigmatic and controversial. Using alanine mutagenesis and rational extrapolation, we identified precise residues where alpha-synuclein binds to the presynaptic protein VAMP2; and also characterized a novel interaction with another presynaptic cytosolic protein, synapsin. Modest over-expression of alpha-synuclein leads to attenuation of synaptic responses, and perturbations of alpha-synuclein binding to VAMP2 or synapsin abolishes this attenuation. Our data support a model where alpha-synuclein cooperates with VAMP2 and synapsin to dampen neurotransmission; suggesting a physiologic role of alpha-synuclein in attenuating presynaptic responses.

The effect of cellular aging on the unfolded protein response in changing environments

Yonatan Savir, Technion

One of the hallmarks of cellular aging is the decline in the ability of cells to cope with intracellular protein aggregates. The unfolded protein response (UPR) plays a significant role in the proteostasis network that protects the cell against proteotoxicity, and its failure play a key role in the onset of neurodegenerative diseases. One of the hallmarks of the UPR sensing of endoplasmic reticulum (ER) stress is its ability to sense, directly, both the levels of unfolded proteins and the levels of chaperons. The role of this dual-sensing in changing environments and throughout aging is still not fully understood. Using mathematical modeling, we showed that dual-sensing has an advantage in systems that has to cope with both chronic low stress and bursts of stress pulses. We use imaging in a microfluidic device to characterize Yeast UPR response dynamics to pulses of ER stress, at the single-cell level. We characterize the effect of chronological age on the UPR response for both chronic and acute stresses and its interplay with amyloid-β levels.

Dissecting the mechanisms that underlie mislocalization and aggregation or RNA binding proteins in neurodegenerative diseases using marker based CRISPR screens

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Mislocalization and aggregation of RNA binding proteins (RBPs) is observed in many neurodegenerative diseases (ND) including Frontotemporal Dementia (FTD), Amyotrophic Lateral Sclerosis (ALS) and Alzheimer's Disease (AD). A notable example is the mislocalization and aggregation of TDP-43. Despite growing evidence, including rare mutations in the protein itself, pointing to the central role of TDP-43 aggregation in the disease etiology of ALS and FTD, the genetic networks that control this event are poorly understood.

Our lab has developed a cellular reporter that enables accurate quantification of TDP-43 aggregation status at the single cell level by flow cytometry using a method called Pulse Shape Analysis. In a preliminary genome-wide CRISPR loss-of-function screen for TDP-43 aggregation in a human cell line we identified many known and novel proteins that affect this process that opened exciting research avenues into the function of new modifiers. We are now preforming secondary screens in neuronal models and also conducting a similar screen for the aggregation of the protein FUS, an additional RNA binding protein that is found as the major component of protein inclusions in ALS and FTD. We plan to use these studies to establish a research program that will aim to systematically map the control network of physiological and pathological aggregation of RNA binding proteins and explore the prospect of modulating this network as a therapeutic approach.

Charting the 3D epigenome in Human Neural Cells to Reveal Contributions of Genetic Variants to Complex Neurological Disorders

Yin Shen
Institute for Human Genetics
Department of Neurology
University of California, San Francisco

Genetic variants associated with complex neurological disorders are located in the non-coding regions of the human genome that control cell fate and cellular function in a highly cell-specific manner. Understanding how exactly non-coding variants contribute to diseases is not straightforward. Regulatory DNA sequences can control target gene far away on the linear DNA sequences, and such regulation is thought to be achieved by DNA looping. I will discuss our efforts on using functional genomics tools including studying the three-dimensional (3-D) DNA structure in distinct neural cell types and CRISPR mediated genetics perturbations to better interpret non-coding DNA function linked to diseases. We found more than half of the disease-associated variants don't regulate their commonly assumed neighboring gene(s) but regulate other genes farther away. This is exciting and significant as such insights can only be gained after examining the DNA sequences in their 3D conformation. We further use genome editing tools to demonstrate that perturbing distal non-coding DNA sequences can affect target gene expression and ultimately contribute to diseases in brain cells. Our study offers significant advantages for identifying disease causal variants, deciphering their functions, and enabling the development of novel diagnostic and therapeutic strategies in otherwise intractable diseases such as Alzheimer's disease.

Single-molecule conformational analysis of Apolipoprotein E

Melissa D. Stuchell-Brereton, Maxwell Zimmerman, Greg DeKoster, Berevan Baban, Gregory R. Bowman, Carl Frieden, Andrea Soranno

The ε4-allele isoform of apolipoprotein E (ApoE4) plays a key-role in Alzheimer's disease and cardiovascular pathologies. A large body of evidence support that conformations of the protein are instrumental in its contribution to function and disease; yet, much remains unknown about the conformational ensemble of the full-length ApoE4 and its role in protein function, largely because of its elevated propensity for oligomerization and its inherent flexibility.

Here, we combine state-of-the-art single-molecule fluorescence spectroscopy and molecular dynamic simulation to access the structural ensemble of the monomeric full-length ApoE4. Our data reveal that ApoE4 does not adopt a unique stable structure but, instead, explores a conformational heterogeneous ensemble where multiple distinct conformers coexist in equilibrium. We further tested the effect of single-point substitution that differentiates ApoE3 from ApoE4, finding that this mutation alters the equilibrium between the different conformers. Our results pave the way to identify the structural differences between ApoE isoforms in their monomeric form, within oligomers, and when bound to lipids. Furthermore, our single-molecule assay can be adapted to test the effect of small compounds on protein conformations.

Title: Association of Cognition to Amyloid- β and Tau in the Vitreous Humor

Author: Manju Subramanian MD
Institution: Boston University School of Medicine

Abstract

Purpose: The purpose of the study was to evaluate levels of beta amyloid-β ($A\beta_{40}$, $A\beta_{42}$), phosphorylated tau (pTau), and total tau (tTau) in human vitreous humor and investigate the clinical predictive role of these proteins as early diagnostic markers of Alzheimer's Disease (AD).

Materials and Methods: A prospective, single-center, multi-surgeon cohort study. Vitreous humor samples from 80 eyes of 80 individuals were measured quantitatively for known biomarkers of AD: $A\beta_{40}$, $A\beta_{42}$, pTau, and tTau. Serum apolipoprotein E (APOE) allelic determination and Mini Mental State Exam (MMSE) was performed on all individuals. Linear regression was used to test associations between MMSE score, APOE genotype, and AD biomarker levels with adjustment for age, sex, and education level of patients.

Results: Lower MMSE scores were significantly associated with lower levels of vitreous $A\beta_{40}$ ($p=0.015$), $A\beta_{42}$ ($p=0.0066$), and tTau ($p=0.0085$), and these biomarkers were not associated with any pre-existing eye conditions. Presence of the ε4 allele and the ε2 allele approached significance with reduced $A\beta_{40}$ level ($p=0.053$) and increased p-Tau level ($p=0.056$), respectively.

Conclusions: Patients with poor cognitive function have significantly lower vitreous humor levels of AD-related biomarkers $A\beta_{40}$, $A\beta_{42}$, and tTau. These biomarkers do not correlate with underlying eye conditions, suggesting their specificity in association with cognitive change. This is the first study to our knowledge to correlate cognition with AD-related proteins in the vitreous humor. Results suggest ocular proteins may have a role for early dementia detection in individuals at-risk for AD.

Next Steps: Current R03 grant funding focuses on recalling patients from this cohort, repeating neuropsychological testing, and procuring and evaluating aqueous humor (which is a more accessible eye fluid) for the presence of Aβ and Tau proteins. Additionally, we will evaluate the vitreous of post-mortem eye specimens to correlate with brain pathology in established AD and chronic traumatic encephalopathy donors from the Boston University Alzheimer's Disease and Chronic Traumatic Encephalopathy Center (ADCTE).

Integrative genomics approach identifies conserved transcriptomic networks in Alzheimer's disease

Vivek Swarup[1,3], Samuel Morabito[2,3], Emily Miyoshi[1,3], Neethu Michael[1,3],

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[2]Mathematical, Computational and Systems Biology (MCSB) Program, University of California, Irvine, CA 92697, USA
[3]Institute for Memory Impairments and Neurological Disorders (MIND), University of California, Irvine, CA 92697, USA

Key words: Transcriptomics, systems biology, genomics, Alzheimer's disease, co-expression analysis

Alzheimer's disease (AD) is a devastating neurological disorder characterized by changes in cell-type proportions and consequently marked alterations of the transcriptome. Here we use a data-driven systems biology approach across multiple cohorts of human AD, encompassing different brain regions, and integrate with multi-scale datasets comprising of DNA methylation, histone acetylation, transcriptome- and genome-wide association studies as well as quantitative trait loci to define the genetic architecture of AD. We perform co-expression network analysis across more than twelve hundred human brain samples, identifying robust AD-associated dysregulation of the transcriptome, unaltered in normal human aging. We further integrate co-expression modules with single-cell transcriptome generated from 27,321 nuclei from postmortem human brain to identify AD-specific transcriptional changes and assess cell-type proportion changes in the human AD brain. We also show that genetic variants of AD are enriched in a glial AD-associated module and identify key transcription factors regulating co-expressed modules. Additionally, we validate our results in multiple published human AD datasets which are easily accessible using our online resource (https://swaruplab.bio.uci.edu/consensusAD) .

Datablitz abstract Title: A Problem Solving Intervention for Post-ICU Cognitive Impairment in Older Adults
Principal Investigator: Judith Ann Tate
Co-Investigators: Jennifer Bogner, Lorraine Mion, Alai Tan
Setting: The Ohio State University
Key Words: Cognitive Impairment, ICU, critical illness, ICU survivorship, Post-Intensive Care Unit Syndrome

Older adults comprise more than half of all intensive care unit (ICU) days and are at risk of delirium, a common acute brain impairment associated with increased risk for dementia and altered trajectories of cognitive recovery. Approximately 80% of mechanically ventilated older adults in the ICU experience delirium and decrements in cognitive function that are profound and persistent. At 1-year post-ICU discharge, two-thirds of ICU survivors experience cognitive impairment comparable to those with mild Alzheimer's disease or moderate traumatic brain injury, regardless of age or pre-morbid chronic illness burden. In addition, post-ICU survivors experience co-occurring physical, cognitive and psychological symptoms known as Post-ICU Syndrome (PICS), a condition that can be profound, persistent and contribute poor quality of life (QoL). It remains unclear whether psychological symptoms of PICS are comorbid, causal or worsened by cognitive impairment.

Critically ill older adults have at least one pre-illness chronic illness most commonly cardiovascular and pulmonary disease, fluid and electrolyte disorders, diabetes, and obesity. Chronic illness self-management requires the cognitive capability to problem-solve, make decisions, use resources, and take action to change behavior. Inability to self-manage chronic illness increases risk of acute illness, functional decline and long-term disability.

Despite the prevalence and persistence of post-ICU cognitive impairment, its association with dementia onset, and impact on chronic illness self-management, few interventions have been tested that help ICU survivors *overcome* cognitive impairment associated with critical illness. Cognitive rehabilitation is a well-established, effective intervention following many acute illnesses or trauma, but the benefit of these programs on cognitive function for ICU survivors has not been determined. **Our goal is to evaluate the feasibility, acceptability and efficacy of a well-established, rehabilitation-based problem solving intervention in the home setting for ICU survivors suffering from post-ICU cognitive impairment.** We will determine the program's effect on cognitive function, chronic illness self-management, affective well-being (anxiety depression), health care utilization and health related QoL.

We propose a small-scale two-group randomized controlled trial (RCT) comparing a ten session **Post-ICU Problem Solving (PIC-UPS)** intervention with a Control Group (CG) for older adult ICU survivors who have cognitive impairment at hospital discharge. The components of the PIC-UPS intervention include (1) in-person, in-home strategy training designed to overcome cognitive problems by employing comprehensive structured problem-solving strategies delivered by trained interventionists and (2) concomitant use of smartphone technology specifically designed to remind and reinforce in-person training.

This pilot study will provide data on processes critical to further hypothesis development and to the successful development of a large RCT to test the effectiveness of PIC-UPS on overcoming to cognitive impairment in ICU survivors. In addition, our pilot will provide infrastructure for a larger trial (e.g., manual of operations, web-based data collection form).

This study addresses the National Institute of Aging goals and the National Alzheimer's Project Act milestone 4.1 to develop a scientific workforce committed to research in Alzheimer's disease and Alzheimer's Related Dementias. Further, this study will test a non-pharmacological intervention (PIC-UPS) to assist older adults to overcome cognitive impairment, a harbinger of dementia, during the post-ICU period.

Impact of KIBRA signaling on memory in tauopathy

Tara E. Tracy[1,2], Grant Kauwe[1], Helen Cifuentes[1], Yaqiao Li[3], Yungui Zhou[3], David Le[3], Anja Holtz[1], Li Gan[3,4,5], Birgit Schilling[1,2]

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[2]USC Leonard Davis School of Gerontology, Los Angeles CA 90089
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Keywords: Tau, KIBRA, Synapse, Alzheimer's disease, Plasticity, Memory,

Tauopathies are age-related neurodegenerative diseases including Alzheimer's disease that are characterized by tau accumulation in the brain and progressive cognitive decline. How pathogenic tau in neurons triggers memory loss in tauopathy is not well understood. Normal cognitive processes such as learning and memory involve the modulation of synaptic strength by plasticity mechanisms in neuronal circuits of the brain. At hippocampal synapses, the induction of long-term potentiation (LTP) enhances actin polymerization in spines and recruits additional AMPA-type glutamate receptors (AMPARs) to the postsynaptic membrane which produces a sustained increase in synapse strength. Tauopathy mouse models with high levels of pathogenic tau have impaired LTP expression at hippocampal synapses which coincides with their Alzheimer's disease related memory loss. To investigate the role of abnormal tau acetylation in Alzheimer's disease we previously generated a transgenic mouse that expresses human tau with lysine-to-glutamine mutations to mimic the acetylation of two lysines on tau (tauKQ). We found that tauKQ-expressing mice had hippocampal LTP and memory deficits that were linked to the loss of a memory-associated protein called KIBRA in postsynaptic spines. KIBRA is a large scaffold protein with several functionally-distinct protein interaction domains which could modulate signaling complexes important for postsynaptic function. Our work suggests that tau triggers memory deficits in Alzheimer's disease by reducing the KIBRA-dependent signaling that is essential for LTP expression. In preliminary studies, we showed that the C-terminal domain of KIBRA (C-term KIBRA) is sufficient to restore postsynaptic AMPAR trafficking during LTP in cultured neurons expressing tauKQ. Moreover, lentivirus-based expression of C-term KIBRA in hippocampus rescued the LTP impairment in tauKQ mice. We plan to test the hypothesis that C-term KIBRA restores LTP through its interaction with postsynaptic proteins that regulate actin dynamics and AMPAR trafficking. In collaboration with Dr. Birgit Schilling, we are using mass spectrometry to identify proteins that bind to C-term KIBRA in hippocampal neurons of tauKQ mice. Then we will investigate the role of these C-term KIBRA interacting proteins in LTP expression. These studies will add a new dimension to Alzheimer's disease research by highlighting the impact of restoring KIBRA-dependent signaling and LTP on the recovery of memory encoding. We anticipate that this work will stimulate the development of new strategies to treat memory loss in Alzheimer's disease.

Datablitz Abstract

Title: Structural basis of CD33 receptor signaling in Alzheimer's disease

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Keywords: CD33, cell surface receptors, innate immunity, microglia, signaling, structural biology

Alzheimer's disease (AD) is a fatal neurodegenerative disorder that affects 10-30% of the population over 65 years old. The pathology of the disease is characterized by the failure to clear extracellular amyloid-β (Aβ) peptides and intracellular neurofibrillary tangles from the brain. In the continued absence of an AD therapy, the disease is persistent, disabling, costly and ultimately fatal. Microglia, the resident phagocytes of the central nervous system, play a major role in the clearance of Aβ aggregates. The activation state and phagocytosis capability of microglia are modulated by the CD33 cell-surface receptor. Specifically, the AD risk allele *rs3865444* is associated with higher levels of CD33 that suppress microglial phagocytosis. In contrast, CD33 inactivation improves phagocytosis and mitigates Aβ pathology. CD33 inhibition may thus represent a novel therapy for AD and, to aid in this endeavor, the current work aims to understand the structural basis of CD33 signaling. To ascertain the mechanism of signal transduction across the cell membrane, the TM domain border, the aggregation state of the TM domain, and the structure and dynamics of the TM and cytosolic domains will be determined by solution NMR spectroscopy. To connect ligand binding and associated biological effects with structural events that provide first insight into the mechanism of TM signaling, the CD33-binding sites and affinities of two cytosolic ligands will be characterized by NMR and calorimetry (ITC). The binding sites further identify the structural and functional roles of the cytosolic receptor tail and provide insight into assembly of cytosolic signaling complexes. Understanding the mechanism of CD33 signaling at atomic resolution further provides avenues to discovering small molecules (drugs) that either lock CD33 in an inactive state or disrupt downstream signaling by interfering with interaction sites of downstream ligands. CD33 belongs to the family of sialic acid-binding immunoglobulin-like receptors (Siglecs) that regulate the function of cells in the innate and adaptive immune systems through the recognition of their glycan ligands. The proposed research provide basic insight into the little understood structural basis of Siglec signaling, identifies targets sites and drugs for the pharmaceutical intervention in CD33 signaling and, thus, offers a direct avenue to therapeutic AD intervention.

An Endolysosomal Transmembrane Protein Regulates Glial Cell Metabolism and ApoE Secretion

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[4] Graduate Program in Cell and Regulatory Biology

Key words: endolysosome, glia, ApoE, cell metabolism

Abstract

Allelic variation in the *APOE* gene is the major risk factor of late-onset Alzheimer's Disease. The metabolic fate of ApoE in brain cells is determined by the vesicular trafficking pathways. To expand our understanding of the vesicular transport of ApoE, we examined potential functional relationship between *APOE* and genes encoding endolysosomal proteins. By analyzing RNA-seq datasets, we found that expression of *APOE* is highly correlated with that of *Tweety Homolog 1* (*TTYH1*), which encodes an endolysosomal transmembrane protein. Although *TTYH1* expression is found to be enriched in astrocytes, its functional role remains undefined. To test it functional relationship with ApoE, we chose to focus on the model organism Drosophila, which expresses *tweety* (*tty*), homolog of *TTYH1* and founding member of the protein family. *tty* mutant flies show glia-specific neuronal phenotypes, sensitivity to oxidative stress, and abbreviated lifespan. Remarkably, glial secretion of ApoE is impaired in *tty* mutant. Using genetically-encoded fluorescent reporters, we also found that *tty* mutant glial cells exhibit defects in metabolic and bioenergetic processes. Our data suggest that Tweety family proteins may mediate the crosstalk between metabolic pathways and ApoE secretion.

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Genetic interaction of PICALM and APOE in Alzheimers disease

Alzheimer's disease (AD) is the most common form of dementia in the elderly, manifesting progressive neurodegenerative conditions including amyloid plaque and neurofibrillary tangle formation, and cognitive impairment. Genetic inheritance is estimated to determine nearly 80% of the AD cases. Besides the well-known familial mutations in *APP*, *PSEN1* and *PSEN2* genes found in early-onset AD cases, over 30 loci or genes are associated sporadic late-onset AD (LOAD) as indicated by recent genome-wide association studies and whole exosome/genome sequencing projects. *APOE* and *PICALM* are among the top of the list.

APOE encodes the lipid carrier apolipoprotein E protein. Among its three major isoforms (ε2, ε3, and ε4), ε3 is the most common isoform, ε4 is unarguably the strongest genetic risk factor for LOAD, and ε2 is the less frequent but is protective for AD. These isoforms also differentially affect molecular and cellular events that are important for amyloid β (Aβ) metabolism and neurodegeneration. On the other hand, *PICALM* encodes the phosphatidylinositol binding clathrin assembly protein, and is confirmed by nearly all GWAS studies as a major AD-associated gene. *PICALM* controls receptor internalization and subsequent intracellular trafficking of clathrin-coated vesicles. It plays key roles in mediating brain clearance of Aβ, regulating activities of β- and γ-secretases for Aβ production, mitigating Aβ toxicity in neurons, and promoting Tau clearance via autophagy. More interestingly, the unique genetic interaction between *APOE* and *PICALM* in AD has been demonstrated based on population studies, as *PICALM* genotypes at multiple AD-associated confer risk predominantly in ε4 carriers, and AD risk *PICALM rs3851179*^{G} allele and *APOE* ε4 allele synergistically affect cortex volume and working memory function in AD patients. Such phenomena truly separate *PICALM* from any other AD-associated genes including *CR1* and *CLU.* However, the mechanism underpinning this interaction in AD is still unknown.

Based on the PICALM's interactome and functions in maintaining cell surface protein functions, as well as our preliminary findings showing impaired APOE lipidation and reduced level of surface ABCA1 cholesterol and phospholipid transporter in PICALM deficient mice, we hypothesize that PICALM may facilitate APOE lipidation and Aβ metabolism by controlling the function of ABCA1 transporter, and therefore risk PICALM rs3851179$_{G}$ and APOE ε4 alleles adversely affect AD pathogenesis. To test this hypothesis, we propose to: i) determine the cellular and molecular mechanisms of PICALM in facilitating APOE lipidation and characterize PICALMdependent internalization and trafficking of ABCA1 transporter (AIM 1); ii) explore the functional impact of PICALM and APOE's synergistic interaction *in vivo* on neurodegenerative phenotypes (AIM 2).

By probing the molecular and cellular mechanism of interaction between *APOE* and *PICALM* both *in vitro* and *in vivo*, we expect to gather first-hand evidence that the risk alleles of two genes synergistic influence AD pathogenesis, and establish the molecular and cellular mechanisms of interaction between *APOE* and *PICALM* both *in vitro* and *in vivo*. The outcomes of the studies will provide new insights into the inheritability, etiology and pathogenesis of AD, and serve as a foundation for future studies to therapeutically target this interaction between *APOE* and *PICALM* for AD diagnosis and treatment.

Social-biological dimensions of ADRD risk and resilience in a Native American cohort
Principal Investigator: Megan Zuelsdorff, PhD

Background: ADRD disproportionately impacts historically disadvantaged populations including racial minority communities. African Americans are up to twice as likely to develop dementia as whites, and evidence suggests that AI/AN are at similarly elevated risk. These disparities are not fully explained by ancestry or cardiovascular risk factors. Disadvantage conferred by intersections of race, geography, and socioeconomic status empirically correlates with chronic stress, and biological stress processes provoke systemic dysfunction and premature morbidity. Modifiable social-biological pathways plausibly link disadvantaged social environments with accelerated aging and ADRD onset. Reducing disparity requires identification of *community-specific* social determinants of risk and resilience. However, few cognitive aging cohorts focus on AI/AN experiences despite evidence that 1 of every 3 older AI/AN will develop ADRD.

Methods: This pilot project builds upon two NIA-funded efforts: the infrastructure and rich cognitive and ADRD biomarker data available through the Wisconsin Alzheimer's Disease Research Center (WADRC), and a research partnership between the WADRC and a local tribal Commission on Aging. This work explores social-biological predictors of ADRD markers in a cohort of 80 AI/AN community members to establish preliminary methods and data for future work, via two aims: **(1)** Examine relationships between social and physiological stress indices (e.g., early and later life adverse events, cortisol dysregulation) and markers of ADRD risk including (i) cognitive decline and (ii) key ADRD biomarkers (e.g. b-amyloid42, white matter hyperintensities), and **(2)** Characterize self-reported social resources (e.g., cultural ties, spirituality) salient to AI/AN populations and examine (i) relationships with ADRD markers and (ii) modification of relationships in Aim 1 by relevant resources.

Results: The Principal Investigator attends monthly Community Advisory Board (CAB) meetings on tribal land and was invited to give a keynote presentation on social connectedness and ADRD resilience at a quarterly intertribal AI/AN Elders meeting. CAB members have contributed to instrumentation that reflects AI/AN experiences, including intergenerational effects of historical traumas (eg, government boarding schools). Recruitment at an expected rate of 3-4 AI/AN participants per month is now underway.

Impact: This study capitalizes on **existing data and infrastructure** as it continues to grow a rich collaboration with local tribes. The work will establish effect sizes for community-specific social determinants of cognitive health disparities and stress-linked biological mediators that can serve as proximal outcomes in risk reduction studies. In so doing, it will inform future longitudinal R01 research on personal and community resources that promote ADRD resilience in historically disadvantaged populations.

Partha Bhattacharyya, PhD
Program Director
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Dr. Partha Bhattacharyya is the Director of The Office of Research Resources (ORR) and also serves as a Program Director in Population and Social Processes (PSP) Branch within the Division of Behavioral and Social Research (BSR).

As the Director for ORR, Dr. Bhattacharyya coordinates, directs, and implements initiatives related to research data and resources supported by BSR and the National Institute on Aging (NIA). He is a project scientist for Understanding America Study, the largest internet panel survey jointly supported by NIA and the Social Security Administration. Additionally, he advises NIA leadership on new developments in data collection, analysis, and data sharing, supporting the NIA mission.

As a PSP Program Director, he primarily oversees NIA's health economics, health services, behavioral economics, and pragmatic trials portfolios. He was instrumental in developing the behavioral economics and subsequent pragmatic trials portfolio for improving care for patients with Alzheimer's Disease and Related Dementias (AD/ADRD). In collaboration with multiple divisions across NIA, Dr. Bhattacharyya leads the development of AD/ADRD Health Care Systems Research Collaboratory, which will bring together health systems, health insurance companies (e.g., managed care plans), home health care providers, and nursing homes systems for research to improve care of persons with dementia.

While in graduate school, Dr. Bhattacharyya worked as an economist and Vice President of Research at Academic Analytics, LLC, in Stony Brook, New York, where he managed the process for database construction, integration, and analysis for FSPINDEX 2005-06, which measures the productivity of approximately 180,000 faculty in Ph.D. programs.

Dr. Bhattacharyya received his Ph.D. in Economics in 2007 and B.S. in Applied Mathematics and Statistics and Economics in 2002 from the State University of New York at Stony Brook.

Tatiana Foroud, PhD

Tatiana Foroud is an internationally recognized genetic researcher and currently the Joe C. Christian Professor Medical and Molecular Genetics, Distinguished Professor and Chancellor's Professor at the Indiana University School of Medicine.

Foroud joined the Indiana University School of Medicine faculty in 1994 and was named the P. Michael Conneally Professor of Medical and Molecular Genetics in 2005. Indiana University appointed Foroud to the rank of Distinguished Professor, the highest academic rank at the university in 2017.

Foroud is director of Hereditary Genomics Division of the Department of Medical and Molecular Genetics, and leads the Genetics, Biomarker and Bioinformatics department at the Indiana Alzheimer Disease Center. She is scientific director of the Indiana Biobank.

Foroud's research is primarily in the area of mapping genes contributing to the susceptibility for common, complex genetic disorders. These include disorders such as Parkinson's disease, Alzheimer's disease, bipolar disorder and alcoholism.

Foroud received her bachelor's degree in biology and mathematics from Fairfield University, master's degree in biomathematics from the University of California, Los Angeles, and doctoral degree in population genetics from the Indiana University School of Medicine.

Walter A. Kukull, PhD
Professor, UW Department of Epidemiology
Director, NACC, National Alzheimer's Coordinating Center

Dr. Kukull's research is focused on the neurodegenerative, vascular and other conditions causing dementia and cognitive impairment. These conditions include Alzheimer's disease, Parkinson's/Lewy body disease, frontotemporal lobar degeneration, and cerebrovascular disease. Since 1999, he has served as Director and PI of the National Alzheimer's Coordinating Center [U01AG016976], an effort to collect and make available to researchers standardized, detailed clinical data from the approximately 30 NIA-funded Alzheimer Disease Centers across the United States. Dr. Kukull works closely with the leadership of the ADRCs and the National Institute on Aging to ensure that scientifically relevant and valid data are obtained and available from our database to any researcher anywhere. In addition to NACC work, he is an investigator with a number of other NIH grants.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Gil Dan Rabinovici, MD

eRA COMMONS USER NAME (credential, e.g., agency login): RABINOVICI

POSITION TITLE: Professor in Residence, UCSF Depts. of Neurology, Radiology and Biomedical Imaging

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Stanford University	B.S.	1997	Biological Sciences
Northwestern University	M.D.	2001	Medicine
Stanford University Medical Center	Intern	2002	Medicine
University of California, San Francisco	Resident	2005	Neurology
UCSF Memory & Aging Center	Fellow	2007	Behavioral Neurology

A. Personal Statement

My research focuses on utilizing multi-modal neuroimaging techniques and other biomarkers to improve early detection and diagnostic accuracy in dementia, and to study mechanisms of neurodegenerative diseases. I lead the PET program at the UCSF Memory & Aging Center, applying novel PET tracers along with structural and functional MRI to a broad spectrum of neurodegenerative diseases. I serve as Study Chair of the national Imaging Dementia-Evidence for Amyloid Scanning (IDEAS) study (~600 sites, 18,200 participants) and co-PI and PET Core Director of the Longitudinal Early-Onset Alzheimer's Disease Study (LEADS) investigating sporadic early-onset AD (15 sites, 600 participants), among other activities. I am Associate Director of the UCSF Alzheimer's Disease Center, and Co-Lead of the Center's Administrative and Imaging Cores.

B. Positions and Honors

Employment

2001 – 2002 Intern in Internal Medicine, Stanford University Medical Center, Stanford, CA
2002 – 2005 Resident in Neurology, UCSF, San Francisco, CA
2004 – 2005 Chief Resident, UCSF Dept. of Neurology
2005 – 2007 Behavioral Neurology Fellowship with Dr. Bruce Miller, UCSF Memory & Aging Center
2007 – 2009 Clinical Instructor, UCSF Dept. of Neurology
2007 – 2013 San Francisco General Hospital Dept. of Neurology, Attending Physician
2009 – 2010 Assistant Clinical Professor, UCSF Dept. of Neurology
2010 – 2014 Assistant Professor in Residence, UCSF Dept. of Neurology
2014 - 2018 Associate Professor in Residence, UCSF Dept. of Neurology
2018 – present Professor in Residence, UCSF Dept. of Neurology
2019 – present Co-appointment, Professor in Residence, UCSF Dept. of Radiology and Biomedical Imaging
2016 – present Global Brain Health Initiative, Faculty member
2016 – present Institute for Neurodegenerative Diseases, affiliated faculty
2016 – present UCSF Weill Institute for Neurosciences, faculty member
2018 – present Lawrence Berkeley National Laboratory, faculty scientist

Honors

- Howard Hughes Summer Research Fellowship, Stanford University, 1996
- Departmental Honors and Distinction, Dept. of Biological Sciences, Stanford University, 1997

- Phi Beta Kappa, Stanford University Chapter, 1997
- Firestone Medal for Excellence in Undergraduate Research, Stanford University, 1997
- Alpha Omega Alpha, Northwestern University Medical School, 2000
- Kathryn Grupe Award for Excellence in Alzheimer's Research, Alzheimer's Association of Northern California and Northern Nevada, 2006
- Henry Newman Award for Research in Clinical Neurology, San Francisco Neurological Society, 2007
- Alzheimer's Association Best Paper in Alzheimer's Disease Neuroimaging: New Investigator, 2010
- American Academy of Neurology Research Award in Geriatric Neurology, 2012
- Christopher Clark Award for the Advancement of Amyloid Imaging, 2015
- Edward Fein and Pearl Landrith Distinguished Professor of Memory & Aging UCSF, 2017
- American Academy of Neurology Abstract of Distinction, 2019

Membership in Professional Organizations

- American Academy of Neurology, Active Member, 2002 – present
- AAN Geriatric Neurology section, Vice-Chair, 2016 - 2018
- International Society to Advance Alzheimer Research and Treatment (ISTAART), 2008 – present
- ISTAART Neuroimaging Professional Interest Group Executive Committee (Chair), 2011-2015
- ISTAART Advisory Council 2014 – 2018
- Alzheimer's Association of N. California, Medical & Scientific Advisory Council, 2013 - present
- American Neurological Association, Fellow, 2012 - present
- ANA Scientific Program Committee, 2017 - present
- Physician & Surgeon, Medical Board of California, 2002 - present
- Diplomate, American Board of Psychiatry and Neurology, 2007 – present

C. Contributions to Science (complete bibliography available at:
https://www.ncbi.nlm.nih.gov/sites/myncbi/gil.rabinovici.1/bibliography/40871522/public/?sort=date&direction=ascending**)**

1. My lab has combined multiple imaging, including amyloid, FDG and tau PET, structural and functional-connectivity MRI to study mechanisms that drive clinical heterogeneity in AD. This work has provided in vivo evidence that the clinical and neurodegenerative phenotype of AD is dissociated from the distribution and burden of amyloid, and may be driven by the spread of tau through vulnerable brain networks.

a. Rabinovici GD, Furst AJ, Alkalay A, Racine CA, O'Neil JP, Janabi M, Baker SL, Agarwal N, Bonasera SJ, Mormonio EC, Weiner MW, Gorno-Tempini ML, Rosen HJ, Miller BL, Jagust WJ. Increased metabolic vulnerability in early-onset Alzheimer's disease is not related to amyloid burden. Brain. 2010 Feb;133(Pt 2):512-28. PMCID: PMC2858015.
b. Lehmann M, Madison CM, Ghosh PM, Seeley WW, Mormino E, Greicius MD, Gorno-Tempini ML, Kramer JH, Miller BL, Jagust WJ, Rabinovici GD. Intrinsic connectivity networks in healthy subjects explain clinical variability in Alzheimer's disease. Proc Natl Acad Sci U S A. 2013 Jul 9;110(28):11606-11. PMCID: PMC3710820.
c. Ossenkoppele R, Schonhaut DR, Schöll M, Lockhart SN, Ayakta N, Baker SL, O'Neil JP, Janabi M, Lazaris A, Cantwell A, Vogel J, Santos M, Miller ZA, Bettcher BA, Vossel KA, Kramer JH, Gorno-Tempini ML, Miller BL, Jagust WJ, Rabinovici GD. Tau PET patterns mirror clinical and neuroanatomical variability in Alzheimer's disease. Brain. 2016 May;139(Pt 5):1551-67. PMCID:PMC5006248.
d. Bejanin A, Schonhaut DR, La Joie R, Kramer JH, Baker SL, Sosa N, Ayakta N, Cantwell A, Janabi M, Lauriola M, O'Neil JP, Gorno-Tempini ML, Miller ZA, Rosen HJ, Miller BL, Jagust WJ, Rabinovici GD. Tau pathology and neurodegeneration contribute to cognitive impairment in Alzheimer's disease Brain. 2017 Dec 1;140(12):3286-3300. PMCID:PMC5006248.

2. A major focus of my research has been assessing the utility of molecular brain imaging techniques for improving the diagnosis and care of patients with neurodegenerative dementia. I led early studies describing the potential of amyloid PET to distinguish between Alzheimer's disease (AD) and frontotemporal dementia (FTD), demonstrating its higher overall accuracy compared to FDG-PET, and illustrating its role in medical decision making. I also played a major role in an international meta-analysis on this topic published in JAMA. Expertise in this line of research has led to my role as principle investigator of Imaging Dementia – Evidence for Amyloid Scanning (IDEAS), a U.S.-wide study of the clinical impact of amyloid PET funded by the Centers for Medicare and Medicaid Services.

a. Rabinovici GD, Rosen HJ, Alkalay A, Kornak J, Furst AJ, Agarwal N, Mormino EC, O'Neil JP, Janabi J, Karydas A, Growdon ME, Jang JY, Huang EJ, DeArmond SJ, Trojanowski JQ, Grinberg LT, Gorno-Tempini ML, Seeley WW, Miller BL, Jagust WJ. Amyloid versus FDG PET in the differential diagnosis of AD and FTLD. Neurology. 2011 Dec 6;77(23):2034-42. PMCID: PMC3236517.
b. Ossenkoppele R, Jansen WJ, Rabinovici GD, Knol DL, van der Flier WM, van Berckel BNM, Scheltens P, Visser PJ, and the Amyloid PET Study Group. Prevalence of amyloid PET positivity in dementia syndromes, a meta-analysis. JAMA. 2015 May 19;313(19):1939-49. PMCID: PMC4517678.
c. La Joie R, Ayakta N, Seeley WW, Borys E, Boxer AL, DeCarli C, Doré V, Grinberg LT, Huang E, Hwang JH, Ikonomovic MD, Jack C Jr, Jagust WJ, Jin LW, Klunk WE, Kofler J, Lesman-Segev OH, Lockhart SN, Lowe VJ, Masters CL, Mathis CA, McLean CL, Miller BL, Mungas D, O'Neil JP, Olichney JM, Parisi JE, Petersen RC, Rosen HJ, Rowe CC, Spina S, Vemuri P, Villemagne VL, Murray ME, Rabinovici GD. Multisite study of the relationships between antemortem [^{11}C]PIB-PET Centiloid values and postmortem measures of Alzheimer's disease neuropathology. Alzheimers Dement. 2019 Feb;15(2):205-216. PMCID: pending.
d. Rabinovici GD, Gatsonis C, Apgar C, Chaudhary K, Gareen I, Hanna L, Hendrix J, Hillner BE, Olson C, Lesman-Segev OH, Romanoff J, Siegel BA, Whitmer RA, Carrillo MC. Association of Amyloid Positron Emission Tomography With Subsequent Change in Clinical Management Among Medicare Beneficiaries With Mild Cognitive Impairment or Dementia. JAMA. 2019 Apr 2;321(13):1286-1294. PMCID: pending.

3. My lab is involved in translating novel radiotracers into clinical populations and developing innovative methodological approaches for analyzing PET data.
a. M Schöll, SN. Lockhart, DR Schonhaut, JP O'Neil, M Janabi, R Ossenkoppele, SL Baker, JW Vogel, J Faria, HD Schwimmer, GD Rabinovici, WJ Jagust. Tau Deposition in the Aging Human Brain. Neuron. 2016 Mar 2;89(5):971-82. PMCID: PMC4779187.
b. Schonhaut DR, McMillan CT, Spina S, Dickerson BC, Siderowf A, Devous MD Sr, Tsai R, Winer J, Russell DS, Litvan I, Roberson ED, Seeley WW, Grinberg LT, Kramer JH, Miller BL, Pressman P, Nasrallah I, Baker SL, Gomperts SN, Johnson KA, Grossman M, Jagust WJ, Boxer AL, Rabinovici GD. 18F-flortaucipir tau PET distinguishes established progressive supranuclear palsy from controls and Parkinson's disease: A multicenter study. Ann Neurol. 2017 Oct;82(4):622-634. PMCID: PMC5665658.
c. Ossenkoppele R, Rabinovici GD, Smith R, Cho H, Schöll M, Strandberg O, Palmqvist S, Mattsson N, Janelidze S, Santillo A, Ohlsson T, Jögi J, Tsai R, La Joie R, Kramer J, Boxer AL, Gorno-Tempini ML, Miller BL, Choi JY, Ryu YH, Lyoo CH, Hansson O. Discriminative Accuracy of [18F]flortaucipir Positron Emission Tomography for Alzheimer Disease vs Other Neurodegenerative Disorders. JAMA. 2018 Sep 18;320(11):1151-1162. PMCID: pending.
d. Ossenkoppele R, Iaccarino L, Schonhaut DR, Brown JA, La Joie R, O'Neil JP, Janabi M, Baker SL, Kramer JH, Gorno-Tempini ML, Miller BL, Rosen HJ, Seeley WW, Jagust WJ, Rabinovici GD. Tau covariance patterns in Alzheimer's disease patients match intrinsic connectivity networks in the healthy brain. Neuroimage Clin. 2019 May 2;23:101848. PMCID: PMC31077982.

4. My lab has worked on single site and multi-site studies evaluating genomic correlates of AD.
a. Yokoyama JS, Wang Y, Schork AJ, Thompson WK, Karch CM, Cruchaga C, McEvoy LK, Witoelar A, Chen CH, Holland D, Brewer JB, Franke A, Dillon WP, Wilson DM, Mukherjee P, Hess CP, Miller Z, Bonham LW, Shen J, Rabinovici GD, Rosen HJ, Miller BL, Hyman BT, Schellenberg GD, Karlsen TH, Andreassen OA, Dale AM, Desikan RS. Association Between Genetic Traits for Immune-Mediated Diseases and Alzheimer Disease. JAMA Neurol. 2016 Jun 1; 73(6):691-7. PMCID: PMC4905783.
b. Schott JM, Crutch SJ, Carrasquillo MM, Uphill J, Shakespeare TJ, Ryan NS, Yong KX, Lehmann M, Ertekin-Taner N, Graff-Radford NR, Boeve BF, Murray ME, Khan QU, Petersen RC, Dickson DW, Knopman DS, Rabinovici GD, Miller BL, González AS, Gil-Néciga E, Snowden JS, Harris J, Pickering-Brown SM, Louwersheimer E, van der Flier WM, Scheltens P, Pijnenburg YA, Galasko D, Sarazin M, Dubois B, Magnin E, Galimberti D, Scarpini E, Cappa SF, Hodges JR, Halliday GM, Bartley L, Carrillo MC, Bras JT, Hardy J, Rossor MN, Collinge J, Fox NC, Mead S. Genetic risk factors for the posterior cortical atrophy variant of Alzheimer's disease. Alzheimers Dement. 2016 Aug; 12(8):862-71. PMCID: PMC4982482.

c. Ossenkoppele R, Mattsson N, Teunissen CE, Barkhof F, Pijnenburg Y, Scheltens P, van der Flier WM, Rabinovici GD. Cerebrospinal fluid biomarkers and cerebral atrophy in distinct clinical variants of probable Alzheimer's disease. Neurobiol Aging. 2015 Aug; 36(8):2340-7. PMCID: PMC4465267.

d. Tan CH, Bonham LW, Fan CC, Mormino EC, Sugrue LP, Broce IJ, Hess CP, Yokoyama JS, Rabinovici GD, Miller BL, Yaffe K, Schellenberg GD, Kauppi K, Holland D, McEvoy LK, Kukull WA, Tosun D, Weiner MW, Sperling RA, Bennett DA, Hyman BT, Andreassen OA, Dale AM, Desikan RS; Alzheimer's Disease Brain. 2019 Feb 1;142(2):460-470. PMCID: pending.

5. I am involved in working groups dedicated to translational neuroimaging and to updating diagnostic criteria for AD.

a. Frisoni GB, Bocchetta, Chételat G, Rabinovici GD, de Leon MJ, Kaye J, Reiman EM, Scheltens P, Barkhof F, Black SE, Brooks DJ, Carrillo MC, Fox NC, Herholz K, Nordberg A, Jack CR, Jagust WJ, Johnson KA, Rowe CC, Sperling RA, Thies W, Wahlund LO, Weiner MW, Pasqualetti P, DeCarli C. Imaging Biomarkers for use in the Context of the Revised NIA-AA and IWG Diagnostic Criteria for Alzheimer's Disease: a Review from ISTAART's NeuroImaging Professional Interest Area (NIPIA). Neurology. 2013 Jul 30;81(5):487-500. PMCID: PMC3776529.

b. Dubois B, Feldman HH, Jacova C, Hampel H, Molinuevo JL, Blennow K, DeKosky ST, Gauthier S, Selkoe D, Bateman R, Cappa S, Crutch S, Engelborghs S, Frisoni GB, Fox NC, Galasko D, Habert MO, Jicha GA, Nordberg A, Pasquier F, Rabinovici G, Robert P, Rowe C, Salloway S, Sarazin M, Epelbaum S, de Souza LC, Vellas B, Visser PJ, Schneider L, Stern Y, Scheltens P, Cummings JL. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol. 2014 Jun;13(6):614-29.

c. Dubois B, Hampel H, Feldman HH, Scheltens P, Aisen P, Andrieu S, Bakardjian H, Benali H, Bertram L, Blennow K, Broich K, Cavedo E, Crutch S, Dartigues JF, Duyckaerts C, Epelbaum S, Frisoni GB, Gauthier S, Genthon R, Gouw AA, Habert MO, Holtzman DM, Kivipelto M, Lista S, Molinuevo JL, O'Bryant SE, Rabinovici GD, Rowe C, Salloway S, Schneider LS, Sperling R, Teichmann M, Carrillo MC, Cummings J, Jack CR Jr; Proceedings of the Meeting of the International Working Group (IWG) and the American Alzheimer's Association on "The Preclinical State of AD"; July 23, 2015; Washington DC, USA. Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria. Alzheimers Dement. 2016 Mar;12(3):292-323.

d. Rabinovici GD, Karlawish J, Knopman D, Snyder HM, Sperling R, Carrillo MC. Testing and disclosures related to amyloid imaging and Alzheimer's disease: Common questions and fact sheet summary. Alzheimers Dement. 2016 Apr;12(4):510-5.

D. Research Support

ACTIVE

R01 AG045611 (Rabinovici) 05/01/2014 – 02/28/2020 (NCE)
NIH/NIA
Early Age-of-Onset AD: Clinical Heterogeneity and Network Degeneration
This study applies multi-modal neuroimaging to assess the relationship between clinical phenotype and the integrity of specific neural networks in clinical variants of Alzheimer's disease.

U01 AG057195 (Apostolova (contact)/Rabinovici/Dickerson/Carrillo) 09/30/2018 – 05/31/2023
NIH/NIA
Longitudinal Evaluation of Early-Onset AD (LEADS)
This is a prospective, multi-site, longitudinal study of 400 patients with early-onset AD and 100 matched controls. The goal is to characterize biomarker changes in this cohort, identify novel genetic risks and optimize outcome measures for future clinical trials.

P30 AG062422 (Miller) 04/01/2019 - 03/31/2024
NIH/NIA
New Approaches to Dementia Heterogeneity
Dr. Rabinovici is Associate Director of the UCSF ADC and Co-Lead of Administrative and Imaging Cores.

R01 AG038791 (Boxer) 03/01/2016 - 02/28/2021
NIH/NIA
The Four Repeat Tauopathy Neuroimaging Initiative

The goal of the project is to collect longitudinal clinical, neuroimaging and biofluid markers on patients with progressive supranuclear palsy and corticobasal degeneration. Dr. Rabinovici is co-investigator responsible for analyzing longitudinal tau PET data.

P01 AG019724 (Miller) 09/01/2017 - 05/31/2022
NIH/NIA
Frontotemporal Dementia: Genes, Images and Emotions
This is the third renewal for this program project grant on frontotemporal dementia and related disorders. Dr. Rabinovici is co-PI for Project 6 and co-investigator for Core E (Imaging).

R01 AG048234 (Kramer) 04/01/2015 - 01/31/2020
NIH/NIA
Effects of chronic inflammation on brain structure and function
The overarching goal of this proposal is to better define the longitudinal impact of chronic inflammation on brain structure and function in the elderly by employing imaging biomarkers of white matter injury and Alzheimer's disease. Dr. Rabinovici is co-investigator and is responsible for PET analyses.

R01 AG032289 (Kramer) 09/01/2015 – 05/31/2020
NIH/NIA
Biological predictors of brain aging trajectories
The overarching goal of this proposal is to better understand the inflammatory, vascular, and neurodegenerative mechanisms that contribute to this clinically important diversity in brain aging trajectories since more precise specification of these relationships will lead to better prediction and prevention of adverse cognitive aging and inform person-specific interventions. Dr. Rabinovici is co-investigator and is responsible for PET analyses.

R01 AG057204 (Sturm) 09/15/2017 – 05/31/2022
NIH/NIA
Neurobiological Basis of Emotion Regulation Trajectories in Early Alzheimer's Disease
The overall goal of the proposed project is to elucidate the neural systems and genetic factors that underlie emotion change in AD. Anatomically-specific markers of emotion could be used to broaden current conceptualizations of early AD phenotypes, identify subtypes at greatest risk for affective symptoms, monitor symptom progression, or track disease-related decline in clinical trials of asymptomatic or mildly symptomatic individuals. Dr. Rabinovici is co-investigator and is responsible for PET analyses.

Beta-Amyloid PET Coverage with Evidence Development (Rabinovici) 06/01/2015 - 12/31/2019
Centers for Medicare and Medicaid Services/American College of Radiology
IDEAS: Imaging Dementia Evidence for Amyloid Scanning
This is a national study to evaluate the clinical utility of amyloid PET scans in ~18,500 patients across the U.S. with diagnostically uncertain MCI or dementia, under the CMS Coverage with Evidence Development program. Dr. Rabinovici is Study Chair.

Research Award (Rabinovici/Jagust) 04/01/2013 - 08/31/2022
Tau Consortium
Human Tau Imaging
This is a pilot project to develop and validate tau-specific PET ligands for human use.

Gerard D. Schellenberg, PhD

Professor of Pathology and Laboratory Medicine
Professor of Pathology and Laboratory Medicine in Genetics
Director, Penn Neurodegeneration Genomics Center
University of Pennsylvania Perelman School of Medicine

Dr. Schellenberg is a leading expert on genetics and gene sequencing with specialties in neuropathology, immunobiology and experimental pathology. Prior to joining the faculty of Penn Medicine, he was a senior research fellow at the University of Washington. He has received numerous awards and honors including the Potamkin Prize for Alzheimer's Disease Research. He is the author of dozens of peer-reviewed papers and publications. Dr. Schellenberg received his BS and PhD degrees in biochemistry and cell biology from the University of California, Riverside.

http://pathology.med.upenn.edu/department/people/496/gerard-d-schellenberg

Dr. Nina Silverberg is the Director of the Alzheimer's Disease Research Centers (ADRC) Program at the National Institute on Aging. She manages and supports the efforts of 31 NIA-funded Centers at major medical institutions across the country.

In addition, Dr. Silverberg is a program officer with a small portfolio covering a variety of dementia research. She strives to reduce health disparities, with the goal of ensuring that people from underrepresented populations receive access to research opportunities as well as research training. She is also a leader in NIA's efforts to educate the public and health care providers about the importance of research participation.

Dr. Silverberg received her Ph.D. in cognitive psychology from the University of Arizona, Tucson. Before joining NIA in 2005, she was a clinical research scientist at the NIA-funded Alzheimer's Disease Center at Banner Sun Health Research Institute in Sun City, Az. There, she coordinated the American Indian outreach program and was the principal investigator on a study assessing the usefulness of various neuropsychological assessment tools in an American Indian population.

Dr. Silverberg is currently working on responding to recommendations for the ADRC Program and supporting the efforts of a national workgroup on disclosure of genetic and biomarker results.

W. A. Kukull

Helpful hints and suggestions for each component section.
These hints are written to focus on an actual NIH grant application rather than specifically on requirements for your class project paper. All of these hints should be considered as you construct your class project paper.

ABSTRACT

- Clear and concise description of "aims" , rationale and method
- Used by CSR to route to study section; "buzz words" like epidemiology, toxicology, genetics, etc., may influence where your grant is reviewed;
- Reviewers read the abstract first; it sets the tone and provides an initial impression of the overall grant; the major Aims/Hypotheses focus reviewers on the potential value of the outcome.
- In the study section meeting, principal reviewers usually read/paraphrase the abstract first to other members before detailed review and discussion begins;
- A poor first impression due to an unfocused, difficult to follow abstract (or an abstract which seems to include different specific aims, from those stated later) can lead to disaster.
- A good abstract alone cannot save a poorly presented proposal, but a bad abstract can sink a proposal.

SPECIFIC AIMS

- **Number your aims** so that reviewers can point to them easily;
- **Do Not** bury your aims in a sea of text;
- **Avoid** including *multiple topics within one aim;*
- **State a broad, overall goal** for the study *either as an intro to the aims or as a concluding paragraph;* this will give context to your aims, and rationale.
- The Specific Aims is where you show the reviewers that you have a clear idea of exactly what the ***key research questions or hypotheses of the study*** are--and that you can communicate them to others. State your aims to reflect the "destination" of your research rather than the "journey" you take to get there.
    - *Good*: To determine whether antioxidant vitamin use decreases risk of Parkinson's disease.
    - *Bad:* 1)To enroll a series of population-based PD cases and controls and to gather self-reported history of use of potential anti oxidants…
- The Specific Aims provide the *focus for the Significance* section of the grant;
- The Specific Aims are *the engine for the Approach* section: There, for each aim, you will describe how data will be collected, what the outcomes (variables of interest) are, which analytic techniques will be applied to answer each aim;
- The Aims are often included verbatim in the Abstract; and also must be addressed in "non-competitive renewals" after the grant is funded (Progress Reports).

SIGNIFICANCE

- Provide evidence which supports your specific topic of investigation as an important contribution to the field; avoid rambling descriptions and exhaustive literature review;
- Start with a paragraph of "classic", defining studies in the field to set the stage for your research question;
- Transition with discussion of a few representative precursor studies more directly related to your question *(be sure to cite similar important studies that you don't discuss in detail especially if one might be written by a potential reviewer with a different point of view);*
- Conclude with a tightly focused discussion of publications which point to the need for your study, gaps in knowledge or controversy, which your study will dispel; try to be current and comprehensive. (You may have one of the PI's you cite as a reviewer and if you miss or misinterpret their relevant study, you may suffer their wrath.)
- Summarize the "significance" of the proposed study; if you do fill the "gaps" and reach your Specific Aims, what will it mean to research in the field or the direction of future research?
- In a real NIH proposal you have about 2-3 pages for this section; *reviewers will almost never read long, broad literature reviews which provide no clear conclusion. This is not an exercise in writing a comprehensive review paper, it is one aimed at providing strong rationale for your proposed study.*

- **Innovation**
- What is novel or innovative about your topic or how you intend to address you Specific Aims? Will you develop new methods or lead the field in a new direction because of your innovative insights?

- **PRELIMINARY STUDIES (if applicable)**

- Must be directly related to the current proposal; do *not* re-state your biosketch and all the things you have done in your career.
- Provides *evidence that laboratory procedures, diagnostic tests, biomarkers* which you plan to use in your study, can actually be accomplished; provide sensitivity/ specificity estimates if appropriate.
- Establishes evidence for *feasibility/validity/reliability* of data collection instruments and methods;
- Supports the current hypothesis through results of *preliminary or pilot studies*; strengthens rationale;
- Shows that Subject *cooperation/participation levels* needed for the current study can be attained; also can be used to show that multi-site collaboration can be accomplished.
- *Preliminary studies give the reviewers information necessary to conclude that your study can be carried out by your research team*;

- **Approach:** a.k.a., DESIGN AND METHODS (1)

- **Introductory statement of general design** e.g., population-based case control study; historical cohort study; Cohort study with longitudinal follow-up; Randomized controlled trial (of intervention or treatment)--be brief but include enough detail so that the reader know about what to expect later;
- **Describe the "study base" population** from which the subjects are obtained, e.g., The residents of King county on Jan 1, 2005; Persons employed at Boeing for at least 10 years with entry date between 1/1/60and 1/1/84; The members of a specific health plan, etc; Try to ***describe this as a sampling frame*** rather than a haphazard, convenience group-- avoid *'persons referred to us from some senior centers and churches in the local area who were STH a neurologic problem' ;*
- **Describe the study process**: enrollment to follow-up; *A flow chart is very useful* since it shows reviewers the sequential process of the study: sampling and identification, consent and intake, exclusions, examinations, interview and data collection, treatment, follow-up, and outcome. This gives the reviewers a road-map that they can easily follow and it provides order for your later detailed description of each stage in the process.
- **Sampling or screening:** describe the sampling frame and *statistical* sampling technique (if used); describe any case-identification screening instruments referencing their use in other studies, include estimates of sensitivity and specificity; estimate briefly the overall number of subjects included (cases and others) -- more detailed discussion will fall in your 'sample size' section. If different sampling screening methods are used for each specific aim describe them there, instead
- **Project participation/refusal/exclusion rates**; strategies to collect data on and characterize refusals, as well as how you intend to minimize their number; for cohort studies emphasize minimization of the "drop-out" rate (subjects who quit after they are enrolled).
- **Case criteria:** diagnostic screening and diagnostic examination; *Use well established, standardized criteria,* if available; describe any reliability/ validity training procedures employed to assure careful and accurate compliance with the criteria; be sure to cite references for development and use of the criteria in similar studies. ***(A similar section should be included to describe Control Selection, in a case-control design. Poorly described control selection criteria and characterization will kill your application)***
- **Exposure Criteria:** what will be the basis for determining who is exposed or unexposed to the risk factors of interest (e.g., biomarkers, employment records, industrial hygienist ratings, proxy report)?
- **Data collection instruments:** describe and reference psychological tests, epidemiologic data interview instruments, medical chart/occupational abstraction forms or techniques; include discussion (pros and cons) of process: personal/telephone interview, use of proxy respondents, self-report questionnaires, record review and abstraction. *Describe interviewer training to maximize reliability and validity* , as possible.
- **Analysis Plan:** List each "Specific Aim" and; after each one list the variables which are

relevant to that aim. Describe the statistical techniques that will be applied and how the hypothesized results might look (if applicable). *List any additional research questions that will be answered or addressed by analysis of each aim.*

- **N.B.** Study Sections always have a hearty laugh when they see a very short Analysis section that simply says: *"our data will be analyzed using Chi Square and logistic regression utilizing SAS and STATA software"*, without reference to individual specific aims.
- **Sample Size/Power:** detailed description of the number of cases and other subjects you expect to enroll: starting with the study-base and showing your estimates of the subject loss due to exclusions, refusals, and other sources of attrition, plus accrual due to known or estimated disease incidence rates, arrive at a working estimate of the number of cases and others (exposed and unexposed) you think you will have available to study. It is almost always best to represent this as a table reflecting a range of power or minimum detectable RR and range of exposure (disease) prevalence, keyed to each Aim (if applicable). Usually investigators choose between "sample size" tables and Power tables/graphs depending on their study needs. It is not necessary to always have both.
- **Construct a paragraph describing data management**: coding, verification, entry, database error checking, loading, updating and security. Reference any database software which will be used and mention the hardware which will hold it.
- **Describe the "limitations"** of your study; there may be some general limitations like potentially underestimating the refusal rate and there may be others that apply only to an individual Aim; describing the limitations by aim may avoid a negative response from reviewers when one Aim has several limitations and others have none. *Avoid being overly negative*, much of this section is to let the reviewers know that you recognize and acknowledge the limitations that are obvious to them. *Win points by discussing how you would minimize the effects of the acknowledged limitations. Consider including some discussion about the value of "negative" results.*
- **Construct a "Time Line"** which shows the overall length of the study (usually 3-5 years) and when each major activity is to start and stop. *Plan to conduct some analyses early in the course so that you can have papers "in press" before you need to write a competitive renewal;* these are often process or descriptive papers rather than major outcome papers.

- Think about how the reviewers will evaluate your application

- **Significance:** Will it "drive the science" or appropriately address gaps in knowledge? Is it a replication of a previous study, if so what will it add?
- **Innovation:** Does the investigator develop or use innovative design or analytic techniques. Is the way, the investigator approaches or identifies research questions novel or innovative and potentially likely to achieve new and valid answers?
- **Investigator:** Does the PI/team have a "track record" of experience in the specific research field? Are necessary experts included to accomplish particular aspects of the

application, e.g. genetics, statistics, Imaging, clinical examination

- **Approach:** Are the methods sound and state-of-the-art? Can they accomplish the work proposed in the grant period. Is the design appropriate to the question? Do they have enough subjects/samples/power? This is usually the area that will make or break a grant and it is what the reviewers spend the most time with.
- **Environment:** Is there some reasonable description of the university or research institute setting which gives confidence that the study can be successfully completed, given the logistical support
- **Human Subjects appropriateness**: Describe the enrollment by Gender and minority status, and whether or not Children are enrolled. Show the proportion of each and provide rationale as to why particular categories may be excluded or may not represent proportions in surrounding geographic location. (Human subjects concerns will usually be addressed separately by your IRB)

PRESENTATION AND FORMATTING -Helpful hints

- Space is short, economize; Do any formatting you can to make the grant more eye appealing; reviewers are more likely to read it carefully.
- Margins and page requirements must be followed exactly as described in PHS 424 (or applicable form) or your grant will not be sent for review.
- If you are responding to an RFA or PA make sure you have addressed all requirements and necessary questions or interest or your application could be discarded as "Non-Responsive".
- White space makes grants more readable; squeezing as much text as possible into the assigned space will guarantee that it will not be read carefully by reviewers—*it will give them eye strain and a headache.*
- Use flow charts, tables and figures when they enhance clarity; synthesize and expand upon them in text but avoid just restating them exactly.
- Use a "Grammar Checker" to eliminate run-on sentences, non-specific modifiers, hanging clauses and other common examples of poor usage. Avoid construction which includes many words from the GRE vocabulary list; instead, try to emulate sentence construction used in the New York Times. *Spell check, too! Too many misspelled words show the reviewers that you are careless and unworthy.*
- **Rule of Tens**: No words longer than 10 letters; No sentences longer than 10 words; No paragraphs longer than 10 sentences. Maybe an exaggeration, but often a very useful guide…
- Pick a font that looks the most readable to you; insure that the size corresponds to the grant guidelines. (Arial or Helvetica 11 or 12 point is usually suggested by NIH).
- Don't allow secretaries/editors/administrators to make editorial changes in the scientific research plan sections, without your specific approval. Sometimes statistical or technical descriptions become nonsense when they are made "grammatical".
- Request draft reviews by technical and non-technical persons: have them mark the

areas that are unclear and indicate why.

- Make sure you check that all pages are present and in correct order before you send out the grant--mistakes like this happen all too frequently and it is very confusing to reviewers when several pages of "methods" are missing yet the included pages are numbered consecutively.