Roster of AD Training Program Mentors – Junior and Senior Mentors

Senior Mentors

William Banks, MD is a Professor in the Division of Gerontology & Gerontology in the UW Department of Medicine and the Associate Chief of Staff-Research and Development VA Puget Sound Health Care System. He has pioneered blood-brain barrier (BBB) mediated brain-body communication, publishing approximately 400 original articles and about 150 reviews and book chapters. Recent reviews have emphasized the BBB as an interface connecting the central nervous system and peripheral tissues via the blood, which form neuroimmune axes and use endocrine-like mechanisms. His lab has shown alterations in BBB function in mouse models of AD using the natural mutant SAMP8 and that the AD phenotype can be largely induced by neuroinflammation. They have shown that triglycerides can induce cognitive impairment, cross the BBB, and induce insulin and leptin resistance in the hippocampus. Treatment of hypertriglyceridemia or with intranasal insulin reverses cognitive impairments in various animal models. Dr. Banks is Associate Chief of Staff for Research & Development at VA Puget Sound and Professor of Medicine in the Division of Gerontology and Geriatric Medicine at UW. He is Editor-in-Chief of *Current Pharmaceutical Design* and served on 20 other editorial boards, including those for *J Pharmacy Expt Therap*; *Endocrinology*; *Peptides: An International Journal*; *Brain, Behavior, & Immunity*; *J Cerebral Blood Flow & Metabolism*, *Fluid and Barriers of the CNS*; and *Experimental Biology and Medicine*. He is the recipient of the Norman Cousins Award, the William S Middleton Award, Milton D Overholser Memorial Lecturer, and is past president of the Psychoneuroimmunology Research Society.
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Elizabeth Blue, PhD, is an Associate Professor in the UW Department of Medicine, Division of Medical Genetics. She received her Ph.D. in Anthropology from the University of Utah, specializing in population genetics, followed by postdoctoral training in statistical genetics at UW. She incorporates tools from population genetics and genetic epidemiology to detect regions of the genome influencing disease. Her long-term research goals are to identify variants influencing disease within and between human populations, as well as to predict and evaluate their functions. Much of Dr. Blue's research focuses on identifying genetic factors influencing risk and age-at-onset of AD, incorporating family- and population-based approaches with functional annotations and predictions of variant pathogenicity. She has also worked to discover genes influencing rare disorders. She is interested in the biology differentiating the genetic underpinnings of Mendelian disorders (single gene, high penetrance) from complex traits influenced by many genetic and environmental factors (e.g., AD, cardiovascular disease), and how genetic modifiers fit within that spectrum. She is an active collaborator, a co-investigator in several large-scale sequencing projects, including the Alzheimer Disease Sequencing Project, the UW Center for Mendelian Genomics, and the Pacific Northwest Undiagnosed Disease Network clinical site.
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Elizabeth Buffalo, PhD, is a Professor of Physiology and Biophysics at UW and Chief of the Neuroscience Division at the Washington National Primate Research Center. She seeks to increase our understanding of the neural mechanisms that support learning and memory. Her studies aim to develop new treatment strategies and better methods of diagnosis for patients with diseases that impair memory, including temporal lobe epilepsy, depression, schizophrenia, and AD. Dr. Buffalo and her trainees use neurophysiological techniques to simultaneously record activity in the hippocampus and surrounding cortex of awake, behaving monkeys that have been trained to perform various memory tasks; Dr. Buffalo and her trainees investigate how changes in neuronal activity correlate with the monkey's ability to learn and remember. These studies attempt to better understand how medial temporal lobe circuits support memory formation. Another focus of the research in the Buffalo laboratory is the investigation of spatial representations and synchronous activity in the hippocampus and adjacent medial temporal lobe cortex.[25] Dr. Buffalo has expertise in using extracellular recording techniques, including spectral analysis techniques, to investigate the role of oscillatory activity and neuronal synchronization in memory formation.
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David Cook, PhD, is a GRECC investigator, Research Associate Professor in the Division of Gerontology and Geriatric Medicine, Dept. of Medicine, UW, and Director of the UW/VA blast laboratory. He has two interrelated research interests: elucidating the role astrocytes play in AD pathogenesis and understanding the mechanisms by which blast mTBI (considered the "signature injury" of the wars in Iraq and Afghanistan) increases the risk for neurodegenerative dementing disorders. Dr. Cook's group has found decreased levels and aberrant expression of glutamate transporters in the brains of AD patients, and these transporters are very important in regulating metabolism in the brain, as well as preventing neurotoxicity. An important goal of this research is to discover new strategies to help astrocytes, which clear most of the glutamate in the brain, do a better job of protecting neurons and synapses from AD-related impairment and loss. To better clarify the relationship between mTBI and neurodegeneration, Dr. Cook's laboratory has developed a battlefield-relevant mouse model of blast-induced mTBI. This research is being done in close collaboration with fellow ADTP Preceptors Drs. Peskind, Kraemer, and Banks. The goal of this work is to better understand the mechanisms of blast-induced repetitive blast mTBI and to provide an *in vivo* platform for testing potential treatments that will forestall blast-related mTBI developing into to aging-related neurodegenerative disorders. Dr. Cook is also using this approach to investigate genetic susceptibility factors that increase the risk of mTBI, particularly those risk factors that are thought to be in common between TBI, AD, and other neurodegenerative diseases.
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Paul Crane, MD, MPH, is a Professor in the UW Department of Medicine and an Adjunct Associate Professor in the UW Department of Health Services. He applies psychometric methods to cognitive tests, including neuropsychological tests used in the elderly. He is a PI, along with Dr. Eric Larson, of the Adult Changes in Thought (ACT) study, an ongoing prospective cohort study that has identified incident dementia and AD cases since 1994 and then followed consenting cases to autopsy. At this time, more than 5,500 participants have been enrolled in the study, with more than 1,000 incident dementia cases identified and 800 autopsies completed. ACT has a wealth of risk factor and cognitive data that have served as research material for graduate students and

postdoctoral trainees. Recent high-profile ACT publications by Dr. Crane have investigated glucose and dementia and anticholinergic medications. Dr. Crane has been on the coordinating committee of the NIA-funded Friday Harbor Advanced Psychometrics Workshop since its inception. This workshop emphasizes educational training of applied researchers at all stages of training, including a special emphasis on postdoctoral fellows. Dr. Crane has been identified as the leader of the Cognition Harmonization Group for the harmonization efforts associated with the Alzheimer's Disease Genetics Consortium and the Alzheimer's Disease Sequencing Project, and his lab serves as the Psychometrics Component for the UW ADRC Clinical Core and for several related grants that are harmonizing cognitive data across multiple studies. All of these initiatives provide numerous potential binding sites for graduate trainees.
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Jose Garcia, MD, PhD, is an GRECC clinical investigator and Associate Professor in the Division of Gerontology and Geriatric Medicine, Dept. of Medicine, UW, focuses on the role of ghrelin, androgens, and other anabolic pathways in different wasting conditions, including aging and cachexia. His basic laboratory work focuses on understanding the molecular pathways involved in the development of muscle wasting, fat atrophy, and anorexia in the context of aging and cachexia, as well as in the development of novel targets for these conditions. Dr. Garcia also conducts human trials in patients with cancer anorexia and cachexia that aim to characterize the pathways involved and to identify the mechanisms of action for several potential therapies. More recently, he has started a program to study hormonal deficiencies in the setting of TBI.
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Richard G. Gardner, PhD, is an Associate Professor in the Dept of Pharmacology at UW and focuses on ubiquitin and ubiquitin-like modifications. These interests and expertise were honed over the last 20 years studying the mechanisms of ubiquitin-mediated protein regulation using a broad collection of genetic, biochemical, cell biological, and molecular methods in the budding yeast *Saccharomyces cerevisiae*. Since the inception of his lab 12 years ago in the Department of Pharmacology at UW, his studies have included elucidating the mechanisms of ubiquitin-mediated misfolded protein degradation in nuclear protein quality control, understanding the functions of ubiquitination in regulating ribosome biogenesis at the level of ribosomal rDNA transcription and RNA polymerase I function, and uncovering novel roles of protein sumoylation in response to cellular stress.
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Thomas Grabowski, MD, is the Director of the UW ADRC, Professor in UW Departments of Radiology and Neurology, UW MBWC/ Director of the UW Integrated Brain Imaging Center. His laboratory in the UW Integrated Brain Imaging Center investigates the functional organization of the human brain using neuroimaging approaches, and applies this knowledge to neurologic disease, especially AD and related neurodegenerative diseases. He has particularly worked to elucidate brain systems supporting lexical-semantic retrieval using PET and fMRI imaging. Current projects focus on functional connectivity measures as preclinical biomarkers of neurodegenerative disease, topographic patterns of degeneration from MRI and tau PET in typical

and atypical AD, and neuroimaging approaches to understanding resilience to AD. This work is closely affiliated with the UW ADRC.
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Jeffrey Iliff, PhD, is Associate Director for Research in the Northwest MIRECC at the VA Puget Sound, and has joint appointments as Professor of Psychiatry and Behavioral Sciences and of Neurology at UW SOM. He currently serves as Co-Lead (along with Dr. Brian Kraemer) of the University of Washington ADRC Research Education Component (REC) and is a member of the ADTP T32 Executive Committee. Dr. Iliff joined the VA MIRECC and UW in June 2019. In his prior position at Oregon Health & Science University, Dr. Iliff was Vice Chair for Basic Science Research in the Department of Anesthesiology and Perioperative Medicine, overseeing research mentorship for graduate and medical students, postdoctoral fellows, medical residents and fellows, and junior faculty throughout a department of over 70 faculty. He was a member of the OHSU Neuroscience Graduate Program and Program in Molecular and Cellular Biosciences teaching faculty, and he served as a faculty mentor for the NIA-funded T32 "Neuroscience of Aging, Neurodegeneration and Alzheimer's Disease" and the NHLBI-funded T32 "Training in Translational Science and Cardiovascular Medicine". Dr. Iliff's lab focuses on the biology of the newly characterized glymphatic system, including using cellular, molecular and imaging techniques to define the glial and vascular contributions to the development of Alzheimer's disease and related dementias.
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Suman Jayadev, MD, is an Associate Professor, UW Dept of Neurology, Director of the UW Neurogenetics Clinic/UW Huntington Disease Center of Excellence, and ADRC Clinical Core PI Clinical Core PI. She is interested in inflammatory mechanisms of neurodegeneration. Dr. Jayadev is a practicing neurogenetics clinician, and one focus of her work is the function of familial AD presenilin gene variants in AD pathogenesis, such as how the immune response to amyloid is influenced by AD gene mutations. She collaborates with a multi-disciplinary team to study how common genomic risk also confers risk for AD using bulk and single cell transcriptomics of human archived brain tissue. She further tests the consequences of AD-associated genomic risk using iPSC derived microglia cells for hypothesis driven in vitro experiments. She collaborates with colleagues in Genome Sciences, Medical Genetics and the Institute for Stem Cell and Regenerative Medicine.
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Matt Kaeberlein, PhD, is a Professor in the UW Department of Pathology Co-Director of the UW Nathan Shock Center of Excellence in the Basic Biology of Aging, Director, Healthy Aging and Longevity Research Institute, and Director of the Dog Aging focuses on understanding the molecular mechanisms of biological aging and how these mechanisms drive age-associated diseases, particularly AD. Age is the single greatest risk factor for AD, and it is clear that changes associated with normative aging are at least permissive for, and perhaps causal in, AD progression. They use both nematode (*C. elegans*) and mammalian (companion dogs) models to study the relationship between normative aging and AD. In nematodes, they have developed and utilized several transgenic models of amyloid beta, alpha-synuclein, and Tau toxicity to identify genetic

and pharmacological modifiers of Alzheimer's-associated toxicity. In companion dogs, they are pioneering studies combining assessment of cognitive function, identification of serum biomarkers, and neuropathological hallmarks of Alzheimer's-like dementia to identify genetic and environmental factors that influence these parameters in a socially-relevant animal model that shares the human environment. Dr. Kaeberlein has won several awards for his research including the Parkin Award, University of Iowa Aging Mind and Brain Initiative Award, and Frontiers in Aging and Alzheimer's Disease Pioneer Award. Dr. Kaeberlein has been elected as a Fellow of the American Aging Association Fellow and a Fellow of the American Association for the Advancement of Science.
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C. Dirk Keene, MD, PhD, is the Director of Neuropathology at UW, Associate Professor in the Department of Pathology,Adjunct Associate Professor in Departments of Ophthalmology and Neurological Surgery at UW. He works to to contribute knowledge and resources to brain aging, neurodegenerative disease and neurotrauma research that lead to mechanistic discoveries and effective preventive and therapeutic strategies. He works towards this goal through neuropathological research and innovation, collaborative science, and education. He is a Board Certified in Anatomic Pathology and Neuropathology and perform hundreds of comprehensive neurodegenerative disease autopsies for diverse clinical and research studies, including the University of Washington (UW) Alzheimer's Disease Research Center (ADRC), the Kaiser Adult Changes in Thought (ACT) study, the Pacific Northwest Brain Donor Network (PNBDN), the Seattle Longitudinal Study (SLS), and the Pacific Udall Center of Excellence (PUC) for Parkinson's disease. As Leader of the UW BioRepository and Integrated Neuropathology (BRaIN) Laboratory and Precision Neuropathology (NP) Core, he supervises a team whose primary goal is to respectfully and expeditiously perform brain autopsies in a manner that maximally and optimally preserves tissues for diverse research applications while providing accurate and timely neuropathological diagnoses according to the latest guidelines. A major goal for my lab is to promote development of technologies that accentuate the scientific utility of human brain tissue and biofluids, and to foster sensible sharing of these data and tissue resources with researchers in the US and internationally to propel scientific discovery and maximize the investment of the donor, his or her loved ones and caregivers, and clinical research teams and studies. Dr. Keene utilizes discoveries derived from these critical tissues to develop and test hypotheses in experimental systems in my own lab, and with collaborators, in pursuit of mechanistic knowledge to drive therapeutic intervention. Finally, as the Director of the UW Neuropathology Fellowship and teacher/mentor for undergraduates, medical and graduate students, fellows, and junior faculty, I devote time and resources on education and community outreach critical to motivate the next generation of clinicians and scientists to join the campaign to solve neurodegenerative disease.
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Eric Larson, MD, MPH, is a Clinical Professor in the UW School of Public Health, Health Services, Executive Director and Senior Investigator at the Kaiser Permanente Washington Health Research Institute, Administrative Core, and Associate Director of the UW ADRC. Dr. Larson was instrumental in establishing one of the first registries of AD patients in the nation (U01 AG006781), which in recent years has evolved into the ACT epidemiologic cohort; this work now

focuses on the characterization of risk factors associated with brain aging and incident dementia. The group's research has described the importance of coexisting dementia and depression, adverse drug reactions causing or exacerbating dementia, the importance of comorbid conditions, the importance of sensory impairments in exacerbating cognitive function, and increased morbidity of falls and fractures in patients with AD. His recent work also has highlighted the relationship between vascular risk factors and the co-occurrence of multiple neurodegenerative processes in late-life brain aging, suggesting strategies for prevention. The "living learning laboratory" of the ACT study has led to impact papers on the effects of critical illness on dementia severity, the relationship between glycemic levels and risk of dementia, and the increased risk of dementia in persons exposed to anticholinergic medications. The ACT study laboratory has been a good place for fellows and those with career development awards to pursue their research interests. Available data include detailed electronic records, ACT study data, extensive chart reviews on autopsied subjects, a neuropathology sample of approximately 600 specimens, extensive genomic data, and, in the next funding cycle, actigraphy and other data.
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Ed Lein, PhD, is an investigator at the Allen Institute for Brain Science and an Affiliate Professor in the Department of Neurological Surgery at UW. He has provided scientific guidance for the creation of large-scale gene expression atlases of the adult and developing mammalian brain as catalytic community resources, including the inaugural Allen Mouse Brain Atlas and a range of developmental and adult human and non-human primate brain atlases. Particular interests of Dr. Lein include using the transcriptome as a core phenotype to understand brain organization at the regional, cellular and functional level, to understand what is unique about human brain, and to understand what is disrupted in brain diseases. He now co-leads the Cell Types program and directs the Human Cell Types department, that aim to create a comprehensive understanding of human cortical cell types and circuits and what is specialized in human cortex, using quantitative single cell transcriptomic, anatomical and functional methods. Dr. Lein. has recently turned his attention to how AD perturbs brain gene expression and organization at the molecular and cellular level.
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Gail Li, MD, PhD, has completed several epidemiological studies investigating the associations between AD and cardiovascular risk or protective factors (e.g., hypertension, hypercholesterolemia, and hyperglycemia) in a longitudinal cohort. In this work, Dr. Li and her colleagues have found that cholesterol-lowering drugs known as statins are associated with both a decreased risk of dementia and a decreased number of neuritic tangles in the brain. Recently, she has expanded her interest to the effect of air pollution on aging brain and AD. She has mentored a PhD graduate student Ms. Rachel Shaffer and published their research findings on association between air pollution and vascular damage biomarkers. She is an integral part of AD fluid biomarker research team.
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Michael MacCoss, PhD. The focus of the MacCoss laboratory is in the development and application of cutting-edge mass spectrometry-based technologies for the analysis of complex

protein mixtures. They are applying these approaches to study AD and ADRD related changes in the CSF and brain proteomes. Dr. MacCoss' primary area of expertise is in protein biochemistry, nanoflow liquid chromatography, mass spectrometry instrumentation, and computational analysis of mass spectrometry (MS) data. He has >20 years of mass spectrometry experience that bridges the fields of protein MS, isotope ratio mass spectrometry, and quantitative MS. His laboratory is also experienced with all aspects of computational analysis of MS data – an essential component of any large-scale proteome analysis. Furthermore, Dr. MacCoss' doctoral training focused on the development of methodology for the measurement of human amino acid and protein metabolism in vivo using stable isotope tracers. The MacCoss laboratory has been actively applying these tools to important areas of biology including, but not limited to, the basic biology of aging, protein-protein interactions, insulin signaling, measurement of protein half-life, transcriptional regulation, characterization of post-translational modifications, proteogenomics, and clinical diagnostics. The MacCoss laboratory is widely known for its expertise in the development and support of proteomics software tools. The laboratory has trained >12 post-doctoral fellows and >9 graduate students in the use and application of MS. The training occurs from both the environment created by the group members, the senior staff, and Dr. MacCoss himself. Dr. MacCoss's trainees are widely sought after and are known as being extremely well trained.
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Abhinav Nath, PhD, is an Associate Professor in the department of Medicinal Chemistry. His research focuses on understanding how highly dynamic and intrinsically disordered proteins recognize small molecules and biological binding partners and how they self-assemble or aggregate in ways important to normal function or pathological dysfunction. His laboratory employs a variety of experimental and computational biophysics techniques, including single-molecule fluorescence, NMR, mass spectrometry, molecular simulations and machine learning. Much of his recent work has focused on microtubule-associated protein tau, a key player in AD, frontotemporal dementias (FTDs), chronic traumatic encephalopathy (CTE) and related dementias. They have developed novel families of tau-binding small molecules, and explored the relationships between chemical structure and their ability to inhibit tau aggregation *in vitro*. Their work has also revealed how different molecular chaperones interact with tau to delay or halt its aggregation, and defined the quasi-ordered nature of certain tau/chaperone complexes. More broadly, they also seek to understand the diverse roles of protein self-assembly in microbial pathogenesis and the host response, the efficacy and disposition of protein-based therapeutics, and the molecular recognition mechanisms of drug-metabolizing enzymes and transporters.
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Daniel Promislow, PhD, is a Professor in the Departments of Pathology and Biology. His laboratory focuses on the genetics and systems biology of aging and age-related traits. His lab uses genetically variable populations of the fruit fly, *Drosophila melanogaster*, to identify genetic and metabolomic signatures of variation. Working in collaboration with other researchers at UW, he serves as PI on an NIH R01 using the fruit fly as a model to identify natural genetic variations that modify the toxic effects of Aβ and tau in the fly brain. In parallel with his fly work, over ten years ago he began epidemiological studies of aging in companion dogs, work that led to an NIA-funded U19 grant to support a long-term longitudinal study of aging in dogs, the Dog Aging Project. As

PI of this project, Dr. Promislow leads a large nationwide interdisciplinary team creating a long-term study of tens of thousands of dogs across the US, focused on the genetic and environmental determinants of aging and age-related disease. A recently funded ancillary study is measuring Aβ and tau in the brains of deceased dogs, and his laboratory is also developing new metrics to allow 'citizen scientists' to measure age-related cognitive decline in their pet dogs. Dr. Promislow's has received the Bennett J. Cohen Award in aging research, the Glenn Foundation Award for Medical Research and he is a fellow of the American Association for the Advancement of Science and a Rhodes Scholar (1986, British Columbia and Merton College, Oxford).
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Murray Raskind, MD's work addresses stress hormone contributions to the pathophysiology and psychopathology of AD, aging, and other neurobehavioral disorders. His research program has combined both clinical research in human subjects, using pharmacologic and physiologic challenge strategies, and basic research in mammalian brain tissue at the receptor and gene expression level. Dr. Raskind's laboratory has demonstrated enhanced hypothalamic-pituitary-adrenal (HPA) axis responsiveness at a suprapituituary level in both normal aging and AD, and provided evidence that suggests decreased HPA axis sensitivity to glucocorticoid feedback inhibition as one mechanism underlying this potentially deleterious phenomenon. Dr. Raskind's work has demonstrated enhanced brain noradrenergic function in AD[61] and elucidated its role in the disruptive agitation that is so common in the middle and late stages of disease. Dr. Raskind serves as Co-PI (with ADTP Program Director, Dr. Peskind) of the NIA and Alzheimer's Association-funded Alzheimer's Disease Cooperative Study national multicenter randomized controlled trial of the centrally active alpha-1 adrenergic antagonist, prazosin, for disruptive agitation in AD. In 2011, Dr. Raskind was awarded the Department of Veterans Affairs John P. Barnwell Award for excellence in clinical research to honor his work on antiadrenergic approaches to treating behavioral disorders. Dr. Raskind has also taken a leadership role in clinical pharmacologic studies of other drugs with potential therapeutic effects in cognition and behavioral problems in AD. For the past two decades, he has been the physician facilitator of the Black Veterans Support Group of Puget Sound and has worked closely with this group to facilitate participation by the African American community in AD research.
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Wendy Raskind, MD, PhD, is Professor of Medicine (Division of Medical Genetics) and Psychiatry and Behavioral Sciences (Joint), and Genome Sciences (Adjunct). She is an affiliate of the Center on Human Development and Disability, Graduate Program in Neurobiology and Behavior, Institute for Stem Cell and Regenerative Medicine, and Cancer Consortium/Cancer Basic Biology Program, UW and Fred Hutchinson Cancer Research Center. She is a member of the UW Huntington Disease Center of Excellence Advisory Board and the Northwest Autopsy Repository Oversight Committee. The focus of Dr. Wendy Raskind's research is to identify and further study the genes that cause neurodegenerative disorders, including AD, unusual parkinsonian disorders, and cerebellar atrophy. In collaboration with ADTP Internal Advisor, Dr. Thomas Bird, and through the UW Neurogenetics clinic, subjects are ascertained, biological samples are collected, and family members are recruited. Candidate causative genes are selected through exome sequencing and further analyzed for co-segregation with disease in the pedigree.

Her laboratory group is actively studying the pathogeneses of multiple diseases whose causative genes they have identified, including a parkinsonian disorder with tauopathy (XPDS) and a movement disorder in which abnormal tau deposits were found in a brain (ADCY5). In addition, they are studying the effect of a missense variant, R47H, in TREM2, a recently identified risk factor of similar magnitude to APOE-□4. Such studies include neuropathologic evaluations of autopsy material when available, functional analyses *in vitro*, generation of iPSCs and brain organoids in which to delineate the process of neurodegeneration and as a resource in which to investigate potential therapeutic compounds.
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May Reed, MD's longstanding research interest has been in defining the effects of aging on tissue repair, the microvasculature, and the extracellular matrix (ECM) in vitro and in vivo. Her early studies were based in structural matrix components, such as Collagen I, and matricellular (regulatory) matrix components, such as SPARC and thrombospondin. In more recent studies of normal aged brains and brains affected by neurodegeneration, Dr. Reed has focused on the ECM component, hyaluronan (HA), a widely expressed non-sulfated glycosaminoglycan that can range from a single disaccharide to thousands of repeating disaccharide units. As the quantity and size of HA determines its effect on surrounding cells and ECM, she is especially interested in matrix components that regulate HA synthesis and degradation such as TSG-6. Dr. Reed has found that the brain and brain microvasculature is rich in HA and TSG-6, and that these components markedly increase during neuroinflammation and neurodegeneration. However, little is known as to the underlying mechanisms of HA accumulation and size changes, and the subsequent impacts on aging and neurodegenerative processes. Dr. Reed's studies use archived human brain tissues from normal subjects and those with AD and amyloid angiopathy, as well as murine and cell culture models, to elucidate the relationship between ECM and brain aging, neuropathology and microvascular dysfunction.
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Stephen Thielke, MD, MSPH 's research seeks to ascertain the optimal treatments for patients with AD dementia, especially as they progress through advanced stages of the disease.[67] Although considerable research has explored the effects of cholinesterase inhibitors in mild to moderate AD, less is known about the effects of these medications for patients who have more profound functional and cognitive limitations. Very little is known about if, when, or how cholinesterase inhibitors for treating dementia can be stopped. It is particularly challenging to study this issue because patients and families consciously use medication and may attribute effects to it during sustained use, and because patients with dementia progressively worsen, making it impossible to track specific medication consequences within individuals. Dr. Thielke's current research applies a placebo-controlled, double-blind discontinuation design. Patients with advanced dementia will either continue on their current cholinesterase inhibitor (in a blinded form) or switch to placebo. The primary outcome is the patient's and caregiver's decision to return to the pre-study dose of medication over a period of six weeks. The results will help direct the pharmacological management of dementia. Dr. Thielke is Director of the VA Puget Sound Geriatric Psychiatry Fellowship, Chair of the VA regional Dementia Committee, and serves on the national VA Dementia Education Workgroup and Dementia Education Training Committees.

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Timothy Thornton, PhD, is the Robert W. Day Endowed Professor of Public Health and an Associate Professor and Graduate Program Director for the Department of Biostatistics at the University of Washington (UW). He is also an Affiliate Investigator at the Fred Hutchinson Cancer Research Center. His research lab develops statistical and computational tools for the analysis of large-scale and high-dimensional data, with an emphasis on methodology for the analysis of genotyping and sequencing data for new insights into the genetic underpinnings of human health and health disparities. His collaborative research is largely focused on identifying genetic and/or environmental factors contributing to variability in clinical outcomes. Dr. Thornton is involved in several NIH-funded projects for the genetics of complex disorders in multi-ethnic populations. He is a co-PI for the Data Coordinating Center for the Trans-Omics for Precision Medicine (TOPMed) Program. He is also a co-investigator for the Alzheimer's Disease Sequencing Project (ADSP) as well as a study for the genomic characterization of AD risk in the Puerto Rican populations. Dr. Thornton is the PI and program director for an NIH/NIGMS funded T32 training program in statistical genetics at UW. In addition, Dr Thornton is an associate editor for the American Journal of Human Genetics.
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Debby Tsuang, MD, MSc, is the Director of the Geriatric Research, Education, and Clinical Center (GRECC). She has directed multi-disciplinary efforts to better understand the biology, genetics, etiology, prevention, and treatment of neurodegenerative disorders. Her research has focused on the genetic and phenotypic characterization of neurodegenerative disorders. Within this context, her recent work uses innovative genomic and bioinformatic technologies to elucidate the complex genetic architecture underlying dementia such as AD and Lewy body disorders (LBD). More recently, she has been involved in big-data analytic projects using the VA's electronic health records system. Given that dementia is underdiagnosed in the Veterans Health Administration (VHA), she has developed machine learning models for dementia diagnosis. Finally, in line with her interests in the earlier detection of dementia, she is leading a pilot study to determine if objective measures of sleep and movement patterns can effectively differentiate between people living with AD and LBD.
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Ellen Wijsman, PhD's research examines genomic data at various levels of resolution to track inherited variability, with the goal of identifying genes of medical importance in humans. She specifically focuses on neurodegenerative, aging, and neurodevelopmental diseases, with studies that focus on both family-based and population-based designs, and with data that span the 'omics possibilities but is grounded in genomics. In this context, her group's research is directed toward the development and application of statistical and quantitative methods for the analysis of human complex traits, including a heavy emphasis on AD. She works on AD data collected in collaboration with other local and external collaborators, as well as aggregated through large consortia including the AD sequencing project. Other investigators provide appropriate clinical and molecular expertise in their respective disciplines to perform research in a strong team-

oriented environment. Late-onset diseases, such as AD and the phenotypes associated with aging, typically are described as complex traits, and provide many statistical and analytical challenges; to address these challenges, Dr. Wijsman's laboratory uses and develops statistical methodologies associated with gene localization, modeling the genetic architecture, genetic inheritance, population structure, linkage disequilibrium and haplotype analyses[77, 78], and genotype imputation[79-81], to provide evidence for causal variants in the context of DNA sequence variability and gene expression associated with disease risk.
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Jessica Young, PhD. The primary goal of Dr. Young's new laboratory at UW is to understand the molecular and biochemical mechanisms underlying sporadic AD, the most common neurodegenerative disorder in elderly adults. She is working with many groups at UW, including the ADRC, to develop a human stem cell model of sporadic AD. This work includes a collaboration with Senior Mentor, Dr. Keene, of the ADRC Neuropathology Core to develop stem cell lines from autopsy tissue (leptomeninges) and a collaboration with Senior Mentor, Dr. Jayadev, to understand cellular and molecular mechanisms of variation in the *SORL1* gene using patient-derived and gene-edited human iPSCs.
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Chang-En Yu, PhD. Dr. Yu's research focuses on the genetics and epigenetics of AD. His laboratory has been working on the *APOE* gene to identify additional functional elements that might contribute biological effects to AD risk. Recently, his lab has identified a circular RNA (circRNA) of *APOE*, which has never been reported before. Their finding on human *postmortem* brain suggests that expression level of this circRNA is associated with both AD disease status and AD age-at-onset. Thus, this *APOE* circRNA has a potential to serve as a new biomarker for early detection of AD. The long-term goal is to apply this knowledge to develop preventive or interventive strategies for AD and other age-related neurodegenerative disorders.
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Cyrus Zabetian, MD, MS. The primary goal of Dr. Zabetian's research program is to elucidate genes that increase risk or modify phenotypic characteristics of Parkinson's disease (PD) and related disorders. This work is accomplished using family-based, case-control, and longitudinal cohort studies. Efforts to discover causative genes are performed using over 200 multiplex PD families enrolled across North America through the Parkinson's Genetic Research Study. Dr. Zabetian leads the PD Cognitive Genetics Consortium and through this endeavor has discovered several genes that modify the rate of cognitive decline and/or the patterns of cognitive dysfunction in PD patients. His group is now using machine learning methods to uncover complex relationships between genotype and phenotype in PD and to build predictive models aimed at identifying patients at high risk for rapid symptom progression.
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Ning Zheng, PhD, is an Investigator of the Howard Hughes Medical Institute and Professor in the Department of Pharmacology at UW SOM. He is a Fellow of American Association for the Advancement of Science. Research of the Zheng laboratory focuses on the molecular and structural mechanisms by which protein-protein, protein-nucleic acid, and protein-small molecule interactions control eukaryotic biology and human diseases. Since its establishment in 2002, his research group has made major contributions to the field of protein ubiquitination and ubiquitin-dependent protein degradation. Through the studies of plant hormone perception, his lab raised the concept of "molecule glue" in chemically-induced ubiquitin ligase-substrate interactions. His group is now actively pursuing the discovery of therapeutic compounds that are capable of promoting the ubiquitination and degradation of tau and other proteins involved in neurodegenerative diseases. A newly established collaboration between his group and Dr. Brian Kraemer's lab holds the promise to reveal the structure-function relationships of mSUT2 and to enable the development of its inhibitor as a therapeutic target for AD.
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Junior Mentors:

Martin Darvas, PhD, is an Assistant Professor in the Department of Pathology at UW. The research goal of his laboratory is to understand structural and molecular bases of cognitive impairment that occurs with age and neurodegenerative diseases like AD and PD. To achieve that goal, his lab primarily focuses on the investigation of the infectious-disease etiology of AD. Dr. Darvas's secondary goal is to develop quantitative and precision molecular neuropathology methods to improve understanding of pathologic changes in clinical samples. He was recently awarded an NIH R01 grant to investigate the infectious disease etiology of AD. Dr Keene will serve as the Senior co-mentor with Dr. Darvas for any ADTP trainees that join his group.
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Shelly Erickson, PhD, explores mechanisms by which systemic inflammation contributes to cognitive dysfunction and dementias such as AD, with a particular focus on the BBB as a disease-modifying interface. One of her lab's projects focuses on mechanisms of CNS dysfunction that may contribute to AD following ozone exposure. Ozone is a widespread toxicant in air pollution, and epidemiological studies have shown that ozone exposure increases AD dementia risk. However, the primary reactions of ozone occur exclusively in the lungs, and so it has been proposed that CNS dysfunction following ozone exposure occurs, in part, through circulating factors that interact with the BBB. She is actively studying one such factor, serum amyloid A, and its contributions to neurovascular dysfunction, neuroinflammation, and amyloid beta accumulation in the CNS in context of acute and chronic ozone exposures in mice. A second ongoing project in my lab utilizes human iPSC-derived models of the BBB to study aspects of BBB dysfunction such as disruption and transporter defects that may contribute to AD. In these models, they are studying how factors in blood from aged humans with vs. without dementia may contribute to different modes of BBB dysfunction. A third project in her lab aims to determine mechanisms by which

senolytic drugs may protect against BBB dysfunction with aging. Dr. Banks will serve as the Senior co-mentor with Dr. Erickson for any ADTP trainees joining her group.
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Caitlin Latimer, MD, PhD, is a neuropathologist by training who has had the opportunity to participate in the neuropathologic evaluation of numerous research brain autopsies from several iconic studies, including the ACT Study, the UW ADRC, the Seattle Longitudinal Study (SLS), the Nun Study (NS), and the Honolulu-Asia Aging Study (HAAS). As a junior faculty member, she received a competitive NIA Career Development Award in Neuropathology Core Leadership through a supplement to the UW ADRC providing her with the opportunity to further develop diagnostic expertise and develop skills in neuropathology core leadership, both at UW and at other nationally renowned neuropathology cores. Her research focus is on neuropathologic changes of age-related neurodegeneration, particularly on the underlying pathophysiology, and potential synergies, of multiple pathologic proteins of late-onset AD. She recently received a career development award which will allow her to develop new skills in utilization of *C. elegans* as a model system for studying the interactions of pathologic proteins and the underlying genetic pathways. This work will address critical gaps in knowledge surrounding the interactions between TDP-43 and tau pathology. Drs. Keene and/or Kraemer will serve as the Senior co-mentor with Dr. Latimer for any ADTP trainees joining her group.
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Nicole Liachko, PhD, is a molecular biologist and research geneticist committed to improving the lives of those afflicted by neurodegenerative diseases of aging including Amyotrophic Lateral Sclerosis (ALS), Frontotemporal Lobar Degeneration (FTLD), and AD. She has built a research program centered on understanding the biology underlying pathological TDP-43: the major protein aggregate in ALS and FTLD-TDP, and a secondary pathology in up to 50% of patients with AD. During the course of these studies, she has developed and characterized powerful models of neurodegenerative disease using the nematode, *C. elegans*, mammalian cultured cells, and mouse primary neurons. She has used these models to identify molecular changes that promote disease and to demonstrate that interventions in these processes provide neuroprotection. Her current projects seek to characterize cellular mechanisms driving TDP-43 neurotoxicity, including the regulation of its post-translational modifications and interactions with other neurodegenerative disease proteins including tau and Aβ. The long-term continuing goal of her research is to leverage these mechanisms for neuronal health through the identification and validation of new therapeutic targets for neurodegenerative proteinopathies. Dr. Kraemer will serve as the Senior co-mentor with Dr. Liachko for any ADTP trainees joining her group.
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Erik Carlson, MD, PhD, is an Assistant Professor at the UW SOM, Department of Psychiatry and Behavioral Sciences, and a Clinician-Scientist at the VA Puget Sound GRECC. Dr. Carlson focuses on understanding cerebellar circuits as they relate to psychiatric and neurodegenerative illnesses and utilizes this knowledge to inform and improve current and novel treatments for psychiatric disorders, primarily in the cognitive domain. His research utilizes mouse behavior, *in*

vivo electrophysiological recordings, gene targeting, viral vector production, translational profiling, chemo- and optogenetic tools, site-specific intracranial viral vector injection, and protein chemistry. As such, he utilizes a multi-disciplinary approach combining genetic, electrophysiological, pharmacological and behavioral techniques. One of his laboratory's discoveries has been the role of a catecholaminergic circuit from the locus coeruleus to the lateral or dentate nucleus, which supports several cognitive functions involved in neurodegenerative diseases such as AD. They are now using specific viral techniques to understand how this circuit is affected by pathological molecules such as hyperphosphorylated tau. He has recently developed rich collaborations with colleagues in Neuropathology, Radiology and Biostatistics to investigate human cerebellar circuitry and function. Drs. Tsuang and/or Kraemer will serve as the Senior co-mentor with Dr. Carlson for any ADTP trainees joining his group.
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James Meabon PhD, studies the role that neuro-immune mechanisms play in brain function during recovery from TBI and how those mechanisms, when left unchecked, may yield ongoing neurodegeneration. The main cells of interest are microglia and peripheral immune cells functioning within the CNS. Using advanced microscopy technologies to follow the behavior of these cells inside the intact brain, Dr. Meabon's laboratory previously showed that myeloid cells (i.e., microglia, macrophages and monocytes) continuously survey their environment and can rapidly contain small vascular injuries that dynamically open and close within a few minutes following TBI. These findings inspired numerous studies aimed at understanding the mechanisms and the significance of such unexpectedly dynamic injury processes for neural repair and dysfunction. Central to this they found that modulation of nitric oxide signaling inhibits immune cell infiltration into the brain, normalizes the BBB, and leads to future functional improvements in measures of brain function. His laboratory has identified microglial transcriptomic phenotypes induced by TBI that are dependent upon the degree and frequency of BBB disruptions within a brain region; a common phenomenon among multiple sclerosis, AD, and stroke. Currently they are developing novel methods for imaging the three-dimensional brain multiplexed with high-dimensional imaging mass cytometry to gain an unprecedented view of the TBI lesion and disrupted BBB microenvironment. These same techniques are then applied to understand how TBI, as the most validated environmental risk factor for AD, may precipitate AD-related pathological processes. Their research goal is to understand how the basic mechanisms of neuro-immune interaction initiated by injury may catalyze latent disease processes in order to develop novel therapeutic targets and strategies for the treatment of TBI and prevention of chronic neurodegeneration. Drs. Peskind and/or Iliff will serve as the Senior co-mentor with Dr. Meabon for any ADTP trainees joining his group.
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Elizabeth Rhea, PhD, is an Assistant Professor of in the UW Department of Medicine, Gerontology Division working to understand brain metabolism. The brain requires insulin to function and acquires it primarily from the periphery. However, for insulin to enter the brain from the blood, it must cross a tightly regulated blood-brain barrier (BBB). In AD, insulin content and signaling in the brain diminishes, which can lead to impairments in cognition. Her work focuses on identifying targets and regulators of insulin BBB transport, including modifiable risk factors

such as diet and exercise, such that brain levels of insulin might be restored. Further work investigates insulin signaling in the CNS in a mouse model of AD following manipulation of CNS insulin levels. Dr. Rhea recently received the 2019 Outstanding Research Mentor Award from the UW SOM. Dr. Banks will serve as the Senior co-mentor with Dr. Rhea for any ADTP trainees joining her group.
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Garth Terry, MD, PhD, is a psychiatrist and research scientist, and a Physician/Research Associate, MIRECC at VA Puget Sound and an Acting Assistant Professor in the departments of Psychiatry and Behavioral Sciences and Radiology at UW SOM. His research interests are two-fold. First, he is dedicated to the development and use of novel radioligands in positron emission tomography (PET) for neuropsychiatric translational and pre-clinical research. He has active projects in the identification of PET imaging biomarkers of neuroinflammation following blast mTBI and development of novel radioligands for CNS targets. Second, he is active as a speaker, educator, and researcher in the field of cannabis and cannabinoid pharmacology and its intersection with mental health (including cannabis use disorder). He has previously co-developed a novel radioligand for imaging the cannabinoid CB1 receptor using PET, and is currently starting a pilot study to assess the feasibility of prazosin in treatment of cannabis use disorder. He is the primary investigator of a VA Career Development Award-2 and multiple pilot grants, and is a co-investigator on multiple projects at the VA. Drs. Peskind and Raskind will serve as the Senior co-mentor with Dr. Terry for any ADTP trainees joining his group.
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Paul Valdmanis, PhD, is an Assistant Professor in the Division of Medical Genetics in the Department of Medicine and adjunct assistant professor in the Department of Genome Sciences at UW. The Valdmanis lab seeks to identify novel genetic contributions to neurodegenerative disease and correct these variants through gene therapy approaches. Dr. Valdmanis has made several key genetic discoveries including the first identification of mutations in TARDBP (TDP-43) in patients with ALS, and mutations in KIAA0196 (Strumpellin) in patients with Hereditary Spastic Paraplegia and RNF170 in a novel form of Autosomal Dominant Sensory Ataxia. During his postdoctoral work, he optimized methods to safely and efficiently reduce target genes through use of adeno-associated viral delivery of small hairpin RNAs and identified a mechanism by which small hairpin RNAs compete with endogenous microRNAs in the liver. His lab uses long-read sequencing technology to interrogate the contribution of repeat expansions in AD and ALS and – through a series of *in vitro* and *in vivo* model systems – is working to understand the mechanism by which repeat expansions can act as modifiers of disease. Dr. Valdmanis is a recent recipient of the Robert F. Schoeni Award for Research from Ann Arbor Active Against ALS. Dr. Jayadev will serve as the Senior co-mentor with Dr. Valdmanis for any ADTP trainees joining his group.
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