From the Chair

Welcome to the Fall 2016 issue of Neurotransmissions, the UW Department of Neurology’s newsletter for colleagues, alumni and friends. I am proud to share the latest exciting developments in our department, including news on research, clinical resources, and education. Looking at this issue, I am reminded again what a promising time this is for our specialty.

Alzheimer’s disease (AD) and related dementias are some of the most pressing health problems confronting society. The prevalence of these diseases increases relentlessly as our lifespan becomes longer. Our Department is meeting this challenge head-on with both comprehensive clinical resources and research programs. Our lead story in this issue describes the UW Memory and Brain Wellness Center (MBWC), our newest clinical program. Led by Thomas Grabowski, MD, Professor of Radiology and Neurology, this is a comprehensive, multidisciplinary program where neurologists, psychiatrists, neuropsychologists, geriatricians, and others collaborate to diagnose and treat patients with dementia. You will be heartened to learn that possible disease-modifying therapies are being studied in the MBWC in conjunction with UW Medicine’s NIH-funded Alzheimer Disease Research Center.

The work of the MBWC is complemented by basic research into the molecular pathologies of AD and other neurodegenerative diseases causing dementia. Here we profile the laboratory of Suman Jayadev, MD, Assistant Professor of Neurology. Dr. Jayadev is focused on understanding the role of neuro-inflammation in AD. She is one of many examples in the department of a ‘triple-threat’ academic neurologist. She is an outstanding clinician, highly successful scientist and an inspired educator.

Please look inside to learn more about her laboratory’s work.

In this issue we introduce a new feature: Swanson’s History of Neurology. Philip Swanson, MD, PhD, Professor of Neurology, has been a member of our faculty since 1964, and was Division Head from 1967 through 1996. Not only is he the institutional memory of our department, Dr. Swanson is also an avid student of the history of clinical neurology. In this inaugural column (titled with tongue-in-cheek “The Bronze Age of Neurology”), he traces the beginnings of our Department. It is a must-read.

In closing, I want to acknowledge the critical role now played by Nicholas Poolos, MD, PhD, in orchestrating the production of Neurotransmissions. He serves as both the creative director of Neurology’s newsletter as well as the ‘spur’ to ensure that we go to press in a timely manner. Nick and I are committed to producing future issues of Neurotransmissions that are both newsworthy and relevant. To do this we need your help. Please contact us with suggestions and advice for future issues.
Philip Culbertson, a retired university professor and musician in Seattle, lives with early symptoms of Alzheimer’s Disease. As a participant in a workshop recently offered by the UW Memory and Brain Wellness Center (MBWC), he shared his story of cognitive challenges with children at a local day camp. His goal is to help raise awareness of memory loss and promote a dementia-inclusive community.

“It's OK to have Alzheimer's Disease. You can go on, you don't have to be shut away,” Culbertson wants to say to the 5 million Americans over the age of 65 who have this neurodegenerative disease, which causes memory loss and cognitive impairment, and eventually leads to dementia.

Fortunately, AD is one of the UW Department of Neurology’s leading fields of clinical care and innovation. Based at Harborview Medical Center, a multidisciplinary team of clinicians in the Departments of Neurology, Psychiatry and Behavioral Sciences, and Division of Gerontology and Geriatric Medicine specializes in diagnosis, individualized treatment, and follow-up care of dementia. The MBWC also unites efforts in community outreach, training of primary care physicians in early detection, and prevention-focused research.

A clinic on a mission

Thomas Grabowski, MD, Professor of Neurology and Director of the MBWC, seeks to reframe Alzheimer’s disease, which is commonly associated with global cognitive impairment and a resulting sense of hopelessness. He encourages recognition of the entire spectrum of disease progression, from the presymptomatic stage, to mild cognitive impairment (MCI), to dementia. People living with MCI typically have the capacity to gain new skills and enjoy fulfilling social activity, but need support and guidance.

“Inspired by our clinic’s large population of patients with early memory loss,” says Dr. Grabowski, “we take a strengths-based approach to disease management, helping the patient and family to leverage remaining abilities and find ways to improve well-being and maintain quality of life as long as possible.”

Neuropsychologist Kristoffer Rhoads, PhD, Associate Professor of Neurology, recently expanded clinic offerings to help patients and caregivers implement lifestyle interventions. He recommends procedures that patients can learn through practice, such as mindfulness meditation. He focuses on evidence-backed applications of mindfulness training, which show potential to stimulate brain plasticity, improve emotional resilience, and reduce cardiovascular risk factors for cognitive decline.

Forming even one new healthy habit can be surprisingly powerful for patients with early- to mid-stage dementia, Dr. Grabowski notes. “We’ve learned that working towards a positive goal can function as a vehicle for adjustment to the diagnosis and journey ahead.”

A Center for Alzheimer’s research

In tandem, researchers in the UW Alzheimer’s Disease Research Center (ADRC) and the Pacific Northwest Udall Center for Excellence in Parkinson’s Disease (PANUC) work to identify genetic factors, biomarkers that track disease progression, and targeted therapeutics. In September 2016, the ADRC won National Institutes of Health
Alzheimer's Disease (AD) and related disorders exact a very high toll on patients, families, and society. Despite the earlier lack of success in developing disease-modifying therapies in most neurodegenerative diseases, we have recently made significant gains in our understanding of disease pathogenesis, often through clues gleaned from genetics. Large genetic population studies have shown repeatedly that there are a number of different pathways to sporadic AD, and therefore not everyone will develop AD for the same reasons. Our group focuses on one important pathway, dysregulation of inflammation, and is using genetic manipulation and patient samples to study those mechanisms at the bench. With the molecular clues from familial forms of neurodegeneration, we can begin to map out the pathways related to neuronal loss, dysfunction, abnormal brain immune cell function, and the interactions between various brain cell types.

**Familial Alzheimer Disease mutations**

We investigate the mechanisms by which familial Alzheimer's Disease (FAD) mutations in the presenilin genes cause AD pathology. We had previously demonstrated an important role for presenilin 2 (PSEN2) in the regulation of microglia, the resident brain innate immune cells. To study the consequences of abnormal immune responses related to presenilins in a more biologically complex system, we have created a transgenic mouse model expressing a presenilin 2 mutation. Microglia isolated from these mutant mice have an exaggerated pro-inflammatory response, similar to those we observed in microglia from animals with genetic deletion of the PSEN2 gene. This supports the idea that a loss of function of PSEN2 results from those mutations that produce AD. Understanding how mutations confer either a loss of function, or a toxic gain of function, is critically important to developing the appropriate disease-modifying therapies in the future.

Clinical and research genetic testing for patients with FAD has contributed to understanding the mechanism of action of AD-causing genes by identifying novel mutations that have different effects on protein structure and function. In parallel to work in mouse models, technologies such as patient-derived stem cell-based disease modeling allows us to investigate mechanisms directly in human tissue.

**Patient-derived tissue to model AD**

Because brain tissue is only available through autopsy or biopsy, it has been challenging to develop a reliable source of human brain cells to study in a dish. However, the recent advent of patient-derived induced pluripotent stem cell (iPSC) technology to study the impact of disease-associated mutations in brain cells has broadened our repertoire of tools. Methods to create neurons from iPSC have been optimized for years, though very few methods exist to do the same for brain immune cells. To address this need, we created a novel method to develop microglia from iPSC. Currently, with collaborator Jessica Young PhD, Assistant Professor of Pathology, we are engineering methods to create mixed neuron-glial neural three-dimensional structures in a dish to better understand how neuronal-microglia dynamics contribute to neuronal injury in AD.

Complementing the brain microglial studies, we are investigating the regulation by microRNAs in peripheral innate immune cells isolated from patients carrying a familial AD mutation in the PSEN1, PSEN2, or amyloid precursor protein (APP) genes. These efforts are in collaboration with Gwenn Garden, MD, PhD, Professor of Neurology, who is performing parallel studies in FAD mouse models. These

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Neurology Residency News

By Arielle Davis, MD and Patricia Oakes, MD, JD, Co-Directors of the Neurology Residency Program

For those of you who have not yet interacted with our new class of adult neurology residents (N1s), we are pleased to introduce them. This year we have an international flavor to the class with residents originally hailing from Poland, Nigeria, Vietnam, and Pakistan. Among them are a former TV documentary film producer (Ami Cuneo, MD), a trained EMT (Justin Granstein, MD), and an aficionado of 3D-printing (Alexander Doud, MD). In addition, this is our first class of eight adult neurology residents, as our program continues to grow.

Please help us welcome the new N1s!

Raima Amin, MD,
University of Washington

Faiza Butt, MBBS,
Fatima Jinnah Medical College, Pakistan

Ami Cuneo, MD,
Brown University

Alexander Doud, MD,
University of Minnesota

Justin Granstein, MD,
Cornell University

Wojciech Gryc, MD,
University of Michigan

Chinwe Ibeh, MD,
Drexel University

Lien Nguyen, DO,
Rocky Vista University College of Osteopathic Medicine

Our N1s at the July resident teaching course. From left to right, Raima Amin, Pin-Yi Ko (a pediatric PGY-3/N1), Ami Cuneo, Faiza Butt, Alex Doud, Chinwe Ibeh, Wojciech Gryc, Justin Granstein, and Lien Nguyen.

Continued from page 3

combined studies in both human and mice will unravel the impact of presenilin mutations on inflammation and neurodegeneration as well as test the potential for manipulating microRNAs to mitigate AD progression.

AD as a complex trait

I lead the UW Alzheimer Disease Research Center’s Therapeutic Pipeline Project (TPP) Genetics project, a translational study investigating the clinical utility and patient impact of exome sequencing for subjects with early onset AD or family histories of AD. Through this philanthropy-funded project, I and Brad Rolf, MS, CGC, a Certified Genetic Counselor, are stratifying AD genetic risk, developing counseling methods for returning whole exome testing results to subjects and their families, and establishing methods to study functional variants in vitro.

Thus, our group focuses on both familial and the late onset “sporadic” AD which are genetically and clinically heterogeneous groups. Knowledge of the genes contributing to AD provides tools and clues to design experiments aimed at unraveling key cellular mechanisms that lead to neurodegeneration. Our hope is to identify pathways to target for drug intervention.
By James Owens, MD, Director of Pediatric Neurology Residency

This was our first year matching three applicants and we couldn’t be more delighted with our new residents:

Jennifer Keene graduated from the Cleveland Clinic Lerner College of Medicine of Case Western Reserve with both her MD and a Masters in Biomedical Engineering with a concentration in neural engineering.

Jessica Hauser earned her PhD in Neurobiology from Harvard with a particular emphasis on understanding the development and regulation of glutamatergic and GABAergic synapses. She received her MD from Baylor College of Medicine.

Benjamin Dean earned his PhD in Neuroscience and his MD from Vanderbilt University School of Medicine. His PhD work focused on the developmental neurobiology of the habenula.

The Division has now grown to 23 faculty members. This fall we welcome Christopher Beatty, MD, Stephanie Carapetian Randle, MD, and Lindsey Morgan, MD to our program.

Our five-year categorical residency training program in pediatric neurology (two years of preliminary training in general pediatrics followed by three years of training in neurology and pediatric neurology) has expanded to three residents per year. The three individuals who matched with us in March 2016 are now interns in pediatrics and will begin their neurological training in July 2018.

The outpatient services provided by the Division of Pediatric Neurology have grown substantially. During the academic year ending June 2016, our program conducted over 12,000 patient visits. These took place through the pediatric neurology clinics at the main Seattle Children’s Hospital site; at multi-specialty clinics in neuromuscular disorders, autism and neuro-oncology; and at the Seattle Children’s regional clinics in Bellevue, Everett, Federal Way, Wenatchee, Olympia, and the Tri-Cities. In addition to these visits, the Division also provides neonatal neurology follow-up services at the University of Washington Medical Center, and outreach clinics in Yakima, Missoula, MT, and four sites in Alaska.

Pediatric electroencephalography (EEG) services have also expanded. Over the past year, the Seattle Children’s Clinical Neurophysiology Laboratory conducted over 4,400 individual studies, including routine outpatient and inpatient EEGs, continuous EEG recordings in the intensive care units, and video-EEG telemetry studies in the Epilepsy Monitoring Unit.

Our three new pediatric neurology residents on Mount Rainier during pediatric orientation this past June. From left to right: Jennifer Keene, MD, PhD; Jessica Hauser, MD, PhD; and Benjamin Dean, MD, PhD.
The UW School of Medicine was established in 1946. In most US medical institutions at that time, the specialty of neurology was considered to be a subspecialty of internal medicine, and usually was administered as a division within the department of internal medicine. The first chair of the UW Department of Internal Medicine was Robert H. Williams, MD, a graduate of the Johns Hopkins School of Medicine who had spent a number of years as an endocrinologist on the Harvard Medical Unit of the Boston City Hospital. As the first chair of Internal Medicine at the UW, Dr. Williams chose excellent individuals to develop specialty areas in his department.

Its first neurologist, Fred Plum, MD, was hired in 1952. Dr. Plum, a graduate of the residency program at Cornell under Harold Wolff, was at that time a young instructor at Cornell who had written several papers on respirator management in patients with poliomyelitis. He was a dynamic, creative physician, who provided care for patients with all types of neurological patients, but especially for those with poliomyelitis, many of whom required respiratory assistance. When he came to Seattle, Dr. Plum obtained a grant from the National Foundation for Infantile Paralysis to develop a regional respirator center, which was located at King County Hospital (now Harborview Medical Center). Patients from the Pacific Northwest, Alaska, Hawaii, Montana, and New Mexico were treated there. The Center, located on the 4 Center wing of the hospital between the Neurology Service (4 North) and the Infections Disease Service (4 South), admitted all patients with acute poliomyelitis as well as patients with severe respiratory problems, many of whom had poliomyelitis.

Dr. Plum became interested in the complications of polio, especially those associated with respiratory insufficiency. He began a series of human and animal studies on a number of clinical problems, such as disturbances in acid-base metabolism. Prominent collaborators were his first resident, August G. Swanson, MD, and Jerome Posner MD, first as a medical student, then as a neurology resident at the UW. Dr. Plum started the neurology residency training program, which was for many years supported by a Clinical Neurology Training Grant from the National Institutes of Health.

Dr. Plum, together with Dr. Posner and others, initiated a series of studies on coma, culminating in 1966 in the widely utilized book: The Diagnosis of Stupor and Coma, by Plum and Posner. As a result of Dr. Plum’s interest in comatose patients, the Neurology Service came to admit all comatose patients, whatever the cause. (Jerome Posner, personal communication).

During the initial years under Dr. Plum, the Chief of Neurological Surgery Arthur Ward, MD in 1954 also hired a neurologist, Richard P. Schmidt, MD to develop electroencephalography (EEG) as part of a goal to establish a research and clinical program in epilepsy, including epilepsy surgery. Dr. Schmidt published papers on EEG in cerebrovascular disease, and studies on tetanus. In 1958, Dr. Schmidt left UW to become head of the Division of Neurology at the University of Florida in Gainesville, followed by a career in medical and academic administration, later becoming President of SUNY-Upstate and later SUNY-Stonybrook.

In 1962, Dr. Plum left Seattle to become chair of the newly established department of neurology at the Cornell School of Medicine and Hospital in New York City, leaving a rather depleted neurological division in Seattle. In the interim, the Neurology Division was headed by Dr. Richard Birchfield, a neurologist who had done fellowship training with Dr. Plum. Dr. Birchfield then left UW to become the first neurologist at the Virginia Mason Clinic in Seattle. He continued for many years to teach as a member of the volunteer clinical faculty. The next Head of Neurology at UW was Dr. Charles N. Luttrell from Johns Hopkins. That will be the beginning of the next segment of this tale.

Philip D. Swanson graduated from Johns Hopkins School of Medicine in 1958, where he also did his neurology residency. From 1962-64 he was an NIH Special Fellow in Neurochemistry at the Institute of Psychiatry at the Maudsley Hospital in London where he earned a PhD degree. He joined the University of Washington Division of Neurology in the fall of 1964, and was Division Head from 1967 to 1996.
FACULTY NEWS
Selected recent publications from Neurology faculty

Compiled by Nadine Waldmann,
Budget/fiscal analyst lead


Neurology Top Docs

Congratulations to the following Neurology faculty who were recognized by Seattle Magazine and Seattle Met magazine in their annual Top Doctors poll. These represent physicians selected by their peers as being outstanding clinicians.

Kyra Becker, MD, Professor of Neurology
Jane Distad, MD, Associate Professor of Neurology
Will Longstreth, MD, Professor of Neurology
Christina Marra, MD, Professor of Neurology
Bruce Ransom, MD, PhD, Professor of Neurology
Ali Samii, MD, Professor of Neurology

Selected New Grants to Neurology Faculty

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Maciej Mrugala, MD, PhD, MPH, Associate Professor of Neurology writes: “It was in August of 2006 when I arrived in Seattle from Boston, ready to start my first real job at the UW. Welcoming me with open arms was Alexander Spence, MD, the “father” of Seattle neuro-oncology, and later my mentor and dear friend. I did not need to wait long to realize I made the right decision to move to Seattle and join the faculty of the Department of Neurology. All of you accepted me, as a colleague and friend, and my clinical and academic life would not have been successful without your support. It was a privilege and pleasure to work along some of the brightest minds in neurology. I have learned so much from all of you and I will always cherish our professional interactions. The ability to work with a team of experts of such magnitude made me a better neurologist and a better human being. For this I would like to thank you all!

I very much enjoyed my role as a teacher and it was a great pleasure to work with our superb residents over the years. I am very proud that since I arrived in Seattle, five of our residents selected neuro-oncology as their career path. I think Alex would have been happy!

I am starting the next chapter of my academic life at the Mayo Clinic. I am sad to be leaving, yet excited about the new opportunities that lie ahead. I have been tasked with building a neuro-oncology program at Mayo Arizona, and I am certain that skills that I acquired at the UW will help me succeed.

I am going to miss you all. I will keep the memories of our time together dear to my heart. I am sure many of us will remain in touch, and who knows, maybe in the future my life journey will bring me back to my beloved Pacific Northwest.”

Kyra Becker, MD, Professor of Neurology writes: “After 20 years at UW Medicine/ Harborview, I’ve made the decision to make time to pursue interests other than stroke/vascular neurology. Chief among these interests is sailing: we plan on exploring environs to the north over the next few years before heading south – and then who knows where.

Despite the change in my role within the Department and at HMC, I will still be attending on the inpatient service from time to time and taking some stroke call – so it isn’t quite goodbye as of yet.