UW Medicine
DEPARTMENT OF NEUROLOGY

SPRING-SUMMER 2019

Neurotransmissions

DEPARTMENT OF NEUROLOGY
UNIVERSITY OF WASHINGTON
SCHOOL OF MEDICINE

1959 NE Pacific St.
RR650 Box 356465
Seattle, WA 98195
Phone 206.543.2340
Fax 206.685.8100
depts.washington.edu/neurolog

Dear Neurology Colleagues and Friends:

I have served as Chair of our Department for 24 years. You have made this the most meaningful and happiest experience of my career. Together, we have succeeded in building a world class Neurology Department that excels in all of our core missions: providing care, discovery and translational investigation, and education. Of equal importance to me is our culture of mutual respect and interpersonal trust, creating a professional environment that fosters comradery. We are justified in pausing to celebrate what we have accomplished together, and how we have gone about doing it.

After a great deal of reflection, I have decided to step down as your Chair, a position I have loved. I have accepted a position at City University of Hong Kong to serve as the founding Chair of a new Department of Neuroscience. Dean Ramsey recent circulated a letter announcing my resignation, and the appointment of **Nicholas Poolos, MD, PhD**, Professor of Neurology, as Interim Chair. Dean Ramsey will address at our next faculty meeting the important issue of the upcoming national search for a permanent Chair.

Bruce R. Ransom, MD, PhD

Serving as your Chair has been a great privilege. There are no words to properly thank you for your unfailing support, advice and friendship. Likewise, I cannot adequately explain how honored I have felt in this role for the last 24 years. The time has truly sped by in a way that is hard for me to comprehend in retrospect. It goes without saying that I will work with our Dean and all of you to ensure the smoothest possible transition in Chair leadership.

Sincerely,

Bruce R. Ransom, MD, PhD
Warren and Jermaine Magnuson Professor and Chairman
Department of Neurology

INSIDE THIS ISSUE

Tresa McGranahan, MD, PhD makes a teaching point on a brain MRI in the ABTC to medical scribe Emanuel Cuevas.

Neuro-oncology at the Alvord Brain Tumor Center

By Lynne P. Taylor, MD,
Clinical Professor of Neurology

Glioblastoma and other primary brain tumors produce immediate and very challenging cognitive, behavioral and communication difficulties for our patients. Caregivers are under tremendous stress because of these changes in loved ones and need a multidisciplinary "home." The Alvord Brain Tumor Center (ABTC) at the University of Washington is a nationally recognized brain tumor program integrating multi-disciplinary clinical care, research and teaching for the optimal care and treatment of patients. Clinical co-directors are **Dr. Lynne Taylor, MD**, Clinical Professor of Neurology; Manuel Ferreira, MD, PhD, Associate Professor of Neurosurgery; and Lia Halasz, MD, Associate Professor of Radiation Oncology. Together, their complementary and diverse expertise in brain tumor treatment enables them to direct the optimal treatment course for their patients with brain tumors.

There were 23,820 new cases of brain tumors diagnosed in 2019 (only 1.4% of all new cancer cases). The percent surviving five years is 32.9%, an increasing percentage compared to years in the past, making the care of our long-term survivors even more important.

Recently recruited to the Department of Neurology and the ABTC are **Tresa McGranahan, MD, PhD**, Assistant Professor of Neurology, who joins us from Stanford, and **Jerome Graber, MD, MPH**, Associate Professor of Neurology, trained at NYU and Memorial Sloan Kettering Cancer Center. Both of them have an interest in clinical trials, neuroprotection of the CNS from the side effects of chemotherapy and radiation therapy, and the care of patients with primary CNS lymphoma. Unusual for a brain tumor program, Drs. Taylor and Graber also have board certification in Palliative Care.

In our multi-disciplinary clinic our patients will see their dedicated nurse, advanced practice provider (APP), neuro-oncologist and neuro-radiation oncologist, often in the same day. We work closely with our colleagues in neurosurgery, rehabilitation medicine, and medical oncology. We also care for patients with secondary complications in the nervous system such as brain metastases and leptomeningeal carcinomatosis. These complications are most often seen in patients with the underlying cancer diagnoses of breast, lung, lymphoma, leukemia and melanoma. In this context, we work closely with our colleagues in medical oncology at UW and the Seattle Cancer Care Alliance (SCCA).

Once our patients are established at our clinic, we usually treat them with combined chemo-radiation therapy after ensuring as complete a surgical resection as possible. We have a dedicated team of advanced practice providers: Brien Barrett, ARNP, Karl Cristie Figuracion, ARNP, Young-Bin Song, PA-C, and Claire Stockhausen, PA-C who provide superb supportive care to help our patients and their caregivers successfully navigate their treatments. We have four dedicated oncology nurses and a nurse manager, a full time dedicated social worker (Katie Sofie, MSW), and a clinical nurse manager, Caryn Leibowitz, RN.

For our patients who wish to get their radiation therapy and chemotherapy closer to home, we partner with our medical and radiation oncology colleagues in other

Continued on page 8

Mitochondrial Medicine Center research

By Russ Saneto, DO, PhD
Professor of Neurology

When I went to medical school and the earth's crust was cooling, the mention of mitochondria comprised a few brief moments discussing intracellular organelles. What I learned was that this small organelle is responsible for producing most of the ATP required for cellular function. Evolving over the last couple of decades, science has learned that mitochondria have their own specialized DNA and replication machinery. There is communication of oxidative radicals and metabolic signals between the nucleus and mitochondria to regulate energy production and other synthetic processes, such as cholesterol synthesis, iron-sulfur metabolism, urea cycle, heme synthesis, and calcium regulation. Even more recently appreciated are the clinical manifestations of these processes inducing mitochondrial dysfunction and disease. The first reported patient with mitochondrial disease occurred in the 1960s, and the initial genetically proven disease was described in 1988.

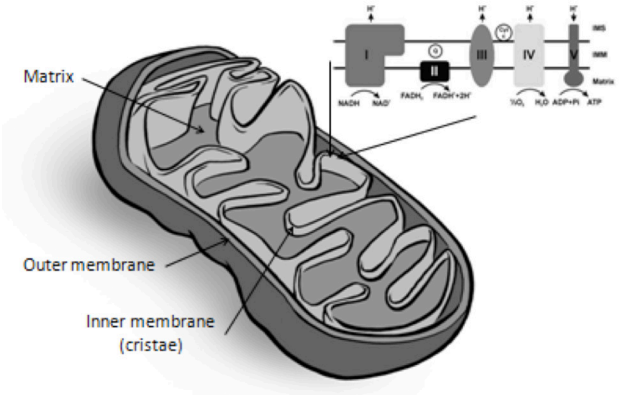
Once thought to be a rare disorder, recent prevalence figures suggest the disease occurs in 1 in 4,500 individuals. Most in the field feel that this number is low. The conundrum of diagnosis lies with the unique physiology of the mitochondria. The interaction of mitochondrial DNA and nuclear DNA produces a wide spectrum of diseases, with alterations within each genome capable of producing disease with various phenotypes. For example, the nuclear-encoded mitochondrial DNA polymerase, polymerase gamma (POLG), can produce medically intractable seizures with rapidly progressive neurodegeneration and early death in a three year old, while the same mutation can induce ophthalmoplegia, dysarthria, sensory neuropathy, and ataxia not presenting until a patient is in his late 60s. Mitochondrial DNA-encoded disease, such as the pathological variant m. 8993T>G, can produce medically refractory seizures and rapidly progressive neurodegeneration in infants, yet in another patient ataxia, sensory neuropathy, and retinitis pigmentosa at age 25 years. The variability in clinical presentation of the over 150 pathological variants in mitochondrial DNA and 200 variants in nuclear DNA has hampered research into diagnosis and treatment of these diseases.

In the early 2000s, Billi DiMauro and Michio Hirano of Columbia University and I obtained an NIH Challenge Grant to document the natural history of various mitochondrial diseases. We have been fortunate to have three renewals from the NIH Orphan Disease Section. During this time, the Mitochondrial Disease Care Consortium was created involving 22 centers, including our center, across the US and Canada. Our site has been involved in multiple pharmaceutical industry clinical trials studying possible treatments for Leigh syndrome and primary mitochondrial myopathies. We are part of the BioElectron Therapeutics clinical trial using a medication for palliation at the end of life for patients with mitochondrial disease. We are also fortunate to be part of the NIH Phase III drug trial using a novel medication, dichloroacetic acid, for the treatment of pyruvate dehydrogenase complex deficiency.

Working with the Seattle Children's Research Institute, we have been studying novel packaging of rapamycin for treatment of mitochondrial diseases and seizures. In the lab of Simon Johnson and labs of Phil Morgan and Margret Sedensky, research has shown that packaging of rapamycin halts the progression of Leigh syndrome in a mouse model. We are currently investigating human fibroblast models of various genetic mitochondrial diseases with this compound. We have begun a Phase I clinical trial looking at this compound in patients with medically refractory seizures after failure of surgical resection. We are also in talks with the FDA to begin a Phase I trial in patients with seizures and genetically proven mitochondrial disease.

This is an exciting time to be studying mitochondrial medicine. Although no reproducible treatments yet exist for

Continued on page 8



Cartoon of the mitochondrion and diagram of the ATP-producing pathway.

Farewell to our graduating residents

Raima Amin, MD

Thank you for the amazing mentorship and training in the diverse fields of neurology over the last four years. I am forever grateful for the amazing neurologists I've met and look forward to being one of them some day soon.

Movement Disorder Fellowship at UW/VA

Faiza Waheed Butt, MD

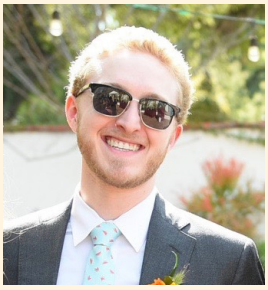
I am extremely grateful to my mentors at UWMC for investing in me and shaping me into a young neurologist. It's been a very humbling, rewarding, and life altering experience. Thank you to my very supportive family for being there every step of the way. I couldn't have done it without them. I am excited to continue to learn and pursue a fellowship in *Movement Disorders*.

Ami Cuneo, MD

UW Neurology has been a wonderful residency experience! I am grateful to the faculty who have infused the joys of teaching and scientific research into morning rounds; to our patients, many of whom have given us the privilege of sharing challenging moments in their own journeys; to my UW Neuro resident colleagues, whose positive energy and consistent hard work make our teams run so well; to Stella, who always has the answer; and to my amazing family, for their enduring support. I look forward to continuing at UW next year in the *Headache Fellowship*.

Alexander J. Doud, MD, MS

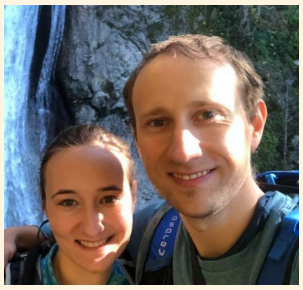
Dr. Doud plans to participate in a newly created fellowship at SCH that combines engineering with clinical neurophysiology and epilepsy under the guidance of Drs. Novotny, Cheng-Hakimian and So.



Justin Granstein, MD, MPH

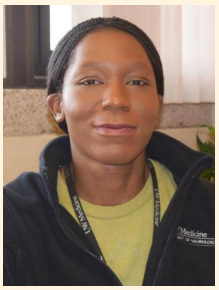
The past four years have been an incredible ride, and a period of personal and professional growth that exceeded all expectations. Thank you to everyone who lent a hand along the way.

Neurocritical Care fellowship, Mount Sinai Hospital.



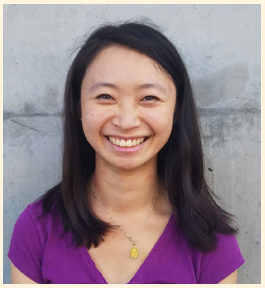
Wojciech Gryc, MD

It has been quite a journey! It was the best of times, it was the worst of times, and I am so grateful for taking this path. I am the most thankful for meeting so many wonderful people along the way, especially my amazing co-residents and exceptional faculty. We have grown to be a great team over those few years. I am very happy about discovering the Pacific Northwest and particularly its beautiful and diverse landscape that I enjoyed during my outdoor escapades. I am tremendously excited to see what the future hold as I move on to the next step in my career as a *Movement Disorders fellow at University of Washington.*



Chinwe Ibeh, MD

Dr. Ibeh leaves us to undertake a *Vascular Neurology fellowship at Columbia.*



Pin-Yi Ko, MD

It has been a humbling and inspiring five years of training--I will always be grateful for the pure serendipity by which I discovered the field of child neurology, for the patients who have made this pursuit worthwhile, for the attendings who have guided me, for my co-residents who have made this experience lighter, and for my family who had no choice but to support me. I am excited to find out where this journey takes me. For now, I will spend this upcoming year here in Seattle completing a fellowship in *Neurophysiology*. Thanks everyone and see you around!

Ava Lin, MD

Dr. Lin (center) says: "Thank you for the wonderful times, the learning, the laughter and memorable moments that helped me be a better neurologist!"

Lien Nguyen, MD, DO

Neurology residency has been a long journey with many ups and downs, stepping stones (sometimes boulders) passed, and now the finish is coming quickly. I feel like there was a significant learning curve and now that I am finishing residency, despite all that I have learned, I feel that there is just sooo much more to learn from all of the wonderful neurologists at the U. I will miss these days and miss the great people that have helped me grow so much these past years - my co-residents, attendings, and Stella for easing everything. Thank you, everyone!

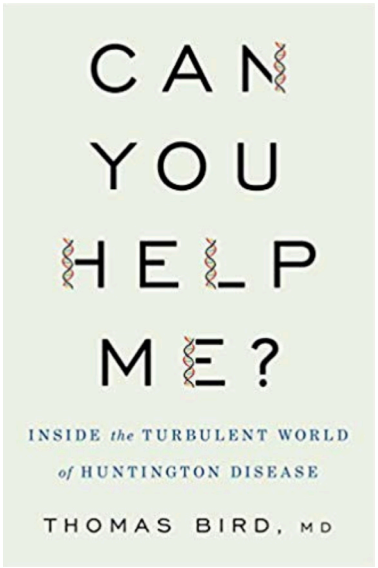
Neurology Faculty News

Top doctors

UW Neurology faculty scored three out of six neurologist citations in *Seattle Magazine*'s annual "Top Doctors" survey. **Will Longstreth, MD**, Professor of Neurology; **Lynne Taylor, MD**, Professor of Neurology; and **Michael Weiss, MD**, Professor of Neurology were all highlighted for their dedication to outstanding patient care and neurological expertise. Congratulations to you all!

Thomas D. Bird, MD, Professor of Neurology, published his first book intended for general readership, *Doctor Can You Help Me? Inside the turbulent world of Huntington Disease* (Oxford University Press). In the Introduction Dr. Bird writes: "Over a 40+ year career I have seen more than 1,000 persons with this disease and have been constantly amazed, puzzled, distressed and impressed by the trials and tribulations of these families coping with it. Dealing with HD has been so moving, so unsettling and so challenging for me that I felt compelled to write about it. Setting these stories down has been therapeutic for me, but I hope it will be both interesting and enlightening for you."

Check out this beautifully written book today at your favorite bookstore or Amazon (5 stars!).



Update from the Division of Pediatric Neurology

By Mark S. Wainwright, MD, PhD
Professor of Neurology, Head of Division of Pediatric Neurology

The Pediatric Epilepsy Monitoring Unit was re-certified this year by the National Association of Epilepsy Centers as a Level 4 Center. This is the highest level achievable and Children's is the only Level 4 Pediatric Epilepsy Center in the WWAMI region. The first patients to undergo epilepsy surgery using the robotic surgical assistant (ROSA) robot completed their surgery at Seattle Children's in early 2019. This new technology will allow minimally invasive and more rapid brain surgeries to be carried out at Children's.

The Tuberous Sclerosis Complex program had its annual fundraising walk on April 28. This program, led by Dr. Stephanie Randle, is in its second year and has successfully established multi-disciplinary clinics for patients with TS Complex. As a measure of its success, the fundraising target of $10,000 for this walk has already been eclipsed with a new goal of $15,000. As a result of the rapid achievement of this target, both **Dr. Rusty Novotny**, Professor of Neurology and myself will be pied in the face.

The Neuromuscular Program will add a second faculty member in July. **Dr. Seth Perlman** from the University of Iowa completed a fellowship in Neuromuscular Medicine at the University of Washington, St. Louis and will also become the Neuromuscular Fellowship Director for the Department of Neurology.

Dr. Fawn Leigh completed the first treatment in the WWAMI of two children with Spinal Muscular Atrophy Type 1 with a novel gene therapy (AVXS-101). This treatment requires only a single intravenous administration of a gene construct which contains a functional copy of the SMN1 gene and promises to open a new era in gene therapies for neuromuscular disorders.

Recent Faculty Publications

Vishnevetsky A, Zapata Del Mar C, Luis Cam J, Cornejo-Olivas M, **Creutzfeldt CJ**. Palliative Care: Perceptions, Experiences, and Attitudes in a Peruvian Neurologic Hospital. *J Palliat Med.* 2019.

Brizzi K, **Creutzfeldt CJ**. Neuropalliative Care: A Practical Guide for the Neurologist. *Semin Neurol.* 2018.

McGranahan T, Therkelsen KE, Ahmad S, Nagpal S. Current State of Immunotherapy for Treatment of Glioblastoma. *Current Treatment Options Oncology* 2019.

Li, A., **McGranahan, T.M.**, Su, E., Kipp, L., and Gold, C. Coexistence of neuromyelitis optica and amyotrophic lateral sclerosis: Case report. *The Neurohospitalist* 2019.

Tenner L, Hlubocky FJ, Blanke CD, LeBlanc, T, Marron, JM, McGinnis M, Spence RA, **Taylor LP.** Let's talk about those herbs you are taking: Ethical considerations for communication with patients with cancer about complementary and alternative medicine. *Journal of Oncology Practice* 2019.

Naydenov A, **Taylor LP**. Leptomeningeal carcinomatosis in chronic lymphocytic leukemia (CLL): A case report and review of the literature. *The Oncologist* 2019.

Graber JJ, Cobbs CS, Olson JJ. Congress of Neurological Surgeons Systematic Review and Evidence-Based Guidelines on the Use of Stereotactic Radiosurgery in the Treatment of Adults With Metastatic Brain Tumors. *Neurosurgery* 2019.

Kennedy T, Guiraud S, Edwards B, Squire S, Moir L, Babbs A, **Odom G**, Golebiowski D, Schneider J, **Chamberlain JS** and Davies KE: Micro-utrophin improves cardiac and skeletal muscle function of severely affected D2/*mdx* mice. *Mol Ther: Methods Clin Dev*, 2018.

Park J, Vohra R, Klussmann K, Bengtsson NE, **Chamberlain JS** and Lee D: Non-invasive tracking of disease progression in young dystrophic muscles using multi-parametric MRI at 14T. *PLoS One* 2018.

Ramos JN, Hollinger K, Bengtsson NE, Allen JM, Hauschka SD and **Chamberlain JS**: Development of novel micro-dystrophins with enhanced functionality. *Mol Ther* 2019.

Hollinger K, Crudele JM and **Chamberlain JS**: Gene replacement therapy for Duchenne muscular dystrophy. In: *Muscle Gene Therapy*, Duan D, ed. 2019, Springer, *in press*.

Wang Y, Andrews J, Jenkins Colon P, **Wundes A**. FDG-PET abnormalities leading to the diagnosis of an unusual case of probable neurosarcoidosis. *Neurol Neuroimmunol Neuroinflamm* 2018.

Arcot Jayagopal L, **von Geldern G**. Anosmia as the initial presentation of neurosarcoidosis. *Neurology*. 2018 Nov 27;91(22):1020-1021

Kuo CC, Tucker DM, Luu P, Jenson K, **Tsai JJ**, Ojemann JG, **Holmes MD**. EEG source imaging of epileptic activity at seizure onset. *Epilepsy Res.* 2018.

Collins KL, Sarma D, **Hakimian S, Tsai JJ**, Ojemann JG. Preserved evoked conscious perception of phosphenes with direct stimulation of deafferented primary visual cortex. *Epilepsy Behav Case Rep.* 2019.

Continued on page 8

New Faculty Awards

Gloria von Geldern
John Hopkins University/ PCORI

A pragmatic trial to evaluate the intermediate-term effects of early, aggressive versus escalation therapy in people with multiple sclerosis

Michael Weiss
Pharmaceutical Research Associates

Refeals ("Effects Of Oral Levosimendan [Odm-109]) On Respiratory Function In Patients With ALS

Margaret Stockbridge/ Bruce Ransom
National Science Teachers Award

Washington Regional Junior Science and Humanities Symposium

Leo Wang
Fulcrum Therapeutics

FSHD Longitudinal Biomarker Preparatory Study

David Tirschwell
Abbott Laboratories

AMPLATZERTM PFO Occluder Post Approval Study

Michael Weiss
Argenx

A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase 3 Trial to Evaluate the Efficacy, Safety and Tolerability of ARGX-113 in Patients with Myasthenia Gravis Having Generalized Muscle Weakness

Nicholas Poolos
American Epilepsy Society

Mass spectrometry of human tau to discover novel epilepsy biomarkers

Continued from page 2

institutions, managing the neurologic problems and re-evaluating every quarter with neurologic examinations and personal review of their brain MRI scans to provide guidance in the appropriate treatment regimens.

All the physicians at the ABTC are actively involved in teaching in our joint clinic work room. At any one time we may have neurology, neurosurgery and radiation oncology residents, and hematology-oncology fellows helping us deliver the highest quality of care. There is now a Neuro-Oncology Fellows Match through the United Council of Neurologic Sub-specialties (UCNS) and we will be joined by our first fellow in July 2020.

In addition to the care that we provide our patients, we are always encouraging enrollment in brain tumor clinical trials. Research coordinators Bryan Kim and Valeria Martin are available to review those trials with patients and support them in their participation. Current trials include proton vs. photon radiation therapy for newly diagnosed glioblastoma patients; temozolomide vs. procarbazine/CCNU/vincristine for newly diagnosed low grade glioma patients with 1p/19q co-deletions; and proton vs. photon radiation therapy for IDH mutant low to intermediate grade gliomas. We have an inhaled perillyl alcohol trial for patients with recurrent glioblastoma. Lastly, there is a very exciting trial of BRAF/MEK inhibitors for patients with papillary craniopharyngiomas, a very rare skull base tumor.

For referrals to the Alvord Brain Tumor Center:**abtcref@uw.edu**.
Or call 206-598-ABTC. (2282)

Our nurses also carry cellphone **206-598-1220** for discussion and triage of more urgent referrals.

Continued from page 3

these diseases, we are rapidly investigating multiple drugs in clinical trials. New gene discoveries occur in the literature every month. We are beginning to understand how dysfunctional intracellular pathways create multiple symptoms. We are trying to push bench research to the patient with the hope that they may benefit from our expanding knowledge.

Continued from page 7

Espay AJ, Vizcarra JA, Marsili L, Lang AE, Simon D, Merola A, Josephs K, Fasano A, Morgante F, Savica R, Greenamyre JT, Cambi F, Yamasaki TR, Tanner C, Gan-Or Z, Litvan I, Mata IF, **Zabetian CP**, Brundin P, Fernandez H, Standaert DG, Kauffman M, Schwarzschild M, Sardi SP, Sherer T, Perry G, Leverenz J. Revisiting protein aggregation as pathogenic in sporadic Parkinson's and Alzheimer's diseases. *Neurology* 2019.

Shi M, Sheng L, Stewart T, **Zabetian CP**, Zhang J. New windows into the brain: Central nervous system-derived extracellular vesicles in blood. *Prog Neurobiol* 2019.

Velez-Pardo C, Lorenzo-Betancor O, Jimenez-Del-Rio M, Moreno S, Lopera F, Cornejo-Olivas M, Torres L, Inca-Martinez M, Mazzetti P, Cosentino C, Yearout D, Waldherr SM, **Zabetian CP**, Mata IF. The distribution and risk effect of GBA variants in a large cohort of PD patients from Colombia and Peru. *Parkinsonism Relat Disord* 2019.

Coughlin, CR III, Swanson, MA, Spector, E, Meeks, NJL, Kronquist, KE, Aslamy, M, Wempe, MF, van Karnebeek, CDM, **Gospe, SM Jr**, Aziz, VG, Tsai, BP, Gao, H, Nagy, PL, Hyland, K, van Dooren, SJM, Salomons, GS, Van Hove, JLK: The genotypic spectrum of ALDH7A1 mutations resulting in pyridoxine dependent epilepsy: A common epileptic encephalopathy. *J Inherit Metab Dis* 2019.

Lo, MD, **Gospe, SM Jr**: Telemedicine and child neurology. *J. Child Neurol* 2019.

Wang LH, Friedman SD, Shaw D, Snider L, Wong CJ, Budech CB, Poliachik SL, Gove NE, Lewis LM, Campbell AE, Lemmers RJFL, Maarel SM, Tapscott SJ, Tawil RN. MRI-informed muscle biopsies correlate MRI with pathology and DUX4 target gene expression in FSHD. *Human Molecular Genetics* 2019.

HAVE SOME NEWS TO SHARE?

A recent grant, publication, or award? Please send it along to Nadine Waldmann (dine33@uw.edu) so we may include it in the next issue of *Neurotransmissions*.