Dear colleagues and friends,

We are honored to share with you some annual highlights of the promising innovations transforming how we care for people affected by nervous system disease. Whether we are wiring homes to track real-time data or challenging traditional concepts of health equity and professional archetypes, we constantly strive to blaze new trails for individualized and compassionate care.

With a strong tradition of collaboration between creative and diverse interdisciplinary teams, we believe OHSU is uniquely positioned to advance human neuroscience. We are committed to improving the lives of Oregonians, knowing our efforts also have far-reaching impact across our region, nation and the world.

Sincerely,

Dennis Bourdette, M.D., FANA, FAAN
Chair and Roy and Eulalia Swank Research Professor, neurology

Nathan R. Selden, M.D., Ph.D., FACS, FAAP
Mario and Edith Campagna Chair, neurological surgery
Carrying the torch

Based in Portland, we have more than 1 million patient visits each year, operate the top-ranked adult and children’s hospitals in Oregon, and secure competitive research funding of over $485 million. As a public corporation, serving the best interests of Oregon and the region, we provide services to the most vulnerable Oregonians as well as outreach that improves health in communities across the state.
# OHSU highlights

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<th><strong>Research</strong></th>
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<tr>
<td><strong>OHSU award dollars:</strong> $486 million</td>
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<tr>
<td><strong>NIH funding ranking:</strong> 28th</td>
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<tr>
<td>OHSU placed in the top 20 of Nature’s Index 2019 Innovation ranking, which measures the quality and quantity of research by institutions and universities worldwide.</td>
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<th><strong>Health care</strong></th>
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<td>One of 11 academic medical centers in the country recognized as a top performer in the 2019 Vizient Quality and Accountability Ranking.</td>
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<td>Awarded 5 stars by Centers for Medicare and Medicaid Services.</td>
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<td>Ranked among the nation’s best in multiple adult and children’s specialties.</td>
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<th><strong>Education</strong></th>
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<td>OHSU helps educate more than 4,500 students and trainees each year.</td>
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<th><strong>Community service</strong></th>
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<td>OHSU has more than 200 community health care programs, reaching out to vulnerable groups in urban areas as well as underserved rural communities throughout the state, and in 2017 had a community benefit contribution of $437 million.</td>
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<th><strong>Facilities and employees</strong></th>
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<td><strong>Employees:</strong> 17,532</td>
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<td>OHSU occupies more than 7.8 million square feet of space on approximately 350 acres.</td>
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The OHSU Brain Institute is dedicated to understanding, healing, and protecting the brain through cutting-edge research, outstanding patient care, innovative public education and training of future neuroscience leaders for Oregon and beyond.

PURKINJE CELLS, captured by Kathleen Beeson, a Ph.D. candidate in the Neuroscience Graduate Program in the Vollum Institute.

ACCOLADES AND ACCREDITATIONS

Ranked 44th in the U.S. for neurology and neurosurgery by U.S. News & World Report

Ranked 29th in the U.S. for pediatric neurology and neurosurgery by U.S. News & World Report

National Parkinson Foundation Center of Excellence

Level 4 Comprehensive Epilepsy Center (Adult and Pediatric)

NIH National Institute on Aging Designated Alzheimer’s Disease Research Center

ALS Association Center of Excellence

Race to Erase MS, Center Without Walls Research Center

Beacon Award of Excellence – Silver, American Association of Critical Care Nurses

DNV-Certified Comprehensive Stroke Center
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<th><strong>NEUROLOGY AND NEUROLOGICAL SURGERY</strong></th>
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<th><strong>RESEARCH</strong></th>
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Expanding personalized care with multimodality, intraoperative awake brain mapping

OHSU is gaining national attention as a center with a high volume of awake craniotomies using sophisticated intraoperative brain mapping to individualize and modify risk factors for patients. In 2016, neurosurgeon Ahmed Raslan, M.D., neurosurgeon/neurooncologist Seunggu Jude Han, M.D., and Barry Oken, M.D., Ph.D., the medical director of Intraoperative Neuromonitoring, collaborated to formalize a program, the only one between Seattle and San Francisco.

From 10 cases the first year, the OHSU awake mapping team expanded to 50 surgeries in 2019, signifying the high level of expertise and strengths of the protocols the team has developed.
Neurosurgeon Seunggu Jude Han, M.D., talks with Bonnie Quick, who is completely awake during her craniotomy, in October 2019. OHSU performs 40–50 awake craniotomies with language mapping annually.
“OHSU has chosen to commit resources to awake mapping in order to provide better outcomes for our patients in both their disease and cognitive function,” Raslan said. “The tension between achieving maximal resection and maximal functional outcome is inherent in neurosurgery for cerebral tumor resection and epilepsy.”
The indications for awake craniotomy continue to expand, and more patients are choosing the option, Raslan added. Han said that historically, surgeons only considered an awake craniotomy when tumor positioning puts language function at risk.

“But what’s pushed the indications beyond that is the impact on other eloquent functions,” he said. “As our understanding of the brain has deepened, it’s changed our thinking about what value awake surgery adds. Also, patients are living longer with disease and the results of surgery. If that means a function a patient wants to preserve is critical for a job or favorite activity, it’s incumbent on us to do everything we can to preserve that. Awake mapping during craniotomy is crucial in preserving these functions and also has the added benefit of advancing the science.”

One innovation the OHSU team has brought to the field is a cognitive visual neglect test, which allows the team to map visual pathways. Until now, this couldn’t be tested during surgical resection. OHSU is also participating in a research consortium with University of California-San Diego and Massachusetts General Hospital/Harvard Medical School to test a high-definition grid to record from the brain surface with astonishing detail. The OHSU Institutional Review Board approved the study and it is moving forward in 2020.

“Finding the exact sweet spot can’t be achieved unless the patient is awake. We believe this program allows us to do a better job for patients while producing a wealth of new knowledge to help other patients.”

Ahmed Raslan, M.D.
Another strength of the OHSU awake mapping team is the addition of neuropsychology to perform neuropsychological evaluations before and during surgery.

“It’s incredibly valuable to have these specialists on board,” Oken said. “The neuropsychologist or speech language pathologist is attuned to testing cognitive function. They are in the operating room using the data signals from cortiQ and traditional networks in the brain beyond what is thought of as speech processing, while giving instructions and taking feedback from the patient one-on-one. Providing surgeons with real-time feedback regarding the patient’s cognitive processing during the craniotomy has increased our ability to perform maximal resection while preserving postoperative functioning. It has also allowed us to track cognitive functions previously untested at a very high level.”

The volume of awake craniotomies at OHSU represents a unique opportunity to do investigations in the neuroscience world with the assistance of patient volunteers.

“No other setting gives us as direct a look at the brain and how it functions, including how it responds to different insults, such as tumors and epilepsy,” Han said.

“We are learning from every patient, and it’s helping us reframe how to personalize every surgery we do. It’s also changing how we define success by not only the tumor removal or curing epilepsy, but preservation of prioritized functions and the patient’s experience through the process.”

Seunggu Jude Han, M.D.
Language mapping for a Spanish monolingual patient

In October 2019, OHSU’s awake mapping team performed its first awake craniotomy for a Spanish-speaking patient.

“It was an impressive feat and a landmark, requiring a considerable amount of preparation and effort,” said Han. “Cases like this speak to our mission as an academic referral center, specifically by improving access to this specialized technique to all who need it. This accomplishment also signifies the growth of the awake mapping program and where we are headed.”

OHSU fellow and neuropsychologist Dana Dharmakaya Colgan, Ph.D., managed the Spanish translation of the cognitive tests and the training of a Spanish interpreter. Colgan’s collaboration in awake mapping has positively impacted the patient experience before, during and after surgery, Han said.

OHSU fellow and neuropsychologist Dana Dharmakaya Colgan, Ph.D., is conducting a qualitative study to foster greater understanding of patients’ subjective experiences while undergoing an awake craniotomy, information that is scarce in scientific literature.
Health Care Equity

Delving into the impact of sexual and gender minority status on neurologic care

OHSU is a recognized national leader in sexual and gender minority (SGM) health care equity at a time when clinicians are hungry for education and training in culturally competent care.

OHSU neurologist Holly E. Hinson, M.D., M.C.R., is blazing a trail for fellow neurologists by leading American Academy of Neurology (AAN) initiatives to improve neurologic care for SGM patients.

“Many of us trained when sexual and gender minority health wasn’t part of the curriculum, so there is an opportunity to educate our medical specialty on how to better tailor care to SGM patients’ individualized needs,” she said.

Hinson co-led a survey distributed April–June 2018 to a random, representative sample of 1,000 U.S.-based members of the AAN to ascertain the attitudes and knowledge of practicing neurologists for serving SGM patients. The survey was the first of any medical specialty or medical professional society to ask members about this topic. Notably, it was also the first survey of any physician group to ask about the sexual and gender identity of the respondents. (About 10% identified as something other than heterosexual/cisgender.)

“The results of the survey showed that most respondents felt comfortable taking a history, performing a physical exam, and providing care to SGM patients,” Hinson said. “But when queried about their understanding of how neurologic care could be impacted, there was a disconnect between comfort and knowledge.”

OHSU shines in Human Rights Campaign’s annual survey

For the eighth year, OHSU scored a perfect 100 and earned the coveted status of “2019 LGBTQ Healthcare Equality Leader” from the Human Rights Campaign Foundation, the educational arm of the nation’s largest lesbian, gay, bisexual, transgender and queer civil rights organization.
More than half the respondents believed that patients’ sexual orientations and gender identities have no bearing on treatment of neurologic illness. Hinson noted several examples contrary to that belief, which she cited from the July 2019 published study:

- **Antiretroviral medications**, such as preexposure prophylaxis (PrEP), can be associated with neuropathy. These medications are increasingly prescribed to those at risk for acquiring HIV.

- **Gender-affirming hormonal therapy**, specifically estrogen, can interact with other important medications, including anti-epileptic therapies like Dilantin.

- Poor understanding of SGM identity can lead to discrimination within long-term care facilities during neurorehabilitation. For example, assisted living facilities may not allow a same-sex couple to live together.

These insights are among the first to surface in this evolving field. In 2016, the National Institutes of Health designated SGM as a health care population worthy of studying, inspiring future high-quality research.

“We are just beginning to understand the ways SGM status impacts neurologic health,” Hinson said.
Aging and Alzheimer's

Advancing meaningful strategies for dementia care and innovative pursuits for the cure

As one of 32 National Institute on Aging Alzheimer’s Disease Research Centers in the U.S., the OHSU C. Rex and Ruth H. Layton Aging and Alzheimer’s Disease Center is a frontrunner in dementia care and research. OHSU scientists and clinicians are leading unique and creative research studies that have immediate translation to clinical care, especially notable in neuroimaging, telemedicine, new therapeutics and collecting objective digital data.

“Our focus is defining the underlying brain changes that lead to cognitive decline in later age and discovering tools that allow us to understand the impact of that progression to develop meaningful treatments,” said Jeffrey Kaye, M.D., the director of the Layton Center. “We are investigating strategies for what we can do today that will impact the lives of current patients while we continue to pursue true cures.”

Pushing the boundaries of research through creative neuroimaging studies

OHSU neuroscientist Erin Boespflug, Ph.D., and neurologist Lisa C. Silbert, M.D., M.C.R., created a leading-edge MRI protocol to advance studies of brain waste clearance through the perivascular compartment in states of neurodegeneration in 2017. This was the first fully automated segmentation method to provide morphological information of enlarged perivascular spaces (ePVS) in whole-brain clinical field strength MRI. Boespflug now uses it to facilitate examination of this system in National Institutes of Health-funded studies of dementia cases from Alzheimer’s centers across the U.S.

Silbert and colleagues are discovering unprecedented details of the neurovascular system by using post-mortem 7T MRI on OHSU brain bank donations from deceased patients, allowing comparative analysis premortem and post-mortem. Through an NIH grant, Silbert and colleague Randy Woltjer, M.D., Ph.D., are using this methodology to study the links of white matter hyperintensity-associated astrocytopathy in Alzheimer’s disease and vascular cognitive impairment.
Experimenting with new delivery methods of telemedicine for dementia care

According to earlier studies, individualized interventions are most effective in aiding caregivers to manage behavioral disturbances in family members with Alzheimer's disease and related dementias. Allison Lindauer, Ph.D., N.P., leads a novel tele-dementia care intervention program, Tele-STELLA (Support via TEchnology: Living and Learning with Advancing ADRD) that provides caregivers eight weekly, hourlong, direct-to-home sessions with a trained consultant via videoconferencing. This unique home-based model for bringing help to homes will be further tested for eventual national scalability in a newly funded NIH pilot in 2019–2020.

OHSU researcher Hiroko H. Dodge, Ph.D., is leading the first-ever internet-based Conversational Engagement Clinical Trial or I-CONECT. Trained interviewers deliver this protocol direct-to-home through personal computers, webcams and a user-friendly interactive interface with a touch screen. The intervention is randomized between daily versus weekly social interactions. The trial examines the efficacy of the intervention on cognitive function. It focuses on octogenarians with mild cognitive impairment and limited opportunities for social interaction. Half the trial participants are from low-income or ethnic minority populations.
Pioneering new pathways in therapeutics

With her expertise in medicinal plants, OHSU researcher Amala Soumyanath, B.Pharm., Ph.D., has shown through extensive experiments in cell culture and animal models that extracts of *Centella asiatica* (an Ayurvedic herb used in traditional botanical medicine for centuries) may stimulate peripheral nerve regeneration and also be useful as a neuroprotective agent in the central nervous system. Data to date has been compelling. The extract has passed safety and toxicology reviews. In 2019, OHSU launched a first-in-human study supported by NIH for patients with Alzheimer’s disease.

The relatively recent discovery of extracellular microRNAs in cerebrospinal fluid raises the possibility that miRNAs may serve as novel biomarkers of Alzheimer’s disease. OHSU researcher Julie A. Saugstad, Ph.D., has developed a panel of microRNAs that are associated with Alzheimer’s disease, which may help identify preclinical cases and monitor mechanisms of disease.

Oregon Brain Bank

OHSU has one of the largest dementia-focused brain banks among National Institute on Aging-designated centers, serving as a rich, shared resource to researchers around the world. In operation for almost 30 years, the bank houses donated brains of well-characterized research participants, providing a wealth of comparative data.
ORCATECH platform shows pathologic correlation between daily activities and Alzheimer’s disease

ORCATECH (Oregon Center for Aging and Technology) is an innovative research center closely integrated with the Layton Aging and Alzheimer’s Disease Center. The focus is developing technologies that can assess home-based activities, providing millions of hours of continuous objective measures in real-world and real-time activity and health data.

ORCATECH director Jeffrey Kaye, M.D., and his team began the program in 2001, and it has evolved to monitor 450 patient homes in the United States and Canada. In 2020, the program will expand to collaborators and patient homes in France and Australia.

Through the generosity of program participants, donated brains of deceased participants have provided the unique opportunity to correlate home-based digital activity patterns with Alzheimer’s pathology.

“We have shown that many of these functional activities and behaviors are clearly driven by Alzheimer’s pathology,” Kaye said. “We have an amazing team of people who have created this huge infrastructure that is unique in the world. This technology enables clinical trials to run more effectively with dramatically fewer individuals. Now we are translating that data into actionable health and wellness outcomes, improving the lives of those who age independently at home.”

Supported primarily by the National Institutes of Health and Veterans Affairs, Kaye’s group at OHSU has grant funding to further develop the remote assessment technology system to enable researchers across the U.S. to use these novel digital tools for their clinical research.
Pituitary

Changing the paradigm for treatment of pituitary disorders

The OHSU Pituitary Center is a progressive and premier multidisciplinary program with high-patient volume, meeting all criteria for a Pituitary Center of Excellence. The center’s clinical observations and research are innovating and changing standards of care in neuroendocrinology and pituitary tumors based on substantial data accumulated through population observational studies and novel patient-reported outcomes.

- Neuroendocrinologist Elena Varlamov, M.D., has been a co-investigator in multiple clinical trials studying pituitary tumors, treatment of acromegaly, Cushing’s disease and growth hormone deficiency.
Cutting-edge personalized treatments

Mirroring cancer treatment’s evolution, the OHSU Pituitary Center is personalizing pituitary treatment using clinical and pathology biomarkers and imaging characteristics to determine the likelihood of success of different therapies and predictors of recurrence. As there is often a delayed diagnosis for many secretory (10 years average) and nonfunctioning pituitary tumors, personalizing therapy for suitable patients shortcuts the trial and error of standard guidelines. Some examples include:

- More frequent follow-up MRIs for patients with silent corticotroph adenomas, which proved more aggressive in a review of more than 800 surgery patients at OHSU.
- More frequent evaluation for men with macroprolactinomas, based on the center’s research which shows these may be more clinically aggressive compared with women, comparable to new pituitary adenomas classification by World Health Organization.
- Screening for symptomatic Rathke’s cleft cyst (regardless of size) for adrenal insufficiency, especially in women. Surgery may not achieve adrenal axis recovery, but it renders a high percentage of headache improvement.

Discovering novel pharmacological agents and new delivery modes for some treatments

OHSU Pituitary Center Director, Maria Fleseriu, M.D., FACE, is leading several international studies into novel drugs for Cushing syndrome (CS) and acromegaly, including:

- Levoketoconazole, the first adrenal steroidogenesis inhibitor drug studied for CS in a worldwide phase 3 trial; published in Lancet Diabetes & Endocrinology in 2019.
- Safety international multicenter trial for daily pasireotide (Signifor), the first pituitary-directed agent approved for use in Cushing’s disease (CD), Frontiers in Endocrinology, 2019.
- Long-term data study on pasireotide LAR (Signifor LAR), Clinical Endocrinology, 2019.
- Oral octreotide, the first oral medication for acromegaly, now in a phase 3 trial.
Investigating recommendations for pituitary diagnosis and treatment

- Elena Varlamov, M.D., and Maria Fleseriu, M.D., showed in OHSU experience and a systematic literature review (the largest to date), a lower than previously reported 68Ga somatostatin receptor PET/CT sensitivity for ectopic CS, especially in occult lesions. Based on their research, this test seems less useful than predicted for ECS. Together with Justin Cetas, M.D., Ph.D., they are currently investigating a different nuclear medicine approach for locating elusive pituitary tumors, particularly for CD.

- Based on recent research (the first in the U.S.) and a new meta-analysis, the OHSU Pituitary Center found that patients with CS have a significantly increased risk of thromboembolism and now recommends clinicians balance the advantages of thromboprophylaxis with risk of bleeding.

Leadership and training in pituitary field

OHSU Pituitary Center team members are actively involved in teaching other physicians the latest treatments in the pituitary arena, speaking at more than 30 national and international conferences a year. Fleseriu, directs the Educational Commission for Foreign Medical Students Pituitary fellowship training program, unique in the U.S. for neuroendocrinology. Chris Yedinak M.N., F.N.P., D.N.P., is the current president of the Endocrine Nurses Association USA and is co-founder and president of the Federation of International Nurses in Endocrinology.
The OHSU Pituitary Center treats more than 500 new patients a year from around the U.S. This high volume facilitates studies to refine treatment. For example, Justin Cetas, M.D., Ph.D., (left) and Maria Fleseriu, M.D., FACE, (right) are collaborating on a new method of locating elusive pituitary tumors.
Leading a "give and go" protocol for acute ischemic stroke intervention

In January 2019, OHSU became the first comprehensive stroke center in the U.S. to include IV tenecteplase (TNKase) in its formulary as the primary thrombolytic agent for treatment of acute ischemic stroke (AIS). As a referring center that receives 80% of stroke patients through transfer, OHSU hopes to set an example for this new protocol.

For AIS, the OHSU protocol is to administer tenecteplase within four and a half hours of the patient’s onset of symptoms, reserving alteplase (Activase, Actilyse) as an alternative solely for patients enrolled in clinical trials that require current standard of care. At this time, the U.S. Food and Drug Administration has not approved tenecteplase for stroke. However, the American Heart Association (AHA) guidelines designate tenecteplase as an equivalent and reasonable alternative to alteplase. OHSU’s accrediting program, DNV Healthcare, accepts the substitution.

For Hormozd Bozorgchami, M.D., associate director of the OHSU Stroke Program, the one-time bolus delivery for tenecteplase is superior to the “drip and ship” bolus plus infusion option of alteplase, which presents logistical challenges and multiple hand-offs.

"Our goal is to expand the use of tenecteplase to our partner telestroke sites, because this ‘give and go’ model has the potential to make transfers safer, easier and more efficient.”

Hormozd Bozorgchami, M.D.
Tenecteplase was already on the OHSU formulary for cardiac arrest. The OHSU Clinical Knowledge and Therapeutics Executive Committee approved the use for AIS after reviewing the OHSU Stroke Program's presentation of AHA's EXTEND-IA TNK trial results and considering the cost savings and ease of administration for tenecteplase.

“Of about a dozen cases, we’ve had zero complications administering tenecteplase at OHSU this year,” said cerebrovascular program manager Noah Jacobson, noting patients thus far also have better functional outcomes measured by median modified Rankin scores at 90 days. “We want to build a body of evidence for the new usage of this medication to develop better and safer systems for treating stroke patients.”

The OHSU Stroke Program is also participating in the phase 3 TIMELESS trial to evaluate the efficacy of tenecteplase given up to 24 hours from symptom onset, potentially broadening the time window for intervention in AIS for patients who meet the criteria.
OHSU neurosciences focuses on improving health care through a breadth of fundamental scholarship. In 2018–2019, OHSU neurosurgery faculty members published a remarkable seven new books, with topics ranging from basic neurophysiology to the history of medical professionalism. Each contribution is aimed at one unifying goal: improving the lives of patients with nervous system disease.

One of these books shines a spotlight on how foundational concepts of Western medicine from ancient Greece are still relevant to physicians today. And yet, it argues, the legacy of ancient Greek medicine also transmits various troubling and destructive assumptions that limit the scope and effectiveness of modern medical practice.

In “The Rhetoric of Medicine: Lessons on Professionalism from Ancient Greece,” Nathan R. Selden, M.D., Ph.D., FACS, FAAP, chair of the OHSU Department of Neurological Surgery, and co-author Nigel Nicholson, Ph.D., Walter Mintz Professor of Classics and Dean of the Faculty at Reed College in Portland, created a very unusual collaboration. Together, the pair delved into the underpinnings of medical professionalism by comparing ancient Greek to modern American medicine.

“Two millennia later, it is surprising how incredibly similar the personal and professional challenges of physicians remain despite the advent of new technologies,” Selden said. “The biggest challenges in medicine aren’t related to the latest drug or gene discovery, but how to deliver health care in a way that truly enhances understanding between patient and provider. Human nature and the human challenges of medicine are amazingly resistant to the influence of new technology.”

This ancient Greek legacy includes the ambiguous role of money in health care, competition between traditional and alternative medicine, and restrictions on political involvement by physicians.
Breadth of scholarship across the field

In 2018–2019, OHSU neurosurgery faculty produced two basic science books, four clinical textbooks, and a book describing the history of professionalism in ancient Greek medicine.


Rather than straying into ethical debates, Selden and Nicholson focus on the permanence of social narratives reinforced across centuries. One embedded narrative Selden calls out is providers seeing themselves as untouchable by illness, which can impair their ability to deliver care.

“The image of selfless physicians over-working themselves to make up for gaps in the health care system is harmful to both doctors and patients,” he said.

“We can fix that and have a healthier workforce, better patient care and, ultimately, less cost. We have to learn about culture like anthropologists of medicine in order to make changes that support modern physicians reaching their full potential and professional success, so they can achieve the best possible outcomes for their fellow community members.”
OHSU supports basic neuroscience research, understanding that seeking the causes of brain disease is paramount to discovering new treatments and cures. The OHSU Brain Institute has nine research institutes in addition to the renowned Vollum Institute, which is dedicated to the study of the molecular basis of nervous system function.
In the 12 years since the recognition of an autoimmune encephalitis that attacks the N-methyl-D-aspartate (NMDA) neurotransmitter receptor in the brain (as chronicled in the patient account “Brain on Fire” by Susannah Cahalan), treatments have been limited to standard modes of therapy for autoimmune diseases. OHSU neuroscientists are hoping to push the science forward through a mouse model of the disease using active immunization with native-like NMDA receptors (holoproteins). With this model, the goal is to provide insights into disease induction and a platform for testing therapeutic approaches.

“Using this model, we can determine the exact time when anti-NMDA receptor encephalitis starts and follow the progression of the pathophysiology to look at what aspects are relevant to the disease in patients,” said Gary L. Westbrook, M.D., a neurologist and senior scientist at the OHSU Vollum Institute. “For example, we hope to investigate where on the receptor antibodies bind. With OHSU’s cryo-EM technology, the goal is to identify where the antibodies bind on the NMDA receptor at the atomic level. Conceivably, this approach could enable therapeutic approaches to block this specific interaction, rather than requiring broad-spectrum immuno-suppression.”

Westbrook and his colleagues have applied to OHSU’s Institutional Review Board to collect anonymous human samples to compare their studies in mice to humans. The ability to replicate the disease in mice offers several tangents of potential therapeutic insight.

“For example, the antibodies interfere with the function of receptors, but we also see neuroinflammation in some affected mice that could contribute to the disease phenotype,” Westbrook said. “The mouse model allows us to study which factors are more important in the disease and which happens first. This could tell us what impact treating the inflammation alone or in sequence might have.”

This breakthrough in NMDA receptor research resulted from a serendipitous collaboration between OHSU structural biologist Eric Gouaux, Ph.D., and Westbrook, who has studied NMDA receptors for several decades. Gouaux, also a senior scientist at the Vollum and an investigator with the Howard Hughes Medical Institute, published an unprecedented three-dimensional view of the NMDA receptor in Nature in 2014. In this project with the Westbrook Lab, they immunized mice with NMDA holoproteins in liposomes (lipid bubbles), resulting in behavioral changes, seizures, histopathology, as well as serum NMDA receptor antibodies that were consistent with the human disease. Brian Jones, a doctoral student in OHSU’s neuroscience graduate program, was the lead author of the study published in Science Translational Medicine in July 2019.
Breakthroughs in Research

Groundbreaking trial of lipoic acid for multiple sclerosis moves to phase 2

Based on research conducted at OHSU, the natural, oral antioxidant lipoic acid may be neuroprotective in progressive multiple sclerosis (MS). After a successful pilot study at the VA Portland Health Care System, lead investigator Rebecca Spain, M.D., MSPH, is launching a multi-site, international follow-up trial to determine if lipoic acid provides a clinical benefit by maintaining walking ability and other neurological functions among those taking lipoic acid.

In the pilot of lipoic acid versus placebo, 51 people with secondary MS showed a 68% reduction in brain atrophy at the end of two years in the group taking lipoic acid.

The second phase of the clinical trial will study 118 people with either primary or secondary progressive forms of MS across the country and a site in Canada, with results expected in 2022. In a related series of clinical trials, Spain is investigating the mechanisms of action of lipoic acid, and determining ways to increase the gastrointestinal tolerance and absorption for lipoic acid in people with MS.

Spain’s study of lipoic acid builds upon more than a decade of research at OHSU. Dennis Bourdette, M.D., the director of the OHSU Multiple Sclerosis Center, was one of the forerunners in this research area. Vijayshree Yadav, M.D., used Bourdette’s research to conduct her own investigations, with a focus on the dosage and safety of using lipoic acid in animal models and its effects on optic neuritis.

This exciting research could offer a low-cost, over-the-counter treatment for people with progressive forms of MS.
Differences in brain atrophy two years between lipoic acid and control cohorts

Annualized percent change brain volume (PCBV) between LA and placebo cohorts using intention-to-treat analysis of 51 participants with secondary progressive MS (A). Two-year PCBV from study completers is shown and demonstrates significantly less PCBV in the LA cohort (n = 22, -0.45% [SEE 0.71]) than controls (n = 24, -1.31% [SEE 1.10], p = 0.001, B). LA = lipoic acid; SEE = standard errors of the coefficient estimate.
OHSU joins aneurysm database study

OHSU is one of 25 clinical centers participating in the Prospective Observational Database Comparing Aneurysm Surveillance and Treatments (PODCAST) study to compare the effectiveness of medical management strategies for patients with unruptured intracranial aneurysms (UIAs). Among the goals of the study is to find consensus in management approaches. OHSU is a high volume center for UIA and has a robust reputation for successfully hosting clinical trials. OHSU’s role begins in 2020, running through 2027.
“Using ferumoxytol will provide an imaging biomarker that can be used to tailor therapy early after starting treatment compared to standard delays of three to six months. If the change is treatment-related, we can continue the course of immunotherapy. If the change is due to tumor progression, we can go with the next line of treatment.”

Prakash Ambady, M.D.
Exercise program shows improvement in balance and walking for Parkinson’s disease patients

An Agility Boot Camp at OHSU’s Balance Disorders Laboratory for people with Parkinson’s disease developed by Fay B. Horak, Ph.D., P.T., and Laurie King, Ph.D., P.T., M.C.R., showed improvements in participants’ balance and walking with exercise intervention. The exercise program focused on both motor impairments and cognitive challenges. Participants attended small-group classes three times a week for six weeks.

Post-exercise, there was significant improvement in walking speed while dual-tasking, foot angle at heel contact with the floor, and torso range of motion. Additionally, there were improvements in patient-reported perceived functional independence, including improved balance confidence and ability to do activities of daily living. The results contribute to the growing body of evidence on the benefits of exercise for people with Parkinson’s disease.
Structural and functional synaptic improvements verified following exercise

Vollum Institute scientists in the Goodman and Westbrook labs reported that even a short period of exercise (mice on running wheels for two hours) causes structural and functional increases in synapses in the dentate gyrus of the hippocampus, a brain region critical to learning and the formation of new memories. Genetic analysis of individual neurons in the hippocampus activated by the exercise revealed a unique role for an understudied, “membrane-bending” gene called Mtss1L. “This research suggests that you don’t have to do regular exercise to enhance acute memory and learning; even one hour at the gym could lead to structural changes in the brain that can last for several days,” said Gary L. Westbrook, M.D. “We took a very broad question of what happens with acute exercise down to a single molecule. This discovery of the role of Mtss1L could be key to understanding the cascade of molecular events that lead to new synapses.”

In the dentate gyrus, exercise for two hours showed a robust increase in neural activity as labeled by the immediate early gene, c-Fos (green dots).
The Accreditation Council for Graduate Medical Education receives nominations from around the United States competing for one resident member appointment to each specialty committee annually. The ACGME board of directors selected sixth-year resident Jacob Bagley, M.D., of OHSU as the sole resident member of the Neurological Surgery Review Committee last year. He will serve in this role through July 2021. Bagley’s current research focus is cerebrovascular neurosurgery. He is involved in endovascular surgery outcomes research and is completing an enfolded fellowship in neurointerventional surgery.

An OHSU pilot initiative is forging a pathway to Ph.D. programs for college graduates from backgrounds underrepresented in science. Scholars accepted as part of this competitive training opportunity receive a mentored research experience as well as tailored support around academic and professional development. The second cohort of three students began in July 2019. Applications for 2020 are open to recent baccalaureate graduates who want to earn a graduate degree in a neurosciences-related field and who identify as an individual from a historically underrepresented group in biomedical sciences, as defined by the National Institutes of Health.

The OHSU Neuroscience Postbaccalaureate Initiative is a collaborative effort between the Department of Behavioral Neuroscience, Vollum Institute and OHSU Research & Innovation and overseen by Letisha Wyatt, Ph.D., director of diversity in research.
Clinical Neuroscience Fellowships at OHSU

**Neurology**
- Epilepsy
- Geriatric and Dementia Neurology
- Movement Disorders
- Multiple Sclerosis and Neuroimmunology
- Neurocritical Care
- Neuromuscular Medicine
- Neuro-oncology
- Sleep Medicine
- Vascular Neurology / Stroke

**Neurosurgery**
- Campagna Endowed Fellowship in Pediatric Neurosurgery
- Skull Base and Vascular Neurosurgery
- Stereotactic and Functional Neurosurgery
- Endovascular Surgical Neuroradiology
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Crom, Raina, Ph.D.
Dale, Marion, M.D.
Recent representative publications

**Neurological Surgery**


Neurology


Stuart S, Belluscio V, Quinn JF, Mancini M. Pre-frontal cortical activity during walking and turning is reliable and differentiates across young, older adults and people with Parkinson’s disease. Front Neurol. 2019 May 22;10:536.