Welcome from the Chair

Dear Colleagues,

I am delighted to present the inaugural edition of the Department of Neurology's quarterly e-newsletter to provide a new venue for sharing our continued progress in research, education, and patient care.

The COVID-19 pandemic reached our doorstep earlier this year, and I am so proud of the contributions that our department made to support and care for our patients. There has been a multitude of departmental projects related to understanding the neurologic consequences of infection led by Professor Serena Spudich, who explored the neurologic consequences of COVID-19 alongside Drs. Lindsay McAlpine and Shelli Farhadian. Similarly, new Assistant Professor of Neurology Tomokazu Sumida studied the immunologic mechanism of COVID-19 infection.

Our department has not been insulated from the social and racial injustice turmoil that has engulfed our nation. I remain deeply troubled by the systemic racism that continues to plague our society, and I stand in solidarity with our black and brown neighbors and colleagues. The department held a virtual town hall to learn from each other's lived experiences with prejudice and discrimination, and we began to explore how we might build a more welcoming and inclusive academic environment. I am immensely proud of our many neurology residents, fellows, faculty, and staff who participated in the White Coats for Black Lives event held recently at Sterling Hall of Medicine, and of our department's development of a Committee for Diversity and Inclusion. Each sub-
committee - Education, Community Outreach, and Recruitment and Retention - will work towards the common goal of fostering diversity and promoting equity and inclusion within our department.

Despite the multitude of challenges we have faced, our department has had a successful year of growth and accomplishments that we can all be proud of. In the sections below, learn more about our faculty's recent research advancements, join us in celebrating their many accolades, and discover the latest news updates from across the department.

Thank you for your continued, thoughtful, hard work. Each person makes our department what it is, and I look forward to a successful 2020-2021 academic year.

Sincerely,
David A. Hafler, M.D.
William S. and Lois Stiles Edgerly Professor of Neurology and Professor of Immunobiology
Chairman, Department of Neurology
Yale School of Medicine
Neurologist-in-Chief
Yale New Haven Hospital

Publications

**Neuro-Immunology**

From David Pitt: **Differential expression of the T-cell inhibitor TIGIT in glioblastoma and MS.** *(Neurology: Neuroimmunology and Neuroinflammation)* Here, we show that TIGIT is expressed on T cells in glioblastoma tissue, but is absent in MS brain, suggesting that anti-TIGIT may be useful to treat GBM.

From David Hafler: **Transcriptomic and clonal characterization of T cells in the human central nervous system.** *(Science Immunol)* T cells were profiled in the CSF of healthy individuals and patients with MS using single-cell RNA and TCR sequences to define CNS immune homeostasis in both healthy patients and patients with MS. In healthy individuals, clonally expanded CSF T cells are largely distinct from those found in the blood with effector, IFNγ, and tissue adaptation signatures, whereas CSF T cells from patients with MS differ from healthy controls with a gene expression signature consistent with elevated activation and cytotoxicity. These findings provide insight into the unique immune environment in the CSF under normal and disease-associated conditions.


**Neurological Infections and Global Neurology**

From Serena Spudich: **Neuropathogenesis and Neurologic Manifestations of the Coronavirus in the Age of Coronavirus**
Disease 2019: A Review. (JAMA Neurology) This narrative review article authored by residents and faculty in the Yale Department of Neurology takes a deep dive into the potential nervous system targets and routes of entry of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and examines how viral invasion as well as host immune responses may underlie neurological signs and symptoms observed in patients with COVID-19.

**Neurodegenerative Disorders**
From Jaime Grutzendler:
Astrocytes and microglia play orchestrated roles and respect phagocytic territories during neuronal corpse removal in vivo. (Science Advances) Using fluorescent markers, the researchers were able to watch for the first time microglia, astrocytes, and NG2 cells communicate and remove dead cells using in vivo time-lapse optical imaging of single brain cells in live mice.

From Carolyn Frederick:
Hippocampal and cortical mechanisms at retrieval explain variability in episodic remembering in older adults. (Elife) Using functional MRI, the researchers show that the effectiveness of hippocampal pattern completion explains variability in memory performance in healthy, older adults.

Tau PET imaging with 18F-PI-2620 in aging and neurodegenerative diseases. (European Journal of Nuclear Medicine and Molecular Imaging) Using 18F-Pi-2620, a new tau PET tracer, researchers show strong differences in the medial temporal lobe, as well as cortical regions known to be impacted in Alzheimer's disease, demonstrating that this tracer has promise for monitoring tau pathology in this illness.

**Human Translational Immunology & Neurology**
From Kevin O'Connor:
Single-cell repertoire tracing identifies rituximab-resistant B cells during myasthenia gravis relapses. (JCI Insight) Disease-relevant B cells during post-rituximab relapse emerge from the unsuccessful depletion of preexisting B cell clones; single-cell transcriptomic phenotyping combined with lineage tracing using paired B cell receptor repertoires identified both persistent antibody-secreting cell, as well as memory B cell subsets.

High-Throughput Investigation of Molecular and Cellular Biomarkers in NMOSD. (Neurology: Neuroimmunology & Neuroinflammation, Under Review) Integrative analyses of cytokines, chemokines, and immune cells in participants with NMOSD highlights CD16+CD56+ NK cells and CX3CL1 as potential novel biomarker candidates.

**Epilepsy and EEG**
From Larry Hirsch:
Up and Down States of Cortical Neurons in Focal Limbic Seizures. (Cerebral Cortex) This study provides the first direct evidence that during focal seizures with impaired consciousness, cortical neurons exhibit the same physiological activity as during deep anesthesia or slow wave sleep.

Realistic driving simulation during generalized epileptiform discharges to identify electroencephalographic features related to motor vehicle safety: Feasibility and pilot study. (Epilepsia) This study uses a realistic driving simulator resembling an automobile to test driving safety during spike wave discharges on EEG, and to determine which EEG features may predict safe or unsafe driving.

**NICU**
From Dave Hwang:
Policies for Mandatory Ethics Consultations at U.S. Academic Teaching Hospitals: A Multisite
Survey Study, (Critical Care Medicine) We demonstrate that, among top-ranked academic medical centers, the existence and content of official policies regarding situations that mandate ethics consultations are variable; this finding suggests that, despite recent critical care consensus guidelines recommending institutional review as standard practice in particular scenarios, formal adoption of such policies has yet to become widespread and uniform.

Concerns of surrogate decision makers for patients with acute brain injury: A US population survey. (Neurology) We demonstrate that, although surrogate decision makers for patients with severe acute brain injury are universally concerned with respecting patient wishes and minimizing suffering when making goals-of-care decisions, certain groups of decision makers highly prioritize specific decisional factors, such as attaining intrafamily consensus, worrying about inaccurate prognosis, and assessing the cost of long-term care; these data can help inform future interventions for supporting ICU decision makers.

From Guido Falcone: Genetically Elevated LDL Associates with Lower Risk of Intracerebral Hemorrhage. (Annals of Neurology) Researchers tested the hypothesis that genetically elevated LDL is associated with reduced risk of ICH. Genetically elevated LDL levels were associated with lower risk of ICH, providing support for a potential causal role of LDL cholesterol in ICH.

Neurogenetics
From Anna Szekely: Revealing ring chromosome formation mechanism by whole genome sequencing and registering clinical and cytogenomic findings for ring chromosome 9. (Under Review) The researchers believe this is the first study of ring chromosome 9 that reveals not only clinical and cytogenomic findings, but also using whole genome sequencing delineates the mechanism of ring formation and permits researchers to map critical regions, candidate genes, and correlated phenotypes.

Synapse Biology
From Thomas Biederer: Synapse-Selective-Control of Cortical Maturation and Plasticity by Parvalbumin-Autonomous Action of SynCAM 1. (Cell Reports) This study investigates critical period plasticity in the cerebral cortex and reveals that thalamocortical inputs to interneurons are a synaptic locus for this form of plasticity. These inputs are organized by the synaptic adhesion molecule, SynCAM 1.

Synaptic Connectivity and Cortical Maturation Are Promoted by the ω-3 Fatty Acid Docosahexaenoic Acid. (Cerebral Cortex) This work provides insights into the profound impact of micronutrients on neuronal connectivity, combining neuronal culture approaches with in vivo recordings to analyze cortical maturation.

VA Connecticut
From Jason Sico: Quality improvement in neurology: Neurology Outcomes Quality Measurement Set. (Neurology) This paper presents the rationale for and development of a quality measurement set, which includes three total measures - one related to patient experience and satisfaction, another regarding quality of life for patients with neurologic conditions, and healthcare utilization as it pertains to EMG for isolated lower back pain - which was developed by neurologists for neurologists to guide the implementation and evaluation of focused quality improvement initiatives within their work units (e.g. small practice, multispecialty group, academic center).

Yale Stem Cell Center
From Jean-Leon Thomas:
VEGF-C driven lymphatic drainage enables immunosurveillance of brain tumours. (Nature) This work reveals the capacity of VEGF-C to promote immune surveillance of tumors, and suggests a new, therapeutic approach, targeting lymphatic vessels to treat brain tumors.

Three-Dimensional Imaging of the Vertebral Lymphatic Vasculature and Drainage using iDISCO+ and Light Sheet Fluorescence Microscopy. (JoVE) We present a novel approach to obtain three-dimensional (3D) and cellular resolution images of CNS-associated lymphatics while preserving the integrity of their circuits within surrounding tissues.

Center for Neuroscience and Regeneration Research
From Steve Waxman:
Differential effect of lacosamide on Nav1.7 variants from responsive and non-responsive patients with small fibre neuropathy. (Brain) Functional testing of Nav1.7 variants from patients with small fibre neuropathy who were responsive or unresponsive to treatment begins to unravel biophysical underpinnings that contribute to the patient's responsiveness to lacosamide, in addition to bringing us closer to pharmacogenomically-guided treatment for neuropathic pain.

Dendritic Spine Dynamic after Peripheral Nerve Injury: An Intravital Structural Study. (JNeurosci) Using two-photon microscopy and whole-animal live imaging with an implanted glass window, we profiled the in vivo dynamics of dendritic spines over time on the same superficial dorsal horn neurons before and after peripheral nerve injury-induced pain to establish a structural-based bioassay for investigating the basis for chronic pain stability.

Hafler Team Awarded $9M ASAP Grant
A team led by Dr. David Hafler is one of two Yale teams to each receive approximately $9 million in grants from the Aligning Sciences Across Parkinson's (ASAP) research initiative. The grant will fund research on the neuro-immune-gut interactions that may drive the progression of Parkinson's disease. This research will build upon Yale's collaboration with the Massachusetts General Hospital and the Broad Institute and exemplifies both YSM and ASAP's commitment to research collaboration.

Research Highlight: CSF Analyses During COVID-19
Although the primary organ dysfunction by SARS-CoV-2 infection is thought to be respiratory, there is growing evidence demonstrating the virus's effects on other major organ systems, including the CNS. Dr. Shelli Farhadian, MD, PhD (Infectious Diseases and Neurology) is a lead clinical-investigator of the IMPACT biorepository at Yale, which is studying various aspects of COVID-19 pathogenesis through patient clinical data and samples. Through IMPACT, Dr. Farhadian is enrolling COVID+ hospitalized patients with neurological symptoms, including intractable headache, seizure, and encephalopathy, for studies of blood and spinal fluid. The team, which includes Dr. Serena Spudich, MD, MA (Neurology), Dr. Akiko Iwasaki, PhD (Immunobiology), and Dr. Laura Glick, MD (Internal Medicine), and Eric Song (MD/PhD candidate), is assessing CSF for evidence of viral neuroinvasion, inflammatory cytokines, and CSF and serum antibody responses during COVID-19. With the help of referring neurologists and other physicians at Yale, they have enrolled COVID-19 patients with a range of neurological symptoms and have begun
analysis of paired CSF and blood samples from these patients. Any COVID-19 patients who are undergoing clinical LP or who may be candidates for research-LP can be enrolled in this study and would help move this important research forward.

**Awards and Grants**

- Dr. Emily Gilmore, MD and the ELECTRO-BOOST team were awarded a $3.25 million grant from the National Institute of Neurological Disorders and Stroke.
- Drs. Serena Spudich, MD, MA (Neurology), Mark Gerstein, PhD (Molecular Biophysics and Biochemistry), and Yuval Kluger, PhD (Pathology) were awarded a $15 million grant from the National Institute on Drug Abuse (NIDA) to establish a Data Center to coordinate, analyze, and make accessible single-cell and other molecular data sets generated by Single Cell Opioid Responses in the Context of HIV (SCORCH) and other NIDA-funded HIV and substance use disorder projects.
- Dr. David Hwang, MD, FAAN (Neurology), FCCM, FNCS was awarded a Presidential Citation from the Society of Critical Care Medicine for serving as the Principal Investigator for the Society's Family Engagement Collaborative.
- Dr. Nils Petersen, MD, PhD, MSc received a NIH K23 Award for his proposal to study precision blood pressure management after endovascular stroke therapy, using real-time autoregulation measurements.
- Dr. Jennifer Kim, MD, PhD was awarded a K23 grant from the NIH/NINDS for her project, "EEG and MRI biomarkers to predict post-traumatic epilepsy."
- Dr. Ben Tolchin, MD, MS received the 2020 Epilepsia Clinical Science Award from the International League Against Epilepsy for the best clinical science published in *Epilepsia*: "Randomized controlled trial of motivational interviewing for psychogenic nonepileptic seizures."
- Dr. Guido Falcone, MD, ScD, MPH received the Robert G. Siekert New Investigator and Bernard J. Tyson Career Development Awards, and was named a Paul Dudley White International Scholar at the 2020 International Stroke Conference.

**NIA Renews Support for ADRC**

We are delighted the NIA has renewed its support for the Yale Alzheimer's Disease Research Center (ADRC) led by Drs. Stephen Strittmatter, MD, PhD and Christopher van Dyck, MD. The ADRC seeks to advance our understanding of Alzheimer's disease with the goal of translating laboratory discoveries into novel, effective, clinical therapies. Severed Cores (Administrative, Clinical, Data, Biomarker, Neropathology, Imaging, and Outreach) and a Research Education Component will work together to achieve this goal. Our unifying theme is a focus on the cell biology of specific neurons, and its heterogeneous disruption in Alzheimer's disease.
Graduation 2020
Congratulations to the Yale Neurology Class of 2020 and award recipients!

Neurology Establishes Committee for Diversity and Inclusion
The Department of Neurology's new Committee for Diversity and Inclusion convened for the first time on Friday, June 26, 2020

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Dr. Emily Gilmore, MD Appointed as Medical Director of Yale Neuroscience ICU

Dr. Joseph Schindler, MD Promoted to Clinical Professor, Department of Neurology

Dr. Kevin O'Connor, PhD Receives Tenure as Associate Professor

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Neurology Goes Social!

Announcing the launch of our official Neurology Department social media accounts! Click on the Twitter, LinkedIn, Instagram, and Facebook icons below, and follow us for weekly updates.