Summer, 2021

Welcome from the Chair

Dear Colleagues,

The Yale Department of Neurology is devoted to providing exceptional patient care, educating medical and graduate students, and advancing neurological research. In our spring 2021 newsletter we are proud to continue our expansion as a world-renowned research, teaching, and clinical center. The tireless efforts of our 138 faculty have resulted in overall percent increases in active grants, ultimately securing a 5th place ranking in total NIH funding in 2020 for Neurology. Once again, we recruited an outstanding class of new residents, in spite of the limitations posed by COVID-19. Our clinical efforts also continue to reach across southern New England.

Our department has made breakthrough advances in clinical and basic neurological research. Key accomplishments over recent years include: an Alzheimer’s Disease Research Award led by Stephen Strittmatter, MD, PhD, AB and Christopher Van Dyck, MD; a Human Immunology Project
Consortium Grant led by Ruth Montgomery, PhD and myself; an American Heart Association Bugher Center Award of Excellence led by Lauren Sansing, MD, MS, FAHA, FANA, Kevin Sheth, MD, and Guido Falcone, MD, ScD, MPH; and a new, $22M, investigator-initiated grant from Genentech to study early immune intervention in patients with multiple sclerosis awarded to Erin Longbrake, MD, PhD. We integrated our translational and research efforts with basic sciences across neuroscience, cell biology, and inflammation in relationship to the new Wu-Tsai Institute for the study of human cognition. We also continue to expand our NIH-funded clinical trial networks: NeuroNEXT, Infinity, StrokeNET Spirit, and ASPIRE, led by Drs. Sheth and Sansing. Neuro-Oncology has also launched a new, investigator-initiated trial for recurrent glioblastoma, led by Antonio Omuro, MD and in partnership with Arcus Biosciences. During this trial, patients will receive the combination of a novel immune-checkpoint inhibitor targeting TIGIT, along with an anti-PD-1 antibody. A robust translational component led by Liliana Lucca, PhD will utilize state-of-the-art, single-cell RNA sequencing technology to characterize this combination in the tumor microenvironment and on immune cells repertoire in the periphery. Additionally, in Neurological Infections and Global Neurology, Serena Spudich, MD, MA was awarded two major grants (UM1 and R01) for her HIV projects, totaling $19.5M over the next five years. Finally, a team led by Le Zhang, PhD, Noah Palm, PhD, Sreeganga Chandra, PhD, and I received a three-year, $9M ASAP grant to investigate the role of inflammation in Parkinson’s disease.

As always, our faculty play a pivotal role in training the next generation of neurologists. The Department’s “hybrid” virtual and in-person education model during the pandemic has allowed for strengthened teaching and learning tools for our residents and clinical fellows. The virtual format also extended to recruitment, which resulted in more than 550 residency applicants. Virtual grand rounds took advantage of Zoom to host renowned speakers, both nationally and internationally. This multitude of expertise and perspectives has facilitated more
comprehensive discussions and proven to be an integral part of our medical education program. We are especially proud that Jeremy Moeller, MD, MSc, FRCP(C) received the 2021 AAN Program Director Award in recognition of his contributions in making the Yale Neurology residency among the best in the nation.

We also continue our massive expansion in Connecticut and neighboring states. A new, multispecialty outpatient clinic was opening in Guilford, CT, where the following services are provided: General Neurology, Headache, Stroke, Epilepsy, Memory Disorders, and Neuromuscular Medicine, including EMG. Likewise, a new infusion center was established at our ambulatory practice in Fairfield, CT. Under Dr. Serena Spudich’s leadership, we also developed one of the first clinics in the country dedicated to the diagnosis and management of neurologic complications in COVID-19, and inpatient services have reached or surpassed pre-COVID levels. The second neurointensive care team now provides consultations to patients after cardiac arrest. A multidisciplinary neurotrauma service has been established under Drs. Emily Gilmore and Bulet Omay’s leadership, and patients with brain trauma are cared for from the acute injury to outpatient follow-up. Our neurovascular service was split in two teams to accommodate an ever-increasing volume of stroke codes within Yale New Haven Hospital and telestrokes in one of our ten spoke hospitals. We were able to enhance the care we provide on our General Neurology services by expanding the team with two advanced practice providers. Neurology inpatient-based services are now available at five of the six YNHHS hospitals, the latest addition being the Neurology program at Bridgeport Hospital led by Dan Brooks as chief of the general service and directors of the stroke program. In collaboration with Neurosurgery, an interventional stroke program has been established at Greenwich Hospital. A third interventional stroke program is being launched at Bridgeport Hospital, where the first patient was recently treated.

I am grateful to every member of our department who continues to make
our work possible, and I look forward to our future accomplishments in the remainder of the year.

Best Wishes,

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

Neurological Infections and Global Neurology
From Serena Spudich:
Lessons from a neurology consult service for patients with COVID-19 (Lancet Neurol) In March 2020, as the number of COVID-19 cases rose throughout the country, the Yale New Haven Hospital Neurology Department created a subspecialty consult service to diagnose and treat an expected wave of patients with novel neurological issues. In reviewing the NeuroCOVID patients, the team observed a striking and disproportionate representation of non-white patients requiring NeuroCOVID consultation. The authors write that the underlying cause of these racial disparities deserves critical investigation from pathogenic and public health perspectives.
Neurodegenerative Disorders

From Jaime Grutzendler:

*Imaging and optogenetic modulation of vascular mural cells in the live brain* ([Nat Protoc](https://www.nature.com/articles/nprot.2016.398)) Mural cells (smooth muscle cells and pericytes) are integral components of brain blood vessels. The authors demonstrate that measurements of diameter and flow within individual brain microvessels, along with calcium imaging and optogenetics, allow the investigation of mural cell physiology and their role in regulating regional cerebral blood flow. The studies demonstrate the utility of these tools to investigate mural cells in the context of Alzheimer’s disease and cerebral ischemia mouse models.

Movement Disorders

From Sule Tinaz:

*Robust Bayesian Analysis of Early-Stage Parkinson’s Disease Progression Using DaTscan Images* ([IEEE Trans Med Imaging](https://ieeexplore.ieee.org/tdom)) This paper proposes a mixture of linear dynamical systems model for quantifying the heterogeneous progress of Parkinson’s disease. The model was fitted to longitudinal DaTscans from the Parkinson’s Progression Marker Initiative, and revealed characteristic spatial progression patterns in the brain, each associated with a time constant, that can serve as disease progression markers.

Neuro-Immunology

From David Hafler:

*Oleic acid restores suppressive defects in tissue-resident FOXP3 Tregs from patients with multiple sclerosis* ([J Clin Invest](https://www.jci.org)) FOXP3+ Tregs rely on fatty acid β-oxidation-driven oxidative phosphorylation for differentiation and function. In this paper, the authors report a new mechanism by which environmental lipids drive cellular-specific metabolic programs that establish a positive feedback loop designed to enhance the stability and function of Tregs via the CD25/STAT5/FOXP3 axis. They show that oleic acid partially restored defects in the suppressive function of Tregs isolated from patients with MS, which further suggests the importance of fatty acid species in counteracting inflammatory signals in the tissue.

*Two genetic variants explain the association of European ancestry with multiple sclerosis risk in African-Americans* ([Sci Rep](https://www.nature.com/articles/srep15637)) Epidemiological studies have suggested differences in the rate of
multiple sclerosis in individuals of European ancestry compared to African ancestry, motivating genetic scans to identify variants that could contribute to such patterns. The authors report that a whole-genome scan in 899 African American cases and 1,155 African American controls identified two variants of MS susceptibility that predict a 1.44-fold higher rate of MS in European Americans compared to African Americans.

**Immune dysregulation and autoreactivity correlate with disease severity in SARS-CoV-2-associated multisystem inflammatory syndrome in children** *(Immunity)* Multisystem inflammatory syndrome in children (MIS-C) is a life-threatening, post-infectious complication occurring unpredictably weeks after mild or asymptomatic SARS-CoV-2 infection in otherwise healthy children. In this paper, the authors define immunopathology features of MIS-C with implications for predicting and managing this SARS-CoV-2-induced critical illness in children.

**Type I Interferon Transcriptional Network Regulates Expression of Coinhibitory Receptors in Human T cells** *(under revision, Nature Immunology)* In this article, the authors report the construction of co-inhibitory regulatory networks induced by IFN-I with identification of unique transcription factors controlling their expression that may provide targets for enhancement of immunotherapy in cancer, infectious diseases, and autoimmunity.

**Human Genetics and Genomics**

From Chris Cotsapas:

**Shared associations identify causal relationships between gene expression and immune cell phenotypes** *(Commun Biol)* The researchers assessed how many associations to different traits in the same locus are due to the same genetic variant, and are thus shared. The also assessed whether or not these associations shared between traits are likely due to a causal relationship between these traits or if horizontal pleiotropy is widespread. They found that only a subset of traits share associations, with many due to causal relationships rather than pleiotropy.

**Epilepsy and EEG**

From Chris Cotsapas:

**Epilepsy risk in offspring of affected parents: a cohort study of the “maternal effect” in epilepsy** *(Ann Clin Transl Neurol)* In this paper, the authors report a prospective population-based study
using the Danish National Patient Register (N = 1,754,742) in order to assess whether the risk of epilepsy is higher in offspring of mothers with epilepsy than in offspring of fathers with epilepsy. The authors found a clear maternal effect on offspring risk of epilepsy from their nationwide cohort study.

**NICU**

From Richa Sharma and Kevin Sheth:

*Excess Cerebrovascular Mortality in the United States During the COVID-19 Pandemic* ([Stroke](https://doi.org/10.1161/STR.0000000000000009)) In this paper, authors quantified the national- and state-level excess cerebrovascular deaths using the US National Center for Health Statistic data and determined that excess cerebrovascular deaths during the COVID-19 pandemic were observed and associated with decreases in stroke-related EMS calls nationally, and mobility at the state level, highlighting the need for public health measures that identify and counter the reticence to seeking medical care for acute stroke during the pandemic.

**Vascular Neurology**

From Lauren Sansing:

*Longitudinal transcriptomics define the stages of myeloid activation in the living human brain after intracerebral hemorrhage* ([Sci Immunol](https://doi.org/10.1126/sciimmunol.abb1169)) The authors leveraged a clinical trial of minimally invasive neurosurgery for patients with intracerebral hemorrhage (ICH) to investigate the dynamics of inflammation and the time course of myeloid activation at the site of brain injury after ICH. They observed a conserved progression of immune responses from proinflammatory to pro-resolution states in humans and identified transcriptional programs associated with neurological recovery.

*Leukocyte dynamics after intracerebral hemorrhage in a living patient reveal rapid adaptations to tissue milieu* ([JCI Insight](https://doi.org/10.1172/jci.insight.136075)) The authors longitudinally profiled blood and cerebral hematoma effluent from a patient enrolled in the Minimally Invasive Surgery with Thrombolysis in Intracerebral Hemorrhage Evacuation (MISTIE III) trial and discovered shifts in the activation states of myeloid and T cells in the injured brain over time. This suggests that leukocyte responses are dynamically reshaped by the hematoma microenvironment and that sensitive methods such as scRNA-Seq would enable greater understanding of complex intracerebral
Neuro-Oncology

From Liliana Lucca:

*Circulating Clonally Expanded T Cells Reflect Functions of Tumor Infiltrating T Cells* (J Exp Med)

In this article, the authors report their investigation of the relationship between tumor and peripheral immune environments and demonstrated that circulating TILs have unique transcriptional patterns that may have utility for the interrogation of T cell function and longitudinal immune monitoring in cancer immunotherapy.

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Drowning Out COVID-19 with Water Bottles

The pandemic has affected nearly every aspect of daily life, from ubiquitous mask-wearing and hand washing to social distancing and remote working and learning. Through our first community outreach fundraiser, we sought to address an overlooked yet critical need among local school children: access to drinking water.

Over the past year, local New Haven schools have had to shut off their water fountains to comply with CDC guidelines, leaving many 6-8th graders without drinking water for the entire school day. The Gentleman’s Leadership Club of the Roberto Clemente Leadership Academy for Global Awareness Magnet School sprung into action and organized a reusable water bottle fundraiser to address this urgent need and reached out to our department for support.
Initiated by the Community Outreach branch of our Committee for Diversity and Inclusion, we raised nearly $3,000 on GoFundMe from both individual and commercial donors, supplying each student and teacher at Roberto Clemente, as well as all 6-8th graders and teachers at Hill Central, John C. Daniels, Truman, and Betsy Ross schools with water bottles.

**TRUMAN SCHOOL**

**THANK YOU YALE SCHOOL OF MEDICINE DEPARTMENT OF NEUROLOGY**

**Education Highlights:**

The 2020-21 academic year was unique in the history of the department. The COVID-19 pandemic posed unprecedented challenges to our education programs, but also provided the opportunity for innovation and growth.
Grand Rounds have been 100% virtual this year, resulting in an all-time high of approximately 100 attendees per session. This virtual format allowed us to invite distinguished speakers from around the world.

The residency recruitment process was also completely virtual for the 2020-21 season. This latest cycle was facilitated by a robust website and social presence, including video tours, resident and alumni interviews, and regular updates about daily life within the department. We hosted 132 incredible applicants for virtual interviews, and the residents hosted highly successful virtual dinners the night before each interview day. Given that virtual interviewing posed no cost to the applicant, we saw a broader, more diverse applicant pool than ever before.

Our clinical training programs have continued to grow, with 30 residents and 25 clinical fellows. Many of these residents and fellows will remain at Yale as faculty members. Our educational program this year has occurred online or in a “hybrid” format with some online learners and some in-person. We have also continued to improve and promote our highly successful learning tools, including our EEG and Movement Disorders online modules and “Neurology Exam Prep Podcast.”

Awards and Grants

- **Jeremy Moeller**: Leah M. Lowenstein Award; AAN 2021 Residency-Fellowship Program Director Recognition Award.
- **Carolyn Fredericks**: Henry F. McCance Yale Scholar.
- **Stephen Waxman**: Mitchell B. Max Award for Neuropathic Pain.
- **Stephen Strittmatter**: King Faisal Prize for Medicine.
- **David Hafler**: Elected to the American Association of Physicians.
- **Sreeganga Chandra**: McKnight Brain Disorders Award.
- **Dave Hwang**: Grevnik Family Award.
- **CT Magazine Best Doctors 2021**: Joachim Baehring, David Hafler, Larry Hirsch, Paul Lleva, David Pitt, Alice Rusk, Joe Schindler, Dario Zagar.
- **Lauren Sansing and Kevin Sheth**: Inducted into the American
Society for Clinical Investigation.

- **Lauren Sansing**: R21 NINDS grant titled “Manipulation of metabolic pathways to enhance human macrophage phenotypes after ICH.”
- **Guido Falcone**: 2021 Michael S. Pessin Stroke Leadership Prize; 2020 American Society for Clinical Investigation Young Physician-Scientist Award.
- **Kevin Sheth**: Association for Clinical and Translational Science (ACTS) Team Science Award; ASA 2021 Stroke Research Mentoring Award.
- **Serena Spudich**: Kevin Robertson Memorial Award; R21 NIMH grant titled “CNS Viral Persistence and Neuropsychiatric Perturbations in HIV: Single cell and molecular interrogation;” R01 NIMH grant titled “PET imaging of synaptic density combined with neuroimmunologic measure to reveal mechanism of HIV Neuropathogenesis during ART.”
- **Nils Petersen**: K23 NINDS grant titled “Precision blood pressure management after endovascular stroke therapy based on real-time autoregulation measurements.”
- **Soumya Yandamuri**: National Multiple Sclerosis Society Postdoctoral Fellowship.

New Appointments

- **Ben Tolchin**: Inaugural Director, Yale New Haven Health System Center for Bioethics.
- **Huned Patwa**: Chief of Staff, VA Connecticut Health. Included in his new role, Dr. Patwa will also serve as Associate Dean for Veterans Affairs for the Yale School of Medicine.
- **Daniel DiCapua**: Acting Chief, Neuromuscular Medicine.
- **Hajime Tokuno**: Interim Chief, Neurology at VA Connecticut.
An Emerging Tool for COVID Times: The Portable MRI

A New Hope for Patients With Epilepsy

CELLO Study to Explore Early Treatment of Multiple Sclerosis

$11.12M Gift Supporting Hemorrhagic Stroke Treatment Launches Innovative Research Network

Yale Neurologists Identify Consistent Neuroinflammatory Response in ICH Patients