UNRAVELING LINKS

Between Chronic Inflammation and Long COVID

Current State, Challenges, and Opportunities

Program Workbook

September 19–21, 2023
Virtual Meeting

Organized by the Trans-NIH
Chronic Inflammation Working Group

NIH NATIONAL CANCER INSTITUTE

U.S. Department of Health & Human Services | National Institutes of Health

Day 1 | September 19: **DEFINING LONG COVID**

All times are noted in Eastern Time

10:00–10:10 a.m.	Welcome and Introduction **Pushpa Tandon, Ph.D.,** National Cancer Institute
10:10–10:40 a.m.	Update on Long COVID and post-COVID research **Keynote Speaker: Josh P. Fessel, M.D., Ph.D.,** National Center for Advancing Translational Sciences
Session 1:	Diagnosing Long COVID and Identifying Risk Factors: Unresolved COVID or Something More? **Chair: Gallya Gannot, D.M.D., Ph.D.,** National Center for Advancing Translational Sciences
10:40–11:00 a.m.	Sars-CoV-2 reservoir: a potential driver of inflammation and other disease mechanisms in Long COVID/PASC **Amy D. Proal, Ph.D.,** PolyBio Research Foundation, Kenmore, WA
11:00–11:20 a.m.	Identifying who has Long COVID in the U.S.A.: a machine learning approach using N3C data **Melissa A. Haendel, Ph.D.,** University of Colorado Anschutz Medical Campus
11:20–11:40 a.m.	The Gastrointestinal Tract and Long COVID **Saurabh Mehandru, M.D.,** Icahn School of Medicine at Mount Sinai
11:40 a.m.–12:00 p.m.	COVID-19 sequelae—Can long-term effects be predicted? **Eleni Gavriilaki, M.D., Ph.D.,** Aristotle University of Thessaloniki, Greece
12:00–12:30 p.m.	Panel Discussion **Moderators:** **Preethi Chander, Ph.D.,** National Institute of Dental and Craniofacial Research **Anju Singh, Ph.D.,** National Cancer Institute
12:30–1:00 p.m.	Lunch Break

Session 2:	**Classifying Long COVID and Potential Mechanisms** **Chair: Joy Liu, M.D.,** National Institute of Allergy and Infectious Diseases
1:00–1:20 p.m.	**Defining the pathophysiology of Long COVID / Long COVID Subtypes (using the RECOVER platform)** **Upinder Singh, M.D.,** Stanford University
1:20–1:40 p.m.	**Immune memory of Long COVID** **Julie J. McElrath, M.D., Ph.D.,** Fred Hutchinson Cancer Center
1:40–2:00 p.m.	**Long COVID: A proposed hypothesis-driven model of viral persistence for the pathophysiology of the syndrome** **Joseph A. Bellanti, M.D.,** Georgetown University
2:00–2:20 p.m.	**Epigenetic memory of COVID-19 in innate immune cells and their progenitors** **Steven Z. Josefowicz, Ph.D.,** Cornell University
2:20–2:50 p.m.	**Panel Discussion** **Moderators:** **Mercy Prabhudas, Ph.D.,** National Institute of Allergy and Infectious Diseases **Leela Rani Avula, Ph.D.,** National Cancer Institute
2:50–3:00 p.m.	**Day 1 Wrap-up** **Gallya Gannot, D.M.D., Ph.D.,** National Center for Advancing Translational Sciences

Day 2 | September 20: ORGAN-SPECIFIC EFFECTS OF INFLAMMATION AND LONG COVID

10:00–10:10 a.m.	**Review from Day 1: Goals and Objectives** **Merriline Satyamitra, Ph.D.,** National Institute of Allergy and Infectious Diseases
10:10–10:40 a.m.	**Organ-Specific Inflammation and Long COVID** **Keynote Speaker: Richard C. Becker, M.D.,** University of Cincinnati
Session 3:	**Neurological Effects** **Chair: Danielle Carrick, Ph.D., M.H.S.,** National Cancer Institute
10:40–11:00 a.m.	**COVID-19: Challenges for Neurology** **Prof. Raimund Helbok, M.D., Ph.D.,** Department of Neurology, Johannes Kepler University Linz, Austria
11:00–11:20 a.m.	**Neuropathogenesis of Long COVID** **Avindra Nath, M.D.,** National Institute of Neurological Disorders and Stroke
11:20–11:40 a.m.	**Post-infectious peripheral neuropathy in Long COVID—mechanisms, diagnosis and mitigation** **Anne Louise Oaklander, M.D., Ph.D.,** Massachusetts General Hospital
11:40 a.m.–12:00 p.m.	**SARS-CoV-2 spike protein, neuroinflammation, and brain fog** **Prof. Theoharis Theoharides, M.D., Ph.D., M.Phil., M.S., FAAAAI,** Nova Southeastern University
12:00–12:30 p.m.	**Panel Discussion** **Moderators:** **Nataliya Gordiyenko, Ph.D.,** National Eye Institute **Christina Liu, Ph.D., P.E.,** National Institute of General Medical Sciences
12:30–1:00 p.m.	**Lunch Break**

Session 4:	Cardiovascular, Respiratory, and Immunological Effects **Chair: Rao L. Divi, Ph.D.,** National Cancer Institute
1:00–1:20 p.m.	COVID-19 Associated Coagulopathy (CAC) **Jim H. Morrissey, Ph.D.,** University of Michigan
1:20–1:40 p.m.	Immuno-proteomics of the post-COVID-19 lung and its link to pathology **James Harker, Ph.D.,** Imperial College London, London, UK
1:40–2:00 p.m.	Cardiac Pathology in Long COVID **James R. Stone, M.D., Ph.D.,** Massachusetts General Hospital
2:00–2:20 p.m.	Prevention and early treatment of the long-term physical effects of COVID-19: a randomised clinical trial of resistance exercise **Prof. Colin Berry, B.Sc., M.B., Ch.B., Ph.D.,** University of Glasgow, Scotland, UK
2:20–2:50 p.m.	Panel Discussion **Moderators:** **Natalie Abrams, Ph.D.,** National Cancer Institute **Ronald Warren, Ph.D.,** National Heart, Lung, and Blood Institute
2:50–3:00 p.m.	Day 2 Wrap-up **Christina Liu, Ph.D., P.E.,** National Institute of General Medical Sciences

Day 3 | September 21: **LIVING WITH LONG COVID**

10:00–10:10 a.m.	Review from Days 1 and 2: Goals and Objectives **Kyung Moon, Ph.D.,** National Institute of Allergy and Infectious Diseases
10:10–10:40 a.m.	The ins and the outs, the long and the short, of complement in COVID-19 **Keynote Speaker: Edward M. Conway, M.D., Ph.D.,** University of British Columbia, Canada
Session 5:	Comorbidities and Long COVID—What Do These Chronic Inflammatory Conditions Mean for Long COVID **Chair: Mulualem E. Tilahun, D.V.M., Ph.D.,** National Institute of Aging
10:40–11:00 a.m.	What does aging mean for Long COVID effects? **Shabnam Salimi, M.D., M.Sc., FAHA,** University of Maryland
11:00–11:20 a.m.	Autoimmune diseases and Long COVID **Divaker Choubey, Ph.D.,** University of Cincinnati
11:20–11:40 a.m.	Long COVID, selection criteria, and representation **Charisse Madlock-Brown, Ph.D.,** University of Iowa
11:40 a.m.–12:00 p.m.	Age of first developing overweight or obesity, COVID-19 and Long COVID in two British birth cohorts **Charis Bridger Staatz, Ph.D.,** University College London, UK
12:00–12:30 p.m.	Panel Discussion **Moderators:** **Joy Liu, M.D.,** National Institute of Allergy and Infectious Diseases **Chiayeng Wang, Ph.D.,** National Cancer Institute
12:30–1:20 p.m.	Lunch Break

Session 6:	Prevention and Treatment **Chair: Johanna Dwyer, D.Sc., R.D.,** National Institutes of Health, Office of Dietary Supplements
1:20–1:40 p.m.	Disparities in Post-Acute Sequelae of COVID-19 (Long COVID) **Dhruv Khullar, M.D., M.P.P.,** Cornell University
1:40–2:00 p.m.	Long COVID and Viral Persistence: Exploring Avenues for Therapies **Linda C. Geng, M.D., Ph.D.,** Stanford University
2:00–2:20 p.m.	Clinical experience with the α2A-adrenoceptor agonist, guanfacine, and N-acetylcysteine for the treatment of cognitive deficits in Long COVID **Amy F.T. Arnsten, Ph.D.,** Yale University
2:20–2:50 p.m.	Panel Discussion **Moderators:** **Rao L. Divi, Ph.D.,** National Cancer Institute **Christina Liu, Ph.D., P.E.,** National Institute of General Medical Sciences
2:50–3:00 p.m.	Day 3 Wrap-up **Pushpa Tandon, Ph.D.,** National Cancer Institute

Amy FT Arnsten, Ph.D.

Albert E. Kent Professor of Neuroscience, Yale Medical School
amy.arnsten@yale.edu

Dr. Arnsten studies the molecular regulation of higher cortical circuits in primates, identifying changes with stress, inflammation, and age that increase the risk of cognitive disorders such as schizophrenia, Alzheimer's disease, and the cognitive deficits of Long COVID. Much of her research focuses on the prefrontal cortex, a recently evolved region that subserves higher cognition. Dr. Arnsten received her B.A. in neuroscience from Brown University in 1976 and her Ph.D. in neuroscience from the University of California, San Diego, in 1981, with postdoctoral studies at Cambridge and then Yale, where she became Assistant Professor in 1986. She is currently the Albert E. Kent Professor of Neuroscience at Yale and a member of the National Academy of Medicine. She received the Goldman-Rakic Prize for Outstanding Research in Cognitive Neuroscience. Dr. Arnsten's research has led to the development of guanfacine (Intuniv™) for the treatment of cognitive disorders and prazosin for the treatment of post-traumatic stress disorder.

Richard Becker, M.D., M.Ed., FAHA

Professor of Medicine, University of Cincinnati College of Medicine
richard.becker@uc.edu

Dr. Becker is a tenured Professor of Medicine at the University of Cincinnati College of Medicine. He is an adjunct Professor of Medicine at Duke University School of Medicine. Prior to his appointment as Chief of Cardiology and director of the Heart, Lung, and Vascular Institute at the University of Cincinnati College of Medicine, Dr. Becker was Director of the Duke Cardiovascular Thrombosis Center at Duke University Medical Center and the Duke Clinical Research Institute in Durham, NC.

Dr. Becker has published extensively in peer-reviewed journals, including Nature Communications, the New England Journal of Medicine, The Lancet, Circulation, and Circulation Research, and contributed 85 textbook chapters and authored 12 textbooks. He is the founding editor-in-chief of the Journal of Thrombosis and Thrombolysis, now in its third decade of publication. His current research focuses on molecular regulation in cardiovascular disease, and organoid and cardioid cellular models to study the cardiotoxicity of chemotherapy drugs, accelerated vascular aging in early-stage breast cancer, biomarkers of post-COVID conditions, and novel platforms for drug development in thrombosis-related conditions.

Dr. Becker established the COVID-19 Recovery and Post-COVID Conditions Clinic in the spring of 2020 in response to a growing number of patients with persisting symptoms after an initial infection. The multidisciplinary clinic includes cardiology, pulmonary, sleep medicine, rheumatology, immunology, neurology, psychiatry, otolaryngology, dermatology, pulmonary rehabilitation, and integrative medicine expertise and has evaluated more than 700 patients from the tri-state region and beyond. The clinic established a data and sample biorepository for future research and is available to investigators.

Joseph A. Bellanti, M.D.

Professor, Department of Pediatrics & Microbiology-Immunology,
Georgetown University Medical Center
bellantj@georgetown.edu

Dr. Bellanti is professor of pediatrics and microbiology-immunology and director of the International Center for Interdisciplinary Studies of Immunology at Georgetown University Medical Center. He received his M.D. degree from the University of Buffalo, followed by residency training at the Children's Hospital of Buffalo, post-doctoral training in developmental immunology at the University of Florida School of Medicine, Gainesville, and viral immunology at Walter Reed Army Institute of Research, Silver Spring, MD. Dr. Bellanti's research team has directed their investigative efforts toward antimicrobial research, evaluation of new vaccine strategies, and developmental immunology. This work resulted in the initial characterization of the IgM response of the newborn, the identification of the antiviral role of secretory IgA in respiratory secretions, and the cellular immune responses to viral infections following immunization or natural infection. He is the recipient of numerous awards and honors, including the prestigious E. Mead Johnson Award for Research in Pediatrics for outstanding scientific contributions, the Humanitarian Award from the American College of Allergists, the Distinguished Medical Alumnus Award from the State University of Buffalo, New York, and the Founder's Day Award from the Georgetown University School of Medicine. Dr. Bellanti has also held numerous leadership positions in national and international organizations, including president, Society for Pediatric Research; president, American Board of Allergy and Immunology; president, INTERASMA; president, American College of Allergy, Asthma and Immunology (ACAAI); president, Association of Medical Laboratory Immunologists (AMLI); and president, American Association of Certified Allergists (ACA). Other roles include editor-in-chief of several journals, including Pediatric Research; Annals of Allergy, Asthma & Immunology; and Allergy and Asthma Proceedings. He has published over 500 scientific articles and abstracts, as well as numerous textbook chapters and his widely acclaimed textbook on immunology, Immunology IV: Clinical Applications in Health and Disease.

Colin Berry, B.Sc., M.B., Ch.B., Ph.D. *(Degrees listed are based on the UK academic system.)*

Professor of Cardiology and Imaging, University of Glasgow

colin.berry@glasgow.ac.uk

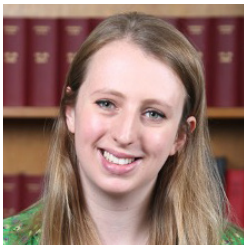
Dr. Berry is a professor of cardiology and imaging at the University of Glasgow, Scotland. He is director of research at the Golden Jubilee National Hospital and a Consultant Cardiologist in this hospital and in the Queen Elizabeth University Hospital in Glasgow.

Professor Berry is currently an Executive Editor of the European Heart Journal, President of the British Society of Cardiovascular Magnetic Resonance, and a member of the Clinical Trials Committee of the Society of Cardiovascular Magnetic Resonance.

Professor Berry studied medicine at the University of Glasgow (1987–1993) and physiology (Maîtrise) at the University of Paris (1989–1990). He was awarded a Ph.D. in cardiovascular science at the University of Glasgow (2002). Dr. Berry trained in cardiology and internal medicine (2001–2006) first in Glasgow and then at the Montreal Heart Institute (2005–2006). While in Montreal, he worked in Jean-Claude Tardif's Atherosclerosis Research Group and used imaging techniques to study stem cells and coronary artery disease. This work was supported by a British Heart Foundation International Fellowship and an International Exchange Award from the Royal Society of Edinburgh. When in Montreal, Professor Berry became the first British clinician to participate in transcatheter aortic valve replacement (TAVR). He then undertook post-doctoral studies (2007–2009) in advanced cardiovascular imaging at the National Heart, Lung, and Blood Institute, Bethesda, MD. This appointment was supported by a Lord Kelvin Adam Smith Fellowship from the University of Glasgow. In 2009, Professor Berry secured a senior fellowship from the Scottish Funding Council.

He is a principal investigator (PI) for the CISCO-19 multisystem imaging study of people after hospitalization for COVID-19 (NCT04403607; PMID: 35606551), the CISCO-21 clinical trial of resistance exercise for prevention and treatment of Long COVID (NCT04900961; PMID: 35606551), and co-PI for UK COVID-HEART (ISRCTN58667920; PMID: 35606551). He has contributed to multiple biomedical and clinical studies in COVID-19.

References: https://pubmed.ncbi.nlm.nih.gov/?term=colin+berry+covid-19



Charis Bridger Staatz, Ph.D.

Research Fellow in Population Health and Quantitative Social Sciences, University College London

charis.staatz.17@ucl.ac.uk

Dr. Staatz is a Research Fellow in Population Health and Quantitative Social Sciences working at the Centre of Longitudinal Studies (CLS) based at University College London. Her research interests are broad, spanning the field of population health and including social inequalities in health, particularly obesity and body composition; COVID-19 and Long COVID; early life shocks from infections; and midlife health and international comparisons.

She is also the co-lead for the Physical Health Theme of research at CLS, and from September 2023, she will take on the role of Research Fellow in Impact Evidence alongside her current position. In her new role, she will be responsible for evidencing the way in which data from the cohort studies hosted by CLS (specifically, the 1958 National Child Development Study, the 1970 British Cohort Study, Next Steps, and the Millennium Cohort Study) have influenced research/knowledge, teaching, policy, and practice.

Divaker Choubey, Ph.D.

Professor Emeritus, University of Cincinnati, College of Medicine
divaker.choubey@uc.edu

Dr. Choubey joined the Department of Molecular Biophysics and Biochemistry at Yale University in early 1986 for his postdoctoral training after completing his Ph.D. research work at the Indian Institute of Science. During the training, he identified a novel family of the type I interferon (IFN)-inducible proteins (referred to as AIM2-like receptor family or ALR-family) and investigated their potential roles in cell growth inhibition. The ALR-family proteins, upon sensing cytosolic DNA, either stimulate the expression of the type I IFNs or activate an inflammasome activity. In 1994, Dr. Choubey joined the MD Anderson Cancer Center, Houston, Texas, as an Assistant Professor to establish his own laboratory to further investigate the role of ALR-family proteins in human cancers. In 1998, he moved to Loyola University Medical Center, Maywood, Illinois, to establish a new research program to investigate the role of ALR-family in cellular aging (senescence) and in lupus disease. In 2007, Dr. Choubey joined the University of Cincinnati (OH), as a tenured associate professor. His laboratory identified a novel role of ALR-family in female sex bias in the development of lupus, and in cellular senescence associated secretory phenotype. In 2010, he received a promotion to full professor. He continues to serve as a reviewer for various grant funding agencies (in the United States as well as internationally) and certain prestigious journals. He has published extensively on the role of ALR-family proteins in chronic inflammation-associated human diseases. Of interest, Long COVID is associated with chronic inflammation. Because the development of Long COVID appears to exhibit a female sex bias and individuals with Long COVID exhibit lupus-like symptoms, Dr. Choubey's recent research interests include investigating the potential roles of the ALR proteins in long COVID-associated chronic inflammation.

Edward M. Conway, M.D., Ph.D.

Professor of Medicine, Centre for Blood Research, University of British Columbia
ed.conway@ubc.ca

Dr. Conway was born and raised in Toronto, Canada, receiving degrees in Electrical Engineering and Medicine at the University of Toronto. He completed clinical and research fellowships in hematology-oncology at Harvard and MIT; he returned to Toronto as a physician-scientist, establishing a research group in vascular biology that focused on delineating mechanisms that regulate hemostasis and thrombosis. He has since pursued studies as a group leader at the University of Leuven in Belgium, and is now a scientist and Professor of Medicine at the University of British Columbia in Vancouver, Canada, where he is the Director of the Centre for Blood Research. There, his research aims to characterize the interplay among the vascular endothelium, coagulation, inflammation, and innate immunity using a range of technologies, from bench to bedside.

Josh P. Fessel, M.D., Ph.D.

Senior Clinical Advisor, National Center for Advancing Translational Sciences, National Institutes of Health
josh.fessel@nih.gov

Dr. Fessel is the senior clinical advisor in the National Center for Advancing Translational Sciences' (NCATS) Division of Clinical Innovation, where he serves as a liaison among basic, translational, and clinical scientists and helps build bridges among multiple stakeholders to ensure that the most innovative clinical science moves forward. He works closely with the Clinical and Translational Science Awards (CTSA) Consortium, with all of the different components of NCATS, across NIH Institutes and Centers, and across US Government (USG) agencies to help streamline existing processes (e.g., single institutional review board operations, clinical trial metrics, data management and sharing) and accelerate innovation in clinical and translational research (e.g., novel trial designs and analytical approaches, incorporation of cutting edge real-world data and digital health methods). In addition, Dr. Fessel has worked on multiple NIH-wide and USG-wide efforts responding to the SARS-CoV-2/COVID-19 global pandemic for both acute COVID and for post-COVID conditions (i.e., Long COVID).

Eleni Gavriilaki, M.D., Ph.D.

Assistant Professor, Aristotle University of Thessaloniki
elenicelli@yahoo.gr

Dr. Gavriilaki is a clinician-scientist with an exceptional record of training and accomplishments. She received her medical degree from the Aristotle University of Thessaloniki, graduating first out of 214 students in 2010 and her Ph.D. (Excellent with Distinction) in Internal Medicine-Hematology with a special interest in thrombosis and hemostasis in 2016. She worked as a postdoctoral fellow at the Johns Hopkins Hospital and then completed her specialization in the Hematology Department, Bone Marrow Transplantation Unit, at the George Papanicolaou Hospital of Thessaloniki, the largest center in Greece and the Balkans. Dr. Gavriilaki has established a unique clinical and research program in the field of complement-related diseases, including COVID-19.

Linda N. Geng, M.D., Ph.D.

Clinical Associate Professor, Stanford University
geng@stanford.edu

Dr. Geng is the co-founder and co-director of Stanford's integrated, multidisciplinary Long COVID clinical and research program. Her area of focus is in advancing the care of patients with complex, puzzling conditions and, since the pandemic, has led multiple research projects on Long COVID and infection-associated chronic illnesses. Dr. Geng is currently co-principal investigator of one of the first clinical trials testing antiviral therapy for Long COVID symptoms and a Stanford site investigator in the NIH RECOVER (Researching COVID to Enhance Recovery) initiative. Dr. Geng also serves on expert advisory councils and collaborative working groups for defining Long COVID care guidelines and advancing Long COVID treatment through innovative research approaches.

Melissa A. Haendel, Ph.D.

Chief Research Informatics Officer, University of Colorado Anschutz Medical Campus
melissa.haendel@cuanschutz.edu

Dr. Haendel is the Chief Research Informatics Officer at the University of Colorado's Anschutz Medical Campus and co-director for the National COVID Cohort Collaborative. Her background is in molecular genetics and developmental biology, as well as translational informatics, with a focus over the past decade on open science and semantic engineering. Dr. Haendel's vision is to weave together healthcare systems, basic science research, and patient-generated data through the development of data integration technologies and innovative data capture strategies. Her research has focused on the integration of genotype-phenotype data to improve rare disease diagnosis and mechanism discovery. Dr. Haendel also leads and participates in international standards organizations to support improved data sharing and utility worldwide.

James Harker, Ph.D.

Senior Lecturer and Associate Professor, Imperial College London
j.harker@imperial.ac.uk

Dr. Harker is a Senior Lecturer and Associate Professor and group leader at Imperial College London with a long-standing interest in understanding immune responses at barrier surfaces. He completed his Ph.D. at St. Mary's Hospital with Peter Openshaw before moving to the United States for 5 years, where he was an Irvington Institute Fellow in Elina Zuniga's Group in San Diego before establishing his team at Imperial in 2013. His team's current research interests revolve around understanding the regulation of T-cells during respiratory infection and inflammation using mouse models and clinical samples. The majority of his work explores how the immune response is shaped by those first antigenic exposures in early life. During the COVID-19 pandemic, his team, in collaboration with those of Professor Clare Lloyd and Professor Pallav Shah, were able to focus on how humans respond to a novel infection, and how this shapes respiratory health.

Raimund Helbok, Ph.D.

Professor of Neurology, Johannes Kepler University, Linz, Austria
Raimund.Helbok@kepleruniklinikum.at

Dr. Helbok is a Professor of Neurology and specialist in Neurocritical Care and appointed as Chair of Neurology at Johannes Kepler University Linz, Austria, since April 2023. After his training in general medicine, tropical medicine, and neurology, he conducted his research fellowship at the Division of Neurocritical Care, Department of Neurology, Columbia University Medical Center, New York City. He was working for more than 15 years at the Medical University of Innsbruck (MUI) in the field of neurology and co-leading the clinical and research group in neurocritical care at MUI.

Dr. Helbok's clinical practice covers the spectrum of neurocritical care, including the management of ischemic and hemorrhagic stroke, subarachnoid hemorrhage, traumatic brain injury, status epilepticus, neuromuscular diseases, autoimmune encephalitis, and neuroinfectious diseases. He is involved in several international trials and societies, and is working for the European Medicines Agency in the field of medical devices and currently co-leading the prospective studies group of the Curing Coma campaign of the Neurocritical Care Society.

Dr. Helbok co-founded the European Academy of Neurology (EAN) Neuro-COVID Registry Consortium (ENERGY) on neurological manifestations of COVID-19, which has over 270 registered sites worldwide. EAN formally collaborates with the Global Consortium Study of Neurological Dysfunction in COVID-19 network and contributes to global data harmonization and collaboration on the neurologic impacts of COVID-19.

Steven Z. Josefowicz, Ph.D.

Associate Professor, Weill Cornell Medicine
szj2001@med.cornell.edu

Dr. Josefowicz is an Associate Professor whose research interests and expertise lie at the intersection of immunology (doctoral studies, Alexander Rudensky, Memorial Sloan Kettering Cancer Center) and epigenetics (postdoctoral studies, C. David Allis, Rockefeller University). Dr. Josefowicz's research laboratory focuses on the role of "signaling to chromatin" pathways in immune cell development and function and their dysregulation in infectious and inflammatory disease and cancer. Work in the lab has revealed pathways for the transmission of extracellular or cytosolic signals to selectively induce stimulation responsive genes in immune cells. The lab focuses on understanding the transmission of cellular signals to chromatin, dedicated mechanisms of simulation-induced transcription, and molecular mechanisms controlling durable cellular memory of inflammation, with a focus on hematopoietic stem cells (HSCs) and their progeny innate immune cells. The lab applies biochemical, epigenomics, and single cell approaches to study fundamental mouse and human HSC epigenetic responses to inflammatory signals. The lab has been recognized for impactful research with the Burroughs Wellcome Fund Pathogenesis of Infectious Disease Award.

Dhruv Khullar, M.D., M.P.P.

Assistant Professor, Weill Cornell Medicine
khd9010@med.cornell.edu

Dr. Khullar is a physician and assistant professor of health policy and economics at Weill Cornell Medical College. He serves as Director of the Physicians Foundation Center for the Study of Physician Practice and Leadership, and his research, which focuses on value-based care, health disparities, and medical innovation, has been published in JAMA and the New England Journal of Medicine. He is also a writer at The New Yorker, where he writes about medicine, health care, and politics. Dr. Khullar earned his medical degree at the Yale School of Medicine and completed his medical training at the Massachusetts General Hospital and Harvard Medical School. He also received a master's degree in public policy from the Harvard Kennedy School, where he was a fellow at the Center for Public Leadership.

Charisse Madlock-Brown, Ph.D.

Associate Professor, University of Iowa
cmadlock@uiowa.edu

Dr. Madlock-Brown is an Associate Professor of Informatics at the University of Iowa College of Nursing. She was formerly an Associate Professor in health informatics and information management at the University of Tennessee Health Science Center (UTHSC). Dr. Madlock-Brown is at the forefront of exploring the impact and power of data management, data mining, and visualization techniques. At the UTHSC Research Pipelines Laboratory, she led a groundbreaking initiative that harnessed the power of distributed computing and storage through an innovative online interface. Her research explores electronic health records, focusing on analyzing data through an artificial intelligence-driven lens. Her work explores social determinants of health, health disparities, and multimorbidity, illuminating crucial insights that foster equitable health care practices.

Margaret "Julie" J. McElrath, M.D., Ph.D.

Senior Vice President and Division Director of the Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Center
jmcelrat@fredhutch.org

Dr. McElrath is a Physician-Scientist and directs the Vaccine and Infectious Disease Division (VIDD) and serves as the Joel D. Meyers Endowed Chair at the Fred Hutchinson Cancer Center. VIDD brings together scientists in translational, quantitative, and clinical research to prevent, vaccinate, treat, and cure infectious diseases of global health importance, including those affecting immunocompromised persons. Dr. McElrath serves as principal investigator of the HIV Vaccine Trials Network Laboratory Center and the Seattle HIV Vaccine Trials Unit. As a key scientific leader in the development of an effective HIV-1 and now SARS-CoV-2 vaccine, she oversees the implementation of high-quality, innovative approaches to reliably interrogate the human immune system on a global scale.

Saurabh Mehandru, M.D.

Physician, Icahn School of Medicine at Mount Sinai
saurabh.mehandru@mssm.edu

Dr. Mehandru is a Physician-Scientist who straddles clinical care and laboratory-based investigation. He completed his residency training in internal medicine at the New York University School of Medicine, where he also served as chief resident. Dr. Mehandru received subspecialty training in gastroenterology at the Icahn School of Medicine at Mount Sinai.

For his laboratory training, Dr. Mehandru undertook post-doctoral training at Rockefeller University, first working in the laboratory of Dr. David Ho and then in the laboratory of Dr. Ralph Steinman, Nobel Laureate in Physiology or Medicine, 2011.

After finishing his postdoctoral training, Dr. Mehandru was invited to join the faculty at Mount Sinai where, in addition to serving as Professor of Medicine, and Vice Chair for Research in Gastroenterology, he has led a laboratory of mucosal immunology since 2013. His laboratory studies the mucosal immune system and the host-microbial interface. He is an NIH-funded investigator who has received multiple awards and was elected to membership of the American Society of Clinical Investigation (ASCI).

During the COVID-19 pandemic, his laboratory defined the expression of ACE2 and TMPRSS2 in the human GI tract during health and inflammation (Gastroenterology, 2020), characterized intestinal immune and transcriptomic responses to SARS-CoV-2 (Gastroenterology, 2021), and identified for the first time, the long-term persistence of SARS-CoV-2 in the intestinal epithelium (Nature, 2021).

James “Jim” H. Morrissey, Ph.D.

Professor, University of Michigan Medical School
jhmorris@umich.edu

Dr. Morrissey has devoted most of his career to investigating how the blood clotting system is controlled in health and disease. He is a Professor of Biological Chemistry and Internal Medicine at the University of Michigan Medical School in Ann Arbor, Michigan, and is the co-editor-in-chief (with David Lillicrap) of the Journal of Thrombosis and Haemostasis.

Beginning with the cloning of tissue factor in 1987, Dr. Morrissey’s research has focused on the biochemical mechanisms by which the blood clotting system is regulated, with a particular interest in understanding how the clotting cascade is triggered, and how protein-membrane interactions regulate blood clotting reactions. In 2006, his laboratory reported the discovery that inorganic polyphosphate, which is released from activated human platelets, is a potent modulator of blood clotting and inflammation, and can help explain the otherwise puzzling role of factor XI in hemostasis. More recently, his lab has reported that platelet polyphosphate is a signaling molecule with potential roles in wound healing and fibrosis. Work from his lab has led to spin-offs with potential clinical applications, including new diagnostic assays. His lab is also working on novel hemostatic agents for treating bleeding and anti-inflammatory/anti-thrombotic agents with reduced bleeding side effects relative to conventional anti-coagulant drugs.

Avindra Nath, M.D.

Clinical Director, National Institute of Neurological Disorders and Stroke, National Institutes of Health (NIH)
natha@ninds.nih.gov

Dr. Nath is the Clinical Director of the National Institute of Neurological Disorders and Stroke (NINDS) at NIH, where he is also Chief of the Section of Infections of the Nervous System and Director of the Translational Center for Neurological Sciences. He specializes in neuroimmunology and neurovirology. Dr. Nath's research is focused on studying the clinical manifestations and pathophysiology and developing treatments for neurological infections with a focus on HIV infection and endogenous retroviruses. In recent years, he has studied the neurological complications of emerging infections, including Ebola, Zika virus, and SARS-CoV-2, and conducts research on patients with undiagnosed neuroinflammatory disorders. Dr. Nath has served on advisory committees to NIH, Centers for Disease Control and Prevention, U.S. Food and Drug Administration, and the World Health Organization. He is the past president and the recipient of the Pioneer in NeuroVirology award from the International Society of NeuroVirology. He received the Wybran Award from the Society on NeuroImmune Pharmacology for contributions to neurovirology. He also received the NIH Director's Award for his work on SARS-CoV-2 and the U.S. Department of Health and Human Services Secretary's Award for his work on Ebola infection. Dr. Nath is an elected member of the Association of American Physicians, an elected fellow of the American Association for the Advancement of Science, and a board member of the American Neurological Association.

Anne Louise Oaklander, M.D., Ph.D.

Associate Professor of Neurology, Harvard University/Massachusetts General Hospital
aloaklander@mgh.harvard.edu

Dr. Oaklander is a Harvard Medical School Associate Professor of Neurology and Assistant in Neuropathology at Massachusetts General Hospital (MGH). After undergraduate studies at Columbia and Cornell, she received M.D. and Ph.D. (neuroscience) degrees from Albert Einstein College of Medicine. After a Rutgers' neurology residency and peripheral nerve fellowships at the Johns Hopkins School of Medicine, she joined Hopkins' faculty. At MGH, Dr. Oaklander directs the Nerve Unit, an NIH and US Food and Drug Administration (FDA)-funded team that researches peripheral neuropathies. Her 130+ publications documented evidence of small-fiber pathology in 40% of fibromyalgia patients, and her team characterized early onset small-fiber neuropathy in children and young adults. She proposed inflammation/autoimmunity as the most common cause of small-fiber neuropathy (SFN) in otherwise healthy children and young adults. In 2018, she published the first large case series showing a benefit from immunotherapy for patients of all ages with dysimmune SFN. She co-authored the first clinical trial for hereditary sensory neuropathy type 1 and founded and directs the multilingual NeuropathyCommons.org website for patients. A fellow of the American Academy of Neurology and the American Neurological Association, her research has been profiled in Science and Scientific American Mind, PBS, and YouTube. Dr. Oaklander has served on NIH's Research Advisory Council and on review and advisory panels for NIH, FDA, American Academy of Neurology, and the Institute of Medicine, and on various editorial boards, currently Neurology® Neuroimmunology & Neuroinflammation.

Amy D. Proal, Ph.D.

President/Chief Scientific Officer, PolyBio Research Foundation
aproal@polybio.org

Dr. Proal serves as President/Chief Scientific Officer of PolyBio Research Foundation and directs the organization's close up to LongCovid Research Consortium (LCRC). She holds a B.S. in biology from Georgetown University and a Ph.D. in microbiology from Murdoch University in Australia. Her work examines the molecular mechanisms by which viral, bacterial, and fungal pathogens dysregulate human gene expression, immunity, and metabolism. In her work with the PolyBio Research Foundation and the LCRC, Dr. Proal conceptualizes conceptualizes and coordinates large-scale collaborative research projects among research teams studying infection-associated chronic illnesses such as Long Covid, myalgic encephalomyelitis, also called chronic fatigue syndrome (ME/CFS). Dr. Proal has written multiple review articles that delineate core biological drivers of both the LongCovid and ME/CFS disease processes. She is a regular speaker at infection-associated chronic disease conferences, including the International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis, LymeMIND, and the International Congress on Autoimmunity.

Shabnam Salimi, M.D., MSc, FAHA

Instructor/Adjunct Assistant Professor, University of Washington/
University of Maryland, Baltimore
ssalimi2@uw.edu

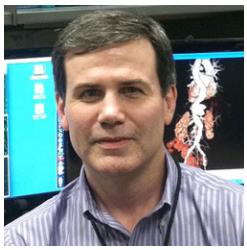
Dr. Salimi is a multidisciplinary scientist studying the mechanism of healthspan and lifespan. She uses clinical and laboratory tools to define health and multimorbidity as the rate of aging and functional decline and response to stress. Her work evolved around determining clinically and biologically meaningful algorithms that measure the rate of aging, "omics" that track healthspan and lifespan, and how they respond to anti-aging modalities and interventions. She has developed BodyClock and Health OctaTool in human and animal models, and PathoClock and PathoAge, PhysiocClock, and PhysiocAge using pathology and physiology measures in mice models. She joined the University of Washington to continue her goals of understanding mechanistic roles in heterogeneous aging patterns in body and brain systems in different contexts.

Upinder Singh, M.D.

Professor and Division Chief, Stanford University
usingh@stanford.edu

Dr. Singh is a Physician-Scientist with clinical training in infectious diseases and research expertise in COVID-19 and post-acute sequelae of COVID-19 or Long COVID. She is professor and chief of the Division of Infectious Diseases and Geographic Medicine in the Department of Medicine, Stanford University School of Medicine. She also serves as the Associate Chair for Faculty Development in the Department of Medicine. Dr. Singh is a fellow of the Infectious Diseases Society of America, a member of the American Society for Clinical Investigation, and a deputy editor for the Journal of Infectious Diseases.

Dr. Singh's research efforts in COVID-19 began with leading multiple investigator-initiated clinical trials in 2020, contributing to leadership of large, national COVID treatment studies, including ACTIV-2, leading the Stanford hub for the NIH RECOVER (Researching COVID to Enhance Recovery) study, and initiating the first study globally to investigate the effect of Paxlovid on the treatment of Long COVID. She also led efforts to establish a Long COVID clinic at Stanford, which launched in May 2021.



James R. Stone, M.D., Ph.D.

Associate Professor of Pathology, Massachusetts General Hospital
jrstone@mgh.harvard.edu

Dr. Stone directs the cardiovascular pathology and autopsy services at Massachusetts General Hospital. He completed medical school at the University of Michigan in the Medical Scientists Training Program, an 8-year program in which he earned both an M.D. and a Ph.D. He then completed residency training in anatomic pathology, as well as a cardiovascular pathology fellowship at Brigham and Women's Hospital and Harvard Medical School. For 3 years, Dr. Stone served as a staff pathologist at Brigham and Women's Hospital practicing cardiovascular pathology, autopsy pathology, and pulmonary pathology. In 2003, he was recruited to Massachusetts General Hospital to direct the Cardiovascular Pathology Service. In addition, he is currently an Associate Professor of Pathology at Harvard Medical School, and teaches cardiovascular pathology to Harvard medical students, as well as pathology residents and fellows at Massachusetts General Hospital. In addition to his clinical and teaching responsibilities, Dr. Stone directs a basic science research laboratory, studying disease mechanisms related to cardiovascular diseases, with a particular focus on atherosclerosis, vasculitis, myocarditis, amyloidosis, and SARS-CoV-2 associated pathologies.

Theoharis C. Theoharides, M.D., Ph.D., M.Phil., M.S., FAAAAI

Professor and Vice Chair, Clinical Immunology, and Director, Institute of Neuro-Immune Medicine, Clearwater, Florida, Nova Southeastern University
ttheohar@nova.edu

Dr. Theoharides is Professor and Vice Chair of Clinical Immunology and Director of the Institute of Neuro-Immune Medicine; Adjunct Professor of immunology at the Tufts School of Medicine, where he was Professor of Pharmacology and Internal Medicine; and Director of Molecular Immunopharmacology and Drug Discovery, and clinical pharmacologist at the Massachusetts Drug Formulary Commission (1983–2022). He received his B.A., M.S., M.Phil., Ph.D. and M.D. degrees and the Winternitz Prize in Pathology from Yale University. He also received a Certificate in Global Leadership from the Fletcher School of Law and Diplomacy at Tufts University and a fellowship at the Harvard Kennedy School of Government. He trained in internal medicine at the New England Medical Center, which awarded him the Oliver Smith Award "recognizing excellence, compassion and service." He received the Tufts Distinguished Faculty Recognition and Excellence in Teaching award multiple times and the Alumni Excellence in Service award. Dr. Theoharides showed that the unique tissue immune cells—mast cells—are critical for neuroinflammation, especially the pathogenesis of autism spectrum disorder, chronic fatigue syndrome, and Long COVID. He has 480 publications (44,904 citations; h-index 103), placing him in the world's top 2% of most cited authors and was rated as a worldwide expert on mast cells and luteolin by Expertscape. He has developed novel dietary supplements containing liposomal flavonoid (luteolin, quercetin) combinations (e.g., BrainGain®, CystoProtek®, FibroProtek®, NeuroProtek®) formulated in olive pomace oil and ViralProtek® (containing eriodictyol and oleorupein). Dr. Theoharides has received 40 patents and trademarks; he was inducted into the Alpha Omega Alpha National Medical Honor Society, the Rare Diseases Hall of Fame, and the World Academy of Sciences (www.mastcellmaster.com; www.algonot.com).

Update on Long COVID and Post-COVID Research

Josh P. Fessel, M.D., Ph.D.
josh.fessel@nih.gov
National Center for Advancing Translational Sciences, National Institutes of Health

By any name—Long COVID, post-COVID conditions, long haul COVID, etc.—the effects of SARS-CoV-2 infection that linger after the acute illness has subsided have been recognized almost as long as it has been possible to do so. In the context of hundreds of millions of SARS-CoV-2 infections, even a low incidence of Long COVID translates to huge numbers of lives and livelihoods affected. Understanding Long COVID presents some unique and complex challenges that are not true of acute COVID. This presentation will discuss those challenges and some components of the NIH's approaches to meeting those challenges and will set the stage for thinking about chronic inflammation as a potential key contributor to Long COVID. Most importantly, this presentation will attempt to highlight some reasons to have hope for continued progress in the understanding, diagnosis, and treatment of Long COVID.

SARS-CoV-2 reservoir: a potential driver of inflammation and other disease mechanisms in Long COVID

Amy D. Proal, Ph.D.
aproal@polybio.org
PolyBio Research Foundation

Several biological factors have emerged as core potential drivers of inflammation in Long COVID or post-acute sequelae of COVID-19 (PASC). One is a SARS-CoV-2 reservoir: Some individuals with PASC may not fully clear the SARS-CoV-2 virus after acute infection. Instead, replicating virus and/or viral RNA—potentially capable of being translated to produce viral proteins—persist in patient tissue. These SARS-CoV-2 reservoirs could modulate host immune responses or release viral protein into the circulation. This presentation reviews studies that have identified SARS-CoV-2 RNA/protein or immune responses indicative of a SARS-CoV-2 reservoir in PASC samples. Mechanisms by which a SARS-CoV-2 reservoir may contribute to PASC pathology, including inflammatory, coagulation, microbiome, and neuroimmune abnormalities will be delineated. Research priorities and methods to guide the further study of a SARS-CoV-2 reservoir in PASC will also be described, with the goal that clinical trials of antivirals or other therapeutics with potential to clear a SARS-CoV-2 reservoir are accelerated.

Identifying who has Long COVID in the U.S.A.: a machine learning approach using N3C data

Melissa A. Haendel, Ph.D.
melissa@tislab.org
University of Colorado Anschutz Medical Campus

Emily Pfaff, Ph.D.; Andrew Girvin, Ph.D.; Richard Moffitt, Ph.D.; Christopher Chute, M.D., M.P.H.

Post-acute sequelae of SARS-CoV-2 infection, or Long COVID, have severely affected recovery from the pandemic for patients and society alike. This new disease is characterized by evolving, heterogeneous symptoms, which not only makes it a challenge to derive an unambiguous Long COVID definition, but hampers clinicians' ability to offer effective and timely treatment. Clinicians and patients report distinct, albeit overlapping, spectra of symptoms, making Long COVID classification difficult for diagnosis and care management, and a gold standard definition of Long COVID remains elusive and even controversial. Electronic health records (EHRs) could aid in rapidly identifying patients with Long COVID; however, the aforementioned overlapping and incomplete spectra of symptoms make harvesting the correct data from heterogeneous EHR databases a significant challenge. The National COVID Cohort Collaborative (N3C) is a partnership across US academic medical centers (>232) to harmonize and link EHR data from >20 million unique patients across research networks. The N3C has implemented an open team science approach to navigate the societal, technical, regulatory, and clinical obstacles to sharing, linking, and analyzing EHR data. Using the N3C, we developed XGBoost machine learning models to identify potential Long COVID patients. We examined demographics, health care utilization, diagnoses, and medications for adult COVID-19 patients. Our models identified potential Long COVID patients with high

accuracy, with important features including the rate of health care utilization, patient age, dyspnea, and other health care utilization, patient age, dyspnea, and other diagnoses and medications. Combinatorial approaches such as these are especially useful in the face of a new disease with different patient trajectories and few treatment options, and can provide the basis for research studies, public health surveillance, and treatment selection. The impact of the N3C data and community has been tremendous, with >200 manuscripts/preprints; changed COVID patient care guidelines (in multiple countries); White House and state requests for data; and the NIH and Federation of American Societies for Experimental Biology DataWorks! Grand Prize.

COVID-19 sequelae—Can long-term effects be predicted / what are the pathological sequelae of Long COVID?

Saurabh Mehandru, M.D.
saurabh.mehandru@mssm.edu
Icahn School of Medicine at Mount Sinai

The gastrointestinal tract (GI) is targeted by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) due to its high physiological expression of ACE-2. During acute COVID-19 infection, the GI tract shows evidence of attenuated inflammation. Additionally, in patients who have recovered from COVID-19, the protracted presence of SARS-CoV-2 proteins and mRNA is noted. This leads to the speculation that lack of sterilizing immunity in the GI tract during acute COVID results in viral persistence, which may fuel manifestations of Long COVID. That said, to date, we and others have not been able to culture replication-competent SARS-CoV-2 from the GI tract. This presentation examines GI involvement in patients with COVID-19 and discusses the underlying pathophysiological mechanisms that include viral persistence and mucosal and systemic immune dysregulation. Due to the complex and potentially multifactorial nature of this syndrome, rigorous clinical definitions and pathophysiology-based therapeutic approaches are warranted.

COVID-19 sequelae: Can long-term effects be predicted?

Eleni Gavriilaki, M.D., Ph.D.
elenicelli@yahoo.gr
Aristotle University of Thessaloniki

Nikolaos Kotsiou, B.Sc.; Styliani Kokkori, M.D., Ph.D.

Given the worldwide impact of COVID-19 and the uncertain long-term sequelae, better understanding of Long COVID-19 predictors is of the utmost importance. Similar to severe COVID-19, endothelial dysfunction might be commonly associated with COVID-19 sequelae. Our group has shown that complement-related variants along with gender differences predict COVID-19 morbidity and mortality. These findings were replicated not only in adults, of Caucasian and other origin, but also in children with severe infections. In an effort to utilize routine diagnostic markers, we created an artificial intelligence model that predicted COVID-19 outcomes with high accuracy. Regarding traditional risk factors, increased body mass index, dyslipidaemia, and decreased physical endurance 6 months after COVID-19 have also predicted a higher risk of metabolic disorders and cardiovascular complications, supporting the hypothesis of endothelial dysfunction as a primary driver of COVID-19 sequelae.

In conclusion, although no accurate prediction models exist for who will develop severe COVID-19 or sequelae, the risk factors of vascular damage have emerged as important predictors. Large and high-quality studies are needed that utilize multidisciplinary teams not only from different medical specialties but also from computational science who could suggest novel predictive models for the development of COVID-19 sequelae.

Defining the pathophysiology of Long COVID / Long COVID Subtypes using the RECOVER platform

Upinder Singh, M.D.
usingh@stanford.edu
Stanford University

Long COVID or post-acute sequelae of SARS-CoV-2 (PASC) is a major public health crisis with estimates of over 25 million PASC cases in the United States alone. PASC

encompasses various conditions and symptoms, such as fatigue, brain fog, and dyspnea, which develop in about 10% of individuals after an acute COVID-19 infection and can last for months or years with a significant impact on quality of life and function. Several hypotheses have been proposed to explain the multiple symptoms present in the post-COVID-19 conditions, including viral persistence, dysregulated immune system, clotting abnormalities, and dysbiosis. NIH launched Researching COVID to Enhance Recovery (RECOVER) as a trans-NIH platform to characterize PASC prevalence, including the symptoms, natural history, and distinct phenotypes of PASC. Additionally, the goal is to define the biological mechanisms underlying PASC pathogenesis. This presentation will outline the study design implemented for RECOVER and share results on symptoms associated most strongly with a PASC phenotype, as well as symptoms that appear to be co-associated.

Immune Memory of Long COVID

M. Juliana McElrath, M.D., Ph.D.
jmcelrat@fredhutch.org
Fred Hutchinson Cancer Center

Rafi Ahmed, Ph.D.; Aarthi Talla, M.S.

In an ongoing longitudinal COVID-19 cohort established early in the pandemic, we evaluated the durability of immune memory and changes associated with Long COVID. Among ~600 participants enrolled, ~25% experienced continued or new symptoms post-infection associated with Long COVID. Among these, ~59% still have Long COVID after 1 year post-infection.

We examined features of immune memory associated with Long COVID vs. COVID recovery. Receptor binding domain IgM and IgA serum antibody responses to natural infection developed faster in Long COVID participants than in those who recovered. No significant differences in the frequencies and decay of IgG, IgM, and IgA spike-specific memory B cells were observed. Moreover, there were no significant differences in the frequencies of spike-specific CD4+ and CD8+ T cell frequencies and half-lives over ~300 days post-symptom onset. Using an unbiased proteomic approach, we identified inflammatory and non-inflammatory subsets of Long COVID at day 60 or soon thereafter. Key inflammatory signatures (IFNg, TNF, and NFkB) persisted over time in those with Long COVID. Validation was observed in a separate COVID cohort.

Studies underway and planned include a deeper dive into the immune memory and immune signatures of Long COVID, understanding the effects of variants and response to potential treatments and eventual recovery in our 3- to 5-year longitudinal cohort study.

Long COVID: A Proposed Hypothesis-driven Model of Viral Persistence for the Pathophysiology of the Syndrome

Joseph A. Bellanti, M.D.
bellantj@georgetown.edu
Georgetown University Medical Center

Following SARS-CoV-2 infection, several clinical outcomes have been identified, ranging from asymptomatic infection or minor symptoms to a devastating form of the disease requiring intensive care and often associated with death. Shortly after the beginning of the COVID-19 pandemic in 2020, another form of the disease appeared with reports suggesting that previously healthy individuals were now experiencing lingering symptoms and were not fully recovering from an initial infection with SARS-CoV-2 (a condition termed *Long COVID,* or *post-acute sequelae of SARS-CoV-2 infection* (PASC). Some of the common symptoms include fatigue, shortness of breath, chest pain, joint pain, brain fog, and difficulty concentrating. Although the precise etiology of Long COVID is uncertain, various mechanisms have been proposed to explain its pathogenesis, including immune system dysregulation, hyperinflammatory states, oxidative stress, autoimmunity, and autonomic nervous system dysfunction. This presentation puts forth a hypothesis-driven model of viral persistence for the pathogenesis of the condition and proposes that Long COVID originates from a state of increased proinflammatory cytokine production resulting from persistence of SARS-CoV-2 or one of its molecular components. Several publications demonstrating the persistence of the SARS-CoV-2 S1 protein in COVID-19 infection support the hypothesis. Long COVID presents a significant challenge for patients and health care providers because it can have a profound impact on a

person's quality of life and ability to work or carry out daily activities. Although no practical diagnostic tests or specific treatments currently exist for the condition, health care providers can play a crucial role in managing patients with Long COVID by providing the necessary support and care modalities. These include early recognition and diagnosis, symptom management, and shared disease management with specialists and other health professionals who can provide supportive measures to help patients regain their quality of life and functionality.

Epigenetic Memory of COVID-19 in Innate Immune Cells and Their Progenitors

Steven Z. Josefowicz, Ph.D.
szj2001@med.cornell.edu
Weill Cornell Medicine, M.S.

Jin-Gyu Z Cheong, M.S.; Arjun Ravishankar, M.D.; Christopher N. Parkhurst*, M.D., Ph.D.; Simon Grassmann, Ph.D.; Paoline Laurent, Ph.D.; Robert E. Schwartz, M.D., Ph.D.; Jason Buenrostro, Ph.D.; Rachel E. Niec, M.D., Ph.D.; Franck J. Barrat, Ph.D.; Lindsay Lief, M.D.; Joseph Sun, Ph.D.; Duygu Ucar, Ph.D.*

Inflammation can trigger lasting phenotypes in immune and non-immune cells. Whether systemic inflammation, such as that caused by severe coronavirus disease 2019 (COVID-19), COVID-19 triggers innate immune memory in hematopoietic cells is unknown. We found that circulating hematopoietic stem and progenitor cells (HSPCs), enriched by peripheral blood, captured the diversity of bone marrow HSPC, enabling investigation of HSPC epigenomic changes following COVID-19. Alterations in innate immune phenotypes and epigenetic programs of HSPC persisted for months to 1 year following severe COVID-19 and were associated with distinct transcription factor activities, altered regulation of inflammatory programs, and durable increases in myelopoiesis. HSPC epigenomic alterations were conveyed, through differentiation, to progeny innate immune cells. Early activity of IL-6 contributed to these persistent phenotypes in human COVID-19 and a mouse coronavirus infection model. Epigenetic reprogramming of HSPC may underly altered immune function following infection and be broadly relevant, especially for millions of COVID-19 survivors.

Organ-Specific Inflammation in Long COVID

Richard Becker, M.D., MEd, FAHA
richard.becker@uc.edu
University of Cincinnati College of Medicine

COVID-19 infection is associated with an acute inflammatory state. The terms *thrombo-inflammation, immune-inflammation,* and *immune-thrombosis* have been used to describe patients primarily in the acute phase of infection but increasingly in the subacute phase or during recovery or in patients following even a mild infection. Early observations during the pandemic identified laboratory signatures of inflammation, including IL-6 and C-reactive protein that correlated with clinical phenotypes and outcomes. Similarly, tissue biopsies and post-mortem examinations revealed inflammation in many organs and organ systems, including small, medium, and large blood vessels. A common theme in acute COVID-19 infection was the presence of nucleotide-binding oligomerization domain-like receptor containing 3 (NLRP3)—an intracellular innate immune receptor that recognizes a diverse range of stimuli, including pathogens, damaged cells, and cellular debris. NLRP3 activation promotes assembly of a large, multi-protein complex known as the NLRP3 inflammasome that, in turn, promotes inflammation, vascular injury, thrombosis, and cell death. Inflammation-related tissue injury can cause irreversible organ damage and dysfunction, contributing to Long COVID phenotypes. An equally or even more common scenario is a heightened state of inflammation or inflammatory signature(s) observed in tissues, blood, and molecular patterns that participates in dysregulation of normal immune, microbiota, vascular endothelial cell, and neurological signaling of the central, peripheral, and autonomic nervous systems. Whether tissue-specific inflammation is a cause of, or a response to, one or more immune-associated triggers (or both) is an important question that requires careful thought and investigation.

COVID-19: challenges for Neurology

Raimund Helbok, Ph.D.
Raimund.Helbok@kepleruniklinikum.at
Johannes Kepler University, Linz, Austria

Since the outbreak of the pandemic in 2020, all medical subspecialties have been challenged in organizational, scientific, socioeconomic, and educational activities. Prof. Helbok will provide some insight into initiatives taken by the European Academy of Neurology, the World Federation of Neurology, and WHO (Global COVID-19 Neuro Research Coalition), among others, to guide clinicians and support science during the acute outbreak and throughout the pandemic. Furthermore, he will elucidate on the role of neurology in understanding neurological manifestations of COVID-19 during the pandemic and ongoing involvement in the care of patients suffering from post-COVID-19 conditions. Finally, the effect of COVID-19 on neurology training programs, telemedicine, and research activities will be discussed.

Neuropathogenesis of COVID-19

Avindra Nath, M.D.
natha@ninds.nih.gov
National Institute of Neurological Disorders and Stroke

A wide variety of neurological manifestations have been reported with SARS-CoV-2 infection. In the acute setting, loss of smell and taste are due to direct infection. Metabolic encephalopathy is often found in sick patients due to end organ damage and vascular complications are related to coagulopathies and endothelial cell damage. In the subacute phase, a number of inflammatory syndromes may occur. This includes acute disseminated encephalomyelitis, transverse myelitis, acute necrotizing hemorrhagic encephalomyelitis, and acute inflammatory demyelinating peripheral neuropathy. In children, a multisystem inflammatory syndrome may occur. Each of these syndromes have distinct immunopathophysiological mechanisms. A subset of individuals with mild acute infection develop a variety of new neurological symptoms after recovery, termed *Long COVID/post-acute sequelae of COVID-19*. These involve cognitive or psychiatric manifestations, exercise intolerance, dysautonomia, or pain syndromes. The pathophysiology of these symptoms is still under investigation; however, persistent infection or persistent innate immune activation are thought to be the drivers. Our studies suggest that these patients have NK cell and monocyte activation, T cell exhaustion, and increased antibody-secreting B cells in the cerebrospinal fluid. They may cause microvascular disease, glial cell activation, and neuronal injury. Autopsy studies from patients who died in the acute or subacute stage with minimal lung involvement found that there is deposition of antibodies on the brain endothelial cells with platelet aggregates, breakdown of the blood-brain barrier, macrophage infiltration, gliosis, and neuronophagia. Importantly, there is a virtual absence of T cells. These studies suggest that there might be multiple potential therapeutic targets for this population that are worthy of consideration.

Post-infectious peripheral neuropathy in Long COVID—mechanisms, diagnosis, and mitigation

Anne Louise Oaklander, M.D., Ph.D.
aloaklander@mgh.harvard.edu
Massachusetts General Hospital/Harvard Medical School

Peripheral neuropathy means abnormalities affecting the nerve cells and their long fibers (axons) that connect our brains and spinal cords to other body parts and the outside world. The symptoms depend on the nerve cell types damaged. In three-quarters of patients, they start in the feet, sometimes ascending upward toward the torso and head. Motor neuropathies cause weakness and muscle atrophy, and sensory neuropathies cause tingling and reduced and abnormal sensations, including chronic pain and itching. Neuropathies affecting the tiny sensory/autonomic axons that control blood circulation and digestion (small fiber neuropathy [SFN]) typically cause hard-to-diagnose chronic fatigue, pain, blood pressure, and gastrointestinal symptoms, including POTS (postural orthostatic tachycardia syndrome) and irritable bowel/bladder.

If the underlying causes of neuropathy are identified and improved, damaged axons typically heal, otherwise they

can degenerate. Viruses and some bacteria occasionally cause neuropathy by infecting nerve cells (e.g., leprosy) or after neurotoxic anti-infective medications. Rarely, infections trigger dysimmune responses that damage neurons, particularly those to which infecting organisms bind to. Pathology studies demonstrate that COVID-incident neuropathy is dysimmune—not infectious—and mostly follows mild COVID illnesses.

Case series, particularly, link Long COVID with SFN, which is plausible as small fibers preferentially bind SARS-CoV-2 and interact with immune cells. Our multi-center study of 17 patients undergoing neuropathy evaluations (mean age = 43.3 years, 69% female, 94% Caucasian, 19% Latino) analyzed standardized symptoms, examinations, neurodiagnostic test results, and outcomes. We identified ≥10 SFN cases. Two had large-fiber neuropathy with weakness. Overall, 59% had ≥1 neuropathy-confirming test. A total of 63% had SFN confirmed by skin biopsy pathology and 50% by autonomic-function results. A total of 17% had abnormal electrodiagnostics. During 1.4y average follow-up, improvement averaged 52% with no complete remissions. Given immunotherapies' proven effectiveness for other dysimmune neuropathies, they are now increasingly considered for Long COVID-associated neuropathies. In our series, 65% received corticosteroids and/or intravenous immunoglobulins. NIH-sponsored controlled trials of immunoglobulins for COVID-incident dysautonomia will begin soon—including at Mass General/Brigham.

SARS-CoV-2 spike protein, neuroinflammation, and brain fog

Theoharis Theoharides, M.D., Ph.D., M.Phil., M.S., FAAAAI
ttheohar@nova.edu
Nova Southeastern University

Post-acute sequelae of SARS-CoV-2 (PASC) or Long COVID can affect 50% of COVID-19 patients who experience fatigue, neuropsychiatric symptoms, and brain fog. Pathogenetic mechanisms of blood-brain barrier disruption, neurovascular inflammation, activation of microglia, and neuronal damage occur without viral invasion of the brain, but we hypothesized that they derive from SARS-CoV-2 stimulating the perivascular immune cells, or mast cells, which can activate microglia and contribute to neurovascular inflammation. We reported that nanomolar amounts of recombinant SARS-CoV-2 Spike protein stimulated cultured human mast cells to secrete the proinflammatory proteases, chymase and tryptase, as well as IL-ß and CXCL8 via activation not of ACE2, but TLR-4, an action augmented by IL-33. We also reported that Spike protein stimulated cultured human microglia to secrete IL-ß, IL-8, IL-18, TNF-a, MMP9, and S100B via activation of different receptors. We show that the luteolin analogue, flavanol eriodictyol, significantly inhibits the effect of the Spike protein. Eriodictyol is combined in a unique dietary supplement (ViralProtek®) with oleuropein, hydroxytyrosol, and sulforaphane, which have potent anti-viral and anti-inflammatory actions.

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COVID-19 Associated Coagulopathy (CAC)

James H. Morrissey, Ph.D.
jhmorris@umich.edu
University of Michigan Medical School

COVID-19-associated coagulopathy (CAC) is an acute, life-threatening complication of infection with SARS-CoV-2 that can result in thrombosis in multiple

organs and tissues. Research on the underlying cellular and molecular mechanisms driving this condition has provided some answers but has also raised many more questions. Current thinking is that CAC derives from interactions between the immune response—particularly, the innate immune system—and coagulation, fibrinolytic and complement pathways, together with contributions from cells such as platelets and the vascular endothelium. A better understanding of the pathogenesis of CAC is required to mitigate the acute thrombotic risk in COVID-19, and this is even more urgent for understanding the contributions of CAC to Long COVID.

Immune-proteomics of the post-COVID-19 lung and its links to pathology

James Harker, Ph.D.
j.harker@imperial.ac.uk
Imperial College London

Bavithra Vijayakumar, Ph.D.; Karim Boustani, Ph.D.; Patricia Ogger, Ph.D.; Artermis Papadaki, Ph.D.; Sara Fontenella, Ph.D.; James Peters, M.D., Ph.D.; Pallav Shah, M.D., Ph.D.; Clare Lloyd, Ph.D.

As the primary site of SARS-CoV-2 infection, the respiratory tract has the complex task of resolving initial infection, establishing long-lasting protective immunity, and repairing tissue damage incurred. In many people, this is achieved successfully; however, in some people, signs of ongoing damage to the lungs and impaired respiratory function can be seen months or years after initial infection. Indeed, respiratory symptoms are among the most common experienced in individuals suffering from post-acute sequelae of COVID-19. By characterizing the immune and protein landscape of the post-COVID-19 lung, we can link distinct immunological or inflammatory events to different respiratory symptoms and highlight how local sampling, but not systemic sampling, reveals these associations. Finally, we identify the factors that might be involved in determining whether respiratory disease post-COVID-19 resolves rapidly, or is sustained for a longer period.

Cardiac Pathology in Long COVID

James R. Stone, M.D., Ph.D.
jrstone@mgh.harvard.edu
Massachusetts General Hospital,
Harvard Medical School

The heart is suspected to play an important role in Long COVID due to its proximity to the lungs and the myriad pathologic changes identified in this organ during the acute phase of SARS-CoV-2 infection, including myocarditis, myocardial macrophage infiltration, pericarditis, microthrombi, acute myocardial strain injury, acute myocardial ischemic injury, and SARS-CoV-2 viral infiltration and infection. Also, some of the symptoms of Long COVID could be explained by cardiac dysfunction. While there have been numerous studies examining the cardiac pathology in the early acute phase and extended acute phase of COVID-19, up to 60 days from infection, there have been very few studies examining the cardiac pathology in the post-acute phase of the disease, beyond 60 days from infection. In the post-acute phase, viral persistence in the myocardium has been shown to be present in some patients. Likewise, cardiac pathological changes seen in the acute phases along with fibrous scarring can be seen in the hearts of patients in the post-acute phase. However, these changes are not entirely specific, and large studies correlating these cardiac pathologic changes and viral persistence with symptoms of Long COVID are needed. In addition, the very low levels of virus being detected in the heart in the post-acute phase will require careful consideration of the methodologies to be best utilized for determining viral persistence and avoiding potential molecular confounders, such as the presence of SARS-CoV-2 vaccines. Finally, transcriptomic analyses should help elucidate the molecular changes of the cardiac tissue response in patients with Long COVID.

Prevention and early treatment of the long-term physical effects of COVID-19 in adults: design of a randomised controlled trial of resistance exercise: CISCO-21

Colin Berry, B.Sc., M.B., Ch.B., Ph.D.
colin.berry@glasgow.ac.uk
Center for Blood Research,
University of British Columbia

CISCO-21 Investigators

Background: Coronavirus disease-19 (COVID-19) infection causes persistent health problems such as breathlessness, chest pain, and fatigue, and therapies for the prevention and early treatment of post-COVID-19 syndromes are needed. Accordingly, we are investigating the effect of a resistance exercise intervention on exercise capacity and health status following COVID-19 infection.

Methods: A two-arm randomized, controlled clinical trial including 220 adults with a diagnosis of COVID-19 in the preceding 6 months. Participants will be classified according to clinical presentation as Group A: not hospitalized due to COVID but persistent symptoms for at least 4 weeks leading to medical review; Group B: discharged after an admission for COVID and with persistent symptoms for at least 4 weeks; or Group C: convalescing in hospital after an admission for COVID.

Participants will be randomized to usual care or usual care plus a personalized and pragmatic resistance exercise intervention for 12 weeks. The primary outcome is the incremental shuttle walks test (ISWT) at 3 months after randomization with secondary outcomes, including spirometry, grip strength, short performance physical battery (SPPB), frailty status, contacts with health care professionals, hospitalization and questionnaires assessing health-related quality of life, physical activity, fatigue, and dyspnoea.

Discussion: The CISCO-21 randomized, controlled trial will provide clinical data on the feasibility, safety, and efficacy of resistance-based exercise over a 3-month period on validated measures of physical and psychological function in people recovering from COVID-19.

Ethical approval has been granted by the National Health Service West of Scotland Research Ethics Committee (reference: GN20CA537) and recruitment is ongoing. Trial findings will be disseminated through patient and public forums, scientific conferences, and journals.

The ins and the outs, the long and the short, of complement in COVID-19

Edward M. Conway, M.D., Ph.D.
ed.conway@ubc.ca
Center for Blood Research,
University of British Columbia

COVID-19 remains a major source of concern, particularly as new variants emerge and with recognition that many patients may suffer long-term effects. Mechanisms underlying SARS-CoV-2 mediated vascular endotheliopathy and organ damage remain poorly understood, hindering new drug development. Here, we highlight selected key concepts of how the complement system, a major component of innate immunity that is dysregulated in COVID-19, may participate in the thrombo-inflammatory response and drive the vascular endotheliopathy and the accumulation in various organs of cytotoxic tissue-resident memory T cells. Based on advances in our understanding of the complement system and its multiple interactions with other biological systems, we will discuss potential targeted therapeutic maneuvers and diagnostic strategies.

Multimorbidity and aggerated COVID-19 symptoms in probability Theory: A predictive tool for Long COVID

Shabnam Salimi, M.D., MSCc, FAHA
ssalimi2@uw.edu
University of Washington/
University of Maryland, Baltimore

Mohammad Sajadi, M.D.

We have devised a novel metric for assessing symptoms through the application of probability theory. This metric allows us to investigate the interconnectedness among individual diseases, specific bodily systems, and the overarching concept of a body clock measured through a probability theory-based symptom metric.

Our hypothesis centers on the idea that the overall health of the body, as indicated by the body clock metric, correlates with an elevated symptom metric, serving as a proxy for accelerated aging. We anticipate observing a positive association between the two.

Furthermore, the symptom metric itself holds potential utility as a predictive tool for Long COVID and can find application in critical care settings and prognostic models.

Autoimmune diseases and Long COVID

Divaker Choubey, Ph.D.
divaker.choubey@uc.edu
University of Cincinnati, College of Medicine

Dysregulated immune responses in autoimmune diseases (ADs) "prime" the immune cells for an increase in the production of proinflammatory cytokines (e.g., the type I interferons) upon an infection. Of interest, the development of certain common ADs (e.g., Sjögren's syndrome, systemic lupus erythematosus, rheumatoid arthritis) exhibits a female gender bias. Furthermore, these ADs exhibit a female gender bias in activation of the type I interferon (IFN) response and an "IFN-signature" (an increase in the levels of type I IFN-inducible mRNAs) in immune cells due to activation of the cGAS-STING pathway by the IFN-stimulatory DNA (ISD). A constitutive activation of the pathway in aged (senescent) cells is associated with paracrine senescence and inflammageing. Notably, senescent cells accumulate in tissues and organs with human aging and in chronic inflammatory conditions. In the SARS-CoV-2 (COVID-19) virus-infected patients, the lung pathology in the late phase of the infection is associated with activation of the ISD pathway, accumulation of senescent cells, and senescence-associated secretory phenotype (SASP). SASP promotes paracrine senescence. Interestingly, COVID-19 virus infection in human cells activated a DNA damage response and the LINE-1 (L1) retrotransposon element (TE). These responses activate the ISD pathway. Consequently, the viral infection leads to activation of the type I IFN response, accumulation of senescent cells, SASP, and chronic inflammation. Therefore, chronic activation of proinflammatory pathways by the COVID-19 virus in individuals with an AD has implications for gender and age-dependent increases in the risk of developing Long COVID. Although the mRNA vaccine against the SARS-CoV-2 virus is safe in AD patients, an improved understanding of the molecular interactions between the virus and proinflammatory pathways has the potential to identify new therapeutic approaches to treat "Long COVID" patients.

NIH RECOVER research identifies potential Long COVID disparities

Charisse Madlock-Brown, Ph.D.
cmadlock@uthsc.edu
University of Iowa

Here, we leverage the largest publicly available HIPAA-limited data set about patients with COVID-19 in the United States to examine the heterogeneity of adoption and use of U09.9, the ICD-10-CM code for "Post COVID-19 condition, unspecified." We undertook a number of analyses to characterize the N3C population with a U09.9 diagnosis code (n = 33,782), including assessing person-level demographics and a number of area-level social determinants of health; diagnoses commonly co-occurring with U09.9, clustered using the Louvain algorithm; and quantifying medications and procedures recorded within 60 days of U09.9 diagnosis. We stratified all analyses by age group in order to discern differing patterns of care across the lifespan. Furthermore, we assessed the impact of inclusion criteria on the representativeness of a multi-site national electronic health record system along gender, race, health care-seeking, and socioeconomic lines. We established the diagnoses most commonly co-occurring with U09.9 and algorithmically clustered them into four major categories: cardiopulmonary, neurological, gastrointestinal, and comorbid conditions. Importantly, we discovered that the population of patients diagnosed with U09.9 is demographically skewed toward female, White, non-Hispanic individuals and individuals living in areas with low poverty and unemployment. Our results also characterize common procedures and medications associated with U09.9-coded patients. We also found that typical selection criteria for Long COVID research biases patient representation across race and gender.

BMI across adulthood, COVID-19 and Long COVID in two British birth cohorts

Charis Bridger Staatz, Ph.D.
charis.staatz.17@ucl.ac.uk
University College London

David Bann, Ph.D.; George Ploubidis, Ph.D.;
Alissa Goodman*, Ph.D.; Richard J. Silverwood, Ph.D.*

Background: Longer exposure to obesity, and thus a longer period in an inflamed state, may increase susceptibility to infectious diseases and worsen severity. Previous cross-sectional work finds higher body mass index (BMI) is related to worse COVID-19 outcomes, but less is known about associations with BMI across adulthood.

Methods: To examine this, we used BMI collected through adulthood in the 1958 National Child Development Study (NCDS) and the 1970 British Cohort Study (BCS70). Participants were grouped by the age they first became overweight (>25 kg/m^2) and first became obese (>30 kg/m^2). Logistic regression was used to assess associations with COVID-19 (self-reported and serology-confirmed), severity (hospital admission and contact with health services), and Long COVID reported at ages 62 (NCDS, n = 7,769) and 50 (BCS70, n = 7,168).

Results: An earlier age at which participants first experienced obesity was associated with increased odds of adverse COVID-19 outcomes, but results were mixed and often underpowered. Those with an earlier exposure to obesity were over twice as likely in NCDS (odds ratio [OR] 2.15, 95% confidence interval [CI]: 1.17 to 4.00) and three times as likely in BCS70 (OR 3.01, 95% CI: 1.74 to 5.22) to have Long COVID. In NCDS, they were also over four times as likely to be admitted to hospital (OR 4.69, 95% CI: 1.64 to 13.39). Most associations were somewhat explained by contemporaneous BMI or self-reported health, diabetes, or hypertension; however, the association with hospital admission in NCDS remained.

Conclusion: An earlier age in which cohort members first experience obesity onset is related to COVID-19 outcomes in later life, providing evidence on the long-term impact of raised BMI on infectious disease outcomes in midlife.

Racial/ethnic disparities in post-acute sequelae of COVID-19

Dhruv Khullar, M.D., M.P.P.
khd9010@med.cornell.edu
Weill Cornell Medicine

During the pandemic, Black and Hispanic individuals have experienced higher rates of COVID-19 hospitalization and death compared with White individuals. Less is known about whether disparities exist with regard to the long-term consequences of infection (Long COVID) or whether the prevalence of new or lingering symptoms varies by racial/ethnic groups. Racial/ethnic minority groups have several risk factors for the development of Long COVID, including differing levels of vaccination, access to medical care, baseline comorbidities, socioeconomic status, viral exposure, and the severity of initial illness.

Recent evidence suggests that there may be meaningful disparities in the incidence of post-acute conditions among both hospitalized and non-hospitalized patients with COVID-19. For example, one study using electronic health record data from health care systems across New York City found that, compared with White patients, Black and Hispanic patients had significantly higher odds of a range of potential Long COVID symptoms and conditions, including diabetes, chest pain, headaches, and dyspnea. These findings are consistent with survey data from the US Census Bureau suggesting that Black and Hispanic individuals have the highest rates of lingering symptoms after acute COVID-19.

More research is needed to understand the reasons for these differences and the mechanisms by which they occur. Researchers, clinicians, policymakers, and health systems should also work to ensure representative enrollment in clinical trials and access to comprehensive post-COVID care for individuals of all backgrounds.

Long COVID and Viral Persistence: Exploring Avenues for Therapies

Linda N. Geng, M.D., Ph.D.
geng@stanford.edu
Stanford University

Hector Bonilla, M.D.; Karen Jacobson, M.D.; Haley Hedlin, Ph.D.; PJ Utz, M.D.; Prasanna Jagannathan, M.D.; Aruna Subramanian, M.D.; Lu Tian, Ph.D.; Upinder Singh, M.D.

Post-acute sequelae of SARS-CoV-2 (PASC), or Long COVID, continues to affect millions of people worldwide. Long COVID encompasses a wide spectrum of symptoms and conditions, and, while models of pathogenesis are crystallizing, there is an urgency to find effective and safe therapeutics to treat patients with Long COVID. SARS-CoV-2 viral persistence has gained traction as a potential mechanism of disease and direct antivirals against SARS-CoV-2 present a promising therapeutic avenue for investigation. In our Selective Trial Of Paxlovid for PASC (STOP-PASC), which is a randomized, double-blind, placebo-controlled signal-seeking study, the primary objective is to assess the efficacy and safety of nirmatrelvir-ritonavir in the treatment of Long COVID symptoms and, in parallel, explore potential biological biomarkers and digital wearable biomarkers of Long COVID. This and other studies will add to the rapidly evolving and growing landscape of clinical trials to address the great unmet need for effective Long COVID therapeutics.

Clinical experience with the α2A-adrenoceptor agonist, guanfacine, and N-acetylcysteine for the treatment of cognitive deficits in Long COVID

Amy F.T. Arnsten, Ph.D.
amy.arnsten@yale.edu

Arman Fesharaki-Zadeh, M.D.

Long COVID is frequently associated with debilitating cognitive deficits, colloquially referred to as “brain fog.” Characterization of these symptoms has revealed a consistent impairment in the functions of the dorsolateral prefrontal cortex (dlPFC), a recently evolved brain region that subserves higher cognition. The dlPFC is needed for abstract reasoning, working memory, and memory recall; the executive functions (e.g., planning and organization); and the top-down control of thought, action, and emotion, including the ability to concentrate and focus, and protection against depression. Research in macaques has shown that the dlPFC has unusual molecular requirements that make it especially vulnerable to inflammatory insults. These include a reliance on N-methyl-D-aspartate and nicotinic alpha-7 receptor neurotransmission, disrupted by kynurenic acid (KYNA) inflammatory signaling, and metabotropic glutamate receptor 3 regulation of potassium channels, which is weakened by glutamate carboxypeptidase-II (GCPII) inflammatory signaling. Studies of animals have shown that N-acetyl cysteine (NAC) and the alpha-2A-adrenoceptor agonist, guanfacine, can restore dlPFC function in aged macaques with naturally occurring KYNA and GCPII inflammation, likely through anti-inflammatory actions, including inhibition of KYNA production, and restoring cAMP regulation in dlPFC, respectively. Our recent, open label data from patients with cognitive deficits from Long COVID suggest that the combination of NAC and guanfacine (1–2mg) can markedly improve cognitive functioning (Fesharaki et al., 2023), suggesting a path forward for those suffering from these symptoms.

If interested, see:

Fesharaki Zadeh A, Arnsten AFT, Wang M. Scientific Rationale for the Treatment of Cognitive Deficits from Long COVID. Neurol Int. 2023 May 31;15(2):725-742. doi: 10.3390/neurolint15020045. PMID: 37368329; PMCID: PMC10303664.

Arnsten AFT, Ishizawa Y, Xie Z. Scientific rationale for the use of α2A-adrenoceptor agonists in treating neuroinflammatory cognitive disorders. Mol Psychiatry. 2023 Apr 7:1–13. doi: 10.1038/s41380-023-02057-4. Epub ahead of print. PMID: 37029295; PMCID: PMC10080530.

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