Cannabinoids/ Terpenes and Pain

Exploring the Mechanisms Underlying Analgesic Properties of Minor Cannabinoids and Terpenes

October 23, 2020
Agenda

NCCIH Workshop 2020:
Exploring the Mechanisms Underlying Analgesic Properties of Minor Cannabinoids and Terpenes

Friday, October 23, 2020

9:45 a.m.–3:00 p.m. ET

9:45–9:50 a.m.  Welcome From the National Center for Complementary and Integrative Health (NCCIH)
David Shurtleff, Ph.D., Deputy Director, NCCIH

9:50–10:00 a.m.  Meeting Overview and Goals
Emmeline Edwards, Ph.D., Director, NCCIH Division of Extramural Research

10:00–11:00 a.m.  Data Blitz Presentations on the Nonclinical Studies Funded by NCCIH Cannabinoids and Pain Funding Opportunity Announcements
Sara Jane Ward, Ph.D., Temple University of the Commonwealth
Analgesic Efficacy of Single and Combined Minor Cannabinoids and Terpenes

Yu-Shin Ding, Ph.D., New York University School of Medicine
Identifying the Mechanisms of Action for CBD on Chronic Arthritis Pain

Andrew D. Ellington, Ph.D., University of Texas at Austin
Synthetic Biology for the Chemogenetic Manipulation of Pain Pathways

Cassandra L. Quave, Ph.D., Emory University
Mechanistic Studies on Analgesic Effects of Terpene Enriched Extracts From Hops

David Sarlah, Ph.D., University of Illinois
Systematic Investigation of Rare Cannabinoids With Pain Receptors

Jenny L. Wiley, Ph.D., RTI International
Minor Cannabinoids and Terpenes: Preclinical Evaluation as Analgesics

Zhigang He, Ph.D., B.M., Boston Children’s Hospital/Harvard Medical School
Mechanism and Optimization of CBD-Mediated Analgesic Effects

Q & A Session on Nonclinical Studies
Moderator: Inna Belfer, M.D., Ph.D., NCCIH

11:00–11:15 a.m.  BREAK
11:15–Noon  Data Blitz Presentations on the Clinical Studies Funded by NCCIH Cannabinoids and Pain Funding Opportunity Announcements

Rajiv Radhakrishnan, M.B.B.S., M.D., Yale School of Medicine
Effect of Cannabidiol on Microglial Activation and Central Pain-Sensitization

Deborah Yurgelun-Todd, Ph.D., University of Utah
Exploring the Mechanisms Underlying the Analgesic Effect of Cannabidiol Using Proton Magnetic Resonance Spectroscopy

Judith Hellman, M.D., University of California, San Francisco
Neuroimmune Mechanisms of Minor Cannabinoids in Inflammatory and Neuropathic Pain

Ziva D. Cooper, Ph.D., University of California, Los Angeles
Analgesic and Subjective Effects of Terpenes Administered Alone and in Combination With THC: Potential THC- and Opioid-Sparing Effects of Myrcene and ß-Caryophyllene

Richard E. Harris, Ph.D., University of Michigan at Ann Arbor
Cannabinoid Interactions With Central and Peripheral Pain Mechanisms in Osteoarthritis of the Knee

Q & A Session on Clinical Studies
Moderator: Angela Arensdorf, Ph.D., NCCIH

Noon–1:00 p.m.  BREAK

1:00–1:30 p.m.  Keynote Presentation (Introduction by David Shurtleff, Ph.D., NCCIH): Cannabis Research in Canada: Opportunities, Risks, and Lessons Learned
Mark A. Ware, M.B.B.S., MRCP(UK), M.Sc., Chief Medical Officer, Canopy Growth Corporation, Canada; Associate Member, McGill University

1:30–1:45 p.m.  Q & A Session for Keynote Speaker
Moderator: Emmeline Edwards, Ph.D., NCCIH

1:45–2:30 p.m.  Panel Discussion on Gaps and Future Directions
Inna Belfer, M.D., Ph.D., NCCIH
Roger Little, Ph.D., National Institute on Drug Abuse (NIDA)
Jeffrey White, M.D., National Cancer Institute (NCI)
Qi-Ying Liu, M.D., M.Sci., National Institute on Alcohol Abuse and Alcoholism (NIAAA)
Smriti Iyengar, Ph.D., National Institute of Neurological Disorders and Stroke (NINDS)
Mi Hillefors, M.D., Ph.D., National Institute of Mental Health (NIMH)
Dominic Chiapperino, Ph.D., U.S. Food and Drug Administration (FDA)
Terrence L. Boos, Ph.D., Drug Enforcement Administration (DEA)
Robert Walsh, R.A.C., NIDA Drug Supply Program
2:30–3:00 p.m.  **Q & A Session for the Panelists**  
Moderator: David Shurtleff, Ph.D., NCCIH

3:00 p.m.  **Adjournment**
9:45–9:50 a.m. Welcome From the National Center for Complementary and Integrative Health (NCCIH)
David Shurtleff, Ph.D., Deputy Director, NCCIH

David Shurtleff, Deputy Director, National Center for Complementary and Integrative Health (NCCIH)

David Shurtleff, Ph.D., is Deputy Director of NCCIH at the National Institutes of Health (NIH). He is also the Acting Scientific Director and Acting Chief of the Clinical Investigations Branch and the Pain and Integrative Neuroscience Branch, Division of Intramural Research. Dr. Shurtleff’s career at NIH has focused on providing leadership and fostering an extensive research portfolio in the basic behavioral and neurosciences—cognitive studies, behavioral economics, decision theory, and risk-taking—and a broad spectrum of research that has contributed to cutting-edge research related to drug abuse, addiction, and their treatment. Dr. Shurtleff came to NCCIH from the National Institute on Drug Abuse, where he helped develop, implement, and manage the institute’s broad grant portfolio. Dr. Shurtleff received his Ph.D. in experimental psychology from American University. Among his many honors and awards are the NIH Director’s Award for outstanding leadership, vision, dedication, and oversight in developing the NIH Blueprint Neurotherapeutics Grand Challenge and the NIH Director’s Award for outstanding contributions to the development and advancement of diverse programs in basic neuroscience and behavioral research.
Meeting Overview and Goals
Emmeline Edwards, Ph.D., Director, NCCIH Division of Extramural Research

Emmeline Edwards, Director, Division of Extramural Research, National Center for Complementary and Integrative Health (NCCIH)

Emmeline Edwards, Ph.D., is director of the Division of Extramural Research of NCCIH. In that capacity, she is responsible for development of scientific programs or areas of science that fulfill NCCIH’s mission as well as planning, implementation, and policy. Prior to joining NCCIH, Dr. Edwards served as deputy director of the extramural program at the National Institute of Neurological Disorders and Stroke. Before coming to the National Institutes of Health, Dr. Edwards earned her Ph.D. in neurochemistry from Fordham University, did postdoctoral research in behavioral pharmacology and neuroscience at the State University of New York, and was a tenured associate professor in the Department of Pharmacology at the University of Maryland. Her research there focused on the neural mechanisms of complex behaviors and characterization of a genetic model of affective disorders. Currently, Dr. Edwards is chair of Women in World Neuroscience, an independent mentoring and networking organization with the primary mission of identifying, promoting, and implementing mentoring and networking opportunities for women neuroscientists across the world.
Sara Jane Ward, Ph.D., focuses her research on the therapeutic potential of nonpsychoactive cannabinoid compounds for the treatment of nervous system disorders, including neuropathic pain, neuroinflammation, and substance abuse. There are two ongoing projects investigating cannabinoid effects on neuropathic pain. The goal of these projects is to elucidate the therapeutic mechanisms by which the nonpsychoactive cannabinoid cannabidiol protects against the development of neuropathic pain. Dr. Ward’s laboratory uses three rodent models of neuropathic pain: 1) a central model of spinal cord injury, 2) a peripheral model of chemotherapy-induced neuropathic pain, and 3) a rat model of orofacial pain. The therapeutic strategy includes understanding the neuroprotective mechanisms of cannabidiol alone and in combination with the psychoactive phytocannabinoid Δ⁹-tetrahydrocannabinol (Δ⁹-THC) and other, minor phytocannabinoids. Experiments are also under way to test the ability of cannabidiol and synthetic analogues of this phytocannabinoid to increase the potency and efficacy of opioid-based pain management while also mitigating opioid abuse liability. Lastly, additional studies are under way to test the efficacy of nonpsychoactive cannabinoids for the treatment of traumatic brain injury (TBI) and the impact of this strategy on concurrent substance abuse associated with TBI.

**Analgesic Efficacy of Single and Combined Minor Cannabinoids and Terpenes**

Data will be presented showing our results to date on the single and combined effects of cannabidiol (CBD) and beta-caryophyllene in male and female mice to prevent chemotherapy-induced neuropathic pain following oral or intraperitoneal administration. Behavioral and immunohistochemical data will be presented. Effects of morphine, CBD, and beta-caryophyllene on acute thermal and inflammatory pain will also be presented.
Speaker: Yu-Shin Ding, New York University School of Medicine

Yu-Shin Ding, Ph.D., is professor of radiology, psychiatry, and chemistry and Distinguished PET Researcher at New York University (NYU) School of Medicine. She has more than 25 years of experience in the development and application/evaluation of novel ligands for translational research. From 1998 until 2005, she was a key member of the positron emission tomography (PET) team at the Brookhaven National Laboratory, rising to the rank of senior tenured scientist. In 2005, as professor of diagnostic radiology and codirector of the Yale PET Center, she led the development and application of novel ligands for PET translational research, investigating functional significance of various molecular targets in neurological and psychiatric disorders. As director of radiochemistry at NYU School of Medicine, she set up a state-of-the-art Good Manufacturing Practices (GMP) radiochemistry lab for PET imaging studies. Dr. Ding received a Ph.D. in medicinal chemistry from the State University of New York at Stony Brook and completed a postdoctoral fellowship in PET medical imaging at the Brookhaven National Laboratory. She has published more than 200 peer-reviewed articles and 30 reviews and book chapters on PET imaging and ligand development.

Identifying the Mechanisms of Action for CBD on Chronic Arthritis Pain

Nearly 27 million U.S. adults have osteoarthritis, a chronic and progressive disease for which pain is the primary symptom, making it a common cause of chronic pain and a leading cause of disability in the United States. The management of pain has often relied on opioid-based pharmacologic interventions, which not only lack long-term efficacy but also carry risks for adverse events and contribute to the national epidemic of opioid misuse. The identification and development of novel strategies for the treatment of chronic pain, therefore, is a high priority and an unmet need. Preclinical studies showed that cannabidiol (CBD) has a wide range of reported pharmacologic effects such as anticonvulsant, analgesic, anxiolytic, anti-inflammatory, hypnotic, antipsychotic, and neuroprotective actions; however, the exact mechanisms of action for these effects have not been examined in chronic osteoarthritis pain. Our study is the first positron emission tomography (PET) imaging study to determine the key targets of CBD that are related to its mechanisms of action on pain treatment in osteoarthritis. The goal of this study is to bolster the evidence base and understand the underlying mechanisms of action of CBD by identifying the neurochemical and behavioral alterations induced by chronic pain in osteoarthritis and their modulation by CBD, alone or in combination with other drugs.
Speaker: Andrew D. Ellington, University of Texas at Austin

Andrew D. Ellington, Ph.D., is the Kathryn M. Fraser Endowed Research Professor of Biochemistry at the University of Texas at Austin. His work is probably best known for his contributions to the discovery and development of aptamers, nucleic acid binding species selected from random sequence populations. His laboratory has also been involved with robust efforts in engineering the catalytic and biophysical properties of proteins. To carry out protein evolution with the same facility as nucleic acid evolution, Dr. Ellington’s lab has developed a number of novel selection methods, based in part on emulsion-based protein expression. Dr. Ellington has also been involved in the development of the field of synthetic biology, which used to be called biotechnology but has the added flair of characterizing genes as “parts” in metabolic or regulatory “circuits.” To expand the reach of synthetic circuitry, Dr. Ellington’s lab has been developing new parts and circuits for the incorporation of unnatural amino acids, including a generalized reengineering of selenocysteine incorporation. Dr. Ellington received a Ph.D. in biochemistry and molecular biology from Harvard University and completed a postdoctoral fellowship in the same field at Massachusetts General Hospital.

Synthetic Biology for the Chemogenetic Manipulation of Pain Pathways

The methods of synthetic biology have transformed practice throughout the biological sciences but have yet to find wide application in neurobiology. To create a wider range of tools for selective cell modulation, we propose to develop directed evolution methods that will generate orthogonal neural receptors that are specifically activated by nonnative ligands and thereby offer multiple different chemogenetic control points across the brain. The proposed methods should yield very High Affinity receptors that have Validated Orthogonalities for their receptor:ligand Couples (HAVOCs). We will use our HAVOCs to examine the gate theory of pain and in consequence serve as a surrogate model for targeted nanodosing strategies to safely promote analgesia and combat addiction. Using our novel directed evolution method, compartmentalized partnered replication, we will initially evolve individual G protein-coupled receptor (GPCR) variants that can interact with high affinity with the unnatural ligands. We will proof the utility of these compounds and their evolved receptors with isolated neurons and directly in a mouse model for pain.
Mechanistic Studies on Analgesic Effects of Terpene Enriched Extracts From Hops

Chronic pain affects up to one fifth of the world population. It is a debilitating health condition with significant socioeconomic costs. Discovery of nonopiate analgesics is urgently needed to provide patients with nonaddictive medicines for the management of pain. Plants of the Cannabaceae family, such as *Cannabis sativa* (cannabis) and *Humulus lupulus* (hops), have a long history of traditional use in the mitigation of pain and inflammation, yet the mechanistic basis for these activities and the identities of the compounds responsible are not well understood. Terpenes are a class of natural compounds produced by plants that may provide a solution. We are investigating the analgesic effects of terpenes from hops in inflammatory and neuropathic pain. Here, we present an update on our progress in the chemical characterization and evaluation of hops terpenes as potential analgesic agents.
Speaker: David Sarlah, University of Illinois

David Sarlah, Ph.D., is an assistant professor in the Department of Chemistry at the University of Illinois at Urbana-Champaign. He obtained his Ph.D. in 2011 with Professor K.C. Nicolaou at The Scripps Research Institute and then joined the laboratory of Professor Erick M. Carriera at ETH Zürich. In 2014, he returned to the United States to start his laboratory, which explores both the chemical synthesis of biologically active natural products and method development. Dr. Sarlah’s research program focuses on the advancement of the science of synthesis. His laboratory is involved in natural products chemistry and synthesis, and reaction innovation and design including asymmetric catalysis. He aims to provide new solutions to the problems encountered at the front line of organic synthesis that benefit chemistry and enable advances in the allied fields of chemical biology, material science, and medicine. Some of his recent accomplishments include a National Science Foundation Career Award, Alfred P. Sloan Research Fellow, 2019 Grammaticakis-Neumann Award, 2019 Bristol-Myers Squibb Unrestricted Grant Award in Synthetic Chemistry, 2019 Amgen Young Investigator Award, 2019 Eli Lilly Organic Chemistry Award, and 2020 FMC New Investigator Award.

Co-Principal Investigator: Aditi Das, University of Illinois

Aditi Das, Ph.D., is a membrane protein biochemist. She studied chemistry at Princeton University with Michael H. Hecht and completed her postdoctoral studies at Northwestern University with Stephen G. Sligar. She is currently an associate professor in the Department of Comparative Biosciences (Pharmacology and Toxicology) at the University of Illinois and an affiliate faculty of the Beckman Institute and Division of Nutritional Sciences. Her research laboratory has made important contributions toward elucidating the biochemical mechanism of human cytochrome P450s and pharmacology of lipid mediators in brain and nervous system (e.g., endocannabinoids). In 2019, she received the Mary Swartz Rose Young Investigator Award, Eicosanoid Research Foundation Young Investigator Award, and Zoetis Research Excellence Award for her studies on endocannabinoid metabolism by cytochrome P450s.

Systematic Investigation of Rare Cannabinoids With Pain Receptors

The primary focus of our research is to prepare rare cannabinoids and elucidate their ability to activate the primary human pain receptors, focusing on the cannabinoid receptors and transient receptor potential (TRP) channels. We have developed synthetic pathways to several minor phytocannabinoids from the cannabigerol (CBG), cannabichromene (CBC), and cannabielsoin (CBE) class, as well as other nonclassified cannabinoids, such as cannabioxepane and cannabifuran, that are not commercially or readily accessible. With these compounds in hand, we initiated biological investigations. Firstly, we studied the antineuroinflammatory properties of 12 naturally occurring rare minor cannabinoids that are structurally similar to cannabidiol (CBD). We demonstrated that some of these minor cannabinoids are more potent than CBD itself in promoting microglial polarization toward an anti-inflammatory phenotype. Secondly, we delved into initial studies on the metabolism...
of CBG by human cytochrome P450s to form oxy CBG metabolites that are also naturally occurring minor cannabinoids. The epoxy-CBG are also more potent toward promoting microglial polarization. This study will culminate by studying the effect of selected minor cannabinoids on the miRNA expression profiles and molecular networks in resting and lipopolysaccharide-activated microglial cells. Thirdly, we have initial studies on the agonism/antagonism of TRPV1 with minor cannabinoids (CBD structural class). TRPV1 is a nonselective cation channel that is involved in pain sensation. Our first-year studies demonstrate the varied response of selected naturally occurring minor cannabinoids with respect to their anti-inflammatory effects and ability to be an agonist/antagonist of TRPV1 receptors. Taken together, these basic in vitro studies on rare minor cannabinoids are critical and will guide the future in vivo studies of their pharmacology and development as potential antipain therapeutics.
Speaker: Jenny Wiley, RTI International

A native Virginian, Jenny Wiley, Ph.D., earned her undergraduate degree at the College of William and Mary and her doctoral degree at Virginia Commonwealth University. She completed a postdoctoral fellowship in the Department of Pharmacology and Toxicology at Virginia Commonwealth University and accepted a faculty position in the department shortly thereafter. She moved up the ranks, achieving the status of tenured professor before moving to North Carolina to accept the challenge of setting up a behavioral pharmacology program in RTI International’s (RTI’s) Center for Drug Discovery. Dr. Wiley is currently a distinguished fellow in pharmacology at RTI. In this capacity, she designs and supervises a program of in vivo research that complements existing strengths of the center, including the synthesis and development of candidate medications and investigation of neural mechanisms underlying substance abuse. She also has independent National Institutes of Health grant-supported research in cannabinoid pharmacology. Dr. Wiley’s primary departmental program area is neuropharmacology. Her areas of expertise include cannabinoid pharmacology and behavioral pharmacology of substances of abuse. She has over 200 peer-reviewed publications and previously served as a member of the board of directors and president of the International Cannabinoid Research Society.

Co-Principal Investigator: Steven Kinsey, University of Connecticut

Steven Kinsey, Ph.D., earned his undergraduate degree in psychology from University of California, Davis, and was a laboratory assistant at the California National Primate Research Center before beginning his doctoral degree in behavioral neuroscience at the Ohio State University. After completing a postdoctoral research fellowship in pharmacology and toxicology at Virginia Commonwealth University, he was assistant and associate professor of psychology at West Virginia University. This past January, he relocated his lab to the University of Connecticut, where he is currently an associate professor in the School of Nursing and director of the UConn Center for Advancement in Managing Pain. His research interests are in pain and substance use disorders, with an emphasis on cannabinoid modulation of pain and inflammation. He serves on the board of directors of the International Cannabinoid Research Society as treasurer and previously served as secretary.

Minor Cannabinoids and Terpenes: Preclinical Evaluation as Analgesics

The overall goal of our project is to provide a comprehensive in vitro and in vivo evaluation of minor phytocannabinoids and terpenoids contained in the cannabis plant to determine their potential efficacy as analgesics. To date, we have concentrated on examination of the effects of selected phytocannabinoids on binding to and activation of CB₁ and CB₂ receptors. Our presentation will focus on description of the strategy we will use to evaluate cannabis constituents and discussion of the results of CB₁ and CB₂ receptor binding and functional assessment. Future directions will be outlined.
Mechanism and Optimization of CBD-Mediated Analgesic Effects

Substantial evidence indicates that cannabis is effective for the treatment of chronic pain but carries adverse psychoactive effects. Minor cannabinoids in cannabis, such as cannabidiol (CBD), have minimal psychotropic activity. However, their analgesic effects are not as potent as those of cannabis, and the neural mechanisms by which minor cannabinoids-mediated analgesia may be optimized remain largely unknown. Our overall objective is to identify the neural mechanisms involved in the in vivo actions of minor cannabinoids in order to optimize their analgesic effects.

In this presentation, we will discuss our specific aims to define the cortical and spinal circuit
mechanisms underlying CBD’s analgesic effects, and determine whether these effects may be modulated by neural inhibitory changes induced by a neuron-specific chloride extruder, KCC2. Identifying the novel circuit targets and mechanisms of minor cannabinoids-mediated analgesia will not only help optimize nonpsychoactive cannabinoid-based therapies but also provide routes to develop effective new treatments with minimal side effects.

Q & A Session on Nonclinical Studies

Moderator: Inna Belfer, National Center for Complementary and Integrative Health (NCCIH)

Inna Belfer, M.D., Ph.D., is a program director in the Basic and Mechanistic Research in Complementary and Integrative Health Branch at NCCIH. She oversees part of the NCCIH pain portfolio, with a focus on mechanisms underlying the effects of mind and body approaches and natural products on pain management. In addition, she leads research programs related to genetic, genomic, and epigenetic mechanisms of complementary and integrative health approaches; neural mechanisms of meditative movement practices such as yoga, tai chi, and qi gong; cannabinoids and pain; and sleep and pain. Dr. Belfer earned her medical degree from the Moscow Medical University in Moscow, Russia and her Ph.D. in neurobiology from Hebrew University in Jerusalem, Israel. She did her postdoctoral training in human genetics and clinical pain at the National Institute of Dental and Craniofacial Research (NIDCR) pain and neurosensory mechanisms branch. Dr. Belfer has served on numerous national and international grant review panels, presented at national and international conferences, and organized seminars, workshops, and roundtables on pain and related conditions.

11:00–11:15 a.m. BREAK
11:15–Noon  Data Blitz Presentations on the Clinical Studies Funded by NCCIH
Cannabinoids and Pain Funding Opportunity Announcements

Speaker: Rajiv Radhakrishnan, Yale University School of Medicine

Rajiv Radhakrishnan, M.B.B.S., M.D., is an assistant professor of psychiatry at Yale University School of Medicine. He received his medical degree from St. John’s Medical College in Bangalore, India. He is board-certified in psychiatry and addiction medicine and serves as an associate editor for *Journal of Dual Diagnosis* and a member of the American Society of Clinical Psychopharmacology Technology Task Force. As a physician-scientist with a research interest in examining the neurobiological effects of cannabinoids, Dr. Radhakrishnan has conducted laboratory studies using delta-9 tetrahydrocannabinol (THC), the principal psychoactive constituent in cannabis, on verbal memory and recall, time-perception, and pain. His expertise is in using positron emission tomography (PET) to understand brain structure and function, and he has conducted studies using radioligands for cannabinoid 1 receptor availability, synaptic vesicle density, and brain microglial activation. His current National Center for Complementary and Integrative Health-funded study examines the effect of cannabidiol on brain microglial activation and central pain-sensitization using PET imaging.

Co-Principal Investigator: Mohini Ranganathan, Yale University

Mohini Ranganathan, M.D., is an associate professor in the Department of Psychiatry at Yale University School of Medicine and codirects the Department of Veterans Affairs (VA)-Yale Schizophrenia Research Program. Her research includes clinical trials and psychopharmacologic studies aimed at probing the cannabinoid system as it relates to cannabis use disorder and psychosis. She has been funded by the National Institute on Drug Abuse to examine the interactive effects of tetrahydrocannabinol and cannabidiol, and has several ongoing studies in collaboration with the Yale positron emission tomography center to examine the endocannabinoid and glutamatergic systems in healthy individuals, patients with psychotic disorders, and patients with cannabis use disorders.

**Effect of Cannabidiol on Microglial Activation and Central Pain-Sensitization**

Drs. Rajiv Radhakrishnan and Mohini Ranganathan will present their National Center for Complementary and Integrative Health-funded study titled “Effect of Cannabidiol on Microglial Activation and Central Pain-Sensitization.” They will provide an overview of the study including the goal and specific aims of the study. They will also discuss the study design, which enables them to examine the effect of cannabidiol on *in vivo* brain microglial activation (a biological mechanism of chronic pain) using positron emission tomography (PET) imaging, and on central pain-sensitization (a physiological mechanism of chronic pain) using intradermal capsaicin. The presentation will also discuss some of the challenges faced due to COVID-19.
Speaker: Deborah Yurgelun-Todd, University of Utah

Deborah A. Yurgelun-Todd, Ph.D., is professor and vice-chair for research in the Department of Psychiatry and Director of the Neuroscience Initiative at the University of Utah School of Medicine. She received her Ph.D. from Harvard University and directed the Cognitive Neuroimaging Laboratory at McLean Hospital, Harvard Medical School between 1998 and 2008. Dr. Yurgelun-Todd is considered an expert in the application of magnetic resonance imaging techniques to characterize neural mechanisms associated with cognitive and emotional processing, pain perception, and traumatic brain injury and during treatment intervention in adult patients. As co-principal investigator of the signature Adolescent Brain Cognitive Development (ABCD) longitudinal neuroimaging study of American adolescents, funded by the National Institutes of Health, she is also recognized for applying imaging techniques to study cortical changes during development in healthy children and adolescents. Data from these investigations have been published in over 300 peer-reviewed journals, reviews, and book chapters. Dr. Yurgelun-Todd has received Federal, foundation, and industry funding and has worked closely with pharmaceutical companies, including Eli Lilly, Johnson & Johnson, Novartis, and GlaxoSmithKline, on the design of clinical trials of agents aimed at improving cognition and clinical symptoms in persons with psychiatric disorders.

Co-Principal Investigator: Perry Renshaw, University of Utah

Perry Renshaw, M.D., Ph.D., is a Utah Science, Technology, and Research (USTAR) professor of psychiatry at the University of Utah School of Medicine; serves as medical director of the Veterans Integrated Service Network (VISN) 19 Mental Illness Research, Education, and Clinical Center (MIRECC); and is the director of the Magnetic Resonance Laboratory at the Brain Institute at the University of Utah. Dr. Renshaw’s training in biophysics and psychiatry has led to internationally recognized authority in the use of multinuclear magnetic resonance spectroscopy (MRS) neuroimaging to identify changes in brain chemistry associated with psychiatric and substance abuse disorders. Over the past 20 years, he has conducted more than 2,500 MRS brain scans of individuals with stimulant dependence or mood disorders, with the goal of characterizing the cross-sectional and longitudinal alterations in brain chemistry associated with these comorbid disorders. With funding by the National Institutes of Health for over 25 years, he has a notable publication record, having served as an author on more than 400 publications. Dr. Renshaw’s current projects are investigating hypoxic stress and depression among female methamphetamine users.

Exploring the Mechanisms Underlying the Analgesic Effect of Cannabidiol Using Proton Magnetic Resonance Spectroscopy

Chronic pain is a prevalent disorder affecting approximately 100 million Americans. Treatment of chronic pain has heavily relied on opioid drugs, a therapy accompanied by significant shortcomings
including lack of efficacy in the long term and the risk for dependence that has contributed significantly to the current national opioid epidemic. A burgeoning body of literature suggests that the cannabis plant may have analgesic properties. The main psychoactive constituent in the cannabis plant, tetrahydrocannabinol (THC), has demonstrated analgesic effects, but its clinical use is limited by adverse psychoactive and cognitive effects. However, cannabidiol (CBD), an isomer of THC, has been shown to demonstrate analgesic properties without psychoactive effects. This study will evaluate changes in brain chemistry after administration of a cannabis extract enriched in CBD using proton magnetic resonance spectroscopy (1 H-MRS). We aim to investigate whether short-term administration of a cannabis extract enriched in CBD can modulate glutamate and GABAergic signaling in critical pain-processing regions of the brain such as the anterior cingulate cortex (ACC) and insula. Furthermore, we plan to investigate the effects of CBD on peripheral and neural markers of inflammation. The successful completion of the study will advance the evidence-based application of CBD as a potential treatment for pain conditions and will also provide substrates that can be targeted to reduce neuroinflammation.
Judith Hellman, M.D., is the William L. Young, M.D., endowed professor and vice chair for research in the University of California, San Francisco Department of Anesthesia and Perioperative Care, and a physician-scientist doing basic-translational research on sepsis, critical illness, and injury. She trained in internal medicine, anesthesiology, and critical care medicine and then did a postdoctoral research fellowship in sepsis and innate immunity. Broad focuses of her research include innate immunity in sepsis and lung ischemia-reperfusion injury, endothelial immune function and inflammatory pathways in sepsis and critical illness, and immune modulation by the endocannabinoid and endovanilloid systems. Dr. Hellman and her colleagues observed that the endocannabinoids N-arachidonoyl dopamine (NADA) and N-oleoyl dopamine (OLDA), and tetrahydrocannabinol (THC) from Cannabis, strongly upregulate circulating levels of the anti-inflammatory cytokine IL-10, while reducing proinflammatory cytokines in mice with acute inflammation or bacterial sepsis. They have determined that NADA and OLDA exert their anti-inflammatory effects via TRPV1 expressed outside of the myeloid compartment, whereas the anti-inflammatory effects of THC are mediated through cannabinoid receptor 1 (CB₁R). They are now exploring the effects of endocannabinoids, minor cannabinoids, and THC on immune function and on acute inflammation and pain.

Neuroimmune Mechanisms of Minor Cannabinoids in Inflammatory and Neuropathic Pain

We previously found that in endotoxemic mice, the endocannabinoids N-arachidonoyl dopamine (NADA) and N-oleoyl-dopamine (OLDA) strongly upregulate plasma levels of the anti-inflammatory cytokine IL-10, while reducing proinflammatory cytokines and lung injury via the pain receptor TRPV1. Treatment with tetrahydrocannabinol (THC) has identical anti-inflammatory and lung-protective effects as treatment with NADA and OLDA but modulates inflammation via CB₁R. The broad goals of our National Center for Complementary and Integrative Health-funded study are to characterize the anti-inflammatory and analgesic properties of minor cannabinoids, focusing on the roles of TRPV1 and CB₁R and neuroimmune mechanisms. We will present in vitro data on the effects of four minor cannabinoids, cannabidiol (CBD), cannabiol (CBN), cannabigerol (CBG), and cannabichromene (CBC). We observed that treatment with CBD induces calcium flux in dorsal root ganglion (DRG; sensory) neurons from C57BL/6 mice, that the calcium responses to CBD between different DRG neurons are heterogeneous in onset and differ in magnitude and recovery profile, that treatment with CBD blocks subsequent calcium responses to capsaicin, and that a small population of DRG neurons responds to CBD but not capsaicin. In human peripheral blood mononuclear cells, CBD reduces HMGB1-induced production of IL-1β and IL-6, but not IL-8 or TNFα. HMGB1 has been implicated in the development of chronic pain. Finally, we observed that treatment with CBD, CBN, and CBG reduces permeability, and CBD, CBN, CBG, and CBC reduce IL-6 production of lipopolysaccharide-activated human endothelial cells.
Speaker: Ziva D. Cooper, University of California, Los Angeles

Ziva D. Cooper, Ph.D., is the interim director and research director of the University of California, Los Angeles (UCLA) Cannabis Research Initiative in the Jane and Terry Semel Institute for Neuroscience and Human Behavior and associate professor in the Department of Psychiatry at the David Geffen School of Medicine, UCLA. Her research involves understanding variables that influence both the therapeutic potential and the adverse effects of cannabis and cannabinoids. Dr. Cooper received her Ph.D. in biopsychology from the University of Michigan in 2007 in preclinical psychopharmacology, experience that informs her focus on translating preclinical studies of cannabinoids to the clinic using placebo-controlled human drug-administration studies. Current projects include understanding the potential for cannabis constituents to reduce reliance on opioids, differences between men and women in their response to the pain-relieving effects of cannabis, and therapeutic effects of cannabinoids in patient populations. Dr. Cooper served on the National Academies committee that published a comprehensive report on the health effects of cannabis and cannabinoids. She is a board director for the College on Problems of Drug Dependence and an associate editor of the American Journal of Drug and Alcohol Abuse.

Analgesic and Subjective Effects of Terpenes Administered Alone and in Combination With THC: Potential THC- and Opioid-Sparing Effects of Myrcene and β-Caryophyllene

Several terpenes found in cannabis are hypothesized to have therapeutic effects on their own and in tandem with cannabinoids, the unique chemical constituents of the cannabis plant. This presentation will describe a novel double-blind, placebo-controlled investigation probing the pain-relieving effects of two terpenes, myrcene and beta-caryophyllene, alone and in combination with tetrahydrocannabinol (THC), in volunteers.
Speaker: Richard Harris, University of Michigan

Richard Harris, Ph.D., is an associate professor in the Department of Anesthesiology and the Department of Internal Medicine at the University of Michigan. He is also the Director for Neuroimaging at the Chronic Pain and Fatigue Research Center at the University of Michigan. His background is in basic science and clinical research in alternative medicine. Dr. Harris received his Ph.D. in molecular and cell biology from the University of California at Berkeley in 1997. He completed a postdoctoral fellowship at the National Institutes of Health (NIH). He is a graduate of the Maryland Institute of Traditional Chinese Medicine and has completed an M.S. in clinical research design and statistical analysis at the University of Michigan. Dr. Harris is currently investigating mechanisms of chronic pain and its treatment with acupuncture and acupressure, focusing on the role of brain neurotransmitters and brain network behavior in chronic pain. He is a member of the National Advisory Council for Complementary and Integrative Health and a co-President of the Society for Acupuncture Research. He serves as associate editor of and scientific advisor for the Journal of Acupuncture and Meridian Studies.

Co-Principal Investigator: Steven Harte, University of Michigan

The research of Steven Harte, Ph.D., leverages preclinical models, human psychophysics, and functional brain imaging to investigate mechanisms of chronic pain and its treatment. Specific areas of interest include multisensory integration and amplification in chronic pain, environmental influences on pain, endogenous pain modulation, and neural mechanisms of pain affect. Dr. Harte is a member of the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP), Symptoms of Lower Urinary Tract Dysfunction (LURN), and AURORA Research Networks, where he leads the development and implementation of multisite quantitative sensory testing methods. Dr. Harte is also involved in the development of novel medical and dental devices, e-Health delivery platforms, and diagnostic algorithms for clinical research and personalized pain management. He is principal inventor on several patents for pain measurement technology.

Cannabinoid Interactions With Central and Peripheral Pain Mechanisms in Osteoarthritis of the Knee

Current research suggests that cannabinoids such as cannabidiol (CBD) and tetrahydrocannabinol (THC) may ameliorate pain, but the mechanisms by which this occurs are largely unknown. In particular, it is uncertain if chronic pain patients with variable central and peripheral pathologies may respond differentially to these compounds. Our approach is to study a population of mixed pain patients diagnosed with knee osteoarthritis (KOA), some of whom will have peripheral joint inflammation driving their pain, whereas others may have brain factors that facilitate their pain. Our hypothesis is that patients with more knee pathology will respond better to CBD, which could reduce circulating inflammatory cytokines, whereas patients with more central nervous system factors may respond better to THC. Our approach is to randomize 140 KOA patients to either CBD,
THC, CBD + THC, or placebo. Following randomization, primary outcomes collected at baseline and after 14 weeks of treatment include circulating interleukin-6 and resting state brain connectivity between the default mode network (DMN) and the insula. We predict that CBD will reduce levels of interleukin-6 whereas THC will reduce insula-DMN connectivity. We currently have Investigational New Drug (IND) approval from the U.S. Food and Drug Administration (FDA), and our protocol is under review by the Institutional Review Board at the University of Michigan. Our sources of CBD and THC are pharmaceutical grade CBD (Epidiolex) and dronabinol, respectively. This circumvented having to get compounds extracted from the cannabis plant, which can be variable from batch to batch and harder to quantify for IND approval by the FDA. Our major stumbling block was trying to find a source for matching placebo for Epidiolex. This compound comes as a liquid and is typically prepared in sesame oil with flavor. The company that makes Epidiolex would not provide us with matching placebo so we resorted to having our matching placebo prepared by an external lab (Dr. ElSohly). Had we known this initially, our progress from proposal submission and IND approval would have been easier.

Q & A Session on Clinical Studies

Moderator: Angela Arensdorf, National Center for Complementary and Integrative Health (NCCIH)

Angela M. Arensdorf, Ph.D., is a health science policy analyst within the Office of Policy, Planning, and Evaluation at NCCIH at the National Institutes of Health. In this role, Dr. Arensdorf is involved in the strategic planning, coordination, evaluation, and implementation of select NCCIH activities. Prior to joining NCCIH in her current role, Dr. Arensdorf was an American Association for the Advancement of Science (AAAS) science and technology policy fellow at NCCIH. She received her B.S. in biology and biochemistry from Clarke University, a Ph.D. in cell and molecular biology from the University of Iowa, and postdoctoral training in cellular signaling at St. Jude Children’s Research Hospital. Dr. Arensdorf’s scientific expertise is in gene regulation, endoplasmic reticulum stress responses, G protein-coupled receptor biology, Hedgehog signaling, and bioinformatics.

Noon–1:00 p.m. BREAK
1:00–1:30 p.m.  
**Keynote Presentation** (Introduction by David Shurtleff, Ph.D., NCCIH):
*Cannabis Research in Canada: Opportunities, Risks, and Lessons Learned*
Mark A. Ware, M.B.B.S., MRCP(UK), M.Sc., Chief Medical Officer, Canopy Growth Corporation, Canada; Associate Member, McGill University

**Keynote Speaker: Mark A. Ware, Canopy Growth Corporation**
Mark Ware, M.B.B.S., MRCP(UK), M.Sc., is chief medical officer (CMO) of Canopy Growth Corporation and an associate member of the Department of Family Medicine, McGill University. Prior to joining Canopy Growth in 2018, Dr. Ware was a tenured associate professor in the Faculty of Medicine at McGill University. He obtained his medical degree at the University of the West Indies and undertook training in internal medicine and secured a master’s degree in epidemiology. He began evaluating the role of cannabis in pain management at McGill in 1999, where he served as director of clinical research of the Alan Edwards Pain Management Unit at the McGill University Health Centre for more than 10 years. Since joining Canopy Growth, Dr. Ware has helped establish the company’s global medical division and led the team responsible for supply and regulatory documentation, clinical development, medical affairs, and global product safety. As CMO, Dr. Ware advises on scientific and ethical aspects of Canopy Growth’s global research efforts and is responsible for the company’s product safety and pharmacovigilance program encompassing all research and development and commercial activities.

*Cannabis Research in Canada: Opportunities, Risks, and Lessons Learned*

With the emergence of cannabinoids as a new therapeutic class, as well as evolving cannabis regulations worldwide, the importance of high-quality research on a range of cannabis topics to inform patients, health care professionals, and policymakers is paramount. Canada has a Federal regulatory landscape that permits cannabis access to patients for medical purposes and adults for nonmedical purposes, and this context offers a unique opportunity to examine research paradigms. This presentation offers a perspective from witnessing two decades of cannabis research in Canada regarding the challenges that clinical researchers face in trying to answer important questions regarding safety, efficacy, and effectiveness. The opportunities and risks that evolving cannabis policies pose to academic research efforts will be explored from a Canadian perspective, recognizing that this is an issue of global importance and pressing need.

1:30–1:45 p.m.  
**Q & A Session for Keynote Speaker**
Moderator: Emmeline Edwards, Ph.D., NCCIH
See bio on page 6.
1:45–2:30 p.m.       Panel Discussion on Gaps and Future Directions

Moderator: Inna Belfer, Ph.D., NCCIH
See bio on page 15.

Panelist: Roger Little, National Institute on Drug Abuse (NIDA)

Roger Little has over 17 years of experience in neuroscience, genetics, and psychiatric and neurological disorders, 10 years of which have been at the National Institutes of Health (NIH). Dr. Little is the deputy director of the Division of Basic Neuroscience and Behavioral Research at NIDA, where he helps oversee the NIDA extramural research portfolio in neuroscience research in addiction, pain, and HIV-AIDS. Previously, he was a senior advisor at the National Institute of Mental Health. He also served as a liaison and coordinator for trans-NIH initiatives and was a program co-lead for the Common Fund Genes, Tissue, and Expression initiative. He led a trans-NIH workgroup that created a federated network of brain banks in the United States called the NIH Neurobiobank. Prior to NIH, he was a postdoctoral fellow at the Centers for Disease Control and Prevention-National Institute for Occupational Safety and Health (CDC-NIOSH), where he conducted basic molecular neurobiology research focused on the neural signaling pathways related to astroglial activation in response to brain injury.

Panelist: Jeffrey White, National Cancer Institute

Jeffrey D. White, M.D., is director of the Office of Cancer Complementary and Alternative Medicine (OCCAM) at the National Cancer Institute (NCI). He has served in various positions at NCI since 1990. From 1995 to 1998, Dr. White also served as an oncology consultant to the director of NIH’s Office of Alternative Medicine. In October 1998, the deputy director of extramural science of NCI, Dr. Robert Wittes, chose him to serve as director of OCCAM, a new office within NCI. The office was created to augment the activities of the different divisions at NCI that were already supporting complementary and alternative medicine research. OCCAM continues to promote and support research and generation of good quality information on the various disciplines and modalities associated with the field of complementary and alternative medicine as they relate to the diagnosis, prevention, and treatment of cancer. Dr. White is a board-certified medical oncologist and a cancer researcher. He received his M.D. from Howard University in 1984. He completed a residency in internal medicine in 1987 and fellowships in oncology and hematology in 1990 at The Washington Hospital Center in Washington, D.C.
Panelist: Qi-Ying Liu, National Institute on Alcohol Abuse and Alcoholism (NIAAA)

Qi-Ying Liu, M.D., is a program director at the Division of Neuroscience and Behavior, National Institute on Alcohol Abuse and Alcoholism (NIAAA), National Institutes of Health. Dr. Liu’s program areas include cellular neurobiology and neurocircuitry, synaptic plasticity, neuroadaptation, and neuromodulation. Before joining NIAAA, Dr. Liu was a program official at the National Center for Complementary and Alternative Medicine (now National Center for Complementary and Integrative Health). Dr. Liu is experienced in overseeing basic, translational, and clinical research in complementary and alternative medicine, alcohol use disorder, neuroscience and neurodegeneration, the cardiovascular system, etc. He also oversaw multicenter consortia and clinical studies ranging from smaller clinical research project grants to large-scale, multisite clinical trials. Dr. Liu’s own research involves neurophysiology and neuropharmacology of the developing and mature nervous system, muscular and neuronal ion channels, and cardiac physiology and pharmacology.

Panelist: Smriti Iyengar, National Institute of Neurological Disorders and Stroke (NINDS)

Smriti Iyengar, Ph.D., is program director for the newly formed Preclinical Screening Platform for Pain (PSPP) program in the Division of Translational Research, National Institute of Neurological Disorders and Stroke (NINDS). She is a neuroscientist with extensive research and drug development experience focused on neurodisorders including pain and headache. Prior to joining NINDS, she was an adjunct senior research professor in the Department of Anesthesia, Indiana University School of Medicine, where her research interests included pain and headache mechanisms and neuroimmune interactions following traumatic brain injury, as well as mechanisms leading to neuropathic pain. She was formerly at Eli Lilly and Company, and before that at G.D. Searle and Company, Schering-Plough Inc., and Ciba Geigy. Her drug discovery expertise includes target, lead, and clinical candidate identification and characterization as well as translational and clinical development, regulatory strategy, launch, and commercialization. Her postdoctoral training was at Rutgers University in the Department of Physiology and Neuroscience, with research focused on central regulation of opioid function and central regulation of neuroendocrine function. She received her Ph.D. from Maharaja Sayajirao University of Baroda, India. She is a fellow of the American College of Neuropsychopharmacology.
Panelist: Mi Hillefors, National Institute of Mental Health (NIMH)

Mi Hillefors, M.D., Ph.D., serves as the deputy director of the Division of Translational Research (DTR) at the National Institute of Mental Health (NIMH), National Institutes of Health (NIH). The DTR directs, plans, and supports programs of research and research training that translate knowledge from basic science to discover the etiology, pathophysiology, and trajectory of mental disorders and develops effective interventions for children and adults. As an integral part of her job, Dr. Hillefors collaborates and communicates with other Government agencies and nongovernmental organizations on a regular basis to optimize NIMH’s and NIH’s research efforts, nationally and internationally. She communicates with NIMH and NIH leadership, the research community, patient advocacy groups and other stakeholders, the U.S. Food and Drug Administration, the media, etc. Previously, Dr. Hillefors served as the program chief for the translational therapeutics program in DTR, overseeing projects in the areas of biomarker discovery and novel treatment development, including early phase clinical drug trials. Earlier in her career, she conducted basic research in neuroscience, molecular neurobiology, and receptor pharmacology of mental health disorders, and practiced psychiatry, geriatrics, and family health care. She received her M.D. and Ph.D. in neuroscience at the Karolinska Institutet, Sweden.

Panelist: Dominic Chiapperino, Food and Drug Administration (FDA)

Dominic Chiapperino, Ph.D., is the director of the Controlled Substance Staff (CSS) at the U.S. Food and Drug Administration (FDA), a group with expertise in the assessment of the abuse potential of drugs. He has worked extensively on FDA policy and regulatory issues involving cannabis and related substances and, prior to CSS, was with the Center for Drug Evaluation and Research’s (CDER) Division of Anesthesia, Analgesia, and Addiction Products, gaining regulatory experience concerning opioid analgesics and drugs indicated for the treatment of substance use disorders. Dr. Chiapperino received his Ph.D. in organic chemistry from the University of Maryland in 2000 and did postdoctoral research with the National Institute of Diabetes and Digestive and Kidney Diseases before beginning his career at the FDA in 2002.
Panelist: Terrence Boos, Drug Enforcement Administration (DEA)

Terrence L. Boos, Ph.D., serves as the Chief of the Drug and Chemical Evaluation Section, Diversion Control Division, Drug Enforcement Administration (DEA, U.S. Department of Justice) and has been in his current position since 2012. He oversees scientific and regulatory programs and shares these responsibilities with a multidisciplinary team of senior scientists. Dr. Boos serves as advisor to the Diversion leadership and DEA officials on matters impacting drug policy development and execution and as a liaison to Federal agencies, international and state governments, and industry. His group facilitates initiatives to improve public health and safety through the collection and evaluation of illicit drug manufacturing and trafficking trends and abuse data to draft and promulgate regulations related to domestic drug scheduling and chemical control. These activities are highlighted by the response to trafficking in new psychoactive substances. The group routinely initiates scientific studies to inform policy and regulatory decisions and works closely with law enforcement and public health officials to identify opportunities to better protect the public. Prior to joining the DEA in 2007, Dr. Boos was a research fellow at the National Institute on Drug Abuse in the Drug Design and Synthesis Section.

Panelist: Robert Walsh, NIDA Drug Supply Program

Robert L. Walsh is Chief of the Regulatory Affairs Branch, Division of Therapeutics and Medical Consequences, National Institute on Drug Abuse (NIDA). He has been with NIDA for 33 years. Mr. Walsh oversees and directs branch activities, including Investigational New Drug (IND), New Drug Application (NDA), and Drug Master File (DMF) submissions. He is responsible for ensuring that all clinical trials are performed in compliance with applicable regulatory requirements. He provides guidance to NIDA investigators and development partners on regulatory issues and consults on clinical support contracts, importation of compounds from foreign sources, and Drug Enforcement Administration (DEA) registration of contract testing facilities. He serves as a liaison to the U.S. Food and Drug Administration, DEA, and other Governmental regulatory agencies. Mr. Walsh is the NIDA Contracting Officer’s Representative for the NIDA marijuana contract program at the University of Mississippi. He is responsible for directing activities under that contract including the production of various chemovars of marijuana, extracts, formulations, and human use material to support IND applications by NIH grantees and others. He also oversees the Marijuana Potency Monitoring Program and serves as a reviewer and authorized approver for the NIDA Drug Supply Program.

2:30–3:00 p.m.  Q & A Session for the Panelists

Moderator: David Shurtleff, Ph.D., NCCIH
See bio on page 5.

3:00 p.m.  Adjournment