National Center for Complementary and Integrative Health

2024 NCCIH Cannabinoids and Pain Research Annual PIs Meeting

Meeting Summary

Fifth Annual Principal Investigators Meeting 2024:
Exploring the Mechanisms Underlying Analgesic Properties
of Minor Cannabinoids and Terpenes
June 4, 2024
Summary

Introduction

Inna Belfer, M.D., Ph.D., deputy branch chief and program director in the Basic and Mechanistic Research Branch of the National Center for Complementary and Integrative Health (NCCIH), welcomed everyone to the meeting. She introduced David Shurtleff, Ph.D., deputy director of NCCIH, for welcoming remarks, followed by Emmeline Edwards, Ph.D., director of the Division of Extramural Research at NCCIH, for the meeting's overview and goals.

Welcome From NCCIH

Dr. Shurtleff welcomed everyone to the fifth and last annual principal investigators meeting since NCCIH initially released a request for applications (RFA): Exploring the Mechanisms Underlying Analgesic Properties of Minor Cannabinoids and Terpenes in 2019 for cannabinoid and terpene research for pain and analgesia. Following an overwhelming response of interest, NCCIH funded nine applications with $3 million, and later more, towards this research.

NCCIH rigorously investigates the fundamental science, usefulness, and safety of complementary and integrative health approaches. NCCIH considers the whole person, and the interventions it studies include physical, psychological, and nutritional approaches, which include natural products, dietary supplements, botanicals like cannabis, and vitamins.

Dr. Shurtleff discussed NCCIH's process for investing in this area of science. NCCIH considers whether there is enough rigorous preclinical research to support further study of a complementary approach, as well as the rates of current use of that approach by the American public. He noted that cannabis and the endocannabinoid (eCB) system have been well studied and characterized, and there is wide public use of cannabis, with an estimated 55 million Americans using marijuana and 8.3 million Americans using cannabis for medical purposes in 2023.

Twenty-four states and the District of Columbia have legalized marijuana for adult and medical use, and 14 states have legalized cannabis for medical use only. Meanwhile, under Federal law, tetrahydrocannabinol (THC) and the cannabis plant have Schedule I restrictions on access and availability, and historically, Schedule I cannabis products were available for research use only through the University of Mississippi. He said that recently, however, additional cannabis growers have been approved by the Drug Enforcement Administration (DEA) for the purposes of supplying cannabis to qualified researchers. For further information about obtaining cannabis and cannabis products from other DEA-approved sources of cannabis, researchers may contact those sources directly.

Dr. Shurtleff said that a variety of cannabis-based products that are not Schedule I have moved forward through the U.S. Food and Drug Administration (FDA), including nabilone, a Schedule II drug; dronabinol, a Schedule III drug; and epidiolex, a Schedule V drug. Many hemp products are also available and unscheduled. He then

discussed challenges related to scheduling classification. He said cannabis is in the process of possibly being rescheduled to Schedule III, noting the impact of rescheduling may help facilitate research efforts.

Dr. Shurtleff reiterated NCCIH's interest in studying the therapeutic potential of the cannabis plant, noting how preclinical research has indicated that minor cannabinoids have target sites relevant to treatment, such as for bone stimulation, as well as potential anxiolytic, anti-inflammatory, analgesic, and antipsychotic properties.

Dr. Shurtleff discussed NCCIH's Notice of Special Interest (NOSI): Promoting Mechanistic Research on Therapeutic and Other Biological Properties of Minor Cannabinoids and Terpenes (NOT-AT-22-027), which has received support from the National Cancer Institute (NCI), National Eye Institute (NEI), National Institute on Aging (NIA), National Institute on Alcohol Abuse and Alcoholism (NIAAA), National Institute of Dental and Craniofacial Research (NIDCR), National Institute on Drug Abuse (NIDA), National Institute of Neurological Disorders and Stroke (NINDS), Office of Dietary Supplements, and Office on Research of Women's Health. Many National Institutes of Health (NIH) Institutes and Centers have cannabinoid research portfolios.

Dr. Shurtleff discussed how NCCIH has continued the momentum by releasing an RFA: Resource Center for Cannabis and Cannabinoid Research (RFA-AT-24-006), which has received a robust response of applications that will be reviewed in July 2024 with funding anticipated in January 2025. He discussed aims to further advance research by providing opportunities for researchers outside of the cannabinoid field to get involved despite the complex regulatory environment.

Meeting Overview and Goals

Dr. Edwards discussed the growth NCCIH has seen in its cannabinoid research portfolio. NCCIH funded 11 studies, 6 of which have been completed, and 5 of which are expected to be completed by 2025. Following the RFA and NOSI, NCCIH has seen growth in its research portfolio to approximately 20 to 25 grants with a number of new collaborations following the principal investigators' meetings. Dr. Edwards expressed enthusiasm for the meeting's upcoming nonclinical and clinical presentations, noting that the duration limit was 5 minutes for each "data blitz" presentation, and the keynote presentation by Daniele Piomelli, Ph.D., entitled "Safety and Efficacy of Cannabis Products," on the safety and efficacy of cannabis-derived products in animal models and in humans. Dr. Edward's ended by asking everyone to save questions for the end of each session.

Session 1: Advances in Nonclinical Studies on Cannabinoids and Pain

Dr. Belfer thanked Dr. Shurtleff and Dr. Edwards for providing an overview of the meeting history and goals and noted a special thanks to Helene M. Langevin, M.D., director of NCCIH. Dr. Belfer said the first session would include 15 principal investigators presenting NCCIH-funded nonclinical studies on cannabinoids and pain.

Analgesic Efficacy of Single and Combined Minor Cannabinoids and Terpenes
Sara Jane Ward, Ph.D., Temple University Lewis Katz School of Medicine

Dr. Ward's laboratory investigated the potential antineuropathic effects of minor cannabinoids and terpenes on chemotherapy-induced peripheral neuropathy and a pulpitis model of dental pain in rodents. Across four studies, they found 1) nuanced, dosing-specific effects of cannabigerol (CBG) on oxaliplatin-induced mechanical sensitivity in rodents, with some synergistic and sub-additive effects; 2) sex-based differences between the peripheral

nervous system (PNS) and the central nervous system (CNS) and in neuroinflammatory markers following paclitaxel administration; 3) beta-caryophyllene (β-CP) was the most effective treatment strategy to prevent the development of inflammation and sensitivity in rodents with orofacial pain from pulp exposure; and, 4) robust, anti-inflammatory effects of β-CP for chemotherapy-induced neuropathic pain, with robust neuroinflammatory effects of β-CP compared to cannabidiol (CBD). Future research should list, rank, and prioritize pain models based on features such as inflammation and systematically test cannabis constituents in a standardized way across laboratories.

Identifying the Mechanisms of Action for CBD on Chronic Arthritis Pain

Yu-Shin Ding, Ph.D., New York University School of Medicine

Dr. Ding's laboratory sought to determine the mechanisms of action of CBD on pain treatment for chronic osteoarthritis (OA) in rodents. They demonstrated CBD binding to the serotonin 1A (5-HT1A) receptor through positron emission tomography (PET) and computed tomography (CT) scans, and they observed higher uptake when administering CBD after OA onset to the rodent's right leg compared to the left leg. In a behavioral assessment study, they observed a reduction in sensitivity from CBD through Von Frey testing; a recovery through daily CBD after high anxiety in the OA state via light/dark box testing; and recovery through daily CBD after an increase in mobility and decrease in locomotor activity through Porsolt forced-swim tests. They noted significant effects only in female rodents across all aspects. They did not observe differences in their combined agonist and antagonist drug treatment study. Future research will help fine-tune mechanistic studies in humans, such as by imaging 5-HT1A modulation and anti-inflammatory effects in humans before and after CBD treatment.

Synthetic Biology for the Chemogenetic Manipulation of Pain Pathways

Andrew Ellington, Ph.D., University of Texas at Austin

Dr. Ellington and his colleagues sought to dissect human neural responses by functionally expressing individual receptors, such as cannabinoid receptor 1 (CB1R), cannabinoid receptor 2 (CB2R), and transient receptor potential vanilloid type 1 (TRPV1), into yeast. They found that dose responses in CB1R and CB2R yeast mimicked mammalian cell expression. Using machine learning, they compiled PubMed and patent literature databases to create compound signatures and English-language correlations, enabling them to confirm and predict the relationships between cannabinoids and receptors. Next steps include 1) using yeast strains to characterize previously unknown structure-activity relationships for cannabinoid compounds for CB1R and CB2R; 2) developing CB2R-specific ligands, enhancing therapeutic effects, and decreasing psychoactive effects; and 3) using yeast sensor strains to explore whether machine learning can predict novel cannabinoids.

Mechanistic Studies on Analgesic Effects of Terpene Enriched Extracts from Hops

Cassandra Quave, Ph.D., Emory University, and Isaac Chiu, Ph.D., Harvard Medical School

Dr. Quave and Dr. Chiu's laboratories sought to investigate mechanisms by which *Humulus lupulus*, or hops, and its extracted terpenes may affect sensory neurons and pain signaling in rodents. They prepared six formulations of hops and, following subjection to mass spectrometry, chose three distinct hops compounds (myrcene, alpha (α)-humulene, and e-caryophyllene) and topically applied the formulations to mice under hot plate conditions. They found that the hops extract formulations had a similar efficacy to CBD in blocking heat pain, and female rodents exhibited greater sensitivity. They also observed effects from a mixture formulation. They did not find effects with cold plate conditions or Von Frey thresholds. These findings may suggest future use of hops, which is unscheduled, as a source of analgesic terpenes for pain management. Future research should explore the mechanisms of receptor sensitization and the potential synergistic effects of extract mixtures.

Systematic Investigation of Rare Cannabinoids With Pain Receptors

Aditi Das, Ph.D., Georgia Institute of Technology, and David Sarlah, Ph.D., University of Illinois Urbana-Champaign

Dr. Das's and Dr. Sarlah's laboratories sought to assess classes of cannabinoids that are not commercially available and characterize their pharmacologic properties related to metabolism and inflammation in rodents. They elucidated the metabolism of the minor cannabinoids CBG and cannabichromene (CBC) by cytochrome P450s (CYP) (i.e., Phase 1 drug metabolizing enzymes) and showed that the metabolites are bioactive. They found that CBG formed epoxides at the 2',3' position and cyclized to cyclo-CBG in rodents, culminating in an anti-inflammatory effect in microglial cells. CBC metabolized at CYP sites in the brain, nasal, and cardiovascular pathways of rodents, producing 6',7'-epoxy-CBC, 8'-hydroxy-CBC, and 6'7'-dihydroxy-CBC; and cyclo-CBG was formed in rodent blood within 30 minutes of CBG administration. Future studies should 1) define the metabolism of CBG, CBC, and cannabinol (CBN) by human CYPs, 2) determine the molecular interactions of cannabinoids with CYPs using biophysical methods and molecular dynamics, and 3) elucidate the interaction of the cannabinoids and their oxidized metabolites with selected receptors and transient receptor potential (TRP) channels.

Minor Cannabinoids and Terpenes: Preclinical Evaluation as Analgesics

Steven Kinsey, Ph.D., University of Connecticut, and Thomas Gamage, Ph.D., The State University of New York Upstate Medical University

Dr. Kinsey, Dr. Gamage, and their colleagues sought to screen and evaluate minor phytocannabinoids and terpenes from cannabis in rodents to determine suitability for developing novel analgesic agents. Using semiquantitative and qualitative measures, they found that delta-8-THC (Δ8-THC) reduced arthritis severity and hind paw edema. Δ8-THC decreased proinflammatory cytokines, such as interleukin (IL)-1β and IL-6, and recovered vascular endothelial growth factor A (VEGF-A). In behavioral assays, the Δ8-THC intervention slightly recovered grip strength and climbing and reduced temperature preference to control levels. They did not observe changes to immobility compared to controls. Δ8-THC was an agonist at CB1R and CB2R. Future research should 1) determine the pharmacology of minor cannabinoids, terpenes, and terpenoids at molecular targets implicated in pain; 2) evaluate drug psychoactivity using Pavlovian discrimination; and 3) compare the anti-arthritic effects of additional minor cannabinoids in both male and female rodents.

Mechanism and Optimization of CBD-Mediated Analgesic Effects

Zhigang He, Ph.D., Boston Children's Hospital, and Kuan Hong Wang, Ph.D., University of Rochester

Dr. He's and Dr. Wang's laboratories sought to identify the actions of CBD and the underlying neural circuit mechanisms for analgesia in rodents. They found robust analgesic and selective inhibitory actions of CBD on neuropathic pain behaviors and hyperactive somatosensory circuits. CBD suppressed tactile allodynia and hyperalgesia in rodents with spared nerve injury, but it did not disturb tactile or nociceptive responses in intact rodents. Additionally, CBD suppressed the hyperactivity of somatosensory corticospinal pain but did not affect its activity in controls. Future research should continue investigating the efficacy and specificity of cannabinoids across mechanistic levels to optimize therapeutic translation, noting the potential for CBD effects across the central neural pathway.

Modulation of Pain Hypersensitivity by Terpenes via Endocannabinoid Release in Descending Circuits

Myra Alayoubi-Rice, Ph.D. Candidate, University of California, Los Angeles

Dr. Alayoubi-Rice and her colleagues sought to elucidate the mechanisms of myrcene's antinociceptive effect on neuropathic pain. In rodents with chronic constriction injury, she observed a dose-response curve for myrcene with greater force-withstanding potential in female mice. She also observed that a CB1 antagonist pretreatment

of myrcene blocked antiallodynic affects. She found differences between myrcene and a CB1 agonist, and myrcene did not modulate the activity of eCBs, 2-arachidonylyglycerol, or anandamide on supine 1 receptors. Future research should 1) investigate myrcene's ability to enhance eCBs using in vivo fiber photometry imaging in the ventrolateral periaqueductal grey, 2) investigate the lateral hypothalamus to ventrolateral periaqueductal gray circuit, and 3) explore sex differences in eCB release.

Session 1: Q&A

Dr. Belfer thanked presenters from the first session and introduced the question-and-answer session. A speaker asked Dr. Ding to clarify whether she displayed PET imaging for rodent knees in addition to brain imaging. Dr. Ding confirmed her laboratory's use of a whole-body scanner for rodent knee and brain imaging.

Session 2: Advances in Nonclinical Studies on Cannabinoids and Pain

Dr. Belfer introduced the second session on advances in nonclinical studies. She introduced the researchers, who provided 5-minute "data blitz" presentations.

Kratom and Cannabinoid Constituents: Mechanisms and Interactive Effects in Neuropathic Pain

Sara Jane Ward, Ph.D., and Scott Rawls, Ph.D., Temple University Lewis Katz School of Medicine

Dr. Ward and Dr. Rawls sought to demonstrate whether the co-use of cannabis and kratom constituents increases positive or potential adverse effects. They tested CBD, CBG, and Δ8-THC individually and in combination with the kratom compound mitragynine in male and female mice. In a chemotherapy-induced peripheral neuropathy (CIPN) pretreatment model, CBG and mitragynine both prevented the development of mechanical sensitivity in female mice, demonstrating protective effects from mitragynine. In a formalin model, CBG and mitragynine both attenuated Phase II licking behaviors in male mice, indicating a possible sedative effect from CBG. In a tetrad model, Δ8-THC and mitragynine both produced catalepsy-like behavior and a significant interactive effect. Finally, in a hot plate model, mitragynine did not have antinociceptive effects but did reduce the latency of Δ8-THC and CBG. Additional clinical and translational research on kratom is needed, as mitragynine effects may not reflect kratom use in humans.

Terpenes from *Cannabis sativa* Relieve Chronic Pain and Block Opioid Reward

John Streicher, Ph.D., University of Arizona

Dr. Streicher's laboratory sought to investigate the therapeutic and mechanistic efficacies of *Cannabis sativa* terpenes in chronic pain models. In a CIPN model, terpenes were highly efficacious in relieving neuropathic pain by activating the adenosine 2A receptor (A2aR) in the spinal cord. In addition to efficacy, the terpenes showed no abuse liability, moderate analgesic tolerance, and an ability to enhance opioid pain relief through a combined approach on neuropathic pain. Additionally, β-CP and α-humulene blocked dopamine release in the A2aR striatum, indicating that a combination therapy with β-CP and morphine may improve pain relief while blocking opioid reward aspects. Future research should 1) continue exploring and clarifying the mechanisms of terpenes on receptors, and 2) explore the therapeutic aspects of terpenes, including drug potential, effects on opioid self-administration and potential for relapse, side effects, and dosing. Dr. Streicher also noted the importance of informing the public with evidence-based findings on cannabis, given widespread claims and misinformation from commercial actors.

Modulation of Pain Mechanisms by Cannabis-Derived Phytochemicals

Reinhold Penner, Ph.D., The Queen's Medical Center, and Ken Mackie, M.D., Indiana University Bloomington

Dr. Penner's and Dr. Mackie's laboratories sought to provide a pharmacologic profile of the effect of cannabis phytochemicals on pro-inflammatory calcium signaling in immune cells and assess the analgesic properties of active cannabinoids in rodent models of inflammatory and neuropathic pain. They found two novel mechanisms inhibited by acidic cannabinoids, including cannabigerolic acid (CBGA), cannabinolic acid (CBNA), tetrahydrocannabinolic acid (THCA), and cannabidiolic acid (CBDA). CBGA was found to be strongly anti-inflammatory in vitro; however, they did not find efficacy in mouse models of pain. Future research should investigate 1) the topical application of CBGA to sites of pain, 2) the efficacy of the spared nerve injury model of neuropathic pain, 3) the development of alternative CBGA formulations, 4) the assessment of serum binding affinities for all cannabinoids, and more.

Cannabidiol and Terpenoid Interactions in Amygdalar Regulation of Pain States

Benjamin Land, Ph.D., University of Washington

Dr. Land's laboratory sought to investigate the efficacy of CBD, α-pinene, linalool, β-CP, and β-myrcene on chronic pain. In a sciatic nerve ligation model, CBD/terpene gelatin pretreatment blocked allodynic effects in mice, but acute treatment had no effect. Additionally, an acute CBD and terpene treatment did not change pain behaviors in mice, while chronic dosing of the combination recovered some behaviors.

AI-Based Mapping of Complex Cannabis Extracts in Pain Pathways

Kent Vrana, Ph.D., Pennsylvania State University Hershey Medical Center

Dr. Vrana's laboratory sought to use an artificial intelligence (AI)-driven platform, drug-target identification based on chemical similarity (DRIFT), to map cannabinoids and terpenoids to molecular targets. Using a CIPN model, they observed acute analgesic effects from chronic CBG administration in mice. In a DRIFT comparison of cannabinoids and terpenes with target predictions, they observed high correlations with THC and tetrahydrocannabivarin (THCV), while CBC indicated potential for a unique biological profile. Incidentally, they found that CBC provided analgesia across inflammatory pain, CIPN, and thermal models, indicating CBC's potential as a novel minor euphorigenic cannabinoid for pain. Regarding future research, Dr. Vrana discussed creating a cannabis database and referred to his team's website, candi.dokhlab.org.

Computation-Assisted Discovery of Bioactive Minor Cannabinoids From Hemp

Jan Frederik Stevens, Ph.D., Oregon State University

Dr. Stevens's laboratory sought to develop hemp products for the mitigation and management of chronic pain. Using a heat map of high-resolution mass spectrometry data and machine learning, they generated bioactivity predictions for 15 compounds, including cannabichromenic acid (CBCA), cannabicyclolic acid (CBLA), and CBDA, among others. Disconnecting the bioactivity data removed predictive effects, indicating that their predictive approach could be used in validation assays. Future research should investigate the interactive effects of compounds on pharmacologic targets relevant to pain signaling, such as TRPV1, cyclooxygenase, and fatty acid amide hydrolase pathways. Dr. Stevens also discussed potential collaboration efforts to expand the Cannabis Compound Database and opportunities to research novel mouse models for noninvasive, continuous monitoring of pain using acoustics.

Biosynthesis and Biological Mechanisms of Minor Cannabinoids

Anna Love, Ph.D., University of California, San Diego

Dr. Love's laboratory sought to discover, characterize, and engineer biocatalysts for the construction of structurally diverse minor cannabinoids and analogs, and to investigate nonclassical and classical cannabinoid receptor interactions. Two *Streptomyces* marine bacterial flavoenzymes, Clz9 and Tcz9, reacted on phytocannabinoid precursors to generate CBC scaffolds, indicating potential for generating cannabinoid molecules and analogs fermentatively in bacteria. Future research should investigate 1) how minor cannabinoids, such as CBC and CBCA, fit into current understanding of lipid G protein-coupled receptor biology; 2) the interplay between phyto- and endocannabinoid pharmacology; and 3) the potential synergistic effects and the mediation of exposure to a mixture of phytocannabinoids.

Session 3: Advances in Clinical Studies on Cannabinoids and Pain

Dr. Belfer introduced Sekai Chideya-Chihota, M.D., M.P.H., program director in the Clinical Research Branch in the Division of Extramural Research of NCCIH, as the moderator of the third session.

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

Deborah Yurgelun-Todd, Ph.D., and Perry Renshaw, M.D., Ph.D., M.B.A., University of Utah

Dr. Yurgelun-Todd and Dr. Renshaw sought to examine the mechanisms by which a CBD-enriched extract impacts brain chemistry in chronic musculoskeletal pain intensity and quality. In a model of daily CBD-enriched extract administration across 5 days, anterior cingulate cortex glutamate levels decreased, and right insula glutamate levels significantly decreased. Lower insular glutamate levels were associated with lower pain sensitivity, and there was a positive association between glutamate and peripheral markers of inflammation. Future research should investigate individualized pain treatments, somatic versus affective components of pain, acute versus chronic responses of pain, and advanced magnetic resonance spectroscopy imaging techniques in the development of novel therapeutics for chronic pain.

Neuroimmune Mechanisms of Minor Cannabinoids in Inflammatory and Neuropathic Pain

Judith Hellman, M.D., and Mark Schumacher, M.D., Ph.D., University of California, San Francisco

Dr. Hellman's and Dr. Schumacher's laboratories sought to study whether minor cannabinoids, including CBD, CBN, CBG, and CBC, modulate inflammation and pain via neuro-immune mechanisms mediated by CB1R and TRPV1. Cannabinoids had diverse actions on multiple sites of action, including PNS neurons, CNS neurons, white blood cells, and endothelial cells. CBD acted indirectly on TRPV1 through transient receptor potential ankyrin 1 (TRPA1), indicating that TRPA1 may play a role in TRPV1 activation. They also observed differences between CBN and CBD; CBN affected larger diameter neurons and did not appear to impact CB1R or TRPV1. Minor cannabinoids affected the inflammatory activation of nonneural cells, including human and mouse leukocytes and human brain endothelial cells, and cannabinoids modulated acute inflammation through CNS-dependent mechanisms. Future research should investigate 1) how minor cannabinoids modulate pain biology through diverse actions on different cell types, and 2) the brain's role in modulating pain and inflammation with minor cannabinoids.

Subjective and Analgesic Effects of Terpenes, β-CP and Myrcene, Vaporized Alone and Combined With THC
Ziva Cooper, Ph.D., University of California, San Francisco

Dr. Cooper's laboratory sought to examine whether myrcene and β-CP dose-dependently decrease pain response with minimal psychoactivity and enhance THC analgesia while reducing adverse effects. Their ongoing Phase I, double-blind, randomized, placebo-controlled study in healthy people who used vaporized cannabis has completed 171 sessions with few minor adverse events related to terpene administration. Next steps include 1) identifying terpene and THC dose combinations that afford maximum pain relief and minimal abuse liability, 2) generating pharmacokinetic analyses, 3) determining ability of the dose combination to decrease opioid doses for pain relief (opioid-sparing effect), and 4) considering alternative modes of administration that have superior clinical utility compared to vaporizing.

Cannabinoid Interactions With Central and Peripheral Pain Mechanisms in Osteoarthritis of the Knee
Steven Harte, Ph.D., University of Michigan, and Richard Harris, Ph.D., University of California Irvine

Dr. Harte and Dr. Harris' laboratories sought to elucidate cannabinoid mechanisms of pain processing to inform the precision of analgesia approaches for chronic pain. In an ongoing double blind, placebo-controlled, randomized controlled trial, they aimed to 1) evaluate the central and peripheral mechanisms by which THC and CBD alone, and in combination, modify pain processing in painful knee OA, and 2) investigate associations between cannabinoid-induced changes in pain/physical function and mechanistic measures. Preliminary data (n = 54 participants) suggested that insula connectivity to the precuneus was amplified in participants with centralized pain or fibromyalgia-like symptoms, indicating that this subpopulation may respond better to a THC intervention, and that participants with low centralization or without fibromyalgia-like symptoms may respond better to CBD for an analgesic effect. Next steps include continuing recruitment and navigating study challenges, such as slow regulatory processes, participant ineligibility from placebo effects, and drug shortages.

Effect of Cannabidiol on Microglial Activation and Central Pain-Sensitization
Cinnamon Bidwell, Ph.D., University of Colorado Boulder

Dr. Bidwell's laboratory sought to use a prospective, naturalistic design to improve their understanding of the therapeutic effects and pharmacology of cannabis edibles for chronic pain in humans. In the 5-year study, they recruited 250 participants interested in using edible THC, CBD, or THC and CBD combined for chronic back pain. Their data indicated a stronger trend of pain relief over time in participants using THC edibles. Within 2 hours post use, higher THC doses provided stronger reductions in self-reported pain severity but a slight increase in negative mood. More drug effects, such as intoxication, were observed in participants who used THC alone and THC and CBD combined. CBD doses in the legally marketed CBD products used by participants did not modify effects. Next steps include analyzing additional data from the study.

Effect of Cannabidiol on Microglial Activation and Central Pain Sensitization
Rajiv Radhakrishnan, M.D., and Mohini Ranganathan, M.D., Yale School of Medicine

Dr. Radhakrishnan and Dr. Ranganathan sought to examine the effect of CBD on in vivo brain microglial activation and central pain sensitization in humans. Through PET imaging, preliminary results demonstrated in vivo evidence of increased brain microglial activation via [11C]PBR28, the binding ligand, following low-dose lipopolysaccharide compared to baseline. THC doses modulated the zone of hyperalgesia following intradermal capsaicin. Next steps include completing the study, and future research should seek to 1) validate findings in patients with chronic pain,

2) identify predictors of responses, and 3) understand the relationship between chronic pain and non-pain related factors, such as sleep, anxiety, stress, and expectancy response.

Sessions 2 and 3: Q&A

Dr. Chideya-Chihota thanked the second and third session presenters and introduced the question-and-answer session.

An observation was made about the preclinical and clinical comparators being used in studies, such as buprenorphine, morphine, and Δ9-THC in nonclinical studies, and fewer comparators in human studies. The speaker asked presenters to consider uniform or systematic ways to have standardized comparators so that cannabis constituents can be assessed for effectiveness and efficacy across pain models. Dr. Belfer acknowledged that this was a wonderful general question. She asked the presenters, especially AI and computational experts, to share opinions or preliminary thoughts on how to standardize in high-throughput ways.

Another speaker raised the issue of blinding. In human studies, participants can know whether they are receiving CBD or placebo because of side effects. In terms of standardization, he said blinding approaches should also be considered.

Another speaker said that, in terms of the drugs, research indicates many targets, noting that he had never seen a clinical drug that effects only one receptor. He discussed the relevance of bioavailability and biological affinity in creating formulations. He expressed how amazing it is to listen to all the studies in this meeting and urged that it is time to connect small molecules to both biological and behavioral effects. He wondered if an initiative could be put together to create a databank of predictive models that can be used to view small molecule effects to adverse effects. Dr. Belfer said that this was a great suggestion and discussed the new Data Management and Sharing Policy (DMSP) for NIH grants, which requires applicants to indicate the database they will use for storing data. She noted that the databases must be continuously accessible and standardized so that the data collection format may be used. She encouraged everyone to consider standardized, uniform, big data sets, especially for NIH-funded studies.

Another speaker commented on machine learning as applied to mouse behavior. While a fair amount of data using Von Frey filament testing was presented at the meeting, a so-called Black Box or noninvasive monitoring that uses machine learning exists and has indicated a divergence. For example, a signal may not be seen through Von Frey, but a reversal of hypersensitivity can be seen using advanced algorithms. As the field advances, some uniformity may be needed to bring together standards for the emerging techniques that have been presented. He also commented that CBC was described as being very unique in one of the studies. In his laboratory's study, CBC showed a discrete dose-response relationship, almost predicting a single site of action, which he also observed to be unique.

Dr. Chideya-Chihota asked Dr. Cooper to elaborate on why the study's vaporized product was not an ideal formulation for the study. From a clinical lens, Dr. Chideya-Chihota wondered how studies can be translated to human use. From her understanding, the majority of people who use cannabis still inhale products, though there is growing evidence that people use edibles. Why is a vaporized formulation undesirable when that is probably closer to how people use cannabis for recreation or pain management?

Dr. Cooper noted a recent publication on the number of older adults in Canada who require emergency treatment following use of edible cannabis products. As more people use cannabis products, she said there is risk with oral use in general. She said she is trained to think that inhaled cannabis, referring to potential toxins that are inhaled when cannabis is combusted, can lead to adverse effects like bronchitis. Regarding pharmacokinetic and pharmacodynamic effects, she said it is known that inhaled Δ9-THC may provide brief but unsustained pain relief with higher rates of intoxication and abuse liability. However, oral Δ9-THC provides analgesic effects for longer periods of time with lowered rates of intoxication and abuse liability. She acknowledged that these are good questions and that NCCIH can reach answers through the funding it is providing.

Dr. Chideya-Chihota asked a follow-up question about why Dr. Cooper chose the vaporized formulation for her study. Dr. Cooper described how she develops grant-funded study ideas based on what is available and feasible. Inhaled terpenes were available and feasible, from an FDA perspective, at that point in time. The study recruited people who were already using inhaled cannabis, so the study did not introduce additional risk to participants. Dr. Chideya-Chihota thanked Dr. Cooper and welcomed one more question.

Another speaker commented that concentration mediates dose and effect, and concentration depends on the formulation being used. He encouraged researchers to explore pharmacokinetics to determine, from a drug's concentration, whether a drug works, and analyze for whom the drug works. He referred to some of the preclinical and human studies he has conducted on hops and described what he has learned about absorption and metabolism from measuring plasma levels.

Dr. Chideya-Chihota thanked everyone and directed attention back to Dr. Belfer.

Discussion on Future Directions in Nonclinical and Clinical Research of Cannabinoids

Dr. Belfer introduced the discussion on future direction priorities, displaying presentation slides that synthesized next steps and challenges as indicated by presenters. She welcomed listeners to share opinions, suggestions, comments, and ideas on new studies, potential for translation from nonclinical to clinical studies, new mechanisms, and resources for basic and pharmacologic studies. Dr. Chideya-Chihota co-moderated the discussion.

A speaker discussed how stroke researchers are standardizing their assays through methods trainings. For example, the sex of investigators is standardized in studies that involve experimental animals, given potential for sex-based impacts on the animals, and the same CBD formulations are used to eliminate variability. She said that standardization introduces both benefits and potential restrictions to novelty and innovation. If researchers agree to keep methods unstandardized, she wondered if the formulations of controlled compounds could be standardized or better characterized.

Another speaker shared that he has spent 20 years working for drug companies and about 10 years in academia, and he expressed feeling struck by the heterogeneity of imaging, which he stated is his area of expertise. He was impressed by how many more investigators are working toward having a compound for clinical use. He said predrug compounds require researchers to ask different questions than compounds that will never become drugs. He noted that drug companies are more likely to invest in compounds that are likely to affect disease or

treatment response. Given the wide range of research interests and goals, he asked how NCCIH considers the funding applications it receives.

Dr. Belfer clarified the steps through which applications are evaluated before NCCIH reviews them. First, applications are reviewed by field colleagues for the study's novelty, mechanisms, plan, and feasibility. She encouraged prospective applicants to check the NIH RePORTER portal for previously funded study areas. Next, NCCIH reviews applications for their alignment with NIH and NCCIH organizational priorities. She noted how this meeting helps to highlight potential research gaps and opportunities for collaboration.

Another speaker discussed harnessing machine learning for compound development and discovery, target discovery, and behavior. As a trained behaviorist, he said there is a preclinical bottleneck effect and discussed his considerations for testing known and new cannabinoid compounds with efficacy in mouse models. He highlighted a colleague's method of using zebrafish and associated benefits. He emphasized that, as the field considers high-throughput measurement in assays, it is important to remember behavioral considerations as well.

Another speaker referred to the previous discussion on vaporized versus oral administration of cannabinoids, asking how much we know about the metabolism of inhaled and oral cannabinoids. She wondered about the potential metabolic differences that may exist. Dr. Chideya-Chihota agreed that this topic area is worth exploring in depth, given known use preferences in the United States.

Another speaker mentioned a study that found that phytol was toxic, which relates to cannabinoid inhalation, and that vitamin E acetate has been reported to have associations with acute lung infections. He expressed support for his colleague's inhalation study methodology and offered caution about adulterated formulations, whether they are used orally or through inhalation. He asked whether there is organizational interest in funding studies on the toxicology and safety of cannabinoids in the context of translational (nonclinical to clinical) use and/or chronic dosing.

Dr. Belfer said this was a great question. She clarified that NCCIH allows a component for adverse effects and toxicity in the context of studying therapeutic potential for cannabinoids. She noted that NIDA is particularly interested in clarifying potential toxicity and adverse effects. If a study is about therapeutic and analgesic potential, it would align better with NCCIH; if the study's main focus is on toxicity, it may potentially align better with NIDA.

Another speaker discussed some limitations and merits of computational predictions in cannabinoid research. He likened computational predictions to hypotheses, noting that these are essentially useless without real-life testing. He said computational predictions can be an incredible resource for prioritizing compounds and combinations to test, and it would be helpful to have a database that combines both computational and experimental data. He discussed how recently developed tools have enabled the screening of billions of compounds each day through machine learning.

Another speaker referred to the new DMSP that Dr. Belfer had mentioned. He discussed the challenge of reaching agreement on where data should be saved. He said that there are existing, general repositories that the researchers could use if an agreement on a general repository is reached. He said that NIH created the DMSP with the hope that this would help congregate data.

Dr. Belfer noted that later there would be a special presentation from her colleague, Patrick Still, Ph.D., program director in the Basic and Mechanistic Research Branch at NCCIH, about the NCCIH Resource Center initiative.

Another speaker said he also feels a push and pull about standardizing methods, noting the difficulty of trying to agree on methodology while technology, such as machine learning, is simultaneously changing. He said that researchers should keep this in mind, especially when reviewing one another's work. He felt unsure of how behavioral assays would change over time.

Dr. Chideya-Chihota noted that she had not heard anyone discuss a topical mode of administration which, from a clinical standpoint and given study considerations for OA, neuropathic pain, and diabetic neuropathy, made her feel curious as to why. She asked if anyone had thoughts about studying topically administered cannabis products.

A speaker said his laboratory has given topical administration a lot of thought and noted that two of his colleagues listening on Zoom have studied topical administration for OA and fracture healing in rodents. He agreed that this is a remarkably rich area to explore. He shared his experience with a human study in which it was unknown how much of the topical intervention would get into the participants' circulation and whether participants might fail a drug test if they use it on their knees. He said he received support from his institutional review board (IRB), while the FDA requested an investigational new drug (IND) application. The speaker said that descheduling or rescheduling should help researchers immensely with this area of research, and he expressed belief that the lipophilicity of cannabinoid molecules will make them marvelous for use in the topical form.

The same speaker raised the topic of pharmacogenomics in cannabinoids research. He discussed how, in the last decade or two, the concentration of THC in the cannabis plant has reached its upper limit of 30 to 35 percent by weight. He discussed some of the side effects his laboratory has been observing, such as psychosis and cannabinoid-induced hyperemesis syndrome. He pointed out that these drugs are metabolized by CYP2C9, CYP2C19, and CYP3A4; for the latter, there are 26 star alleles that compromise the activity. He said some people are ultra-metabolizers, extensive metabolizers, intermediary metabolizers, and non-metabolizers, but researchers cannot predict these yet. He asked others to consider: 1) What are the genotypes of our participants? 2) How does genotype influence how participants will respond to cannabis? 3) Will participants have side effects? and 4) Does it work for the participant? The speaker noted that ultra-metabolizers may experience fewer benefits, while non-metabolizers may experience more side effects.

Dr. Belfer noted that this is another point that goes with the list of challenges and potential complexities for clinical trials. She agreed that thinking about therapeutic biomarkers and how we can predict who will respond faster and better to interventions through individualized approaches would be essential steps in clinical trials.

Another speaker expressed curiosity about the translational question. She said that many of the presenters' nonclinical studies seemed to use synthetic cannabinoids, but this is not what her laboratory's participants buy from their dispensaries. She asked whether we have good evidence that synthetics work in the exact same way, biologically, as natural products do in terms of pharmacodynamics. How do we know what doses to use in human participants? Do nonclinical studies elucidate clinical doses?

Another speaker added that she wishes a database existed with pharmacokinetic data from mouse, rat, and human studies comparing doses, methods of administration, and effects. She referred to her CBD dose preferences in mice, but she agrees that it is a challenge to translate this information to humans. She noted that bigger differences may follow from formulation types, concentrations, and routes of administration rather than the use of synthetic versus natural interventions.

Another speaker discussed experiences of working with pain in humans, including athletes, veterans, and Native American/Indigenous populations. She noted the importance of culture for assessing pain, pain tolerance, and goals, and she said this needs standardization, too. She agreed with previous comments and emphasized the importance of bringing an awareness of the lifetime of experiences.

Marsha Lopez, Ph.D., chief of the Epidemiology Research Branch at NIDA, introduced herself and discussed a new project called the Cannabis Health Research Initiative, which seeks to gather, centralize, and disseminate patient-centered information. She noted that this may be of interest to clinical researchers and encouraged listeners to contact her for help with finding more information. Her email is Marsha.Lopez@nih.com.

Dr. Belfer thanked everyone and commented that it has been a phenomenal meeting so far with wonderful data and ideas. She encouraged listeners to discuss potential collaborations for NIH applications.

Keynote Presentation

Dr. Shurtleff introduced Daniele Piomelli, Ph.D., distinguished professor of anatomy and neurobiology in the University of California, Irvine (UCI) School of Medicine, and director of the UCI Center for the Study of Cannabis.

Safety and Efficacy of Cannabis-Based Products

Daniele Piomelli, Ph.D., University of California, Irvine School of Medicine

Dr. Piomelli said that the purpose of his presentation was to 1) discuss methodological issues in cannabis research, including bias, causality, and confounders, and 2) present two example case studies, including a study on cannabis and psychosis and another on cannabis as an analgesic.

Dr. Piomelli acknowledged that the debate on cannabis is dichotomous and polarized. While some consider cannabis to be one of the most toxic substances on the planet, others consider it to be a cure-all and a panacea for all ailments. Meanwhile, scientists are in the middle, "between a rock and a hard place," and unknowingly influenced by the dichotomy. This deeply rooted dichotomy is unique to cannabis, unlike with plants that can be made into morphine, cocaine, and scopolamine. Historically, cannabis was approved as a medication in the United States in 1850, but it was delegalized with the Marihuana Tax Act of 1937.

Dr. Piomelli said there are hidden consequences to this dichotomy, including bias. As an example, he referenced a Meier et al. (2012) paper, "Persistent Cannabis Users Show Neuropsychological Decline from Childhood to Midlife," which concluded that cannabis decreased participants' intelligence quotient (IQ), and a Rogeberg (2013) paper, "Correlations Between Cannabis Use and IQ Change in the Dunedin Cohort Are Consistent With Confounding From Socioeconomic Status," which concluded that cannabis use and IQ were confounded by participants' socioeconomic status. Dr. Piomelli emphasized that there is biased attention towards the Meier et al.

paper, which had been cited 1,996 times at the time of his presentation, while the Rogeberg paper had only been cited 132 times, despite the similarity of study topics and publication dates.

Dr. Piomelli discussed strategies for addressing bias in cannabis research through: 1) self-awareness through acknowledging bias, reflecting on your experiences, and seeking feedback; 2) learning about different types of bias, such as "white hat" bias and anchor bias; 3) mindful decision making through pausing, reflecting, and considering alternatives; 4) interacting with other groups, with better communication among advocates, physicians, and scientists; and 5) cultivating an open mindset by not ignoring published studies that challenge your ideas.

Dr. Piomelli further noted that the Meier et al. paper title implies causality, while the Rogeberg paper's title starts with the word "correlations." He emphasized that correlation is not causation. From Galileo Galilei's (1612) *Discourse on Floating Bodies,* Dr. Piomelli quoted, "Cause is that which is placed, the effect follows; and removed, the effect is removed." In philosophy, this is called an "interventionist approach," which is more difficult to apply in disciplines that rely primarily on observation. He emphasized the importance of observation in cannabis research.

Dr. Piomelli discussed strategies for addressing causality in cannabis research, including: 1) discordant sibling/twin study design, by which researchers can compare outcomes when homozygotic twins are discordant in their cannabis use; 2) Mendelian randomization, by which researchers can exploit genetic variants associated with cannabis use as a variable to test the causal effect of cannabis on an outcome; 3) quasi interventions, by which researchers can study how an external event or intervention affects cannabis use in one population but not another; and 4) experimental studies, including controlled studies with subjects randomized to the administration of a defined quantity and type of cannabis or cannabinoid.

Dr. Piomelli discussed how cannabis product diversity, with differences in mode of use, excipients, and potency, is a confounder. He compared cannabis product diversity with potato chip product diversity, and he emphasized how the existence of THC has led to today's meeting. He discussed a Watts et al. (2021) paper from the Netherlands titled, "Cannabis Labelling Is Associated With Genetic Variation in Terpene Synthase Genes," the results of which indicated that cannabis plant strains, sold as *C. indica* or *sativa*, are genetically and chemically the same. This study would not have been possible in the United States due to restrictions.

Dr. Piomelli discussed strategies for addressing cannabis diversity in research. He said: Ignore marketing ploys; the terms *indica, sativa,* and "entourage effect" have been hijacked by the industry for marketing and sales purposes. Don't ignore the "feel"; organoleptic properties (aroma) have functional consequences (e.g., placebo effect, study blinding issues). Pay attention to potency, given that THC drives the pharmacology of cannabis, and its concentrations matter; route of administration, since mode of use can affect THC concentration, bioavailability, and actions; and excipients, which can affect bioavailability, interact functionally with THC, or have effects of their own.

Dr. Piomelli addressed the question of whether cannabis can cause psychosis. He refined the question into two related questions: 1) Can cannabis cause acute psychotic symptoms? 2) Can persistent cannabis use cause schizophrenia and/or other psychotic disorders? Dr. Piomelli acknowledged that while cannabis can produce perceptual disturbances (e.g., visual illusions), "cannabis-induced psychosis" relies on distinguishing that

hallucinations occur in the absence of intact reality testing, according to the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5).

Dr. Piomelli discussed a study by Andréasson et al. (1987) titled, "Cannabis and Schizophrenia: A Longitudinal Study of Swedish Conscripts," which famously indicated that using cannabis during adolescence was associated with a sixfold increase in the risk of developing psychosis in adulthood. Dr. Piomelli contextualized how, at the time, society was hearing that the use of cannabis makes people go crazy. As an example, he referred to a news headline, "Evil Mexican Plants That Drive You Insane," which stated, "Not long ago, a Mexican of the lower class […] who had smoked a marijuana cigarette, became insane and killed a policeman and badly wounded three others." Dr. Piomelli emphasized that these problematic ideas pervade in media today.

Dr. Piomelli reviewed conclusions from "The Health Effects of Cannabis and Cannabinoids" by the National Academies of Sciences, Engineering, and Medicine (NASEM, 2017), which stated, "There is substantial evidence of a statistical association between cannabis use and the development of schizophrenia or other psychoses, with the highest risk among the most frequent users." He emphasized the text's careful use of "substantial" rather than "conclusive," noting that the text also concludes, "There is moderate evidence that, among individuals with psychotic disorders, there is a statistical association between a history of cannabis use and better cognitive performance." Dr. Piomelli said this suggests inverse causality.

Dr. Piomelli also discussed a longitudinal study by Schaefer et al. (2021) titled, "Associations Between Adolescent Cannabis Use and Young-Adult Functioning in Three Longitudinal Twin Studies," which suggested that cannabis use is causative for negative socioeconomic outcomes (i.e., educational attainment, occupational status, and income), but not for IQ or schizophrenia. He said this paper had only been cited 38 times at the time of his presentation.

To address the causal nature of the link between cannabis and schizophrenia, Dr. Piomelli suggested Mendelian randomization and quasi-intervention studies on large human cohorts. Human or animal experimental studies are unlikely to be useful due to the complexity of schizophrenia.

Dr. Piomelli then addressed the question of whether cannabis is a safe and effective analgesic. He discussed a paper by Abrams et al. (2007) titled, "Cannabis in Painful HIV-Associated Sensory Neuropathy: A Randomized Placebo-Controlled Trial," which indicated that a small number of patients with HIV who smoked low levels of cannabis experienced less pain during the treatment period. Abrams et al. (2007) based their study on the "Commentary on the Pharmacopoeias of Great Britain and the United States, 1848" by Robert Christison, which stated that a cannabis intervention had a "cessation of pain" effect, as well as side effects such as "a pleasant numbness in the limbs, giddiness, a rapid succession of unassociated ideas and impossibility to follow a train of thoughts, frequent intervals of sleep, and slight increase in the force of the pulse." Dr. Piomelli quoted NASEM (2017), which concluded, "There is substantial evidence that cannabis is an effective treatment for chronic pain in adults." Nonclinical scientists convened and arrived at the same conclusion in Finn et al. (2021), "Cannabinoids, the Endocannabinoid System, and Pain: A Review of Preclinical Studies."

Dr. Piomelli mentioned a paper by Cooper and Haney (2016), "Sex-Dependent Effects of Cannabis-Induced Analgesia," which sought to address causation. The paper concluded that in both men and women, THC produced

an analgesic effect on pain sensitivity (i.e., latency to report pain) and pain tolerance (i.e., latency to withdraw hand from cold pressure). Both human and animal data support the notion that cannabis causes analgesia.

Dr. Piomelli then addressed the questions: 1) How do we address the causal nature of the link between cannabis and analgesia? and 2) Is cannabis both safe and effective as an analgesic? Researchers can determine answers by developing appropriately powered, placebo-controlled, randomized controlled trials of chronic pain in adults, and animal studies and human trials can aid in the selection of one or more suitable chronic pain condition(s).

Dr. Piomelli encouraged listeners to download the NASEM (2017) report for further reading.

Keynote Presentation: Q&A

Dr. Edwards welcomed questions for Dr. Piomelli. The question-and-answer session was moderated by Dr. Edwards and Dr. Shurtleff.

A speaker expressed that he loved Dr. Piomelli's comment to not let marketers influence one's terminology. He offered that his pet peeve is the term "nutraceutical," saying he hates this term despite its wide use. Dr. Piomelli agreed, commenting that all we can do is make suggestions.

Dr. Shurtleff asked if Dr. Piomelli can apply what he is saying about cannabis to other drugs. Are we trying to get at risk/benefit for any pharmaceutical at this point? Dr. Shurtleff said the brain does not know if a drug is illicit or not; and, referring to the opioid crisis, he said that opioids provide an analgesic effect, as well as respiratory depression, high risk for overdose and death, and abuse potential. Dr. Piomelli responded that we can, and should, look at drugs as cultural phenomena. Though it is complex, every drug has to be treated differently, and opioids are an excellent example. He said we have shaped our view of analgesics based on opioids; when we look for a new analgesic, we look for something that does what opioids do. However, opioids are very peculiar in the way they produce analgesia, and they are also highly addictive and can kill people. He said it is always good to have conversations about and consider the cultural significance of drugs (e.g., Prozac), even as scientists.

Another speaker commented that many people take drugs for recreation, maybe as self-medication to maintain their way of living. The speaker asked Dr. Piomelli: do you think there is a reason to study cannabis use in healthy individuals and the impact on their health in general, rather than just looking at how to mitigate some diseases? Dr. Piomelli said this was an excellent question that raises more questions, such as: What is health? How healthy is a healthy individual? For example, there has recently been an increase in cannabis use among people aged 55+ years. Why? According to surveys, Dr. Piomelli said, people in this demographic use cannabis to alleviate pain and/or to facilitate sleep. He said health, our perception of health, and our actual health change over time, and recreational substances, including cannabis, alcohol, and coffee, are used in this context.

Another speaker commented that, as a pharmacologist, he recognizes that it is important to consider the concentration of cannabis. He said when the FDA approves a drug, a dose-response curve must be shown, but cannabis researchers do not do or consider this. Dr. Piomelli agreed this is a challenging problem. He referred to the research team that is helping the California Department of Public Health deal with the problem of high-potency cannabinoids and cannabis products, noting that it is difficult to define "high potency." If a plant contains 26 percent of THC, how much of that 26 percent will go into the person? What is the real dose? He said he has not

seen data showing whether titration occurs, though he believes there is a study in Colorado working to elucidate this. Dr. Piomelli suggested a step approach: establish how much THC people actually use, and then policy decisions can be made.

Another speaker pointed out that Dr. Piomelli began his presentation by stating that we are here because of THC. She noted how, for the first half of the meeting, the discussion focused on cannabis constituents that are not THC. She asked Dr. Piomelli what he thinks will happen in the next 10 years. Will the conversation related to medical cannabis and cannabis constituents shift from THC to other constituents? Or do you think this is really about THC?

Dr. Piomelli said, depending on the population using cannabis, he estimated that 97 percent of use cases are about THC. Compared to anxiolytic effects of CBD, THC provides feelings of euphoria, relaxation, changes in senses, and increased sensorial experiences, which feel good to users, like how a glass of wine feels good. Thanks to research, we have learned that there is a cannabinoid system in the brain, and cannabis is a fantastic "chemical factory" plant. It is a lucky discovery that cannabis has potential to be used to create new medications, regardless of the other purposes for which people use it, which he considered happenstance.

Dr. Piomelli thanked everyone for their time. Dr. Belfer thanked Dr. Piomelli for his presentation and Dr. Edwards and Dr. Shurtleff for co-moderating.

Session 4: New Initiatives and Resources for Cannabis Research

Dr. Belfer introduced the fourth session and its moderator, D. Craig Hopp, Ph.D., deputy director of the Division of Extramural Research at NCCIH.

NCCIH-Led Resource Center for Cannabis and Cannabinoid Research (RFA-AT-24-006)
Patrick Still, Ph.D., NCCIH Basic and Mechanistic Research Branch

Dr. Still briefly discussed NCCIH's background for developing the Resource Center for Cannabis and Cannabinoid Research (RFA-AT-24-006) in partnership with NIDA, NIA, and NCI. The purpose of the Resource Center is to address barriers to cannabis research (e.g., Schedule I status, challenges in maintaining licensing), which exist despite the widespread availability of cannabis products and its established pharmaceutical potential. He discussed the initiative's three core components: 1) regulatory guidance, which aims to link to existing or updated DEA/FDA guidance; 2) research standards, which aims to provide standards for cannabis products appropriate for research; and 3) the research support core, which will provide seed funding for regulatory support and research application development. Dr. Still said there are numerous seed funding activities that are within scope for the participating NIH Institutes and Centers, for seed funds dispersed by the Resource Center, to which applicants can respond within the RFA.

NIH-Wide Collaborations and Resources
Angela Arensdorf, Ph.D., NCCIH Office of Policy, Planning, and Evaluation

Dr. Arensdorf began by also recommending the NASEM (2017) paper, "Health Effects of Cannabis and Cannabinoids," for further reading. She shared a line graph on NIH's yearly funding totals for cannabis/cannabinoid-related research from 2018 to 2022, noting increasing trends for both therapeutic and nontherapeutic research areas.

Dr. Arensdorf discussed the Therapeutic Cannabinoid Research Working Group (t-CReW), which was established with the goal of collaborating to expand the cannabis/cannabinoid research community. tCReW activities include 1) strategizing how to work within current regulatory guidelines to increase cannabis/cannabinoid research; 2) discussing and collaborating on Institute- and Center-specific funding initiatives; 3) sharing cannabis/cannabinoid-related information, workshops, and conferences; and 4) developing and strengthening interest in cannabis/cannabinoid research across NIH Institutes and Centers.

Dr. Arensdorf discussed current results from collaborative efforts, including increased communication across agencies. She displayed the NIH-Supported Research on Cannabis, Cannabinoids, and Related Compounds webpage and pointed out links to specific research interests, funding opportunities, NIH contacts, and resources.

Role of the NIDA Drug Supply Program in Providing Cannabis Products for Research
Mary MacDonald, Ph.D., NIDA Chemistry and Pharmaceutics Branch

Dr. MacDonald introduced the NIDA Drug Supply Program (NDSP), which provides drugs, research chemicals, and cannabis to researchers free of charge. The NDSP inventory comprises items that are DEA controlled, commercially unavailable, uncommon, and/or expensive for researchers on budgets. The program is administered through a series of contracts. The program's primary activity involves reviewing requests to the drug supply program and communicating with researchers to understand their needs. Other activities include maintaining the inventory, monitoring the literature and reports from the DEA/forensics to find out about new compounds that could be of use to researchers, analytical services, method development, and more. She noted various drugs and chemical classes, including cannabinoids, in the NDSP inventory.

Dr. MacDonald discussed NDSP's process for obtaining cannabis through the University of Mississippi. The DEA has approved additional cannabis suppliers for researchers, and her presentation slide displayed the logos of Groff North America, Biopharmaceutical Research Company, Scottsdale Research Institute, Royal Emerald Pharmaceuticals, Bright Green Corporation, Maridose, and Irvine Labs Incorporated. She emphasized that researchers who have been supported by Federal funds must obtain their cannabis through a federally approved supplier.

Dr. MacDonald discussed the 2023 cannabis contract and products, including cannabinoids Δ9-THC, Δ8-THC, THC-A, CBD, CBG, CBN, and CBC for human use, and placebo plant materials for human use. All products have certificates of analysis showing that the products meet FDA specifications and details on growing conditions. She encouraged listeners to contact the NDSP inbox at NDSP@rti.org for inquiries and information on how to submit a request.

Biopharmaceutical Research Company Supplier Update on Cannabis Products for Research
Hunter Land, Ph.D., Biopharmaceutical Research Company

Dr. Land, vice president of research and development at Biopharmaceutical Research Company (BRC), introduced BRC as a federally legal pharmaceutical cannabinoid development company that seeks to address unmet medical needs using cannabinoid therapeutics safely and effectively. He displayed BRC's list of six DEA active licenses and noted BRC's ability to manufacture under good manufacturing practices and under Federal compliance. He said

BRC has systems for correct management and spoke to the reputability of the BRC team, board of directors, and advisors.

Session 4: Q&A

Dr. Hopp welcomed listeners to participate in the question-and-answer session. To introduce the session, he asked Dr. Land to elaborate on the types of cannabis materials provided by the company to researchers. Dr. Land clarified the company's production process and material types.

A speaker asked how the rescheduling of cannabis would potentially affect NIH's U24 Resource-Related Research Projects Cooperative Agreements and NIDA's drug supply. Dr. Hopp responded that the answer is currently unclear, noting that the regulatory environment has not yet changed, and only a proposed change exists, which will take at least one year to enact. Dr. Hopp said he suspected that NIDA is discussing potential effects from regulatory changes.

Another speaker pointed out that the Notice of Proposed Rulemaking has been published with a 60-day open period for comments. He encouraged researchers to submit a comment to inform the Department of Justice about how the notice affects their research on cannabis, such as through study registration and access to dispensary products. Dr. Hopp supported the speaker's point and further noted that the language of the rescheduling rule will affect whether researchers can use products from local dispensaries for federally funded studies.

Another speaker asked how NCCIH envisions that the Resource Center will provide support to researchers. At these types of meetings in the future, will there be Resource Center representatives who can answer questions and provide guidance (e.g., submitting INDs, where to procure products) to researchers? Dr. Hopp confirmed that the Resource Center was created in response to researchers' stated needs. Although the Resource Center will not be testing products or submitting INDs on researchers' behalf, the vision is to provide detailed guidance in support of researchers.

The same speaker followed up by asking whether the Resource Center has the infrastructure to work with related agencies. Dr. Hopp clarified that the Resource Center has a cooperative agreement between NCCIH and partners, including NCI, NIA, and NIDA. The Center will have a steering committee and open lines of communication with agencies like the FDA and the DEA to support the consistency of guidance. The Center will also aim to address barriers among researchers who are new to studying cannabis/cannabinoids.

With no additional questions from listeners, Dr. Hopp thanked everyone for participating. Dr. Belfer thanked all speakers, with special thanks to non-NIH and non-principal investigator (PI) speakers.

Session 5: New and Existing Legislation, Policies, and Regulatory Oversight for Cannabinoids

Dr. Belfer introduced Wendy Weber, N.D., Ph.D., M.P.H., branch chief for the Clinical Research in Complementary and Integrative Health Branch in the Division of Extramural Research at NCCIH, who moderated the fifth session.

Impact of Cannabis Policy on NIH-Funded Research

Jennifer A. Hobin, Ph.D., NIDA Office of Science Policy and Communications

Dr. Hobin provided a broad overview of the policy landscape, its impact on NIDA-funded researchers, and resources available to help researchers navigate the complex regulatory environment. From a regulatory and scientific perspective, she discussed the complexities of the cannabis plant, cannabinoids, and constituents with possible medical benefits and harms, alone or in combination. Data from the NIDA-supported Monitoring the Future study found in 2023 that 11 percent of 12th grade students in the United States had used Δ8-THC in the past year. She emphasized the importance of research on how people are using cannabis and its impact on public health.

Dr. Hobin discussed Federal policy for cannabis according to the Controlled Substances Act and the Agriculture Improvement Act of 2018. As of March 2024, 38 states and the District of Columbia had passed various medical cannabis laws, and 24 states and the District of Columbia had various adult use laws. She discussed regulatory challenges for research on cannabis, noting that cannabis with more than 0.3 percent Δ9-THC dry weight content has Schedule I status. She acknowledged additional challenges to researchers related to study registration, expense, regional and organizational requirements, and confusion over the regulatory status of cannabis products. She noted that hemp-derived Δ8-THC is not controlled, while non-hemp-derived Δ8-THC is controlled. She noted additional challenges, including cannabis product purchasing and handling and NIDA-supplied research-grade cannabis.

The Medical Marijuana and Cannabidiol Research Expansion Act, passed by Congress in 2023, aimed to expand research on cannabis and cannabis products. Dr. Hobin noted that it would not address researcher access to state authorized dispensary products. She referred to NIDA's Frequently Asked Questions about Conducting Research with Cannabis and Hemp webpage and encouraged listeners to contact regulatory agencies with regulatory questions. NIDA, the Centers for Disease Control and Prevention, and NCI are sponsoring a NASEM study on the Public Health Consequences of Changes in the Cannabis Policy Landscape; the report of this study is expected to publish by the end of 2024.

Current Practices in Reviewing Investigational New Drug Applications Involving Cannabis and Hemp Products

Chad Reissig, Ph.D., FDA Center for Drug Evaluation and Research

Dr. Reissig started with the disclaimer that the presentation does not represent the FDA's view, policies, or endorsements of/for the products he mentions. He discussed the FDA's product regulation responsibilities, including those for prescription and nonprescription drugs, and the FDA's process for the research and development of cannabis and cannabis-derived products, which includes the submission of an IND application. He shared the following relevant guidance resources: "Cannabis and Cannabis-Derived Compounds: Quality Considerations for Clinical Research," published in 2023, and "Botanical Drug Development Guidance for Industry," published in 2016.

Dr. Reissig reviewed three basic types of IND applications: 1) Investigator, 2) Emergency Use, and 3) Treatment. He noted that the two categories for IND applications are commercial INDs, by which the sponsor intends to seek marketing approval for the unapproved drug, and research INDs, by which a sponsor intends to not seek marketing approval for the unapproved drug.

Dr. Reissig discussed FDA requirements for IND applications, including 1) pharmacology and toxicology studies, or data to permit an assessment on whether the product is reasonably safe for initial testing in humans; 2) manufacturing information; and 3) clinical protocols and investigator information. Following an IND submission, by Day 30, the FDA will determine whether a study may proceed or requires placement of a clinical hold; if a study using Schedule I cannabis material is authorized to proceed, the investigators may proceed with DEA protocol registration.

Dr. Reissig discussed sources for cannabis research and product formulation, noting that cannabis and cannabis-derived compounds are held to the same regulatory standards as any other botanical raw material, botanical drug substance, or botanical drug product. He emphasized that sponsors must meet all FDA requirements to conduct human clinical trials, regardless of the source of cannabis under study. Sources for cannabis include the NIDA Drug Supply Program, grown under contract by the University of Mississippi at the National Center for Natural Products Research, and some new DEA registrants.

Dr. Reissig further discussed botanical drug development by referencing chemistry, manufacturing, and controls (CMC) and current good manufacturing practices (CGMP) regulations for human pharmaceuticals. He concluded by summarizing previous points and referencing additional resources provided in subsequent presentation slides.

Dr. Weber explained that the final presentation on the DEA and Approval Processes was cancelled at the last minute due to unforeseen circumstances. Dr. William Heuett, chief of the Schedule I research and international control unit at the Drug and Chemical Evaluation section, has provided contact information at DPEScheduleIResearch@dea.gov for anyone interested in conducting research with Schedule I controlled substances and associated guidance. Dr. Weber introduced the next question-and-answer session.

Session 5: Q&A

Dr. Weber introduced the session by asking whether there is a good place for researchers to find information on public use of cannabis compounds. Dr. Hobin discussed the annual NIDA-supported Monitoring the Future surveys on drug use, attitudes, and perceptions in youth, and the Substance Abuse and Mental Health Services Administration's (SAMHSA) National Survey on Drug Use and Health. Another speaker discussed how a Δ8-THC measure was added by the University of Michigan Institute for Social Research, noting that the investigators are open to discussing other measures to add.

A speaker asked if it is possible to formally request an IND waiver from the FDA. Dr. Reissig confirmed that FDA IND exemptions are possible but rare, mentioning the FDA's drug use and classification considerations.

Another speaker asked about the type of preclinical toxicology data, existing or needed, that meets minimum FDA standards for exploratory pilot cannabinoid studies. Dr. Reissig said that the FDA's toxicology team may have a better answer but noted International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines. He emphasized the importance of demonstrating that the proposed intervention will not expose subjects to risk or harm, such as through existing literature, for the FDA to review and make case-by-case decisions.

Dr. Weber asked whether researchers could cite references that might use cannabis as a whole but specify the amount of an individual constituent and then propose an intervention within that dose range for the FDA to review. Dr. Reissig noted the challenge of isolating compounds from whole plants while eliminating effects, such as a protective, entourage effect. He mentioned running a study on kratom and having similar challenges. Dr. Weber added that when studying a single component, the compound will be taken in much higher doses than in other studies. Dr. Reissig discussed the FDA's preference for a standard, ascending dose study, noting the ability to see adverse effects in a dose-dependent manner for safety.

Another speaker noted legislative distinctions between naturally derived cannabinoids (e.g., THC or CBD extracted from a plant) versus synthetic cannabinoids (e.g., THC or CBD made in a laboratory). He asked: Is there anything we can do to convince members of Congress that these are the same molecules? Dr. Hobin agreed that clarity and education are needed to support policy making. She noted that there are opportunities for researchers and scientific societies to engage with Congress and weigh in on policy making.

Another speaker commented that, in the past year, she has successfully navigated the FDA IND process for a hemp-derived CBD product. She asked for insight and advice for researchers navigating the FDA for an experimental study using a THC product from the NIDA drug supply, in which the focus is not on a therapeutic indication, but on risk or abuse potential. Dr. Reissig reinforced that this study falls under FDA's purview because THC is a drug. There was a follow-up question: is there any option where an experimental study in the laboratory without focus on a therapeutic indication could get an FDA exemption, or would it be run through the whole IND process? Dr. Reissig said that the researcher's outcome measures probably would be a structure-function claim as it investigates people's liking of the drug, which means it is a clinical investigation and drug trial that requires an IND. There was another follow-up question: have there been THC-based studies that have met the criteria for exemption? Dr. Reissig said that an FDA-approved THC product would not require an IND in an indicated population.

Dr. Weber noted that the same process and questions apply to NCCIH-funded research on botanicals. NCCIH considers whether the product is being used to treat, mitigate, prevent, cure, or diagnose a disease. If a researcher is using the product for any of these reasons, whether for marketing or a new drug application (NDA), the published study can be used by someone else to make an indication. Many of these considerations apply to all botanicals and are not necessarily unique to cannabis, other than elements related to hemp-derived products.

Another speaker asked Dr. Reissig to describe how controlled substances staff, botanical staff, and review division staff coordinate during an IND review. Dr. Reissig said that once the FDA receives an IND, it is assigned a project manager and a primary review division, such as the divisions of psychiatry, anesthesia, analgesia and addiction products, or neurology. The division assembles a large internal team, including physicians, chemists, toxicologists, statisticians, and controlled substances staff. There is a meeting with 15 to 20 multidisciplinary reviewers who follow protocol to consider the IND and determine hold issues, which are generally related to safety. If the IND is placed on hold, the FDA drafts and sends a hold letter within 30 days. When the FDA receives a response to the hold, reviewers may reconvene. From a controlled substances perspective, marijuana, cannabis, and THC have well-characterized abuse liability. Controlled substances staff may refer applicants to the DEA for scheduling concerns. NDAs have a longer review process.

Dr. Weber asked whether the FDA's protocols are in a standardized template. Dr. Reissig clarified that the protocols come from many industries and look different, but as a clinical protocol, they generally have the information expected.

Dr. Weber then invited the presenters to share any additional advice for those wanting to do research in this area. Dr. Reissig encouraged researchers to Google the 1301.08 Code of Federal Regulations concerning Schedule I research protocols, noting that sections will contain bolded requirements. While INDs are generally reviewed by divisions, the Schedule I portion is quickly reviewed by controlled substances staff within 30 days. Dr. Hobin noted that the DEA can assist researchers navigating that [Schedule I] process.

Another speaker asked for general thoughts and opinions on the Ninth Circuit's decision on Δ8-THC. As a chemist and a pharmacologist, he noted that Δ8-THC is pharmacologically pretty equivalent to Δ9-THC, yet the Ninth Circuit decided that Δ8-THC is legal, while Δ9-THC is not. Dr. Reissig expressed personal agreement that a molecule is a molecule, and he would think that impurities are the focus during extraction processes. Dr. Reissig noted that he has never seen evidence that an extracted molecule performs differently than a synthetic molecule. Dr. Hobin noted that she is not a pharmacologist, so she would not comment.

Dr. Weber thanked all speakers and invited Dr. Belfer to announce the final session.

Session 6: Overview of NIH Support for Cannabis Research and Institute-Specific Priorities

Dr. Belfer thanked all speakers and Dr. Weber for moderating and invited her colleagues to participate in the brief overview of NIH interests in cannabis research. Dr. Belfer said that when an application is submitted to NIH, it will go to a specific Institute or Center based on the programmatic priorities and mission. NCCIH's interest is to encourage research on terpenes and minor cannabinoids in model organisms and/or human subjects as it relates to pain, nociception, and analgesia. She said that, among people who use complementary interventions, including natural products like cannabis, most of them use the interventions for pain relief. She then reviewed four high-priority areas: 1) mechanisms by which minor cannabinoids and terpenes may affect pain cellular and molecular signaling pathways, neuroimmune interactions, or other innovative regulatory pathways; 2) interaction between the microbiome and minor cannabinoids or terpenes; 3) how specific terpenes may influence potential analgesic mechanisms of understudied minor cannabinoids; and 4) multimodal approaches to analgesia that include minor cannabinoids and terpenes. Dr. Belfer noted that NCCIH's goal is to prompt interdisciplinary collaboration by experts from multiple fields, such as immunology, pharmacology, chemistry, pain, and neuroscience.

Dr. Belfer discussed the NOSI: Promoting Mechanistic Research on Therapeutic and Other Biological Properties of Minor Cannabinoids and Terpenes (NOT-AT-22-027), published by NCCIH together with nine Institutes, Centers, and Offices of NIH. They seek to support highly innovative basic and/or mechanistic studies in appropriate model organisms and/or human subjects aiming to investigate the impact of minor cannabinoids and terpenes on mechanisms underlying their therapeutic effects. The NOSI expires July 1, 2025. Dr. Belfer welcomed presenters for other Institute and Center perspectives.

Cannabinoids and the Eye: Biology and Therapy
Houmam Araj, Ph.D., National Eye Institute

In Dr. Araj's absence, Dr. Belfer summarized NEI's interest in investigating the treatment potential of cannabinoids for glaucoma, keratitis, uveitis, dry eye, and diabetic retinopathy.

National Institute of Mental Health (NIMH) Perspective on Cannabinoid Research
Steven Zalcman, M.D., NIMH Division of Translational Research

Dr. Zalcman discussed NIMH's preclinical and clinical research priorities. For preclinical research, NIMH is interested in supporting projects aimed at understanding how endogenous cannabinoids influence cellular and circuit-based mechanisms implicated in mental health-relevant behaviors and studies identifying and testing potential therapeutic targets acting on the endogenous cannabinoids system. He noted that preclinical research on marijuana and its constituent compounds would be low priority. For clinical research, NIMH's priority is in studying how pharmacologic manipulation of cannabinoids or cannabinoid receptors can influence CNS function in psychiatric disorders. Because of the target-based orientation of NIMH's clinical trials, Dr. Zalcman noted that access to the cannabinoid system should be performed using pharmacologic agents with good safety profiles, specificity, and selectivity to test them in early-stage pharmacokinetic and/or pharmacodynamic trials, using trial designs that incorporate a CNS pharmacodynamic measure associated with the pharmacologic target.

NOSI: Targeting the Endocannabinoid System for Brain Health and Acute and Chronic Diseases
Da-Ting Lin, Ph.D., NIDA Behavioral Neuroscience Research Branch

Dr. Lin discussed NIDA and NCCIH's shared interests in pain. He noted that the NIDA Behavioral Neuroscience Research Branch focuses more on brain and neural interactions. He discussed active (NOT-DA-22-048, NOT-DA-22-003) and not active (RFA-DA-22-028, NOT-DA-20-039) initiatives and encouraged listeners to view both for NIH's perspective on existing and recent research gaps. Dr. Lin said that the fact that an initiative has expired does not necessarily mean the science has been completed. He concluded by noting NIDA's close working relationship with NCCIH.

National Institute of Neurological Disorders and Stroke Interest in Cannabinoid Research
Michael Oshinsky, Ph.D., NINDS Office of Preclinical Pain Research

Dr. Oshinsky said that the NINDS interest in cannabinoid research is focused on the therapeutics and pathological conditions, including epilepsy, Alzheimer's disease, amyotrophic lateral sclerosis, pain and headache, Huntington's disease, and Parkinson's disease, that fall under the NINDS mission. NINDS's mission is to seek fundamental knowledge about the brain and nervous system and to use that knowledge to reduce the burden of neurological disease for all people. He commented that he watched the previous data blitz presentations with tremendous interest, as there is really great work happening. He noted that NINDS strongly supports the use of data transparency and rigor icons. He discussed NINDS divisions and clinical trial networks for neurological disorders. Dr. Oshinsky welcomed listeners to reach out with questions about NINDS funding opportunities or with ideas about projects aligning with the NINDS mission.

National Institute on Alcohol Abuse and Alcoholism Interests

Qi-Ying Liu, M.D., NIAAA Division of Neuroscience and Behavior

Dr. Liu discussed NIAAA's focus on exploring 1) the role of endocannabinoid systems in alcohol misuse and alcohol use disorder (AUD), including comorbidity and polysubstance use studies; 2) medication development for alcohol misuse and AUD targeting eCB pathways mediated by both CB1R and CB2R; 3) potential for CBD and other minor cannabinoids and terpenes for the treatment of AUD; and 4) brain mechanisms shared by AUD and other substance use disorders, including cannabis use disorders. Regarding comorbidity and polysubstance use studies, he provided examples such as cannabis use on alcohol craving and consumption, and prenatal cannabinoid and alcohol coexposure and fetal brain development. He also noted NIH's portfolio in this area is small with fewer than 10 active research grants.

The Trans-NCI Cannabis and Cancer Research Interest Group Interests

Andrew Freedman, Ph.D., Joe Ciccolo, Ph.D., NCI Clinical and Translational Epidemiology Branch

Dr. Freedman started by noting that a 2017 study at Washington State found that one in four cancer patients were using cannabis or cannabinoids during their treatment. He said the Cannabis and Cancer Research Interest Group's (CCRIG) goals are to 1) assess cancer patients' use of cannabis, identify benefits and harms, and examine tobacco co-use; 2) understand basic mechanisms of cannabis and cannabinoid action in cancer; 3) contribute evidence to clinicians and patients; and 4) provide information to design and conduct clinical trials. He discussed CCRIG activities, including its 2020 Cannabis, Cannabinoids, and Cancer Research Symposium and Journal of the National Cancer Institute (JNCI) Monographs publication. Dr. Freedman discussed funding 10 comprehensive cancer centers to do a cross-sectional survey of 1,000 cancer patients on their use of cannabis; results will be published across 14 articles in the JNCI. He noted that the results indicated that one in three cancer patients are using cannabis during their treatment. Dr. Freedman also discussed recent funding opportunities (NOT-CA-22-070, NOT-CA-22-085, RFA-CA-22-052) and five funded cannabis cancer cohorts.

National Institute on Aging: Cannabinoid Research Priority Areas

Alexis Bakos, Ph.D., M.P.H., R.N., NIA

In Dr. Bakos's absence, Dr. Belfer summarized NIA's interest in supporting research to study the processes underlying the potential contributions or adverse effects of minor cannabinoids and terpenes to relieve symptoms and improve quality of life in older adults experiencing pain, age-related cognitive decline, weight loss, cachexia, sarcopenia, insomnia, multimorbidity and polypharmacy, and palliative and end-of-life care. Dr. Belfer encouraged listeners to contact Dr. Bakos with questions at Alexis.Bakos@nih.gov.

National Institute of Dental and Craniofacial Research Interests

Lorena Baccaglini, D.D.S., Ph.D., NIDCR

Dr. Baccaglini discussed the distribution of TRP channels and/or cannabinoid receptors in the human oral mucosa, salivary glands, periodontal ligament, synovial tissue of the temporomandibular joint, and immune and central nervous system cells. She referenced NOSI: Promoting Mechanistic Research on Therapeutic and Other Biological Properties of Minor Cannabinoids and Terpenes (NOT-AT-22-027) and explained that NIDCR is interested in mechanistic, preclinical or clinical studies on the analgesic, immune-mediating, anti-inflammatory, apoptotic, or other potential therapeutic properties of minor cannabinoids and terpenes for dental, oral, and craniofacial diseases or conditions, and in the interaction with the oral microbiome. For a clinical intervention trial,

researchers can apply through UG3/UH3 and contact the FDA. Dr. Baccaglini encouraged listeners to contact her with any questions at Lorena.Baccaglini@nih.gov or her colleague Melissa Ghim, Ph.D., at Melissa.Ghim@nih.gov.

Session 6: Q&A

Dr. Belfer introduced the question-and-answer session, but there were no questions. Dr. Belfer welcomed researchers to find the right program officer for their applications. She thanked her colleagues, noting that supporting this research is only possible by doing it together. She invited Dr. Shurtleff for closing remarks.

Closing Remarks, Next Steps

Dr. Shurtleff noted that 5 years ago there was no cannabis research program at NCCIH, and now there is a burgeoning, growing, developing program with more to do. He acknowledged that researchers have laid the foundation for important future work, as cannabis is now thought of as a manufacturing machine for a variety of natural products including 120 minor cannabinoids, many terpenes, and other chemicals that the plant provides in a wealth of opportunity to develop. THC research has enabled this progress, and now other compounds can be studied for potential therapeutic benefits. He said we have learned about many areas for next steps related to pharmacogenetics, artificial intelligence, and other new technologies for studying cannabis at NCCIH and NIH. He thanked researchers for helping start NCCIH in this direction.

Dr. Shurtleff thanked all NIH colleagues in the process of furthering research, funding, and opportunities for studying minor cannabinoids, terpenes, and other aspects of the cannabis plant for therapeutic development for many conditions. He thanked Dr. Belfer for her work in organizing this meeting and the PIs for offering their generous contributions, research, and ideas. He thanked the NIH Institutes and Centers, as well as FDA and DEA for their important roles in regulating cannabis research. He offered a special thanks to all NIH staff and those working behind the scenes, including Courtney Peterson, Ph.D.; Sahar Fakhruddin; Ryan Garrison-Linder, IT specialist; and Beta Lear, science writer. He said he hoped everyone had opportunities to speak to fellow colleagues and that collaborations started as a result of the meeting.

Dr. Belfer extended thanks to the keynote speaker, the NCCIH Office of Communications and Public Liaison, registrants, all colleagues, and everybody who has helped with this important work. Dr. Belfer adjourned the meeting.