The rapid evolution of UC cannabis research

At campuses across the UC system, cannabis researchers are grappling with questions that have accompanied legalization.

In 2016, when voters approved Proposition 64, they set the stage for radical change across California’s cannabis landscape. Licensed, regulated cannabis stores would soon throw open their doors. A flood of novel cannabis-derived products would make their way to market. The state’s vast cannabis industry would begin to emerge from illegality, though unlicensed operations would surely persist.

UC researchers immediately understood that cannabis legalization would present California with pressing new questions, along numerous dimensions, that could only be answered through rigorous, broad-ranging research. How would legalized cannabis cultivation affect the state’s water, wildlife and forests? How might impaired driving, or interconnections between cannabis and tobacco, influence public health? How would tax and regulatory policy affect the rate at which cannabis cultivators abandoned the illegal market? These questions and many more are now the subject of research around the UC system, and multiple campuses are establishing centers dedicated to cannabis research. This article surveys UC’s emerging architecture for cannabis research in the legalization era — and presents a sampling of notable research projects, both completed and ongoing.

Multiple UC campuses are establishing centers in which researchers will study the effects of legalized cannabis cultivation on water, wildlife, forests and public health.

UC Berkeley

The Cannabis Research Center (CRC) at UC Berkeley is an interdisciplinary program that, bringing together social, physical and natural scientists, evaluates the environmental impacts of cannabis cultivation; investigates the policy-related and regulatory dimensions of cultivation; and directly engages cannabis farmers and cannabis-growing communities. The center, according to Ted Grantham — one of three CRC co-directors and a UC Cooperative Extension (UCCE) assistant specialist affiliated with UC Berkeley’s Department of Environmental Science, Policy, and Management — is “focused on cannabis as an agricultural crop, grown in particular places by particular communities with unique characteristics.” For Grantham and the center’s co-founders, establishing the program was “a chance to develop policy-relevant research at the time of legalization and a time of rapidly shifting cultivation practices.”

The center’s co-directors, in addition to Grantham, are Van Butsic — a UCCE assistant specialist affiliated with UC Berkeley’s Department of Environmental Science, Policy, and Management — and Eric Biber, a UC Berkeley professor of law. Other CRC researchers are associated with entities such as the
One UC Berkeley project is motivated by an urgent need to understand the environmental threats posed by noncompliant farms and the reasons that some farms successfully navigate state regulations while others fail.
UC Davis

Research into the environmental aspects of cannabis is also underway at UC Davis, where Mourad Gabriel is a research associate member in UCD’s School of Veterinary Medicine. In 2018, Gabriel and co-authors, including Robert Poppenga — a professor of molecular biosciences at the California Animal Health and Food Safety Lab at UC Davis — published the results of their research on the effects of rodenticides on owls in northwestern California forests (Gabriel et al. 2018). The researchers, working on privately owned timberland in Humboldt and Del Norte counties, investigated the prevalence of anticoagulant rodenticides in areas characterized by illegal cannabis cultivation. Anticoagulant rodenticides, used by some cannabis cultivators to control pests, are known to affect nontarget species in urban areas and recently have been shown to affect carnivores in California’s remote forest areas as well.

Gabriel and his co-authors undertook to determine whether the northern spotted owl, a threatened species, is exposed to anticoagulant rodenticides in the study area — and also to determine if barred owls, a common species, can be used as a surrogate to determine exposure levels in northern spotted owls. The researchers analyzed liver samples from 84 barred owls and 10 northern spotted owls. (The barred owls were removed by other researchers for an unrelated project, with appropriate permits; the carcasses of northern spotted owls were discovered opportunistically.) Within the study area, 70% of northern spotted owls and 40% of barred owls tested positive for anticoagulant rodenticides. The researchers hypothesize that cannabis cultivation in the area is the main source point for the presence of dangerous rodenticides. They also determined that barred owls are a suitable surrogate for determining rodenticide levels in the threatened northern spotted owl.

In a reclamation project conducted this May at 16 illegal cannabis cultivation sites in the Shasta-Trinity National Forest, a team representing 11 governmental and nongovernmental entities worked at 16 cultivation sites within eight large cultivation complexes, removing 6,000 pounds of trash, which included rodenticides and more than 5 miles of irrigation lines. Mourad estimates that removal of the irrigation lines restored more than 500,000 gallons of water — daily — into affected watersheds. Agencies including the California Department of Fish and Wildlife and the Law Enforcement and Investigations arm of the U.S. Forest Service have provided grant funding for 170 such projects, 112 of which have already been completed.

In an entirely different vein, UC Davis—based cannabis research has been conducted since 2016 at the UC Agricultural Issues Center (AIC), a UC Agriculture and Natural Resources statewide program operating since 1985. The center’s broad mission is to provide research-based information on the economic dimensions of emerging issues in agriculture. Cannabis, then, is right in the center’s wheelhouse.

Dan Sumner, the center’s director, reports that AIC began pursuing cannabis-related work after the 2015 passage of a set of laws known collectively as the Medical Marijuana Regulation and Safety Act. This legislation laid the groundwork for state regulation of medicinal cannabis and ultimately of the recreational cannabis industry. The lead agency in regulating commercial cannabis licenses for distributors and retailers, among other business types, is the Bureau of Cannabis Control (BCC) — for which, between 2016 and 2018, the AIC prepared a Standardized Regulatory Impact Analysis (UC Agricultural Issues Center 2018). In the process, the AIC advised the BCC on the economic dimensions of various regulatory scenarios — and the bureau used the center’s analysis to inform the final cannabis regulations that it issued on Jan. 16 of this year.

According to Sumner, a principal insight that the AIC furnished to the BCC was that, since illegal cannabis continues to be attractive to retail buyers because it is cheaper than cannabis from regulated (and taxed) retailers, “much of the cannabis sold in California [after legalization] would remain in the illegal segment.” Moreover, regulations that generate benefits for consumers at lower costs will help sustain the legal marketplace.

In this issue of California Agriculture, three AIC researchers — Pablo Valdes-Donoso, a postdoctoral scholar; Robin S. Goldstein, principal economic counselor; and Sumner — present their research on California’s rather stringent system for testing cannabis that enters the legal market (see page 154). All cannabis sold legally in the state is tested for more than 100 contaminants. Of those contaminants, 66 are pesticides — and tolerance for 21 of those pesticides is set at zero.
In many cases, allowable levels of cannabis contaminants are lower than those established for food sold in the state. The researchers, drawing on data provided by testing laboratories and manufacturers of testing equipment, estimated how much it costs to test a pound of cannabis under California’s regulatory regime, as well as the cost of collecting samples. They concluded that the need to destroy batches of cannabis that fail testing accounts for a large share of testing costs. The researchers argue that, though the availability of certifiably safe and legal cannabis products may prompt some customers to join the regulated market, other customers will remain in the cheaper illegal market. They speculate that, over time, increased availability of data about cannabis testing and sales will allow for greater certainty about the effect of the testing regime on cannabis prices and demand for legal cannabis.

Meanwhile, UC Davis is establishing a dedicated center for research into psychoactive cannabis and industrial hemp — the Cannabis Research Initiative. According to Cindy Kiel, executive associate vice chancellor for research administration at UC Davis, the initiative will draw on the comprehensive strengths of UC Davis faculty in areas ranging from agricultural and environmental impacts to legal, economic and policy outcomes to human and animal health. In particular, the initiative will benefit from UC Davis’s strong emphasis on agricultural issues such as soils, water, genomics and plant science and from faculty interest in two-way interactions such as those between cannabis and the environment. Funding is envisioned to flow from the UC Davis budget, from research funds established in Proposition 64 and from outside sources such as industry partners. Funding could also flow from the federal government via the National Institutes of Health. The initiative will be headed by co-directors (not yet chosen) representing the agricultural and medical sides of cannabis research.

In May, UC Davis faculty members including Chemistry Professor Mark Mascal, along with colleagues from the University of Reading in the United Kingdom, published an article (Mascal et al. 2019) demonstrating that a synthetic analogue of cannabidiol (CBD, a nonpsychoactive component of cannabis) is as effective as CBD in controlling seizures in rats — and that it provides several benefits in comparison to CBD. The synthetic analogue is cheaper than herbal CBD, cannot be converted into psychoactive tetrahydrocannabinol (THC) and is not restricted by the Drug Enforcement Administration’s “scheduling” apparatus. Meanwhile, the UC Davis-affiliated Western Center for Agricultural Health and Safety is studying issues such as workplace safety for cannabis workers, who face risks that include unhealthy pesticide exposure.

For students, UC Davis has offered cannabis courses including the graduate-level Cannabis sativa: The Plant and Its Impact on People — and, for undergraduates, Physiology of Cannabis.

Song reports that the center’s work will fill gaps in knowledge about cannabis intake behavior; epidemiological data is spotty, she says, because many people won’t admit to engaging in behavior that has historically been illegal and continues to be federally illegal. The researchers are also keen to understand the interconnections between tobacco and cannabis — emerging data indicates that perceptions of tobacco risk are related to perceptions of cannabis, and the relationship between the two may affect individuals’ future tobacco use. “These are the things we are trying to disentangle,” Song says. (The center is conducting a parallel research project that focuses on American Indians in the same study area.)

The center was founded with a $3.8 million grant from the Tobacco-Related Disease Research Program, a state initiative administered by the UC Office of the President, which dispenses funds derived from the Tobacco Tax Increase Initiative, a proposition approved by California voters in 2016.
Cannabis institutes at three UC campuses in Southern California — UC San Diego, UC Irvine and UC Los Angeles — conduct research on the health effects and medical uses of cannabis and its derivatives. But they differ greatly in their approach. The program at UC San Diego focuses closely on medical cannabis research and public safety issues. The UC Irvine program brings together medicine and law. The UCLA program has set itself the ambitious interdisciplinary task of exploring how cannabis affects society along the medical, legal, economic and social dimensions.

The UC Center for Medicinal Cannabis Research (CMCR) at UC San Diego, the oldest of the three institutes, was established when California Senate Bill 847 (the Marijuana Research Act of 1999) enabled UC to establish a program to “enhance understanding of the efficacy and adverse effects of marijuana as a pharmacological agent.” Today, the center’s cannabis research covers a broad range of clinical conditions such as neuropathic pain, autism, bipolar disorder and early psychosis — as well as public safety issues surrounding the use of cannabis and cannabinoids.

A notable current CMCR study, authorized by the 2015 Medical Marijuana Regulation and Safety Act, seeks to determine how multiple dosing strengths of cannabis affect driving and for what duration driving impairment continues after cannabis use. The research also seeks to determine if saliva or breath tests can substitute for blood samples in determining cannabis intoxication and if sobriety tests administered with iPads can supplement standard field sobriety tests. The study is led by Thomas Marcotte, a professor of psychiatry at the UCSD School of Medicine.

Another notable CMCR study, tentatively set to begin at the end of the summer, concerns autism. The research, which includes both a clinical trial and a basic science component, investigates the effect of CBD on severe autism spectrum disorder, a condition that affects one in every 68 U.S. children. In the clinical trial — overseen by Doris Trauner, a professor of neuroscience and pediatrics at UCSD — researchers will administer oral doses of CBD or a placebo to 30 children who have been diagnosed with moderate to severe autism. CBD interacts with the endocannabinoid system, a network in the human body that regulates various physiological and cognitive processes. Researchers will attempt to determine whether CBD is safe for the study population to use, whether it addresses their symptoms, whether it alters neurotransmitters or improves brain connectivity, and if so, how.

In the basic science component of the study, researchers will use cells from the skin and blood of participants and, in Grant’s words, “re-engineer these cells to be neurons — to create little brain organoids, if you will.” This feat of re-engineering will allow researchers to observe how the cells function and, if CBD has benefited the subjects of the clinical trial, to investigate the associated mechanism of action. The study will be conducted with funding from the Wholistic Research and Education Foundation.

Grant notes that Proposition 64 allocates $2 million annually to the CMCR. The center intends to use the funding partly to support its core facility and partly to fund small-scale pilot studies that might be conducted at the center itself, at other UC campuses or at campuses of other universities in California.

UC Irvine

A much newer entrant into medical cannabis research is UC Irvine’s Center for the Study of Cannabis (CSC). As an interdisciplinary venture involving UC Irvine’s School of Medicine and School of Law, the center includes basic medical science, clinical science and jurisprudence in its purview. Daniele Piomelli, director of the center — as well as a professor of anatomy and neurobiology at the UC Irvine School of Medicine — calls cannabis “a quintessential multidisciplinary problem.” Because much existing cannabis law was...
written when medical knowledge about cannabis was scarce, he says, new knowledge to underpin new legislation is urgently needed.

Piomelli further argues that because cannabis encompasses, for example, commercial and cultural dimensions, researchers across disciplines must engage with each other (and with policymakers) to find realistic solutions to cannabis-related problems. “If medicine and science and law don’t talk to one another,” he says, “we’ll never have sensible legislation.” In that spirit, the center has two directors — Piomelli representing the medical side of the interdisciplinary undertaking and Robert Solomon, a clinical professor of law at UC Irvine School of Law, representing the legal side. About 30 faculty members across law and medicine are involved in the center’s work.

The centerpiece of the CSC’s work so far is an ongoing preclinical study called Impact of Cannabinoids Across the Lifespan. Piomelli, who directs the study while a team of UC Irvine principal investigators conducts the bulk of the research, characterizes it as a broad research project with many components, from which a stream of independent discoveries and publications is expected over the next 3 or 4 years. Piomelli reports that the study’s main purpose is to study THC’s effect on adolescents — and particularly on the adolescent brain. The human brain routinely produces neurotransmitters known as endocannabinoids — molecules, similar to cannabis derivatives, that are important in learning, memory and experiencing emotion.

The key questions that the study addresses are these: Does exposure to THC, in a persistent way, change the brain’s endocannabinoid system? If so, what changes at the cellular and molecular level explain the alterations? Does exposure to THC during adolescence carry lasting implications for learning and emotion? The study has received a $9 million Center of Excellence Grant from the National Institute on Drug Abuse.

UC Los Angeles

Another new entrant into cannabis research is the UCLA Cannabis Research Initiative, founded in 2017 with a broad remit — “to understand how cannabis affects bodies, brains and society.” The initiative, encompassing an interdisciplinary team of 40 faculty members from 15 university departments, aims to function as an education, research and service organization that leads public discussions of cannabis, policy and health.

The initiative got its start in the months before Proposition 64 was approved by voters. According to Jeffrey Chen, the initiative’s director, leadership at the Semel Institute for Neuroscience and Human Behavior (which partially funds the initiative) anticipated that legalization would soon create the world’s largest market for recreational cannabis — and that California and particularly Los Angeles would “play an outsized role in establishing normative behaviors” around cannabis. Los Angeles, in Chen’s view, has become the world’s cannabis capital overnight. He and his colleagues hypothesize that, given the city’s status as a major tourist destination and an exporter of culture, “what happens in Los Angeles is very likely to be transmitted around the world.”

So far, Chen says, the initiative’s research remains mainly oriented toward health-related issues. One study — soon to start, and led by Kate Wolitzky-Taylor, an assistant clinical professor in UCLA’s Department of Psychiatry and Biobehavioral Sciences — seeks to develop and evaluate a behavioral treatment for young adults who exhibit cannabis use disorder and who use cannabis to cope with anxiety, depression and the like. Cannabis, according to the researchers, is the most commonly used drug among young adults, and it can be harmful when its use qualifies as a “maladaptive way” of contending with negative experiences.

Wolitzky-Taylor reports that the research project is a randomized clinical trial focusing on participants’ reactions to the anxiety and depression that might lead them to use cannabis. The treatment, she says, will draw on strategies such as “mindfulness, cognitive reappraisal skills, problem solving and … gradual exposure to distressing but objectively safe stimuli.” The treatment was developed in an iterative manner — an early version has already been tested with a small group of patients and further refinements may be made after the clinical trial is complete. The research is funded by a 3-year, $450,000 grant (in direct costs) from the National Institute on Drug Abuse. Individuals with cannabis use disorder, if they are 18 to 25 years old, are encouraged to email the project’s coordinator, Nick Pistolesi (npistolesi@mednet.ucla.edu), regarding participation in the study.

A second example of the initiative’s work is decidedly nonmedical. Brett Hollenbeck, an assistant professor of marketing at the UCLA Anderson School of Management, analyzed — along with Kosuke Uetake of Yale University — a large dataset of cannabis transactions in the state of Washington to learn about firm and consumer behavior in legal cannabis markets (Hollenbeck and Uetake 2018). Their goal was to provide policymakers, including in California, information useful for optimal development of cannabis taxation and regulation — optimal in the sense of maximizing tax revenues, safeguarding public health and discouraging a black market for cannabis.

Washington created a legal framework for growing and selling cannabis in 2012. Legal sales began there in 2014. Since then, every cannabis transaction in the state has been recorded in an administrative dataset. The researchers used the data to model consumer demand for cannabis products and measure price elasticity. Their
analysis, covering the period from November 2014 to September 2017, indicates that Washington's strict cap on cannabis retailers — some 550 are allowed in the entire state — has permitted retailers to command high prices and behave like local monopolies.

The researchers report that when prices for regulated cannabis rise in Washington, consumers often switch to cheaper cannabis alternatives available from regulated retailers, rather than seeking out black-market cannabis. Indeed, the researchers argue that Washington's 37% sales tax rate for cannabis, though it appears high, does not drive down tax revenue, and in fact the state could generate higher revenue by raising the tax rate to 40% or higher. Further, the researchers calculate that Washington could substantially increase its revenue if it acted as the state’s sole cannabis retailer, as it did for alcohol sales until 2012, and could do so without causing an increase in cannabis prices.

UC Riverside

UC Riverside, though it has established no dedicated cannabis program, will soon host cannabis research for the first time. Nicholas DiPatrizio — a UC Riverside assistant professor in the School of Medicine's Division of Biomedical Sciences who is newly equipped with a DEA Schedule I license — is set to begin research investigating the effects of long-term cannabis use on metabolic diseases, including type 2 diabetes. DiPatrizio’s lab, using technologies such as tandem mass spectrometry, will study how cannabis use affects glucose homeostasis (the stable equilibrium of glucose) in wild-type mice — and will also investigate whether long-term cannabis use is sometimes associated with positive health outcomes such as increases in high-density lipoproteins (often called good cholesterol).

DiPatrizio’s research has received more than $700,000 in funding from the Tobacco-Related Disease Research Program, the same entity that provides funding for the UC Nicotine and Cannabis Policy Center at UC Merced. DiPatrizio reports that, though his research will not specifically investigate cannabis-tobacco interactions, it is eligible for the program’s funding because type 2 diabetes is a tobacco-related disease.

UC San Francisco

Returning now to Northern California, a team of UC San Francisco researchers led by Gregory Marcus — a professor of medicine at the UC San Francisco School of Medicine — recently published an article based on their research into the influence of cannabis legalization on health care utilization (Delling et al. 2019). The researchers, analyzing a medical-coding database that contained information on 16 million hospitalizations between 2010 and 2014, sought to determine if and how Colorado’s 2012 cannabis legalization had changed health care utilization in the state (with data about Oklahoma and New York providing points of comparison).

The data revealed that, after legalization, motor vehicle accidents increased by 10% in Colorado, while rates of alcohol abuse and overdoses resulting in injury or death increased by 5%. (Marcus explains that the database’s codes for overdose indicated that a patient had suffered an injury related to use of some drug — not that patients had overdosed on cannabis per se.) Diagnoses of chronic pain, however, decreased, and the overall result was that utilization of health care services remained level. In Marcus’s view, his team’s research demonstrates that the repercussions of public policy tend to be complex and nuanced. In particular, even if new legislation results in certain harmful health effects, it can prove beneficial to society in other ways. No one has yet attempted an analogous study in California — adult-use legalization is still very new in the state, and the availability of datasets tends to lag real-world events by several years. Marcus and his team, however, would be eager to take on the job.

— Lucien Crowder

References


