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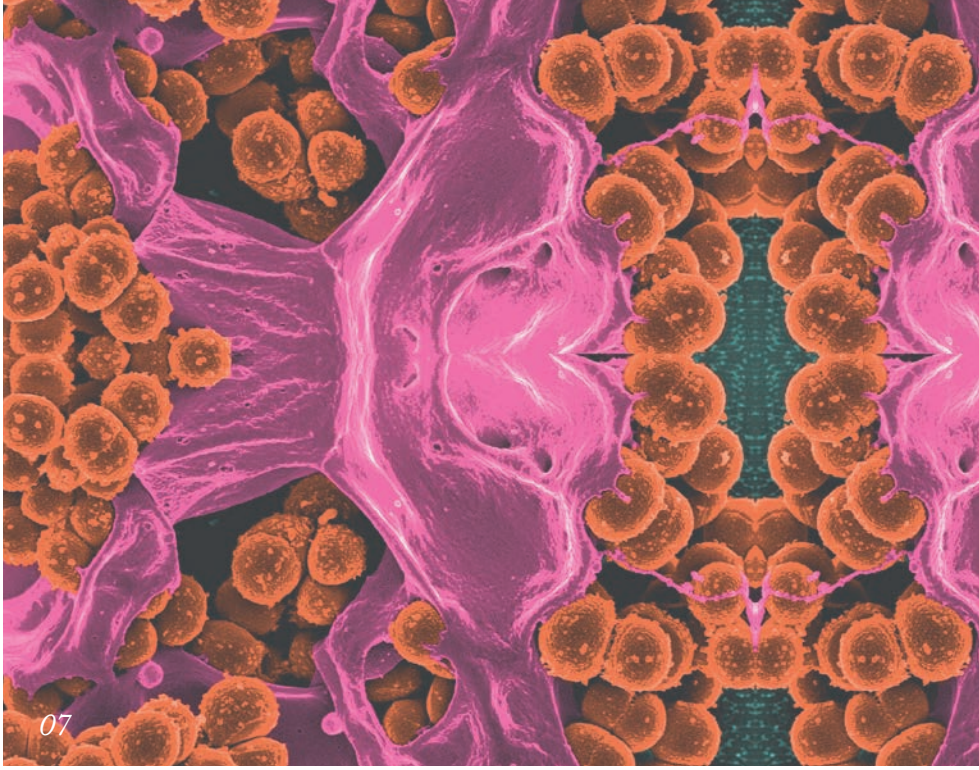






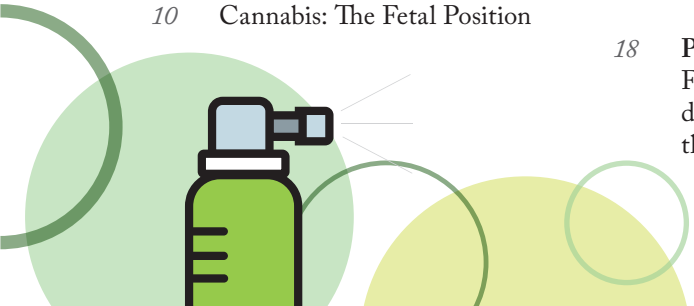

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# Cannabis Conversations

*As interest in medical cannabis ramps up, the need for open and ongoing discussion between scientists, clinicians, regulators and patients has never been clearer.*

The medical cannabis landscape is changing fast. And there are few people who can fully understand the ramifications of shifting policy – be it complete legalization, limited access or absolute prohibition. How will these three approaches play out against a backdrop of growing demand?

Stories in the press cover everything from barriers to access ("A mother's fight to get medical cannabis for her son" – FT) to squabbles over the role of celebrities in the ongoing debate ("Longtime medicinal cannabis advocate warns Pete Evans involvement invites 'controversy'" – News.com.au). The upshot? The seemingly interchangeable terms "medical cannabis" and "medicinal cannabis" are increasingly entering the public consciousness, fueling curiosity. Patients are looking for (the right) answers.

The reality is that, after such a lengthy spell of limited-to-no research, the scientific community has got some serious catching up to do – especially when it comes to "whole-plant" extracts and any entourage effects.

Those working in the pharmaceutical industry are well aware of the typically long, sometimes painful and always costly road to approved medicines. Despite the risk, GW Pharmaceuticals has put all its eggs in the cannabinoid basket. And it has seen success; the FDA approval of Epidiolex (CBD) in 2018 being one example.

The FDA press release for its first cannabis-derived drug approval makes for interesting reading, with Commissioner Scott Gottlieb praising the trusted route: "Controlled clinical trials testing the safety and efficacy of a drug, along with careful review through the FDA's drug approval process, is the most appropriate way to bring marijuana-derived treatments to patients."

But we covered Pharma's "takeover" in the last issue (1). What about the rest of the medical cannabis industry? How do we apply both good science and common sense in a field where the heterogeneity of plant products – and human beings – may result in an almost miraculous treatment for one patient and zero effect in another?

As we navigate the myriad complexities – scientific, clinical, ethical, political, legal, societal – we must come together to discuss the impact of scientific discoveries, learn from clinical trial results, consider unmet need from a medical practitioner's perspective, and allow patients to share their experiences (both negative and positive). There's a lot to talk about – and we all need to be honest and open in those medical cannabis conversations.

**Rich Whitworth**
*Content Director*

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# Upfront

*Reporting on research, personalities, policies and partnerships that are shaping cannabis science.*

*We welcome information on interesting collaborations or research that has really caught your eye, in a good or bad way. Email: charlotte.barker @texerepublishing.com*

## Off the Hook?

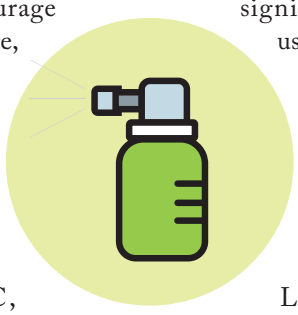
### Repurposing nabiximols to tackle cannabis dependency

"The concept of prescribing patients a safer form of the drug they are dependent on is not novel; it is routinely used to treat tobacco and heroin addiction," explains Nicholas Lintzeris, a researcher at New South Wales University, Australia, and part of a team that hopes to apply the same logic to cannabis dependency (1). "The process can encourage behavioral 'lifestyle' change, which is necessary to stopping addiction."

A previous study (2) had already demonstrated promising results with nabiximols (Sativex) – an oromucosal spray, containing THC, CBD and specific minor cannabinoids, which has been approved in "over 25 countries outside the USA for the treatment of spasticity (muscle stiffness/spasm) due to [muscular sclerosis]" (3).

"We found that a short course of nabiximols was effective in helping patients' complete withdrawal and minimizing discomfort," says Lintzeris. "However, most patients relapsed within several weeks, returning to regular cannabis use. Hence, we wanted to determine if a longer exposure to nabiximols would produce longer-term benefits."

In the randomized, double-blind, controlled trial, patients received either nabiximols or placebo, dispensed weekly and with individually adjusted doses. In addition, patients were provided access to counseling, nursing and medical input to address other health and social issues. The aim? To mimic real life experience as much as possible. "Patients in both the nabiximols and placebo groups reduced their cannabis use, but those that received nabiximols demonstrated significantly greater reductions," says Lintzeris. "The medication was well tolerated with few side effects, and patients did not report significant intoxication when using nabiximols."



In these rapidly changing times, who dares predict the scale of need for so-called "drug replacement therapy" for cannabis dependence – or what form it may eventually take? Lintzeris remains confident in their work: "Our findings indicate considerable promise in this treatment approach – and we might one day consider this a routine part of treatment for cannabis dependence."

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# New Drugs for Stubborn Bugs

## Novel antibacterial agents are needed… Could CBD fill the void?

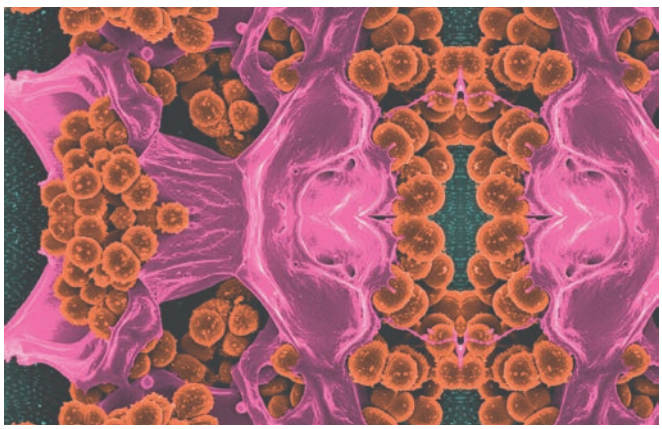
The rise of antibiotic resistance has been dubbed the "antibiotic apocalypse." It's an alarming turn of phrase that has sent scientists scurrying off to discover new compounds for our antimicrobial armamentarium in the least likely of places – from cockroach brains (1) to the Atacama Desert (2). Now, cannabis joins the fight.

The activity of CBD against Gram-positive bacteria (a group including the Staphylococcus and Streptococcus families, and the notorious superbug MRSA) was documented in the 1970s, but only now is this activity being fully characterized by Mark Blaskovich and colleagues (3). The team has conducted assays of cell viability, explored bacterial biofilms through confocal microscopy, and treated skin infections in immunocompromised mice; research was conducted in collaboration with Botanix Pharmaceuticals at the University of Queensland, and was funded by an Innovation Connections grant from the Australian government.

In each case, the results have impressed Blaskovich, who cites three unexpected findings: "i) the breadth of activity against a range of Gram-positive bacteria, including strains highly resistant to existing antibiotics, ii) the lack of development of resistance to CBD after long periods of exposure, and iii) the mechanism of action, which did not appear to involve membrane disruption." The combination of widespread activity and slow development of resistance are promising fundamental features, while the proven capacity of CBD to disrupt biofilms further increases the promise of CBD to treat tricky infections.

Human studies are being planned – particularly for topical application, but the researchers also want to investigate the use of CBD for systemic infections in mice. At the same time, the team hope to uncover CBD's mechanism of antibacterial action. Thinking forward to the most likely applications, Blaskovich says, "At a minimum, CBD could help replace decolonization agents like mupirocin, which are used to disrupt biofilms before surgery to reduce postoperative complications."

The more ambitious hope? That CBD-based medicines could serve as reinforcements in the ongoing fight against resistance. The battle waged in the "golden age of antibiotics" may be behind us, but the war rages on.



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# Not as Advertised

**Apples to oranges... to cannabis. Strain classifications in US dispensaries are not always what they appear**

Product consistency is an accepted consumer expectation. "Take apples, for example," says Anna Schwabe, a Research Coordinator at Mile High Labs. "Consumers have a level of expectation of what a Granny Smith apple is: green, crunchy, and tart. Each apple is not identical, but there are common features that make a Granny Smith apple a Granny Smith apple."

When it comes to cannabis, plants labeled as a given strain should demonstrate a similar phenotype – and thus exert similar effects when consumed – somewhat irrespective of the seller… in theory.

Schwabe first became suspicious of dispensary claims when her friend found a cannabis strain she adored, and yet experienced different effects when buying "the same strain" from other sellers. Later, "the same strain" from the original dispensary wasn't quite hitting the spot. Given a background in population genetics, Schwabe is well aware that some phenotypic variation is a given. "Phenotype is a product of the environment and the genotype. We know that grow facilities don't follow the same protocols; plants are grown under slightly different conditions (soil, water, nutrients, harvest time, storage, and so on), and that can lead to variation in phenotypes (as with Granny Smith apples), but to what extent?" asks Schwabe. "And what if it isn't just different growing conditions? What if dispensaries really do have plants that are genetically different but labeled with the same name? And, if they do, how would they even know?" She decided to explore (1).

With co-investigator Mitchell McGlaughlin, Schwabe collected 122 cannabis samples of 30 strains from 20 recreational and medical dispensaries across Colorado, California and Washington. When asked why they didn't declare the nature of their study to the dispensaries, Schwabe says, "We wanted to know what consumers were being provided with – and we believe this research is especially valuable for those using cannabis for medicinal purposes."

DNA was extracted from each sample and assessed for genetic similarity within labeled strains. Their alignment with purported proportions of genes belonging to typical Sativa- and Indica-type plants were also assessed to investigate the true value of these distinctions among tested strains.

So, what did they find? Some strains were cohesive – though Schwabe notes that would probably not be the case if further samples were added for under-represented strains. Specifically, Jack Flash (n = 2), Island Sweet Skunk (n = 3) and Chemdawg (n = 7) all displayed over 90 percent similarity. Blue Dream (n = 9) and Durban Poison (n = 9) samples were 89 percent similar – but the two strains each harbored one genetic outlier. Schwabe summarized: "27 of 30 strains had at least one genetic outlier, indicating there are substantial genetic differences within strains that are largely propagated from cloning methods."

Sativa, Indica and hybrid plants were also poorly defined at a genetic level. The likely reason? "Extensive hybridization and selection leading to homogenization and erased evidence of potentially divergent historic phenotypes," says Schwabe.

The extent of genetic variation observed highlights the need for aligned product verification in the cannabis industry. Schwabe offers a solution for part of that problem: "Industry standard regulatory checks should be implemented in the form of genetic testing to provide consistency, especially for medical applications [...] How will you ever provide consistency without first making sure you have what you think you have?"

As for Schwabe's friend… "She is still hunting for the elusive perfect strain she found so many years ago."

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# Stemming Epilepsy's Effects

## A dose-escalation study aims to quantify the value of CBD in children with epileptic encephalopathy

Mounting evidence suggests that CBD acts as an antispasmodic therapy for children with otherwise intractable epilepsy. In many cases, however, this research is yet to leave the lab – in part because of insufficient dosage data. Now, a dose-escalation trial – the Cannabidiol in Children with Refractory Epileptic Encephalopathy (CARE-E) study – provides some of the first pharmacokinetic data (1).

Richard Huntsman and colleagues conducted a clinical study of cannabis herbal extract in seven children with epileptic encephalopathy, and preliminary results – albeit in a small sample – are promising. "We saw a correlation between dosage and reduced seizures," says Huntsman. "There seems to be a correlation between the levels of plasma CBD and clinical efficacy." Importantly, there was no indication of intoxication in any of the children.

Huntsman recalls many sleepless nights caused by the research. "I'd find myself awake at 3 o'clock in the morning asking myself why I was doing this." Navigating the bureaucracy surrounding the use of cannabis herbal extract in this vulnerable group was apparently the easy part – the challenge came from opposition within academia itself. "We faced a lot of resistance from the ethics board and academic administration," says Huntsman. "It took a lot of convincing for people to believe this was a safe study."

But, with promising preliminary results, the team are confident they can maintain momentum. "We are looking to establish an international trial, with sites in the UK and the USA," says Huntsman. "We realized early on that we've just scratched the surface – there is so much more to explore, firstly in treating epilepsy but also in many other areas."

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# Cannabis: the Fetal Position

**Cannabis exposure during pregnancy could have adverse effects on brain development – but where is the data to prove it?**

The negative consequences of tobacco smoking during pregnancy are widely acknowledged and supported by evidence. Equivalent studies for cannabis smoking, however, have been historically lacking, and most published studies have provided conflicting or difficult-to-interpret results. With the number of expectant mothers choosing to take an occasional puff rising across the US (2.37 percent in 2002 to 3.85 percent in 2014 [1]), the rationale to conduct such studies has never been clearer.

Heeding this call, Daniel Corsi and Mark Walker conducted a study of over 600,000 pregnant women in Ontario, Canada, and were able to demonstrate a significant association between cannabis exposure and the probability of preterm birth (2); the rate of preterm births doubled from 6 percent to 12 percent with exposure. We spoke to Corsi and Walker to find out more.

### What do we know about the effects of cannabis exposure during development?

*Corsi*: We know from adolescent populations that there is a link between development and cognitive function and an increased risk of psychiatric conditions when exposed to cannabis. There are a few studies, particularly in Ottawa, that have followed children born to mothers who consumed cannabis during pregnancy. Though the study was quite small and the data now quite dated, it is very robust.

*Walker*: We know that fetuses are incredibly sensitive – it's a major time for brain growth and development, especially during the late first and early second trimester. We know that there are cannabinoid receptors in the brain – but we don't know what the long-term outcome and safety of exposure will be.

### How did you conduct the study?

*Corsi*: Our source was the provincial registry of pregnancy and births in Ontario. It was established in 2012, so there are nearly a million recorded pregnancies. We also captured the use of cannabis for that dataset. Of course, it is also true that there is a correlation between cannabis use and use of other drugs, including tobacco and alcohol. As a result, we had to control for these confounding factors. We looked at a number of things independently, including preterm birth, small size at birth, and admission to the neonatal unit. These primary outcomes helped us to be more confident that our findings were not related to other factors.

### How does cannabis exposure cause these effects?

*Walker*: To be honest, we are not entirely sure – we lack knowledge about the pathways that trigger labor. One answer might be that it has something to do with the cannabinoids – in particular THC – affecting smooth muscle receptors. And that might influence the signaling cascade that induces labor.

*Corsi*: There have been a few studies on tobacco that suggest it is the method of consumption that affects preterm birth – in particular, smoking. As cannabis is often smoked, it might be related to that. However, it is possible that independent associations with components of cannabis are involved.

### What are the next steps?

*Crosi*: We are now trying to develop a research platform in this area. We've begun some larger studies with the hope of following up children exposed at an earlier date. Some of our datasets go back to around 2007, which gives us 12 years' worth of data to work with. We also hope to look at childhood outcomes, including developmental delays and learning disabilities, and would like to reproduce our findings on an international scale – we are already working with datasets in the US and UK.

*Walker*: The key questions for us are quite practical: how much cannabis is being consumed? How frequently? During which trimester? And by what mode of exposure? As ingestible cannabis products become more popular, we'll need to assess whether they are safer or more harmful than smoked cannabis. The development of larger networks of data will be really enlightening.

### What impact will this work have in the clinic?

*Corsi*: If cannabis can be seen in at least a similar way to cigarettes, that would be a good outcome. Now that we have seen cannabis legalized in Canada, we would like to see labeling and warming signs attached to packaging. There's really a public health message that we need to get out there. The general perception of cannabis is that, because it is a natural product and not synthetic, it may be 'nature's own remedy'. The awareness of the effects of cannabis during pregnancy has not reached the public domain as much as we would like.

*Walker*: We want to avoid the delay that we saw during the recognition of fetal alcohol exposure. It took a generation or two to witness fetal alcohol syndrome and other effects before a strong public health message was out there. What we hope to do is more research to look at the long-term effects of cannabis exposure, and then get the message out there as quickly as possible.

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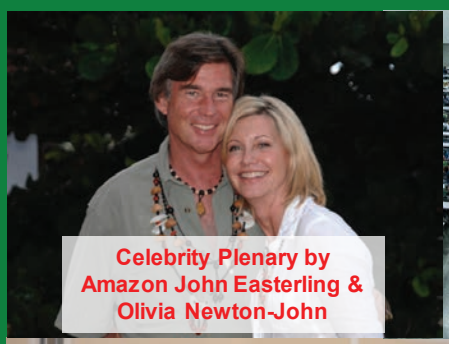







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# In My View

*In this opinion section, experts from across the world share a single strongly-held view or key idea.*

*Submissions are welcome. Articles should be short, focused, personal and passionate, and may deal with any aspect of analytical science. They can be up to 600 words in length and written in the first person.*

*Contact the editors at charlotte.barker @texerepublishing.com*

## Knowledge Is Power – and Progress

**Scientists must come together to share experiences, accumulate evidence, and bring about change in cannabis policy.**

*By Paul Mavor, Director at Health House International, Perth, Australia.*

When I saw data outlining the toll of pharmaceutical opiates in the US, I knew that an alternative was desperately needed – over 30,000 largely avoidable deaths in a single year. As a pharmacist who dispenses opiates myself, I couldn't help but feel partly responsible. Conversely, there are little-to-no recorded deaths associated with cannabis abuse. And that got me thinking.

The rise of the global medical cannabis industry has been equated to the dot-com boom of the late nineties. We've seen explosive growth that has been spurred on in part by financiers, but also by the opioid crisis itself and the need for novel chronic pain treatments. The resulting wave of legalization across the globe and strong investment have been tempered by regulators with the same mindset that saw cannabis banned for the last 80 years. Nevertheless, legislation is changing and research is booming, gifting us with a strong evidence base for the use of cannabis across multiple medical indications.

Now, diverse products are starting to hit global markets, including oils, capsules, creams and inhalers. Many of these are entering clinical studies to compare efficacy and safety with existing drugs and placebos.

Some medical professionals are beginning to view cannabis as a valid treatment option for patients with chronic illness. And yet, stigma persists. I myself was guilty of holding negative presumptions at one time; I expected my first cannabis event – the Cannabis Science Conference in Portland (or Pot-land, as I like to call it) – to consist almost entirely of fire-twirling, tie-die-wearing hippies doing relatively little science. What I found, however, was a focused community of scientists and clinicians – and that changed my perception of the field.

*"Perhaps some of the best speakers were patient advocates, who really brought the story to life by highlighting the human impact of the field."*

*"As a community, we need to come together to separate fact from fiction by providing empirical evidence for cannabis in all its medical applications."*

In part inspired by the people we met there, my wife, Sharlene, and I returned home to set up a non-commercial seminar series to combat misinformation and to raise the profile of cannabis within the Australian medical and scientific communities. Our seminars featured a range of healthcare professionals who presented the positives and negatives of medical cannabis – all based on scientific evidence. An array of incredible speakers came out of the woodwork to participate – some of whom had been studying cannabis for up to 30 years.

The response to our seminars was amazing, with even more speakers emerging to participate in the second and third rounds. Question and answer sessions were extremely popular – and often led to extended conversations that spilled over into local bars until the late evening. Perhaps some of the best speakers were patient advocates, who really brought the story to life by highlighting the human impact of the field. All things considered, the seminars taught me that people are hungry for information on this topic. And who can blame them?

Off the back of this success, we're starting a grassroots (excuse the pun) network of UK healthcare professionals interested in medical cannabis. Seminars are once again part of our strategy, with upcoming events in London, Manchester and Glasgow (for more information, visit http://mcuk.org/events). We hope to open up sensible conversations on what cannabis can treat – but also what limitations exist. The current prohibition-style access scheme in the UK needs to change. But change will only come when health professionals embrace cannabis as another treatment option rather than see it as fringe medicine – and, for that, they need evidence and an open dialogue with the community.

The UK may be the start of its journey. Australia, on the other hand, is three years into its legal-medical cannabis framework; recreational cannabis remains illegal and medical cannabis is just starting to get traction. In this time, the system for prescribers has been streamlined considerably – from multiple processes over two months to an online form often approved within 24 hours. What's more, we've seen a massive growth in the amount of prescriber information and educational courses. The overall result? An exponential increase in patient approvals – we expect to see 20,000 by the end of 2019 in Australia.

As a community, we need to come together to separate fact from fiction by providing empirical evidence for cannabis in all its medical applications.

# Culture Shock

## Microbial safety: why viability testing fails to protect patients.

*By Kyle Boyar, Field Application Scientist, Medicinal Genomics, Beverly, Massachusetts, USA.*

Cannabis is used to treat a huge variety of conditions, some of which are immunocompromising, so it is of paramount importance to ensure that products are free of microbial contaminants.

At present, microbial testing requirements for cannabis differ widely from state to state – some call for molecular methods while others rely on culture-based technologies such as plating. Some regulations require total counts, while others focus on known human pathogens, and others require a mixture of the two. Testing methods used in food are commonly being adapted to cannabis; however, cannabis is a unique matrix in itself and has myriad alternative matrices (for instance, concentrates and infused products), which further complicates the picture.

In 2015, the Medicinal Genomics team sequenced the cannabis microbiome of a variety of cultivars, revealing the presence of numerous mycotoxic fungi in dispensary-grade cannabis (1). Further work has demonstrated that many of these pathogenic fungi are endophytes, meaning that they reside inside the cannabis plant (unlike epiphytes, which colonize the surface of the plant) (2–3). Some of these pathogens include

Aspergillus, Fusarium, and Rhizopus, all of which produce mycotoxins and have been implicated in a number of cases in which people became ill – or even died – after using cannabis, with immunocompromised patients most at risk (5–11).

Endophytes are a major blind spot for culture-based systems. The methods used to collect samples for culture are predominantly designed to pick up surface microbes, and typically only capture a very small proportion of endophytic communities.

Furthermore, some microorganisms of concern, like Aspergillus, do not grow well in culture-based systems and have a propensity to clump and produce macrocolonies, making the standard colony-forming unit an inaccurate measure. To further complicate the picture, different species of Aspergillus can be morphologically very similar, making the distinction between what is pathogenic and not extremely challenging. In one instance, the state of Alaska had to step in to referee a disagreement between two labs over misidentification of A. niger (pathogenic) for A. brasiliensis (non-pathogenic).

The Medicinal Genomics team has also observed a large discordance between different culture-based platforms, as well as how these two platforms compare to quantitative polymerase chain reaction (qPCR), a DNA-based test. In a follow-up study, our team demonstrated that the act of culturing produces a skewed image of the cannabis microbiome and that many of culture-based systems lack specificity and grow off-target microorganisms, leading to inflated total counts (12). Furthermore, there were many instances when qPCR would yield signal while the plates were clean and vice versa. Sequencing of the colonies on these plates and the amplicons generated from qPCR demonstrated the presence of an endofungal bacteria called Ralstonia. This is problematic for non-molecular methods because these bacteria take residence inside of fungal cells and therefore the cell must be lysed to know if they are present. Ralstonia is a pathogen to both plants and humans, causing wilt in the former and lung infections in the latter (13–14).

*"Even if a product appears to be free of viable contaminants according to culture-based techniques, many known endophytic and endofungal pathogens could be missed."*

Even if a product appears to be free of viable contaminants according to culture-based techniques, many known endophytic and endofungal pathogens could be missed. Plus, there is no good way to homogenize samples without lysing cells. Grinding will lyse cells in a non-uniform manner and anything that lyses a plant cell could also lyse a microbial cell. Therefore, relying on techniques that only measure viable cells can lead to increased failure rates for products that are perfectly safe while failing to detect underlying microbial threats.

There are numerous challenges that face the accurate quantification of microbial hazards in cannabis; in my view, molecular methods are best able to address them and ensure consumer safety.

While total count tests can give you some information about the microbial load in a sample they lack specificity and do not differentiate between what is hazardous and what is benign, which puts growers who use beneficial microbes in a tricky spot. This is why I am a strong advocate for species-specific testing. Targeting known threats is a much better way of ensuring a product is safe without penalizing cultivators for organic practices. Carefully designed qPCR primers are one way to resolve this issue of specificity. Some industries under the jurisdiction of the US FDA are taking things a step further and are beginning to sequence contaminated product to better understand the exact serotype of the pathogens encountered during outbreaks.

As we begin to shape policy for newly legal states – and eventually federal legalization – I hope that regulators take these important factors into consideration. Ultimately, the safety of consumers relies on implementing scientifically sound approaches.

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# Taking Back Cannabis Control

**Ill-considered regulations have resulted in an analytical race to the bottom. If you aim for best rather than worst, you have a part to play in shaping the future of our cannabis-testing field.**

*By Reggie Gaudino, President, Director of R&D, and Director of Intellectual Property, Steep Hill Labs, Berkeley, California, USA.*

Over the last few years, cannabis testing has seen serious change – and it has become a very "interesting" business. Years ago, when there were no regulations, some labs, like Steep Hill, were bringing the best science possible to the table so that we could help provide the industry with the information it needed to move onwards and upwards. But as more stringent regulations have come online, what we've witnessed is akin to the top blowing off a pressure cooker.

The regulators entered the game with their own views and ideas. They didn't pay a great deal of attention to the existing testing landscape; in truth, they were somewhat ignorant to the groundwork already laid out – and there was very little discussion with the labs that had helped establish testing in the industry; for example, Steep Hill, SC Labs, and CW Analytical Laboratories. And so, we were suddenly subjected to regulations that appear to have been constructed in a vacuum – or at least without a lot of forethought. Imagine laying out regulatory framework for an industry without performing in-house checks to ensure suitability – or even possibility…

Well, when the Californian regulations hit, the state didn't have its own reference laboratory. The scuttlebutt? As the scientists at California's Bureau of Cannabis Control (BCC) attempt to meet the same regulations handed down to us, those regulations are starting to change. Go figure!

Terpenes, for example, are extremely labile – they are volatile organic compounds, after all; in most other industries, recovery acceptance criteria for a standard in a batch run would be ± 30–40 percent. The BCC wanted ± 20 percent – almost impossible for most of the compounds. It was later changed to ± 30 percent, when the BCC acknowledged the issue, and some compounds like volatile monoterpenes are still difficult to get within the ± 30 percent acceptance criteria. And this is not an isolated example.

Some of those wayward regulations have been modified, but there are still others that make no sense. The microbial testing regulations are one example. Consider Aspergillus, E. coli or salmonella – the acceptance criteria state: "not detected in one gram." But what on God's green earth does that mean? Not detected by what methodology and on what measurement scale? There is no other regulated testing space where an action threshold is defined as "not detected in 1 gram", this is akin to trying to prove a negative.

For pesticides, some regulations state that your instrumentation must be capable of attaining a limit of quantitation (LOQ) of at least 100 ppb. But here's the crazy part: if you can meet that LOQ, you have to fail product on any level detected – whatever the limit of detection (LOD) of your analytical setup. At the LOQ, where you've got a signal-to-noise ratio of 10 to 1, everything is hunky-dory – the calls you make are the correct calls. But at the LOD, which means you are barely above the "noise" or background, hence the word "limit", you're working at a ragged edge that produces false positives and false negatives at a fairly significant rate by definition.

With such ambiguous or ill-defined regulations, there is a dire consequence. The industry has been sent down a "lab shopping" pathway, where some growers seek those labs with the worst equipment for pesticides and the least sensitive microbial tests! We are losing clients because we are able to detect pesticides at a lower level than other labs. It's a race to the bottom.

As I said in my Sitting Down With interview in the previous issue of The Cannabis Scientist (1): "Good science is not necessarily the order of the day in the current regulatory framework." And I'll be honest: it's been a somewhat disheartening journey. At Steep Hill, we want to be able to do the best science that we can do – that's why and how we began. We want to earn our stripes because we offer the best service and help our customers identify potential problems before they become truly problematic. And I am sure we are not alone. Current regulations are stifling these ambitions.

What can we do? Well, I now think standardization is looking like a very attractive option. I'm planning to join relevant working groups at the Association of Official Analytical Chemists (AOAC) and American Oil Chemists' Society (AOCS) to help craft the future direction of regulations and testing methodology in our industry. And I urge my science-driven colleagues in cannabis testing to do the same.

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# PERSPECTIVES ON PAIN

From early-stage research to clinical practice, four experts offer their take on the potential of cannabis-based pain relief.

If you conducted a straw poll on the medical indications of cannabis, pain will likely shoot to the top of the list. With a relatively solid safety profile, legalization advocates claim that cannabis-based treatments may be a magic bullet for the chronic pain that plagues as many as 1 in 5 Americans – and thus an answer to the country's deadly opioid epidemic. Notably, an estimated 67 percent of US cannabis prescriptions are already for chronic pain relief (1).

But beyond the anecdotes and hyperbole, there is mixed evidence for the efficacy of cannabinoids in the treatment of pain (2, 3) – perhaps unsurprising given the huge range of causes and types of pain. We spoke with four experts working across the spectrum of pain research to get a clearer idea of the state of the field – from biologists shedding light on the role of the endocannabinoid system in pain and inflammation, through to doctors running (tightly-regulated) clinical trials and assessing the impact on their patients.

# THE CELL BIOLOGIST

With E. Alfonso Romero-Sandoval, Associate Professor of Anesthesiology at Wake Forest School of Medicine, Wake Forest University, North Carolina, USA.

*What is the focus of your research?*

We use animal, cellular and molecular models to better understand whether engaging the endocannabinoid system is beneficial in conditions causing pain or inflammation (4, 5). We investigate synthetic cannabinoid molecules selected to specifically target cannabinoid receptors found on immune cells (rather than neuronal cells) and help damp down excessive inflammatory processes, while avoiding psychotropic effects. We use models that mimic the effects of cannabinoids applied topically (through the skin), assessing their impact on skin cell function under inflammatory conditions. Our work is a long way from the clinic, but our initial results have been promising.

*What do we already know about cannabinoids and pain?*

Not enough! Research efforts so far have focused on enhancing the activity of endocannabinoids to reduce pain signaling. This has proven challenging – for example, some components of the system seem to attenuate the inflammatory processes, but we do not know whether this is clinically relevant. Nevertheless, when the whole cannabis plant is used, particularly when inhaled, some patients suffering from chronic neuropathic pain report partial relief (6). Our current drugs to treat neuropathic pain (pain caused by alterations in the nervous system) are only partially effective and only in a portion of patients so any new therapeutic options would be exciting.

The evidence suggests that THC is necessary to induce an effect in these patients. Interestingly, the concentrations of THC required are rather small – in the order of 5 percent or less, in some cases up to 10 percent, but certainly not higher. By contrast, cannabis used recreationally is highly potent (> 15 percent THC).

So far, we do not have any quality scientific evidence that CBD is helpful for pain conditions. The fact that CBD does not produce intoxicating effects (in contrast to THC) has created the false perspective that it is the "medicinal" cannabinoid. As a result, it has been highly marketed for multiple conditions for which there is no clinical evidence that it is useful. We need to have more studies on CBD to better understand the risks and real potential. CBD has proven to be effective in patients with specific severe epileptic syndromes that do not respond to classic treatments. We do not have that evidence for any other condition, including pain.

## THE NEUROPHARMACOLOGIST

With Richard J Miller, Professor of Pharmacology and Psychiatry and Behavioral Sciences at the Feinberg School of Medicine, Northwestern University, Illinois, USA.

*Tell me about your background…*

My work is focused on understanding how drugs interact with the nervous system. Over the years, I've worked on a wide variety of drugs and conditions; more recently, I've become involved in several projects that are focused on pain and the drugs used to treat it, including cannabis – a decision that has emerged naturally from the growing scientific and societal interest in the drug.

People have been using cannabis for thousands of years and have long remarked on its medicinal properties, including pain relief. Up until the 19th century it was freely available at pharmacies, and the idea that it should be an illegal substance only really surfaced in the 1930s, driven by political considerations. Now that we are moving away from prohibition, we are rediscovering the plant as a medicine. The difference now is that we have much more sophisticated technology, which allows scientists to evaluate claims about its efficacy.

*How do pain and cannabis intersect?*

There are cannabinoid receptors – specifically CB1 receptors, which bind THC – that are expressed in neurons responsible for sensing pain in the peripheral nervous system. CB1 receptors are also present in the central nervous system, including the neurons that decode these sensations into conscious experience (7). Given the locations of these receptors, it is not entirely surprising that their activation (by the body's own endocannabinoids) may have something to do with pain control.

The question arises: if we introduce THC into the body, will that impact pain perception? The current evidence suggests that it does. To be sure, we need to apply the gold standard in testing drug efficacy, the clinical trial – but that's difficult to do when the substance you want to administer is illegal in many countries and states.

*What evidence do we have?*

There are certainly some interesting case studies. Recently in the UK, the case of Jo Cameron gained significant attention (8). Cameron has two genetic mutations that cause her to express very high levels of endocannabinoids; she is also completely unable to feel pain. Based on this and evidence from observational studies over the years, it does seem entirely possible that cannabinoids, particularly THC, could offer pain relief.

*What's next for research in this field?*

It's a very exciting time – changes in the law have led to the re-emergence of real scientific interest in the field. There is a long road ahead to develop effective, safe cannabis-based drugs but I expect to see a huge amount of new scientific evidence emerge over the next decade. Already, promising studies are being published in cancer and osteoarthritis. Eventually, I think cannabis will once again become a widely-used medicine around the world.

# Can Cannabis Help Control the Pain Epidemic?

## PAIN IS A PERVASIVE PROBLEM

**1 in 5**

Americans suffer from chronic pain (1).

**1.5** *billion*

people globally suffer from chronic pain (2).

## PATIENTS PREFER CANNABIS

**828**

patients were asked if they preferred cannabis or opiates for their pain treatment (4)

**80%**

found cannabis more effective than opiates for pain management

**93%**

would use cannabis as a substitute if available to them.

**92%**

found the side effects of cannabis more tolerable than those of opiates.

## CANNABIS IS WIDELY USED

**1 in 7**

Americans are cannabis users (3)

Medical cannabis patients who reported taking the drug for chronic pain **67.5%**

## WHAT'S THE EVIDENCE?

> "There is conclusive or substantial evidence that cannabis is effective for the treatment for chronic pain in adults."

*Committee on the Health Effects of Marijuana, National Academies of Sciences, Engineering and Medicine*

*Sources: (1) S Keyhani et al., Ann Intern Med, 169 (2018) (2) NIH Report "Defining the Prevalence of Chronic Pain in the United States. (3) Institute of Medicine (US) Report "Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research". (4) A Reiman et al., Cannabis Cannabinoid Res, 2 (2017).*

## THE CLINICAL RESEARCHER

With Albert Dahan, Professor of Anesthesiology at Leiden University Medical Centre, the Netherlands, Founder and Head of the Anesthesia and Pain Research Unit at Leiden University, the Netherlands.

*What is the goal of your research?*

We focus on the effects and side-effects of opioids. In the US, the misuse of opiates has reached epidemic proportions. The situation here in the Netherlands is not so severe, and yet we still have what I would describe as a "silent epidemic." We started by comparing different opioids, and once the severity and prevalence of opioid side-effects became apparent, we started to look at alternatives. That's how we began working with medicinal cannabis – there is some evidence that cannabis may be effective for pain so we got in medical-grade cannabis growers Bedrocan and began discussions about how we might work together.

Our most recent publication (9) is the result of a rather complex pharmacokinetic and pharmacodynamic study.

*Please, tell us more about that study…*

We wanted to understand how cannabinoids – and in particular THC and CBD – affect pain processes. We decided to work with fibromyalgia patients because they are a large population of patients experiencing severe chronic pain. It's a very heterogeneous group with very few treatment options. To establish whether CBD and/or THC had an impact on pain we carried out an experimental pain study, using a selection of pain tests. This is in contrast with the majority of studies on cannabis for pain, which take an observational approach.

*What did you find?*

Firstly, there was a huge difference in the effect of CBD and THC on pain – CBD had no analgesic effect; in contrast, THC had a powerful effect. We were surprised by this result, because many pain patients use CBD oil and report a good effect. It might be that they do not experience true pain relief, but rather an alteration in mood or quality of life. It should also be noted that this was a small study (20 patients) and we only tested a single application – one inhalation of cannabinoid extract for about five minutes, followed by five to six hours of follow-up.

What was even more significant was the observation that when you combine the two cannabinoids, CBD appeared to enhance THC uptake. We have a couple of explanations for this; we think that CBD uptake might increase flow across the blood brain barrier, thus driving uptake of THC. Alternatively, some CBD might be metabolized into THC.

Next, we will look at the interaction between cannabis and opioids to see if they might interact synergistically. You would hope to see pain relief but with reduced toxicity and side-effects, and reduced abuse potential.

# THE PAIN CONSULTANT

With Attam Singh, Consultant at The Medical Cannabis Clinic, London, and The London Pain Clinic, UK.

*How did you get interested in medicinal cannabis?*

It is an area that everybody seems to be talking about – especially doctors in the pain sector. We are dealing with a symptom that is highly subjective and that makes it difficult to measure. Often, we will hear very positive reports about a medication from patients, but when we try to transpose that into a clinical trial with a much more formalized processes and management, the results often do not match up to the expectation.

*Can cannabis really be a viable therapeutic?*

There are a lot of unknowns. As physicians, our first rule is to do no harm. When we try any new intervention, we are very cautious. One of the things I see from my colleagues in the pain field is a desire for more evidence. They want to be educated about cannabis and to know more about what they can prescribe. They also want to see it in action before they start prescribing. Once we start supporting the field – in meetings, in conferences, in studies and clinical trials – it should help steer us towards pioneering these treatment options.

*How are you supporting research?*

All of our patients at The Medical Cannabis Clinic are enrolled in clinical trials because we think it is important to get as much high-quality evidence as possible. Particularly here in the UK, there is a really big push to determine exactly what conditions these products are beneficial for. We want concrete clinical evidence – with guidelines for prescription and precaution – before we see more widespread adoption of cannabinoids as a medical treatment. I do feel that we will get there, and I think we are making a positive first step. When medical cannabis eventually takes off, I can see the market exploding into life.

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# Pesticide Analysis in Oil-Based Cannabis Products using UCT's LipiFiltr®

Cannabis testing laboratories face the difficult task of removing a variety of unwanted matrix components from their samples prior to LC-MS or GC-MS analysis. High-lipid samples, in particular, pose a major challenge when testing for a large number of pesticide residues that have different physicochemical properties and need to be detected at very low concentrations. To overcome these challenges, UCT recently introduced a new product for the quick cleanup of fatty samples – LipiFiltr®. The ability to obtain significantly cleaner extracts, ease of use, and time and cost savings make the new LipiFiltr® push-thru cartridges an attractive option. This featured application note outlines the performance benefits achieved using LipiFiltr® for the analysis of pesticides in oil-based cannabis products. The pesticides evaluated in this study include those listed in the Oregon monitoring list (~60 pesticides). CBD oil was used as the representative matrix. A comparison of pre- and post-LipiFiltr® clean-up using full scan GC-MS is also presented to demonstrate the removal of lipid co-extractives.

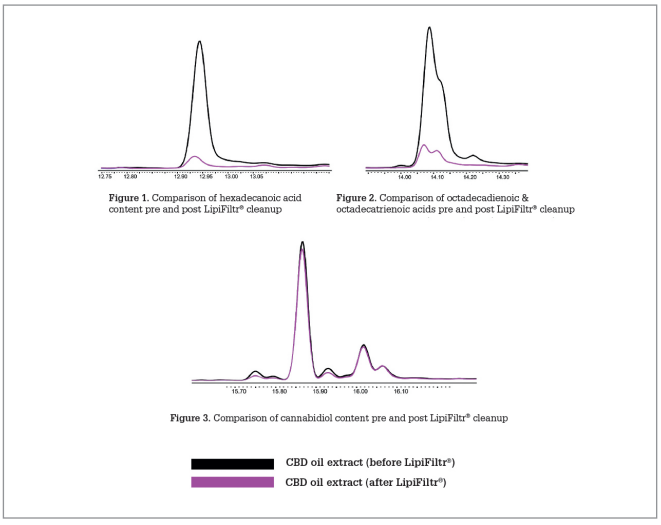



**Figure 1.** Comparison of hexadecanoic acid content pre and post LipiFiltr® cleanup

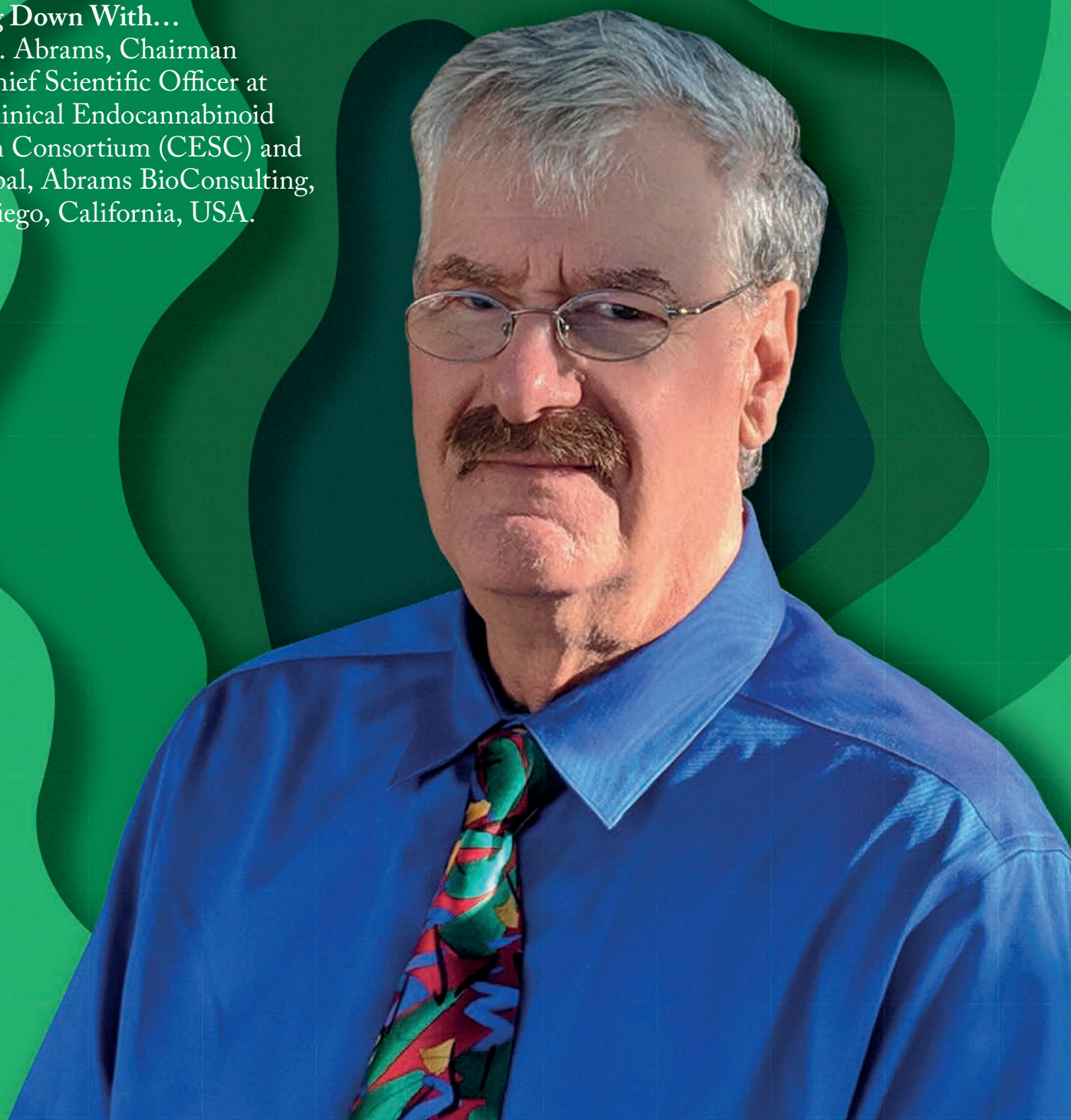
**Figure 2.** Comparison of octadecadienoic & octadecatrienoic acids pre and post LipiFiltr® cleanup

**Figure 3.** Comparison of cannabidiol content pre and post LipiFiltr® cleanup

*Download UCT's full application note for oil-based cannabis clean-up using LipiFiltr® here: tcs.txp.to/UCT0819*

# Cannabinoid Collaborator

**Sitting Down With…**
John S. Abrams, Chairman and Chief Scientific Officer at The Clinical Endocannabinoid System Consortium (CESC) and Principal, Abrams BioConsulting, San Diego, California, USA.



What is your scientific background?

I've been in biotech and pharma for over 40 years. The discovery of monoclonal antibodies came while I was at grad school in the 1970s, and as a budding immunologist it was natural to turn my focus towards these revolutionary new therapeutics. I rode the antibody technology wave, creating tools and reagents for the immunology field.

Today, biologics are blockbuster drugs, but initially they were treated with skepticism – luckily, I was never afraid to go against the grain. During the 1990s, my lab invented a therapeutic antibody that ultimately became a registered drug worldwide for severe asthma and, along with several other important drugs, pushed the pharma industry into recognizing antibody therapeutics as a valid product.

How did you go from biopharma to cannabis?

Growing up in the Bay Area in California in the late 1960s and then at the University of California, Berkeley in the early 1970s, cannabis was very prevalent, and I was fascinated by how people "get high" – what neural circuitry is responsible for altered states? Back then, you couldn't pursue such questions, so I put that on the back burner and thought perhaps I would come back to it when the time was right…

By the 2000s, medicinal use of cannabis had become a hot topic. Cannabis science had progressed immensely since my college days and a whole vocabulary of receptors and endogenous ligands had sprung up – the endocannabinoid system. Like a moth to the light, I started to gravitate towards the field.

I came across a publication that documented methods for analyzing the various active ingredients in cannabis by liquid chromatography and felt that this would be my route into the space.

What was your first foray into cannabis science?

While there were a few publications coming out, there was no formal training and no certification for cannabis analysis back then. But there were garage analytical labs that would test cannabis for growers – and so I found myself networking in the back alleys of San Diego, sharing my scientific expertise with early-stage labs in exchange for learning more about the field.

Nearly a decade on, I act as a consultant to help groups and organizations who are working towards making label claims for cannabis-related medicines. In addition, I now have the chance to explore the question that intrigued me early on – what are the biological mechanisms behind the mental and physical effects of cannabis?

How did the Clinical Endocannabinoid System Consortium (CESC) come about?

Like so many of the best ideas, it originated in a conversation over a beer. As I explored the nascent cannabis industry, I became acquainted with one of the leading cannabis clinicians in California – Jean Talleyrand. He commented that one of the biggest issues he faces in prescribing cannabis is the lack of information on dosing. That's how the Dosing Project was born, and we formed the nonprofit CESC as a home for it.

Tell us more about the Dosing Project…

It is an anonymous observational study, tracking the type and dose of medical cannabis taken by patients. We targeted patients smoking cannabis flowers for pain and disordered sleep. By combining patient-reported information about THC:CBD ratio, the height and weight of subjects and the number of "hits" taken, we have been able to estimate the dosage required to achieve a response – typically one milligram per kilogram. We are now expanding the project to include more indications, adverse event data and detailed potency information.

How did you become Scientific Director of the Emerald Conference?

During my tenure with the garage labs, Emerald Scientific was moving into the cannabis testing space and decided to set up a scientific conference – they held the first event in San Francisco, and approached me to speak. I'd been giving scientific talks in the immunology space for years, but speaking in public about cannabis science was a new experience for me – I have presented every year since. Last year, they asked me to become the scientific director – a great honor and a wonderful opportunity to meet other scientists in the field.

I was trained at the DNAX Research Institute (Schering-Plough) by Nobel laureates, including Arthur and Roger Kornberg and Paul Berg, who were at the forefront of immunology and molecular biology and expected absolute scientific rigor. I want to bring that attitude to cannabis science and events like the Emerald Conference are an important step.

Collaboration is vital to scientific progress, and next year's Emerald Conference will feature a pre-conference online portal to help connect researchers.

What is the biggest misconception about medical cannabis?

That it will cure everything! The expectation needs to align with reality, guided by sound scientific studies. We have the luxury that we don't have to do first-in-man studies – because cannabis has been used by humans for millennia. That should mean that we can go faster, further and harder.

*The next Emerald Conference takes place on 26–29 February, 2020 in San Diego, California, www.theemeraldconference.com*

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