MAY 2019 # 07

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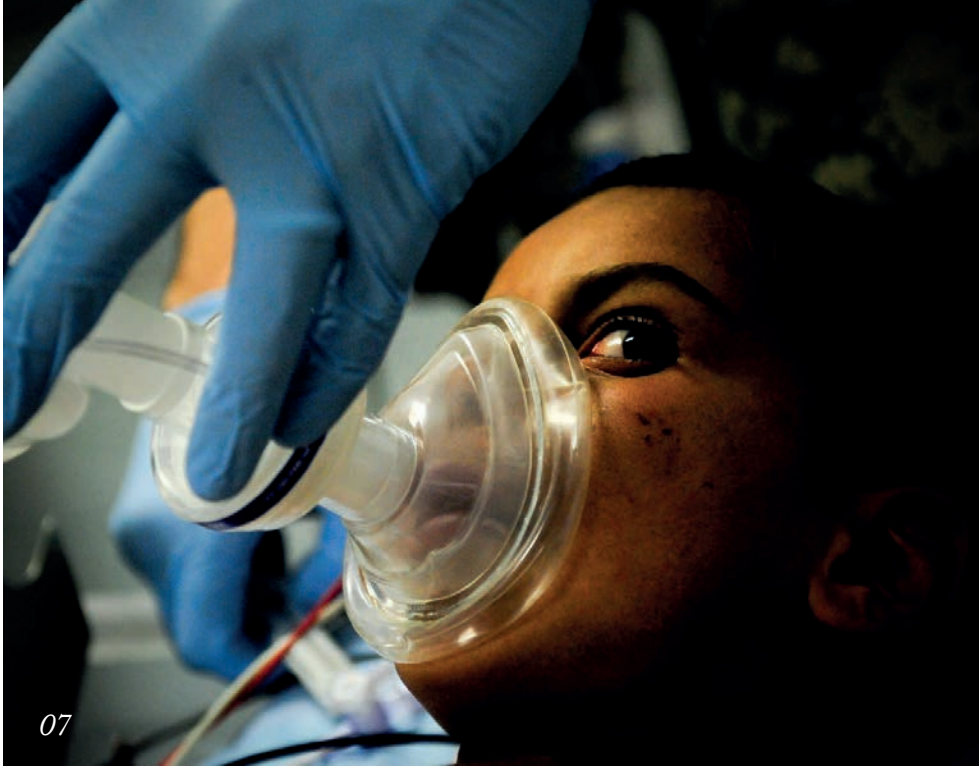

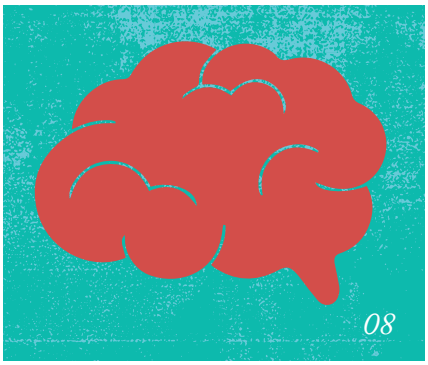

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Under Attack

How will the cannabis industry respond to space invaders – fight or flee?

The cannabis universe is expanding. New centers of gravity are forming. New stars are bursting into life. New discoveries are popping up on the scope every day. The Cannabis Scientist blinked into existence in reaction to the rapidly rising levels of excitement and expectation resulted from the explosive growth.

But among the bright points of light in our cannabis universe, there is darkness – and thus doubt and fear. Some uncharted areas are simply waiting for ambitious explorers – scientists willing to do the legwork needed to unravel a whole galaxy of new information.

Threats also lurk out there in the gloom and confusion, slowly uncoiling.

I spoke at length with Steep Hill's Reggie Gaudino for the Sitting Down With interview on page 26. Our conversation moved apace, and we only have room in the printed version for perhaps half of the resulting article (fear not; you can read the full version at tcs.txp.tpo/0519/gaudino.) We also touched upon three topics that require more space and more time (more space-time, if you wish to continue the opening analogy).

First, the evolving regulatory landscape is currently fueling an analytical race to the bottom, where cannabis-testing labs with less sensitive instrumentation (or lower levels of expertise) are being rewarded with the business of growers who, perhaps unsurprisingly, prefer higher limits of detection. As Reggie says, "Good science is not necessarily the order of the day."

Second, traditional approaches to pheno-hunting – rubbing stems and sniffing fingers – retain a curious and loveable "plant whisperer" vibe but, as internal competition heats up and as Big Agribusiness targets a new cash crop in earnest, a more scientific approach must be applied to all aspects of cannabis cultivation. As Reggie says, "If the cannabis industry doesn't step up and do it – somebody else will."

And third, Big Pharma too is flexing its muscles (see page 14) and the lines between pharmaceutical and medical cannabis are blurring. "Prior art" is a sketchy subject in the cannabis science world, where research has historically been hampered. How will the industry be affected by (overly) broad patents? As Reggie says, "There's a storm brewing."

It seems to me that science plays a critical role in all three of these issues. The expanding cannabis universe needs more intrepid explorers, like Reggie, who can navigate the dark matter and black holes – and guide us all into the light.

Rich Whitworth
Content Director

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

Fishing for Answers

Clues from zebrafish suggest a key role for cannabinoid receptor 2 in behavior

The zebrafish (Danio rerio) has a long history as a model organism in genetics studies, thanks to its quick reproductive cycle, small size, and the similarity of their genetic makeup to human systems.

Agnes Acevedo-Canabal and colleagues recently used this unique organism to investigate how cannabinoid receptor 2 (CB2), a component of the endocannabinoid system, affects behavior (1). CB2 is thought to be the receptor responsible for many of the medicinal properties of cannabis, in part due to its role in reducing inflammation.

The team used CRISPR-Cas9 technology to produce zebrafish offspring lacking functional CB2 receptors ('CB2 knockouts') and compared their behaviors with those of normal ('wild-type') zebrafish in a number of tests, including assessment of their responses to light and their tendency to occupy a predefined central area of their tank. The tests were then repeated while exposing the fish to two drugs: valproic acid, an anxiety-reducing drug, and pentylenetetrazol, an anxiety-inducing drug.

A number of differences were observed in the behavior of the CB2 knockout fish versus their wild-type counterparts. First, CB2 knockout fish travelled significantly less when exposed to light and significantly more in the dark. Second, CB2 knockout fish avoided the center of the tank, preferring to stick to the edges. And third, they were affected differently by the drugs administered; valproic acid did less to reduce swimming activity in CB2 knockouts, for example, while pentylenetetrazol led to increased hyperactivity among knockout fish when transitioning from dark to light. The authors write, "We showed that larvae lacking CB2 behave differently in complex behaviors that can be assimilated to anxiety-like behaviors. Mutant larvae responded differently to valproic acid and pentylenetetrazol treatments, providing in vivo evidence of CB2 modulating complex behaviors."

The research provides new clues to the wide-reaching functions of cannabinoid receptors, and the authors add that their approach could potentially be scaled up for use in drug discovery.

Reference

1. *A Acevedo-Canabal et al., "Altered swimming behaviors in zebrafish larvae lacking cannabinoid receptor 2," Cannabis Cannabinoid Res, Online ahead of print, DOI: 10.1089/can.2018.0025, (2019).*

I Wanna Be Sedated

Frequent cannabis users may be less responsive to commonly-used clinical sedatives

With an ever-growing number of cannabis users attending medical services, Mark Twardowski and colleagues were interested in the effect cannabis use might have on patient response to sedatives – THC binds to the body's cannabinoid receptors, which can interact with opioid and benzodiazepine receptors.

The researchers studied the medical records of 250 patients undergoing an endoscopic procedure in Colorado, 25 of whom were daily or weekly cannabis users and 225 of whom were non-users (1). The sample was reviewed in terms of age, sex, alcohol habits, and receipt of benzodiazepines and opiates. The amount of sedation required in cannabis users versus non-users was assessed using the t-test and Mann-Whitney U test.

In this group, cannabis users required 14 percent more fentanyl, 20 percent more midazolam and 220 percent more propofol than non-users to achieve optimum sedation for their procedure. The numbers demonstrate a clear trend, but what implications do these findings have for the treatment of cannabis users in everyday clinical practice?

As cannabis users were more likely to receive close to the maximum recommended dose of each drug than non-users, they may be more likely to experience dose-dependent adverse effects. There is particular concern that the increased sedative dose may increase the risk of suppressed respiratory function.

The authors suggest that healthcare providers consider specifically asking patients about cannabis use prior to administering sedation, concluding "Determining cannabis use before procedural sedation can be an important tool for planning patient care and assessing both medication needs and possible risks related to increased dosage requirements during endoscopic procedures."

Reference

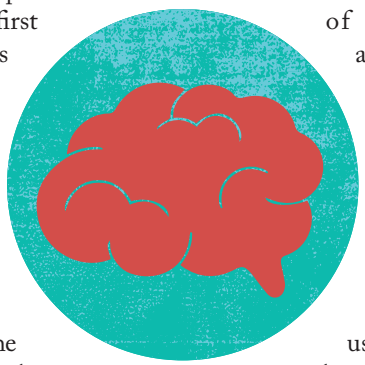
1. *MA Twardowski et al., "Effects of cannabis use on sedation requirements for endoscopic procedures," J Am Osteopath Assoc, 119, 307–311 (2019). DOI:10.7556/jaoa.2019.052*

Cannabis on the Brain

Frequent use of high-potency strains is linked to a five-fold increase in psychotic disorder risk

Claims of adverse effects from cannabis range from cardiovascular disorders to abnormal brain development. But perhaps the most frequently discussed health impacts are those affecting mental health – and a recent study adds compelling new evidence (1).

The aim of the case–control study was to investigate the link between cannabis use and incidence of psychotic disorders. The researchers focused on patients presenting with their first psychotic episode across several sites in Europe and Brazil, and used logistic regression models based on Europe-wide and national data on the expected concentration of THC in different types of cannabis to uncover the potential associations. "A higher incidence of daily cannabis use and more frequent use of high-potency types led to a greater number of new cases of psychosis per person-year," says lead author Marta Di Forti. The findings, she says, tally with her own clinical experience as a psychiatrist in London, where high-potency cannabis is widely available.



When using high-potency cannabis, the study demonstrated a risk of psychotic disorders approximately five times higher for daily users compared with those who never use the drug. When not considering cannabis strength, the risk was approximately three times greater for daily users. The team estimate that roughly 30 percent of cases of first-episode psychosis in London and 50 percent in Amsterdam could be prevented, if high-potency cannabis was no longer available.

Asked about the significance of high- versus low-potency strains, Di Forti drew an analogy to alcohol: "It is like the difference between beer and vodka in terms of liver damage. More potent cannabis has more THC, the cannabinoid associated with psychotic symptoms." Continuing the comparison, Di Forti believes that the results will be applicable to any culture in which cannabis is accessible, just as the health impacts associated with alcohol use are apparent wherever alcohol is found.

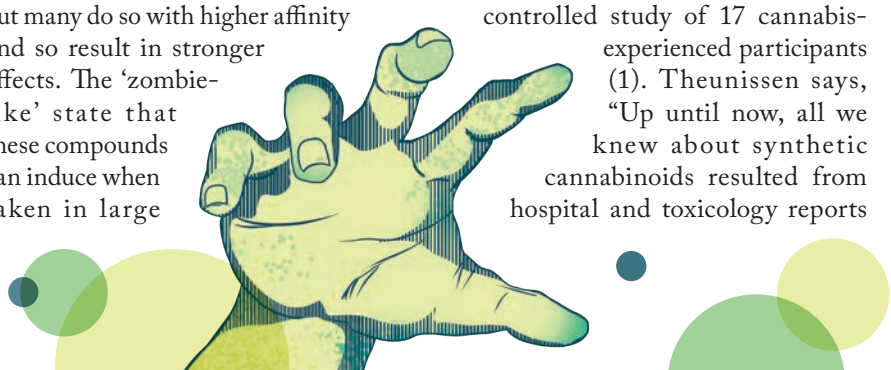
Reference

1. *M Di Forti et al., "The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study," Lancet Psychiatry, 6, 427–436 (2019). DOI: 10.1016/S2215-0366(19)30048-3*

Dawn of the (Synthetic) Dope

Exploring the 'zombifying' effects of synthetic cannabinoids

Synthetic cannabinoids, such as "Spice" or "K2", have exploded in popularity over the past decade. Over 150 synthetic cannabinoids are now known, each with differing potencies. These novel psychoactive substances bind to the same cannabinoid receptor as THC, but many do so with higher affinity and so result in stronger effects. The 'zombie-like' state that these compounds can induce when taken in large doses has become notorious.



To better understand the effect of synthetic cannabinoids on users, Eef L. Theunissen conducted a placebo-controlled study of 17 cannabis-experienced participants (1). Theunissen says, "Up until now, all we knew about synthetic cannabinoids resulted from hospital and toxicology reports

and animal research. These are valuable, but to have a full-scale risk assessment, a well-controlled experimental study in humans was needed."

Participants were given doses ranging from 2–6.2 mg of JWH-018 – a synthetic cannabinoid four-to-five times as potent as THC – or a placebo. A test of subjective experience was performed and participants were subsequently classified as "responders" or "non-responders". Among responders, serum concentrations of JWH-018 were higher, reaction times were slower, and levels of confusion, amnesia, dissociation, derealization and depersonalization were higher. In terms of physical effects, both heart rate and blood pressure were increased following administration of JWH-018 versus placebo. There was substantial variability in the subjective responses of participants, with some suffering impairment even at low doses.

Theunissen says, "We have been able to show how concentrations of the drug relate to the behavioral effect, which is valuable information for their risk assessment." Yet, the outcomes of the study are likely an underestimation of the real-world effects of synthetic cannabinoids, especially for those using smoking mixtures. "These usually contain a mixture of different synthetic cannabinoids, with much higher potencies than used in this study," says Theunissen. Therefore, Theunissen believes similar studies with newer and more potent synthetic cannabinoids are needed to form a complete picture of their effects.

Reference

1. *EL Theunissen et al., "Neurocognition and subjective experience following acute doses of the synthetic cannabinoid jwh-018: responders versus nonresponders," Cannabis Cannabinoid Res, 4, Online ahead of print (2019). DOI: 10.1089/can.2018.0047*

In the News...

The latest cannabis science hitting the headlines

The Cannabis Philanthropist

The founder of a Manhattan-based global equity firm, Bob Broderick, has donated $9 million to Harvard and MIT to further academic research in cannabis. Broderick hopes that his donation will help strengthen scientific evidence on the health impacts and medicinal properties of cannabis.

Read more: https://bit.ly/2H51zbk

Smoke and Mirrors

A new study reveals genetic differences between the cannabis used in US research studies and commercial strains from dispensaries. US cannabis scientists must use cannabis grown for the National Institute on Drug Abuse (NIDA) at a single facility; however, many say that this bears little resemblance to strains sold in dispensaries. The new study lends weight to this assertion, suggesting that NIDA-supplied cannabis may be genetically closer to hemp than to commercially available strains.

Read more: https://go.nature.com/2PL4LwW

Cash Injection

Australian philanthropists Barry and Joy Lambert have donated two million dollars, dubbed the Lambert Innovation Fund, to Philadelphia's Jefferson University to fund research into medical uses for industrial hemp and its derivatives.

Read more: https://bit.ly/2V7r4Tv

Heavy Lifting

In a questionnaire-based study, cannabis users reported that the drug motivates them to participate in exercise. Not only did those who smoke cannabis before or after the gym spend more time working out, they also reported that they enjoyed their workouts more.

Read more: https://bit.ly/2H7t4CI

Munchie Myths

Despite the much-discussed appetite-stimulating effect of cannabis, a recent study reviewing data from 33,000 people in the US found that cannabis users were less likely to be overweight or obese compared with non-users, when assessed by BMI.

Read more: https://bit.ly/2Wr1DJf

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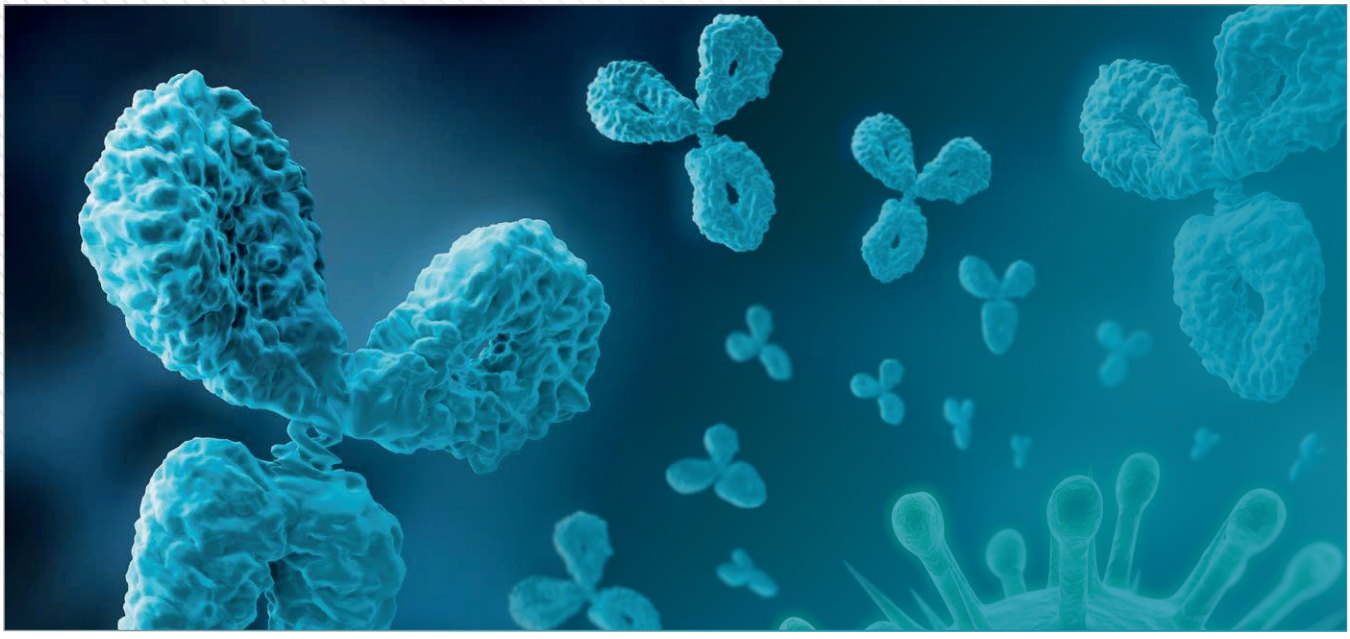

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1. Discover a ground-breaking tool for fast ADCC activity assessment.
2. Learn what FcR receptor affinity tells us about mAb glycoforms.
3. Find out how antibody research, development, and production can benefit.

the Analytical Scientist

TOSOH

Time for Testing

Swetha Kaul is the Chief Scientific Officer at Cannalysis, a state-licensed and ISO-accredited lab in Orange County, California, and an advocate of rigorous, scientific approaches to cannabis testing. We caught up with Swetha to discuss regulation, evolution and the need for nuanced debate.

What was your route into the cannabis industry?

I've always been enthralled by discovering how things work – typical of a scientist – but my first love is method validation. After graduating with a Masters in pharmacology and toxicology and a PhD in analytical chemistry, I worked at Allergan, where I was part of the drug product development team for Botox and other drugs. Though I enjoyed my work at Allergan, the corporate world wasn't for me, and when I met the co-founders of Cannalysis, I saw a perfect opportunity to apply the skills I'd developed. I agreed to help with the initial validation tests, and later joined the company as CSO – it is the most fun I've ever had!

What is it that excites you about the cannabis industry?

The fact that the science is so young. We don't yet have standardized, validated methods, and being involved in developing those standards was very attractive to me as a scientist. It's a huge change from the tightly regulated environment of the pharmaceutical industry. There is tremendous passion within the cannabis industry, but the level of scientific knowledge is quite varied. I think that's what we need to focus on more as an industry – educating each other about the science.

Do you think we need more industry collaboration to standardize methods and best practices?

We definitely do. To date, most labs haven't been sharing information with each other for fear of giving away proprietary information. In some ways, that's understandable, but although specific optimization might be unique to each lab, the basics of these techniques are well established. We are at a point where we need to share information on methods and good practice, if we are to evolve as a field. For example, it's often said that cannabis testing labs give inconsistent results, but by comparing our results with several of our competitors, we have found that there is in fact good correlation in data.

That said, I think we are a long way away from standardized methods. I appreciate the efforts of the AOAC and others, but I think until regulatory requirements are standardized across regions it will be challenging to apply universal methods.

How is changing legislation impacting the industry?

It has had a huge impact. California went into a regulated market on January 1, 2018. As we have made the journey from emergency regulations to final regulations, we have seen changes to many aspects of testing, including the analytes tested for, the limits of quantification (LOQs), and the quality control specifications.

The cannabis industry has sometimes been rather quick to say that new regulations won't work or to paint regulators as "the enemy." It's true that there are challenges within the regulatory framework; these regulations were made without testing standards being available, so there are elements that might not be feasible in the lab. However, I think we will receive a better reception for our concerns if we can have a reasonable dialogue with agencies, rather than taking an adversarial stance. As the industry matures, I think it stands to gain from attracting employees from more traditional industries – especially those who are used to working with EPA and FDA.

People in California are often surprised to hear that 70 percent of the cannabis market in the state is still unregulated, which suggests a need for more education about how the licensing system works and the requirements for testing.

What are the hot topics in cannabis testing at the moment?

Heavy metal testing is one topic at the forefront of everyone's mind. Failures from heavy metal testing are still pretty rare – under 5 percent – but it is a source of concern for growers. An important question is how much of any heavy metals detected comes from packaging versus the cannabis itself.

Another emerging topic is how to test edibles that come from industries with different standards to cannabis. For example, the standards for pesticide testing in cannabis are higher than many food products (because they were set with inhalation in mind). A product that might pass testing in the olive oil industry might actually fail in the cannabis industry. We are going to have to figure out how to address that.

What are the main challenges faced by cannabis testing laboratories?

The biggest challenge is accounting for matrix effects. In most industries, you're looking at a single product and a single matrix. In the cannabis industry, we have thousands of different matrices –

What's Next?

We asked speakers and exhibitors at Emerald Conference 2019 to gaze into their crystal balls and offer their predictions for the industry.

"I think one area that will see a lot of growth in the next few years is cannabinoid synthesis or development from non-plant sources. Whether produced chemically or via yeast or some other organism, there is a lot of research on alternate routes of cannabinoid production, which could allow precise custom blends of different cannabinoids for therapeutic use."

Shawn Helmueller, Chief Scientific Officer, Deutsche Process, Charlotte, North Carolina, USA.

"As methods become more standardized, we will be able to compare data sets from different laboratories, different regions, different states and different products, which will really benefit this industry. We don't test every wine for its flavour profile chemicals, we don't test all of our food for every pesticide that we look for in cannabis – the volume of information we're gathering on cannabis is immense - and that data will give us unparalleled knowledge of the plant."

Savino Sguera, Founder and Chief Scientific Officer, Digamma Consulting, Oakland, California, USA.

"I predict a lot of lab mergers in coming years. The laboratory industry is very expensive to operate in terms of instrumentation, consumables and staffing, making economies of scale important – and smaller, less sophisticated labs are unlikely to survive in a highly regulated environment."

Chris Hudalla, Founder and Chief Scientific Officer, ProVerde Laboratories, Milford, Massachusetts, USA.

"I believe we need to look toward the diagnostic industry, who are increasingly using automation and robotics to ease bottlenecks – that kind of innovation might be a few years away but I think it is coming to this industry."

Swetha Kaul, Chief Scientific Officer, Cannalysis, Santa Ana, California, USA.

apart from the flower, oil and tinctures, we have a huge variety of edibles, beverages and topicals. How can you standardize testing if the matrix keeps changing? The challenge is even greater because the industry is very sensitive to the cost of testing.

In California, the big challenge for testing labs this year will be ISO accreditation requirements coming into effect. Although our lab is ISO accredited, most labs with temporary licenses are still working towards full accreditation, and some may struggle to achieve the standards required.

How have perceptions of the cannabis industry changed in recent years?

The legitimization of this industry has been ongoing. The field attracts some big personalities, and I hope that's something we never lose, but it's good to see that in many ways we are now just like any other industry.

As medical research progresses, I would like to see the narrative move on from the idea that CBD is the medicinal cannabinoid and THC just gets you high. The reality is likely more nuanced. That said, I think we also need to be more open and realistic that cannabis is not a panacea and not suitable for all patients. In this industry, we have been reluctant to talk about potential harm from cannabis, because there is so much negative messaging from opponents of legalization. But it seems clear that, for example, young people with developing brains shouldn't be consuming psychoactive drugs. We need to be able to discuss these issues from a scientific standpoint, without taking sides.

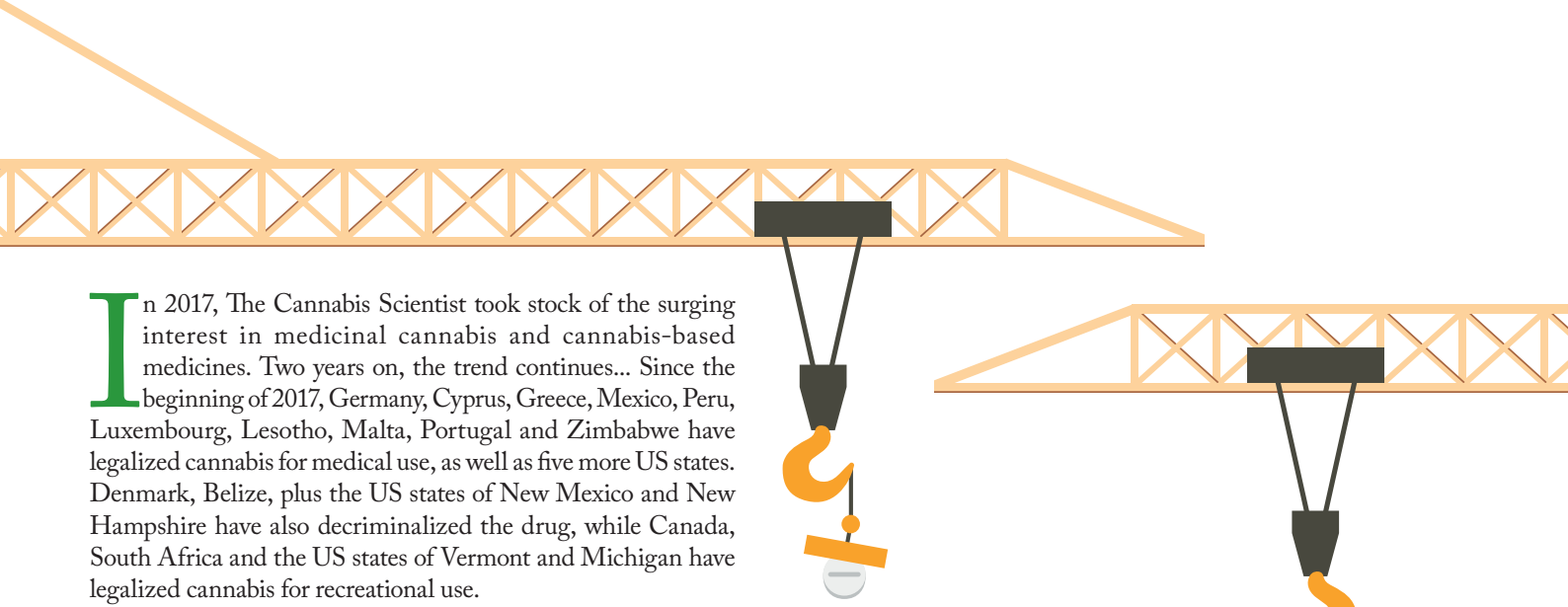
Final thoughts?

Testing labs have a serious responsibility. It's not just about meeting regulatory compliance requirements – we are the sole barrier to unsafe products entering the supply chain. Analytical excellence is just as important for us as it is for testing labs in any other field, but right now we have a lot of different actors within the lab industry with varying levels of experience, knowledge and accreditation. We need to set standards – for example, ISO accreditation and third-party proficiency tests – that customers can trust.

PHARMA TAKEOVER: UNDER CONSTRUCTION?

With medicinal cannabis now legal in many territories, can pharma improve upon nature with cannabis-based drugs? And how will drugmakers entering the fray deal with the dosage, delivery and bioavailability challenges of cannabinoids?

By James Strachan



In 2017, The Cannabis Scientist took stock of the surging interest in medicinal cannabis and cannabis-based medicines. Two years on, the trend continues... Since the beginning of 2017, Germany, Cyprus, Greece, Mexico, Peru, Luxembourg, Lesotho, Malta, Portugal and Zimbabwe have legalized cannabis for medical use, as well as five more US states. Denmark, Belize, plus the US states of New Mexico and New Hampshire have also decriminalized the drug, while Canada, South Africa and the US states of Vermont and Michigan have legalized cannabis for recreational use.

With recreational cannabis legal in 10 US states and medical cannabis legal in 32 states, cannabis has become big business. One study found that, in the US, manufacturers and distributors, on both the recreational and medicinal sides, created 64,389 new jobs in 2018 – making it the fastest-growing labor market in the US (1). Sales of recreational cannabis are expected to grow 18.4 percent yearly, from $3.2 billion in 2018 to $12.5 billion in 2025, while sales of medical cannabis are expected to grow 11.8 percent per year from $5.1 billion in 2017 to an estimated $12.5 billion in 2025 (2).

But what about cannabis-based medicines? With medicinal cannabis becoming more widely accepted, will an increasing number of pharma companies seek to explore the therapeutic potential of the plant? Or does the "medical" or "medicinal" label only create confusion (and competition) for companies whose products are held to much higher standards of evidence by pharmaceutical regulators?

The FDA approval of GW Pharmaceuticals' Epidiolex was seen as a watershed moment for the industry, potentially ushering in a new era of cannabinoid medicines. Indeed, a number of companies are now addressing the manufacturing challenges of working with the cannabis plant to create safe and effective cannabis-based pharmaceutical drugs: is extraction or chemical synthesis the way to go? What about bioavailability? What about regulatory hurdles?

IS SYNTHETIC THE REAL DEAL?

A handful of cannabis-based medicines have already received regulatory approval, namely Sativex, Epidiolex (both from GW Pharma) and Dronabinol (marketed as Marinol and Syndros). The active ingredient in Epidiolex is cannabidiol (CBD), which is extracted and purified via crystallization from the cannabis plant, whereas Dronabinol is synthetic delta-9-tetrahydrocannabinol (THC`). There is some debate as to which route holds most promise for the cannabis-based medicines industry.

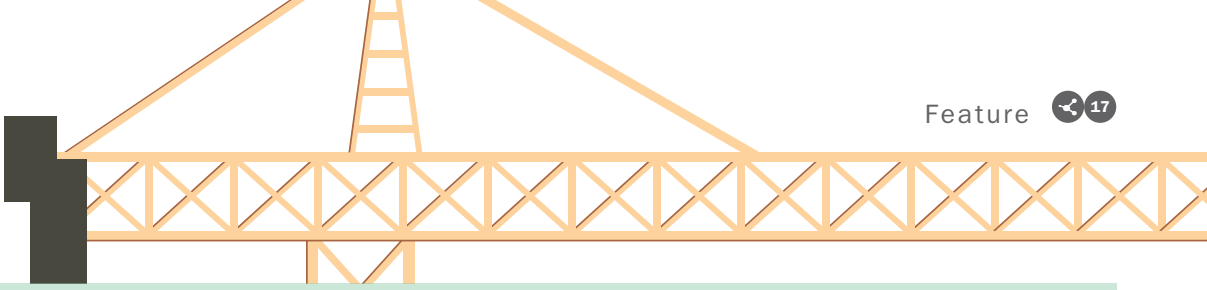
"GW has developed extensive expertise in the growing, extraction, and manufacture of cannabinoids for use within these medicines," says Chris Tovey, Chief Operating Officer at GW Pharmaceuticals. "We believe this tried and tested approach, honed over 20 years, allows us to develop a safe, consistent, and standardized product that patients and clinicians require/demand."

Tovey believes that plant-based cultivation is not more costly nor less efficient than synthetic production. "There are a number of different aspects to synthetic manufacturing that can make it a very costly process; for example, extensive equipment and chemical processes where maintenance and clean-up to remove toxic by-products can be difficult and expensive," says Tovey. "It is not uncommon for a medicine to be derived from plant-based material due to the inherent biological advantage in the synthesis of specific chemical isomers."

Johnson Matthey, which has over 15 years of developing and commercializing cannabinoids, focuses on the synthetic route for its cannabinoids, such as THC and cannabidiol. "Synthetic routes reduce problems with yield and impurity that arise through botanical extraction," says Kevin Hennessy, Global Director, New Business Development at Johnson Matthey. "Methods that rely on botanical extraction could have a high-degree of variability because of crop-to-crop differences." Synthetic routes may also provide for more reliable regulatory compliance, especially where GMP manufacturing is required. "There are no issues with raw material traceability and compliance, whereas farms could be resistant to GMP audits and issues with regulatory bodies," he adds.

Alyn McNaughton, Technical Director for Lonza Pharma, Biotech & Nutrition at its Edinburgh site points out that synthetic cannabinoids do have an advantage over plant-derived products because most plant-derived cannabinoids are classified as controlled substances unless they can be purified to a point where the psychoactive components are below the threshold at which they would be considered controlled (which can create some additional legal hurdles).

But Andrew Badrot, CEO of C^2 Pharma, which manufactures and distributes APIs extracted from plants, including cannabis, objects to the idea that synthetic APIs and naturally extracted APIs



THE CANNABIS TRAILBLAZERS

A short introduction to GW Pharma, the company behind the world's first approved cannabis-based medicine.

By Chris Tovey, Chief Operating Officer, GW Pharmaceuticals.

GW Pharmaceuticals is a UK-based company born in the late nineties – a time when similar conversations to those we have today – about the potential medical benefits of the cannabis plants – were taking place. Indeed, just as in 2017, patients marched on parliament to demand access to cannabis for medical purposes.

In 1998, the House of Lords Science and Technology Committee delivered a report on cannabis and cannabinoids. They concluded that, although cannabis and its derivatives should "continue to be controlled drugs" due to their potential harms, "Clinical trials of cannabis for the treatment of MS and chronic pain should be mounted as a matter of urgency" (1). The message was clear: go forth and seriously study the potential therapeutic benefits of the plant through the usual scientific channels and create a bonafide medicine. And that was the challenge that Geoffrey Guy – who remains chairman – embraced, working alongside Brian Whittle, to found GW Pharmaceuticals that year.

Together, they set out to properly investigate the cannabis plant and 100-plus cannabinoids contained within. They were originally based in Kent Science Park, where the company still maintains a strong presence. For the first 5-10 years, the focus was on research and development, but that work eventually led to the world's first cannabis-based pharmaceutical medicine: Sativex, a cannabis extract administered as a mouth spray, for the treatment of multiple sclerosis – thus directly responding to the original challenge set by the Lords committee.

Sativex, originally approved in the UK in 2010, is now approved in over 25 countries. It is 50/50 CBD and THC, and is a natural plant-based material. Subsequent work focused on a cannabidiol oral solution, Epidiolex; and, in 2015, we initiated Phase III clinical trials for treatment of two orphan conditions in children – Dravet and Lennox-Gastaut syndromes. GW also received fast track designation from the FDA to treat children with epilepsy, which was given FDA approval in June 2018. This was a key milestone for the cannabis medicines industry – the first cannabis-based medicine approved in the US. Sativex isn't yet approved in the US, but we're hopeful that will change in the next couple of years. And we're also hopeful of an EU approval of Epidiolex in the coming months, which would be the first centrally approved cannabis medicine in Europe. We're also looking at additional indications, such as tubular sclerosis (TSC), where we have a pivotal study coming out soon.

The first 10 years or so of research was really the groundwork for our exploration of new therapeutic areas. We see promise in other areas of neurology, oncology and psychiatry, including autism spectrum disorder. Today, we have nearly 6000 patients involved in our clinical trials around the world, we've published 80 articles in peer-reviewed journals and we have generated 80,000 years' worth of safety data.

GW obviously generates a lot of interest because of the plant we're working on. But I'd like to point out that first and foremost, we are a pharmaceutical company trying to develop medicines that will make a difference to patient lives. It just so happens that we work with the cannabis plant. We believe passionately in the potential of the cannabis plant and that the best way to unlock that potential is to subject it to traditional pharmaceutical scrutiny so that we can ensure that the highest standards of safety, quality and efficacy are met.

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are "different." He says, "So long as we are talking about the pure compounds and not an 'extract,' which may contain a combination of hundreds of different compounds, from a chemical standpoint, there is no difference," he says. "The molecule is the molecule." Badrot believes the only difference for API manufacturers is the starting material and the work up methods and purification of the compound versus having to produce it synthetically. "There are different costs and considerations associated with the manufacturing methods employed for synthetic versus naturally extracted APIs," he explains.

Badrot argues that for pharmaceutical companies, the difference will be with the impurity profiles of the API obtained naturally versus synthetically, given the different processes through which they are obtained. "The synthetic API will typically be 'cleaner' and only contain the target cannabinoid; therefore, especially for pharmaceutical indications, the plant extract will need to be purified in such a way that the level of 'immaterial' cannabinoids left in the extract are below the limit of 0.02 percent," he says.

"WHETHER EXTRACTING AND PURIFYING OR CHEMICALLY SYNTHESIZING CANNABIS COMPOUNDS, THERE ARE A NUMBER OF MANUFACTURING CHALLENGES FACING COMPANIES."

MAKING THE MEDICINE

Whether extracting and purifying or chemically synthesizing cannabis compounds, there are a number of manufacturing challenges facing companies. For C^2 Pharma, the challenges aren't at the API level, but rather those around regulations and how to grow and manage cannabis crops. "Hemp can be grown as a crop in certain locations, but with limitations regarding concentrations of THC in the plant," says Badrot. "We are still facing a very fluid landscape, and governmental organizations

BUSINESS-EYE VIEW

By Kris Krane, President at 4Front Ventures

HOW DID YOU BECOME INTERESTED IN CANNABIS POLICY?

It is an issue I have cared about since I was quite young, as my father used medical cannabis to help treat a rare form of emphysema that ultimately took his life when I was eight years old. As I got older, I became an advocate for medical cannabis policy reform, helping found Students for Sensible Drug Policy (SSDP) (add a one liner about what this is) while a college student at American University in Washington DC. I later went on to work at the National Organization for the Reform of Marijuana Laws before taking over as executive director of SSDP in 2006. I formally entered the cannabis industry in 2009.

HOW WOULD YOU CHARACTERIZE THE STATE OF THE CANNABIS-BASED MEDICINES MARKET?

There has been a real increase in attention to and business activity around cannabis-based medicines. The FDA approval of GW Pharmaceuticals' Epidiolex was seen as a watershed moment for cannabis-based medicines in the US, and is expected to usher in a new era of cannabinoid-based pharmaceuticals. The massive success of state-legal medical marijuana markets in the US has already proven a demand for these products. But the federal government's classification of cannabis as a schedule 1 substance has made it extremely difficult for pharmaceutical companies to do research on cannabis-derived medicines, let alone gain approval.

ARE MOST COMPANIES LOOKING AT SYNTHETIC CANNABINOIDS OR CANNABINOIDS EXTRACTED FROM THE PLANT?

Most of the work being done on cannabis medicine seems to focus on plant-derived cannabinoids rather than synthetics. There is an increasing awareness that the entourage effect of the multitude of cannabinoids found in cannabis is more effective for most conditions than isolated cannabinoids. That said, there are a few companies out there like Teewinot Life Sciences, which is looking to produce either synthetic cannabinoids, or cannabinoids bred into and extracted from plants like tobacco, or grown in yeasts.

HOW IS LEGALIZATION IMPACTING THE CANNABIS-BASED MEDICINES SPACE?

Legalization is bringing about more public acceptance for the idea of medical cannabis and cannabis-derived medicines. It is also making it easier for researchers to access cannabis from somewhere other than the tightly controlled and inferior quality cannabis grown by the federal government at their University of Mississippi farm.

Kris Krane is President of 4Front Ventures, which operates in the medical cannabis industry, offering consulting services to companies in the areas such as cannabis cultivation, retail distribution and production, technology.

are not in-sync with each other. As the industry matures, and organizations see the broad range of potential, we believe all those things will be ironed out."

Another key problem that manufacturers face is removing unwanted cannabinoids during the extraction of APIs. "THC presents a real challenge for purification because it is naturally a non-crystalline oil. Impurities are chemically closely related, and prone to thermal and oxidative degradation," says Hennessy. "Purity is critically important as even trace amounts of THC are discouraged by our customers and regulatory bodies." Johnson Matthey invested early in large scale super-critical fluid chromatography (SFC), which Hennessy says works well for water insoluble lipophilic compounds, such as THC.

McNaughton agrees with Badrot that the major challenge in manufacturing synthetic cannabinoids is not necessarily in the chemistry. He sees three main challenges facing cannabis-based medicine manufacturing. The first is in handling and the regulatory aspects. "The non-psychoactive cannabinoids do not always fall under controlled substances regulation, but for those products that still retain their controlled drugs status, the strict controls

around handling and transport means that development activities are extra challenging," he says.

Tovey agrees. GW's growing facilities and protocols, therefore, require highly stringent logistical and regulatory controls. "We are inspected by health regulators like the UK MHRA and the US FDA, and require further inspection and a special license from the UK Home Office to operate," says Tovey. Much like all medicines, cannabis-based medicines are in accordance with "Good x Practices" (GxPs) during their development, which continue beyond regulatory approval and throughout the lifecycle of a medicine. "For us, these include Good Manufacturing Practice (GMP) and Good Agricultural Collection Practices (GACP)," says Tovey. "These GxPs are policed and enforced by statutory bodies with the legal powers to revoke licenses when not followed or adhered to."

Tovey notes that achieving batch-to-batch consistency for plant-derived drugs shouldn't be underestimated. "Due to the differences in cannabis starting materials and methods of manufacture used to prepare cannabinoid/cannabis-based medicines, the chemical profile of the extracts and finished products have the potential to vary enormously – both in terms of the presence of desired components (cannabinoid profile) and undesired components (impurities, degradants and potential adulterants [fungal or bacterial contaminants, pesticides, heavy metals, and so on])," says Tovey.

Cannabinoids are present in the cannabis plant as acids and are inherently unstable in this form at room temperature. According to Tovey, the instability means that it is important to control the extraction and other processes within the manufacturing method (for example, decarboxylation) carefully, as these can affect the content and stability of the resulting extract or product. "It can be challenging to control all of these parameters to maintain batch-to-batch consistency and stability. Achieving a highly bioavailable, convenient, stable dosage form of an appropriate size to allow appropriate titration is therefore a significant challenge when it comes to cannabis-based medicines or cannabinoid/cannabis-based products," Tovey explains.

"MANY CANNABINOIDS ARE LIPOPHILIC AND EVEN IN THEIR PUREST FORMS ARE EITHER OILS OR OILY SOLIDS, RATHER THAN THE WHITE POWDERS SO COMMONLY SEEN WITH MORE TYPICAL PHARMACEUTICAL APIS."

McNaughton echoes the same problems – especially bioavailability – as a second challenge. Many cannabinoids are lipophilic and even in their purest forms are either oils or oily solids, rather than the white powders so commonly seen with more typical pharmaceutical APIs. And that poses challenges for dosage, delivery and bioavailability. "Most cannabinoids suffer from first-pass metabolism and are broken down in the liver before they reach general circulation," says McNaughton. "Consequently, the oral bioavailability of cannabinoids is generally in the region of four to 20 percent, resulting in most of the material swallowed having no effect on the body. Lipidic formulation enables the transformation of oily material into an emulsion that is miscible with water and, therefore, better absorbed by the body. In addition, because these materials are so greasy and have such a high affinity for oils, lipids can also be used to promote lymphatic absorption, which bypasses liver degradation but still delivers the drug substance to the bloodstream."

Tovey adds, "For complex plant-based extracts (such as cannabis extracts), the presence of other non-cannabinoid, typical plant-based components, such as waxes, flavonoids, terpenes, sesquiterpenes and so on, all add to the complexity and solubility issues when trying to find an appropriate formulation."

Finally, according to McNaughton, the dosage form also needs to be adapted to the oily liquid nature of these formulations. "Liquid filled hard capsules and soft gel capsules are ideally suited for this family of medicines," he says.

MEDICINAL, MEDICAL AND RECREATIONAL

Following the legalization of cannabis in Canada, South Africa and several US-states, a big question for pharmaceutical companies in this space is whether debates around legalization and scheduling would make it easier to develop and manufacture cannabis-based medicines. C^2 Pharma sees its business as being totally separate from debates around legalization. "We are talking about two different things," says Badrot. "If you take caffeine as an example, it is applied in both social and pharmaceutical markets, and each one can create their own value stream. Like caffeine, the cannabis market has plenty of space to thrive, but

"EVEN IN COUNTRIES, SUCH AS CANADA, WHICH HAVE ALREADY DECRIMINALIZED CANNABIS, THERE IS STILL VARIATION IN THE INDIVIDUAL PROVINCE OR TERRITORY LEGISLATION."

our interest remains on the pharmaceutical side."

Lonza, on the other hand, has found that differences in legislation can create some logistical problems. "The controlled drugs laws are a large complication in the development of cannabinoids; firstly, as there is a lot of variation in these laws from country to country or even state to state, such as in the US," says McNaughton. "Even in countries, such as Canada, which have already decriminalized cannabis, there is still variation in the individual province or territory legislation. Transporting products to legal zones without impacting areas where it remains illegal is a logistical challenge."

GW Pharma has been asked a lot over the last couple of years whether the legalization of cannabis would make their lives easier. The answer, according to Tovey, is that it wouldn't make a big difference. "Ultimately, because we have chosen to go down the traditional pharmaceutical path, we're almost entirely removed from the debate around legalization and even scheduling, to a certain extent," he says. "We've never had a notable issue in getting the licenses to grow and research cannabis, to do all of the clinical trials and to turn it into a medicine and get regulatory approval." Although Tovey does admit that there were some challenges. "It required a lot of expertise, time and attention to detail. And you have to constantly ensure that you've got your licenses up to date. But we have shown that it is possible to do all of this work within a system in which cannabis isn't legalized, and even where cannabis was schedule one."

Tovey has many good things to say about the environment in the UK for manufacturing and developing cannabis-based medicines – despite the legal status of the plant. "The UK government and regulators have always been supportive in the way they approach things, and we've found the UK to be a conducive and attractive environment for growing and manufacturing cannabis and cannabis-based medicines." He believes that his experience is similar to that of other companies in the UK that hold licenses for growing cannabis and undertaking cannabinoid research. "The UK should be proud that the country is a world leader in cannabinoid research, partly through GW's work, but also through the extensive network of academics we work with."

COMBATING CONFUSION AND CONFLATION

Despite GW's success in the field, there are some misconceptions that pharma companies face.

"We are looking at products derived from a plant that has substantial social implications. Some people believe that anything related to the plant is to be avoided, while others may believe that cannabis-derived compounds will heal everything from your head to your toes," says Badrot. "What we are looking to do is to create a realistic balance between realizing the potential of cannabis and its constituents, and delivering patient solutions that work. Over the next decade, we expect to see a lot of progress in the space and are excited to be one of the trailblazers in the market."

For McNaughton, a major misconception is that all cannabinoids are psychoactive, which isn't the case. In fact, most are not psychoactive at all (cannabidiol, for example). "In some cases, the psychoactive effects may have therapeutic advantages in disorders such as depression, but there is also an increasing body of evidence for the potential for the non-psychoactive cannabinoids as therapies," he says.

He believes that his experience Another major misconception noted by Hennessy arises out of conflating cannabis-based medicines with "medical marijuana" and even recreational pot smoking. "Unlike some of the cannabis-based products that are more readily available in states where they are offered, cannabis-based pharmaceutical medicines have gone through rigorous clinical testing to prove that they are safe and effective," says Hennessy.

"Unfortunately, the science around the active compounds of cannabis – CBD and THC mainly – is still nascent, and even more so when you consider interactions between the two," Badrot adds. "Legally, the term 'medical cannabis' is open to interpretation."

Within the cannabis space, there is a broad array of different products that are commonly referred to as medicinal cannabis or medical cannabis. Tovey says, "That might include some of

the finished products you see being sold in the US or Canada, but it could include some of the CBD products on the shelves, or even people smoking a joint for purported medical reasons. This whole category of products vary greatly in their safety, quality and efficacy, but none have been subjected to double-blind placebo controlled trials – what the pharmaceutical industry would consider hard evidence." He also adds that the term "medical cannabis" is sometimes deliberately conflated with cannabis-based medicines. "There isn't a strong evidence base for those products and we cannot extrapolate from data generated by cannabis-based medicines to a whole group of products," he says.

In a Q&A note, the FDA has stated it "continues to be concerned at the proliferation of products asserting to contain CBD that are marketed for therapeutic or medical uses although they have not been approved by FDA [...] Unlike drugs approved by FDA, products that have not been subject to FDA review as part of the drug approval process have not been evaluated as to whether they work, what the proper dosage may be if they do work, how they could interact with other drugs, or whether they have dangerous side effects or other safety concerns" (3).

Tovey points out that the evidence for GW's cannabidiol oral solution should not be extrapolated to other cannabidiol containing product formulations. "Each product needs to be assessed on its own merit through thorough pre-clinical and clinical evaluation. The safety and efficacy demonstrated in pre-clinical and clinical trials of approved or late-stage investigational

"THERE IS ALSO A COMMON MISCONCEPTION THAT RANDOMIZED CLINICAL TRIALS CANNOT BE CONDUCTED WITH CANNABIS DERIVED MEDICINES."

medicines does not equate to the same efficacy or safety profile in different products of similar or the same cannabinoid composition – doing so assumes different products have been grown and manufactured to exactly the same standards."

There is also a common misconception that randomized clinical trials cannot be conducted with cannabis derived medicines, according to Tovey. "With Epidiolex and Sativex, we have shown that this is not the case." The current lack of randomized controlled trials performed with cannabinoid/cannabis-based products, says Tovey, is due to the lack of quality investigational products. "This is as a result of the challenges around the ability to manufacture and supply a consistent, stable product which can be reproduced throughout a medicine's development and life cycle after market authorization."

Despite this, Badrot believes that the medical cannabis industry is breaking down stigmas, which can only encourage more companies to enter the cannabis-based medicines industry. "The stigma that has been created since the 1920s and the initial ban of 'Indian hemp' during the International Opium Convention is starting to loosen, particularly in a time where we see a critical gap in the pain medication market and the crippling effects of the opioid epidemic. Cannabis offers great potential for safe, effective solutions," he says. "Cannabis is effective, but it is also misunderstood."

As public interest grows in the space, Badrot believes more pharmaceutical companies are willing to explore the opportunities that cannabis presents. "We are just starting to explore what the full potential could be."

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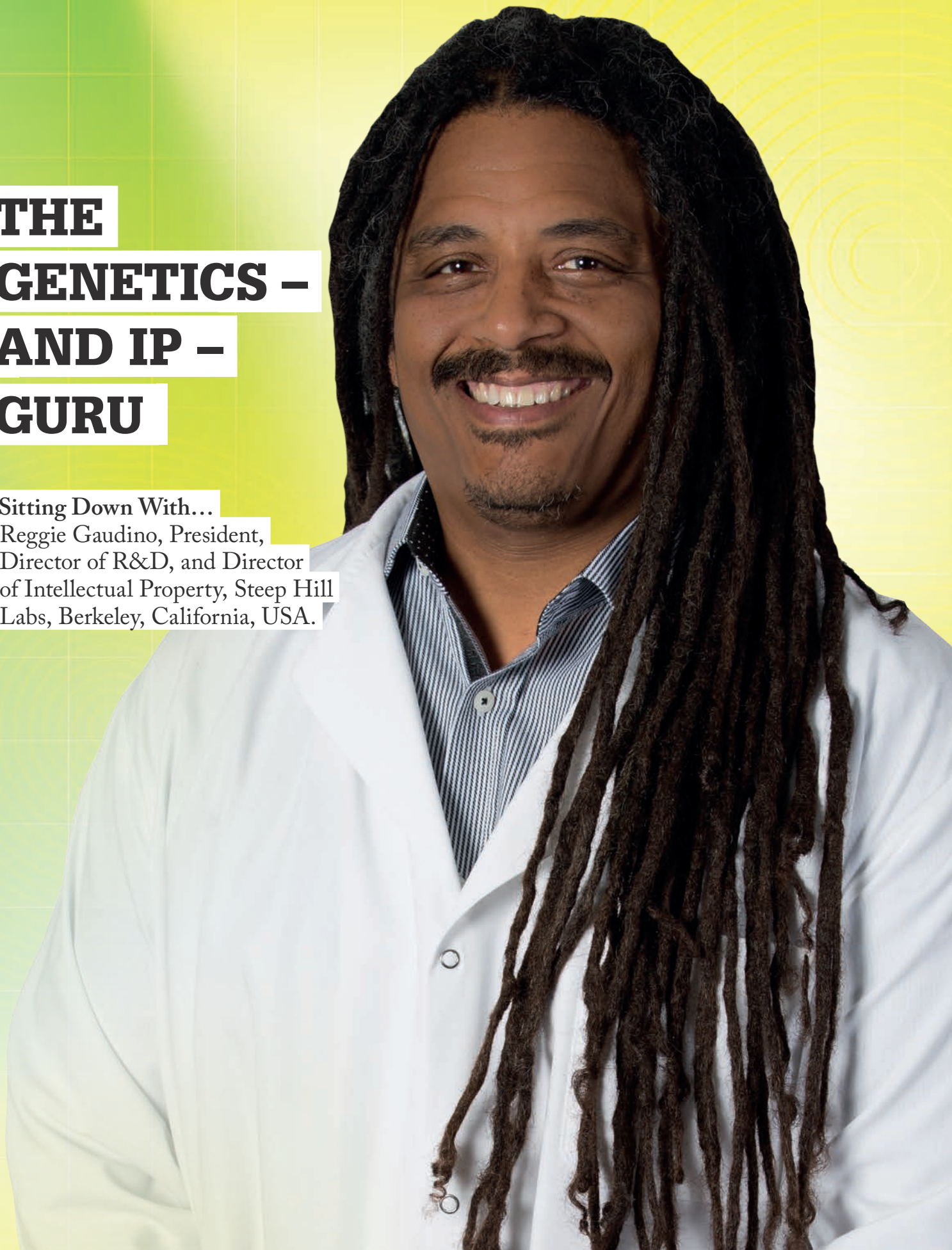
THE GENETICS – AND IP – GURU

Sitting Down With…
Reggie Gaudino, President, Director of R&D, and Director of Intellectual Property, Steep Hill Labs, Berkeley, California, USA.



Genetics researcher and "the patent guy"... What triggered your move into the cannabis industry?

Back in 2014, I was contacted by Steep Hill to do an intellectual property review of their science – to see if they had anything patentable. I starting digging into what amounted to a treasure trove of data that nobody was looking at – real IP. I asked, "Are you doing any research based on this?" And they looked at me like I had a third eye. At that point, they offered me the position of Director of Genetic Analysis and Intellectual Property…

Sounds like a cool position to be in – like a child in a giant sandbox!

It was a dream job – all scientists yearn for such positions, I guess. But it's hard to run a successful business when you're dumping lots of money into a bottomless R&D pit. We operate on small margins, and doing research so that we can first educate and then offer services to the industry becomes an expensive proposition. Going back to the analogy, my bosses hired me and gave me a huge sandbox to play in – but they didn't realize how expensive my toys were!

But you've still done some fine research…

It is true that we have done a lot of great work. But we were horribly underfunded at an important time (and I know I'm not the first or last scientist to say that!). I believe we put our market-leading position in jeopardy because of a lack of investment in R&D; we stagnated and others caught up. Now, we have a much more focused game plan. Science often happens in fits and starts... And we're about to publish some very interesting research in the terpene synthase gene space that I like to think will make an epic splash and help regain our position at the head of the pack.

How does your R&D filter back into service offerings?

There's a direct correlation between R&D and the genetics services we offer. Our sequencing and ongoing search for gene targets allows us to build markers – or at least assign genes to functions. In essence, we can help producers get to where they want to go. On the chemistry side, the link is less clear. There's a lot of interesting chemistry in the plant that contributes to aroma and flavor – and possibly effect – but until the industry understands (and cares about) the importance of these compound classes, we'll struggle to translate such knowledge into a service offering.

And are you applying knowledge from other areas of agricultural research?

Absolutely. With genetics, you build on what's gone before. We always go back to well-studied plants; for our terpene work, we explored many other aromatic plants – basil, strawberry, tomato… In short, we learned that terpenes are really complicated. Across the board, we still have a lot to learn. We have to sequence a lot of strains, do a lot of chemical analysis, and throw it all into the blender (my word for big data crunching) – and see what comes out at the other end.

Steep Hill is perhaps best known as a cannabis testing lab. How's the regulatory landscape looking?

The short answer: good science is not necessarily the order of the day in the current regulatory framework. The reasons are complex and evolving, and I'm becoming more actively involved in making sure that we have appropriate – and feasible – guidelines. We want to do the best science that we can do, and earn our stripes because we helped the industry identify problems preemptively. I'll write my long answer for your next issue's In My View section!

"Leading the Science of Cannabis. Globally" is a Steep Hill motto. Where are you leading us, Reggie?

We need to go deeper down the rabbit hole. Conversations are still centered around THC, CBD, and a few terpenes, which means we've really not progressed that far in the last few years. We need more chemistry knowledge. And not only that, we need to pay more attention to the plant in the field.

"For me, it's always been about uncovering knowledge and sharing it."

You've become an influential figure in the field. How?

I've been thrust into this somewhat uncomfortable position where people see me as some sort of a guru – but that's a pretty foreign concept for me. For me, it's always been about uncovering knowledge and sharing it.

When I first came into the field, my father suffered a very serious stroke. Someone in the lab put me in touch with a company called GI Grow; two days later, I had a box of oil (for free). My father was recovering slowly, but recovered much faster with the high-CBD formula oil. Over the years, as I did more research, I started asking the formulator: how about a little CBC or CBG? And every time I made a suggestion – using my father as a guinea pig (I am a scientist, after all) – they would assist without hesitation. Now, that's personalized medicine!

The experience changed my view of the industry. I wanted to ensure that we released as much knowledge into the world as we could – to help the whole industry improve and make better medicine. I hope that's my legacy.

Reggie discusses patents, pheno-hunting and more in the full online version of this interview: tcs.txp.to/0519/Gaudino

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