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April/May 2020

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PhD

Jim DeMesa, MD, MBA

Eduardo Muñoz, MD, PhD

FASHION
FROM HEMP

INDUSTRY
SUSTAINABILITY

HEMP
DISTILLED
SPIRITS

A Note from **MACE MEDIA** CEO, Celeste Miranda



Every issue of *CBD Health & Wellness* is crafted with care to bring you the latest in the cannabidiol (CBD) industry regarding updates in policy and regulatory news alongside recent breakthroughs in cannabinoid applications, research, and medicine. While we aim to deliver the most cutting-edge and trustworthy information from industry experts in every issue, some issues affect our team more personally than others. As is the case here.

Our cover and feature article are dedicated to the cannabinoid-based compounds being developed by Emerald Health Pharmaceuticals to treat multiple sclerosis (MS). Not only might this new compound help address MS-related symptoms but it also may be able to reverse neural damage caused by the disease, considered the “holy grail” of MS, of which no treatment to date has been able to accomplish.

When many people like myself are diagnosed with MS, it’s strange news to process. MS is a neurodegenerative disease that will be with me all my life but its course is varied and there’s no way to know what the trajectory will be like. And finding the right medication is not easy. Luckily I was able to find a treatment that works for me after failing on two others,

one that nearly caused a rare brain infection. But controlling my MS symptoms doesn’t stop with one medication.

MS brings with it terrible muscle spasticity that causes severe pain. After taking muscle relaxers that caused me to constantly feel knocked out, I was recommended CBD gum. At first a skeptic, within 10 minutes of taking it, my spasticity was completely gone. And so started my life with CBD.

As a lifelong marketer, I had started working with clients in the cannabis space around the same time as my diagnosis. And I soon realized that there was a lack of science-based cannabis educational information available to the public. That’s when I founded *Terpenes & Testing Magazine*, *Extraction Magazine*, and the publication in your hands. The magazines inspired the launch of the CBD Expo Tour, which is grounded in education and aims to facilitate collaboration across the industry.

My commitment to the CBD and cannabinoid industry is a personal one. And that’s why I am so happy to share the latest update in medical cannabinoid research with you in this issue.

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How Cannabidiol and Cutting-Edge Science Could Help Achieve the Holy Grail of Multiple Sclerosis

By Loren DeVito, PhD

“Have any of your patients used cannabinoids to treat their pain?”

I sat straight up in my seat. My eyes darted across the room until squarely landing on the doctor who spoke those words. I wanted to shout, “Yes! They are so helpful, let’s talk!”

The room responded with silence and the moderator went on to address another topic. I sighed and went back to typing.

As a medical writer, I often attend advisory board meetings where key opinion leaders, or leaders in the field of different medical specialties, meet to discuss challenges and triumphs they experience in treating their patients. While medical writing takes me across different disease states, as a former lab neuroscientist, I’m grateful when I have the opportunity to work on a project in neurology, as was the case with this particular meeting.

Surrounding me were about a dozen multiple sclerosis (MS) specialists discussing treatments they used to help manage the disease in their patients. MS, a progressive neurodegenerative autoimmune condition, presents in many different forms, making disease course unique to each individual—and making it that much more difficult to treat. While there were once only a few treatments available, those with MS and their neurologists now have over fifteen different medications to choose from. Many of these work quite well to improve some symptoms and reduce risk of relapses.

But, as with most medications, many of these treatments come with serious side effects, which could make things

much worse for patients, a key reason why many neurologists hold off on treating MS aggressively. Due to this safety consideration, it’s quite surprising that the majority is often quiet about a very safe and effective treatment that can help address MS-related symptoms—cannabis.

And so explains my surprise and joy hearing from an esteemed specialist about the potential of cannabinoids to treat pain—and then disappointment when it was met with silence from the group.

Cannabinoids possess a multitude of beneficial properties that make them quite favorable for use in MS. Cannabidiol (CBD) has anti-inflammatory properties, while tetrahydrocannabinol (THC) can be a powerful pain reliever. And these are not based on anecdotes alone—there is significant clinical evidence demonstrating the positive effects of cannabinoids on MS.

Sativex® is a 1:1 CBD:THC oromucosal spray developed by GW Pharmaceuticals that is approved in the UK to treat MS-related spasticity. Clinical studies have shown that the medication is effective in reducing muscle stiffness and in improving quality of life.[1] Furthermore, a review published by the American Academy of Neurology showed that the clinical evidence supporting the use of cannabinoids in MS was the strongest compared to several other neurological conditions.[2]

While Sativex is unfortunately unavailable in the US, MS is included as a qualifying condition under the majority of state medical cannabis programs.

Nature has provided us with quite the bounty of extraordinary cannabinoids. However, researchers are studying how to leverage the chemical structure of these compounds to more effectively target certain systems in the body.

For example, while CBD is effective on its own, the compound affects so many different pathways in the brain and body that achieving a targeted effect is incredibly challenging. And when developing a compound to treat a certain condition, specificity is key.

A research group in Spain, led by Eduardo Muñoz, MD, PhD and Giovanni Appendino, PhD, has spent many years studying the chemical structures of cannabinoids to better understand how they might be enhanced or modified to target specific diseases. Over a decade of diligent work, making hundreds of manipulations to two well-known cannabinoids, CBD and CBG (cannabigerol), has, to date, resulted in the development of a portfolio of 25 different molecules, 14 derived from CBD and 11 from CBG.

Emerald Health Pharmaceuticals (EHP) acquired this portfolio in 2017 and is currently developing two of these molecules, with one already in clinical trials, targeting MS as well as systemic sclerosis, a severe form of scleroderma.

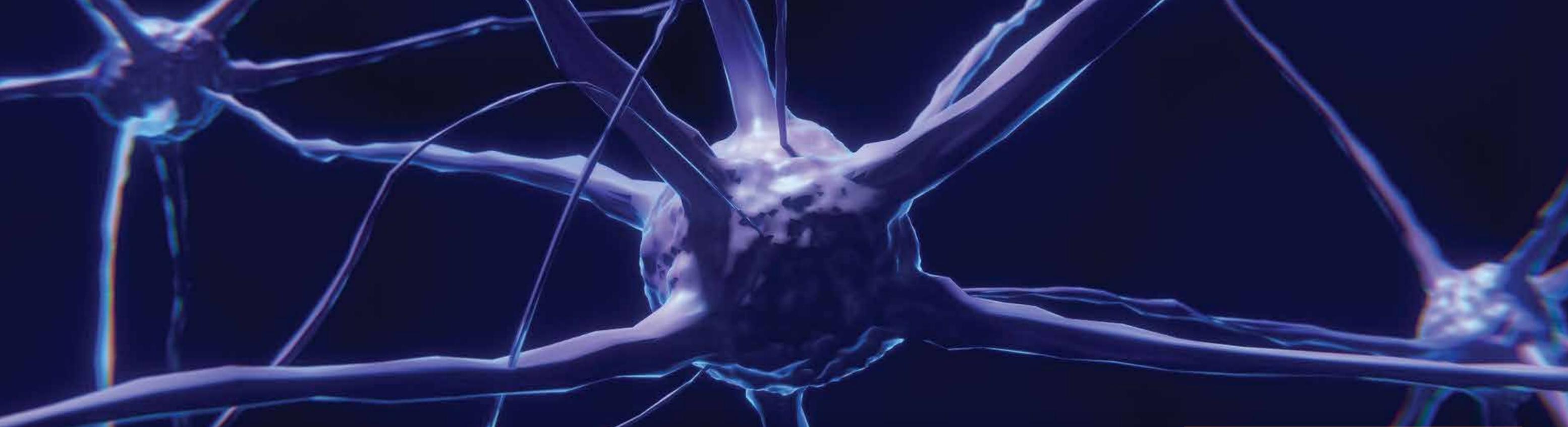
To learn more about this work, I spoke with Jim DeMesa, MD, MBA, President and Chief Executive Officer. Dr. DeMesa has extensive experience in medicine, research, and the business side of the healthcare industry but was new to the cannabis industry when he joined the newly-formed company

three-and-a-half years ago. He was drawn to EHP by their outstanding technology and the people working passionately to find treatments for diseases that currently have no cure.

While many companies are exploring different cannabinoid formulations for various medical conditions, Dr. DeMesa noted that EHP’s approach is unique in that they are not just creating synthetic versions of CBD and CBG but, rather, entirely new molecules derived from CBD and CBG. Therefore, EHP aims to “expand the capabilities through rational drug design by modifying the basic cannabinoid molecules so that they can affect not only targets directly related to the endocannabinoid system (ECS) like cannabinoid type 2 (CB₂) receptors but also targets outside the ECS.”

The uniqueness of EHP’s molecules is supported by the fact that, unlike CBD and CBG, which are classified as controlled substances in the US, the Drug Enforcement Administration (DEA) has determined that EHP’s molecule is not a controlled substance. The same determination has been made in Canada and the United Kingdom.

The molecules developed by Dr. Muñoz and Dr. Appendino were modified to be more powerful than botanical cannabinoids due to their enhanced ability to activate various biologic receptors and physiologic pathways in the body that are targets for various diseases. Some examples are the peroxisome proliferator-activated receptor gamma (PPAR-gamma) and CB₂ receptors, as well as the hypoxia inducible factor (HIF) pathway, which play important roles in neuroinflammation and neuroprotection.[3] Their lead compound, EHP-101, an oral



formulation of a novel synthetic CBD derivative, is currently being studied in systemic sclerosis and MS, while EHP-102, an oral formulation of a novel synthetic CBG derivative, will be evaluated in Parkinson's disease and Huntington's disease.

"Part of our overall strategy is to address diseases like MS and systemic sclerosis, which are primarily autoimmune diseases, with our CBD-derivative (EHP-101), based on its mechanism of action," noted Dr. DeMesa. "Our CBG-derivative (EHP-102) focuses more on neurodegenerative diseases due to its specific (and different) mechanism of action."

Extensive pre-clinical testing of EHP-101 has demonstrated a good safety profile, which is vital for patients and regulatory bodies that evaluate new chemical entities. In fact, they were able to administer doses many times higher than what would be used clinically without finding significant adverse effects. And safety and tolerability were also established in a recent Phase 1 human trial in healthy volunteers, reflecting years of careful study that has led to the development of this compound.[4]

EHP-101 will first be evaluated in patients with systemic sclerosis, with a Phase 2 trial for MS shortly following. The initial MS trial, which will be conducted over six months, will assess safety and tolerability in patients with MS, as well as early treatment effects determined by magnetic resonance imaging (MRI), disease progression, disability status, relapse

rates, and other MS symptoms. They will also be measuring a promising MS biomarker (a substance that indicates disease activity) called neurofilament light chain, or NfL.

For those who have taken cannabinoids for MS-related symptoms, EHP-101 will not be another CBD formulation to ease pain or improve mobility. Pre-clinical evidence has indicated that this compound may do what all other current MS medications cannot—slow the progression of the neural damage caused by the disease or, ideally, even possibly *reverse* it.

MS symptoms result from demyelination of neurons in the brain. While healthy cells are wrapped in a fatty substance called myelin that keeps electrical signals moving across the brain (like the coating on a wire), in MS, this substance is gradually stripped away. And so cumulative damage contributes to disease progression over time.

The "holy grail" of MS is to find a treatment that could reverse this damage, slowing progression and potentially *curing* the disease.

According to Dr. DeMesa, "In our pre-clinical studies to date, we've not only been able to show a significant improvement in symptoms, but also a reduction in the demyelination process of MS and even remyelination of the damaged neurons. As one of our clinical advisory board members said, 'if this can be shown in humans, it's a game changer.'"

Even though the data he is referring to comes from pre-clinical testing, it is certainly reason for optimism as EHP-101 moves into further testing in humans.[5]

Others with interest in the treatment of these diseases have taken notice of the transformative research EHP is pursuing. One analyst described EHP's work as the unique convergence of cannabinoids, science, and biology that really nobody else is doing.

"We're taking it a step further through the manipulation of the cannabinoid molecules to address the biology—the ECS, the PPAR-gamma system, the HIF pathway activation—and use these in combination to create something that is unique," added Dr. DeMesa.

We certainly agree and look forward to seeing data readouts from these trials.

While some cannabis-savvy physicians have come to understand the importance of integrating cannabinoids into their patients' treatment regimens, they likely never imagined one day using a unique, new CBD-derived medication as a *primary* treatment.

While we are not there yet, as this medication is still in development, the research being pursued at EHP could make this scenario a real possibility within the next few years and get us closer to that MS "holy grail."

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