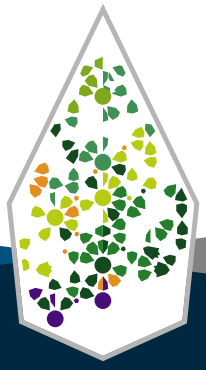

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THE EMERGENCE OF BIOPHARMACEUTICAL CANNABINOIDS FROM RESEARCH & DEVELOPMENT TO CLINICAL TRANSLATION

SYMPOSIUM REVIEW

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BACKGROUND

The 2nd annual Avicanna Symposium, “The Emergence of Biopharmaceutical Cannabinoids – From Research & Development to Clinical Translation”, was held at the MaRS Discovery District (Canada’s premium launchpad for start-ups), Toronto, Canada on 25th March 2019. The Symposium was the first to be held in Canada by Avicanna, with the inaugural Symposium taking place in Santa Marta, Colombia, May 2018.

The purpose of the Symposium was to highlight the current state of the medical cannabis industry in Canada and abroad as well underlining the key areas of research that are currently active. The event brought together clinicians, researchers, regulatory affairs specialists, investors, members of the pharmaceutical industry as well as players in the Canadian cannabis space.

A wide range of topics were covered at the symposium including the research gaps in medical cannabis (specifically quality control, safety and efficacy concerns), as well as the challenges that this rapidly evolving industry faces. In addition, the most recent and exciting developments in cannabinoid research including an overview of cannabinoids as active pharmaceutical ingredients (APIs), progress in formulation development and their potential role in several therapeutic areas were covered.

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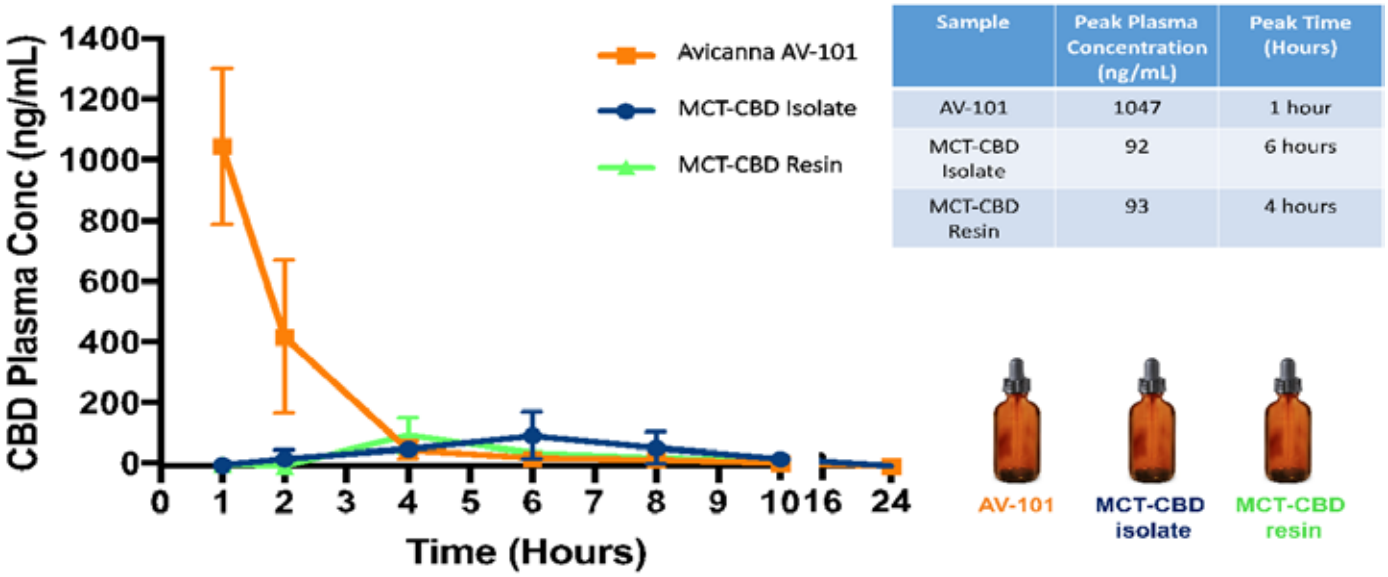
WELCOME AND KEYNOTE REMARKS

Christine Allen, PhD
Professor, *Leslie Dan Faculty of Pharmacy, University of Toronto* and
Chief Scientific Officer, *Avicanna Inc.*

The global cannabis market has enormous fiscal potential, with some financial institutions predicting that it could be valued at nearly $200 billion in the next seven years [1]. While a significant portion of this valuation may be attributed to the recreational space, increasing investment in this area will only serve to augment interest and research in the medical space. There is a vast array of cannabis products currently on the market including cosmetics, gummies, suppositories, cannabidiol (CBD) water as well as various inhalation products. Depending on the jurisdiction, a lot of these products are not subject to strict regulations and there are a lot of parallels between such products and other consumer goods including over the counter (OTC) drugs, tobacco and alcohol, some of which have a long history of litigation. Well publicized critical incidents involving such goods have laid the foundations for regulatory change in the way these products are manufactured, marketed and sold (for example, a string of deaths in Chicago in 1982 from contaminated Tylenol products forced the pharmaceutical industry to develop tamper-resistant packaging [2]). Taking the history of such products into account, it is imperative that researchers, clinicians and industry members involved in the cannabis space do the heavy lifting upfront and take a proactive approach with regards to encouraging quality, safety and education.

It is important to remember that legal and natural is not equitable to safe and effective and there is a temptation in the cannabis area for people to self-medicate. It is not difficult to understand why this might be the case, when a simple search on Dr. Google would imply that cannabis is the panacea for a plethora of indications including (but not limited to) cancer, stress, dementia and even the common cold. There is a real risk of patients swapping prescribed medications in lieu of recreationally available cannabis on the basis of such articles. A real-world example of where this becomes particularly troubling is if one considers the treatment of morning sickness with "self-prescribed" cannabis products. A recent study of 400 dispensaries in Colorado showed that 69 % of them recommended cannabis products to pregnant females for the treatment of morning sickness [3]. This is despite the fact that many of the relevant clinical bodies including the Society of Obstetricians and Gynecologists of Canada (SOGC) and the American College of Obstetricians and Gynecologists (ACOG) have recently published press releases in which they do not recommend cannabis consumption (and discourage continued consumption) for pregnant or breastfeeding mothers [4, 5].

Another major challenge is the quality and consistency of the cannabis products that are currently being sold. **Many of the "medical" cannabis products on the shelf do not go through rigorous (if indeed any) in vitro and in vivo analysis that commonly take place during the early stages of drug development. Such measures lay the foundation for ensuring quality, safety and efficacy of a developing product.** A simple comparison of some of the CBD oral formulations on the Canadian market with an advanced formulation (AV-101) developed in collaboration between the University of Toronto and Avicanna is summarised in **Figure 1**. These results highlight that AV-101 demonstrates enhanced absorption and a more rapid onset in a rodent model compared with the standard oil-based formulations widely available.



Sample	Peak Plasma Concentration (ng/mL)	Peak Time (Hours)
AV-101	1047	1 hour
MCT-CBD Isolate	92	6 hours
MCT-CBD Resin	93	4 hours

Figure 1: Plasma profiles of CBD in Sprague Dawley rats over 24 hours following a single administration of a CBD oral formulation via gavage (n=4).

The FDA has sent out warning letters to many companies that produce CBD products. These letters state that often times, the CBD content does not match what is specified (in some cases, the cannabinoid content can be less than 1 % of what was described). A report generated by Scientus Pharma has claimed that a lot of the cannabis oils on the market have such low levels of cannabinoids, that they are merely acting as placebos [6, 7].

The conventional drug development process is long, typically taking up to 15 years and encompassing extensive scientific rigour, with the products requiring a high level of quality and safety. It is important that level is brought to the medical cannabis industry.

In conclusion, the cannabis industry has substantial market value, with the fates of the medical and recreational space intertwined. It is important to remember that these products will likely be utilised by millions of people, so it is imperative that we have appropriately designed experiments and clinical trials to generate data that increases confidence in the development and commercialisation of these products.

SECTION 1:
CANNABINOIDS AND FORMULATIONS

AN INTRODUCTION TO CANNABINOID FORMULATION DEVELOPMENT

Frantz Le Dévédec, PhD
Senior Vice President, Research and Development *Avicanna Inc.*

It is important for cannabinoids to be regarded as Active Pharmaceutical Ingredients (APIs) and there is a need to isolate cannabinoids for pharmaceutical applications. However, isolated cannabinoids have limited aqueous solubility which can make absorption into the systemic circulation challenging. **In order to enhance the pharmacokinetic profile and overall performance of cannabinoids, it is essential to have a well-designed drug formulation.** In implementing the design of novel cannabinoid formulations, one needs to consider the route of administration. For example, while smoking results in rapid absorption and bypasses first pass metabolism, oral delivery is generally more gradual and is attributed to a lower level of bioavailability of cannabinoids. The indication to be treated will essentially dictate the formulation that will be required. For example, an indication like epilepsy requires fast absorption and rapid action.

It is desirable to develop formulations that will have an extended release profile following administration (red line, **Figure 2**). This will allow for the drug to be maintained within the therapeutic window; i.e. the range of dose at which a drug is effective, without demonstrating any toxicity. This will also allow for the administration of fewer doses, such as with conventional formulations (green line, **Figure 2**), which is advantageous for the patient.

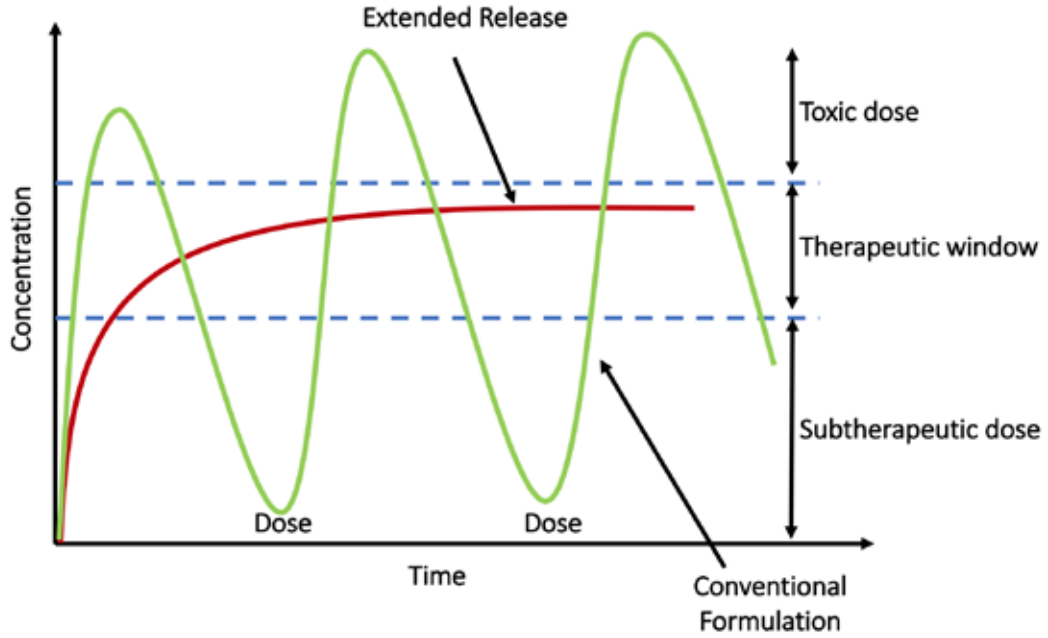


Figure 2: Plasma profile of drug following the administration of conventional formulations (green line) versus an extended release formulation (red). The extended release formulation allows the drug to be maintained within the therapeutic window for a longer period of time with fewer doses.

Many of the cannabinoid formulations currently approved are simple by design. Cesamet and Marinol are examples of approved cannabinoid drugs that have basic formulations made up of safe and FDA approved excipients [8, 9]. However, some of the approved formulations can come with large price tags. For example, Epidiolex (a CBD isolate formulation recently approved for the treatment of two rare forms of Epilepsy; Lennox-Gastaut and Dravet syndromes) can be expected to cost a patient in the US up to $32,000 a year [10].

There is a need for advanced drug delivery systems (lipidic and polymer-based) that will allow for better control of the levels of cannabinoids in the blood. There are many examples in the published literature of advanced formulations that have been designed for cannabinoids. One example is PTL401; an oral emulsion-based system that generated a superior pharmacokinetic profile relative to Sativex [11]. This was further enhanced by the inclusion of the permeation enhancer, Piperazine to the formulation [12]. In addition, the use of FDA-approved polymers in combination with cannabinoids to form polycaprolactone (PCL) microparticles has been shown to demonstrate the sustained release of CBD and tetrahydrocannabinol (THC) over seven days [13].

In conclusion, formulation design can enhance efficacy, reduce side effects and offer an overall improvement in the quality of life for the patient.

TOXICOLOGY AND PHARMACOLOGY OF CANNABINOIDS

Ruth Ross, PhD
Chair, Department of Pharmacology and Toxicology,
University of Toronto

"The Mixture Makes the Medicine"; when it comes to cannabis, it is important that we consider the mixture of chemical components (i.e. cannabinoids, flavonoids and terpenes among others) and how this effects the efficacy, toxicity profile and overall performance of the cannabis "medicine". As our current level of knowledge stands, we need a greater body of evidence to validate this statement. In order to achieve this, it is imperative that we understand the function (if any) of every component that makes up these therapeutics.

In addition to the application of exogenous phyto-cannabinoids for the potential treatment of various indications, it is also important to understand the role of the endocannabinoid system (ECS) and endogenous cannabinoids such as anandamide (AEA) and 2-arachidonoylglycerol (2-AG). These play a role in regulating appetite, pain processing, stress and anxiety and learning and memory [(14)].

One of the main aims of cannabis research today, is to assess the safety and efficacy of the major phyto-cannabinoids, THC and CBD, in the treatment of a range of indications. These factors can be better understood by elucidating the mechanisms of action of the cannabinoids at the molecular level. In the case of THC, its effects can be explained largely by acting via CB1 receptors. However, in the case of CBD, its mechanism of action is still largely unknown.

The efficacy of CBD has been assessed in controlled clinical trials for childhood epilepsy and psychosis. However, as has been previously stated, CBD is ubiquitous in the Canadian population and is currently being used by large swathes of the public to self-medicate for a wide range of indications. This has led to very high doses of CBD being used by patients with no epidemiology data to hand regarding safety for chronic use of such a high dose. Since the mechanism of action of CBD is not fully understood, it is possible that the compound acts on various receptors, which may lead to an undesirable outcome. Another concern is the potential for CBD-drug interactions. Indeed, CBD has been shown to inhibit the activity of certain CYP enzymes (these are a class of liver enzymes that are responsible for metabolising the majority of the drugs that we consume) [(15)]. By inhibiting these enzymes, CBD can potentially increase the levels of other drugs in the blood following administration. There are currently three sides to the cannabis narrative; the good is in relation to the positive effects that we have seen in treating epilepsy, pain in MS patients as well as its anti-nausea and appetite stimulating effects. There is a bad side to cannabis relating to its negative impact on short-term memory, learning skills, driving as well as various other cognitive functions, **There is also an ugly side to cannabis pertaining to the potential for psychosis and schizophrenia in vulnerable patients, the potential for cannabis use disorder, as well as its well documented negative effects on a developing foetus and breastfeeding child following maternal use.**

The body synthesizes endocannabinoids in response to environmental factors and is regulated in response to exercise, stress, hunger and pain. This leads to responses such as stimulation of appetite, pain relief as well as instilling mechanisms to deal with stress and anxiety. It is a highly adaptive system, for example, stress induces the expression of endocannabinoids which can reduce the levels of the stress hormone cortisol, with repeated episodes of the same stress reducing levels of cortisol while simultaneously increasing the levels of endocannabinoids expressed.

Considering the regulation of the ECS to promote homeostasis in the body, we need to know when to go against this natural order and to understand the effects that the exogenous administration of phyto-cannabinoids may have. Many of the other parameters that also need to be considered include; dose, components, route of administration as well as frequency of administration. In conclusion, we need more evidence for the medicinal effects and measurement of side effects in specific illnesses. There is a need to design and implement placebo- controlled double-blind clinical trials for safety and efficacy. Finally, we need more research and education on the potential harms to the public of recreational cannabis use.

SECTION 2:
REGULATORY AFFAIRS AND THE EMERGING INDUSTRY

CANADA'S LEADERSHIP POSITION IN THE EMERGING GLOBAL INDUSTRY

Aras Azadian
Chief Executive Officer, *Avicanna Inc.*

The Cannabis industry can be broken down into four main areas; a) medical cannabis, b) pharmaceutical cannabis, c) recreational cannabis and d) CBD infused products. Canada is at a critical advantage in becoming leaders in this industry. This is demonstrated by Canada becoming the first G7 country to legalise first medical, and now recreational cannabis with the Canadian stock exchange being the first to approve cannabis listings.

The combined market capital for the top five Canadian cannabis companies is valued at over $40 billion, and in 2018, Canadian cannabis firms raised approximately $11.8 billion. While the cannabis industry is currently a thriving market, there are some risks and concerns that should be addressed if we are to maintain our competitive advantage. **These include addressing environmentally unsustainable practices, relatively low investment into R&D and clinical development, limited product offerings, prioritization of the recreational market, public health concerns and limited intellectual property protection.** There is a real need to merge science and business in order to overcome these limitations and ensure Canada maintains its leadership position in this market.

The current cultivation practices of cannabis in Canada typically include capex heavy indoor facilities that are both environmentally unsustainable, due to their massive energy consumption, and globally uncompetitive (**Table 1**).

Table 1: Summary of the commonly used cultivation practices for cannabis with respect to both economic and environmental factors.

Cultivation Practice	Cost/kg	Yield	CO2 +/-	Environmental Impact	Climate Control	Lighting
Indoor	High	High	+	High		
High Tech Green House	Medium - High	High	+	Medium - High	Medium -	
Low Tech Green House	Low	Medium - High	-	Low - Medium	None - Low	Natural
Outdoor	Low	Low	-	Low - Medium	None	Natural

The cost per kilogram (kg) of cannabis flower in Canada today can range from $1500-$2000. This is in stark contrast to optimal climate zones (such as Colombia) where the cost per kg ranges from $50-$100 due to the use of "low tech" green houses that are less reliant on energy to supplement both lighting and climate conditions (Figure 3).

Figure 3: An example of a "low tech" greenhouse (also referred to as a shade house), where optimal climate conditions negate the use of indoor growing. Image published with permission from Avicanna Inc.

The cannabis industry also offers many exciting prospects. There is an opportunity to build a sustainable future for the Cannabis sector, to develop and sustain a competitive edge in an emerging global industry through investment, development and management of competitive research projects, IP transfer and commercialization. There is an opening to build and enhance sustainable agricultural practices in developing countries, adding value through socially responsible projects while having a positive impact on the environment. In addition, there is amazing potential for the research community in Canada, being the only G7 country that currently permits federally approved pre-clinical and clinical development of cannabis-based products. Canada already has world class research institutions that are motivated and open minded. The aim now is to establish a sustainable cannabis industry in Canada for the research community and create long-term biopharmaceutical jobs.

Finally, there is an opportunity to architect a modern industry that is diverse, fast growing, innovative in medicine and agriculture, environmentally sustainable and socially responsible. There will eventually be a segregation between the medical and recreational cannabis industries, with Canada hopefully taking the lead on this. In conclusion, it is important to remember that Canada will not be the only country that is able to do cannabis research forever. Others will follow, and it is imperative that we take advantage of the lead that we currently have by generating long term intellectual property.

CANADIAN REGULATORY LANDSCAPE

Edith Gorecki, MD
Regulatory Consultant, *Dicentra Cannabis Consulting*

It is fair to say that Canada is leading the world with regards to cannabis reform. In June 2018, the Senate passed Bill C-45, known as the Cannabis Act and in October 2018, **Canada became the second nation in the world (after Uruguay) and the first G7 nation to legalize recreational cannabis.** Even though it is legalized, in order to conduct cannabis-based research, authorization must be obtained "by applying for a federal license from the Cannabis Legalization and Regulation Branch of Health Canada" [16]. A research license is granted for a specific research project and requires certain criteria to be met prior to its approval.

Researchers hoping "to conduct clinical trials with cannabis, using either human or animal subjects, must also receive authorization under the Food and Drugs Act" [16]. In order to receive authorization, sponsors must file "a clinical trial application (CTA) to Health Canada" or receive "an Experimental Study Certificate for certain veterinary trials" [16]
.
Once approved the research license permits (for the purpose of research), the possession, production, transporting or delivering of cannabis between sites highlighted in the license. In addition, the research license authorizes the sale of cannabis plants and seeds and the distribution of cannabis, cannabis plants (and seeds), to other specific license holders and persons under the Cannabis Regulations. As well, it authorizes the administration and distribution of cannabis to a research subject.

Clinical evidence supporting the safety and efficacy of cannabis and its constituents for therapeutic purposes is growing but remains limited. While Health Canada has previously authorized health products containing cannabis (such as Sativex), there remains significant uncertainty regarding the pharmacology and safety of the majority of the cannabinoids included in such products. Post-marketing data generated by these products in the Canadian market have allowed for increased knowledge of the safety and efficacy of cannabinoid-based therapies. However, significant gaps in science coupled with limited market experience highlights the need for a precautionary approach with such products.

CLINICAL DEVELOPMENT PLAN FOR CANNABINOIDS

Humberto Reynales, MD, PhD
Chief Executive Officer, Centro De Atención E Investigación Médica (CAIMED)

Cannabis has demonstrated potential in the clinic for the treatment of a number of several different indications. Sativex (CBD:THC sublingual spray) and Marinol (synthetic THC capsule) are examples of cannabinoid formulations with marketing approval that are used in the treatment of neuropathic pain in MS and chemotherapy-induced vomiting respectively [8, 17].

Further clinical studies have demonstrated that cannabis could be effective in the treatment of other disorders such as anxiety, schizophrenia and psychosis. However, these studies have only been carried out in very small groups, thereby compromising the power for detecting significant differences or significant effects. Other potential therapeutic uses that require further inquisition may include (but are not limited to); Parkinson's Disease, IBS and autism spectrum disorder.

One of the major challenges for clinical trials, the "Achilles heel of medical cannabis research, is inadequate blinding of placebo-controlled trials" [18]. Casarett summarizes several approaches to address this challenge, including; adding a psychoactive control, making sure all patients involved in the trial are naïve to cannabis, assessing the adequacy of blinding and using enriched or isolated CBD (this diminishes the psychoactive effect observed with THC) [18]. Casarett concludes by highlighting that "until the problem of inadequate blinding is solved, there is a risk that clinical trials of medical cannabis could overestimate its benefit" [18].

Another limitation is that other cannabinoids need to be considered and studied for potential therapeutic applications such as cannabigerol (CBG) and cannibichromene (CBC). Many of the trials that have been carried out are conducted using whole plant extracts and not purified cannabinoids. This means that the results may be based on synergistic ratios between cannabinoids and minor cannabinoids/terpenes, termed the "entourage effect". However, more work needs to be conducted to validate this phenomenon.

Despite the public perception, it is important to note that CBD is not risk free. It can cause adverse events which include somnolence, hepatic toxicities and potential drug interactions [19]. CBD has been shown to increase levels of transaminase enzymes (indicative of liver damage) and further studies are needed to assess its impact on suicidal ideation [19].

Therefore, despite the psychoactive effects that cannabinoids have invariably demonstrated, they also display "a broad range of potential therapeutic benefits" with advances in formulation and preparation development making " these prospective therapeutic agents" [20].

HEALTHCARE PRACTITIONER PERSPECTIVE

Alex Chan, R.Ph., B.S.Phm., MBA
PharmAct Health Solutions

In 2001, the Federal government of Canada passed the Marihuana for Medical Purposes Regulations (MMPR) allowing people who had obtained medical authorization to access dried marijuana. Some of the current prescription cannabinoid products with marketing approval in Canada are Nabilone and Sativex, used for the treatment of vomiting and advanced cancer pain respectively [9, 17].

Since the enactment of MMPR, some of the issues that healthcare practitioners have seen include off-label use for adjunctive pain management, high costs associated with such products as well as problems with the distribution of medical cannabis and the removal of pharmacists from the process. There is an opportunity to involve healthcare practitioners in the cannabis patient's circle of care and to ensure each patient receives proper education about medical cannabis, the products available and the value of non- drug identification number (DIN) medications.

The medical cannabis products that healthcare practitioners prescribe to their patients need to be proven to be safe and effective. Adopting Good Manufacturing Practices (GMP) is the foundation for success as it ensures that the manufacturing process will yield products that are of high quality, consistency and free from any potential contaminant. The use of GMP practices also allows for Health Canada to regulate and monitor the products being manufactured, which will only increase the overall quality of the product. More research and development are required in order to standardize the formulation and dose of medical cannabis products. Healthcare practitioners need to be able to readily alter the dose for the patient in order to suit the patient's needs. It is also important that different routes of administration are available including oral, inhalation and sublingual.

Another issue that healthcare practitioners are facing is patient compliance, with nearly 50% of medical cannabis patients shown to be non-compliant. This can be due to unsatisfactory treatment outcomes (either real or perceived) and the dosing frequency. It is therefore important to be able to educate the patients on how long a treatment will take to demonstrate efficacy and what the potential side effects can be. Patient monitoring and follow-ups can help with this. In order to improve care for the patient, it is optimal that all healthcare practitioners work as a team. It is therefore imperative that pharmacists (which for many patients act as medication management experts) are not removed from this process.

In conclusion, in order to validate the need for and increase access to medical cannabis, it is imperative to have data from head-to-head clinical studies, that the treatments are readily available (this necessitates qualified prescribers as well as strong distribution networks) and that the therapy is reimbursed (whether this will be by private or public players remains to be seen).

NATURAL CANNABINOID ACTIVE PHARMACEUTICAL INGREDIENTS: FROM SEED TO API

Samantha Watt, MSc
Vice President, Scientific Affairs
Avicanna Inc.

Endogenously, cannabinoids are present within the cannabis plant to act as a defence mechanism by warding off herbivores. In addition to cannabinoids, the cannabis plant has a highly complex chemical composition, including compounds such as terpenes and flavonoids responsible for aroma and color respectively (**Figure 4**).

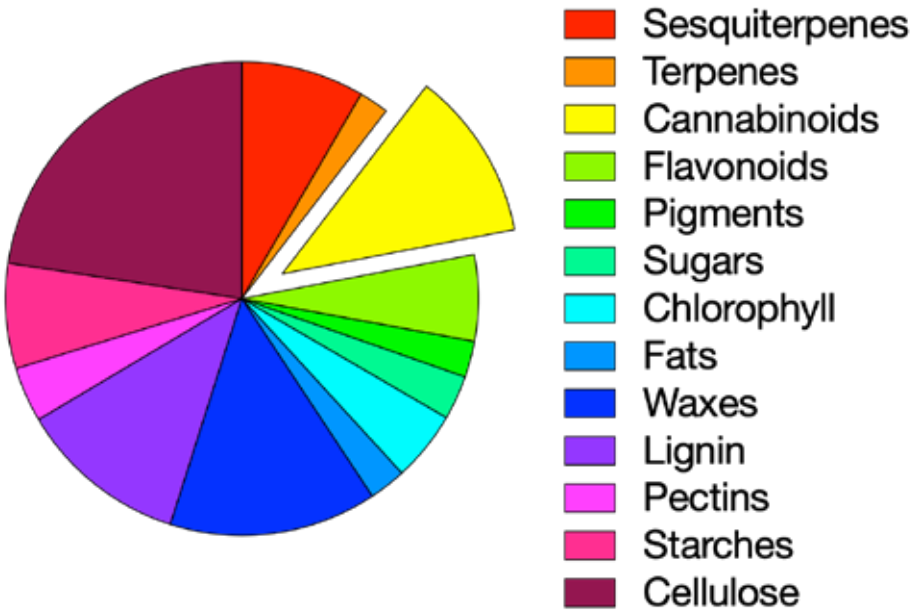


Figure 4: Composition of cannabinoids typically found in the cannabis plant. Cannabinoids are one of many different classes of compounds contained within the cannabis plant. Others include terpenes, cellulose, fats and chlorophyll. Information for chemical composition was modified from [21].

The medicinal compounds of the cannabis plant are present within the bud of the flower, in particular, the trichomes; the hair-like appendages that defend against predators due to their bitter taste and strong aroma (**Figure 5**). The trichomes themselves can act as a rudimental surrogate marker to determine the predominant cannabinoids present. Growers can optimise the cannabinoid content obtained from the plant by harvesting based on the appearance of the trichomes. For example, transparent trichomes can signal predominantly precursor cannabinoids, cloudy trichomes can signal the presence of fully mature THC and amber can signify that degradation to non-psychoactive compounds has been initiated. Damaged trichomes will significantly impact the cannabinoid yield and efforts should be adopted to minimally effect any negative impact on the integrity of these structures.

Figure 5: Microscopic image of the trichomes of a cannabis plant. The trichomes presented are healthy with gland heads intact. Image published with permission from Avicanna Inc.

The area of micropropagation (propagation of plants under in vitro conditions) has only recently been applied to cannabis research. These methods aim to allow the grower to select for the plant with the most desirable genetic profile, and therefore cannabinoid composition, of interest. While these methods minimise the potential for microbial contamination as well as producing genetically identical species of plant, they can lead to random and unavoidable mutations.

Endogenously, the cannabinoid content of the plant is very diverse and can range anywhere between 2-30 % depending on the cannabinoid in question. Further refinement to resins generates a cannabinoid content of up to 85 % with isolates generally demonstrating ≥ 98 % purity. Following cultivation, the next step in raw material processing, is harvesting of the plant. At this stage, the cannabinoids are present in their less active, acidic form. Plant material is milled and then decarboxylated (by heat) to form the active compounds. The two main forms of extraction are CO2 and solvent extraction. CO2 extraction involves the use of liquid CO2, at low temperatures. This allows for the breaking apart of the trichome membrane, which releases among other things, cannabinoids, with the cannabis oil/resin being collected at the end of the system. The main advantage of this system is that it negates the use of solvents, and as it is conducted at low temperatures, minimises degradation of the cannabinoids.

In solvent extraction, solvents such as ethanol are used to dissolve the trichome membrane and release the cannabinoids. Altering the solvent itself, temperature at which the extraction occurs etc., can have a huge impact on the composition of material that is released. Prior to the removal of the solvent, it may be necessary to carry out winterization, a process by which the material is stored at -20°C in order to allow for the removal of waxes and lipids. The solvent can then be removed by heating at low pressure.

The isolation of individual cannabinoids is challenging. This is due to the fact that many of the compounds have similar chemical properties (e.g. similar boiling points). Crystallization is an example of a method that has been utilised to generate highly pure CBD. Advances in propagation, harvesting, extraction and purification can minimise the inconsistencies previously seen in cannabis products and can offer consumers and patients more reproducible goods.

SECTION 3:
THERAPEUTIC AREA FOCUS

CANNABINOIDS IN DERMATOLOGY

Elena Pope, MSc, FRCPC
The Hospital for Sick Children

Recent studies have highlighted the presence of a functional ECS in the skin and its implication in various biological processes [22]. Endogenous cannabinoids (AEA and 2-AG) have been shown to act on various cutaneous targets including immune cells, sweat glands, sensory nerves as well as hair follicles.

There is a strong consensus within the dermatology community that CBD has some medical benefit, with 86 % of clinicians agreeing with its medical use. However, the vast majority (94 %) feel that more research needs to be conducted in the area, with approximately 50% concerned about the stigma that is associated with proposing cannabis treatments [23].

Several studies encompassing in vitro, animal and in some cases, even human data highlight the potential that cannabinoids may have in the treatment of various dermatological conditions (e.g. fibrosis, cell proliferation, inflammation, pain and itch). The topical application of cannabinoids has been shown to reduce pain and have an analgesic effect in patients with pyoderma gangrenosum and epidermolysis bullosa [24, 25]. Cannabinoids have also been shown in murine models to downregulate the production of proinflammatory cytokines [26, 27]. This has translated into human patients where the topical application of cannabinoids has been shown to improve wound healing in EB patients [24]. In addition, in a pilot murine model of melanoma (one of the most dangerous forms of skin cancer), treatment with CBD results in both a reduction in melanoma tumour growth rate and in survival of the mice [28]. Such studies offer a glimpse into the vast potential that appropriately designed cannabinoid formulations may have in the dermatology space.

In conclusion, cannabinoids target many pathogenic mechanisms implicated in skin disorders. This makes them attractive for the treatment of various dermatological diseases. However, more research is needed to fully elucidate the mechanism of action, the ideal formulations as well as determining the optimal dosage to be administered.

CANNABINOIDS IN EPILEPSY

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Epilepsy can be defined as recurrent, unprovoked seizures due to abnormal electrical discharges in the brain. These seizures can be focal (60%) or generalised (40%) in onset. It is a condition that affects more than 65 million people worldwide, with 20-70 new cases diagnosed per 100,000 people, with the majority of new cases occurring in children and elderly. Approximately 30-40% of people with epilepsy respond poorly to currently available treatments [29]. Epileptogenesis is a term used to describe the process by which a previously n ormal brain becomes functionally altered and progressively epileptic following an insult or injury (for example a stroke).

In a nation-wide survey in Australia it was found that "15% of adults and 13% of children were currently using or had previously used cannabis products to treat epilepsy. 90% of these adults and 71% of parents reported a reduction in seizure frequency" [30, 31]. The main reason people cited for using medical cannabis was "to manage treatment resistant epilepsy and obtain a more favorable side effect profile versus standard anti-epileptic drugs" (AEDs) [30]. In addition, "the number of past AEDs tried was a significant predictor for medical cannabis use" [30]. It is important to note that many of the currently available AEDs have undesirable toxicity profiles (for example, Lamotrigine contains a black box warning from the FDA; the strictest of such warnings placed on prescription drugs in order to highlight reasonable evidence of a serious hazard).

There is some limited preclinical data available that highlights the evidence for the anti-epileptic activity of cannabinoids. Blocking CB1 receptors in epileptic rats has been shown to result in an increase in the frequency and duration of seizures [32]. In rodent models of epilepsy, THC has been shown to have anti-convulsant properties [33].

Using cannabis for the treatment of epilepsy is complex. For example, multiple compounds in whole-plant extracts have varying effects on different receptors. Interactions between these compounds themselves may manifest in the so-called "entourage effect." As a result of this, looking at single cannabinoid isolates is the simplest way to begin.**"There is Class 1 evidence that adjunctive use of CBD improves seizure control in patients with specific epilepsy syndromes" (Lennox-Gastaut and Dravet syndromes)** [34-36] (**Table 2**). However, it is currently unknown whether seizure control is a "direct action of CBD or mediated by drug interactions with concomitant medications"[36].

Table 2: Summary of the results of two clinical trials (GWPCARE1 and GWPCARE4) that demonstrate the efficacy of CBD as an adjuvant therapy in reducing the frequency of seizures in 2 rare forms of childhood epilepsy (a= 59, b= 61, c= 85, d= 86 patients). Table is generated from data reported in [34] and [35].

Clinical Trial		GWPCARE1 B [34]	GWPCARE4 [35]
Indication		Dravet syndrome	Lennox-Gastaut syndrome
% Reduction in monthly seizure frequency	Treatment Groups		
	Placebo	13[a]	22[c]
	CBD (20mg/kg)	39[b]	44[d]

Recent high-quality research is supporting earlier anecdotal studies of the positive health implications of cannabis in treating epilepsy. Moving forward, cannabinoids (either alone or as part of a combination) will eventually find their place in the epilepsy therapeutic regimen, but they should not be viewed as a replacement for already efficacious treatments.

In conclusion, it is generally anticipated that high quality, consistent medicinal grade formulations will increase the acceptability of CBD and other cannabinoid products as medicine. Finally, it is also of great interest to "explore the potential role of other cannabinoids (such as CBG or CBC), either alone or in combination, for the treatment of epilepsy " [30].

CANNABINOIDS IN ONCOLOGY

Alejandro Berlin, MD, MSC
Princess Margaret Cancer Centre

Cancer care is extremely complex and touches so many people. Oncology has changed drastically in the last 10-15 years from the transition of non-specific chemotherapeutic agents, to highly specific agents with a single molecular target (a prime example being Herceptin for the treatment of HER2 positive breast cancer). These agents work off the principle that cancer is highly dependent on very specific molecules. A report published in 2017 by the National Academies of Science, Engineering and Medicine highlighted the current state of evidence for cannabinoids in a wide range of indications including cancer [37]. The report essentially concluded that "there is insufficient evidence to support or refute the conclusion that cannabinoids are an effective treatment for cancers, including glioma" [37].

One area in the cancer treatment regimen where cannabinoids have exhibited some promise is the area of chemotherapy-induced nausea. Twenty-three randomized controlled clinical trials (RCTs) conducted between 1975 and 1991 highlighted that cannabis-based medicines may be useful in treating chemotherapy-induced nausea. However, none of these trials involved a comparison with newer anti-emetic drugs (e.g. ondansetron and aprepitant) [38].

There is a lot of compelling biological rationale from current preclinical research as to why the use of cannabinoids for the treatment of cancer is an exciting area. This research suggests that cannabinoids can exert an anti-tumour effect via various mechanisms. For example, CBD has been shown to exert a potential anti-proliferative effect via increasing reactive oxygen species (ROS) and decreasing levels of the DNA binding protein inhibitor, ID-1 [39].

Many preclinical studies have demonstrated the superior anti-tumour efficacy of cannabinoids in animal models of various cancers. The vast majority of these studies utilize tumours derived from cancer cell lines, or from the patient themselves (so called patient-derived xenograft (PDX) models). These studies usually demonstrate enhanced tumour inhibition and survival time of animals (usually mice). However, the transition of these efficacy studies to the clinic has yielded very limited evidence for an anti-tumour effect in patients.

One of the first clinical studies to support the use of cannabinoids (in this case, THC) was for the treatment of recurrent glioblastoma, administered intracranially. In this study, researchers demonstrated a decrease in tumour cell proliferation upon administration of THC in two of the nine patients treated [40]. Following on from this several clinical trials have been undertaken to assess the efficacy of cannabinoid treatments in cancer, usually in conjunction with existing therapies (either chemotherapy or radiation) (e.g. NCT03246113).

In summary, while preclinical evidence for cannabinoids in cancer therapy is necessary, this in and of itself is not sufficient and we need robust, well-designed clinical trials to characterize efficacy and safety profiles.

CANNABINOIDS IN PAIN MANAGEMENT

Hance Clarke, MD, PhD
University Health Network

In a systematic review looking at evidence for the treatment of non-cancer pain with cannabis, 18 studies met the inclusion criteria. Of these, 15 demonstrated a modest analgesic effect, with no serious adverse or drug related side effects being reported. The mild side effects reported included sedation, dizziness, dry mouth and nausea. This review highlights that cannabis could therefore be used as a safe potential therapeutic in the management of chronic pain [41]. A recent update from the Canadian Pain society with regards to the management of chronic neuropathic pain moved cannabinoids from a fourth line therapy to third, still just after Tramadol and controlled-release opioid analgesics [42].

A recent study looking at the attitudes of perioperative patients to the use of cannabis for the treatment of pain determined that approximately one-third of patients strongly agree that they would use cannabis for chronic pain if prescribed by a physician, believe that cannabis is effective for pain after surgery or acute injury and would use cannabis for pain after surgery or acute injury pain if prescribed by a physician (the actual values being 35.5, 27 and 35.1 % respectively) [43].

A major limitation with regards to the management of pain is determining the correct therapeutic dose in order for the patient to receive the desired effect. In addition, the level of dosing will also determine the extent and nature of the side effects. At standard dosing, the side effects of CBD include; dry mouth, drowsiness, light headedness and fatigue. At high doses (20mg/kg) the side effects include diarrhea, vomiting and abnormal results on liver function tests. It is important, therefore, to find the right dosage for each patient. THC side effects are well-documented and include cognitive impairment, paranoia, tachycardia and anxiety.

For patients that are naïve to cannabis it is important that they "start low and go slow" and it is also critical to remember that not all pain is the same (e.g. neuropathic vs. inflammatory). In conjunction with their clinician, new patients must also decide what the overall goal of treatment is; whether that is to help with pain interference or to reduce the current use of other medications. For experienced cannabis users, it is important to understand what they consume and to work out a daily effective dose, with the aim being to identify a strain that effectively manages their symptoms.

It is critical that the public perception of THC changes from that of a "bad molecule that gets you high" to one with potentially therapeutic applications. A patient visiting Dr Clarke's clinic with radicular neck pain (who had previously failed with 1st and 2nd line agents) tried CBD oil in the hopes that it would ameliorate her neuropathic pain symptoms. However, the CBD oil was found to be ineffective. Working with Dr Clarke, they identified a ratio of CBD:THC (15:11) administered in oil that offered her symptomatic relief and improved function. Examples such as this highlight the value of including THC in a treatment regimen as well as identifying an optimal dose and ratio.

In conclusion, the use of cannabis to manage pain could result in a reduction in the use of opioids and over the counter painkillers. However, it is important that we bring a greater level of scientific rigour to the table with regards to more evidence and education that will reduce the numbers of patients substituting prescription medications for cannabis.

CONCLUSIONS

The 2nd annual Avicanna Symposium highlighted the many opportunities and challenges that the medical cannabis field has to offer. The main conclusions from the symposium are as follows;

- More research is required to determine the long-term health effects of chronic cannabinoid administration (particularly regarding consumption of long-term high doses of CBD). It is important that this research is conveyed to the public as it becomes available.
- There is a need for advanced formulations of cannabinoids in order to optimize overall performance; this will allow for the improvement of the pharmacokinetic profile, toxicity profile and efficacy of the therapeutic.
- It is important that the optimal dose for each indication is identified and administered to the patient.
- More indication-specific evidence is needed on the mechanism of action of each of these cannabinoids. In particular, we need to understand how these will affect the endogenous ECS as well as potential interactions with other drugs.
- There is a need for harmonized processes from seed to final product. This includes the use of standardized extraction methods, analytical techniques, formulation preparation, stability testing etc. Adopting systems like this will increase the quality and consistency of the final product for patients.
- Finally, it is imperative to have a robust clinical trial design in order to mitigate the placebo effect and to identify the conditions for which cannabis has a therapeutic future (and conversely to identify those in which it does not).

BIOGRAPHIES

Christine Allen, PhD
Professor, *Leslie Dan Faculty of Pharmacy, University of Toronto* and Chief Scientific Officer, *Avicanna Inc.*

Christine Allen is a Professor in the Leslie Dan Faculty of Pharmacy at the University of Toronto and Chief Scientific Officer at Avicanna Inc. At the University of Toronto, Dr. Allen's research is focused on the design and development of new materials and technologies for drug delivery with over 130 peer-reviewed publications in this area. She has received career awards from CIHR-Rx&D, CSPS and AFPC. Christine completed her doctoral research in the Department of Chemistry at McGill University and post-doctoral research in the Department of Advanced Therapeutics at the B.C. Cancer Agency. She joined University of Toronto from Celator Pharmaceuticals Inc. Christine is President Elect of the Canadian Society for Pharmaceutical Sciences (CSPS) and a member of the Governing Council for the Natural Sciences and Engineering Research Council of Canada.

Frantz Le Dévédec, PhD
Senior Vice President, Research and Development *Avicanna Inc.*

Frantz has over 15 years of experience in academic and industrial R&D projects, including material sciences and drug delivery formulations. He is author of over a dozen research papers and patents. His background is in biochemistry, with a PhD in applied polymer chemistry, and expertise in analytical and pharmaceutical sciences.

Ruth Ross, PhD
University of Toronto

Ruth Ross obtained a PhD in Pharmacology from The University of Edinburgh in 1990. In 2008 she became Chair in Molecular Pharmacology at The University of Aberdeen. In 2013 she relocated to The University of Toronto to take up the position of Chair of the Department of Pharmacology & Toxicology and Director of the Centre for Collaborative Drug Research. Dr Ross has been engaged in cannabinoid pharmacology research since 1994. Her research focuses on understanding the molecular pharmacology of the endocannabinoids, phytocannabinoids (cannabis) and new small molecules targeting the system. She has expertise in understanding the effects of cannabis. This includes both the potential harms of recreational use and the safety and efficacy of cannabis as a medicine for the treatment of various illnesses.

Aras Azadian
Chief Executive Officer*, Avicanna Inc.*

Aras brings extensive senior management experience in the biotechnology and financial sectors including his involvement in several successful start-up companies. In addition to his international experience in corporate development, his diverse roles include his previous position as the president of an investment corporation in the cannabis space and former Chief Operating Officer of an oncology company. Aras holds a Bachelor of Economics degree from York University in Toronto, and an International Masters in Management degree from EADA Business School in Barcelona, Spain.

Edith Gorecki, MD
dicentra Cannabis Consulting

Dr. Gorecki joins dicentra with over 8 years of clinical medicine experience in various therapeutic areas and patient care settings. After completing her family medical internship in the United States, she pursued her passion of helping others by participating in a Medical Mission in the Caribbean, followed by Oncology Research at the Geisel School of Medicine at Dartmouth in New Hampshire. Since 2015, Edith has been working with various Clinical Research Organizations in the Pharmaceutical and Nutraceutical industries. She has experience with organizing, managing and executing clinical trials (phases I-III) under ICH GCP guidelines in the US and Canada.

Humberto Reynales, MD, PhD
Centro De Atención E Investigación Médica

Dr. Reynales is an MD in Internal Medicine. He holds a MSc in Epidemiology an MBA from Duke University and a PhD in Preventive Medicine from the University of Sao Paulo, Brazil and has completed a Global Clinical Scholars Research Training Program at Harvard Medical School. He has more than 15 years of experience in the pharmaceutical industry with Merck & Co in the area of Clinical Research. Since 2009, he is the founder and Executive Director of CAIMED, a private clinical research organization with operations in eleven sites and four countries in Latin America, and a leader in clinical trials implementation as well as design and conduct of clinical studies in several therapeutic areas.

Alex Chan, R.Ph., B.S.Phm., MBA
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Alex is a licensed pharmacist and a graduate of the Faculty of Pharmacy, University of Toronto. He has worked for over 30 years in practically all aspects of pharmacy field —hospital pharmacist, community pharmacist manager, pharmacist owner, teaching assistant, PEBC examiner and admission interviewer (MMI) at the Faculty of Pharmacy, U of T. Alex has provided input to the Ontario Ministry of Health on pharmacy related issues. His academic achievements include MBA from the Ivey School of Business, University of Western Ontario. Combined experience as a pharmaceutical sales representative and 10 years in Marketing has provided unique insights and expertise in the therapeutic areas of OTC, ADHD, OAB, pain management and opioids. As a Marketing Director at Purdue Pharma, Alex launched seven products and designed provincial formularies reimbursement agreements with successful listings, among other accomplishments. Alex managed a portfolio of opioid pain products with sales of $300 million. Alex is the owner of Solara Pharmacy with two locations that serve Etobicoke and Thornhill. In addition, he is a managing partner of Enhanced Care Medical Services, a preferred provider of medical clinic and physician services to McKesson Canada.

Samantha Watt, MSc
Vice President, Scientific Affairs
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Samantha's experience investigating human physiology and cellular biology has allowed her to develop sophisticated laboratory and project management skills that contribute to Avicanna's competitive edge in the department of Research and Development. More specifically, Samantha has been published on several different occasions and has also lead various conferences and presentations related to plant gene manipulation and cloning. Samantha received a Master of Science degree in from the University of Guelph.

Elena Pope, MSc, FRCPC
The Hospital for Sick Children

Dr. Elena Pope is a Professor in the Department of Paediatrics at the University of Toronto. In 2003, she became the Director of the Section of Dermatology, Division of Paediatric Medicine at the Hospital for Sick Children, Toronto, Ontario, Canada. She received her medical training at The Institute of Medicine and Pharmacy, Bucharest Romania and the University of Toronto, and completed her training in Paediatrics and a fellowship in Pediatric Dermatology at the Hospital for Sick Children, Toronto. Since becoming Director of Paediatric Dermatology, Dr. Pope has instituted innovative approaches to the care of paediatric dermatological conditions by establishing interdisciplinary clinics in Epidermolysis Bullosa, Cutaneous T-cell lymphoma, Vascular Tumor Clinic, Morphea and Genodermatoses. She is a Project Investigator at the Research Institute, Hospital for Sick Children and is involved in numerous research projects stemming from her clinical interests focused on new interventions for rare and common pediatric dermatology conditions.

Amza Ali, MBBS, DM, MSc, FRCP, FACP, FAAN, FAES, MBA
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Dr. Amza Ali MD, FRCP, trained in neurology and clinical neurophysiology in both the United Kingdom and in the United States. He has received international recognition for his work in the Caribbean related to advancing the care of patients with epilepsy and was recently chosen as an Ambassador for Epilepsy by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). The development of a sustainability model in his current doctoral program, at the Henley Business School in the United Kingdom, drives his interest in new pharmacological solutions for epilepsy and other neurological conditions. Dr. Ali holds a Masters in Business Administration from the Rotman School of Management, University of Toronto. He is a Fellow of the American Epilepsy Society and the President of the Epilepsy Society
of the Caribbean.

Alejandro Berlin, MD, MSC
Princess Margaret Cancer Centre

Dr. Berlin trained in Chile, Israel and Canada, and currently works as a staff Clinician-Scientist Radiation Oncologist at the Princess Margaret Cancer Centre. His practice focuses in the characterization of malignancies with MRI and molecular imaging, and original applications of combinatorial approaches using systemic agents, stereotactic and MRI-guided ablative treatments. He is particularly interested in the design of innovative clinical trials, translational oncology, and genomic-based biomarker discovery, conveying his clinical and research expertise towards novel treatments for patients with cancer.

Hance Clarke, MD, PhD
University Health Network

Hance Clarke is a staff anesthesiologist and the Director of Pain Services and the Pain Research Unit at the Toronto General Hospital. Dr. Clarke is currently the knowledge Translation Chair For the University of Toronto Centre For the Study of Pain and in 2016, Dr. Clarke was awarded an early Career Award from the Canadian Pain Society. He has been recognized internationally for his research productivity and improvements to patient care such as the development of the Transitional Pain Program. Dr. Clarke has also played a leading role in educating the Canadian public about pain control, risk factors for chronic opioid use, alternatives to opioids as a pioneering strategy at TGH, misconceptions about opioid use, and the need for further studies on understanding the beneficial and adverse effects of cannabis. He is a strong public champion of evidence-based solutions for the opioid crisis and a national pain and addictions strategy.

Chandra Panchal, PhD
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Dr. Panchal has been the Chief Executive Officer of Axcelon Biopolymers since 2008, has authored over seventy scientific papers, holds several patents in oncology, diagnostics, biopolymers and microbiology, and is an Adjunct Professor in Chemical and Biochemical Engineering at the University of Western Ontario. Dr. Panchal currently sits on the board of directors of both an oncology company known as Medicenna Therapeutics (MDNA), and Canadian Oil Recovery and Remediation Inc. (CVR) as well as Pure Global Cannabis Inc. (PURE). Dr. Panchal holds a Master of Science degree in Molecular Biology and a Ph.D. in Biochemical Engineering from the University of Western Ontario.

James Evans, PhD
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James Evans has close to 10 years' experience in formulation and drug development. He graduated in 2016 from University College Cork, Ireland with a PhD in Pharmaceutical Sciences. He is currently working as a Postdoctoral Researcher in Dr Christine Allen's group at the Leslie Dan Faculty of Pharmacy, University of Toronto. In his current role, James manages the research projects of Dr Allen's group and works closely with Avicanna Inc. to design and evaluate novel cannabinoid-based therapies for a variety of indications.

Javier Hasse
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Javier Hasse is a Latinx cannabis-focused writer and author of the best-selling book, "Start Your Own Cannabis Business," published via Entrepreneur Media. In addition, Javier is an award-winning reporter with more than 4,700 unique articles published across numerous mass media outlets including CNBC, Playboy, Forbes, Entrepreneur Mag, TheStreet.com, High Times, Leafly, Dope Magazine, Benzinga, CNN Money, Yahoo Finance, MarketWatch, MSN Money, Morningstar, and many others. In addition, Javier serves as the Managing Director of Benzinga's Cannabis division, hosts and produces multimedia shows, sits on advisory boards at cannabis companies in emerging markets, has recorded songs that were featured on Billboard charting albums with big names like Wu Tang Clan's RZA and Twista, and publishes his photography very often.

Michael Astone, CPA, CA
BMO Capital Markets

Michael Astone is a Vice President in the BMO Capital Markets Diversified Industries Investment Banking Group. Michael is one of the co-founders of the cannabis practice and has been around the globe working for some of the largest cannabis players. Michael has worked on 15+ transactions in the cannabis sector alone, a few notable deals include: Tilrays IPO, Aurora's acquisition of Medreleaf, Michael has been advising leading public and private clients for over 11 years and is a licensed CPA. Michael graduated in the top 10% in Canada on the CPA exams and earned an Honors Bachelor of Business Administration from the University of Guelph.

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Kaivan Talachian holds a doctorate in pharmacy (Pharm.D., R.Ph.) and is a practicing pharmacist in Canada with more than 20 years of diverse experience in pharmaceutical, medical device and healthcare information technology. He has conducted numerous educational sessions on medical cannabis across the country. Kaivan is the vice president of professional services at CannTrust, in this capacity he is responsible for medical business and advocacy relationships.

Lakshmi Kotra, B.Pharm.(Hons), PhD
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Dr. Kotra is an academic entrepreneur with expertise in drug discovery and development. Kotra group specializes in the areas of medicinal chemistry, preclinical and clinical development of small molecule and natural product-based drugs. Dr. Kotra authored/co-authored over 120 peer-reviewed articles and book chapters, and delivered over 110 scientific and plenary talks globally. Kotra research group has contributed to a number of research programs in the areas of infectious, metabolic and neurodegenerative diseases. Dr. Kotra is a recipient of several awards including the Premier's Research Excellence Award from the Province of Ontario (Canada), R&D Health Research Foundation Research Career award, GlaxoSmithKline/Canadian Society for Pharmaceutical Sciences Young Investigator Award. Dr. Kotra leads an international consortium with India for the development of novel chemical classes of drugs targeting malaria—a consortium of public and private organizations in Canada and India.

Janeth Mora, PharmD
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Dr. Mora is an executive within the pharmaceutical industry, with broad and qualified experience in regulatory affairs and marketing across emerging markets. Dr. Mora began her career with the Colombian Regulatory Agency, INVIMA, and then continued in the pharmaceutical industry with Merck & co. She later joined Pfizer Inc. in 1997 where she held different positions of increasing responsibility in regulatory affairs, and then subsequently in marketing for specialty/orphan products. Dr. Mora currently acts as a Strategy and Business Development Advisor for companies in LATAM interested in developing businesses in the region. Janeth also holds degrees in Management, Marketing and Negotiation.

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Dr. Zuluaga is a full professor and senior researcher at Department of Pharmacology and Toxicology and he has been dedicated to research on aspects related to pharmacology, pharmacokinetics and pharmacodynamics, pharmacometrics, immunopharmacology, rational use of drugs, substance abuse and misuse, development of animal models of Therapeutic efficacy, chronic osteomyelitis, study of generics and biosimilars, dose optimization and software development.

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Alan Friedman is the founder and CEO of Rivonia Capital, a Canadian finance and capital markets advisory firm. Alan is also a co-founder of or investor in several publicly traded companies across diversified industries. He participated in the seed financing and assembling of these companies and has been responsible for facilitating various subsequent finance rounds post the going-public process. Alan is a South African qualified attorney and previously worked at a top 5 South African bank.

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Carlo earned his Bachelor of Science in Pharmacy from the University of Toronto in 1981 and completed a Hospital Pharmacy Residency at Sunnybrook Health Sciences Centre in 1982. He graduated with a Doctor of Pharmacy from the State University of New York at Buffalo in 1984. From 1985 to 2011, Carlo was the Clinical Pharmacy Coordinator for Oncology at Sunnybrook Odette Cancer Centre and is currently the Oncology Pharmacy Clinician Scientist at the Odette. He is an Assistant Professor at the Leslie Dan Faculty of Pharmacy, University of Toronto where he co-coordinates the third year Oncology Therapeutics Course. Carlo has given numerous presentations at local, national and international meetings on various oncology related topics.

Carlos Maldonado, MD
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Dr. Carlos Enrique Maldonado Muete is a physician, pharmacologist and professor of pharmacology who contributes his experience in biotechnology, pharmacovigilance, clinical studies and knowledge of the medical community and regulatory authorities, as a local and international lecturer. Among other roles, he has participated in medical and regulatory issues related to the approval and commercialization of several new medicines. Dr. Muete has achieved results through his role as a former Medical Director of international pharmaceutical companies and as an external advisor.

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Dr. Irene Lara-Corrales is an Associate Professor of Pediatrics at the University of Toronto and a staff physician in Pediatric Dermatology at the Hospital for Sick Children in Toronto, Canada. She completed her medical training and pediatric residency at the University of Costa Rica, in San Jose, Costa Rica and her pediatric dermatology training at the Hospital for Sick Children. She obtained a Master in Science degree from the University of Toronto. She is involved in numerous clinical and research endeavours, as well as in teaching commitments. She co-directs the Genodermatoses, Epidermolysis Bullosa, Vascular Tumors and Café-au-Lait. Screening clinics at SickKids. She is also the co-chair of the hospital's Wound Care Committee. Her research interests include genodermatoses, inflammatory diseases and vascular anomalies.

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Dr. Mauricio Torres Pradilla is a Dermatologist with a specialization in pediatric dermatology. He has been involved in research on Atopic Dermatitis, Psoriasis, Epidermolysis Bullosa and Hemangiomas in Europe and South America. Mauricio has several publications on these topics, individually and in collaboration. He is currently the Head of Dermatology at Fundación Universitaria de Ciencias de la Salud in Bogota, Colombia and is a Dermatologist at Debra Colombia, dividing his time among three major teaching hospitals and private practice.

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Justin Grant, PhD, MBA
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Dr. Justin Grant has over fifteen years experience in leading pharmaceutical research in sustained drug release formulations. He held academic appointments at the University of Toronto's Faculty of Pharmacy and UHN's Techna Institute for the Advancement of Technology for Health. For over 10 years, he has managed a $50M preclinical cancer research facility (the STTARR Innovation centre) at Princess Margaret Cancer Centre. Justin is currently the Chair of the Scientific Advisory Board for Avicanna.

Zohar Koren, PhD MBA
SciCann Therapeutics Inc.

Dr. Koren is the co-founder and CEO of SciCann Therapeutics Inc., a Canadian-Israeli speciality pharmaceutical firm dedicated to the development of cutting-edge technologies in the pharmaceutical cannabinoid space. He is the VP BD of Mor Research Applications, commercial unit of Clalit Healthcare Services, World's second largest HMO, with 14 hospitals and $6B annual turnover. Dr. Koren is also the VP BD of Talent Biotechs, a developer of CBD based drugs for the treatment and prevention of GVHD (Graft Vs Host Disease). Dr. Koren is also the co-founder and CEO of Cannabics Pharmaceuticals Inc. (OTCQB:CNBX), a developer of cannabis based therapies for oncology patients. He is the director of Business Development at Aposense Ltd (TASE:APOS), a developer of novel pharmaceutical products in the oncology, CNS and metabolic disease fields. Dr. Koren holds a Ph.D. and M.Sc. in Protein science and computational biology from the University of Haifa, and a B.Sc. in Mathematics, Physics and Biology from the Hebrew University in Jerusalem. Dr. Koren is a veteran of the prestigious "Talpiyot" program of the Israeli Defence Forces, an elite unit designed to qualify the top technology officers of the IDF.

David Kideckel, PhD
AltaCorp Capital Inc.

Prior to joining AltaCorp Capital, Dr. Kideckel was at another leading independent investment dealer, in his role as Director of Healthcare & Biotechnology, Institutional Equity Research. Dr. Kideckel is a seasoned industry executive, having spent over 10 years in international pharmaceutical, biotechnology, and medical device companies where he held executive roles in sales, marketing, medical affairs and international business development. Dr. Kideckel holds a PhD and MBA from the University of Toronto's Institute of Medical Science and Rotman School of Management, respectively. He is a university Gold Medalist and a recipient of the Canadian Institutes of Health Research Science to Business Award.

Ignacio Peralta, PhD
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Dr. Ignacio Peralta currently works at the Institute of Chemistry and Drug Metabolism (IQUIMEFA), National Scientific and Technical Research Council. Ignacio does research in Ethnobotany, Phytochemistry and Pharmacology and teaches Pharmacognosy and Phytotherapy at the School of Pharmacy and Biochemistry of University of Buenos Aires. Their most recent publication is ' Food Preservation by Larrea divaricata extract: Participation of Polyphenols'.

Alan Ridgway, PhD
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Alan Ridgeway has worked as a publishing research analyst for more than 10 years. Prior to joining Sprott Capital Partners he was a top ranked analyst covering the Canadian healthcare sector at Scotiabank. Prior to working in the capital markets, Mr. Ridgeway held a postdoctoral fellowship at Harvard Medical School where he performed cancer research. Mr. Ridgeway holds a PhD in Biochemistry from Western University, an MBA from Queen's University, and is a CFA® Charterholder.

Rahul Sarugaser, PhD, MASc, MBA
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Rahul is an equities research analyst covering the biotechnology, healthcare, and cannabis sectors at Paradigm Capital. Rahul holds a PhD and MASc in biomedical engineering from the University of Toronto, and an MBA from the University of Oxford. Prior to Paradigm, his roles included Director of Business Development at the Centre for Commercialization of Regenerative Medicine, Investment Manager with the Toronto-based MaRS Investment Accelerator Fund, and Strategic Marketing Analyst with GE Healthcare's headquarters in the U.K.

Peter Carlen, MD, FRCP(C)
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Peter L. Carlen, MD, FRCP(C), was trained in Medicine and Neurology at the University of Toronto. He studied cellular electrophysiology for three years at the Neurobiology Department of the Hebrew University of Jerusalem. He then returned to Toronto where he was a staff neurologist and researcher at the Toronto Western Hospital and the Addiction Research Foundation starting in 1975. In 1989, he was appointed Director of the Playfair Neuroscience Unit and Neuroscience Research at the University Health Network for a 10 year term, where he is now a senior scientist and neurological clinician, focussing on epilepsy. He is also a Professor in the Departments of Medicine (Neurology), Physiology and Institute of Biomaterials and Biomedical Engineering of the University of Toronto. His main research interests are the fundamental mechanisms of neural synchrony and entrainment (epilepsy), neuropharmacology and neuroprotection.

Lawrence Hirsch, MD
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Dr. Hirsch completed medical school and internship at Yale University, neurology residency at Columbia University in New York City, and a two-year fellowship in Epilepsy and EEG at Columbia. He remained at Columbia on the faculty from 1997-2011. He moved to Yale University in 2011 as Professor of Neurology, Chief of Epilepsy and EEG, and Co-Director of the Yale Comprehensive Epilepsy Center. He has had leadership roles in multiple societies, including the American Clinical Neurophysiology Society, the American Epilepsy Society and the American Academy of Neurology. Dr. Hirsch has published more than 200 peer-reviewed manuscripts and more than 100 invited reviews, editorials or chapters. His research interests and publications are on topics such as brain monitoring with EEG in the critically ill, status epilepticus, brain stimulation for epilepsy, epilepsy surgery, seizure semiology, electrocorticography, brain mapping, effectiveness and tolerability of antiepileptic drugs, seizure clusters, and sudden unexpected death in epilepsy (SUDEP). Dr. Hirsch has directed symposia and lectured at many national and international epilepsy and neurology meetings, and has won multiple teaching awards.

Robert Bonin, MD, PhD
University of Toronto

Rob Bonin is an Assistant Professor in the Leslie Dan Faculty of Pharmacy at the University of Toronto. He holds the Canada Research Chair in Sensory Plasticity and Reconsolidation and is a Scientist with the University of Toronto Centre for the Study of Pain. Dr. Bonin is exploring the synaptic changes in the spinal cord that contribute to abnormal sensory processing and is developing new models to study natural pain behaviour in animals.

Mohit Kapoor, PhD
University of Toronto

Dr. Mohit Kapoor is the Director of Arthritis Research Program (the largest multidisciplinary Arthritis Research Program in Canada) at the University Health Network (Toronto), where he is directing basic, clinical, and translational research in arthritis. He is the Tier 1 Canada Research Chair in the Mechanisms of Joint Degeneration. Dr. Kapoor's translational research program is directed towards: (1) Understanding the complex cellular and molecular mechanisms associated with joint destruction during osteoarthritis; (2) Identifying reliable biomarkers for early identification of patients with osteoarthritis to enable early intervention; (3) Identifying novel therapeutic targets to stop/delay osteoarthritis and restore joint function. His research is funded by various research organizations including the Canadian Institute of Health Research (CIHR), Canada Research Chair Program, Canadian Foundation for Innovation (CFI), Natural Sciences and Engineering Research Council of Canada (NSERC), Krembil Foundation, The Arthritis Society, Stem Cell Network, etc. He also sits on review panels & boards of various research/funding organizations across the globe. He has published over 80 research articles, reviews, and book/book chapters. His research work has been published in journals including Nature Medicine, Science Translational Medicine, Annals of The Rheumatic Diseases, Nature Reviews Rheumatology, etc.

Sefi Kronenberg, PhD, MD
The Hospital for Sick Children

Dr. Sefi Kronenberg is a psychiatrist within the Department of Psychiatry at The Hospital for Sick Children (SickKids) and an Assistant Professor of Psychiatry at the University of Toronto. Dr. Kronenberg completed his academic training at Tel-Aviv University (Israel) receiving both an MD and a PhD in pharmacogenetics. After which, he completed a five-year residency in child and adolescent psychiatry at Schneider Children's Medical Center of Israel and Ge'ha Mental Health Center. Upon graduation, he worked as the head of the paediatric ER at Ge'ha Mental Health Center. Kronenberg joined SickKids in 2013. He came onboard as a fellow focusing on the clinical and biological aspects of obsessive-compulsive disorder (OCD). Since 2016 he has been working principally with SickKids' pain services including: acute, transitional, and chronic pain services. Kronenberg is also a member of the chronic pain intensive rehabilitation program at Holland-Bloorview Kids Rehabilitation Hospital (Get Up and Go Program). In 2017, Dr. Kronenberg became the mental health lead of the chronic pain service.

Karim Ladha, MD, MSc
St. Michael's Hospital

Dr. Karim Ladha is a clinician-scientist and staff anesthesiologist at St. Michael's Hospital and the University of Toronto. Dr. Ladha received his medical degree from the Johns Hopkins University School of Medicine. He then completed his anesthesia training at the Massachusetts General Hospital and obtained a fellowship in cardiac anesthesia in Toronto. He also holds a Master's degree in clinical epidemiology from the Harvard School of Public Health. His program of research uses mixed methodologies to obtain a multifaceted view of acute and chronic pain including retrospective analyses of administrative databases, prospective observational studies, and multi-center randomized controlled trials. His research has been published in top-tier journals including JAMA, BMJ, British Journal of Anesthesia and Anesthesiology. This past year, he received the prestigious International Anesthesia Research Society Mentored Research Award for his potential to influence the field of Anesthesia.

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