The CCIC Podcast
September 25th, 2015

This month: Dr. Jonathon Page
Interview by Dr. Mark A. Ware

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Introduction

Hello and welcome to the CCIC Podcast. The CCIC Podcast is a series of in depth interviews with leading experts and opinion leaders in the world of medical cannabis and cannabinoids.

In this edition of the podcast we are delighted to welcome Dr. Jon Page from the botany department at UBC and the plant biotech company Anandia labs, talking about the importance of genomics in developing cannabis medicines:

"…genomics can help actually standardize the types of cannabis that are being used clinically, whether for trials or clinical treatments"

and discussing the cannabis indica-sativa debate:

"…we found that even though in some cases the strain was labeled at 100% indica, the genotype that we were able to attain using the DNA sequencing technique didn't support that…"

Jon Page is an Adjunct Professor in the Botany Department at UBC and founder of a Vancouver-based plant biotechnology company, Anandia Labs, which focuses on plant breeding and the development of new cannabis-based medicines.

We spoke on September 15th, 2015.

Dr. Ware — Thank you Jon for joining me for this Podcast. My first question is quite introductory. How did you first get involved in research on cannabis?

Dr. Page. — Thanks for having me, its great to be able to talk on this podcast. So my research on cannabis started in 1999. I did my doctoral work at UBC in Vancouver, went to Munich as a post doctorate researcher, and my PhD had been on the biochemistry of medicinal plants and the specifically antibiotic compounds from members of the sunflower family, and I went off with an NSERC postdoctoral fellowship to Munich to work in a lab that was investigating the biosynthesis of

plant metabolites. Biosynthesis is sort of the biochemical process by which organisms- not just plants but organisms in general- produce molecules. The lab in Munich, their "claim to fame" and research study was the opium poppy, on the biosynthesis of morphine and codeine and other alkaloids. They had research exemptions and research licenses to work with controlled substances, so they had cannabis plants legally growing as research materials in the lab. My initial postdoctoral project, which I started midway through 1998, wasn't bearing very interesting fruit, wasn't progressing and so I actually talked to the supervisor of my postdoctoral work about switching over to a project that would investigate how THC and other cannabinoids are made in the cannabis plant. It made sense, I had always had an interest in medicinal plants, it was kind of where my career was going, and specifically I was always interested in plants that have cultural value, medical value, and cannabis kind of fit the bill. At the time in 1999, very little was known about even the biochemistry of how cannabinoids like THC were formed, so I jumped on a project, which was really attempting to understand one of the enzymes so called polyketide synthase, that was at the heart of the biochemical pathway.

Dr. Ware So you became interested through a pathway in other plants. How did working with cannabis differ from, or what particular challenges did you face, working with herbal cannabis as a plant material for this work?

Dr. Page. It was interesting in those early days as a postdoc in Germany. I wasn't fully versed on the challenges of controlled substances, licensing and specifically the obstacles that I was much more acquainted with later in my career, the obstacle of working on plants that had a drug status. Most plant molecular biology or plant biochemistry is either done on model organisms, so these would be the lab rats of the plant world like *Arabidopsis*, or valuable large acreage agricultural crops like corn and canola and wheat. Cannabis on the other hand is really neither. It's an illicit drug controlled by UN conventions, most countries in the world restrict its use, and so the challenge on working with herbal cannabis was really bureaucratic, and that is getting the ability to bring it into the lab, and use it as an organism of study. So in Germany in 1999 as I mentioned, I was there until 2003 before moving back to Canada and working at the National Research Council in Saskatoon. I lived in kind of a bubble where we had the license, it was renewed annually, the German government was supportive of the lab having the licenses, and it was pretty much un-fettered access to the plant for research purposes. On the other hand, when I returned to Canada, I wanted to continue my work on cannabis, because I was making good progress in the lab, and it was still very

much an unsolved question about how cannabinoids are formed, and I was working for NRC in Saskatoon as I said, the subject of institutional support for that plant came up, and it was clear that there wasn't much support from the management from that particular institution, and the licensing of the project was also challenging in the sense that licensing for work on cannabis takes a lot of lead time and a lot of security and details around how you are going to control the plant in the lab. I wasn't really prepared at the time for the challenges of getting that licensing.

Dr. Ware But you were able to proceed, you were part of a team that first cloned and published the cannabis genome as a result of that work. I want to ask you something about the clinical implications of that finding. Now that we've sequenced the cannabis genome, what do you see as the clinical implications of that work?

Dr. Page I think with an audience like the CCIC membership, I look at the context of genomic work we are doing towards clinical relevance, and that I think is mainly related to two areas. One is that standardization for materials for medical use or clinical trials is obviously very important. At one level, there is standardization of the chemistry, so for example if there is going to be a clinical trial on a particular type of cannabis for neuropathic pain, you'd want the same amount of THC and cannabidiol in the material that is being used in the clinical trial, otherwise you are just going to introduce variability into that experiment. In the sense of the genomic investigation, we are also seeing that this work sheds light on the exceptional diversity of the genus *Cannabis*, and the various types of cannabis that are available for medical treatment, for example indica and sativa, I might talk about that in more detail after, but the genomics can help actually standardize the types of cannabis that are being used clinically, whether for trials or clinical treatments, in the sense that we will know more about an individual strain or type and we can make sure it is being used by all the patients who are being treated for something. I think down the road, genomics will start to shed light on the entity of the individual strain, in the sense that if you have a strain of marijuana that is being used medically, and it is grown by one producer, under one particular name, there might be another producer who grows the same strain of marijuana, same name, but genetically they might be different because at this point it's a very confused situation with respect to strain names and the identity of particular strains. I think genomics is going to help provide a standardization of strain names as it relates to their medical use. So I guess I hope this would mean strains could be identified and used by patients in different parts of the country and they'd know what they're dealing with. There may be some variation in chemistry there because of the way the plant is

grown, but it would be the same thing in all places, and really genomics and genetic analyses is going to be the most helpful thing for that kind of standardization. And just as an example, cannabis is sort of unique in the sense that it's a medicine in the form of a herbal product, but there are other types of plants that strains or varieties are very important. You look at apples, there are varieties of apples you find in the grocery store that have names like Red Delicious and Cox's Orange Pippin and Honey Crisp, and we know what they are, they're the same in Halifax as they are in Vancouver because there is that strict variety registration and control of the product. Same thing goes with wine; you have Pinot Noir and Cabernet Sauvignon etc. and there is no difference in those grapes whether they are grown in France or Chile, but in cannabis that's not the case. We don't if Purple Kush grown by one producer is the same as Purple Kush grown by another producer, but we really need to get that standardization towards its medical use because they will then have a more easily traced, standardized medicine for patients. Does that make sense?

Dr. Ware It makes perfect sense. My limited understanding of the cultivation of cannabis has led me to realize that it's a very sensitive plant to environmental conditions and I'm just wondering if you have any thoughts on the epigenetic modifications; so it may be that we identify the genetic fingerprint, as it were, but is the plant then- even if it were genetically identical- is it still possible to end up with a very different cannabinoid phenotype based on environmental growth conditions and so on, or are you likely to see the same strain emerge if the genetics are identical?

Dr. Page I think there will be still lots of variation introduced by the environment, in the way that you know, growing conditions, the amount of light, even in licensed producers in Canada right now, outdoor cultivation is not really possible, in some cases greenhouse cultivation is used, but the difference between outdoor and indoor, maybe different hydroponic growing versus soil growing, these will all introduce types of large plants versus sea-of-green small plants, these kinds of details of cultivation potentially will introduce variation, which would mean, even though the genetics provide the rough determination of where the chemistry will go, the environment will still give the specifics. That will not mean that a high THC line will suddenly switch to CBD dominant or something like that, I would be more sort of finer changes, like maybe the potency will differ between 18% and 22% or something like that. So I think we still see within certain varieties of grapes for example, quite a variation, and that's based on the region they're grown, the terroire of the site in that region, the way they're treated. Of course if its wine, it's the ability of the wine makers to produce this product, so you still introduce all

those things into the marijuana side as well, and I notice the environment is one thing, but there is also the post harvest treatment of cannabis in the sense that there's this elaborate trimming and manicuring and drying and storage regimes, and they all have an impact on chemistry as well. So its not like genetics is going to give us this absolute standardized product from coast to coast, but it is going to hopefully provide a clearer foundation at least for strains, and why people may attribute certain affects or therapeutic properties to those strains.

Dr. Ware The other part of the taxonomy debate is the cannabis indica-cannabis sativa debate and there are strong public and patient reports that indica strains differ in their clinical effects from sativa strains and so on. You've recently published some work that helps to inform this debate. I wonder if you can comment on how we are ever going to get some resolution to this story?

Dr. Page: The paper we just published, came out a couple weeks in the journal PLoS One, was really the work that I did together with a lab at Dalhousie Sean Miles who's a population geneticist there, and really a person who spends his career looking at the genetic diversity of different organisms mainly plants, but animals as well. And that collaboration was a project to analyze genetic variation in a large number on marijuana samples, so the DNA from 81 different marijuana strains and the DNA from 43 hemp strains, which is a non-psychoactive agricultural crop, which is the same species of marijuana, but with different uses. So that was the first study really looking at cannabis as a genus from this genetic variation perspective, using modern DNA sequencing technologies so that really gave us unparalleled and an in-depth look at the genetic differences between different cannabis plant. Part of our analysis, which was talked about a lot in the media in the last couple for weeks was the fact that we tried to make sense of what we called the reported ancestry as this indica or sativa designation, for those 81 marijuana samples we analyzed, and we found that even though in some cases the strain was labeled at 100% indica, the genotype that we were able to attain using the DNA sequencing technique didn't support that, it didn't provide that clear cut delineation between the two types. So as someone who has worked with cannabis as a researcher for a number of years, I am inclined to believe that there are differences between indica and sativa plants, and certainly the morphology, the look of the plant, with indica being shorter, wider leaflets, maybe darker green, and as you mentioned the affects are attributed. People say its more sedative, more of a "body stone", versus sativa being taller, lankier, narrower leaflet. I think there are those differences, but in terms of the amount of mixing we have seen in cannabis in the last maybe five or six

decades and that is interbreeding with all different types throughout the globe towards high THC recreational strains. I think we are seeing a very complex system where it's hard to tease apart what is indica anymore and what is sativa. If you look on the websites of licensed producers in Canada, many times will distinguish between indica and sativa types, and I think they are working on the best information they have available, but I think its much more confused than being able to say if a plant is 100% indica or sativa, or lots of times you see 60% sativa and 40% indica mixed. I think our study is finding that the situation I not as clear as that. So our paper, if we distill it down, really identified the problem. We said it was really mixed up, confused and we need a solution, and I think our solution for this is a two-fold. One is more research. We have to start doing more sequencing, and more chemical analyses on different types of cannabis, in order to figure out some of these differences, and there have been chemical analyses on sativa and indica types that point to the differences. On the genetics, we just scratched the surface with the 81 marijuana strains. We need to do many more, including strains that are still in their natural environment in Afghanistan, and Western China and India. Places where marijuana is a central origin are good places to do genetic analyses on, and also going into old samples in herbaria, these are plant collection sites like at Kew and other places, whether we can get an older material that may have existed before the amount of breeding between different types we see in a lot of modern strains. I guess the relevance to CCIC, what's the clinical relevance of indica and sativa, and so as a bio-chemist and a geneticist I can start to tease apart the plant on the basis of chemistry and genetic variation, but it still doesn't bring it to the patient or the clinic, so I think we need to start investigating. Whether the effects of indica and sativa are actually born out in the clinic, or are they more related to subjective analyses by the consumer on what they're smoking. I think the vernacular taxonomy, is so widespread, I have no reason to doubt the fact that patients can distinguish between types of marijuana they are using, and that they can lump them together into these two types. To really put some data around that in the clinic is the next logical step we need to take before we can lay this classification issue to rest.

Dr. Ware I am wondering whether you have done any work on the genetic drivers behind terpene production, if that is to play a role on the pharmacology of the drug outside of the cannabinoids. Have you had any thoughts on whether terpene regulation could be genetically modified, and that there could be differences between strains in that approach?

Dr. Page My lab is active in this area, on the sense that our focus for the longest time has been cannabinoids and cannabinoid production glandular

trichomes, but in those trichomes, which are little hairs on the surface of the female cannabis flower where cannabinoids are formed, the cannabinoids co-occur with the terpenoids, and we are starting now to delve into the biochemical events that give rise to terpenoids. One of the things we know is that different strains of marijuana, that may be fairly consisted in the fact that they're high THC and low CDB, often differ a huge amount by their terpenoid profile, so there will be different terpenoids that are dominant, so you will have citrus smells or pine smells, so there seems to be a lot more variation in the terpenoid components compared to the cannabinoid components. I'm not really looking at the regulation, more what's there in terms of the enzymes that produce the end product, and how we can start looking at things like if there are terpenoid differences between indica and sativa, how that relates back to the enzymes that produce the terpenoids, and we have really not dug deep enough in the lab to answer these questions. One of the theories about indica type plants is that they contain more of a monoterpene, so that a simple small terpenoid called myrcene, which is sort of one of the characteristic smells of cannabis. Maybe the sedative properties of indica types is related to the amount of myrcene, and so this would be really interesting to dig into, and figure out if we are seeing genetic differences between indica and sativa, and we're seeing them broadly across the genome of the plant, and do they have specific impact on how the plant affect the terpenoids. So in those studies we are starting to make some of that progress in the lab, but we're not really far along yet, but it's a logical next focus. We haven't really solved cannabinoid production, but we have a much better understanding since I started in 1999 how cannabinoids are made, but terpenoids, we know how they are made in other plants, we just don't have all the details for the cannabis plant yet.

Dr. Ware Any reflections or thoughts on the need for science to inform the exploding field of medical cannabis from your perspective?

Dr. Page The fact is, it's a medicine that is going to remain plant-based for sometime to come, and what we need to know is about the chemical diversity in the plant, and how that relates to the fine tuning and differentiating the different effect, and Mark, as a physician you know how much emphasis that patients and the medical marijuana community puts on strains and the differences between strains, and the fact that strains could be useful for treating different conditions, and I think we need more work on the plant side and what that variation and chemistry is, and hopefully in the clinic and pharmacology labs relating it to how the plant exerts those effects, and then backstopping that, what are the genetic differences, and what can we learn from the genome about why those differences in

chemistry arise and give the different effects, and then we can start thinking towards optimization of some of these effects, so if there is a particular component identified in a strain of cannabis, that seems to be related or helping tin the treatment of a condition. What we know about cannabis breeding, is that its mainly been focused on producing more and more THC, and THC levels have been increasing through that breeding effort, but could we breed toward optimize strains, cannabinoids or terpenoids or other plant chemicals that are useful in treating certain conditions, so I think the future is going to give us much finer detail on the variation, and then we can use that variation to optimize and standardize strains. At the same time, the evidence just isn't there, the research hasn't been done, we're not sure if all those strain differences that people are always talking about, if there's a whole bunch of truth in there, or some small details that are not as important as all the weight we are giving them right now, and so I see that as one future direction. I think the other direction, which is not as much about plant biology, but does encompass the field I am actively working in right now which is genomics. I think what we may see, because cannabis and medical cannabis and cannabinoid pharmaceuticals, are really coming of age and becoming increasingly widespread, just as we're seeing this dawn of personalized genomics coming to pharmacy and to medicine, and that is how does the individual patient and their genetics govern how they react to medications. We already know that some people prefer to use cannabis, where other people don't respond well, or don't respond at all to its use for whatever ales them, and this could be governed by their genetics and how the metabolize the drugs that they are receiving or how their receptors are set up to receive those drugs, so with personalized genomics we may start to be able to say, "this is a patient who actually is not well matched for use of a cannabinoids in an analgesic setting" and I think in five to ten years from now, when genome sequencing and medicine is much more wide spread, we'll probably see it linked to medical cannabis and cannabinoid pharmaceutical use as well. We already know about some of the other plant compounds that people use for example codeine and morphine, we know there are people who metabolize, and convert codeine to morphine very rapidly, and it could be a very dangerous situation for breastfeeding mothers who are receiving codeine, and then actually produce a lot of morphine obtained by their breastfeeding child, so that's an example of a genetic difference, and how people metabolize drugs. Right now we really don't have a lot of information about how the genetic variation in human populations impacts the metabolism, or how their cannabinoid receptors respond, but I think we will have much more information about that soon, and hopefully as we see research coming up on cannabinoids in general, these are expensive studies to do, but they are important studies none the less. Outside the

medical field they will have relevance to the abuse of cannabis in certain people, and the potential addiction in certain individuals. Genetic studies and genomic studies may help shed light on those as well.

Jon, it's fascinating talking with you; I feel like I could talk with you forever! You have a tremendously fertile mind and clearly green thumbs and hands too, so I want to thank you for taking the time to speak with us today and for sharing some of your thoughts and insights, and to congratulate you on your pioneering work and wish you the best of luck moving forward.

Dr. Page Thank you Mark, and thanks for the opportunity to speak to the CCIC

Dr. Ware It's my pleasure, Jon. Take care.

Dr. Page Bye for now.

That was Dr. Jon Page, speaking to us from Vancouver, British Columbia.

Thank you for joining us.

Tune in next month to the CCIC podcast.

The approximately 20 minute audio podcast of this interview is available online at www.ccic.net/podcast and are also available on iTunes

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