The CCIC Podcast

February 24, 2015

This month: Prof. Steve Alexander
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.

The CCIC Podcast is brought to you by CannTrust™, a Canadian licensed medical cannabis producer.

In this edition of the podcast we are delighted to welcome Prof. Steve Alexander from the University of Nottingham, talking about the use of the endogenous cannabinoid system in clinical therapeutics:

"…we've got fine tuning possibilities, and that's certainly possible with modifying the enzymes that synthesize or degrade the endogenous cannabinoids"

and finding ways to take cannabinoid research more seriously:

"…there are people from every walk of life who have an opinion on cannabis, and so you can exploit that as a way of getting into their heads, in a way"

Professor Steve Alexander is Associate Professor of Molecular Pharmacology at the University of Nottingham Medical School, in Nottingham, UK. He is also the President of the International Cannabinoid Research Society.

We spoke on February 16th, 2015.

Dr. Ware: Was there a particular person or event that got you interested in doing cannabinoid research?

Dr. Alexander: In the early 90's when anandamide was first identified, I had a colleague in pharmacy, a medicinal chemist, who was very keen on collaborating with pharmacologists. He identified that the chemical synthesis of anandamide was fairly easy. He came across and we had a conversation and it developed from there. It has developed from Raphael Mechoulam and colleagues identifying the first endogenous cannabinoid molecule and us getting together and identifying

that it is something we could look at. We could combine the medicinal chemistry with in vitro pharmacology and it developed from there.

Dr. Ware: So the pieces were all in place in your laboratory and it was a fortuitous combination of collaborators?

Dr. Alexander: We had to develop the cannabinoid side of things. Our first interest was trying to see if these things changed transmitter release. That was the endpoint, if you like, of cannabinoid function in the central nervous system (CNS). That was looking at dopamine release, at acetylcholine release, and striatal reparations and using that as a mechanism of seeing whether these novel endogenous cannabinoids and their structural analogues were effective in those assays. It then expanded from there.

One of the things that is good about cannabinoid research is that it has its own way of moving through the population. Although cannabinoids are conventionally looked at as being addictive, I have a colleague who believes that they are viral - you just pass them on by contact. Your interest develops because people become infected by the cannabinoid area.

Dr. Ware: The cannabinoid CB1 antagonist rimonabant struggled after approval with safety considerations and it was taken off the market. Do you see a future with drugs modifying the endocannabinoid system, as opposed to phytocannabinoids, the plant based drugs?

Dr. Alexander: There are avenues and opportunities of both. Certainly, there is a lot of scope in modifying the endocannabinoid system itself. Possibly the issue is that we don't want it to be too aggressive a change. Physiology is all about adaptation. If you put too much stimulus then things adapt and you possibly don't get the best benefit. Whereas when you have got the fine-tuning ability, which is certainly possible with modifying the enzymes that synthesize or degrade endogenous cannabinoids, maybe then tweaking the system a bit rather than having a very aggressive way of hitting the system then maybe you have got things that will be a bit more successful.

Dr. Ware: Looking at the broad scale of cannabinoid research now, obviously the plant based work and some of the human clinical agenda has been driving some of our clinical approaches, do you see the basic science research agenda continuing to inform clinical development of cannabinoids in this way?

Dr. Alexander: I think so from a variety of angles; certainly the endocannabinoid system is not complete. We have got a good grasp maybe of 10 to a dozen enzymes and mechanisms involved in the function of the endocannabinoid system. In terms of what goes on from the plant derived sources, we have got to a surface with

THC, CBD and maybe in a couple of years THCV, but the remainder of the panoply of stuff, the plant generates, we don't have an understanding of how might that be useful.

I do not expect that all the compounds produced by the cannabis plant will be useful but it will be interesting to see how widespread some the impact of some of the more recently purified and investigated, on the molecular level at least, cannabinoid compounds proved. There are two different strands here: picking apart the endogenous cannabinoid system; and also looking at how maybe the abundance of interesting chemicals that the cannabis plant produces might be put to use.

Dr. Ware: As the president of the largest community of cannabinoid researchers, the International Cannabinoid Research Society (ICRS) what do you see as the role of the ICRS in addressing issues of the use of cannabinoids in medical practice?

Dr. Alexander: It is kind of two fold. It is a forum for discussion and it's and a forum for the dissemination for information. One of the things people want is not just saying that this is good for you or this is bad for you but adding justification to that. Almost all of the time we are not in a position to be either black or white, it just doesn't happen, we have shades of grey. One of the things we have to do is to say, there is risks associated with everything we do. There are risks in life, there are risks in the use of medicinal drugs, and what we try to do is minimize those harms. One of the things we are trying to do is make sure there is an open discussion about the potential uses of cannabinoids, from either the plant or endocannabinoids and their exploitation for mammalian systems.

Dr. Ware: If you could put your crystal ball in front of you and look down the road 10 years from now, what do you think we will be looking at in terms of cannabinoid research?

Dr. Alexander: Apart from the cannabinoid receptors which are very well established, CB1 and CB2, I say well established because we have known about them for 15 to 20 years so they are getting on a bit in comparison, there are at least three further G-protein coupled receptors which are related in terms of either the endogenous ligands that activate them or the possibility that some of the plant derived cannabinoids may influence their activity. There are other G-protein coupled receptors which are on the horizon that might be part of the wider family of cannabinoid receptors. There are the TRP family of ion channel related receptors, of cannabinoid receptors. So there is a possibility that we may be able to exploit some of those, which may be acutely important in terms of pain relief. The long history of cannabinoid exploitation and the association with

analgesia, part of that may also be mediated through these mechanisms. The enzymes that we are looking at, at the moment, may well have a lot further to go in terms of the exploitation. We have a few selective tools, which may be useful in identifying in how these enzymes may be important in terms of physiological functions, but we haven't really got into the pathological mechanisms. Of course what we are after is drugs that treat sick people, not drugs that treat healthy people. There is a big jump into the pathological area to try and identify the dysfunction that might be associated with the endocannabinoid area, with a view of maybe exploiting that to therapeutics.

Dr. Ware: Do you have a position on the endocannabinoid deficiency hypothesis? Have you had a chance to look at this in any more detail to see whether it may explain some of the clinical syndromes, rather than using them as a therapeutic tool, explaining some of the rather peculiar symptoms we see in these generalized pain disorders?

Dr. Alexander: It is a real problem knowing how to address that deficiency syndrome. The methodologies we have for quantifying those endocannabinoids are really not going to be useful for central human issues. There are ways in which we can make use of markers and take blood samples and identify what's going on there. So much of what is known about the endocannabinoid system suggests that it is a very local system and that we can't really do a great deal by taking peripheral samples of what is going on in the spinal cord. Thus it's very difficult to tweak those apart. It is one of those situations where maybe a step change in technology would allow us to have some surety about that. Whether that is making use of imaging techniques or something that we haven't yet thought of. That awaits the future really.

Dr. Ware: Finally, stepping away from the hard science, by now you must be aware of the giggle factor around the use of cannabis, you must have been exposed to this in the past – how do we get to take cannabinoid research more seriously?

Dr. Alexander: Sometimes it is an advantage because there are people from every walk of life who have an opinion on cannabis, so you can exploit that as a way of getting into their heads in a way. It is there already, they have prejudices already, that's for sure. We all have anecdotes we can pass on about cannabis. One of things that is useful for, is then to exploit what is the science behind that. So you can use those anecdotes and those observations to explain why there may be benefit to exploitation of the endocannabinoid area. I think that's actually quite an advantage.

Dr. Ware: I think you are right. I want to thank you for taking the time to share these ideas with us. It has been tremendous chatting with you. Thanks for taking the time

with us today Steve. Any final comments or thoughts that you want to pass along before we wrap up?

Dr. Alexander: I am genuinely quite enthused about the next five to ten years because I think there are real opportunities. As you mentioned already, the history of cannabinoids has not been great from the pharmaceutical industries perspective, but I think there are beginning to be things which will prove maybe a bit more nuanced, maybe a bit more subtle, which could then have a greater measure of success. Trying to do things by a bit too 'sledgehammer to crack a nut' version is not the way to go for successful medicines. Maybe a bit more subtlety is required. I think that there is definitely a chance for the future exploiting the cannabinoid system to that end.

Conclusion: Thank you very much, Steve; it's been a pleasure.

That was professor Steve Alexander, speaking to us via Skype from Nottingham, UK.

Thank you for joining us.

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[Alexander, Steve. Interview by Mark A. Ware. CCIC Podcast, Feb 2015. Web: www.ccic.net/podcast]

Recorded on Skype using ECAMM software

Transcription by Daniel Ziemianski

Edited and produced on GarageBand by Mark and Gabriel Ware

Music by Gabriel Ware