Interview with Dr. Ruth Ross

UTMJ Interview Team (Mana Modares and Jeff Park)

Dr. Ruth Ross

Dr. Ruth Ross, PhD, is a professor and the Chair of the Department of Pharmacology and Toxicology at the University of Toronto. Her background is in pharmacology, having completed both her undergraduate and graduate degree at the University of Edinburgh in Scotland. After a five-year career break, in 1995, Dr. Ross applied to the Career Reentry Fellowship and met a mentor who has been a long-standing expert in the field of cannabinoid pharmacology. Ever since, Dr. Ross has been immersed in cannabinoid pharmacology research. Her research is directed at gaining insight into the deleterious effects of cannabis use and the therapeutic potential for cannabis to be used as a medicine. Dr. Ross is also on the steering committee for the of the Toronto Cannabis and Cannabinoid Research Consortium (TC3), a newly launched partnership of researchers from the University of Toronto and its affiliated hospitals to investigate the health effects of cannabis and its related compounds.

UTMJ: What is it like to have your research area receive so much attention, especially now that cannabis has been legalized?

RR: People get involved in science not because it is a widely popular area of interest, but because it is something they find fascinating, and you never know what direction it is going to go in. It is fascinating to see how this has evolved into something that everyone is interested in, which is a nice place to be, but it is also quite strange because everyone thinks they are an expert. Based on what they read on the internet. There are a few people who have been working on this for a long time who have maybe a bit more breadth and depth of knowledge. However, it is nice for your research area to be something that everyone is interested in.

UTMJ: Could you give us some insight into your research?

RR: The endocannabinoid system is a key homeostatic system, particularly in the brain and in many other physiologies. It's involved in mood, memory, pain, metabolism, sleep, and more. One of the key receptors is the CB1 receptor. It is one of the most highly expressed receptors in the brain, but it's also everywhere. And if a receptor is everywhere, it's a kind of like blessing and a curse. Or, both an opportunity and a threat You could potentially target this receptor to a number of things like improving sleep and alleviating pain, but because it's everywhere, you've got to deal with the side effects as well. So people are taking THC, which is a CB1 agonist. Inevitably, it can be tricky to separate the medical benefits, if there are any, from the potential side effects. You can't always extricate them. In pharmacology, we are often looking for something like "subtype selective beta 2-adrenergic molecule" rather than something that hits all of the receptors throughout the body.

What I have been working on is understanding the CB1 receptor to find out ways to harness some of its therapeutic benefits without some of its side effects. We discovered what is known as an allosteric binding pocket on the receptor. When molecules bind to the allosteric binding pocket on the CB1 receptor, they either tune the endocannabinoid signaling up or down. In some diseases like fatty liver disease, the endocannabinoid system seems to be overactive and what you want is to tune the system down to reduce the liver problems. And in other cases, you might get an underactive endocannabinoid system, in which case you may want to tune it up. In pain, what happens is that your system is producing a whole bunch of endocannabinoids to enable analgesia, and we want to find a way to tune that system up to get more benefits. That is what we are working on in our lab. Number one, we are trying to understand the endocannabinoid system, how it works, when it is overactive, and when it is underactive. Number two, we are trying to make molecules that are more selective to be able to tune the effects up or down as desired. Oh, and I forgot to mention, I am also looking at preclinical models of psychosis. We have genetic models of psychosis. We are looking at the effects of THC and CBD in these models, because right now there is a lot we don't know about the effects of cannabidiol and THC in psychosis.

UTMJ: How do you think your research has highlighted some of the benefits and harms of cannabis and cannabinoids?

RR: Cannabis is not just one thing. There are 60 different cannabinoids in cannabis. Pharmacologically speaking, we know that THC acts on the CB1 receptors. If you take THC out of cannabis, a lot of the effects associated with cannabis disappear, so we know that quite a lot of effects

are mediated by THC acting on the CB1 receptors. But then there are many other effects of cannabidiol that we don't understand. We are not sure what those molecular targets are. Other effects may be due to the whole plant extract but again, we don't fully understand it yet. The whole plant extract might have different effects from the individual components alone.

The most clearly established medical use of cannabis is with pain. But even if cannabis is established to work, you still have to ask how it compares to the standard of care. For instance, how does THC compare to something like gabapentin in treating multiple sclerosis? It's not just whether or not it works, but also whether it is actually better. I think that still remains to be seen. Some patients find that cannabis works well for their pain. It might be helpful for certain patients in certain situations, but as of this moment, we are still working all of that out. Certainly in palliative care, it helps people sleep, helps stimulate appetite, and helps with some analgesia. Those are specific circumstances in which it is useful. People have been talking about using cannabis in anxiety, PTSD, depression, autism, and in all sorts of things, but we do not have the data yet on the safety and efficacy of cannabis use in these contexts. People are also using very high doses of cannabidiol. We have no data, no epidemiology on what happens with high doses of CBD. People have just started using high doses of CBD. We don't know what the effects on the population or the individual would be, and this will probably only emerge with time as we start to get more data. So we are really in the dark. High doses of CBD don't seem to cause much in terms of acute toxicities but there are other concerns around the liver effects, especially in older people. What we don't know is whether there will be unintended consequences from side effects 10 or 20 years down the road. Other harms include potential risk of psychosis and symptom exacerbation. Cognitive impairment and memory are probably not affected permanently but is affected short-term during cannabis use. Also in young people, particularly adolescents and those under the age of 25, high dose and frequent use are associated with various outcomes like developing depression later in life. Those are some of the things we are aware of.

UTMJ: The popular belief is that cannabis is not addictive or not as addictive as other substances. Can you give us a little more insight into how addictive cannabis really is?

RR: We use the word "dependence" with cannabis because it's not as physiologically addictive as opioids. One recognized potential harm of non-medical cannabis use is cannabis use disorder, which occurs in 10% of people using cannabis. That's when you want to stop using it but you can't; it's affecting your life, your motivation, your grades, and your mood. This is called a dependence and not an addiction. People definitely suffer from withdrawal, like anxiety, trouble sleeping, and craving cannabis, but it's not the same debilitating withdrawal someone would have with opioids or nicotine. Data is showing that young people are using it as coping mechanism to help with anxiety or stress. there is data to show that young people who use cannabis to self-medicate to relieve stress may be more likely to become dependent on it. The endocannabinoid system is an adaptive coping mechanism; your endocannabinoid system gets activated when you are in a stressful situation to reduce stress. We adapt to stress and learn how to develop healthy coping mechanisms. The endocannabinoid system is involved in that. But if you are using something like THC to dampen your stress, you are switching off your own endocannabinoid system as well as your adaptive stress coping mechanism because now it's got a CB1 agonist on board. So that's maybe how people can become dependent. Next time something stressful happens, the coping mechanism is to use cannabis rather than our own healthy coping mechanism. With that said, the latest figure we have is that 10% of all cannabis users develop dependence, but that number is as high as 17% in younger people. That's millions of people. The higher the dose, the higher the frequency, and the earlier you start using cannabis, the more likely you will develop problematic cannabis use

UTMJ: What do you think is least understood about cannabis use that is not being emphasized enough to the public?

RR: People are using much higher doses [of THC] than before. There was a study published recently by a group of psychiatrists looking at whether there is an increased incidence of psychosis in London, Amsterdam, and Paris because of the availability of high dose cannabis. There are lower doses in Paris, whereas in Amsterdam and London the doses are high. They defined "high dose" as >10%, but now most of the licensed producers are often selling 20-25% [THC], which is a very high dose. That is another thing, how are we judging the dose? Should we be dialing it right back to the 4% people were using? People say that the epidemiology shows [that cannabis is safe] and therefore, it is safe to use, but the epidemiology is based on 30 or 40 years of maybe 4-5% [THC], it's not based on 30 years of 20% [THC]. That is another total unknown - what are the consequences of the higher doses? The advice is always "start low and go slow" but what "go" implies is that you can keep [increasing the dose], but I would say if you are going to use it "start low and stay low". But people develop tolerance and desensitization. They would no longer feel its effects with a low dose because they have become tolerant. Inevitably they increase the dose, which is not good because the higher the dose the more likely [it is to precipitate] harmful consequences and also more likely [for the user] to develop dependence. It is important to stay at a low dose and use infrequently.

People say it has been used as a medicine for thousands of years but the reality is that the medical use previously would have been, for example, for premenstrual pain for a specific length of time, at a low dose, and a specific formulation. Now we're in the realm of medical cannabis being used at high doses chronically, which is very different from saying that we have been using it for thousands of years as a medicine. I think we need to understand what the effects are of acute vs. chronic use. What is a medical dose? Is it 20-25% [THC], or is that too high? What happens when users develop tolerance - can you really use this as a medicine if people are going to develop tolerance very quickly? These are the questions that need to be asked.

UTMJ: What do you think about the timeline of cannabis legalization?

RR: We urgently needed to decriminalize because there were inequalities and harms from people having criminal records due to possessing small amounts of cannabis. What has very much concerned me is the rush to legalize in a "for-profit big cannabis" model like "big tobacco". We could have decriminalized as a first step, and then we could have slowly looked at potential ways in which we could legalize, and made sure we had more information in place before we legalized. I have been very concerned about the rate at which legalization happened, how quickly it happened, and also with the idea of creating a billion-dollar industry. Legalization per say is not necessarily bad - what I would like to see is legalization with public health at the absolute heart of it. I would like to see legalization with the goal of reducing the number of problematic cannabis users, not increasing 'the market', with people not starting using until they are a lot older if at all, keeping at a really low dose, and medical use only being based on evidence of safety and efficacy with no over-inflated claims of efficacy. People are free to choose to use cannabis, but it really important that they have as much information as possible on the effects. Keeping cannabis out of the hands of young people has not really been addressed at all by legalization because it is still illegal for young people, and if they see normalization and sophisticated products among young adults, is that going to make them more likely to use later? I don't think that issue has been addressed either. Decriminalization followed by regulated not-for-profit legalization would have potentially provided a safe source of cannabis that was not from the criminal market and wasn't laced with other products.

The good news is that everyone's now interested in it - people now want to know if it is safe. Is it effective? More research funding is becoming available, which is great. We will eventually answer some of these questions about safety. Canada has the second highest use in the world next to America. It is a good thing that the research is happening and that some funding is being made available, but we will need significant amounts of funding to conduct good clinical studies on medical use in various conditions. These trials cost many millions of dollars.

It is interesting from a patient perspective because the reality is that for some people with certain illnesses, cannabis could be an important therapeutic. The question I have is: who is going to spend the money on those clinical trials now that it's legal? Companies can now sell cannabis without the very strong evidence that would have been required before had it been, through a more medical regulatory framework. Then patients would have been prescribed a product that someone had spent millions of dollars on to know if it's safe and effective. Whereas now, what is the incentive to spend money on these clinical trials? Patients are going to be the ones not getting the information that they need. Patients [and physicians] really need to know if it works or not and if it does [then physicians] should absolutely be prescribing it, but maybe [they] are reluctant to prescribe it because no one spent money on the clinical trials. I'm concerned that we keep medical use in patients as a real priority for gathering evidence.

UTMJ: Can you tell us a little about Toronto Cannabis and Cannabinoid Research Consortium?

RR: Toronto Cannabis and Cannabinoid Research Consortium (TC3) is comprised of researchers from CAMH, UHN, and various University of Toronto departments. There are three pillars: the preclinical research to understand the chemistry and biology of cannabis and cannabinoids; the clinical research; and public health. The goal initially is to get people together, have research days, talk to one another and share ideas. We are all in this one giant Canadian 'experiment'. For example, we have people taking high doses of CBD but we don't know what the consequences are. Public health researchers might start to identify some populations that may be exhibiting some symptoms as a result. We then need to get basic scientists looking into this with preclinical models in place in order to identify the mechanism of action and the molecular target. The consortium has over 60 principal investigators. University of Toronto's research network, particularly that of the Faculty of Medicine, is just huge. There is just so much opportunity to answer some of the key questions around the safety, the harms, and the mechanisms. We hope to use some preclinical models to identify key dosing regimens and key risks and then quickly get that information to people working in clinic. Another example is maternal use of cannabis. We are really concerned about people using cannabis when they are pregnant or breastfeeding because it crosses the placenta and the brain blood barrier. We urgently need to get some really good information on what the public health implications of that are. These are some of the things that the consortium will enable us to do. We

have some really important questions to which we need answers really quickly.

UTMJ: What do you think are future directions in cannabinoid research or questions that remain unanswered that should be explored further?

RR: Key research questions include: understanding the endocannabinoid system - how is it regulated? How does it change in different diseases and in different individuals? For example, recently a woman was identified in Scotland who had an abnormal gene for FAAH, which is the gene for the enzyme that metabolizes one of the endocannabinoids. This is an example of a really interesting polymorphism that tells us something about the endocannabinoid system. She doesn't feel any pain and any wounds heal very quickly, but her memory is not very good.

The other big questions are around the idea of the effects of cannabis - does it really work as a medicine? Is it safe? In what conditions does it work in and in which medical conditions is it contraindicated? There are big questions around cannabidiol. Everyone is taking CBD and we need to start to identify what the molecular target is. We know the molecular target for THC and once you know the molecular target, you immediately have information about the safety because you know that target is expressed in certain diseases, or organs, and you can start looking at that. With cannabidiol all we have this polypharmacology, and we don't know what the target is. All the other questions I have already mentioned around maternal use, and mental health concerns are also important. There is a lot of debate around the age of use - how risky is it? Is the risk inflated at 21 vs. 31 [years]?

UTMJ: What is one piece of advice or words of wisdom you would want future medical professionals to know about the use of cannabis in their practice?

RR: Don't do anything that is not based on solid evidence. We need to get the evidence and make sure the source of information is unbiased with no conflict of interest. Many medical prescribing disasters have been caused by misinformation, prescribing drugs based on the information that was misleading or incorrect – provided by people marketing and profiting from sales. We need to make sure that doesn't happen again. Clinical professionals need good unbiased information Let's not repeat history by overstating benefits and understating harms. We can do better than that.