New Developments in Cannabinoid-Based Medicine: An Interview with Dr. Raphael Mechoulam

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(adapted from Mavericks of Medicine by David Jay Brown)

Dr. Raphael Mechoulam

Raphael Mechoulam, Ph.D., is the Lionel Jacobson Professor of Medicinal Chemistry at the Hebrew University of Jerusalem, where he has been working on cannabinoid chemistry (a term he coined) for more than forty years.

Dr. Mechoulam is recognized as one of the world's experts on cannabinoid-based medicine. In addition to his groundbreaking discoveries, he has authored hundreds of scientific papers on his cannabinoid research as well as a book, *Cannabinoids as Therapeutic Agents*, which provides an early review of the research in this area. Dr. Mechoulam was President of the International Cannabinoid Research Society and has received numerous honors and awards for his outstanding contributions to the field. He is a member of the Israel Academy of Sciences, and among the numerous prizes that he has received for his work, is the highest national scientific prize in Israel—the Israel Prize.
In 1964, Dr. Mechoulam and colleague, Dr. Yehiel Gaoni, were the first to identify and synthesize delta-9-tetrahydrocannabinol (THC), the primary psychoactive compound in cannabis. Their discovery provided new insights into how the brain functions and opened the door to medical research exploring, not only the therapeutic potential of THC (marketed as Marinol in America), but other natural and synthetic cannabinoids as well.

Dr. Mechoulam, along with pharmacologist Dr. Habib Edery and colleagues, went on to isolate and elucidate the structures of most members of the cannabinoid group of compounds in the cannabis plant. Twenty-eight years after discovering THC, in 1992, Dr. Mechoulam, along with Dr. William Devane and Dr. Lumir Hanus, identified the brain's first endogenous cannabinoid (or endocannabinoid)—the brain's natural version of THC—which they named "anandamide," from the Sanskrit word "ananda," which means "eternal bliss" or "supreme joy."

Research has since revealed that the brain is richly populated with cannabinoid neurotransmitters and receptors. Just as the active compound in opium, morphine, led to the

discovery of the endogenous morphine or endorphin system in the brain, research investigating the active compound in cannabis, THC, led to the discovery of the brain's endocannabinoid system. Later Dr. Mechoulam and colleagues identified the THC metabolites and, more recently, along with Dr. Lumir Hanus and Dr. Shimon Ben-Shabat, he discovered a second endocannabinoid known as 2-arachidonylglycerol (2-AG). These findings have profoundly advanced our understanding of cannabinoid systems.

The Endocannabinoid System

The endocannabinoid system is a ubiquitous lipid signaling system that we now know appeared early in evolution and has important regulatory functions throughout the body in all vertebrates. It consists of a family of G-protein-coupled receptors, the cannabinoid receptors (CB1 found in the brain and many peripheral tissues, and CB2, primarily found in immune cells); endoligands to activate these receptors; and two enzymes, the fatty acid amide hydrolase and the monoacylglycerol lipase, to metabolize the endoligands. The endoligands of the cannabinoid receptor system, small molecules derived from arachidonic acid, are called endocannabinoids.[1] [2]

The main endocannabinoids, anandamide (arachidonoylethanolamide) and 2-arachidonoylglycerol, bind primarily to CB1 and CB2 receptors, but also to the vanilloid receptor[3] [4] producing a wide diversity of effects since they function as agonists, antagonists and partial antagonists. (Cannabinoids function as antagonists to the vanilloid receptor, *a.k.a.* the capsaicin receptor, since it can be activated by capsaicin and is involved in the transmission and modulation of pain.)

Neuromodulatory Effects

Cannabinoid receptors (primarily CB1), which are found in higher concentrations than any other receptor in the brain, are densely distributed in both neuronal and glial areas, and the endocannabinoids are thought to play a critical neuromodulatory role. Cannabinoid CB1 receptor activation is known to modify the release of several neurotransmitters, including glutamate and gamma-aminobutyric acid, and to be involved in motor control, cognition, memory consolidation, emotional responses, motivated behavior and homeostasis.[5]

The CB1 receptor is expressed in the hypothalamus and the pituitary gland, where its activation modulates all the endocrine hypothalamic-peripheral endocrine axes, including the hypothalamic-pituitary-adrenal (HPA) axis. Endocannabinoids have been found to mediate the glucocorticoid-induced inhibition of the release of corticotrophin-releasing factor within the paraventricular nucleus of the hypothalamus, leading some researchers to postulate that alterations in the normal "tone" of the endocannabinoid system might be associated with the development of stress-related diseases, including anxiety, depression and obesity.[6] [7]

Recent studies show that vigorous exercise stimulates the release of anandamide, and even exercise of moderate intensity activates the endocannabinoid system in the brain, inducing beneficial changes in mental status including analgesia, sedation, anxiolysis, and a sense of well-being.[8] [9]

Neuroprotective Effects

Cannabinoids have been found to be neuroprotective agents against excitotoxicity in vitro and acute brain damage *in vivo*. 2-Arachidonoyl glycerol (2-AG), specifically, has been shown to significantly reduce brain edema, infarct volume and hippocampal cell death after closed head injury in mice, resulting in significant improvements in functional recovery.[10]

Cannabinoids have also been shown to downregulate microglial production of cytokines of the IL-2 family, lessening neuroinflammatory processes involved in demyelinating diseases such as multiple sclerosis.[11,12]

In other research, cannabinoids have demonstrated neuroprotective antioxidant effects, specifically, an upregulation of mRNA levels of Cu,Zn-superoxide dismutase, a key enzyme in endogenous defenses against oxidative stress. In these studies, cannabinoids provided neuroprotection against the progressive degeneration of nigrostriatal dopaminergic neurons occurring in Parkinson's disease.[13]

Synthetic cannabinoids (HU-210, WIN-55,212-2, and JWH-133) have been able to block amyloid-beta peptide induced activation of microglia and its resulting neurotoxicity, preventing cognitive impairment in rats and offering promise as agents in the treatment of Alzheimer's disease.[14]

Widespread Effects beyond the Brain

Outside the brain, the endocannabinoid system has been found to be activated in virtually every physiological system researchers have investigated, playing a critical role in the modulation of the autonomic nervous system, the immune system, reproductive and gastrointestinal tracts, sympathetic ganglia, arteries, lung, heart and endocrine glands.

Gastrointestinal Effects

Both CB1 and CB2 receptors are found in the gastrointestinal tract on enteric nerves, and pharmacological effects of their activation include gastroprotection via reduction of abnormally high gastric and intestinal secretion, intestinal motility and inflammation. The digestive tract also contains the endogenous cannabinoids (i.e., anandamide and 2-aracidonylglycerol) and mechanisms for endocannabinoid inactivation (i.e., endocannabinoids' uptake and enzymatic degradation).

This combination of actions has led researchers to suggest that pharmacological modulation of the endogenous cannabinoid system could provide new treatments for GI diseases including gastric ulcers, irritable bowel syndrome, Crohn's disease, secretory diarrhea, paralytic ileus, and GERD. Cannabinoids (e.g., nabilone and THC) are already in use clinically as anti-emetics helping to prevent cachexia in cancer patients.[15] [16] [17]

Insulin Modulation

Cannabinoid compounds may one day play a role in the treatment of type 2 diabetes. In the pancreas, both CB1 and CB2 receptors are found on pancreatic islet cells where CB1

stimulation has been shown to enhance insulin and glucagon secretion, while CB2 activation lowers glucose-dependent insulin secretion.[18] [19] [20]

Anti-inflammatory Effects

Cannabinoids' anti-inflammatory actions may render these agents helpful in the treatment of arthritis. Several recently developed synthetic cannabinoid agonists (including HU-210 and WIN-55,212-2) have been shown to inhibit the expression of iNOS and COX-2, and the resulting activation of NF-kappaB, thus protecting the cartilage matrix from degradation induced by cytokines and attenuating joint damage in animal models of arthritis.[21]

Potential Clinical Applications

Controlled studies have revealed therapeutic potential of cannabinoid agonists/antagonists and cannabinoid-related compounds in the treatment of multiple sclerosis and other spasticity ailments, neurodegenerative disorders (Parkinson's disease, Huntington's disease, Tourette's syndrome, Alzheimer's disease), schizophrenia, asthma, rheumatoid arthritis, glioma, cancer chemotherapy side-effects, chronic pain, glaucoma, AIDS wasting syndrome, seizure disorders such as epilepsy, obesity, and metabolic syndrome-related disorders.[22]
Properties of CB receptor agonists that are of therapeutic interest include analgesia, muscle relaxation, immunosuppression, anti-inflammation, anti-allergic effects, improvement of mood, stimulation of appetite, anti-emesis, lowering of intraocular pressure, bronchodilation, neuroprotection and anti-neoplastic effects. Currently, a main focus of clinical research is cannabinoids' efficacy in chronic pain and neurological disorders.

Cannabinoid analgesics have generally been well tolerated in clinical trials with acceptable adverse event profiles. Sativex, an oromucosal spray containing equal proportions of THC (a CB1 receptor agonist) and cannabidiol (a non-euphoriant, anti-inflammatory analgesic CB1 receptor antagonist) was approved in Canada for treatment of central neuropathic pain in multiple sclerosis in 2005, and for intractable cancer pain in 2007. Numerous randomized clinical trials have demonstrated safety and efficacy for Sativex in central and peripheral neuropathic pain, rheumatoid arthritis and cancer pain. In the U.S., the FDA approved an Investigational New Drug application for Sativex to conduct advanced clinical trials for cancer pain in January 2006.[23]
CB receptor antagonists are also under investigation for medical use in nicotine addiction and obesity. CB1 antagonists have been shown to decrease nicotine self-administration in rodent models of nicotine dependence.[24] While CB1 agonists increase feeding in rats and humans, CB1 antagonists have been shown to have the opposite effect, significantly suppressing rats' food intake regardless of type of diet (standard lab chow, high fat or high carbohydrate). While some CB1 antagonists also induce nausea and malaise, others have been shown to suppress feeding without these negative side effects.[25] [26] [27]

Additional potential for CB receptor antagonists has been proposed for the treatment of alcohol and heroine dependency, schizophrenia,[28] [29] conditions with lowered blood pressure, Parkinson's disease[30] and memory impairment in Alzheimer's disease.[31] [32]

Cannabinoid Analogs Currently in Drug Development

While the political controversy over medical marijuana continues in America, pharmaceutical companies—such as G.W. Pharmaceuticals in the United Kingdom and Sanofi-Synthélabo Recherché in France—are busy researching and developing a wealth of new medications based on cannabinoids. A wave of new drugs are currently being developed from cannabinoid analogs—both agonists and antagonists of cannabinoid receptors in the brain—from new types of pain killers and neuroprotective agents for head trauma and stroke victims, to appetite stimulants and appetite suppressants.

Recently, one of the synthetic compounds (HU-211) from Dr. Mechoulam's lab completed phase 2 clinical trials against head trauma with evidence of neuroprotective effects. Another synthetic cannabinoid investigated by Dr. Mechoulam's team, HU-331, may be a new potent anticancer drug. HU-331, a highly specific inhibitor of topoisomerase II, has been found to be highly anti-angiogenic, and when compared to doxorubicin, was significantly less cardiotoxic while producing a 30% greater reduction in tumor burden than doxorubicin and other topoisomerase inhibitors.[33] [34] [35] [36] Yet other cannabinoid agonists, specifically HU-210 and JWH-133, have been found to promote the differentiation of glioma stem-like cells (one of the potential origins of glioma), and to inhibit malignant glioma formation *in vivo*.[37]
The pace of cannabinoid research has been significantly accelerating over the past few years, and Dr. Mechoulam—who has been at the forefront of this research since the beginning—thinks these new cannabinoid analog drugs are just the tip of the iceberg.

An Interview with Dr. Mechoulam

Dr. Mechoulam is mentally energetic, kind, and generous. He spoke with David Jay Brown about how he came to discover THC and anandamide, the role that endocannabinoids play in the brain, natural ways to increase the brain's production of anandamide, and the great potential of cannabinoid-based drugs currently being developed.

Q: What do you think the functions of anandamide and other endocannabinoids are in the brain?

Dr. Mechoulam: The endocannabinoid system acts essentially in just about every physiological system that people have looked into, so it appears to be a very central system. Actually, the cannabinoid receptors are found in higher concentrations than any other receptor in the brain, and they are found in very specific areas. They are not found all over, but rather in those places that one would expect them to be—such as areas that have to do with the coordination of movement, emotions, memory, reduction of pain, reward systems, and reproduction. So, I

believe that this is a very central and essential system that works together and communicates with many other systems.
Exercise has been shown to elevate endocannabinoid levels in the brain, and this probably accounts for what jogging enthusiasts refer to as the “runner’s high.”

Q: Do you think that increasing the amount of natural cannabinoids in the brain has any health benefits, and if so, what are some other ways that you think might increase the brain's natural production of endocannabinoids?

Dr. Mechoulam: A good friend of mine was involved in that research. The results were a little bit on the marginal side, not tremendously high.
They saw a little bit more anandamide than normal. I would have expected much more. There was just this one paper, so people have not gone into that very thoroughly. It's probably true, but I think that we have to do a little bit more work on that. I talked to Dr. Piomelli, who was one of the people on that paper, and I believe he also thinks one should see a little bit higher levels.

But there are many ways in which the endocannabinoid levels go up, and this is something quite specific for endocannabinoids. Generally, they are present in very low amounts. They are just not there. If you take a mouse and put it in a very low temperature (around one hundred degrees below zero) the mouse dies, the brain stops functioning immediately, and you'll find essentially no anandamide. The anandamide is formed on demand when needed, and in only those areas that need that particular compound at the moment.

For example, during pain it will be produced in certain areas. The endocannabinoids are not produced all over, and they will not go into the bloodstream like hormones. They will stay around that particular area where they are supposed to be formed. One of the functions is neuroprotection. Now, I'm speaking about mice because I'm not sure what happens with humans. I'm not working with humans and, obviously, it's not ethical to do that. If you take a mouse and cause slight damage to the skull of the mouse, or even to the brain, and if you leave the mouse, it will recover within thirty days. But if you look at the brains of the mice, you find that at least one of the endocannabinoids goes up 1,000%, so we thought that maybe they have a neuroprotective role.

So, we took mice of this type that had been injured, and we injected them with synthetic endocannabinoids—2-AG, the second compound—and we saw that the damage went down very significantly. And there has been a lot of work on that. There has been some excellent work in California by Greenberg,[38] and they find the same thing in other models. So, everybody now believes that these compounds play a role in neuroprotection.

Q: What are your thoughts about using cannabinoids as a treatment to help prevent cancer or retard tumor growth?

Dr. Mechoulam: There are several groups that have found it effective in reducing tumor growth. This is probably due to the same mechanism as before with the neuroprotection. It's probably not only neuroprotective; it's probably a protective agent in general. So, to a certain extent, the endocannabinoid system can be compared with the immune system.
Now, the immune system obviously guards us against protein effects, viruses, and microbes, but not all damages. So, just as our body protects itself with the immune system against microbes or viruses, it also tries to protect itself with other systems—and the endocannabinoid system is one of them.

So, I believe that it certainly acts against cancer cells. There is a very important group in Spain that has done some excellent work on that, and they're actually going into human work now with some cancers found in the brain. We have also done a little bit on that, and there is an Italian group that has done a lot of work on that. So, basically, it seems that this is one of the routes that our body uses to try and protect itself—by acting on cancers using several different mechanisms, not just one.

Q: Can you talk a little about the research that's currently going on with cannabinoid analogs and the development of new pharmaceutical drugs, such as in the areas of neuroprotection and pain management?

Dr. Mechoulam: THC itself is approved in the U.S. by the FDA, and it is used in many other countries for the prevention of vomiting during cancer chemotherapy, and for appetite enhancement. We, and many others, have found that not only THC does that, but also the endocannabinoids. This is one of the main reasons for high endocannabinoid levels during hunger and so on. Now, THC can be used, and is being used, for these two things.[39] [40]
Sanofi-Synthélabo Recherché in France is doing some interesting work. They have a compound, which is an antagonist of the cannabinoid system, and they have tested it in about 8,000 obese people. They have found that it is extremely useful. Their appetite goes down slowly, as it should, and they lose weight. They plan to introduce the compound in twelve months time, I think. They're doing a lot of work in the field, and they expect huge sales. [NOTE: This drug, rimonabant, which is no longer available in the U.S. under the trade name Accomplia, was authorized in the European Union since June 2006, to be used in combination with diet and exercise to help obese and overweight patients lose weight. Human clinical trials showed an average loss of 10% of bodyweight, plus beneficial improvements in HDL, cholesterol ratios and triglycerides. However, the European Medicines Agency (EMEA) issued warnings that rimonabant should not be used by patients who are severely depressed or taking anti-depressants as it heightens risk of suicide among this group.]

There are compounds that are being tried by many companies. I think that just yesterday a new mixture of THC and CBD (cannabidiol), which is made by a company in England called G.W.

Pharmaceuticals as a spray under the tongue, was approved in Canada. So, they will be marketing it in Canada for the prevention of all kinds of multiple sclerosis effects, and they will probably get it approved in England.

Here we have several things going. There is a compound which was found to be pretty good for prevention of cognition-lowering after heart surgery. After heart surgery, in some cases, there is some cognition lowering, and we found that it certainly does something to that. Initially, we found this same compound was very good in the prevention of brain trauma, but large-scale experiments have not been positive. I'm not sure why. I think that it was a technical mistake, but that's another thing.

I'm part of the faculty at the medical school here, and at Hadassah Hospital, and we use THC for a variety of things. It has to be approved in every single case by a committee at the hospital. We have used it for a very wide variety of things. We found it effective in fighting hiccups, for example. You'll be surprised how if somebody has hiccups constantly for months how terrible it is. And it works fine. We've used it for Tourette's Syndrome, which is a very nasty neurological disease.

This was based on work by some colleagues in Hannover, Germany.[41] It works very well indeed. We've tried it in cases of multiple sclerosis. We've tried it, obviously, with appetite. We gave it four hundred times to children undergoing cancer chemotherapy in order to prevent them from vomiting, and to help with the terrible situation associated with treating children for cancer and so on.[42] They're happier, and the families are happier, so we've been very glad about it. So, we try it in various diseases, where there is sufficient literature.

Q: What are some of the new drugs and treatments that you foresee being developed from cannabinoid analogs in the future?

Dr. Mechoulam: First of all, there are those things that have been approved already, such as for improvement of appetite. That's good for cancer and AIDS, and is widely used. The other one of course is vomiting. The new drugs, I'm sure, will have to do with neuroprotection, and with certain kinds of pain—neuropathic pain, not acute pain. It doesn't work with acute pain. It works mostly with neuropathic pain, long-term pain.[23] [43]

It may also work in the suppression of memory. This is something that I hope we'll be able to start shortly. There's something called post-traumatic stress disorder (PTSD), which is due to upsetting memories that stay around too long. Normally, when there is trauma, people slowly forget it. This is true for humans, and it's true for animals. But if the animals do not have an endocannabinoid system, they do not forget bad memories, and this was shown in a paper by a German-Italian group. In collaboration with the Canadian group, we have done some work on that, and in a different model, we have seen the same thing. So, I expect that the endocannabinoid system is not in good shape in those post-traumatic patients, and chances are that it will work in treating them. We are just about to develop a treatment. People who have

PTSD claim that the only thing that helps them is smoking marijuana, so chances are that cannabinoid treatment may help them.

Q: You once said that "Whatever THC does, anandamide does as well." What is the reason that synthetic anandamide isn't used therapeutically as an alternative THC?

Dr. Mechoulam: That's a very touchy subject. Many years ago when insulin was discovered—I think it was in the early 1920s—it was in the clinic within six months. When cortisone was discovered fifty years ago, it was in the clinic within two years, and it became a very successful drug. We discovered anandamide twelve years ago, and it still has never been officially administered to a human. Neither has 2-AG.

Q: Why is that?

Dr. Mechoulam: The laws have changed. I cannot give anandamide to a human because the toxicology research is not there, and the toxicology research is millions of dollars to do. So somebody has to pay for that. I've asked the National Institute of Drug Abuse (NIDA) many times.

Q: But isn't it an endogenous substance?

Dr. Mechoulam: Yes, but the law is that even a human endogenous substance has to be tested for toxicology and all these things. So, I have asked them; I begged them actually, please do it—because a company will not, and obviously an academic person cannot do it. It's a technical thing. It's something that's quite obvious that should be done, yet it has not been done, either with anandamide or with 2-AG. So, nobody has ever given anandamide or 2-AG to a human, period.

Q: Why do you think that there has been so much political resistance to the notion of cannabinoids as medicine?

Dr. Mechoulam: I'm not sure that there is that much nowadays. It used to be much more. No company would ever touch anything like that many years ago. If they did, they did it kind of quietly. Now, this not so. Sanofi is going to introduce that antagonist on a very wide scale in the States. Actually, most of the major U.S. companies have cannabinoid programs. I know that Smith, Kline & Beecham has one, and so does Pfizer and Merck. So, possibly the other companies are actually waiting for people to come on the market, so they won't be the first ones. Now that Sanofi is going to be on the market, and THC is already on the market, chances are that the other companies will come too. After all, most of the drugs on the market—the new drugs over the last twenty years let's say—are based on being agonists or antagonists of receptors of endogenous compounds like dopamine and so on.

Q: Besides weight loss, what would be other uses for a cannabinoid antagonist?

Dr. Mechoulam: One of them is nicotine withdrawal, which has some nasty symptoms. Mark Twain once said, "It's easy to stop smoking; I've done it many times." So, apparently this antagonist may help with that. That's one thing, and I'm not sure that there are not many others. Possibly, it may help with some of the withdrawal symptoms for other drug abuse agents, like heroin perhaps, or maybe cocaine. I'm not sure because not enough work has been done. But those are the two major things that I can see.

Another big field will be agonists specific to the CB2 receptor. The CB2 receptor is in the periphery. We synthesized a CB2 specific agonist that has nothing to do with the CB1, which is present in the brain. It is very good for all kinds of digestive system disorders. THC is excellent for treating Crohn's disease and things of that sort. It's not on the market yet, but quite a few groups are working on it. So, it will definitely be very useful in those cases.

There are other things. For example, many years ago, we elucidated the structure of a compound called cannabidiol, which is present in very large amounts in cannabis. It's more than THC, and it is anti-inflammatory. It is excellent against rheumatoid arthritis, at least in animals. We worked together with a London group—real top of the field people in rheumatoid arthritis—and they have never seen anything as good as that. So, chances are that this particular compound, cannabidiol, can be used in rheumatoid arthritis. And it has no psychotropic effects, as a matter of fact, because it does not bind to the receptors. Maybe it has something to do with the metabolism of anandamide. Maybe it blocks the anandamide breakdown. Maybe.[44] This is something we saw, but whether it's relevant to its activity, frankly I don't know. So, this compound possibly will be used for rheumatoid arthritis. A company is already working on that, so it is not only the endocannabinoids as such, but also other compounds which are in the vicinity. There is also another receptor that we haven't found yet.

People are working on a third receptor, and we have a compound which binds to this questionable receptor actually. It has to do with peripheral action and vasodilatation. It causes vasodilatation. We have not published that yet, but I have talked about it at meetings. So vasodilatation is important, and the story is actually just starting.[45] [46] [47] I hope that more and more people will join in elucidating these things.

Q: What do you think should be done to help improve medical research in general?

Dr. Mechoulam: Quite a few things. Maybe the rules are becoming more and more rigid, and now with several compounds being taken off the market, and the FDA being under a lot of pressure, chances are that it will be even more difficult to develop new drugs because a drug has to have side-effects. There is no possibility of a drug not having a side-effect. Aspirin would not be approved today. So, chances are that we'll see a slump in new compounds coming out. I hope I'm wrong, but I'm afraid I'm not. It is not a question of money so much. I believe there is enough money. Well, there is never enough money, but there is a reasonable amount of money for medical research.

My group has had enough support for over thirty odd years, even more. We have been supported by the U.S. National Institute of Health (initially Mental Health) and then the National Institute of Drug Abuse for a long period of time. And although we are not an American group, obviously, they have decided it's okay, we should be supported. I had to reapply for it, but I was supported for that period of time, and they have never pushed me into any direction. They have been very liberal.

I've known most of the directors, and they are frequently very good scientists. The present director is an excellent scientist. Actually, she was not born in the U.S.; she's Mexican, and she's an excellent scientist by any standard. So, in this respect, I can't say that I've been pushed towards proving that it's terribly bad, and that it will kill everyone. I think nothing of that sort. I've been doing my science, and they've been, I hope, happy with it.

Q: What are you currently working on?

Dr. Mechoulam: In collaboration with a group at N.I.H., we're working on a new transmitter which binds to a recently discovered receptor. Whether this particular transmitter is a neurotransmitter, a transmitter of another sort, or only a vasodilator, it's an important new compound. Actually, there are quite a few other compounds in the brain which are closely related, so we're working on that. We also have some new anticancer cannabinoid compounds which seem to be pretty good.
We recently published something about this research. These new compounds work on an enzyme called topoisomerase, and these are compounds which are very close in action to some of the known anticancer compounds. But the known compounds of this sort cause damage to the heart, and with our compounds, so far, we have seen no such damage in animals. So, hopefully this new type of cannabinoid will come out on the market. There is also a possibility that cannabinoids can be used to reduce temperature, and sometimes it's important to reduce temperature because that prevents brain damage during a heat wave or heatstroke.

Q: Is there anything that we haven't discussed that you would like to add?

Dr. Mechoulam: We've been lucky to work in a field where originally there wasn't anyone else, so we could work on our research slowly, without any major competition. Now it's a field in which there is a large group of very good people working. In the States, there are several excellent groups. There are also some excellent groups working on this in the U.K., Germany, Spain, and Italy. Though one always hears about competition between scientists, I haven't seen it that much in this field. We are a large group that is working without really competing, and we are exchanging information all the time. So, it's a pleasure to be working in such a field. Maybe it has something to do with ananda.

References

1. Akbas F, Gasteyger C, Sjödin A, et al. A critical review of the cannabinoid receptor as a drug target for obesity management. *Obes Rev*. 2008 Aug 20. [Epub ahead of print]. ↥
2. Scholten WK. [The mechanism of action of cannabis and cannabinoids] . *Ned Tijdschr Geneeskd*. 2006 Jan 21;150(3):128-31. ↥
3. Martínez-Orgado J, Fernández-López D, Lizasoain I, et al. The seek of neuroprotection: introducing cannabinoids. *Recent Patents CNS Drug Discov*. 2007 Jun;2(2):131-9. ↥
4. Pazos MR, Sagredo O, Fernández-Ruiz J. The Endocannabinoid System in Huntington's Disease. *Curr Pharm Des*. 2008;14(23):2317-25. ↥
5. Pazos MR, Núñez E, Benito C, et al. Functional neuroanatomy of the endocannabinoid system. *Pharmacol Biochem Behav*. 2005 Jun;81(2):239-47. ↥
6. Cota D. The role of the endocannabinoid system in the regulation of hypothalamic-pituitary-adrenal axis activity. *J Neuroendocrinol*. 2008 May;20 Suppl 1:35-8. ↥
7. Pagotto U, Marsicano G, Cota D, et al. The emerging role of the endocannabinoid system in endocrine regulation and energy balance. *Endocr Rev*. 2006 Feb;27(1):73-100. Epub 2005 Nov 23. ↥
8. Sparling PB, Giuffrida A, Piomelli D, et al. Exercise activates the endocannabinoid system. *Neuroreport*. 2003 Dec 2;14(17):2209-11. ↥
9. Dietrich A, McDaniel WF. Endocannabinoids and exercise. *Br J Sports Med*. 2004 Oct;38(5):536-41. ↥
10. Panikashvili D, Simeonidou C, Ben-Shabat S, et al. An endogenous cannabinoid (2-AG) is neuroprotective after brain injury. *Nature* . 2001 Oct 4;413(6855):527-31. ↥
11. Correa F, Docagne F, Mestre L, et al. Cannabinoid system and neuroinflammation: implications for multiple sclerosis. *Neuroimmunomodulation*. 2007;14(3-4):182-7. ↥
12. Correa F, Mestre L, Molina-Holgado E, et al. The role of cannabinoid system on immune modulation: therapeutic implications on CNS inflammation. *Mini Rev Med Chem*. 2005 Jul;5(7):671-5. ↥
13. García-Arencibia M, González S, de Lago E, et al. Evaluation of the neuroprotective effect of cannabinoids in a rat model of Parkinson's disease: importance of antioxidant and cannabinoid receptor-independent properties. *Brain Res*. 2007 Feb 23;1134(1):162-70. Epub 2006 Dec 28. ↥
14. Ramírez BG, Blázquez C, Gómez del Pulgar T, et al. Prevention of Alzheimer's disease pathology by cannabinoids: neuroprotection mediated by blockade of microglial activation. *J Neurosci*. 2005 Feb 23;25(8):1904-13. ↥
15. Di Carlo G, Izzo AA. Cannabinoids for gastrointestinal diseases: potential therapeutic applications. *Expert Opin Investig Drugs*. 2003 Jan;12(1):39-49. ↥
16. Wright KL, Duncan M, Sharkey KA. Cannabinoid CB2 receptors in the gastrointestinal tract: a regulatory system in states of inflammation. *Br J Pharmacol*. 2008 Jan;153(2):263-70. ↥
17. Massa F, Storr M, Lutz B. The endocannabinoid system in the physiology and pathophysiology of the gastrointestinal tract. *J Mol Med*. 2005 Dec;83(12):944-54. Epub 2005 Aug 26. ↥
18. Juan-Picó P, Fuentes E, Bermúdez-Silva FJ, et al. Cannabinoid receptors regulate Ca(2+) signals and insulin secretion in pancreatic beta-cell. *Cell Calcium*. 2006 Feb;39(2):155-62. ↥
19. Bermúdez-Silva FJ, Suárez J, Baixeras E, et al. Presence of functional cannabinoid receptors in human endocrine pancreas. *Diabetologia*. 2008 Mar;51(3):476-87. ↥
20. Rodríguez de Fonseca F, Del Arco I, et al. The endocannabinoid system: physiology and pharmacology.*Alcohol Alcohol*. 2005 Jan-Feb;40(1):2-14. Epub 2004 Nov 18. ↥

21. Mbvundula EC, Bunning RA, Rainsford KD. Arthritis and cannabinoids: HU-210 and Win-55,212-2 prevent IL-1alpha-induced matrix degradation in bovine articular chondrocytes in-vitro. *J Pharm Pharmacol*. 2006 Mar;58(3):351-8. ↥
22. Kogan NM, Mechoulam R. Cannabinoids in health and disease. *Dialogues Clin Neurosci*. 2007;9(4):413-30. ↥
23. Russo EB. Cannabinoids in the management of difficult to treat pain. *Ther Clin Risk Manag*. 2008 Feb;4(1):245-59. ↥
24. Shoaib M. The cannabinoid antagonist AM251 attenuates nicotine self-administration and nicotine-seeking behaviour in rats. *Neuropharmacology*. 2008 Feb;54(2):438-44. ↥
25. McLaughlin PJ, Winston K, Swezey L, et al. The cannabinoid CB1 antagonists SR 141716A and AM 251 suppress food intake and food-reinforced behavior in a variety of tasks in rats. *Behav Pharmacol*. 2003 Dec;14(8):583-8. ↥
26. McLaughlin PJ, Qian L, Wood JT, et al. Suppression of food intake and food-reinforced behavior produced by the novel CB1 receptor antagonist/inverse agonist AM 1387. *Pharmacol Biochem Behav*. 2006 Mar;83(3):396-402. ↥
27. Sink KS, McLaughlin PJ, Wood JA, et al. The novel cannabinoid CB1 receptor neutral antagonist AM4113 suppresses food intake and food-reinforced behavior but does not induce signs of nausea in rats.*Neuropsychopharmacology*. 2008 Mar;33(4):946-55. ↥
28. Roser P, Vollenweider FX, Kawohl W. Potential antipsychotic properties of central cannabinoid (CB(1)) receptor antagonists. *World J Biol Psychiatry*. 2008 Feb 7:1-12. ↥
29. Zuardi AW, Crippa JA, Hallak JE, et al. Cannabidiol, a Cannabis sativa constituent, as an antipsychotic drug. *Braz J Med Biol Res*. 2006 Apr;39(4):421-9. ↥
30. Papa SM. The cannabinoid system in Parkinson's disease: multiple targets to motor effects. *Exp Neurol*. 2008 Jun;211(2):334-8. ↥
31. Grotenhermen F. Cannabinoids. *Curr Drug Targets CNS Neurol Disord*. 2005 Oct;4(5):507-30. ↥
32. Bisogno T, Di Marzo V. The role of the endocannabinoid system in Alzheimer's disease: facts and hypotheses. *Curr Pharm Des*. 2008;14(23):2299-3305. ↥
33. Kogan NM, Schlesinger M, Priel E, et al. HU-331, a novel cannabinoid-based anticancer topoisomerase II inhibitor. *Mol Cancer Ther*. 2007 Jan;6(1):173-83. ↥
34. Kogan NM, Schlesinger M, Peters M, et al. A cannabinoid anticancer quinone, HU-331, is more potent and less cardiotoxic than doxorubicin: a comparative in vivo study. *J Pharmacol Exp Ther*. 2007 Aug;322(2):646-53. ↥
35. Peters M, Kogan NM. HU-331: a cannabinoid quinone, with uncommon cytotoxic properties and low toxicity. *Expert Opin Investig Drugs*. 2007 Sep;16(9):1405-13. ↥
36. Kogan NM, Blázquez C, Alvarez L, et al. A cannabinoid quinone inhibits angiogenesis by targeting vascular endothelial cells. *Mol Pharmacol*. 2006 Jul;70(1):51-9. Epub 2006 Mar 29. ↥
37. Aguado T, Carracedo A, Julien B, et al. Cannabinoids induce glioma stem-like cell differentiation and inhibit gliomagenesis. *J Biol Chem*. 2007 Mar 2;282(9):6854-62. Epub 2007 Jan 2. ↥
38. Kim SH, Won SJ, Mao XO, Jin K, Greenberg DA. Molecular mechanisms of cannabinoid protection from neuronal excitotoxicity. *Mol Pharmacol*. 2006 Mar;69(3):691-6. ↥
39. Mechoulam R, Hanu L. The cannabinoids: an overview. Therapeutic implications in vomiting and nausea after cancer chemotherapy, in appetite promotion, in multiple sclerosis and in neuroprotection. *Pain Res Manag*. 2001 Summer;6(2):67-73. ↥
40. Machado Rocha FC, Stéfano SC, DE Cássia Haiek R, et al. Therapeutic use of Cannabis sativa on chemotherapy-induced nausea and vomiting among cancer patients: systematic review and meta-analysis. *Eur J Cancer Care (Engl)*. 2008 Jul 3. [Epub ahead of print]. ↥

41. Müller-Vahl KR, Schneider U, Prevedel H, et al. Delta 9-tetrahydrocannabinol (THC) is effective in the treatment of tics in Tourette syndrome: a 6-week randomized trial. *J Clin Psychiatry*. 2003 Apr;64(4):459-65. ↥
42. Mechoulam R, Hanu L. The cannabinoids: an overview. Therapeutic implications in vomiting and nausea after cancer chemotherapy, in appetite promotion, in multiple sclerosis and in neuroprotection. *Pain Res Manag*. 2001 Summer;6(2):67-73. ↥
43. McCarberg BH. Cannabinoids:their role in pain and palliation. *J Pain Palliat Care Pharmacother*. 2007;21(3):19-28. ↥
44. Mechoulam R, Peters M, Murillo-Rodriguez E, et al. Cannabidiol--recent advances. *Chem Biodivers*. 2007 Aug;4(8):1678-92. ↥
45. Hoi PM, Visintin C, Okuyama M, et al. Vascular pharmacology of a novel cannabinoid-like compound, 3-(5-dimethylcarbamoyl-pent-1-enyl)-N-(2-hydroxy-1-methyl-ethyl)benzamide (VSN16) in the rat. *Br J Pharmacol*. 2007 Nov;152(5):751-64. Epub 2007 Sep 24. ↥
46. Herradón E, Martín MI, López-Miranda V. Characterization of the vasorelaxant mechanisms of the endocannabinoid anandamide in rat aorta. *Br J Pharmacol*. 2007 Nov;152(5):699-708. Epub 2007 Aug 20. ↥
47. McCollum L, Howlett AC, Mukhopadhyay S. Anandamide-mediated CB1/CB2 cannabinoid receptor--independent nitric oxide production in rabbit aortic endothelial cells. *J Pharmacol Exp Ther*. 2007 Jun;321(3):930-7. Epub 2007 Mar 22. ↥