Sanofi Keeps Hope Alive for Cannabinoid Antagonist Drug

Researchers Share Findings at ICRS Meeting in Chicago— Input From Users of the "Crude Plant" is Increasing

By O'Shaughnessy's News Service

The International Cannabinoid Research Society (ICRS) held its 2009 meeting last July at a golf-oriented resort outside Chicago. Some 250 scientists employed mainly by academic institutions and drug companies attended —a slight fall-off from previous years, attributable to the recession (universities are limiting their travel allotments) and the advent of other conferences devoted to the cannabinoids.

There was a corresponding rise in registrants from California's medical cannabis movement/industry. UC Berkeley sociologist Amanda Reiman gave a paper on cannabis as an alternative to alcohol, based on a survey taken at the Berkeley Patients Group (BPG). Kristen Peskuski presented a poster describing her regimen of raw cannabis as a treatment for multiple medical problems. William Courtney, MD, had a poster proposing an alternative nomenclature for the endocannabinoid system.

Courtney was one of six pro-cannabis MDs who attended from California. There was a large BPG contingent, and observers from the Farmacy, a Los Angeles dispensary chain, which has since expanded to Colorado, and General Hydroponics, the Sebastopol-based plant nutrient manufacturer. Starr Hergenrather sold specially designed hemp shirts commemorating the conference.

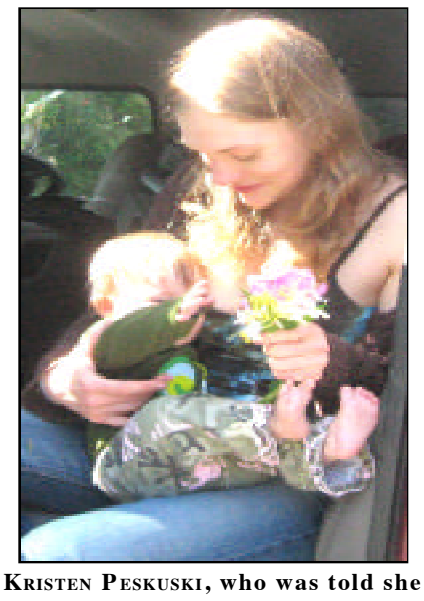
The ICRS

The ICRS was founded in 1991 by a group of scientists —mainly pharmacologists— who had been following each other's work in journals and holding rump sessions at various conferences. As befit its members' reliance on funding from the National Institute on Drug Abuse (NIDA), the first ICRS conference was a "satellite meeting" of the College on Problems of Drug Dependence.

At annual meetings in the years that followed, the discovery of the body's endogenous cannabinoids, anandamide and 2-AG, was reported, as were other breakthroughs in the emerging field of cannabinoid science.

The "C" in ICRS originally stood for "Cannabis." But in 1995, because so few members were actually conducting research with the plant, a vote was taken to change the C-word to "Cannabinoid," which refers to chemicals from three sources —extracted from the plant, synthesized in the lab, or produced by the body.

Conferences such as the ICRS meeting enable researchers to report their latest findings and to network. Speakers have 15 minutes to summarize their studies and answer questions. Giving a talk at a conference is equivalent to publishing a paper in a peer-reviewed journal because the content has been evaluated and deemed worthy by fellow scientists (appointed by the conference organizers). A poster is considered a slightly less prestigious format, but posters often describe the progress of significant studies.



KRISTEN PESKUSKI, who was told she couldn't bear children, with baby Zahila.

Drug Development

ICRS scientists, in general, accept the constraints of marijuana prohibition and seek to develop drugs that deliver the medical benefits of the herb without any psychoactive effect. They employ roundabout strategies.

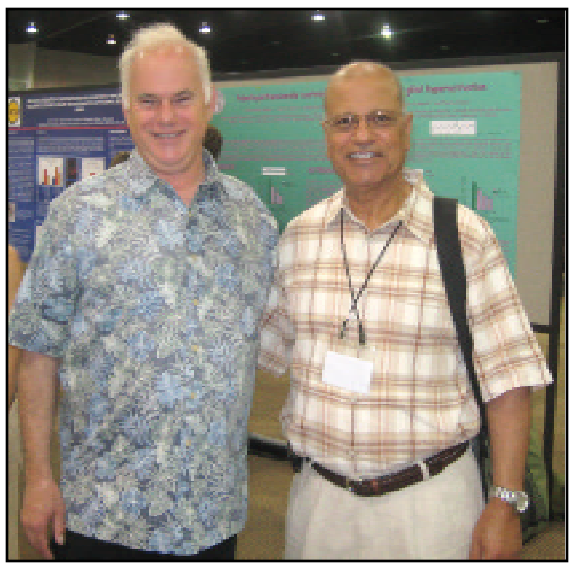
For example, at the Chicago meeting a team from Abbott Laboratories described the development of compounds (isolthizolyidene amides and thiophene bisamide derivatives) that bind only to the CB2 receptors, which are scant in the brain and central nervous system (CNS). These compounds "are anticipated to minimize CB1-mediated CNS events, such as sedation, euphoria, and appetite stimulation that have plagued the clinical utility and development of non-selective cannabinoid agonists for managing pain..."

The approach at several labs has been to target FAAH, the enzyme that breaks down anandamide.

The approach at several labs has been to target FAAH, the enzyme that breaks down anandamide (a compound made in the body that activates receptors also activated by plant cannabinoids such as THC). The less FAAH breaking down anandamide, the more anandamide available to activate the cannabinoid receptors. *(See "Enzymes and the Endocannabinoid System" by Martin Lee, O'Shaughnessy's Summer 2009).* It is hoped that FAAH inhibition will lead to pain relief and other desired effects unaccompanied by "euphoria."

At the Chicago meeting, investigators led by Kay Ahn of Pfizer announced the discovery and characterization of PF-3845, a FAAH inhibitor 10-to-20 times more potent than its predecessors. PF-3845 "displays remarkable in vivo selectivity for FAAH... and raises brain anandamide levels for up to 24 hours, resulting in profound cannabinoid receptor-dependent anti-hyperalgesic effects... PF-3845 has excellent pharmacokinetic properties, including high oral bioavailability." Maybe Pfizer can market it someday as "Faah-out." As in "Faah out your pain with..."

A Spanish group led by Lourdes Ruiz-Valdepenas (plus the ubiquitous Benjamin Cravatt from Scripps Research Institute) crossed a strain of mice bred to exhibit Alzheimer's Disease symptoms with mice unable to produce FAAH (known as "FAAH knockout mice"). The offspring had fewer Beta amyloid deposits in the cortex, hippocampus and thalamus, leading the investigators to "postulate that FAAH ablation and subsequent enhancement of the endocannabinoid tone may delay the development of amyloid pathology in the animal model of AD."



Larry Brooke of General Hydroponics, a California plant-nutrient maker, with Mahmoud ElSohly, America's only legal cannabis grower (under federal law). ElSohly supervises a garden at the University of Mississippi. He has a contract with the National Institute on Drug Abuse.

Patricia Reggio and colleagues at the UNC Greensboro are investigating how anandamide, after binding at a CB1 receptor on a cell membrane, gets transported to the FAAH enzyme located within the cell's endoplasmic reticulum (ER). Anandamide is lipid (fatty), and slipslides along the membrane onto the receptor. But the cell's internal environment is watery —so how does anandamide proceed to the ER?

The answer, published earlier in 2009 by Martin Kaczocha, Sherrye Glaser and Dale Deutsch of Stonybrook University, is a "transporter molecule" known as a fatty acid binding protein. Reggio's team has "begun to study, in atomic detail, the binding mechanism of anandamide to FABP."

Kaczocha et al found that inhibition of two fatty acid binding proteins doubled the time it took for anandamide to break down within the cell. "Inhibiting FABPs could potentially raise the levels of AEA in the brain's synapses," says Dale Deutsch. "Naturally occurring AEA levels have been shown to curb pain without the negative side effects, such as motor coordination problems, of molecules like THC that can also bind the cannabinoid receptor."

NIDA reported the finding by the Stonybrook team in a press release headlined "NIDA research could lead to better treatment for pain and marijuana addiction."

Here's the factual part: "Researchers had long suspected that endocannabinoids needed a specific transporter that would ferry them to the location where they are broken down. This study successfully identified a couple of previously known fatty acid binding proteins (FABPs) as capable of carrying the endocannabinoid anandamide (also known as AEA) from the cell membrane, through the cell interior, to the location where it is destroyed.

Here's the propaganda from Dr. Nora Volkow, the director of NIDA: "This approach could be used for treating marijuana addiction. Compounds that inhibit FABPs could produce an effect similar to nicotine patches for smokers or methadone for opiate replacement. This line of research may also be important for other types of addiction, such as chronic alcohol abuse, which also affects AEA levels."

And to think this bureaucrat is the great-daughter of Leon Trotsky!

Add drug targets: MAGL

The enzyme that degrades the body's other known cannabinoid, 2-AG, has been identified as Monoacylglycerol Lipase (MAGL). MAGL offers the drug developers another target in their quest to achieve the beneficial effects of cannabis. Jonathan Z. Long of the Scripps Research Institute in La Jolla gave a paper on a MAGL inhibitor, JZL184, which raises 2-AG levels eight-fold and reduces pain in mice while having no effect on anandamide levels.

For some the highlight of ICRS 2009 was a report by a Belgian-French team led by Geoffray Labarl on the X-ray structure of MAGL. The exact, atom-by-atom depiction of the MAGL molecule will facilitate development of more selective MAGL inhibitors.

Rimonabant: the dream dies hard

Sanofi-Aventis, the world's fifth largest pharmaceutical company, has spent more than a billion Euros trying to market a drug that blocks ("antagonizes") the CB1 receptor. Synthesized in the early 1990s by pharmacologist Gerard Le Fur, the antagonist compound was called SR (for "Sanofi Recherche") 1716A, and sold to labs investigating the function of the receptor.

It was soon determined that blocking the CB1 receptor suppresses appetite, among other things, so Sanofi redefined SR1716A as a therapeutic drug and geared up to test it for weight-loss and smoking cessation. They would call it "Rimonabant" in some countries and "Acomplia" in others.

At the ICRS meeting in 2004 Sanofi scientists reported that Rimonabant had proven safe and effective as a weight-loss drug in clinical trials involving 13,000 patients. The company launched a pre-market campaign notifying doctors about a disorder called "Metabolic Syndrome," a cluster of risk factors for diabetes that Sanofi defined as a disease unto itself —a disease that could be treated by blocking the CB1 receptor!

In this period Sanofi became the number-one financial backer of the ICRS, and many cannabinoid researchers got grants from Sanofi and/or the National Institute on Drug Abuse to study the potential of antagonist drugs. John McPartland was one of the few ICRS scientists to openly question the safety of Rimonabant. Jeffrey Hergenrather and other California doctors warned that blocking CB1 would almost certainly result in serious adverse effects.

"The consequences of interfering with the cannabinoid receptor system have not been evaluated in normal human physiology," Hergenrather was quoted in *O'Shaughnessy's (Fall 2004)*. He suggested that before Sanofi marketed Rimonabant, "It would be ethical to design longitudinal studies to assess the

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consequences of interfering with the cannabinoid system."

On behalf of the Society of Cannabis Clinicians, Tod Mikuriya, MD, wrote a letter to the U.S. Food and Drug Administration advising against approval. To the FDA's credit, a panel of physicians would unanimously turn down Sanofi's application 2007. (Their decision was influenced by the recently revealed fatal effects of Vioxx.)

Scientists at the MD Anderson Cancer Center reported that mice treated with Rimonabant developed potentially cancerous colorectal polyps at a higher rate than controls.

In October 2008 the European Medicines Agency ordered Sanofi-Aventis to stop selling Rimonabant. (Also that month Merck abruptly canceled five clinical trials of a cannabinoid-blocker called Taranabant.) Data from ongoing clinical trials showed that Rimonabant users suffer depression, anxiety, insomnia and aggressive impulses at twice the rate of subjects given placebo. In one study there were five suicides among Rimonabant users compared to only one among subjects on placebo.

Although Rimonabant was ostensibly removed from the market because of its adverse psychiatric effects, one study conducted by scientists at the MD Anderson Cancer Center found that the drug caused mice to develop potentially cancerous colorectal polyps at a higher rate than controls. We do not know of other published data on adverse effects involving cancer, seizures, and other illnesses that the cannabinoid system plays a role in suppressing.

Given Rimonabant's withdrawal from the market, it was surprising that a block of four talks at ICRS 2009 was devoted to the therapeutic potential of cannabinoid-receptor blockers for treating metabolic syndrome and cirrhosis of the liver. Antagonist drugs of the next generation will be designed, it was explained by George Kunos and others, to not cross the blood-brain barrier. Thus they will exert their effects only on receptors in the body's "periphery," and they will not induce suicidal ideation or other changes of mood.

Several speakers mentioned that Rimonabant had been withdrawn due to adverse psychiatric effects —as if the MD Anderson Cancer Center study had no significance! Drs. Hergenrather and McPartland shook their heads just as they had at the ICRS conference in 2004 when the antagonist dream was unveiled by scientists funded by Sanofi and NIDA.

No sooner does White Man discover the function of the body's cannabinoid signaling system than he dreams of how to block it! It's incredible —but true.

Huntington's Disease

Michele Glass and colleagues at the University of Auckland School of Medical Sciences have been studying cannabinoid receptors and in a mouse model of Huntington's Disease. She noted that the onset of Huntington's can be delayed dramatically by providing the mouse with an interesting ("enriched") environment, which raises anandamide levels.

Activation of CB1 receptors may be protective in HD, but the mechanism is not yet understood.

A Substitute for Alcohol

Amanda Reiman described the study she conducted between August and October 2008 at the Berkeley Patients Group. She surveyed 350 patients ages 18 to 81, about 2/3 male and White. Of the 180 respondents currently drinking alcohol, 40% reported using cannabis to limit their drinking; 26% used it as a substitute for hard (illicit) drugs; and 65.8% used it to reduce prescription drug intake. "Fewer adverse side effects" was the primary reason for choosing cannabis as an alternative, followed by "better symptom management." Some 12% used cannabis because it has "greater social acceptance" than alcohol. (Today, Berkeley, tomorrow the world!)

Amanda Reiman

"Three hundred and fifty is a large sample compared to typical clinical samples," Reiman observed in a post-conference interview. "I think that's one reason my data was taken seriously."

Reiman helped staff the BPG table. "There was a really wide range of reactions to us," she reported. "We had Ed Rosenthal's *Big Book of Buds* right there on the table so there was no question about the kind of botanicals we were into. Some people kind of scowled as they walked by, as if we didn't belong there. But most people were interested and took some of our literature. A few took it almost in a giddy way, as if it was something naughty.

"Samir Ross from the University of Mississippi told me that he really liked my presentation and that he was very interested in what I was doing. He took a copy of the entire report. He was looking at the *Big Book of Buds* and asked 'Is this real?' And Debby [Goldsberry, director of BPG] said, 'Oh yes, those are different varieties of cannabis that we have in California.'

"He asked about the THC percent in our strains, and Debby said, 'Our high grade could range from 18 to 25 percent. What's your high grade?' And he said, 'Eleven to 12 percent.' He was just blown away. He offered to help us on the chemistry if we ever needed help.

"The first day at breakfast a young woman asked, 'Why would you use cannabis as a substitute when cannabis itself is harmful?' I got that question from a couple of scientists. And I would explain the idea of harm reduction. Nobody seemed to be close-minded but they had been following a line of 'truth' that maybe isn't so true. I understand that completely. Because when you rely on grants for your livelihood and you study something for the government you know

"People seemed very open to thinking about things in a different way and a little envious that we could enroll so many subjects in our study."

that you have to phrase things a certain way to get funded. You have to toe the line. And I don't blame anyone for toeing the line because they have to feed their families and do what they need to do to get by. It's understandable.

"But overall people seemed very open to thinking about things in a different way and a little envious that we could enroll so many subjects in our study."

Cannabinoids Kill Cancer Cells

Jahan Marcu personifies the merging interests of the medical marijuana move-

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Dr. John W. Huffman

The Inadvertent Inventor of "Spice"

John W. Huffman, a founding member of the ICRS who runs a lab at Clemson University, is a mild-mannered pharmacologist who does not use cannabis medicinally or otherwise. (His drug of choice is alcohol.) The talks Huffman gives at ICRS meetings are far removed from the clinical realm. In Chicago, for example, his paper was called "Structure-Activity Relationships at the CB1 and CBS Receptors for 1-Alkyl-3(1-Napthoyl-4 And 8-Halogen Substituted) Indoles."

But Huffman has become something of a counter-culture hero, thanks to his development in 1995 of a synthetic cannabinoid that he dubbed JWH-018. In 2008 some bootleggers concocted a batch which they sprinkled on various herbs and marketed as an intoxicant known as "Spice." ("K2" and other knock-offs of Spice have since proliferated.)

At the 2009 ICRS meeting Huffman seemed bemused by his unsought celebrity. He recalled, "The compound was made by an undergraduate named Michele Phillips as part of a program to look at structure-activity relationships in cannabimimetic indoles. The structure was finally published in 1997 or 98 in a paper by Jenny Wiley from Virginia Commonwealth. It was just another somewhat potent research tool...

"In early December 2008 I had an email from a blogger in Germany who included a pdf file of a paper from *Die Spiegel*. I read enough German that I was able to gather that people were adding our compound to herbs and it had become 'Spice Gold.' People were smoking it.

"Subsequently I had email from a woman at the University of Cologne in their forensic chemistry department, she wanted a copy of the mass spec, which I was able to send her. And ultimately I was able to send her a sample.

"I have heard from some other people in Germany, including the Luftswaffe. They don't want their pilots getting high on Spice Gold and I can't blame them.

O'Shaughnessy's: Where did it surface first?

JWH: Apparently, it was first in Austria. Then Germany. Then it was declared illegal in Germany. I also heard from somebody in Japan. And of course I have heard from the DEA —from their science people, not the enforcement people. They just wanted to confirm the physical properties because some of the stuff that winds up in the smoked product is pretty impure.

O'S: How do people obtain JWH-018?

JWH: It is sold by a Korean company as a plant growth stimulant.

O'S: Could it possibly be a plant growth stimulant?

JWH: I very much doubt it. But that's a good excuse. I have seen websites where it's been advertised. When I first heard from this German lady, my wife Googled JWH018 and there were like 26 hits. That was in December. Last time I googled it was in early May and there were 26,000. It has certainly become a legendary, infamous compound.

O'S: What effects do people report?

JWH: I don't know. They seem to like it.

O'S: And burning it doesn't destroy the potency?

John W. Huffman

JWH: No. It's a very simple compound —a two-step synthesis by somebody who knows what they're doing... The advice that I have given all of these people —including the two zillion emails I've gotten about how do I take this stuff— is, 'You shouldn't. You're stupid if you do because we have nothing about the pharmacokinetics, we have nothing about toxicity, we have nothing about the nature of the metabolites. I am sure some of them are carcinogenic.

"We have nothing about the nature of the metabolites. I am sure some of them are carcinogenic."

O'S: Is the Korean distributor allowed to go on or has somebody cracked down?

JWH: I have no idea. I think the website has been taken down.

O'S: Are you entitled to royalties?

JWH: No, because we never patented it. Alex Makryanis patented it but his patent is not valid because we reported the compound at the 1997 ICRS meeting, and then Jenny published the paper in '98 and Alex's patent was filed in 2000. If you want to patent something in the U.S., you have one year after you publish it to patent it.

O'S: Were any of the emails of special interest?

JWH: I had one interesting one that I responded to. It was obviously from somebody with a synonym, using a Yahoo address. Apparently they were bootlegging it at night at a pharmaceutical company somewhere. The English was perfect so I assumed it was the UK or Ireland. They had made a variation of JWH018. It was actually a variation on one of our petyl acetyl indoles. They picked the most potent one. And then they stuck the Winthrop-Makryannis side chain on it, and it's very potent. Apparently they've done some real pharmacology with it. These guys are good.

O'S: What's their goal? To get another psychoactive compound?

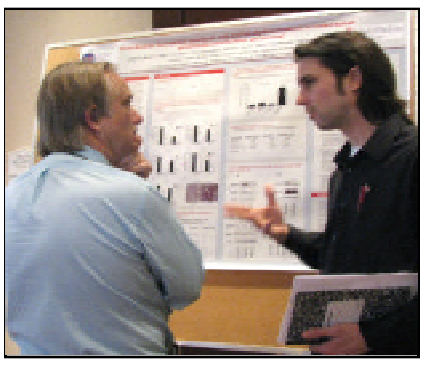
JWH: I think the goal is to get another psychoactive compound that is not illegal. Because Spice is now illegal all over Europe...

I have universally told people: "Do not use this stuff. *(Whispering)* If you want to get high, use marijuana."

ICRS Meeting *from previous page*

ment and the cannabinoid research establishment. While Marcu was doing graduate work at California Pacific Medical Center Research Institute in San Francisco, his mentors included researchers Sean McAllister and Mary Abood —and he was romantically involved with Alex Franco, an organizer for Americans for Safe Access. Marcu and Franco are now married and living in Philadelphia, where he is doing research in the lab run by Abood (who moved from CPMC to Temple University Medical School.)

Marcu's poster at the ICRS meeting —which won the highest award given to grad students— was based on research begun with McAllister. It showed that a combination of THC and CBD is much more efficient at killing cells from an aggressive brain cancer, glioblastoma multiforme, than either cannabinoid on its own. Marcu got the idea to test cannabinoids in combination because the plant itself deploys them in combination, and he entitled his poster "Plant Wisdom: CBD Synergizes with THC to Inhibit GBM Proliferation and Survival."



William Courtney (left) and Jahan Marcu

Marcu explains, "Looking at chromatograms of plant samples, I noticed that certain cannabinoid ratios were showing up frequently. THC to CBD in a 10-to-1 ratio was very common. So I thought a 10-to-1 ratio would be more effective than either compound alone. Sean McAllister suggested that we start by testing the cannabinoids individually, and that's what we did —starting with the precursor compound CBG— to see how well they killed cancer cells in the petri dish."

Marcu measured the efficacy of THC and THC acid, CBD and CBD acid, cannabinol and cannabichrome. Then he started testing various combinations — "and that's when we started seeing surprising results," he recounts. "Doses that literally did not kill a statistically significant amount of cancer cells were suddenly obliterating everything in the petri dish in three days."

The most efficient combination turned out to be a 4-to-1 ratio of THC to CBD. Whether that THC-to-CBD ratio is optimal only in the case of one particular cell line, or holds true in treating other glioblastomas, or other cancers, remains to be studied.

Marcu, McAllister *et al* also determined that cannabinoids in combination kill cancer cells by a different pathway than cannabinoids acting solo. Marcu's analogy for the layman: "Instead of choking the victim, 'you hold his arms while I punch him in the stomach.'"

Individually or in combination, cannabinoids kill cancer cells by inducing apoptosis —"programmed cell death."

Cannabinoids in combination kill cancer cells by a different pathway than cannabinoids acting solo.

Cannabinoids in combination induce apoptosis earlier in the cancer cell's life cycle —which is good news, given the goal of preventing metastasis.

The cells go through three phases: initial growth, synthesis of DNA, division. "Cancer cells grow and divide, grow and divide, and soak up all the nutrients around them," says Marcu. "You want to inhibit them in the growth phases, if possible. And that's what the combination of cannabinoids does, we found."

Marcu was outside smoking a cigarette when his first prize was announced at the ICRS awards banquet. "I have since tried to quit," he says ruefully. Marcu applauds the work of Antonio Luchini, the grad student whose presentation took second place. Luchini showed that inhibiting FAAH can reduce the cocaine reward response.

And the nicotine reward response?

New Hope in the War on Zits

Cannabidiol as a Treatment for Acne?

Accutane is one of the deadliest drugs in the aptly named "armamenture" of Western medicine. Could a cannabis-based medicine be safer and more effective in treating acne? At the 2009 ICRS meeting, Tamas Biro gave an intriguing talk entitled "Cannabidiol as a Novel Anti-Acne Agent? CBD Inhibits Lipid Synthesis and induces Cell Death in Human Sebaceous Gland-Derived Sebocytes."

Acne involves the overproduction of sebum, a lipid (oily substance) excreted by the sebaceous glands to create waterproofing of the skin. Conversely, lipid production is too low in dry-skin conditions such as seborrhea, eczema and itching (which can lead to inflammation). It has been learned in recent years that the sebaceous glands and hair follicles (which also produce oil) have endocannabinoid receptors, as do the surface keratinocytes.

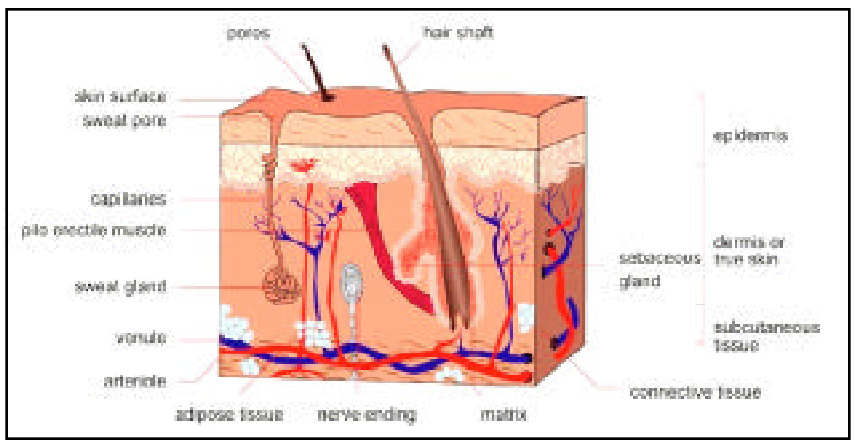
At his lab at the University of Debrecen (Hungary) Department of Physiology, University of Debrecen, Biro works with a line of cells derived from human sebaceous glands. Applying endocannabinoids to the cells, he observed, results in the CB2 receptors dramatically "upregulating" lipid production. Blocking the endocannabinoids with an antagonist drug dramatically suppresses lipid production. Biro wondered, "If the endocannabinoids are so important for the work of the sebaceous glands, how would phytocannabinoids affect that process?"

Biro started with CBD rather than THC for several reasons, he explained in an interview. "CBD is not banned in Hungary —there's no restrictions on its use, you can buy it from Sigma and other sources. Because it's non-psychoactive, if we turn up a potential good drug, it will be much easier to market with CBD." Moreover, CBD had been shown by Audra Stinchcomb at the University of Kentucky College of Pharmacy to penetrate the skin readily through a transdermal patch.

Biro and colleagues applied CBD to cells that had been treated with anandamide, expecting that CBD would further stimulate lipid synthesis. "To our surprise," he recounted, "Anandamide in the presence of CBD was unable to produce a lipid synthesis! CBD does exactly the opposite of the endocannabinoids. It does not stimulate but inhibits lipid synthesis, especially if the lipid synthesis was previously upregulated, as for example in acne. It was very surprising," he reiterated, "that a phytocannabinoid could prevent the action of the endocannabinoids."

Biro has been investigating the mechanism by which CBD works. His data show that CBD "does not target the 'classical' CB receptors but rather certain ion channels expressed on the sebocytes. When activated by CBD, these channels open and permit the influx of calcium to the cells which, in turn, inhibit lipid synthesis. We are working to elucidate the exact mechanism.

"Acne can also be considered as an inflammatory disease in which the skin within the zit is highly inflamed. We know from the literature that CBD has anti-inflammatory properties but it had never been tested on the skin cells. If it really works as an anti-inflammatory, then we would be getting two birds with one stone.



SKIN IN CROSS-SECTION: The sebaceous glands, which have endocannabinoid receptors, produce sebum that lubricates the skin and hair.

"Acne is a human-specific disease. We don't have too much fur. Animals with fur may not need the oily cover for the surface of their skin because they don't have uncovered skin. No hair — only around the paw and the genitalia region, the nose, the very tips... Sebaceous cells from animals may operate differently than human ones. So there is no good animal model for acne."

Biro applies CBD in a methanol-ethanol solution. He is considering how best to formulate it for acne patients. "The vehicle should be the easiest possible," he said. "Think about the psychology of it. If you're a teenager you don't want to put creams on your face, you want a clear solution.

"There will be no trouble getting volunteers for clinical trials. Acne is not a life-threatening disease, but the impairment of quality of life is tremendous. You do not want to socialize. You close the door. It's your face! And the scars can establish an extreme cosmetic problem. The current medications are variably effective —topical gels combined with oral antibiotics and even hormone drugs for severe cases."

The average US incidence of acne is 10%. "Very difficult to say the actual cause," Biro says. " They call it a 'multifactorial' disease. Genetic background plays a role, hormones —that's why we see acne starting with adolescents as they enter puberty. There can be local inflammatory factors —some specific pathogens, the Propionibacteria that can accumulate and cause inflammation..."

Diet? "A fat-rich diet (chocolate is fat-rich) and extremely spicy foods —if the other factors are present. Some say even smoking can aggravate... Stress is an important factor. We say not only the eyes but the skin is the mirror of our soul and our spirit." Dermatologists studying the interaction of brain and skin, Biro says, "have found real mediators coming from the nervous system and acting on the skin cells."

We asked Biro about the possible anti-acne effects of THC —does THC stimulate lipid production in the skin, like anandamide, or decrease it, like CBD? He said it had not been studied, but was on his to-do list for 2010.

At the ICRS meeting in Chicago Biro met several other researchers interested in testing various cannabis-plant compounds. "We think CBG [cannabigerol] might have an effect [on lipid production]," he said. "Once you've found that there's something in the plant, why not see if there's other things in the plant that might be effective?"

CBD, he hastened to add, "is very efficient —actually, in our model system, it was much more efficient than the Vitamin A derivatives like Accutane. Of further importance, CBD was universally inhibitive of lipid synthesis. It was able to inhibit not only the actions of endocannabinoids but also the effects of other inflammatory mediators such as steroid hormones that stimulate fat production in these cells.

"Another important result: we found that low concentrations of CBD were very effective in inhibiting lipid synthesis but did not affect the viability of cells. This was also in contrast to the effects of Vitamin A derivatives which inhibit the fat production of sebocytes by killing them."

We asked Biro what happens to the normal cells surrounding the zit? He said, "We found that at the right non-toxic concentration, CBD doesn't suppress basal lipid synthesis in normal cells. Why bother those guys that are okay? It would create dry skin. Dry skin and itching —that's also impairment of quality of life. At the right concentration you get only the cells that are pathologically increased."

We also asked about baldness. "Currently, there is no effective treatment against hair loss," said Biro. "However, as we published before, THC and the endocannabinoid anandamide applied to cultured hair follicles were found to inhibit hair growth, most probably via the activation of CB1 in the hair follicle. In good accord with these data, a single animal study has shown that orally administered CB1 antagonists accelerated hair growth in mice. Perhaps someday a version of Rimonabant can be developed to promote hair growth."