

Studies Confirm Beneficial Effects of CBD, Terpenes

By Fred Gardner

THC —delta-9 tetrahydrocannabinol— is not the only active ingredient in cannabis.

At least five other cannabinoids exhibit biological activity, and so do some terpenes and flavonoids. All these compounds are produced in the plant's glandular trichomes, and are chemically related. They have been the focus of attention at recent researchers' conferences.



THC predominates in plants bred for psychoactivity (as cannabis plants have been bred for generations in California and elsewhere).

Cannabidiol —CBD— is the predominant cannabinoid in plants typically bred for fiber. There are only trace quantities of CBD in high-THC plants because one form of the same gene codes for THC synthase and another codes for CBD synthase. Thus growers selecting for high THC content get low CBD.

California growers hoping to develop plants with a high CBD-to-THC ratio have been stymied by lack of access to an analytical test lab. In surreptitious tests, "high grade" buds were reportedly in the range of 15-20% THC and 0.1% CBD.

CBD was placed on Schedule 1 although it has no known adverse effects and doesn't induce "euphoria."

The U.S. Drug Enforcement Administration has placed CBD on Schedule I even though CBD has no known adverse effects and doesn't induce "euphoria."

The most dire effects attributed to marijuana —tachycardia (accelerated heartbeat), panic, confusion, anxiety, even psychosis— are effects of THC that CBD has been shown to mitigate!

By listing CBD as a Schedule 1 substance and denying growers the means to develop high-CBD plant strains, the government is protecting the American people from an immunomodulator with anti-inflammatory, anti-convulsant, anti-psychotic, anti-oxidant, and neuro-protective properties. In whose interests could that possibly be?

Europe Takes the Lead (from U.S.)

A high-CBD cannabis strain was de-

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veloped in the 1980s by David Watson and Robert Clarke, American naturalists who founded a company called Hortapharm in Amsterdam to develop plant strains for different purposes. In 1998 Hortapharm sold its seed stock to a British start-up, GW Pharmaceuticals, which has since developed a strain that expresses 97% of its cannabinoid content as CBD.

GW Pharmaceuticals is formulating plans for clinical trials of its high-CBD extract as a treatment for rheumatoid arthritis, inflammatory bowel diseases, psychotic disorders, epilepsy, and possibly other conditions.

GWP mixes its high-CBD and high-THC strains in a 1:1 ratio to make Sativex, a plant extract formulated for spraying under the tongue that has been approved in Canada and elsewhere to treat neuropathic pain associated with multiple sclerosis.

CBD evidently bolsters the pain-killing effects of THC while moderating its psychoactivity. In various studies, patients with severe pain have reported getting significantly more relief from Sativex, the mixture, than from GW's high-THC extract.

The 2007 ICRS Meeting

CBD was the subject of several talks and posters that generated buzz at the 17th annual meeting of the International Cannabinoid Research Society, held June 26-30 at a ski resort in Saint Sauveur, Quebec.

Among the most promising studies: "CBD and the Neural Correlates of Anxiety," by Jose Alexandre Crippa and colleagues at King's College, London, and the Universidade de Sao Paulo. They measured blood flow in various parts of the brain as subjects viewed upsetting images and found that those who had been given an oral dose of CBD had markedly reduced responses.

Iddo Magen's team at Hadassah Hebrew University in Jerusalem showed that CBD and 2-AG (one of the body's own cannabinoids) improved cognition

member. Although he referred to the group collectively as "the lab wonks," he liked and admired Raphael Mechoulam, Sumner Burstein, and many other members. At the 2002 meeting Mikuriya presented a poster calling for classification of cannabis as an "Ease-ment" —a unique class of drugs, as befits its unique mechanism of action and relaxant effects on the mind and body. The pharmaceutical scientists were just beginning to characterize the endocannabinoid system as the body's master modulator.

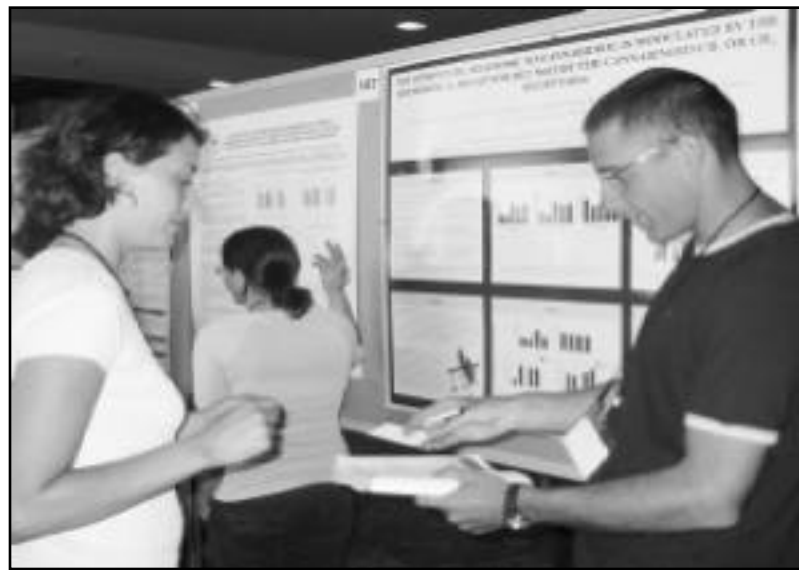
As this year's meeting came to an end, the organizers projected a photo of Mikuriya that elicited sustained applause from his assembled colleagues.

Dr. Tod's Last Paper

A poster by Tod Mikuriya, MD, was presented posthumously at the ICRS meeting. It listed "Atraumatic Autoimmune Disorders Treated With Cannabis." Co-author Laura Galli, RN, reviewed 35,232 patients' records on file at the Oakland Cannabis Buyers Cooperative and found 7,776 cases involving inflammation that met Mikuriya's criteria. AIDS-related illness was the most common (1,884 cases) followed by hepatitis C (723 cases), degenerative arthritis (577), asthma (470), fibromyalgia (447), cancers (444), and premenstrual syndrome (404).

Mikuriya was a longtime ICRS

Cannabidiol improves cognition, reduces anxiety



NETWORKING AT POSTER SESSION: Erica Carrier and Iddo Magen, who both reported on experiments involving CBD at the 2007 meeting of the International Cannabinoid Research Society. Magen and colleagues at Hadassah Hebrew University in Jerusalem showed that CBD and 2-AG (one of the body's own cannabinoids) improved cognition and neurological function in mice with liver damage. Carrier and co-workers at the Medical College of Wisconsin, Milwaukee, determined how CBD —which binds poorly to the known cannabinoid receptors— exerts its anti-anxiety effects.

and neurological function in mice with liver damage.

Erica Carrier and co-workers at the Medical College of Wisconsin, Milwaukee, determined that CBD exerts its anti-anxiety effects by activating the adenosine receptors. Anxiety in mice is evidenced by their remaining in the closed area of an elevated maze instead of exploring its open arms. Mice treated with CBD spend more time in the open arms. Carrier's group showed that CBD does not exert its anti-anxiety effect on mice pre-treated with a drug that blocks a receptor for the neurotransmitter adenosine. They also showed that mice bred to lack this adenosine receptor become no less anxious when treated with CBD.

Some 350 scientists from university and drug-company laboratories attended.

Merck, Pfizer, Eli Lilly, Bristol-Myers Squibb, AstraZeneca, and Allergan (maker of Botox and silicone breast implants) were among the corporate participants. They are all trying to develop synthetic drugs that confer some of the health benefits of cannabis without the psychoactivity. The studies described by representatives of these companies tend not to involve their most promising drugs; or else the speakers are not wholly forthcoming about the structure of the drugs involved.

Other participants included Cayman Chemical (which supplies various companies' products to research labs), Valeant (now marketing a synthetic cannabinoid called Nabilone, developed by Eli Lilly in the 1980s), ElSohly Labora-

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The Naulls Case(s): Nanny State Snatches Kids From Devoted Mom and Dad

Which psychological torment would you rather be spared (bearing in mind that you don't know how or when it will end):

1. Being made to wear panties and chained to a heap of fellow prisoners while gross foreigners insult you. Or,
2. What Ronald Bradley Naulls endured after his house and his Corona, California cannabis dispensary were raided by the DEA July 17, 2007?

Naulls' torment was amplified because his wife Anisha was put through it, too, and their children were the very instrument by which it was applied. On the day of the raids Aaliyah, Amaiyah,

and Aryanna Naulls —ages 5, 3, and 1, respectively— were taken from their home and placed in foster care at a location undisclosed to their parents. In the name of "family values" these healthy, well-cared-for little girls —impressionable, frightened little girls— were taken from their mother and father because the raiders had found edible marijuana stored in a refrigerator in the Naulls' garage.

The rip-off of the Naulls kids was described to *O'Shaughnessy's* in late July, 2007, by James Anthony —a former assistant city attorney in Oakland

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THE NAULLS FAMILY —Ronnie and Anisha with Aaliyah, Amaiyah, and Aryanna Naulls— reunited in September, 2007. For how long is uncertain; Ronnie is facing five years in prison for operating a dispensary in Corona, CA.

Seeking drugs that will heal without the high Researchers focus on CB2 Receptor

By Martin A. Lee

"Why are you traveling to Canada? For business or vacation?" the Customs officer at Calgary airport inquired.

"I'm a journalist," I replied. "I'm attending a conference on medical science in Banff."

"What conference specifically?" she probed.

I handed her a print-out titled "CB2 Cannabinoid Receptors: New Vistas."

She examined the conference flyer and asked: "Are you bringing any into Canada?"

Before I could respond, she winked and waved me through, explaining somewhat apologetically, "I have to ask that question."

In that brief encounter, I heard more about cannabis the plant than I would from most of the speakers at the CB2 conference itself (held May 31 - June 2, 2007).

Of the more than 30 scientists who presented their findings, few spoke directly about cannabis or its widely acclaimed medicinal benefits. Instead, the focus was on cannabinoid receptors — specialized protein molecules embedded in cell membranes— and how these receptors are activated (or blocked) by various synthetic compounds that have been concocted in academic and drug-company laboratories.

Specifically, the discussion focused on the second-to-be-discovered cannabinoid receptor, dubbed CB2, which is distinct from (but 45% identical to, in terms of chemical structure) the CB1

The CB2 receptor is present in the gastrointestinal tract, liver, spleen, heart, kidney, lymph and immune cells, bones, endocrine glands, and throughout the peripheral nervous system.

cannabinoid receptor that was first identified by Allyn Howlett and a team of researchers at St. Louis University in 1988.

When triggered by endogenous agonists, phytocannabinoids, or more powerful synthetic analogues, CB1 and CB2 receptors transmit chemical signals that have been shown to regulate a broad range of biological functions.

Whereas CB1 receptors are concentrated in the brain and central nervous system, the CB2 receptor, discovered in 1993 by S. Munro of Cambridge University, is now known to be present in the gastrointestinal tract, liver, spleen, heart, kidney, lymph and immune cells, bones, endocrine glands, and throughout the peripheral nervous system.

Several drug companies dispatched representatives to participate in the CB2 conference, which was sponsored by Big Pharma heavyweights such as Abbott, AstraZeneca, Wyeth and Amgen, as well as the U.S. National Institute on Drug Abuse (NIDA). All are keen to sculpt synthetic novelties that possess some of the therapeutic attributes of marijuana without altering mood or thinking.

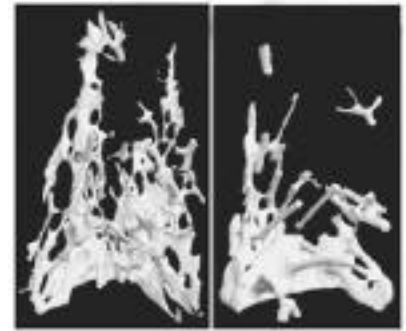
Nearly 100 people attended the event — a very large number for a first-time conference on a seemingly arcane academic and corporate researchers from 15 countries and four continents, along with a trio of Northern California physicians affiliated with the Society of Cannabis Clinicians and your intrepid reporter from O'Shaughnessy's.

Rather than discrediting cannabis, NIDA inadvertently helped underwrite a revolution in medical science.

In addition to sponsoring the conference, NIDA subsidized the work of several scientists who spoke at the gathering. Initially, NIDA had funded such studies in an effort to prove the harmful effects of marijuana. But rather than discrediting cannabis, NIDA inadvertently helped underwrite a revolution in medical science.

Citing the diversity of professional expertise among attendees —biologists, chemists, neurologists, physiologists, etc., conference co-host Keith Sharkey —a professor in the Department of Physiology and Biophysics at the University of Calgary—emphasized in his welcoming remarks the importance of interdisciplinary communication and sharing.

"I have never seen such a strong corporate presence at a cannabinoid conference, and I've been to several of these meetings," a veteran U.S. researcher



Bone tissue lacking CB2 showed serious density loss (right) compared to normal bone tissue with CB2 receptors (left) in studies conducted by Itai Bab and colleagues at Hebrew University.

commented.

In his keynote address, Benjamin Cravatt from the Scripps Research Institute in San Diego provided an overview of the endocannabinoid system and its three principal components: cannabinoid receptors; endogenous cannabinoid ligands that bind to and activate these receptors; and enzymes involved in the biosynthesis and degradation of endocannabinoids.

Scientists are currently experimenting with synthetic enzyme-inhibitors that indirectly prolong the effects of endocannabinoids and thereby amplify the expression of CB1 and CB2 receptors. Tweaking the endocannabinoid system by inhibiting enzymatic breakdown "offers exciting possibilities," according to Cravatt, "for the development of next-generation therapeutics for a range of human disorders."

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Oaksterdam U. Offers Cannabis-Oriented Curriculum

Activist/businessman Richard Lee, founder of the Bulldog Café, proprietor of the Coffeeshop Blue Sky, creator of the *Oaksterdam News*, owner of the Oaksterdam Gift Shop, and a key backer of Oakland's legalization effort, "Measure Z" —has launched an educational enterprise: Oaksterdam University.

The classes cover every aspect of running a dispensary.

The OU curriculum covers every aspect of running a dispensary. The basic classes are taught over the course of a week-end. Advanced classes are offered the following weekend (see box at right).

OU Classes are held in a one-room schoolhouse—a storefront in downtown Oakland—that seats 40. The first session, held in early January, was given rave reviews by the students who attended and even got favorable coverage from Fox News. One about-to-open dispensary sent six prospective employees for training at the second session. February, March and April classes were already filled as we went to press. Night



OU STUDENTS at a class on "Growing Cannabis Responsibly."

classes will be added, Lee says.

Faculty members include Frank Lucido, MD, who lectures on both the medical uses of marijuana and legal aspects of the dispensary-physician relationship; Dennis Peron, founder of the San Francisco Cannabis Buyers Club and the world's greatest maitre d'; Ed Rosenthal, a successful businessman and authority on cultivation; and attorney Robert Raich, who explains how to set up and run a business (both for-profit and non-profit structures).

"I was extremely impressed by the Oaksterdam students," Raich commented. "These were focused, serious people who want to do things right."

Decentralized Production

Lee opened the Bulldog Café on Telegraph Ave. soon after Prop 215 passed. His interest in training medical-cannabis users to grow their own was both political and economic. As an organizer he wanted to involve as many people as possible in the movement. As a retailer he wanted to be supplied by as many ven-

OU hitches the entrepreneurial zeal that energizes capitalism to a social goal—ending the marijuana prohibition by overgrowing the government.

dors as possible and to have the assurance—which only decentralized production could provide—that a few busts wouldn't disrupt the pipeline through which product arrived.

In 2002 Lee hired landscaper Andrew Glazier to teach a cultivation class. "Years of dealing with powdery mildew on roses helped me prepare for the same on cannabis," says Glazier, who helped plan the OU curriculum. "Soil chemistry is soil chemistry no matter if one grows tomatoes or cannabis. Temperature, humidity and pH—you need to understand their role whatever you're growing."

Glazier recalls Lee's approach at the



OU CLASSES WERE BOOKED four months ahead as of late January.

Basic Classes

Politics/Legal Issues

Overview of laws regulating medical-marijuana distribution, cultivation, possession, and use; plus an introduction to Oakland's Measure Z and the issue of legalization for consumption by adults.

Horticulture/Production

Production of cannabis flowers and starter plants. Pest control, smell abatement, security, hydroponics, organic techniques, indoor/outdoor, and drying/curing will be covered.

Budtending

Bartending for the cannabis industry. Learn how to effectively and responsibly dispense cannabis by understanding strain differences, their effects, and their use in treating various medical conditions.

Cooking

The fine art of baking and cooking with cannabis. Hundreds of edible cannabis products have been developed, including: confections, cheesecakes, salad dressings, and drinks. Learn about regulating dosages.

Advanced Classes

Packaging/Distribution

Getting cannabis from producers to retailers. Product grading, weighing, storage, and safe transportation.

Retail Management

Security, managing personnel, community relations, and customer service.

Starting a business

Obtaining city, county, state permits and licenses. Payroll and sales taxes, workman's compensation, health insurance, and other requirements for operating a business.

Horticulture 102

Hydroponics and other advanced cultivation techniques



CB2 Receptor from page 1

CB2 receptors counter inflammation by regulating immune cell migration.

Most prominent among these disorders are inflammatory and autoimmune diseases. It appears that inflammatory stimuli trigger the production of endocannabinoids, which reduce neuronal excitability and normalize overstimulated organ systems. CB2 receptors play a crucial role in this process by regulating immune cell migration. By elucidating how the body's "inner cannabis," so to speak, choreographs immune response, several studies discussed at the conference implicitly shed light on how and why marijuana can benefit people with autoimmune ailments.

The M-word was rarely invoked at the conference. NIDA-allied drug warriors continue to allege that marijuana weakens the immune system. It turns out that one of the main reasons marijuana is therapeutic is precisely because it can inhibit immune cell migration, thus easing inflammatory conditions!

A number of drug companies, large and small, are seeking to develop synthetic CB2 agonists that are far more potent than naturally-occurring cannabinoids (endo- and phyto-) as a novel treatment strategy for osteoporosis, rheumatoid arthritis, chronic pain, irritable bowel syndrome, and other inflammatory maladies.

Using genetically-engineered "knockout" mice that lack CB1 and/or CB2 receptors, researchers have proven that cannabinoid agonists can alter disease progression and attenuate experimentally-induced symptoms.

An "animal model" of osteoporosis

Oaksterdam U. from previous page

Bulldog: "They carefully selected the best strains and released them as clones—exact reproductions of desired female plants. Imagine a pharmacy which sells you medicine and then gives you the recipe, too. It was revolutionary. Folks from Southern California came north to get the best genetics."

According to Glazier, "In the early 1990s seed companies had begun shipping cannabis seeds all over the world. This was great for folks living in rural areas but they still had to separate male from female plants and look out for hermaphrodites. With clubs releasing clones of sexed females and offering instruction, decentralized production could become the norm."

Decentralized Distribution

In Oaksterdam U., Lee has created an institution that furthers decentralized distribution. Why would a capitalist—which Lee is, wholeheartedly—create competition for his own dispensary business? "I'm about politics and changing the laws," he says matter-of-factly.

He's being modest. Oaksterdam U. is a brilliant idea on every level. It hitches



Indoor garden with a college education.

is created in normal mice and in mice without CB2 receptors. Itai Bab of the Hebrew University of Jerusalem reports that when HU-308, a synthetic CB2-specific agonist, is given to both groups of osteoporotic mice, the agonist mitigates bone damage in the normal mice but has no effect on rodents missing CB2 receptors—meaning that CB2 receptors are instrumental in maintaining healthy bone density.

This conclusion was confirmed by several speakers, including Andreas Zimmer from the University of Bonn, who indicated that CB2 activation restrains the formation of bone reabsorbing cells, known as osteoclasts, by downregulating osteoclast precursors, thus tipping the balance in favor of osteoblasts, cells that facilitate bone formation.

Similar experiments with knockout mice highlight the extent to which CB2 receptors are involved in ameliorating skin rashes, intestinal ulcers, acute brain injuries, multiple sclerosis, ALS ("Lou Gehrig's Disease") and other neurological illnesses.

University of Calgary scientist Marnie Duncan spoke on the role of the CB2 receptor in the enteric (digestive) nervous system and how cannabinoids regulate intestinal motility. Based on experiments with a synthetic CB2 agonist in animal models of colitis, she determined that CB2 receptors have "novel protective qualities . . . in the GI tract."

According to Karen Wright of the University of Bath, CB2 receptor agonists modulate intestinal pain and inflammation associated with Crohn's Disease.

Michael Meyer, from Abbott Laboratories cited studies involving CB2 agonists and knockout mice that "demonstrated efficacy in preclinical models of inflammatory, moderate-to-severe post-

operative, and neuropathic pain."

The fact that neuropathic pain is difficult, if not impossible, to treat with conventional analgesics underscores the importance of CB2 research that could yield a new class of medicinal compounds for pain and inflammatory ills.

University of Georgia neuroscientist Andrea Hohmann predicted that analgesics targeting CB2 would not be psychoactive or addictive because CB2 receptors "are localized predominantly outside the central nervous system and are upregulated in the central nervous system by traumatic nerve injury."

At the forefront of the effort to create a non-addictive painkiller without adverse side-effects is Pharmos, an Israeli start-up firm, which has already conducted Phase I and Phase IIa clinical trials with "Cannabinor," a promising CB2 receptor agonist. Noting that his company has generated "a pipeline of CB2 agonists with a variety of selectivities," Arnon Aharon, director of clinical development at Pharmos, says that Cannabinor is "safe and well tolerated" with rapid onset and long duration and has a measurable analgesic effect.

While much of the research discussed at the conference lent credence to anecdotal reports of medical marijuana users, some of the scientific studies pointed to new possible clinical utilities for cannabinoid remedies.



Maccarrone

One of the most fascinating presentations was given by Mauro Maccarrone of the University of Teramo in Italy, who explored the role of CB2 receptors in reproductive biology. Depicting the endocannabinoid system as the "guardian angel" or "gatekeeper" of mammalian reproduction, he stated that CB2 receptors play an essential role in both male and female fertility.

Endocannabinoid signaling figures decisively throughout the reproductive process, from spermatogenesis to fertilization, oviductal transport of the zygote, embryo implantation, and post-implantation embryonic growth. CB2 receptors proliferate in the placenta and facilitate neurochemical "cross-talk" between the embryo and the mother.

A misfiring of the endocannabinoid system, Maccarrone explained, could result in serious problems, including ectopic pregnancy and miscarriage. He hopes that his research will lead to therapeutic applications with "CB2-dependent endocannabinoid signaling as a target for correcting infertility and improving reproductive health in humans."

Risk factor for cirrhosis?

Several studies suggest a complex interplay between CB1 and CB2 receptors. If CB1 receptors are blocked by a selective antagonist, then endocannabinoid ligands seemingly compensate by gravitating toward CB2 receptors, which are formed "on demand" in areas of need. THC binds both to CB1 and CB2 receptors, though only weakly to the latter.



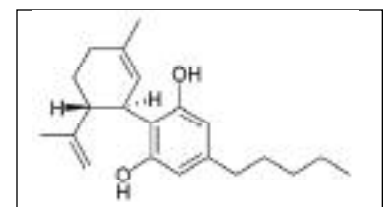
Ken Mackie and Andrea Hohmann

French scientist Sophie Lotersztajn warned that THC's activation of CB1 receptors can contribute to liver cirrhosis and that cannabis may therefore be a risk factor in patients with fibrotic liver disease. But knockout mice experiments

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some terms

phytocannabinoid A 21-carbon compound unique to the cannabis plant. ("Phyto" specifies "plant." There are also endogenous and synthetic cannabinoids). Phytocannabinoids have three six-carbon rings and three additional carbon atoms, with side-groups attached that give them different binding characteristics. Some 66 phytocannabinoids have been found in plants from around the world, over time, but not all are present in a given plant. The most prevalent cannabinoids in the plant are THC, CBD, CBN, CBG and CBC.



cannabidiol (cbd)

endogenous cannabinoid Two cannabinoids produced by the body have been identified: **anandamide (AEA)** and **2-arachidonyl glycerol (2-AG)**. They are synthesized from the membranes of numerous cells in the body and released to signal neighboring cells to slow down the rate at which they are transmitting chemical messages.

synapse Gap between cells that signaling molecules cross. AEA and 2-AG transmit from "post-synaptic" cells and activate **cannabinoid receptors** embedded in the membranes of "pre-synaptic cells." The cannabinoid receptors are linked to proteins that trigger events within the cell leading to a slowed release of neurotransmitters. The process by which the cannabinoids work is called "**retrograde signaling**."

CB1 receptor was found originally in the brain, where it is very abundant (more so than opioid receptors). The **CB2 receptor** was first found in spleen cells in 1993. It has since been found in the stomach, liver, heart, kidney, lymph and immune cells, bones, endocrine glands, and throughout the peripheral nervous system. Research in recent years suggests that two other receptor types in the body might be activated by cannabinoids.

agonist A molecule that activates a receptor. Sometimes referred to as a **ligand**. An **antagonist** occupies the receptor and displaces endocannabinoids. An **inverse agonist** acts on the receptor, producing its own effects.



OU's Richard Lee: the businessman as political organizer

ICRS, IACM Meetings from page 1

tories (Mississippi-based, the only company authorized by the DEA to grow cannabis in the U.S.), Bedrocan BV (which grows cannabis for the Dutch Ministry of Health, Welfare and Sport), Cannasat (a Canadian company with three plant-based products in their pipeline), and GW Pharmaceuticals. Bayer Health Care, which distributes GW's Sativex in Canada, had set up a large exhibit in one of the rooms dedicated to posters.

Adieu, Rimonabant (for now)

The meeting's primary sponsor was Sanofi-Aventis, the world's third-largest drug company, which had suffered a major setback in mid-June when an FDA advisory panel voted 14-0 against recommending approval of Acomplia (also known as Rimonabant), a weight-loss drug that works by blocking the CB1 receptor. Acomplia has been approved for sale in the UK and elsewhere, and Sanofi and most securities analysts had projected it to be a blockbuster in the U.S. But the FDA advisors were troubled by the number of suicides and seizures in the clinical-trial data.

California clinicians warned that reversing the effects of the body's own cannabinoid system was very likely to cause health problems.

When Sanofi first announced at the 2004 ICRS meeting that Rimonabant was proving effective in large-scale trials in Europe, Jeffrey Hergenrather, MD, and other California clinicians warned that reversing the effects of the body's own cannabinoid system was very likely to cause health problems. O'Shaugh-

More Evidence that CBD Reduces Anxiety



DR. JOSE ALEXANDRE CRIPPA explains his poster, "CBD and the Neural Correlates of Anxiety," to Drs. Geoffrey Guy and William Courtney at the 2007 meeting of the International Cannabinoid Research Society. Crippa measured blood flow in various parts of the brain as subjects viewed upsetting images. Those who had been given an oral dose of CBD (cannabidiol) had markedly reduced responses.

nessy's had published a piece quoting Hergenrather, slugged "Danger! Danger! Danger!" So it was a little awkward to encounter the charming scientists from Sanofi at this year's meeting, knowing they had just lost out on millions and might hold us partly responsible (when it fact we are under the radar and politically impotent).

Rimonabant has been used by more than 100,000 people in Europe and Sanofi contends that the safety profile may yet turn out to be satisfactory. They're also trying to figure out ways to prevent those most obviously at risk—people with epilepsy, MS, a history of serious depression, etc. etc.—from taking Rimonabant.

Sanofi-funded researchers had tried to exclude people with a history of these conditions from the clinical trials. Nevertheless, an FDA analysis showed, subjects taking 20 mg of Rimonabant experienced a 1.8 fold increase in suicidality (ideation and attempts) compared to those on placebo.

Rimonabant takers were also at greater risk for seizures and MS exacerbations. Frequently reported side effects included nausea, dizziness, depression, headache, diarrhea, anxiety, vomiting, and insomnia (all conditions known to be eased by cannabinoids activating the CB1 receptor).

Sanofi's marketers wish they could sell Rimonabant only to patients with a condition called "metabolic syndrome" (high glucose levels, obesity, and other risk fac-

They dream of applying "genomics" (analyzing every patient's genetic make-up before prescribing).

tors for diabetes and/or cardiovascular disease, which Sanofi defines as a disease itself). They dream of applying "genomics" (analyzing every patient's genetic make-up before prescribing). But the reality is a world in which doctors can prescribe for off-label uses and everyone wants to lose 10 pounds.

California doctors, although skeptical that blocking the CB1 receptor could produce a safe drug, hoped that Sanofi's marketing push would educate the profession and the public about the endocannabinoid (eCB) system. Philip A. Denney, MD, says that in the past two years he received "at least a half dozen pieces of expensively produced literature" linking the CB1 receptor and "metabolic syndrome."

Dr. John McPartland views the promotion of "metabolic syndrome" as a case study in "disease mongering." In a stinging critique circulated among fellow researchers, McPartland accused Sanofi of unethical marketing practices, including publication of medical-journal supplements in which influential doctors wrote favorably—or lent their names to ghost-written articles—about Rimonabant without revealing that they had gotten support from the company.

"A theme of positive bias emerged from articles authored by Sanofi-sponsored physicians, such as biased statements regarding Rimonabant's efficacy and safety profile..."

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CB2 Receptor from previous page

THC is cardioprotective at a dosage lower than the dose required to experience psychotropic effects.

also show that THC-responsive CB2 receptors attenuate liver injury and enhance liver regeneration.

Cardioprotective effects

Francois Mach, from Geneva University, found that the oral administration of small doses of THC significantly inhibits the progression of heart disease in mice "as demonstrated by reduced atherosclerotic plaque development within aortic roots." It turns out that the cardioprotective properties of THC are largely CB2-dependent and are best harnessed when the dosage level of THC is less than the dose required to experience psychotropic effects. Thus, THC may offer an effective treatment modality for human atherosclerosis, a chronic inflammatory condition affecting the large arteries, which is a primary cause of heart disease and stroke.

Atherosclerosis is also an adverse side-effect of widely used blood thinners, such as coumadin. Mach did not comment on whether THC, in herbal or synthetic form, could provide a viable means of countering the negative, long-term consequences of blood thinners.

Indeed, none of the speakers were inclined to bite the NIDA hand that feeds by openly endorsing the use of medical marijuana. But excitement was palpable among those who participated in the first-ever conference devoted primarily to the CB2 receptor. Immersed in a vi-

brant, challenging, and diverse area of study, these scientific trailblazers were buzzed on being in the vanguard, on being at the cutting-edge of something momentous and portentous that could lead to a treasure trove of new, non-toxic, and highly selective remedies for a wide array of infirmities, including, at long last, a painkiller without abuse potential.

The commercial success of government-approved cannabinoids could depend on how vigorously pot prohibition is enforced.

Tinkering with molecules that activate the CB2 receptor, which (unlike CB1) has not been linked to psychoactivity, conjures the prospect of healing without the high—a prospect that intrigues pharmaceutical firms and seems acceptable to drug war bureaucrats. Both appear to have a vested interest in the continued prohibition of the natural plant. The commercial success of government-approved cannabinoids could depend on how vigorously pot prohibition is enforced.

But the market is enormous, and there should be ample room to accommodate both natural and synthetic cannabinoid medicines. For numerous patients, medical marijuana, whether smoked, vaporized, eaten, sprayed, or applied topically, is the safest and most

effective way to treat their conditions, far superior to any prescription medicines currently available. Many others, however, are not comfortable with the psychoactive ef-

fects of cannabis, which can induce anxiety and disorientation; they could benefit substantially from the healing potential of CB2-activating compounds.

British Journal of Pharmacology Publishes Special Issue on CB2 Receptor

Contents of the January 8, 2008 issue of the *British Journal of Pharmacology*, which was devoted to the CB2 Receptor, reveal the range of research activity:

- Pharmacology and therapeutic potential of CB2 receptor inverse agonists by Charles Lunn
- Mapping the effects of CB2 agonists on regional brain activity using pharmacological magnetic resonance imaging by Gerard Fox
- Cannabinoids receptors and bone function by Itai Bab
- Role of CB2 receptors and mechanisms of action of CB2 receptor agonists in neuropathic pain by T P Malan
- Role of CB2 receptors in inflammatory pain, wind-up and in arthritis by Andrea Hohmann
- CB2 receptor in the enteric nervous system and its role in intestinal motility and inflammation by Keith Sharkey
- Antifibrogenic role of the CB2 cannabinoid receptor in the liver by Sophie Lotersztajn
- CB2 receptors in reproduction by Mauro Maccarrone
- The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: D9-tetrahydrocannabinol, cannabidiol and D9-tetrahydrocannabivarin by Roger Pertwee
- Targeting the cannabinoid CB2 receptor: modelling and structural determinants of CB2 selective ligands by John Huffman
- CB2 Cannabinoid receptor agonists attenuate TNF- induced human vascular smooth muscle cell proliferation and migration by Ken Mackie
- Cannabinoid CB2 receptors in human brain inflammation by Julian Romero
- CB2 receptor-mediated migration of immune cells: it can go either way by Nephi Stella
- CB2 receptors in the brain: role in central immune function by Guy Cabral
- CB2 cannabinoid receptors as an emerging target for demyelinating diseases: from neuroimmune interactions to cell replacement strategies by Eduardo Molina-Holgado
- Cannabinoid receptors in acute and chronic complications of atherosclerosis by Francois Mach



ICRS, IACM Meetings *from previous page*

Maintaining a 'hedonic tone' via a functional eCB system may be critical for maintaining personal optimism.

McPartland reminds his colleagues that "Activation of CB1 in the meso-limbic system drives the motivational and rewarding aspects of food as well as drugs of abuse. Suppression of the drug-reward pathway has been a research focus by NIDA researchers. Conversely, maintaining a 'hedonic tone' via a func-

tional eCB system may be critical for maintaining personal optimism and society productivity in the face of chronic stress and an ultimately unrewarding consumer culture. CB1 blockade is irrational in an obese patient who is stressed and consumes a fast-food diet full of white flour, refined sugars, and *trans*-fatty acids, and lacks fiber, vegetables, omega-3 fatty acids, and exercise."

THCV: a kinder, gentler antagonist?

The consensus among ICRS scientists is that downward modulation of the

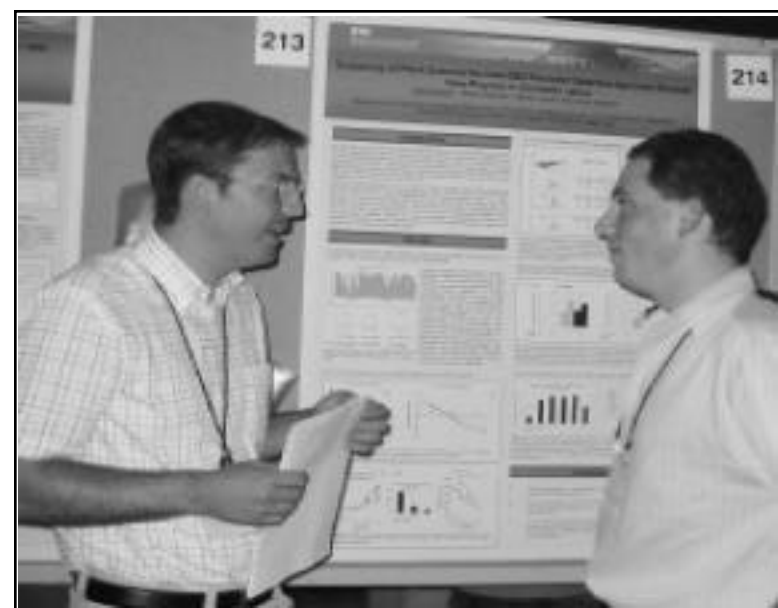
CB1 receptor remains a feasible strategy for treating obesity, but that Rimonabant —an "inverse agonist" that doesn't simply block the receptor but achieves a reverse effect on endocannabinoid tone throughout the body— was too strong a drug.

"Inverse agonists of the endocannabinoid system may not exist in nature," observes Ethan Russo, MD. "Pharmaceuticals that act in such a manner may be outside physiological parameters. The normal order calls for more subtlety of function."

GW Pharmaceuticals is beginning to test a plant strain high in THCV, a "neutral antagonist" that lightly occupies the receptor but doesn't reverse its effects on endocannabinoid tone.

A poster at the ICRS meeting by Michael A. Cawthorne and colleagues at the University of Buckingham and GW's Porton Down Science Park concluded that pure THCV and a THCV plant extract produced anti-obesity effects in mice "mainly by increasing energy expenditure rather than reducing food intake. Such effects merit further study."

CANADIAN ACTIVIST-ENTREPRENEURS at the ICRS meeting included Sara Lee Irwin (below left) of Cannasat, which owns a stake in the company that grows cannabis for the Canadian government and has three products in development —one a cream and one a pill, reportedly; Boris St. Maurice (below right) of the Montreal Medical Cannabis Dispensary; and Philippe Lucas, director of the Vancouver Island Compassion Society (right). Lucas presented a poster describing the options available to Canadians seeking to medicate with cannabinoids.



JÜRIG GERTSCH (left) of the Department of Chemistry and Applied Biosciences, ETH Zurich, had two posters to explain at ICRS 2007. One reported that certain components of purple coneflower —Echinacea, bottom left— selectively bind to and activate the CB2 receptor. These compounds —N-alkyl amides— represent "a new class of cannabinomimetics." Gertsch also led a group that tested the essential oil of cannabis —a concentrate obtained by distillation, consisting only of terpenes and other compounds that give cannabis its smell, no cannabinoids. A component of the oil efficiently displaced a radioactively-tagged synthetic cannabinoid at the CB-2 receptor. Gertsch and his colleagues also screened various plant-extract libraries and got hits from *Piper nigrum* (black pepper, bottom right), *Smyrniun rotundifolium*, and *Juniperus*. They found that "certain ubiquitously occurring sesquiterpenes of the humulan and caryophyllan types [notably beta-caryophyllan] show selective affinity to CB2 over CB1." They concluded: "Our data provide the first proof of CB2-selective functional agonists in Cannabis sativa other than cannabinoids. This finding may therefore have implications for the therapeutical applications of Cannabis sativa extracts containing sesquiterpenes."



"Intriguing Mystery:" Cannabis Smoke Damages Lung Epithelial Cells But Doesn't Cause Cancer

"The tar collected from even one cigarette —and marijuana's even worse than tobacco— is just so horrible looking and smelling that trying to work with it, you find it incredible that people put this stuff inside of them," says Dr. Theodore Sarafian of the Division of Pulmonary and Critical Care, Department of Medicine, UCLA.

Sarafian says that components in marijuana smoke may contribute to bronchitis and chronic infection by slowing down the migration of immune cells to the site of the pathogens, a process called "chemotaxis."

Sarafian has worked with UCLA pulmonologist Donald Tashkin on studies that failed to establish an anticipated link between marijuana smoking and lung cancer. How does he explain their results?

"It is most likely the anti-inflammatory effects of THC and CBD," says Sarafian. "The smoke contains lots of cancer causing chemicals," he reiterates. "It's possible that THC prevents elements of inflammation that block the malignant transformation into cancer. It needs to be investigated more. There's some intriguing mystery there and it's probably very significant."

Sarafian notes that "One negative aspect of the negative cancer results is on funding. Funding becomes much tougher to get when we show that there



THEODORE SARAFIAN reported that THC suppresses the repair process in lung epithelial cells.

"Funding becomes much tougher to get when we show that there isn't as much harm."

isn't as much harm. My grants were rejected for several years by people who said there's no evidence of injury in the lungs for marijuana smokers. So even though the scientific proposals I had were strong, they said there probably wasn't clinical significance to the research." The study Sarafian reported on at the ICRS meeting, "Over-Expressing CB2 Receptor Uncovers Its Role in Regulating Lung Epithelial Cell Chemotaxis," was supported by grants from the National Institutes of Health.

ICRS 2007: Talks of Special Interest

By Dr X.

This year's "top 10" included a mix of basic science and clinical science. There were no big break-through studies; rather, it was a year of "consolidating our knowledge," as Dr. Geoffrey Guy put it.

Andrea Hohmann gave the annual ICRS Young Investigator Award lecture, entitled "Endocannabinoid mechanisms of pain suppression." In an hour tour-de-force, she swept through 13 years of research, which began shortly after the discovery of anandamide in 1992. Hohmann provided behavioral, neurophysiological, and neuroanatomical evidence to demonstrate that cannabinoids suppress nociception and pain via CB1 and CB2 receptors at peripheral, spinal, and supraspinal levels. Her recent work has focused upon "stress-induced anal-

gesia" (SIA). This phenomenon, exemplified by trauma victims seemingly devoid of pain, has long been attributed to the endorphin system. Hohmann's research demonstrated that the endocannabinoid system is also responsible for SIA.

Scott Graham startled everyone at the symposium by saying the Emperor wears no clothes, "Cannabinoid receptor antibodies are not all created equal!" When scientists want to prove that CB1 is present in a tissue or cell line, they use antibodies that bind specifically to the CB1 protein. The antibody-CB1 interaction can be visualized by tagging the antibody to a fluorescent compound, or to a peroxidase enzyme that catalyzes a color-producing stain. Graham showed that most commercially-available CB1 antibodies do not bind specifically to CB1, and in many cases do not bind to CB1 at all. His lecture was the talk of the town, and may herald a resurgence of alternative techniques, such as radioligand CB1 binding assays.

Lisa Gauson and colleagues in Roger Pertwee's lab, and Jürg Gertsch and colleagues in Zürich



Andrea Hohmann

continued on next page

Dr. X's Top Talks from previous page

continue to support the argument that "cannabis is more than just THC." Gauson reported that cannabigerol (CBG) has affinity for both CB2 and CB1, and behaves as a partial agonist at both receptors. Last year, her colleagues in Pertwee's lab showed that cannabidiol (CBD) acts as an inverse agonist at CB1, as does tetrahydrocannabinol (THCV).

Pertwee's work with cannabis constituents dates to 1970, when he showed that cannabis extracts devoid of cannabinoids nevertheless synergized with THC. In agreement (35 years later), **Jürg Gertsch** showed that one such non-cannabinoid cannabis constituent, (E)-bicyclic cannabinol, has affinity for CB2. This has therapeutic implications regarding inflammatory diseases and immune functions.

Meliha Karsak and 15 high-powered colleagues (including Raphael Mechoulam, Vincenzo Di Marzo, Andreas Zimmer, and Ben Cravatt) showed how allergic contact dermatitis is attenuated by the endocannabinoid system. The discovery was classic science, beginning with Karsak's accidental observation that double-knockout CB1-CB2-deficient mice developed a rash around their i.d. tags. But as Pasteur said, "Chance favors the prepared mind." For the next six years Karsak elegantly dissected a mechanism involving the proinflammatory chemokine gene CCL8 (also known as MCP-2), which ties the story to multiple sclerosis, rheumatoid arthritis, osteoarthritis, and perhaps the inflammatory component of atherosclerosis. And for clinicians in the crowd, she demonstrated

that THC, administered topically or subcutaneously, decreased allergic contact dermatitis in mice.

Erica Carrier and colleagues in Ceci Hillard's lab, and **Iddo Magen** and colleagues in Israel elaborated upon the CBD-and-adenosine receptor story. Carrier showed that the anxiolytic effects of CBD were mediated via adenosine A1 receptors and not CB1 or CB2 receptors. CBD blocks the uptake of adenosine through competitive binding to the ENT1 adenosine transporter, thereby enhancing signaling at adenosine receptors. Thus CBD shares a mechanism with ethanol, another ENT1 transport inhibitor. (In contrast, caffeine is an adenosine A1 receptor antagonist.)

Magen showed that CBD (as well as endogenous 2-AG) improved cognition

and neurological function in a rodent model of hepatic encephalopathy. CBD worked via interleukin (IL-1b) signaling and adenosine receptors.

Mark Ware and colleagues at McGill University in Montreal showed that smoking 25 mg (one puff) of 9.5% THC herbal cannabis three times daily can successfully treat patients with neuropathic pain and improve their sleep. This might sound obvious, but Ware's study is only the second randomized placebo-controlled crossover clinical trial to demonstrate that smoked cannabis is an effective pain-relieving medicine! (Earlier this year, Donald Abrams published a randomized placebo-controlled study regarding HIV-associated sensory neuropathy. See story on page 35.)



Esther Fride

Matt Hill

Pertwee and Gertsch

John McPartland

Rik Musty

Hodaya Dahan

ICRS Talks of Special Interest —A Second Opinion

By Dr. Mirage

The two plenary lectures at the 2007 ICRS meeting were both excellent. The Kang Tsou Memorial Lecture was delivered by Jean-Pierre Després, an engaging, dynamic speaker and lead author of the *New England Journal of Medicine* study on Rimonabant. He provided compelling evidence that society's obsession with weight (and specifically the Body Mass Index, or BMI) is misguided, when the real target should be visceral fat. This can be quantified with scanning, but more cheaply and easily with a simple tape measure. (How early 20th century!) Certainly, a strong case was made for addressing this as an important outcome measure in clinical trials of CB1 antagonists and other weight loss approaches.

The Young Investigator Award was delivered by the eminently deserving Andrea Hohmann, who outlined the amazing progress in elucidating cannabinoid mechanisms of analgesia.

Two stunning facts require consideration: 1) Cannabinoids are 10-fold more potent than morphine in wide dynamic range neurons mediating pain, and 2) Hohmann published 14 journal articles during graduate school. Which of the two is the more amazing, our panel of judges will need to ponder.

Scott Graham of Michelle Glass' "Kiwi Crew" deflated many scientists' confidence by his convincing demonstration that many commercial CB1 antibodies employed in research are substandard or worse. There may be a lot of checking and revision necessary in labs across the globe in coming months.

Matthew Hill (elected student representative to the ICRS) expanded on prior work examining the role of endocannabinoids in memory consolidation, this time, in its relationships with the adrenocortical axis of stress. This is the common ground between memory, anxiety and other emotion.

Mark Ware presented results of his clinical study of 21 subjects each smoking single inhalations of Prairie Plant Systems cannabis supplied by Health Canada three times a day. No changes

were noted in acute neuropathic pain scores, but over the course of the study 14% reported 30% pain relief (the current regulatory standard for efficacy of analgesic drugs). These results are modest, at best, and indicate the tremendous effort required from this stage if smoked cannabis is to meet licensing standards for efficacy required to make it a legitimate prescription pharmaceutical. Whether this is even possible given obvious political roadblocks is another serious question.

Chemotherapy-induced nausea and vomiting remain important pitfalls in cancer treatment, and come in three forms: acute, delayed and anticipatory. Current miracle drugs (ondansetron and its relatives) fail utterly in allaying anticipatory symptoms. As discussed by **Linda Parker**, the synthetic URB597, and phytocannabinoid cannabidiol were quite successful, in contrast, in a rat model of the syndrome. Important help may be on the way for cancer patients.

Ester Fride added to her important body of work in demonstrating the key role played by endocannabinoids in early mammalian feeding patterns, and an endogenous deficiency in the system in "non-organic failure-to-thrive." The research points out the hopeful possibility of employing cannabinoid agonists in human neonatology to spur on infant feeding and growth.

Meliha Karsak summarized six years of painstaking research to elucidate the key role that cannabinoid mechanisms and systemic or topical THC can play in treatment of contact dermatitis allergic reactions. The story began with a chance finding that double knockout mice lacking both CB1 and CB2 receptors reacted to ear tags containing nickel, with allergic inflammation, scratching and even tissue necrosis. Through a systematic analysis using histology, gene knockout technologies and application of various cannabinoid agonists, antagonists and combinations, a much clearer understanding has emerged with potential importance

to many dermatological conditions. This work was published in *Science* in June 2007.

John McPartland presented a very interesting poster examining rates of evolution of endocannabinoid system components, and demonstrated that active changes are continuing, particularly in the primate line (meaning you, human). These findings could have important implications in understanding human-environment interactions, and what our bodies seem to be highlighting as areas under evolutionary pressure. This may point the way toward particular areas where new medicines are needed.

Greg Gerdemann extended prior work in demonstrating the key role that the endocannabinoid system plays in consolidating memory of new task learning, and how SR141716A/rimonabant/Acomplia/Zymulti may interfere with the process. European pharmaceutical dieters beware: You may be dumbing down in an effort to lose that weight!

Raffaella Tonini demonstrated award-winning poster form in presenting a study that investigated the long-term potentiation and depression of cannabinoids. The findings extend current knowledge in a way that may enhance our ability to understand problems of memory, emotional control, and chemical dependency.

Natasha Grimsey, another member of the Kiwi Crew, was also lauded for her poster that explored mechanisms of intracellular trafficking of the CB1 receptor. As it turns out, different drugs produce varying effects and duration of receptor internalization, thus having important implications for duration of action, and whether they will be prone to inducing dependency issues. As usual, more research is needed.

One of the final posters in the final session of the final day was quite a revelation. **Jürg Gertsch** demonstrated that caryophyllene, a terpenoid component of cannabis, is a selective CB2 agonist. Thus, its inclusion in cannabis-based medicines certainly may enhance their

analgesic and anti-inflammatory benefits. So much for better living through chemistry; sometimes Mother Nature does it better!

A few trends were noteworthy in the proceedings. Several studies of nabilone (Cesamet®, a 20-plus-year-old synthetic cannabinoid approved for treatment of chemotherapy-associated nausea), were presented in support of company efforts to move into the pain treatment area. However, none of these were advanced randomized clinical trials that are necessary for approval.

A few NIDA-funded studies of potential adverse effects associated with cannabis employing mega-doses of THC were staged, but increasingly, these were challenged, if not ridiculed by European researchers.

GPR55 remains uncommitted as to whether it qualifies to be renamed as the third cannabinoid receptor. The jury is still out for another year.

All things considered, the 2007 ICRS meeting was stimulating and enjoyable, benefited greatly by a congenial group that enjoys social interaction in a collegial atmosphere free of the competitive pressure all too prevalent at scientific gatherings.



Mark Ware (right, with *Volcano* designer **Markus Storz**) presented his findings at both the ICRS and IACM meetings.