Input from the lab has already resulted in growers improving their operations, according to Rick Pfrimmer, Harbor-Continued on page 18

Bad News, Good News

Buds high in cannabidiol (CBD) are from "Soma A" plants grown indoors in the Bay Area. Testing in the lab will enable growers to develop strains with various CBD-to-THC ratios by conventional selection methods or by genetic methods.

CBD: a Treatment for Breast Cancer?

By O'Shaughnessy's News Service

When California Pacific Medical Center took a half-page ad in the San Francisco Chronicle to announce a public forum on October 7, 2008, it may have been the first time in history that a hospital pitched its cannabidiol research program to prospective patients. "From Water Bottles to Marijuana Derivatives," the text called out, "Latest Discoveries About Breast Cancer."

The ad convinced about 100 women who dislike the effects of high-THC cannabis. According to Jeffrey Hergenrather, MD, examine a chromatogram showing learning how the sophisticated testing apparatus and refining their procedures under the tutelage of a sympathetic university-connected chemist.

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CBD for Breast Cancer

From page 1

...ing different combinations of cannabinoids—and other components of the plant—as anti-cancer agents.

McAllister: We’re about to publish the results of the work we’ve done in vitro, combining THC and CBD against glioblastoma multiforme, an aggressive form of brain cancer. We found a synergistic increase in the ability of the compounds to induce apoptosis—programmed cell death. That finding is going to be presented at the ICRS [International Cannabinoid Research Society] meeting. I was quite surprised at how well the combination worked. Now we’re trying to get the funding to do the experiment in vivo.

I proposed to look at many different combinations. I started with THC and CBD because they’re the most abundant. We found that in two out of three aggressive brain-cancer cell lines that we looked at, when you added CBD at a lower concentration than THC, we saw a synergism in terms of its ability to induce cell death.

Q: What was the most effective ratio of THC to CBD?

McAllister: About fourfold less CBD than THC. This occurred in more than one cell line. And we have discovered a molecular mechanism that may explain why if you add THC and CBD together, they might synergize.

Q: Could you explain the mechanism?

McAllister: There is a family of signaling proteins called mitogen activated protein kinases (MAPKs). These proteins control cell growth and survival. Depending on how they function, they can either stimulate cell growth or, if you stimulate them for too long in cancer cells, you can cause the cells to undergo programmed cell death, which is a desirable property in a cancer drug. We found that when you add either component at lower concentrations alone you produce either no effect or marginal effects on certain MAPK. But when you combine them, you get a dramatic change that leads to increased cell death and reductions in proliferation. This ties in a little to Guzman’s work. [A 1998 paper by Manuel Guzman and colleagues documented anti-cancer effects of THC and inspired McAllister to test other cannabinoids for similar effects.] He showed that modulation of MAPK was essential for THC’s ability to increase cell death. So we’re carrying on with that story and looking at the different components and seeing which can help. Which fits in with the theory that the endogenous cannabinoids have an “entourage effect.” One component is not the whole story.

We really want to follow up in vivo now. We have access to actual primary brain tumors from patients—not just cell lines that have been passed for a long time. The problem with cell lines can be that when you pass them for years and treat them with semi-artificial high-serum and all the things that you do in cultures their genetic profile can change so that they’re not the same as the original primary tumor.

But now we have techniques where you can actually take the tumor out of the patient and keep it under conditions where years down the road it would have the same genetic profile as the original tumor. Which gives you a real model to test the efficacy of whatever treatment you’re testing.

The in vivo work we’ve done so far looks promising in regard to CBD being able to inhibit metastasis. And now we’re going to combine it with THC. It makes sense to attack cancer with multiple types of treatments that target different pathways. That’s a classical approach with cancer treatments.

Q: At the forum you said you had begun using a mouse model.

McAllister: We use a mouse model of aggressive breast cancer. We treat the mice every day with a very reasonable concentration—5 milligrams per kilogram [of body weight]. We injected it systemically. These mice get a primary tumor in the breast and just like the common human progression, after a certain amount of time it metastasizes to the lung. We found that if we treat it with the drug, you get significantly less metastasis to the lung.

Q: Are you still on track to have clinical trials less than two years away?

McAllister: STI pharmaceuticals is talking to clinicians in the UK that do these kinds of trials. They’re looking at the data. Yes. We’re definitely getting closer.

Q: Who has the IND [license to conduct the trial] in the UK?

McAllister: STI pharmaceuticals. That’s where we’re thinking the trial will be.

Q: Women in California will be disappointed.

McAllister: We’re going to try and do a parallel trial here as well. I don’t think it will be a problem.

Q: What will that trial look like?

McAllister: I need to collect data for about another six months to a year and talk with physicians in order to propose a trial design. I have questions with regard to dosing. In the model we’ve been working with, the mice have a functional immune system. Vincenzo Di Marzo’s group did a study using a human cell line with a compromised immune system. I’ve read several CBD modulates the immune system, which raised some concerns. I want to try a couple of different dosing schedules. Do we want to give these patients a systemic dose every three days? Every four days? Would oral administration be effective? It is difficult to truly extrapolate between mice and humans but we need more detailed in vivo data before we can proceed.

Q: Who provides your CBD?

McAllister: NIH. They synthesize it.

Q: You know that a high CBD strain has been located in California.

McAllister: I have a DEA license here and I’m working towards getting standardized plant extracts from Arno Hazenkamp in the Netherlands to try. It’s always been my goal to work with extracts. But it’s not easy to find a place to give you extracts with quality control. To do an experiment in a sound, scientific manner you have to know exactly where the material’s coming from, and its make-up.

There’s so much to learn about how these components interact. It was just a few years ago that they found CB-2 agonists in terpenes. And there’s probably even more structures in the extracts that might modulate the activity, depending on whatever physiological effects you’re looking for.

Q: How do the cannabinoids exert their anti-cancer effects?

McAllister: In the breast cancer model, CBD appears to target two major pathways, resulting in modulation of MAPK and an increase in production of reactive oxygen species. Both changes lead to damaging effects in cancer cells. That’s different than

AGGRESSIVE BREAST CANCER CELLS lose ability to invade through an extracellular matrix. Cells left at untreated controls; at right cells treated with CBD. Invasive ability is an indication of the cells’ metastatic potential in the body. Photomicrographs by Sean McAllister

in the brain tumor model where the majority of the drug’s effect is inducing cell death. With breast cancer it looks like there are two primary pathways.

Q: If and when high-CBD strains become available to cannabis users in California and people start using it for various reasons—with or without input from their doctors—is there a downside, a downside to that?

McAllister: Yes. I’ve actually seen this in my own experiments. There’s definitely a specific dose-response occurring with CBD. If you’re too low or too high you won’t see an effect. You need to be within specific therapeutic window. If the treatment is not formulated and you don’t really know what dose you’re getting, you might not see any effect.

Q: If somebody’s using high-CBD cannabis for, say, spasm, they could titrate and figure out an effective dose—two puffs, or three, or four...

McAllister: They probably could. One problem would be the placebo effect. You wouldn’t really know if the effect was due to the drug or the placebo effect on that person.

Q: I’ve heard it suggested that the placebo effect itself might involve the endocannabinoid system.

McAllister: Why not? When it came to reduction of pain, the placebo effect involved the endorphin system—this system was discovered through research on opiates/opium. So why couldn’t the placebo effect for spasticity involve the endocannabinoid system? It makes sense. And there’s nothing wrong with the placebo effect. But for cancer it’s going to be important to have the correct dosing schedule.

PhRMA Denial Campaign Continues, But...Hormone Replacement Therapy

Link to Breast Cancer Confirmed

In July 2002 the Women’s Health Initiative reported that women taking Wyeth’s blockbuster HRT drug Prempro—a combination of estrogen and progesterin—had a heightened incidence of breast cancer. Wyeth and their allies in the medical establishment challenged the WHI data, claiming that a drop in the rate at which women were getting mammograms led to fewer breast cancers being detected. But millions of women stopped taking Prempro, and when the data for 2003 was analyzed, the U.S. breast cancer rate, which had been rising for decades, was shown to have dropped 2% from 2002 new cases to fewer than 190,000. This excellent news was reported by researchers at the M.D. Anderson Cancer Center, and again Wyeth et al tried to downplay it.

Now the numbers through 2005 have been analyzed in The New England Journal of Medicine (“Breast Cancer After Use of Estrogen Plus Progestin in Postmenopausal Women,” by Chlebowski et al). The conclusion: “The increased risk of breast cancer associated with estrogen-plus-progesterin therapy declined markedly soon after discontinuation of the therapy and was unrelated to a change in the use of mammography.”

Chlebowski estimates that HRT caused breast cancer in 200,000 women between 1992 and 2002. “About 22 percent of women who get breast cancer die from it,” according to medical writer Virginia Hopkins, “so by extrapolation we can infer that some 44,000 women died during that decade due to taking synthetic HRT.” HRT also increases the risk of breast cancer, stroke, heart disease and gallbladder disease and dementia. The evidence linking breast cancer probably explains why Marlin County has had an elevated breast cancer rate: it’s a function of more and “better” health care available to the affluent...